PAINFUL HIV-ASSOCIATED SENSORY NEUROPATHY IN THE ERA OF EFFECTIVE ANTIRETROVIRAL THERAPY

Cherry C.
Painful HIV-associated sensory neuropathy in the era of effective antiretroviral therapy
Australia

Up to 40% of HIV infected individuals will develop a painful distal symmetrical polyneuropathy. The neurotoxicity of some of the original agents used in highly active antiretroviral therapy (HAART) has been linked to the stubbornly high rate of the peripheral neuropathy since the wide-spread introduction of HAART. Yet, there is accumulating evidence that the substitution of these neurotoxic antiretroviral agents with less neurotoxic agents has not been associated with significant reduction in the rate of the neuropathy. Thus, HIV-associated sensory neuropathy continues to cause significant pain-related disability in the era of modern HAART. Moreover, the condition has proven resistant to traditional analgesic therapies for painful peripheral neuropathy. The lecture will cover: i) the epidemiology of HIV-associated sensory neuropathy since the introduction of HAART, focusing on the continuing high rate of the neuropathy with modern treatment options, and ii) the evidence-base for pharmacological analgesic treatments of this treatment-resistant neuropathy.
NEUROPATHIC PAIN IN CANCER

Bennett M.

Neuropathic pain in cancer

UK

The session will outline the different types of pain arising in cancer, focusing on neuropathic pain, which is experienced by 20% of people with cancer. There are several different mechanisms of neuropathic pain in cancer, some arising directly as a result of the tumour, and others as a result of treatment. It is important to distinguish between these pain types and causes, in order to address and treat pain effectively. Recent and current work, including high profile research by the speaker, will be reviewed to describe the epidemiology of cancer-related neuropathic pain, and evidence on effectiveness of available treatments. Neuropathic pain in cancer demands some important differences in assessment and therapeutic approach from other types of neuropathic pain, though many similarities also exist.
While much has been learned about neurobiology of pain, translation of novel mechanisms into therapies has been disappointing. Many hurdles exist to develop new pain therapies. At the preclinical level, one challenge is measurement and mechanistic evaluation of ongoing or spontaneous pain. Pain is aversive and elicits a strong motivation drive to escape. The motivational drive resulting from the unpleasantness of ongoing pain has allowed exploration of mechanisms with possibly increased translational relevance. Relief of ongoing pain is rewarding in humans and this is likely to be true in animals. Accordingly, manipulations that provide pain relief produce conditioned place preference (CPP) for a context associated with relief. This approach allows the unmasking of ongoing or spontaneous pain and the dissection of underlying mechanisms. Drugs that are effective clinically produce CPP in nerve-injured rats, whereas ineffective treatments fail to do so. Thus, drugs that are not rewarding in the absence of pain become rewarding in the presence of ongoing pain. This approach allows investigation of neural circuits that contribute selectively to affective dimensions of pain. Understanding these circuits and molecular targets may increase confidence in advancing to clinical studies, speeding the discovery of novel therapies for the treatment of pain.
CHANGING MEANING AND MOOD IN NEUROPATHIC PAIN

Moseley L. (Chair and speaker)
Reconceptualising the problem in neuropathic pain

Edwards R.
Changing meaning and mood in people with pain

Jensen M.
Hypnosis for chronic pain - facilitating change in meaning and mood

This workshop speaks directly to the theme of the symposium by discussing how we can improve a patient's understanding of their pain problem in order to help them overcome it. A compelling body of data clearly show that the way in which an individual conceptualizes their pain modulates the pain itself. Catastrophic thought processes about pain, and depression have been shown to upregulate the pain system and increase the risk of chronic pain and disability. That is, meaning and mood seem to be important modulators of neuropathic and other chronic pains, importantly, are viable targets for treatment. This workshop will present the fundamentals and recommendations for practice of three important approaches to changing these cortical factors in neuropathic pain. Prof Moseley will discuss reconceptualization of the problem - the concept of "explaining pain" and its integration within a wider rehabilitation approach. Dr Edwards will focus on current concepts in cognitive therapy aimed at changing catastrophising and improving mood. Prof Jensen will discuss mechanisms and practical application of hypnosis for chronic pain. There will be an emphasis on the evidence-base for these interventions, practical tips and speculate on possible future directions for brain-targeted cognitive interventions.
COMPARATIVE STUDY BETWEEN SELECTIVE NERVE ROOT INJECTION AND PULSED RADIOFREQUENCY (PRF) FOR SCIATICA, A ONE YEAR FOLLOW UP STUDY

M. Yosry, Egypt

I reported the 1-year results of a study evaluating the efficacy of a single nerve root injection of depot steroid versus pulsed radiofrequency (2 cycles, 120 sec. each) for sciatica. My aim is to evaluate the long-term efficacy of depot steroid versus PRF in patients with sciatica secondary to herniated disc.

Methods: The study is performed on 200 patients. Inclusion criteria were unilateral Lumbar sciatic pain with a single level disc herniation. Criteria included (in addition to a disc herniation in MRI) neural entrapment (straight leg raising [SLR] = 60º). 100 patients were allocated to a single injection of 40 mg methylprednisolone diluted in lidocaine and hypertonic saline 2.7% and the other 100 patients are candidates for PRF by transforaminal approach. Differences in the clinical examination parameters (straight leg raise [SLR], sensory defects), patient-reported symptoms (leg and back pain using a visual analog scale [VAS]), sick leaves, number of discectomies, and adverse effects.

Results: No significant differences in baseline variables existed. 85% of patients in the PRF reported no pain by the end of the year compared with 75% in the selective Nerve root injection group ($P = 0.73$). Similar efficacy was observed between treatment groups for other outcomes. 10 patients required surgery (4 in PRF-group and 6 in Nerve root-group). No adverse reactions were encountered in any of the groups.

Conclusions: The long-term results of this study do not support the use of PRF for sciatica over nerve root injection for lumbar Radicular pain in patients with sciatica.
MECHANISMS OF PAINFUL DIABETIC NEUROPATHY

Castro-Lopez J. (Chair and speaker)
Chair

Bierhaus A.
Role of advanced glycation end products in neural damage

Russell J.
Role of reactive oxygen species in neural damage

Calcutt N.A.
Neuroprotection in the prevention of diabetic neuropathy
Portugal, Germany, USA

Alternative speakers:

Peter Reeh, Erlangen, Germany (as an alternative for Angelika Bierhaus)

Makoto Tominaga, Okazaki, Japan

ML Flonta, Bucharest, Romania

AJM Boulton, Manchester, UK

Solomon Tesfaye, Sheffield, UK

Hans-Peter Hammes, Mannheim, Germany

Tim S Kern, Cleveland

Misha Backonja, Madison, USA
ASSESSMENT AND TREATMENT OF DIABETIC NEUROPATHY

Perkins B.A. (Chair and speaker)
Chair

Madras V.
The diabetes epidemic: implications for neuropathic pain

Malik R.A.
Intravital corneal microscopy vs. punch skin biopsy

Ziegler D.
Evidence-based treatment of painful diabetic neuropathy
Canada, India, UK, Germany

Alternative speakers:

Makoto Tominaga, Okazaki, Japan
ML Flonta, Bucharest, Romania
AJM Boulton, Manchester, UK
Solomon Tesfaye, Sheffield, UK
Hans-Peter Hammes, Mannheim, Germany
Tim S Kern, Cleveland
Misha Backonja, Madison, USA
Nerve injury or trauma can produce sustained activity in peripheral afferents that results in significantly increased excitability of spinal cord neurones and higher centres, producing central sensitisation. There is increasing evidence for a significant role of supraspinal excitatory influences in the development and maintenance of abnormal sensitivity in neuropathic pain- particularly the brainstem rostral ventromedial medulla. The brainstem mediates bulbar relay of descending modulatory projections that facilitate or inhibit spinal neurotransmission. This brainstem-spinal pathway provides multiple pharmacological targets for analgesia, including those for antidepressants, opioids and gabapentinoids. Animal data and imaging and clinical studies in humans have revealed an essential role of the brainstem in mediating pro-nociceptive changes in central excitability- namely enhanced excitatory events and/or reduced inhibitory controls. Associated changes in various neurotransmitter systems are key to setting the scene for long-term sensory changes that promote ongoing pain.

This workshop will provide a clear understanding of the role of these spino-bulbar interactions in producing and maintaining neuropathic pain. Recent preclinical and clinical data will be used to discuss changes that occur and the neurotransmitters involved within the spinal-brainstem loop of descending modulation, which ultimately leads to enhanced central excitability that underlies the abnormal sensory phenotypes of neuropathic patient.
A SURGICAL SOLUTION OF POST TRAUMATIC AND POST SURGICAL NEUROPATHIC PAIN

S. Akhtar, R. Singh, UK

**Aim:** We propose that post surgical and post traumatic neuropathic pain has a physical cause and can be improved by surgery.

Such pain has a profound effect on quality of life and social function, thus we were compelled to offer a surgical solution.

Within our department we present a case series that have achieved successful outcomes following our surgical treatment.

**Method:** Our indications for surgery were:

- Pain along the sensory distribution of the nerve
- Positive Tinel's sign
- Painful neuroma in the nerve
- Neuropathic pain

23 patients either post traumatic or post surgical in aetiology were treated between 2007 and 2011. Pre and post-operative disease specific outcome measures of pain and paraesthesia (VAS) and General Health state specific outcome measure (Nottingham Health profile score) were taken as outcome measures.

The surgical treatment, carried out by a single surgeon, consisted of nerve exploration, decompression, neurolysis, or neuroma excision.

Our follow-up was conducted by a single non blinded observer (not the original surgeon).

**Results:** Post-operative VAS and Nottingham Health scores were significantly improved in the vast majority of cases, many displaying immediate improvement.

**Pain scores** improved: from 8 to 0 (p< 0.001) and **Paraesthesia** improved from 7 to 0 (p=0.005)

Nottingham health profiles improved from 71% to 100% with marked improvements in pain and sleep. Overall quality of life improved significantly (p< 0.001).

**Conclusion:** Surgical treatment of neuropathic pain secondary to trauma or surgery dramatically improves patient disease specific and quality of life outcomes.
PKMZETA: ITS REGULATION AND CONTRIBUTION TO THE MAINTENANCE OF SPINAL NOCICEPTIVE PLASTICITY

Coderre T.J. (Chair and speaker)
Role of PKMzeta in the maintenance of spinal nociceptive plasticity: Regulation by PIN-1 and effects on AMPA receptor trafficking

Price T.J.
Role of PKMzeta in the maintenance of spinal nociceptive plasticity: Regulation by BDNF

Marchand F.
Role of PKMzeta in the maintenance of spinal nociceptive plasticity: Interactions with NR2B subunits and PSD-95

Canada, USA, France

While it is known that spinal PKMzeta is key in maintaining spinal plasticity underlying persistent pain, the mechanisms controlling PKMzeta are unknown. Dr. Price will examine the role BDNF plays in regulating PKMzeta. He will show that BDNF stimulates PKMzeta formation and phosphorylation at spinal synapses. Using behavioral studies with BDNF sequestration or TrkB blockade he will show BDNF is key to the initiation and maintenance of chronic pain states. Dr. Marchand will examine the interaction of NMDA receptors, scaffolding proteins and PKMzeta. He will show, using immunoprecipitation, that there is a novel interaction of NR2B subunits and PSD-95 with PKMzeta. He will show that perturbing interactions between PSD-95 and spinal NR2B subunits, or inhibition of PKMzeta, reduces wind-up of spinal sensory neurons, as well as formalin-induced spinal neuronal activity, spinal c-Fos and pain-related behaviours. Dr. Coderre will examine the role of protein interacting with NIMA 1 (PIN-1) in the regulation of PKMzeta. He will show that an inhibitor of PIN-1, enhances mechanical allodynia in animal models of persistent nociception by enhancing PKMzeta activity. He will also present evidence that the nociceptive effects of PKMzeta depend on enhanced trafficking of AMPA (GluR2) receptors to the plasma membrane of spinal neurons.
EPIDEMIOLOGY OF NEUROPATHIC PAIN: NEWER PREVALENCE AND QUALITY OF LIFE STUDIES

Attal N. (Chair and speaker)
The specific disease burden of neuropathic pain in the general population

Christian D.
Edonis: a French national study of the epidemiology of neuropathic pain after surgery

Petersen K.
Herpes zoster and PHN: prevalence, natural history and impact on quality of life
France, USA

A better knowledge of epidemiology of neuropathic pain is important to better delineate the problem and guide therapeutic decisions. In recent years, several studies have emphasized the importance of NP in terms of prevalence in the general population (Bouhassira et al Pain 2008; Torrance et al J Pain 2006), but also in terms of specific impact on quality of life (Attal et al Pain 2011). Similarly well designed studies have addressed the natural history of postherpetic neuralgia (Petersen et al submitted; Thyregod et al Pain 2007) and of postsurgical neuropathic pain (Dualé et al, submitted).

This workshop will review the latest epidemiological studies of NP in general or in specific conditions. Nadine ATTAL (France) will show that the burden of illness of neuropathic pain is higher than that of non neuropathic pain in the general population. Karen Petersen (USA) will address the prevalence, natural history and impact of postherpetic neuralgia. Christian Dualé (France) will present the results of a large scale French epidemiological study about the prevalence and impact neuropathic pain after various surgeries.
GENETIC ASSOCIATION STUDIES OF NEUROPATHIC PAIN STATES: PERSPECTIVES AND CAVEATS

Kamerman P. (Chair and speaker)
Genetic diversity: pitfalls and benefits

Kim H.
Back to Basics: avoid common fumbles in genetic association studies

Smith B.
Defining and ascertaining a neuropathic pain phenotype for population-based genetic studies
South Africa, USA, UK

There has been a rapid increase in the number of genetic association studies of complex neuropathic pain states over the past decade. Despite some success, the field is complicated by inconsistent findings. Many of the inconsistencies result from methodological differences between studies, with potential bias being introduced at multiple stages from study design to data analysis and interpretation.

This workshop will address common issues that complicate the undertaking and interpretation of genetic association studies on neuropathic pain conditions.

Upon completion of the workshop, participants will:

1. have gained an understanding of issues related to accurate case ascertainment in genetic studies, and the need for robust and practical consensus guidelines on the phenotyping in genetic association studies of neuropathic pain conditions (B. Smith).
2. have learned about the principles of genetic association studies, from study design to data analysis. These include selection between candidate gene and genome-wide approaches, appropriate sample sizes, correction for multiple comparisons, and study replication (H. Kim).
3. have learned about the confounding effect population genetic heterogeneity has on selecting appropriate genetic markers and interpreting the findings of association analyses (population stratification). (P. Kamerman)

The workshop will conclude with open debate and discussion amongst the audience and the panelists.
IS COMPLEX REGIONAL PAIN SYNDROME NEUROPATHIC? - INSIGHTS FROM RECENT INVESTIGATIONS INTO THE ROLE OF THE IMMUNE SYSTEM

Baron R. (Chair and speaker)
Is CRPS neuropathic - the state of the debate

Goebel A.
CRPS as a Regional Autoimmune Disorder

Huygen F.
CRPS and Inflammation
Germany, UK, The Netherlands

The question of whether CRPS is neuropathic remains open. Recent research has emphasized the importance of both autoimmune-, and inflammatory processes in the CRPS pathophysiology. We will set out the state of the current debate on neuropathy in CRPS, and highlight how our understanding about an immune involvement is likely to impact on this debate.

Prof. Baron will provide an historical overview, in which he will outline pertinent points in support and against the idea that CRPS is neuropathic.

Dr. Andreas Goebel will summarise current evidence in support of the concept of CRPS as an ‘autoantibody-mediated autoimmune disorder with regional restriction and predominantly functional impact’; he will review results from recent clinical trials, and ongoing research on autoantibody target epitopes, and discuss the implications of these findings for the debate on whether or not CRPS is neuropathic.

Dr. Huygen will highlight evidence supporting the involvement of inflammation in CRPS, and will discuss the relevance of these findings for the questions of a) the central versus peripheral cause for CRPS, b) the neuropathic versus nociceptive nature of CRPS.
Baron R. (Chair and speaker)
Mechanisms and assessment of mixed neuropathic pain

Bouhassira D.
How neuropathic is low back pain?

Perrot S.
Low back pain with or without radicular pain: A difficult management
Germany, France

Low back pain (LBP) with or without lower limb pain is one of the most challenging chronic pain disorders to treat, due in part to its heterogeneity, probably reflecting multiple underlying mechanisms. This heterogeneity may account for the poorer results obtained in clinical trials of treatments for chronic lumbar radiculopathy than for other neuropathic pain (NP) conditions (Attal et al 2010). Both neuropathic and nociceptive mechanisms are thought to contribute to the pain experienced in patients with low back and lower limb pain. However, the current definition of "neuropathic LBP" remains vague, with no consensus concerning its best clinical determinants. This may probably account for the difficulties in management. This workshop will present new data about definition, mechanisms, clinical diagnosis and assessment and treatment of low back pain with or without lower limb pain and the links between low back pain and neuropathic pain.
REPETITIVE TRANSCRANIAL MAGNETIC STIMULATION FOR THE TREATMENT OF NEUROPATHIC PAIN: IS IT REALISTIC IN CLINICAL PRACTICE?

Bouhassira D. (Chair and speaker)
rTMS for the treatment of neuropathic pain

Lefaucheur J.-P.
rTMS to predict the efficacy of implanted cortical stimulation

Ciampi de Andrade D.
Mechanisms of action of rTMS in chronic pain
France, Brazil

Noninvasive brain stimulation techniques are novel techniques for stimulating the cerebral cortex, which have raised an increasing interest in recent years for the treatment of various pain conditions. The potential advantages of these techniques in the treatment of pain are related to their safety and relative lack of side effects. This symposium will address the relevance of repetitive transcranial magnetic stimulation (rTMS) for the treatment of neuropathic pain, either as standalone techniques or to predict the efficacy of implanted motor cortex stimulation. The recommendations, mechanisms of action and clinical efficacy data of these techniques in neuropathic pain after single or multiple experimental sessions will be presented and commented.

Daniel Ciampi de Andrade (Brazil) will review the mechanisms, recommendations and principles of rTMS and tDCS in analgesia.

JP Lefaucheur (France) will show newer data about the relevance of rTMS to predict the response to invasive cortical stimulation in NP.

Didier Bouhassira (France) will perform a state of the art presentation of the efficacy of rTMS in the treatment of chronic pain including notably neuropathic pain.
MORPHOMETRICAL ANALYSIS OF THE COMMON PERONEAL NERVE, DURING ITS COURSE THROUGH THE FIBULAR TUNNEL USING US IMAGING

L. Meylaerts, F. Weyns, Belgium

Introduction: Peroneal neuropathy is caused by entrapment of nervus fibularis communis (NFC). This condition is associated with rapid and marked weight reduction and results in foot drop. NFC descends along lateral side of fibular head, where it enters fibular tunnel. Because NFC runs subcutaneously, it can be visualised using ultrasonography (US). Purpose of this study is analyze morphometry of NFC, giving a better view of the NFC anatomy.

Materials and methods: Ultrasonography was performed on 50 patients, none with peroneal neuropathy (25 males, 25 females; 18 - 80y). US images were taken at three positions in both legs: where NFC winds around fibular neck, proximal and distal to this location. Morphometrical characteristics (transversal NFC surface area, distance between fibula and NFC, etc.) were measured on US.

Results: Morphometrical analysis shows no significant differences between both legs, except for transversal surface area of fibular tunnel. Surface area of tunnel in left leg was significantly larger than surface area in right leg (P=0.004). Transversal surface area of NFC, distal to fibular neck area, was significantly larger than proximal (P< 0.001). The latter was positively correlated with weight (P< 0.001) Body Mass Index (P< 0.001) and subcutaneous fat, covering peroneal nerve (P=0.003). Surface area of fibular tunnel was positively correlated with weight (R=0.368; P< 0.001) and BMI (P< 0.001). Statistical correlation existed between transversal surface area of tunnel and NFC (P< 0.001).

Conclusion: This study showed that weight, BMI and subcutaneous fat, covering NFC, were statistically correlated with parameters in NFC anatomy.
QST (QUANTITATIVE SENSORY TESTING): USEFUL FOR DIAGNOSTICS IN AN INDIVIDUAL CASE?

Backonja M. (Chair and speaker)
Introduction, Summary

Bouhassira D.
QST: Useful for diagnostics in an individual case? NO!

Maier C.
QST: Useful for diagnostics in an individual case? YES!
*USA, France, Germany*

The use of QST for individual diagnostics in an individual case is still under debate, because it is a psycho-physical assessment tool, which means, the response depends e. g. from the patient’s motivation. Other crucial issues are the cut-off lines between normal and abnormal for some parameters, particularly in older patients. On the other side, QST is the only non-invasive, but standardized assessment for the early stage of neuropathy and the only one for detection of impaired small fiber function as well as for the differentiation and quantification of different types of hyperalgesia. The aim of this workshop, which will be organized in the form of a debate, will be to present the different QST approaches and then the pros and cons for their use in clinical research and in daily practice.
NEUROPATHIC PAIN IN DEVELOPING COUNTRIES

Kamerman P. (Chair and speaker)
Painful HIV-associated sensory neuropathy in Africa: epidemiology and treatment

Seltzer Z.
Neuropathic pain in Cambodian limb amputees: suffering in silence.

Hietaharju A.
Burden of chronic neuropathic pain in leprosy patients
South Africa, Canada, Finland

Nerve damage resulting from infection, certain diseases or trauma only accounts for a small proportion of the overall rate of chronic pain in developed countries. However, they occur at disproportionately higher rates in developing countries, affecting an enormous proportion of the population of the world, contributing significantly to personal suffering, and to societal and economical burdens in these regions. Almost nothing is known about the rates of neuropathic pain syndromes in developing countries, its etiologies, patterns, the dysfunction they cause and the treatments used.

This workshop will address three common causes of neuropathic pain in developing countries, namely, antiretroviral toxic neuropathy, leprotic neuropathy and neuropathic pain following traumatic amputation.

Upon completion of the workshop, participants will:

1. have gained an understanding of the epidemiology and management of antiretroviral toxic neuropathy in low-resourced settings in Africa. (P. Kamerman)
2. have learned about the prevalence and characteristics of neuropathic pain following traumatic limb amputation, primarily as a result of landmine injuries, in Cambodians. (Z. Seltzer)
3. have learned about the epidemiology, assessment and mechanisms of chronic neuropathic pain in leprosy patients who have completed multi-drug therapy. (A. Hietaharju)

The workshop will conclude with an open debate and discussion.
NEUROPATHIC PAIN SCREENING TOOLS: CONTROVERSIES IN CLINICAL PRACTICE AND RESEARCH

Torrance N. (Chair and speaker)
Screening instruments in research

Bouhassira D.
Screening instruments in clinical practice

Bennett M.
Screening instruments in cancer pain

UK, France

Several brief screening tools exist for identifying pain with neuropathic features. These generally show reasonable sensitivity and specificity in pain clinic populations, and are designed for use in secondary or primary care, with a view to influencing treatment decisions. They have also contributed importantly to population research estimating prevalence, distribution and determinants of neuropathic pain. There are important variations between the instruments, but also many similarities. Despite many papers advocating their use in clinical practice or reporting their epidemiology, positive predictive value (compared with specialist examination) in patient samples outwith the pain clinic is uncertain, and we lack specific evidence of their influence in improving patient outcomes.

The speakers, who are experts in the development and use of these instruments, will review the similarities and differences between available instruments, and the evidence for their use as clinical and research tools. They will consider their performance in some specific patient and population groups, and particularly in cancer-related pain. Workshop attenders will debate arguments for and against their continued use or further development.

Didier Bouhassira: Screening instruments in clinical practice

Nicola Torrance: Screening instruments in research

Michael I. Bennett: Screening instruments in cancer pain

Blair H. Smith: Chair and discussion
PAINFUL HIV-ASSOCIATED SENSORY NEUROPATHY: RECENT ADVANCES IN ANIMAL MODELLING, UNDERLYING MECHANISMS, THERAPEUTIC STRATEGIES, AND GENETICS

Huang W. (Chair and speaker)
Refined animal models of HIV antiretroviral drugs induced peripheral sensory neuropathy

Hoke A.
Mechanisms of distal axonal degeneration using in vitro and in vivo models of HIV-SN

Kamerman P.R.
Recent advances in understanding the influence of genetic polymorphisms in mitochondrial and nuclear DNA on the risk of developing HIV-SN

UK, USA, South Africa

The most frequent neurological manifestation of HIV infection and its treatment is the development of a peripheral sensory neuropathy (HIV-SN) that is frequently painful. The combination of the increased use of neurotoxic antiretroviral agents and the resulting improved patient survival has resulted in HIV-SN becoming an increasing problem in resource poor countries. Despite the increased use of less neurotoxic antiretroviral drugs in the developed countries with rich resource, HIV-SN prevalence has remained high. Conventional neuropathic pain agents are ineffective in HIV-SN. Consequently painful HIV-SN remains a large world health problem. In this workshop, we intend to discuss the progress in the past few years in the use of refined animal models of HIV-SN to closely mimic clinical scenarios, in understanding the mechanisms underlying HIV-SN using human studies and animal models with an emphasis on the importance and relevance of mtDNA mutations and mitochondrial "aging" to explain the preferential distal degeneration of axons, in the development of therapeutic strategies based on the mechanistic findings, and updates on the genetic aspects of HIV-SN such as the influence of polymorphisms in mitochondrial and nuclear DNA on the risk of developing HIV-SN and population-dependent differences and consistencies in these genetic findings.
Neuropathic pain can result from primary dysfunction of peripheral nociceptive sensory neurons. This pain outlasts the early stage of injury and frequently leads to debilitating disorders that are not responsive to conventional analgesic drug therapies. It has been suggested by a number of groups that regulation of voltage-activated calcium channels may contribute to hyperexcitability of the primary afferent neuron associated with chronic pain states. An emerging approach to treating neuropathic pain is to target ion channels on sensory neurons that play a role in neuronal excitability and neurotransmitter release. Two candidate ion channels have been shown to control neuronal excitability and neurotransmitter release in peripheral sensory neurons: the T-type and N-type calcium channels, respectively. Biological, genetic, and clinical evidence provide validation for voltage-gated calcium channels as therapeutic targets for chronic pain. In this workshop, we will present novel strategies to curbing calcium channel function to ameliorate pain in rodent models (Khanna), targeting of a specialized type of calcium channel - the low-voltage activated T-type calcium channel in pain (Zamponi), and regulation of the calcium channel auxiliary subunit alpha2 delta (α2δ) subunits in neuropathic pain (Dolphin).
IS PERIPHERAL OPIOID ANALGESIA A Viable STRATEGY FOR THE TREATMENT OF NEUROPATHIC PAIN?

Sweitzer S. (Chair and speaker)
Using Herpes Simplex Virus mediated Gene Therapy to Enhance Peripheral Opioid Analgesia in the Treatment of Neuropathic Pain

Schaefer M.
Sensory neuron opioid responsiveness varies as a function of pain condition: Implications for systemic versus peripheral opioid therapy

Webster L.
A Role for Novel, Orally Available Mu-Opioid Agonists with Both Centrally and Peripherally Mediated Analgesia in the Treatment of Neuropathic Pain
USA, Germany
Chair: Dr. Srinivasa Raja, MD

Present therapies for neuropathic pain, including opioids, are limited by their side effects. Although the efficacy of opioids for neuropathic pain has been shown by randomized trials, their clinical use remains controversial, in part, due to their centrally mediated side-effects (sedation, cognitive dysfunction, potential for abuse). Therapies targeting peripheral opioid receptors have been postulated as potentially useful for neuropathic pain with peripheral opioids, such as morphine-6-glucuronide, showing efficacy in human pain states. This workshop will highlight the preclinical and clinical evidence for the potential beneficial effects and limitations of peripheral opioid analgesia. Dr. Michael Schafer will discuss the basic mechanisms of peripheral opioid analgesia in different pain conditions and the relative contributions of supra-spinal, spinal and peripheral mu-opioid receptors (MOR) to the antinociceptive effects of centrally acting versus peripherally selective opioids. The utility of gene-based therapies, such as herpes viral vectors expressing MOR and ligands, in preclinical neuropathic pain models will be presented by Dr. Sarah Sweitzer. Dr. Lynn Webster will discuss the clinical results with two novel orally bio-available, MOR agonists that have been engineered to have a significantly reduced rate and extent of CNS exposure relative to standard opioid agonists.
CHEMOTHERAPY-INDUCED PERIPHERAL NEUROPATHIES: CAUSAL MECHANISMS AND NOVEL THERAPEUTIC STRATEGIES

Hoke A. (Chair and speaker)
Molecular mechanisms of axonal degeneration in chemotherapy-induced peripheral neuropathy

Bennett G.
Mitochondrial toxicity as the cause of chemotherapy-induced peripheral neuropathy

Flatters S.
Assessing mitochondrial function in paclitaxel-induced painful peripheral neuropathy

USA, Canada, UK

The most common dose-limiting side effect of chemotherapy is toxicity on the peripheral nerves. Chemotherapy-induced peripheral neuropathy (CIPN) is often painful, causing difficulty with mobility and adversely affects quality of life in cancer survivors. Furthermore, several analgesics with established efficacy in other painful neuropathies have failed to show any efficacy in double-blind, placebo-controlled RCTs of patients with CIPN. Although underlying molecular mechanisms that initiate the axonal degeneration are likely to be different among different classes of chemotherapeutic drugs, a common final pathway that results in distal axonal degeneration may exist. Recent advances in the field put mitochondria and mitochondrial toxicity of common chemotherapeutic drugs at the center of this common final pathway. These new molecular mechanisms of axonal toxicity open up new therapeutic targets for development of neuroprotective drugs to prevent CIPN or to treat neuropathic pain using a novel drug target.
DEVELOPMENTAL PLASTICITY IN MICROGLIA-NEURON SIGNALING FOR NEUROPATHIC PAIN

Beggs S.
Developmental plasticity in microglia-neuron signalling in neuropathic pain

Canada

This talk would focus on recent work by the proposed speaker demonstrating that there are enhanced neuroimmune response seen in neonatally primed animals which lead to increased pain hypersensitivity in the adult. This discovery implies that early life injury may predispose individuals to enhanced sensitivity to painful events.
COMBINATION PHARMACOTHERAPY FOR NEUROPATHIC PAIN

Gilron I. (Chair and speaker)
Combination pharmacotherapy for neuropathic pain: Clinical trial design

Dickenson A.
Preclinical research on mechanistic aspects of combination therapy

Jensen T.S.
Clinical aspects of combination pharmacotherapy in routine practice
Canada, UK, Denmark

Following an introduction and foreword on the basis and rationale for combination pharmacotherapy, Professor Dickenson will illustrate the therapeutic potential of combination pharmacotherapy by highlighting mechanistic aspects of additive and synergistic analgesic interactions through various preclinical investigations. Rationale for picking certain targets to combine will be presented as well as issues of combining two different drugs or using single agents with more than one mechanism of action. Professor Gilron will discuss design of clinical trials that evaluate analgesic drug combinations and compare their efficacy to those of single-agents. Review of published trials will facilitate appraisal of the current evidence base for combination pharmacotherapy and highlight knowledge gaps in this area. Professor Jensen will discuss contemporary approaches to implementing evidence-based results into safe and effective pain management practices by discussing known adverse drug interactions and clinical settings where combination pharmacotherapy is of particular benefit. The limitations of combination therapy with available drugs will also be presented. In particular the narrow therapeutic window due to cognitive side effects represent an obstacle and calls for rethinking. An interactive audience-panel discussion on future advances in combination pharmacotherapy for pain will focus on how to better harness the potential of this treatment strategy.
NEW EPIDEMIOLOGICAL DATA AND HOW TO REDUCE THE RISK OF CHRONIC PAIN AFTER SURGERY

Stubhaug A.
New epidemiological data and how to reduce the risk of chronic pain after surgery

Chronic pain after surgery is mostly neuropathic pain. The Tromsø study (13000 interviewed persons) have new data, showing the true prevalence. See: Johansen A, Romundstad L, Nielsen CS, Schirmer H, Stubhaug A. Persistent postsurgical pain in a general population: prevalence and predictors in the Tromsø study. Pain. 2012 Mar 23. [Epub ahead of print] PMID:22445291


Audun Stubhaug delivered an excellent plenary lecture at the Scand Assoc for the Study of Pain scientific meeting in Århus April 21, 2o12, convincingly focusing on what we can do and what is not effective in reducing the risk of chronic postsurgical pain. This is a vitally important topic.

Audun Stubhaug is Professor of Anesthesiology, Pain Medicine and Pain Research, chairman of the Department of pain management and research, Oslo University Hospital,

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PAIN MODULATION PROFILE: ALL YOU NEED TO KNOW ABOUT

Yarnitsky D.

Pain modulation profile: all you need to know about

Israel

The processing of experimental pain, administered to non-affected body parts and modulated by patient's nervous system, reveals the individual properties of handling pain at large, regardless of the specific pain syndrome that patient is suffering from. Pain modulation profile consists of patient's ability to (i) inhibit pain, as assessed by the conditioned pain modulation (CPM) profile, (ii) enhance pain, as assessed by pain temporal summation, and (iii) describe pain sensitivity, as assessed by supra-threshold magnitude estimation of nociceptive stimuli. Data on pain modulation has been shown to reveal important clinical points, such as the risk of acquiring future neuropathic or non-neuropathic pain, and the prediction of efficacy of anti-neuropathic pain drugs. It will be proposed that exploring pain modulation profile (PMP) is essential for understanding pain pathophysiology, providing, amongst other aspects, important data on the correct selection of anti-neuropathic pain drugs. State of the art of research and novel findings on PMP and its clinical relevance will be presented.
Neuropathic pain is associated with severe and debilitating affective states, which include clinical manifestations of anxiety and depression. Both evolve with chronic pain and significantly impact treatment efficacy, suggesting that neuropathic pain alters mechanisms mediating adverse affective states. This workshop will examine this hypothesis by presenting recent research on the relationship between neuropathic pain and affective states from a clinical to a mechanistic perspective. Jennifer Haythornthwaite (Johns Hopkins Medical Centre, Baltimore USA) will review the relationship between affective disorders in long-term pain patients using a biopsychosocial model that outlines the deleterious role of catastrophizing. Using a mouse model of neuropathy induced by sciatic nerve cuffing, Michel Barrot (Institute of Cellular and Integrative Neuroscience, Strasbourg France) will present evidence that affective consequences of neuropathic pain evolve over time. Anatomical and molecular investigations in this model reveal that substrates mediating both anxiety- and depressive-like behaviors are independent of the hypothalamic-pituitary-adrenal axis system. Anna Taylor's (UCLA, Los Angeles USA & Queen's University, Kingston Canada) research extends this line of inquiry by investigating how neuropathic pain modifies affective responses to analgesic drugs. She will present evidence that neuropathic pain produces a switch from dopamine-independent to dopamine-dependent systems, a process that depends on microglia activation.
Despite the plethora of drug targets for neuropathic pain which have emerged over the past few decades, very few effective new drugs have reached the clinic. This high rate of attrition of development compounds which appear to have efficacy in animal models but which “fail” in clinical trials is not sustainable. This workshop will examine three crucial areas of drug development:

Rice will critically appraise animal models of neuropathic pain for predictive validity. He will discuss: advances in developing clinically relevant models reflecting the range of conditions associated with neuropathic pain. He will describe more sophisticated outcome measures than the simple assessment of withdrawal response. Finally, he will address experimental design and bias.

Petersen will describe developments in the use of experimental pain models in healthy volunteers and patients in phase 1 studies to provide proof of concept prior to embarking on phase clinical trials.

Dworkin will describe an analysis of trial design factors in studies where analgesic treatments examined in randomized clinical trials have failed to show superiority to placebo in conditions in which their efficacy had previously been demonstrated. He will then discuss how we can use this information to improve the sensitivity of neuropathic pain trials.
OPIOID THERAPY FOR NEUROPATHIC PAIN: A CHALLENGING LONG TERM COMMITMENT?

Stannard C.F. (Chair and speaker)
Effectiveness of opioids in the management of neuropathic pain

Katz N.
Endocrine effects of opioid therapy: implications for clinical management

Ballantyne J.C.
Long term opioid therapy: ethical challenges
UK, USA

Neuropathic pain remains challenging to treat. Opioid therapy has become established in the repertoire of treatments for neuropathic pain but the hazards of long-term therapy are increasingly recognized and concerns about opioid treatment have, in many countries, prompted a critical appraisal of the benefits and harms of therapy.

There has been a sustained rise in the prescription of opioids in the US, Europe, Australia and elsewhere and data from the US demonstrate that there has been a parallel increase in misuse of prescription opioids, related overdose and death. This has focused the need for clinicians and policy makers to appraise opioid therapy not only in relation to the individual being treated but also as a public health issue.

The workshop will discuss the evidence for effectiveness of opioids in the management of neuropathic pain. Endocrine dysfunction in patients taking long-term opioid therapy is well characterized and the hormonal effects of opioids in males and females and strategies for screening and management of endocrine disturbance will be presented. These discussions will then be set in the broader context of individual and societal misuse of prescribed opioids and the difficult ethical challenges in relation to opioid prescribing will be presented for debate.
COMPLEX REGIONAL PAIN SYNDROME - A REGIONAL OR GENERALIZED DISORDER?

Birklein F. (Chair and speaker)
CRPS is more than a central disease: the complex pattern of peripheral inflammation in CRPS

Terkelsen A.J.
Global autonomic disturbances and generalized hypersensitivity to sensory stimuli in CRPS

Maier C.
CRPS is more than a peripheral disease: the complex pattern of CNS alteration in CRPS

Complex Regional Pain Syndrome (CRPS) is a condition with continuing pain disproportionate to any inciting event. In most cases the involvement is unilateral. However, signs and symptoms may spread to more proximally sites or extend past the painful area of the affected limb in a hemisensory distribution or with affection of all four limbs. This workshop present clinical data showing bilateral hyperexcitability to thermal, mechanical, and chemical stimuli in unilateral CRPS together with a global autonomic dysfunction. Possible mechanisms for this generalized dysfunction are discussed. Firstly, peripheral changes play a role. Posttraumatic CRPS starts unilaterally after limb trauma as an exaggerated posttraumatic inflammation. Exaggerated cytokine release, mast cell accumulation, exaggerated neurogenic inflammation, and the related local symptoms, spread to the distal limb. If CRPS is not adequately resolved systemic/spinal inflammatory cytokines could contribute to widespread nociceptive sensitization and systemic autoantibodies against autonomic nervous system structures may play a role. Secondly, central changes are involved with cortical reorganization, including shrinkage of the cortical limb representation, bilaterally disturbed inhibition of sensory and motor stimuli, neglect-like syndrome, and signs of altered body schema. Pain relief e.g. by sympathetic block immediately recovers the cortical S1-associated changes, demonstrating that some of the alterations are reversible.
It is now well established that normal pain sensitivity and its abnormalities following injury, diseases, toxins and certain drugs, as well as the response to analgesics, are heritable traits controlled by polymorphic loci in the genomes of mammals and even in evolutionarily ancestral species. While recent studies slowly unravel the identity of such polymorphisms, their combined effect-size is small, suggesting that many more genes remain to be discovered. Moreover, heritable determinants explain only about half of the variance in these traits, urging us to develop better tools to identify epigenetic factors and the way they interact with the genome. This workshop will present an update on these aspects by reviewing recent published and unpublished studies from the pain literature and progress made in other fields that bears relevance to the genetics and epigenetics of pain. The session will be chaired by Ze’ev Seltzer, who will also present current advancements in human genetics of neuropathic pain. Jeff Mogil will follow with a review of recent and upcoming findings in pain genetics that use rodent models of painful neuropathies. Stephen McMahon will introduce the concept of epigenetics, and present experimental approaches to studying it in humans and animal models, and recent findings.
Allodynia in chronic pain: Clinical manifestations and mechanisms

Denmark

Allodynia = pain produced by a stimulus which is normally not painful is seen in many chronic pain states including injury to the peripheral or central nervous system. Allodynia is considered to be a manifestation of a general hypersensitivity state irrespective of underlying disorder and patients are treated unspecifically with antihyperalgesic agents. However, the clinical presentation of allodynia differs remarkably between damage to nerve tissue and other tissues and it is also distinct from that seen in idiopathic pain states such as fibromyalgia. The question is if the mechanisms for these allodynic phenomena are different and if specific treatments should be tried.
SENSORY TESTING IN THE DIAGNOSIS AND CLASSIFICATION OF NEUROPATHIC PAIN

Finnerup N.B. (Chair and speaker)
Chemotherapy-induced neuropathy

Rice A.S.C.
HIV neuropathy

Aasvang E.
Post-traumatic neuropathy
Denmark, UK

In this workshop, sensory abnormalities in neuropathic pain conditions will be discussed including implications for diagnosis and treatment and correlation to epidermal innervation, pain characteristics, symptom clusters and quality of life. The speakers will present data from phenotyping studies according to standardized QST protocols, like the one developed by the German Neuropathic Pain Network and compare across pain conditions.

Rice will discuss the pattern of sensory abnormalities in HIV sensory neuropathy, which afflicts 40% of patients infected with HIV even in this era of effective antiretroviral therapy. In general there is a loss of function pattern across most sensory modalities. However, there are sub-groups of patients with gain of function, especially wind-up and those with pin-prick hyperalgesia who respond to pregabalin. Aasvang will discuss the benefits of the surgical models thoracotomy, mastectomy and groin hernia surgery in assessing the contribution of nerve damage and sensory dysfunction in pain. The presentation will include identification of predictive factors and will illustrate that the pain population is heterogenous. Finnerup will present prospective questionnaire and QST data from patients with chemotherapy-induced neuropathy following docetaxel and oxaliplatin, which clinically present with different symptoms.

The studies are part of the Innovative Medicine Initiative EUROPAIN, www.imi.europa.eu
ANTIDEPRESSANT TREATMENT OF NEUROPATHIC PAIN: STILL LOOKING FOR THE MECHANISM(S)

Barrot M. (Chair and speaker)
A peripheral beta2-adrenergic mechanism for antidepressant antiallodynic action

Courteix C.
Spinal mechanisms involved in the analgesic action of antidepressants

Berrocoso E.
Effect of analgesic antidepressants on locus coeruleus neurons: Implications for neuropathic pain

France, Spain

Antidepressant drugs are among the recommended first-line treatments for neuropathic pain. While their clinical efficacy was established more than 30 years ago, the underlying mechanism still remains elusive. However, understanding this mechanism could help to improve treatments, or even lead to new therapeutic approaches. In the past years, preclinical research highlighted potential actors and led to different hypotheses concerning the putative therapeutic mechanism. During the workshop, the 3 speakers will present experimental data supporting different hypotheses for the potential therapeutic mechanism(s). This will open a debate on major questions concerning this mechanism of antidepressant drugs: is it noradrenaline or serotonin-mediated? Which one of the adrenoceptors or serotonin receptors is critical for the therapeutic action? Is the mechanism central, spinal or supraspinal, or is it peripheral? Is the delayed therapeutic action due to drug pharmacokinetic or to drug-induced plasticity? Is the opioid system part of the mechanism? From this debate, a consensus may emerge on some of these points, while very different viewpoints may be present on others, which should foster interesting discussion and future research on antidepressant’s relief of neuropathic pain.
WHAT DOES BRAIN IMAGING TELL US ABOUT NEUROPATHIC PAINS?

Davis K.D. (Chair and speaker)
Brain abnormalities and neuropathic pain in ankylosing spondylitis

Borsook D.
Functional brain imaging of neuropathic pains

Modaie M.
Structural brain imaging can aid in the neurosurgical diagnosis and treatment of pain
Canada, USA

Brain imaging is now widely used to study the impact of chronic pain on the brain. In particular, MRI-based technologies are now providing insight into brain and peripheral nerve abnormalities in structure and function within focal areas and across functional networks associated with chronic neuropathic pains. Furthermore, brain imaging approaches are starting to disentangle issues of individual vulnerabilities, the capacity of the brain to undergo reversal of maladaptive plasticity following treatment, and may provide clinical utility. The workshop will present 1) an overview of the latest approaches to imaging brain gray and white matter, functional connectivity, and evoked functional responses, 2) neuroimaging data of brain abnormalities in various neuropathic pains, including trigeminal neuralgia, multiple sclerosis and ankylosing spondylitis, and 3) neuroimaging evidence for plasticity of brain abnormalities following treatment, and 4) the effects of neurosurgical lesions and prognostic value of neuroimaging in patients with neuropathic pains.
Trigeminal neuralgia and post herpetic neuralgia are well recognised neuropathic pains of the face. However, there are other forms of neuropathic pain in the orofacial region. There is now growing evidence that trauma from dental procedures such as endodontics, implants and extractions can result in neuropathic pain often called atypical odontalgia. Whether trigeminal neuropathic pain is central or peripheral is still being debated. The criteria are now more clearly defined and neurophysiological testing will often confirm nerve damage. The condition is poorly recognised by both GPs and dentists and often results in repeated irreversible dental treatment. Burning mouth syndrome, a condition especially affecting perimenopausal women has also been shown to probably be a neuropathic pain. As these conditions are poorly recognised they often result in significant co morbidity especially depression. These conditions are managed as neuropathic pains with antidepressants and anticonvulsant drugs. However they benefit from concurrent use of psychological therapies. These include identifying treatment goals and determining factors that would affect their response to treatment e.g fear, negative thoughts, depression.
NEW PERSPECTIVES ON MICROGLIAL REGULATION OF NEUROPATHIC PAIN

Beggs S. (Chair and speaker)
Microglial purinergic signaling in neuropathic pain

Bennett D.
The inflammasome; a critical intracellular mediator of neuropathic pain

Ji R.R.
Ani-inflammatory modulation of microglial activity by resolvins
Canada, UK, USA

Neuropathic pain, whether as a consequence of nerve trauma, disease or infection is a highly debilitating condition that can be extremely resistant to conventional treatment. Therapeutic strategies typically target neuronal mechanisms, and while there is clear evidence for a neuronal component in neuropathic pain, the lack of efficacy of these drugs is consistent with the more recent and growing body of evidence that non-neuronal mechanisms have a major functional contribution to the etiology of chronic neuropathic pain states.

Glial cells adopt a reactive phenotype in response to peripheral nerve injury and in this workshop we will elucidate how the adoption of specific phenotypes by these non-neuronal cells contributes directly to the development and maintenance of neuropathic pain. The role of innate and adaptive immune responses in modulating neuronal synaptic plasticity within the nociceptive circuitry of the spinal cord will be described. We will present new evidence for a neuroinflammatory basis of neuropathic pain through the activity of TNF-alpha release, intercellular purinergic receptor-mediated signaling, the intracellular contribution of the inflammasome and discuss how the pro-resolution resolvins modulate glial reactivity.

This workshop will present the latest important basic science findings and highlight the molecular and cellular complexity of spinal neuropathic pain mechanisms.
REFINED PRECLINICAL MODELS AND ENDPOINTS TO ENHANCE PREDICTION OF CLINICAL EFFICACY FOR NOVEL ANALGESICS IN NEUROPATHIC PAIN

Rutten K. (Chair and speaker)
Alternative endpoints and novel behavioral paradigms for assessment of neuropathic pain and complex behavioral changes in rodents with neuropathic pain

Doods H.
Validity of “new” animal models for neuropathic pain

Serra J.
Translational value of microneurographic identification and quantification of spontaneous activity in neuropathic pain

Germany, Spain

Despite a significantly improved understanding of neuropathic pain mechanisms in recent years, and despite large investments in preclinical pain research, only very few new clinically effective compounds have been introduced into the market. This has led to a re-evaluation of the preclinical animal models and endpoints in neuropathic pain research. The pharmaceutical industry requires animal models for neuropathic pain that have a better predictive validity for clinical efficacy and academic groups are in search of animal models for neuropathic pain with enhanced construct validity. Two approaches have been taken: 1) development of novel animal models and novel non-evoked behavioral test paradigms for neuropathic pain that reflect the complexity of the pain syndrome; and 2) detection and quantification of spontaneous activity in peripheral nociceptors through novel techniques of microneurography that may provide an electrophysiological correlate of ongoing neuropathic pain in rats. This workshop will provide an overview of the joint efforts of the Innovative Medicine Initiative (IMI) consortium EUROPAIN, which is a European collaboration between industry and academia forged to establish and validate novel state of the art animal models and novel endpoints. The overall goal of this collaboration is to bridge the gap between preclinical and clinical pain research.
CLINICAL USEFULNESS OF NOVEL NON-INVASIVE ELECTROPHYSIOLOGICAL APPROACHES TO ASSESS THE FUNCTION OF NOCICEPTIVE PATHWAYS

Mouraux A. (Chair and speaker)
A novel and robust approach to record and characterize C-fiber laser-evoked potentials in humans

Baumgartner U.
Cold and mechanical pinprick evoked potentials as clinical tools to study specific subtypes of peripheral nociceptive afferents

Hatem S.
Clinical usefulness of an automated analysis of laser-evoked potentials to assess nociceptive pathways

Belgium, Germany

Laser-evoked brain potentials (LEPs) are used increasingly as a routine clinical tool to assess nociceptive pathways in patients, in particular, for the diagnostic workup of chronic pain. Indeed, brief infrared laser pulses applied onto the skin can be used to selectively activate heat-sensitive Aδ- and C-fiber nociceptive afferents and, thereby, elicit time-locked neural responses. However, LEPs recorded using conventional stimulation techniques only reflect the activity elicited by rapidly-adapting heat-sensitive Aδ-fiber nociceptors. Hence, there is currently a need for novel techniques to study the neural responses elicited by other types of clinically-relevant nociceptive afferents, such as C-fiber afferents and cold-sensitive afferents.

The aim of this workshop is to present electrophysiological methods and tools to explore human nociceptive pathways that are currently being developed in basic research, and to discuss their potential clinical usefulness. The first two talks will focus on novel approaches to activate specific subtypes of nociceptive afferents, such as cold and mechanical pinprick stimulation, selective thermal stimulation of low-threshold C-fiber afferents using feedback-controlled laser stimulation and intra-epidermal electrical stimulation using concentric electrodes. Finally, the third talk will present the clinical usefulness of an automated single-trial analysis of event-related potentials and discuss its potential for clinical pain studies.
CENTRAL SENSITIZATION IN NEUROPATHIC AND NON-NEUROPATHIC PAIN CONDITIONS

Woolf C. (Chair and speaker)
Preclinical aspects of central sensitization

Sullivan M.
Psychological aspects of hypersensitivity

Hansson P.
Hypersensitivity in neuropathic and non-neuropathic pain conditions

USA, Canada, Sweden

Numerous clinical studies report hypersensitivity in areas remote to a focal pain condition. Frequently such a finding is explained in terms of "central sensitization". This, however, lacks support in the preclinical literature and other psychological explanations have been explored to some extent (catastrophizing, anxiety, depression, hypervigilance etc) and were found to be related to some pain parameters. The session should cover preclinical aspects of central sensitization, hypersensitivity (remote and local) in clinical conditions and psychological aspects of pain sensitivity.

Woolf has accepted.

Sullivan is asked but has not replied.
PLACEBO EFFECTS IN NEUROPATHIC PAIN CONDITIONS

Vase L. (Chair and speaker)
Experimental studies of anti-nociceptive and anti-hyperalgesic placebo effects

Dworkin R.
Prediction of placebo group responses and assay sensitivity in analgesic clinical trials

Tracey I.
Lessons from brain imaging studies of placebo analgesia effects
Denmark, USA, UK

The major part of placebo research has been conducted in relation to nociceptive or idiopathic pain but recently there has been a growing interest in understanding the magnitude and the mechanisms of placebo effects in relation to neuropathic pain conditions.

Experimental studies show that large anti-hyperalgesic effects can be obtained in relation to neuropathic pain conditions. There are indications that anti-hyperalgesic placebo effects may involve different mechanisms than placebo effects in relation to nociceptive and idiopathic pain and currently the psychological and neurophysiological mechanisms involved in these effects are being investigated.

The magnitude of the placebo response appears to be increasing in clinical trials. Neuropathic pain trials reported to the FDA are currently being investigated in order to specify some of the factors that may influence the magnitude of the placebo response in neuropathic pain trials.

In the workshop, the magnitude and the mechanisms of placebo effects in relation to neuropathic pain conditions will be discussed and emphasis will be given to future design of clinical trials as well as to specific mechanisms of anti-hyperalgesic placebo effects.
OROFACIAL NEUROPATHIC PAIN: RECENT ADVANCES IN ASSESSMENT, MANAGEMENT AND CLARIFICATION OF UNDERLYING MECHANISMS

Sessle B. (Chair and speaker)
New insights into processes that modulate trigeminal central sensitization following orofacial nerve injury

Iwata K.
Role of non-neural as well as neural processes in animal models of orofacial neuropathic pain

Svensson P.
Advances in assessment and management approaches for orofacial neuropathic pain
Canada, Japan, Denmark

This Workshop will address recent advances in our understanding of mechanisms underlying the development and maintenance of neuropathic pain in the orofacial region as well as recent advances in the assessment and management of orofacial neuropathic pain conditions. Dr. Peter Svensson (Denmark) will review recent research from studies in humans that have applied assessment techniques involving QST, brain imaging and other biomarkers for these conditions, as well as provide details on recent studies of pharmacologic and non-pharmacologic approaches to manage them. Dr. Koichi Iwata (Japan) will present recent research findings pointing to the involvement of non-neural (e.g. glia) as well as neural processes in animal models of orofacial neuropathic pain, and also point out emerging insights into some of the molecular mechanisms involved. Dr. Barry Sessle (Canada) will chair the Workshop as well as review recent findings of processes that modulate trigeminal central sensitization following orofacial nerve injury in animals and that may explain some of the clinical findings in orofacial neuropathic pain patients; he will also present new findings of the effects on trigeminal central sensitization of recently introduced drugs that may account for their clinical efficacy in the management of these conditions.
CANNABIS FOR NEUROPATHIC PAIN: DEBATING THE MERITS OF CANNABIS AS MEDICINE

Moulin D. (Chair and speaker)
Cannabis for Neuropathic Pain: Debate chair

Ware M.A.
Cannabis for Neuropathic Pain: 'pro'

Rice A.
Cannabis for Neuropathic Pain: 'con'
Canada, UK

This session will consist of a debate on the utility of cannabis as a therapy for neuropathic pain. This topic is often politically charged, with scientific, legal, regulatory, ethical and social dimensions. Perfect for a lively and engaging debate!

The debate will be chaired by Professor Dwight Moulin (Western). Dr Mark Ware and Professor Gary Bennett (McGill) will argue for the cannabinoids, and Professor Andrew Rice (UCL) and his seconder (TBD) will lead the opposition. Each team will present in 10 minute presentations in a classical debate format: Proposer, then Opposer, followed by the seconders for both sides. A 30 minute session of statements from the floor will follow, then each side will prepare concluding remarks (5 minutes each).

Participants in this session will become aware of the scientific background information on the endocannabinoid system, the preclinical and clinical data in support of or refuting the efficacy of cannabinoids in the treatment of neuropathic pain, safety data and clinical options. Attendees will reflect on their own attitudes and opinions, interact with the debators, and there will be a final vote to make it interesting. The speakers are experts in their fields, great speakers, and everyone attending will win.
MODULATORY ACTION OF BOTULINUM NEUROTOXIN TYPE A ON NEUROPATHIC PAIN

Gazerani P. (Chair and speaker)
The modulatory role of Botulinum neurotoxin type A on endogenous pain mediators: human experimental pain models

Luvisetto S.
Modulatory action of Botulinum neurotoxin type A on neuropathic pain: behavioral and immunohistochemical studies in animal models

Cairns B.E.
Botulinum neurotoxin type A for management of chronic pain

OnabotulinumtoxinA has recently been approved for treatment of chronic migraine. This has increased the interest in understanding the mechanism by which Botulinum neurotoxin type A (BoNTA) can reduce chronic pain in other painful conditions. The potential use of BoNTA to treat pain is mainly derived from the observation that patients treated with BoNTA for musculoskeletal disorders often experienced reduction of pain. Although the mechanisms of the analgesic effect of BoNTA are still not completely elucidated, several investigations have shown that the analgesic effects may be attributed to the neurotransmitters’ release inhibition along nociceptive pathways.

This workshop will open with Dr. Luvisetto addressing the role of BoNTA in neuropathic pain. Evidences from animal behavioral studies and basic immunohistochemical data will be presented. The modulatory role of BoNTA on endogenous pain mediators will be reviewed by Dr. Gazerani with a special emphasis on the effect of the toxin in human experimental pain models. Dr. Cairns will then discuss the relevance of basic animal and human experimental findings to clinical conditions of pathological pain and modulatory action of BoNTA.
HOW CAN WE APPLY THE IASP CRITERIA IN CANCER NEUROPATHIC PAIN?

Bennett M. (Chair and speaker)
Reliability of current diagnostic approaches and the need for better clinical assessment

Rolke R.
Which QST assessments are most useful for clinical practice?

Caraceni A.
Proposal for a consensus on assessment of cancer neuropathic pain

UK, Germany, Italy

This workshop will focus on reliable assessment of cancer neuropathic pain in clinical practice. The first session will review 31 current studies in cancer neuropathic pain and will examine their assessment methodology against the IASP criteria for neuropathic pain diagnosis. The second session will present clinical data from QST studies in cancer neuropathic pain and identify which bedside tests are most useful to apply in practice. The final session will summarise data on best practice approaches, propose a modified assessment system for cancer neuropathic pain and consider how this fits with a broader cancer pain classification system.
LOST IN TRANSLATION: DRUG DEVELOPMENT LESSONS LEARNED FROM STROKE

Macleod M.

Lost in Translation: Drug Development Lessons Learned From Stroke

UK

The proposed speaker, Malcolm Macleod, is an expert in stroke medicine who works with animal models and who also undertakes clinical research and practice. Together with his colleagues in the CAMARADES consortium (www.camarades.info) he has extensively analysed the potential for, and impact of, experimental bias confounding interpretation of efficacy of novel therapeutics tested in animal models of experimental stroke. Uncontrolled (as well as unrecognized) bias has been shown to be among contributing causes of efficacy overestimation of such compounds, leading to poor translation of efficacy to clinical trials as well as patients being unnecessarily exposed to ineffective compounds. Malcolm will describe various types of generic bias that can compromise animal studies of novel therapeutics in fields beyond stroke. Importantly, he will then describe experimental design techniques that have been shown to reduce the impact of such biases, leading to improved methodological quality, such that systematic review and meta-analysis of animals studied now can be performed. He will describe easy-to-use reporting guidelines that have been adopted by the major journals in the stroke field. Pain scientists and clinicians involved in all stage of analgesic drug development can learn many important lessons from what the stroke field has embraced in this regard.
DOES EXPERIMENTAL BIAS CONTRIBUTE TO POOR BENCH TO BEDSIDE TRANSLATION OF NOVEL PAIN THERAPEUTIC AGENTS?

Macleod M. (Chair and speaker)
Does Experimental Bias Contribute to Poor Bench to Bedside Translation of Novel Pain Therapeutic Agents?

Knopp K.
Does Experimental Bias Contribute to Poor Bench to Bedside Translation of Novel Pain Therapeutic Agents?

Mogil J.
Does Experimental Bias Contribute to Poor Bench to Bedside Translation of Novel Pain Therapeutic Agents?

Porreca F.
Does Experimental Bias Contribute to Poor Bench to Bedside Translation of Novel Pain Therapeutic Agents?

UK, USA, Canada

It is a well-appreciated fact that despite major advances in the understanding of pain biology and signaling pathways as well as identification of many key underlying mechanisms, chronic pain remains a large unmet need with few new drugs successfully developed. As a result, significant discourse has focused on the apparent poor predictive validity of preclinical pain behavioral models as a primary cause for poor bench to bedside translation. A variety of animal pain models, endpoints, and methodologies, including genetic knock-outs, have been used to demonstrate often compelling efficacy as validation of mechanistic targets. Likewise, the model methodologies are well-documented and often standardized across laboratories; however, it has been reported that a significant proportion of pain behavioral studies are not reproducible. Together, this suggests that uncontrolled, and possibly unrecognized, sources of variability may be contributing to both poor preclinical data reproducibility and clinical translation. In this session, four scientists representing academic, industrial and clinical pain research will debate the extent to which various forms of experimental bias may negatively impact study design and implementation and whether increased efforts are warranted toward more transparent reporting of blinding procedures, subject randomization and inclusion/exclusion criteria, as well as the value of reporting negative results.
SPINAL CORD STIMULATION FOR THE TREATMENT OF NEUROPATHIC PAIN:
TRANSLATIONAL RELEVANCE OF NEW INSIGHTS ON MECHANISMS

Guan Y. (Chair and speaker)
Intensity and frequency-dependent features of spinal cord stimulation-induced analgesia: Behavioral and electrophysiological evidence in neuropathic rats

Joosten E.A.
Spinal Cord Stimulation in Neuropathic Pain: Modulation at the Spinal Gate

Saadé N.E.
Spinal cord stimulation: Gating at spinal and various supraspinal levels
USA, Netherlands Antilles, Lebanon

Organizer/Chair: Dr. Srinivasa N. Raja.

Treatment of neuropathic pain continues to be a significant unmet medical need. Spinal cord stimulation (SCS) represents an alternative approach to alleviate neuropathic pain when standard pharmacological interventions have failed. However, knowledge about the biological mechanisms of SCS-induced pain relief has been limited, and has been a barrier to the clinical advancement of this technology. This workshop includes three international speakers whose work has focused on the studies of SCS analgesia, using pre-clinical models of neuropathic pain as well as studies in human. Dr. Srinivasa N. Raja will firstly provide a clinical overview of SCS for neuropathic pain and introduce the speakers. Dr. Elbert A. Joosten will review their recent anatomical, molecular and behavioral studies on the pain modulatory effect at the spinal gate, and discuss the potential clinical applicability of experimental findings (20 min). Dr. Yun Guan will present behavioral and electrophysiological data about the intensity and frequency-dependent features of SCS analgesia (20 min). Dr. Nayef E Saadé will close the session with reviewing electrophysiological and behavioral data about supraspinal effects of dorsal column stimulation, and give a panoramic review of the effects and a comparison between spinal and supraspinal mechanisms (20 min).
THE COMPARATIVE COST-EFFECTIVENESS OF SPINAL CORD STIMULATION VERSUS ALTERNATIVE TREATMENTS

North R.B. (Chair and speaker)
Improving the cost effectiveness of SCS for neuropathic pain

Taylor R.S.
Analyzing the cost of healthcare

Shipley J.
The evidence on the comparative cost-effectiveness of SCS versus alternative treatments in the treatment of neuropathic pain

USA, UK

Discussion of 1) various ways to analyze the cost of healthcare, including modeling studies, 2) the strengths and limitation of these methods, and 3) cost outcome measures (e.g., incremental cost effectiveness ratios, incremental cost-utility ratios, quality-adjusted life years, maximum willingness to pay threshold, the cost-effectiveness plane, economic dominance, etc.).


Presentation of ways to improve SCS cost effectiveness, including how to design an SCS comparative cost-effectiveness study and how to improve cost effectiveness by adopting best practices (i.e., to improve outcomes and reduce complications).
Can visceral pain be of neuropathic origin?

Cervero F.
Can visceral pain be of neuropathic origin?

Surprisingly, visceral pains are not usually considered to be neuropathic despite the fact that it would appear very likely that at least in some cases injury to and/or other pathological changes to visceral primary afferent nociceptors and/or the central pathways mediating visceral pain cause or contribute to the pain. Dr. Fernando Cervero is a world renowned expert in the basic neuroscience of visceral pain and would be able to provide a thorough and insightful discussion of this important topic.
There is increasing evidence that nociceptive information and pain are processed in a cortical network aimed at detecting and reacting to sensory stimuli that are salient enough to represent a potential threat for the body. This implies that nociceptive inputs are integrated with sensory information originating from other sensory modalities (e.g. vision, proprioception) in order to form a global representation of the body and the space nearby. As an example, the manipulation of visuospatial perception was shown to influence the central processing of nociceptive stimuli. On the other hand, chronic pain can lead to a distortion of spatial perception. The scope of this workshop is to provide an overview of the recent data obtained in healthy participants, patients suffering from chronic pain and patients with cortical lesions, and to present the neuro-cognitive mechanisms supporting the multimodal and peripersonal integration of nociception and pain in the human brain. In addition, the workshop will outline the therapeutic potential of cognitive manipulation of spatial perception and body posture for alleviating neuropathic pain. Indeed, this topic reveals a fertile breeding ground for original experimental and clinical studies and the development of new rehabilitation procedures.
Peripheral neuropathy may induce not only pain but also various emotional and cognitive co-morbidities that significantly influence life of patients. So far, little is known about the neurobiological mechanisms of neuropathic pain-associated emotional and cognitive disturbances. In this workshop, the speakers approach this problem using an experimental animal approach. Dr. Pertovaara will describe peripheral neuropathy induced changes in sensory- and affective-like behavior as well as accompanying in the amygdala and its efferent actions on the pain-regulating system. Dr. Leite-Almeida will describe how peripheral nerve injury influences both affective and cognitive behaviors and how these changes vary depending on whether the nerve injury is on the left or right side. Dr. Noverjarque-Gadea will describe anatomical studies documenting the pattern of neuronal activation of neurons in the various subdivisions of the amygdala in neuropathy animals and demonstrate how these changes are directly correlated with thigmotactic (anxiety-like) behavior as measured in the open field paradigm. She will also describe associated changes in amygdala protein and gene expression obtained using “-omics” techniques. By way of comparison with other pain types, the results of parallel experiments in a model urinary bladder inflammation will be described.
CENTRAL PAIN: CLINICAL CHARACTERISTICS, MECHANISMS AND DIAGNOSTIC CHALLENGES

Klit H. (Chair and speaker)
Central post stroke pain

Roosink M.
Post-stroke shoulder pain: A neuropathic pain?

Wrigley P.
Spinal cord injury neuropathic pain - brain mechanisms and treatments
Denmark, The Netherlands, Australia

Central neuropathic pain is a common complication after stroke and spinal cord injury. About 8% of patients with stroke and 50% of those with spinal cord injury suffer from persistent neuropathic pain that cannot be relieved by currently available treatments. Often classification of pain is challenging. The goal of this topical workshop is to discuss the problems related to the diagnosis, classification, and assessment of central pain. In addition, tools to unravel the mechanisms underlying central pain will be discussed.

Klit will discuss the epidemiology, clinical characteristics and diagnostic challenges in central post-stroke pain. Roosink will discuss post-stroke shoulder pain as a multi-factorial pain syndrome and discuss if and how it can be classified as neuropathic or not. Wrigley will focus on neuropathic pain following spinal cord injury. Recent research on the brain changes associated with this condition and implications for treatment will be presented. Early work on a number of novel treatment approaches and assessment measures will also be discussed.
TRUE ANALGESIC EFFICACY - ACCESSING ALL THE DATA

Rowbotham M.
True Analgesic Efficacy - Accessing all the data
USA

Obtaining results on analgesic efficacy beyond those published is difficult, but necessary from an ethical and cost perspective. Mostly positive trials make it to the peer-reviewed journals, while equivocal or negative results end up in the 'grey literature' or are never published. This lecture will discuss strategies on how to access all data and discuss the 'real' versus the published analgesic efficacy of compounds used to treat neuropathic pain.
MANY YEARS AFTER. ACHIEVEMENTS AND FAILURES OF LASER EVOKED POTENTIAL STUDIES IN ASSESSING PAIN PATIENTS

Garcia-Larrea L. (Chair and speaker)
Central pain and psychogenic pain

Truini A.
From distal polyneuropathy to trigeminal pain

Baumgaertner U.
Experimental studies: patients are another matter!
France, Italy, Germany

After the times of lab-produced laser stimulators, and their success in physiological studies, commercial laser stimulators with fibreoptic guidance became available and the studies in pain patients multiplied. Nowadays the method of Laser Evoked Potentials (LEPs) has been applied in over 1,000 patients.

What have we achieved?

Even complying with the rigid rules of evidence-based classification, there have been several class-I studies that allowed sound meta-analyses and evaluation of sensitivity/specificity in the main neuropathic pain conditions (polyneuropathy of various etiology, focal neuropathy, postherpetic neuralgia, trigeminal neuralgia, syringomyelia, multiple sclerosis, stroke), as well as in idiopathic/putative conditions (CRPS I, fibromyalgia) and psychogenic pain. According to recent guidelines the LEPs are the most reliable neurophysiological method of assessing nociceptive system function in neuropathic pain.

However, these achievements mostly refer to the assessment of A-delta fibres. Unfortunately, after many years no high-quality studies about the unmyelinated (C-fibre) system have appeared. Except for the trigeminal territory, where the conduction distance is so short, it would appear that nobody has so far been able to develop a method of stimulation that reliably yields C-related LEPs from the limbs. Given the importance of C-fibres in pain pathophysiology, should we search for an alternative method?
DIFFERENCES IN NEUROPATHIC PAIN PHENOTYPES: DIAGNOSTIC CHALLENGE, POTENTIAL THERAPEUTIC OPPORTUNITY

Scholz J. (Chair and speaker)
Phenotype Variation in Diabetic Polyneuropathy

Finnerup N.B.
Distinct Subtypes of Central Pain after Spinal Cord Injury

Rolke R.
Phenotyping Strategies for Neuropathic Pain
USA, Denmark, Germany

Patients with neuropathic pain may present with different symptoms and signs even if the underlying etiology of the pain is the same. This raises diagnostic problems. How important are these phenotypic differences clinically? Do they indicate the activity of different pain mechanisms? How shall we measure and document variations in pain-related symptoms and signs? Do they require adjustments in pain management? We provide evidence of phenotypic diversity from prospective clinical studies on peripheral pain caused by diabetic polyneuropathy and central pain after spinal cord injury. We compare different strategies for capturing interindividual variations in the manifestation of neuropathic pain, such as pain questionnaires, physical bedside tests developed for diagnosis and phenotypic evaluation, quantitative sensory testing and screening tools used in epidemiological surveys. Although diagnostically challenging, phenotypic differences may offer insight into the diversity of mechanisms in neuropathic pain. Based on our clinical findings, we review how genetic studies on neuropathic pain and experimental models of diabetic neuropathy and spinal cord lesions are suited to inform about the relationship between pain manifestations and neurobiological pain mechanisms, and discuss potential therapeutic implications.
TRIGEMINAL NERVE STIMULATION

V. Petruzelli, Italy

Background: These are two cases of two different patients who have been subjected to the peripheral nerve stimulation of the second branch of the fifth cranial nerve by the placement of an electronic underarm device with persisting stimulation (intervals every two months). The two patients were subjected to a vascular decompression surgery. The first has been treated with the “termorizotomia” whereas the second with “fenolizzazione” for several years.

Methods: After that, they were tested for subcutaneous stimulation on the 2nd branch of the sinister trigeminal nerve. They were no longer complaining about a shooting pain lasting a few minutes but they were complaining about a more persistent kind of pain (trigeminal neuropathy), NRS = 10. An octopolar electrode was positioned on the periosteal surface of the cheekbone with the distal end on the nose’s side and placed in the subcutaneous area hidden by the ear. The electrode was fixed with sixty days absorbable sutures. The NRS resulted 0 during the stimulation and 10 with the ENS off. After a month of testing a rechargeable IPG was set up. The follow-up were performed at 2 months, 4 months and 6 months. In one case there was a surgical complication after six months: electrode decubitus behind the auricle. For this reason, the electrode was removed to allow the drainage of the subcutaneous tissue. In the three-week elapsed before planting the new electrode, the patient has never complained about the pain so that we have continued to hold off the IPG.

Result: The period of temporary well-being lasted about two months.
Results of studies on glucocorticoids for treatment of neuropathic pain are contradicting.

In a nerve injury rat model, reversal of the existing neuropathic pain state and glial activation was obtained after continuous IT infusion methylprednisolone. However in another nerve injury model opposite effects were observed; IT delivery of dexamethasone did not inhibit the activation of microglia or reduce pain-like behavior after SNI in rats. There is even a report stating that the glucocorticoid receptor antagonist RU486 produced antinociceptive effects in mice.

In clinical studies positive results were obtained; IT betamethasone caused pain relief in cancer patients with vertebral metastasis, IT methylprednisolone acetate (MPA) reduced pain in 95% of chronic postherpetic neuralgia patients. But also reports of inefficacy were published.

Glucocorticoids have also been applied local, epidural and systemically with varying results. Recently reports appeared on pro-inflammatory effects of glucocorticoids. In dogs receiving four IT injections with MPA, dose dependent inflammatory processes were seen. Cortisone potentiated allodynia and increased spinal IL-1β and IL-6 protein after IT lipopolysaccharide (LPS) treatment in rats. Also decreases of mechanical thresholds in normal rats after triamcinolone acetonide were observed.

In this workshop mechanisms of action, clinical use and toxicity of spinal glucocorticoids will be discussed.
TARGETTING CHLORIDE HOMEOSTASIS FOR THE TREATMENT OF NEUROPATHIC PAIN

De Koninck Y. (Chair and speaker)
Potentiators of the potassium-chloride co-transporter KCC2 as novel therapeutics for neuropathic pain

Prescott S.A.
Dynamics of intracellular chloride regulation: insights from computer simulations

Price T.J.
Pharmacological strategies to mitigate limitations of GABAergic modulation for the treatment of neuropathic pain

Canada, USA

Impaired chloride extrusion due to a loss of the potassium-chloride co-transporter KCC2 in spinal dorsal horn neurons has been identified as a major substrate of pain hypersensitivity in several preclinical models replicating symptoms of neuropathic pain. These include: different models of nerve injury-induced pain hypersensitivity (Coull al Nature 2003, 2005; Miletic & Miletic, Pain 2008; Janssen et al, Neuroscience 2011); painful diabetic neuropathy (Jolivalt, Pain 2008) and spinal cord injury-induced pain (Lu et al, J.Physiol. 2008; Cramer et al, Mol.Pain 2008). While the main effect of this disruption in chloride homeostasis in neurons is impaired inhibition, the consequences of such a mechanism of disinhibition are complex and deserve to be examined in details to understand its impact for therapeutic strategies. Theodore Price will present data illustrating how altered chloride homeostasis mitigates the efficacy of certain benzodiazepines for the treatment of neuropathic pain. Steven Prescott will present modeling work exploring the complex impact of impaired chloride transport on processing of input by neurons and how this can explain the mitigated therapeutic efficacy of drugs enhancing GABA\ receptor-mediated transmission. Yves De Koninck will present an innovative analgesic strategy based on the discovery of novel compounds aimed at enhancing KCC2 activity.
QUANTIFYING PAIN IN HUMANS USING NOVEL OBJECTIVE MEASURES: FROM QUANTITATIVE SENSORY MEASURES TO NOCICEPTOR SPIKES AND GAMMA BAND OSCILLATIONS

Serra J. (Chair and speaker)
Quantification of nociceptor discharges in animals and humans

Treede R.-D.
Quantifying pain in humans: a need and a challenge

Iannetti G.D.
Novel approaches to capture nociceptive-specific cortical activity in humans
Spain, Germany, UK

There have been huge efforts to develop standardized tools for quantitative sensory testing. The main aim has been to detect specific sensory profiles. However, there still is a lack of objective measures of spontaneous pain intensity. Several electrophysiological tools and imaging techniques have been proposed as methods to quantify pain intensity, but there is still no agreement on their utility.

Generation of ectopic impulses in nociceptors may constitute a major underlying mechanism for spontaneous pain. Important steps have been made to not only identify such discharges, but also to quantify them, in an attempt to obtain an objective measure of peripheral nociceptive system activity.

When detected with traditional analysis approaches, most of the neural activity measured using currently available functional neuroimaging techniques (like EEG and fMRI) in response to a transient nociceptive stimulus does not reflect pain perception per se, but the unspecific detection of novel salient events. Hence, the neural correlates of the actual pain experience remain elusive. We will describe innovative approaches to explore functional neuroimaging data to identify brain activities specifically related to the conscious detection of nociceptive stimuli and thus provide biomarkers of pain perception.
Diagnosis of neuropathic pain requires documentation that somatic sensory system is adversely affected by injury or disease and this is achieved on the basis of sensory symptoms and signs. Sensory signs are elicited on the basis of bedside application of stimuli of specific properties, such as brush or pin, or in a quantitative manner when stimuli have predefined characteristics and are administered to provide stimulus-response type of information. Role of these two types of information in the process of diagnosis of neuropathic pain will be presented and discussed by Dr’s Treede and Hansson.
PREDICTION OF CHRONIC PAIN FOLLOWING ACUTE NERVE INJURY

Finnerup N. (Chair and speaker)
Neuropathic Pain following injury: A matter of loss or gain?

Petersen K.
Natural history of pain

Aasvang E.
Nerve injury and neuropathy - a sufficient factor in development of persistent pain?
Denmark, USA

Trauma and surgery affecting the somatosensory nervous system are associated with a risk for development of neuropathic pain. This workshop will discuss predictors of chronic pain. Karin Petersen will discuss the natural history of pain following melanoma surgery and herpes zoster and how longitudinal studies can help us understand the resolution of pain. Eske Aasvang will discuss nerve injury as a risk for the development of persistent postsurgical pain and the relation between pain and neuropathy. Nanna Finnerup will discuss the role of sensory loss and gain as predictors for chronic neuropathic pain following surgery.
THE EFFECTS OF PRENATAL MORPHINE EXPOSURE ON PAIN RESPONSE
A. Alijarahi, M.H. Esmaeili, Iran

Background: Drug abuse during pregnancy is a growing problem in all developed countries of the world. Maternal drug abuse affects the developing system and its long-term effects can persist till adulthood so it can decreases the rate of their maturation. Since endogenous opioid induced analgesia, and morphine can interact with it, Thus the present study was designed to determine whether the exposure to the morphine during gestation permanently alter pain response.

Objective: To determine the effects of prenatal morphine exposure on pain response.

Materials and methods: 12 Pregnant rats were divided to morphine and control groups. Morphine was administrated (S.C) to female rats twice a day (08h and 20h) on gestational days 11-18, (5 mg/kg morphine for 3 days and 10mg/kg for 5 days). Analgesic response of pups (P90, n=6) were tested by formaline test.

Finding: The results of our experiment demonstrated that prenatal morphine exposure rats exhibited significantly lower pain thresholds.

Conclusion: Prenatal morphine exposure impair pain sensitivity.
Patients with neuropathic pain are often refractory to pharmacologic and non-interventional treatments. Evidence-informed recommendations for the interventional management of NP were developed by evaluating systematic literature reviews, clinical trials, and existing guidelines at a consensus meeting.

The role of neural blockade in the treatment of herpes zoster will be reviewed. Epidural blocks with local anaesthetics combined with steroids soon after onset of herpes zoster can result in a decrease in pain and allodynia and appear to shorten the time to complete resolution of pain.

Treatment of Post Herpetic Neuralgia by interventions. Despite favourable results reported for intrathecal local anaesthetic and steroid in patients with refractory PHN, the authors believe that concerns about the reproducibility of results of this single RCT and potential risk of adhesive warrant an "inconclusive" recommendation.

Three of six observational studies on the effectiveness of sympathetic blocks and majority of cohort studies with epidural local anaesthetics alone or combined with steroids reported a reduction in acute pain in herpes zoster patients. Several non-randomized trials of the efficacy of sympathetic blockade in PHN have been conducted and all failed to demonstrate benefit. Based on the available evidence the use of sympathetic nerve blocks should generally be avoided.
LOSS OF GABAERGIC INHIBITION AT THE LEVEL OF THE SPINAL CORD

Braz J.M. (Chair and speaker)
Chair

Zeilhofer H.U.
Speaker

De Koninck Y.
Presenter
USA, Switzerland, Canada

Loss of GABAergic inhibition at the level of the spinal cord is a major contributor to the development of peripheral nerve injury-induced neuropathic pain. This Workshop will address both mechanistic and novel therapeutic approaches to addressing the GABAergic dysfunction. Dr. Yves De Koninck will describe studies demonstrating alterations of the spinal cord GABAergic system in the setting of nerve injury and the implication of microglia in the hypersensitivity characteristic of neuropathic pain. Dr. Hanns Zeilhofer will describe new avenues in the development of subtype-selective modulators of GABA A receptors. Not only are these novel approaches to the pharmacotherapy of neuropathic pain directed at enhancing inhibitory controls, but the objective is to address the existing problem of adverse side effects of existing therapies, which limit the use of effective doses. Finally, Dr. Joao Braz will present a novel, non-pharmacological therapeutic approach for the treatment of chronic pain that aims at restoring GABAergic inhibition through transplantation of precursors of GABAergic cells.
Rehabilitation has changed a great deal in the last 10-15 years. No longer are rehabilitation clinicians simply targeting musculoskeletal strength and general fitness, or solely attempting to correct faulty biomechanics or aberrant joint forces. Rehabilitation strategies now reflect the monumental advances that have been made in our understanding of the role of the nervous system, including the brain, in neuropathic pain. Psychophysical and brain imaging studies show clear relationships between changes in brain structure and function, and clinical variables such as the duration and intensity of pain, mechanical hyperalgesia and sensory processing deficits. Interactions between immune and neural mechanisms in the periphery have raised the possibility for new attempts to improve the health of the entire nervous system. Prof Moseley will present an overview of the current concepts in training the brain - attempts to reinstate cortical inhibition within neural representations of the body and the space around it. A/Prof Coppieters will present an overview of the state of the art in neurodynamics for pain states, evidence and recommendations for practice. Prof Vlaeyen will overview exposure therapy, including recommendations for practice. This workshop is relevant to anyone involved in rehabilitation of people in neuropathic, or chronic non-neuropathic, pain.
Pain is a biopsychosocial problem. Cognitive factors relate to pain severity and functional impact in people with chronic and neuropathic pain. Research suggests that brain states, as measured by the absolute and relative magnitude of brain wave bandwidth activity, also relate to the presence and severity of pain. Non-pharmacological interventions with demonstrated efficacy for decreasing pain may operate, at least in part, by facilitating changes in brain states associated with the experience of pain. Non-pharmacological pain treatments (hypnosis, meditation, neurofeedback, and transcranial direct current stimulation) are associated with a unique pattern of changes in brain activity, and in pain intensity. This type of finding opens up new opportunities for the treatment of people with neuropathic pain. In this talk, Prof Jensen will outline the current state of the art as it relates to cognitive factors in neuropathic pain and overview non-pharmacological treatments and their possible cortical effects.
RAPID DIAGNOSIS OF DIABETIC POLYNEUROPATHY: SELECTION OF ACCURATE SYMPTOMS AND SIGNS IN AN OUTPATIENT CLINICAL SETTING

R. Aghili, M.E. Khamseh, M. Malek, S.M. Aghili, L. Najafi, Iran

Objective: Clinical assessment of distal symmetric polyneuropathy (DPN) involves evaluation of symptoms and signs. Although there are numerous tools to evaluate DPN, there is still a need to determine the most sensitive, specific, and accurate tests to detect DPN at its early stage in a busy outpatient clinical setting.

Methods: One hundred and seven type 2 diabetic subjects were examined using the Michigan Neuropathy Screening Instrument (MNSI). The total score of the instrument was used as the standard to calculate sensitivity, specificity and diagnostic accuracy of every single item of MNSI to find the most accurate and applicable test for evaluation of DPN.

Results: In history, the most sensitive (99.4%) and accurate (78%) tests were muscle cramp and weakness. Numbness and prickling respectively had lower sensitivity (72.6% and 67.9%) but higher specificity (65.2% and 47.8%).

In physical assessment, the most accurate tests were appearance of feet (81.3%), ankle reflexes (67.2%), and vibration perception (63.5%). Monofilament had sensitivity of 16.7%, accuracy of 31.7% with specificity of 87%.

Conclusions: The findings show that symptoms such as muscle cramp, weakness, numbness, and prickling, as well as signs such as ankle reflexes, appearance of feet, and vibration could be used as the most accurate tests for rapid diagnosis of DPN. In addition, the results suggest that monofilament may not be the optimum test to detect high risk subjects.
PITFALLS IN DIAGNOSIS OF TRUNCAL NEUROPATHY

R.T. Ibitoye, S.M. Rajbhandari, UK

Introduction: Pain over the chest or abdomen is a common presentation of intrathoracic or intra-abdominal pathology. Truncal neuropathy is an uncommon but important cause. Clinical experience suggests that such patients have multiple unnecessary investigations prior to diagnosis.

Aim: The aim of this study was to review diagnostic workup in patients with truncal neuropathy to gain insight into diagnostic pitfalls.

Methods: In this single centre retrospective study, electronic records of patients seen over an 8 year period were searched for ‘neuropathy’ and ‘neuritis’. Case records of patients with truncal neuropathy were reviewed to identify: comorbidities, investigations performed and treatment response.

Results: Out of 7 patients identified 4 had diabetes. Extensive investigation performed in 5 patients included chest radiography (5), abdominal ultrasonography (4), echocardiography (3), abdominal computed tomography (2), oesopha
gastroduodenoscopy (2), coronary angiography (2), pulmonary function testing (1), nuclear medicine bone scintigraphy (1), barium swallow (1), barium follow-through (1), flexible sigmoidoscopy (1) and colonoscopy (1). In two patients in whom truncal neuropathy was suspected at first presentation, focused clinical examination and early treatment avoided unnecessary investigation. Treatment was gabapentin in three patients, duloxetine and pregabalin in one and duloxetine with amitriptyline in another. Two patients required no treatment. All symptoms were well controlled with this therapy.

Conclusions: Truncal neuropathy is an important cause of atypical pain. Failure to consider the diagnosis leads to unrewarding extensive investigation and patient anxiety. Diabetes remains the single most common clinical association and should be considered. Clinical suspicion and focused clinical examination are essential to diagnosis.
Background and aims: Neuropathic pain is often worse at night, however, little is known about pain rhythmicity during waking hours. We aimed to replicate previous observations of diurnal pain progression, evaluate associations between diurnal rhythmicity and clinical factors and evaluate the impact of diurnal rhythmicity on treatment response.

Methods: We performed exploratory analyses of two trials (NEJM 2005;352:1324; Lancet 2009;374:1252) in diabetic neuropathy (DPN) and postherpetic neuralgia (PHN). Pain recorded at 8am, 4pm and 8pm, at baseline and during drug treatment was examined.

Results: Data from the latest trial replicated our previous observation of diurnal pain progression with a relative pain intensity difference of 33% between 8am and 8pm. This pattern was preserved during treatment with gabapentin, nortriptyline and their combination. Pooled multivariable analyses suggested that difference in pain intensity from 8am-8pm was more pronounced in females (versus males) and in DPN (versus PHN). The degree of baseline pain rhythmicity failed to predict treatment response.

Conclusions: These observations suggest that neuropathic pain progressively increases throughout the day with clinically relevant morning-evening differences and further indicate that sex and underlying etiology may be important determinants of diurnal rhythmicity in neuropathic pain. Consideration of these clinical clues may guide improved therapeutic strategies and stimulate new directions of research that will improve our understanding and treatment of neuropathic pain.
The primary goal of the current study was to evaluate the efficacy of flurosscopic guided epiduroplasty with and without epiduroscopy (EDS) in failed back surgery syndrome (FBSS).

FBSS patients were allocated randomly into two groups; the Non-EDS group in whom patients underwent caudal epiduroplasty by flurosscopic guided insertion of Racz catheter and the EDS group in whom patients underwent caudal epiduroplasty by flurosscopic guided insertion of Racz catheter assisted with EDS. Pain severity was measured by visual analogue score for chronic radicular leg pain and functional activities were assessed using Waddell and Main score with a followup to 6 months whereas, satisfaction was observed at 3 and 6 months.

There was significant reduction in leg pain score (P< 0.001) at 1, 3, and 6 months when compared to the preprocedure baseline values in both groups. Also there was significant reduction in leg pain score in EDS group (P< 0.001) at 3 and 6 months compared to the Non-EDS group. The function abilities and satisfaction scores showed statistical significant improvement (P< 0.001) at 3 and 6 months in both groups. No complications recorded and side effects were minimal.

Epiduroplasty by flurosscopic guided insertion of Racz catheter with or without epiduroscopy assistance reduce monosegmental unilateral radicular leg pain, improve patient functional abilities and satisfaction but with more long term leg pain and functional abilities improvement in epiduroscopic assisted patients, with minimal side effects in FBSS patients.
CIGUATOXIN-INDUCED COLD ALLODYNA IS AN ACQUIRED PERIPHERAL CHANNELOPATHY INVOLVING PREFERENTIAL ACTIVATION OF TRPA1-EXPRESSING NOCICEPTORS

I. Vetter, F. Touska, R. Hinsbey, S. Sattler, A. Lampert, A. Sharov, L. Collins, P. Cabot, J. Wood, V. Vlachova, P. Reeh, R. Lewis, K. Zimmermann, Australia, Germany, UK, Czech Republic

Ciguatera is a common form of fish intoxication that typically involves several painful neuropathy-like syndromes including cold allodynia, arthralgias and myalgias. At the molecular level, ciguatoxin (CTX) is the most potent known activator of voltage-gated sodium channels. Despite the exquisite sensitivity of neurons to CTX, the precise sensory neuronal populations activated by CTX have not been determined. Specifically, it remains uncertain how CTX causes pain or how it modulates sensory inputs by altering the activity of Na\textsubscript{v} subtypes expressed in different types of dorsal root ganglion neurons.

The neuronal population activated by low concentrations of CTX may be responsible for the persistent cold-allodynia caused by ciguatera. In this study we sought to identify the sensory neuronal populations mediating these symptoms and to elucidate the cellular and molecular basis of ciguatoxin-induced cold allodynia. Consistent with reports of CTX-mediated cold sensitization in a subset of C-fibers and A\textsubscript{\delta}\textsubscript{\delta}-fibers as well as CTX-mediated CGRP release, we show that the CTX-responsive neuronal population consists of myelinated (A\textsubscript{\delta}) and unmyelinated (C), predominantly CGRP-positive DRG neurons. Peripheral activation of this neuronal population by CTX is sufficient to elicit cold allodynia in animals. This establishes a peripheral site of action for ciguatoxins and reveals that altered excitability of peripheral sensory neurons can be sufficient for the development of cold allodynia.
IMPROVEMENT OF PARAESTHESIA IN PRESURGICAL CARPAL TUNNEL SYNDROME WITH A COMBINATION OF PALMITOYLETHANOLAMIDE (PEA) AND THE PATIENT’S USUAL MEDICAL TREATMENT

M. del Cerro, J. Saus, P. Presa, M. Marfil, J.L. Fernández, A. García, F. Márquez, Spain

Background and aims: PEA is a natural substance that is synthesised and metabolised by the body in response to cellular stress. It has an antagonistic inhibitory effect on agonist-stimulated mast cells. In animals with compression neuropathy, oral administration of PEA reduced the formation of oedema and hyperalgesia, modulated mast cell activation and provided partial activity in rats with intraneural oedema of the sciatic nerve and hyperalgesia. An improvement was also observed in patients with chronic neuropathic pain secondary to lumbar sciatica and median nerve entrapment.

Methods: This is a prospective, multi-centre study that included 62 patients divided into two groups: usual treatment (NO PEA) and usual treatment plus PEA (PEA). The following tests were performed at baseline and after 30 days: Phalen’s Test, Durkan’s Test, Carpal Tunnel Syndrome (CTS) self-administered Boston Questionnaire, VAS (0 to 10), and doctor’s and patient’s Clinical Global Impression (CGI).

Results: The two groups have been compared in terms of the mean improvement achieved between baseline and day 30. In the PEA group, the paraesthesia-associated symptoms improved (p< 0.05) in relation to the NO PEA group (CTS self-administered Boston questionnaire). As regards pain (VAS), no significant improvement was observed between the groups.

Conclusions: The combination of PEA and the patient’s usual CTS treatment improves paraesthesia. Given the characteristics of the pain experienced by patients, it seems likely that PEA will not improve this symptom.
MULTIPLE FUNCTIONS OF THE P75 NEUROTROPHIN RECEPTOR IN THE NERVOUS SYSTEM

G. Tabrizi Kahoo¹,², Iran

Background: The P75 neurotrophin receptor (p75NTR) is a trans membrane protein that binds the nerve growth factor (NGF) and implements multiple functions in the nervous system. It is expressed widely during the development of the nervous system although its expression is dramatically decreased at adulthood. Though the P75 neurotrophin receptor has been identified more than 35 years ago, our knowledge about its structure and function has barely increased.

Materials and methods: In this review various methods are used to search databases and reliable scientific resources have been reviewed to give an up-to-date panoramic picture of the protein expression, structure, function, and its interaction with other known molecules.

Results: P75NTR not only in neurons but also in various types of glial cells is expressed. In addition to NGF, this receptor can also bind the tropomyosin kinase receptors. Some pathological conditions such as neurodegenerative diseases and nerve damages are followed by the considerable increased expression of p75NTR.

Conclusion: In this study, the role of p75NTR in the nervous system of human beings has been investigated and it has been illustrated that how spinal cord repair can improve by blocking of p75NTR. It seems that in addition to p75NTR, some other homologues are also involved in this pathway. Further studies are required to elucidate more details about the role of p75NTR in the development and function of the nervous system.
Aims & objective: We present series of three patients who had electric injury.

Methods: All had incidental direct touch of electric source followed by brachial plexus involvement. Patients had isolated upper limb paralysis in next 12 hours to 24 hours.

Results: Patients had sensorimotor weakness, with power 0/5 on MRC scale and Sensory loss in involved limbs in neuropathic pattern which involved (pain, touch, vibration and temperature) in median, ulnar and radial distribution. Patients were screened by neuroimaging (MRI) examination for brain and spinal cord which was normal. Nerve conduction velocity was normal in sensory motor conduction. Inj. Methylprednisolone (1gram/ day IV for 5 days) was given which started on day 3 of injury. No improvement was noted in motor power or sensory involvement. By the end of first week, patient started having intense, sharp, tearing pain in involved limb, which was Scale 8 on pain rating scale and severe to very severe on verbal pain intensity scale. Patient did not showed any improvement in neuropathic pain, inspite of Cap Pregabaline, Tab Amytryptaline. Repeat nerve conduction test showed loss of F wave in Median, ulnar and Radial Nerves in affected limbs, with normal sensorimotor conduction. Repeat MRI test showed edematous Brachial Plexus in all patients on the affected side. Pain reduced to 6 on pain rating scale at the end of 8 week.

Conclusion: Post electric brachial plexus involvement presents with severe neuropathic pain and motor weakness and prognosis is guarded.
PERSISTENT PAIN SYNDROME IN PURE THALAMIC STROKE: REPORTS OF 34 PATIENTS

R.N. Chaurasia, V.N. Mishra, D. Joshi, India

Aims: To study clinical profile of pain syndromes in post stroke patients.

Introduction: Thalamic pain syndrome is a condition developed after a stroke causing damage to thalamus. Weeks to months later, numbness can develop into severe and chronic pain that is not proportional to an environmental stimulus, called dysaesthesia or allodynia.

Methods: Series of 34 pure thalamic stroke patients, who got recovered of their motor weakness, but persisted with central neuropathic pain syndrome. Thirty four patients of pure thalamic stroke presented in neurology outpatient department with complaints of persistent central neuropathic pain on the hemiparetic side. Patients were in age group 45-78 years, out of these 20 were female and 14 male. Twenty three patients were more than 65 years of age. Out of 34 patients, 18 had both hypertension and diabetes, 6 had diabetes and 5 had hypertension. Nine patients presented with sensorimotor deficit, 17 presented with isolated thalamic pain and 8 patients presented with pure motor deficit, at the time of presentation. Twelve had hemorrhage and rest had infarct, with 21 had right thalamic involvement and rest had left thalamic involvement. Patient had persistent annoying pain in which 56% were on scale 6, 27% on scale 8 and rest on scale 5 of pain rating scale

Results and conclusion: Patients were given various symptomatic treatments. Seven patients were referred to pain clinic for intervention pain management. 34% patients continued with persistent pain syndromes in 3 month follow-up and these were having predominantly posterior thalamic lesions
TO EVALUATE THE ROLE OF PREGABALIN AS PREEMPTIVE ANALGESIC FOR ATTENUATION OF POSTOPERATIVE PAIN UNDER SPINAL ANESTHESIA

S. Sahu, S. Sachan, A. Verma, P.K. Singh, India

Background: Pregabalin is currently used in the treatment of neuropathic pain and fibromyalgia etc. It binds to the alpha-2 subunit of calcium channels which reduces the influx of several neurotransmitters causing a decrease in neuronal hyperexcitability. Studies show a considerable overlap between the mechanism of chronic and acute pain. A preemptive analgesic attenuates sensitization of pain before surgery so as to reduce postoperative hyperalgesia and allodynia. It is of considerable interest, whether preemptive pregabalin can alter central sensory processing to reduce post surgical pain.

Material and methods: After institutional ethical clearance and written informed patient consent, 70 patient of ASA I-II between 18-60 yrs of both sexes were randomly divided into two groups. Group I, received placebo capsules 12 hrs before surgery and 1 hr before surgery. Group II received pregabalin 150 mg, 12 hrs before surgery and 1 hr before surgery. All cases for below umbilical surgeries were included and conducted under spinal anaesthesia. After giving spinal anesthesia patients were assessed every two hours for first twenty four hours for pain score by VAS scale, NIBP, PR, RR, rescue analgesics demand (injection tramadol 1 mg/kg IV as per protocol) and side effects if any.

Result and observation: Patients in Pregabalin Group had significant lower mean VAS postoperatively and lower rescue analgesic consumption than placebo group (P < 0.05).

Conclusion: A 300 mg preemptive pregabalin in two divided doses before surgery provides better pain control than placebo and reduces the demand of rescue analgesic.
EFFECT OF CERVICAL TRACTION IN MANAGEMENT OF RADIATING NECK PAIN

A.O. Ojoawo, C. Mbada, A. Olabode, A. Badru, Nigeria

Background: Radiating neck pain is a common episode that affects almost everybody with poor prognoses. The purpose of this study was to examine the effect of cervical traction on patients with radiating neck pain.

Method: A total number of 31 patients (18 males and 13 females) diagnosed with radiating neck pain participated in the study after obtaining their consent. Visual analogue scale (VAS) and Neck Disability Index (NDI) were used as outcome measures for pre test and post test assessment. Cryotherapy, soft tissues massage with methyl salicylate ointment and active exercise were baseline treatment. Participants were then divided randomly into 2 groups. Group A (16 patients; 9 males 7 females) was treated with cervical traction using a head halter sling with a weight of 25% of total body weight and Group B (15 patients; 9 males, 6 females) had no additional treatment. The treatment lasted for 6 weeks with assessment every week. Descriptive and inferential statistics were used to compare the pre and post treatment assessments and post treatment of group A and B. Result revealed that there were significant differences (p < .05) between the pre and post treatment assessment of VAS and NDI for group A and B. There was a significance difference between post treatment assessment when VAS of group A was compare to VAS of group B. The study concluded that cervical traction can be useful in ameliorating radiating pain and disability of patients with neck pain.
COMPARATIVE STUDY OF THE EFFECT OF DRY AND MOIST DRESSING ON PAIN BURN WOUND

M. Seyedalshohadadee, F. Rafii, A.F. Hoseini, H. Karimi, Iran

Background and aims: Consistent with recent scientific advances in wound treatment and pain management, modern dressing, using technology and knowledge were designed and produced. Such a dressing can provide an appropriate environment for moisturizing wound healing by maintaining and controlling moisture along with other conditions. This study aims to compare the effect of dry and moist dressing on burn wound healing.

Material and methods: It was a quasi experimental research. Sampling was done constantly according to inclusion criteria.

The final sample consisted of 60 patients hospitalized in Shahid Motahari burn center with second degree burn and a TBSA less than or equal to 10% on both hands or legs. Data collection tools included demographic information form and observation checklist. Part of the burned area was covered with a dry dressing according to hospital routine and the other part covered with the wet dressing of NA ultra. The stage and duration of wound healing was observed and recorded in the third, seventh, thirteenth and twenty-first days. Data was analyzed using descriptive statistics and pair t-test by SPSS-PC (v. 13).

Results: There was a significant difference between the mean scores of the stage (P< 0.001) and duration (P=0.004) of burn wound healing.

Conclusion: According to the findings, the use of wet dressings in treating and pain burn wounds is advisable.
FACTORS ASSOCIATED WITH DEPRESSIVE SYMPTOMS IN PATIENTS WITH CHRONIC LOW BACK PAIN

J.Y. Ha, Republic of Korea

Introduction: Depressive symptoms as well as organic lesions in patients with chronic low back pain are very important for patient management. Therefore, factors associated with depressive symptoms need to be understood to consider treatment for chronic low back pain.

Objective: To investigate depressive symptoms and their related factors in patients with chronic low back pain in Korea.

Methods: A cross-sectional study using data from the fourth Korea National Health and Nutrition Examination Survey (KNHANES IV) 2009 was undertaken. The sample consisted of 1,426 participants with chronic low back pain. Multifactorial regression analysis was used to identify the association between depressive symptoms and socioeconomic demographics and other chronic diseases.

Results: Among the 371 (26.0%) patients with depression, significant factors associated with depressive symptoms were female gender (odds ratio [OR], 2.691; 95% confidence interval [CI], 1.724-4.199), medical aid beneficiary (OR, 1.371; 95% CI, 1.039-1.810), a dependent group for activities of daily living (OR, 1.570; 95% CI, 1.180-2.087), 'not good' in the perceived health category (OR, 2.309; 95% CI, 1.730-3.081) and in a cancer group (OR, 1.803; 95% CI, 1.051-3.093).

Conclusions: This study provides the foundation for managing patients with chronic low back pain and depressive symptoms. Clinicians managing chronic low back pain should consider risk factors for depressive symptoms.
GABAPENTIN VERSUS PREGABALIN IN RELIEVING EARLY POSTSURGICAL NEUROPATHIC PAIN IN PATIENTS OPERATED DUE TO LUMBAR DISC HERNIATION


Background and aim: Patient outcome after lumbar discectomy for neuropathic pain is variable. Many patients have started suffering from pain in an early postsurgical period. Gabapentin and pregabalin are anticonvulsant agents and may decrease perioperative central sensitization and early postsurgical neuropathic pain. To study the modeling a multimodal acute neuropathic pain management plan to decrease the conversion of acute to chronic pain.

Methods: Prospective, controlled, randomized, study based on personal interviews. Eighty patients undergoing lumbar discectomy and partial medial facetectomy associated with neuropathic pain at early postsurgical period were included (Table 1). The assessment included the Leeds Assessment of Neuropathic Symptoms, and Signs scale (LANSS), preoperatively and three days, 6 and 12 months after surgery. Among these patients, fifty-four patients complained of neuropathic pain and treated with gabapentin (group 2) and pregabalin (group 3).

Results: In the gabapentin group, while LANNS scores increased to 14 points at post-op 3rd day. With gabapentin treatment, the patients improved both neurologically and LANNS score, which decreased 10 points at post-op 6th month and 4.5 points at post-op 1st year (p< 0.001). In pregabalin group, LANNS scores increased from 12 to 16 points at 3rd post-op day. With pregabalin medication, the patients improved more than gabapentin treatment and LANSS scores decreased 12 and 5 points at post-op 6th month and post-op 1st year, respectively (p< 0.001), (Fig 1), (table 3-4).

Conclusion: Pregabalin administration is associated with less neuropathic pain in the early postsurgical period. Both gabapentin and pregabalin were very effective agents for relieving of neuropathic pain at 1st year follow-up after discectomy.
ELECTROCHEMICAL DETERMINATION OF GLYCINE RELATIVE TO NEUROPAIN TRANSMISSION BY USING A NOVEL ELECTRODE MODIFIED WITH NANOPARTICLES

Y. Wang, J. Wang, H. Peng, J. Zhu, China

Introduction: Amino acids play key roles in many neuro-chemical response mechanisms, such as pain transmission. Direct electrochemical detection is a subject of great interest. However, the electrode of noble metal fouling is a great problem due to the strong adsorption and accumulation of intermediate products.

Objectives: Establish a novel electrochemical assay method for detection of glycine with highly accuracy, quick response and low cost.

Methods: Glycine electrochemical sensor was fabricated by ZnO and Ni(OH)$_2$ nanoparticles coated multi-walled carbon nanotubes (MWNTs). Amperometric method was used for the determination.

Results: Fig.1 represents the chronoamperogram of the sensor obtained in 0.1 M KOH solution at 0.5 V by successively adding aliquots of glycine. The cyclic voltammograms in the absence and the presence of 1 mM glycine and calibration curve is also shown as the insert (linear response range: 0.1 - 1.2 mM, sensitivity: 1.1 µA mM$^{-1}$, RSD: 5.5%). Interferent tests illustrated that 0.2 mM of L-arginine, L-glutamic acid, α-leucine and L-alanine didn’t have effect on the determination of glycine.

Recovery and levels of glycine detected in discrete brain area of rats were listed in Table 1 and 2, respectively. The results confirm that the sensor reaches the needs of glycine determination in the animals.
[Fig. 1 Chronoamperogram, cyclic voltammograms and ]

<table>
<thead>
<tr>
<th>Spiked (µM)</th>
<th>Detected (µM) (n=5)</th>
<th>% Recovery</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.10</td>
<td>0.11</td>
<td>110</td>
</tr>
<tr>
<td>0.50</td>
<td>0.48</td>
<td>96</td>
</tr>
<tr>
<td>1.00</td>
<td>1.05</td>
<td>105</td>
</tr>
</tbody>
</table>

[Table 1 Recovery of glycine in the assay]
<table>
<thead>
<tr>
<th>Level (µg/g)</th>
<th>Amygdala</th>
<th>Hypothalamus</th>
<th>Brainstem</th>
</tr>
</thead>
<tbody>
<tr>
<td>The sensor</td>
<td>204 ± 5</td>
<td>250 ± 8</td>
<td>646 ± 21</td>
</tr>
<tr>
<td>HPLC</td>
<td>198 ± 3</td>
<td>258 ± 6</td>
<td>671 ± 11</td>
</tr>
</tbody>
</table>

Table 2 Comparison of levels of glycine detected

**Conclusion:** A novel glycine sensor based on nanoparticles has been successfully fabricated. The results illustrate it can be used for the determination of glycine in rats tissue with accuracy, quick response and low cost, which provides a powerful tool to investigate neuro-pain transmission mechanisms.
SARTANS, AT1 RECEPTORS AND NOCICEPTION: CONNECTING THE MISSING LINKS

L.B. Badgujar, G. Khanvilkar, M.N. Saraf, India

Introduction: There is an ambiguity regarding the role of AT receptors in modulation of pain pathways, to explore this present study is designed.

Objective: To study the Neurochemical & biochemical pathways involved in the antinociceptive effect of AT1 receptor antagonist.

Methods: Sprague-Dawley rats (180-200g) were anesthetized under ketamine-xylazine (80:20, intraperitonially), chronic constriction injury (CCI) was performed (Bennett and Xie, 1988). Vehicle (1ml), Candesartan (3, 10 & 30 mg/kg) and irbesartan (3, 10 & 30 mg/kg) were administered from day 1 to day 28 after recording the behavioral observations. Behavioral observations were recorded on 7,14,21 & 28th day. Animals were sacrificed on 29th day and brain and sciatic nerve were isolated for biochemical estimations.

Results: CCI rats displayed a significant mechanical allodynia (P< 0.0001) and a significant increase in time of immobility (P< 0.001). As time of swimming was unchanged, immobility was increased at the expense of climbing behavior (P< 0.001). Candesartan 10 & 30 mg/kg and irbesartan at all the doses decreased the mechanical allodynia (P< 0.05). Similarly both the agents were decreased the time of immobility at an expense of climbing behavior at doses of 10 & 30 mg/kg. Repeated administration of candesartan & irbesartan did not produce any effect on motor behavior. Brain monoamine and Biochemical estimations are in process.

Conclusion: Antinociceptive effect of noradrenalin & sartans have been recently established. The present study explains the underlying mechanism by elucidating the probable neurochemical pathway involved in the pain transmission, which could be mediated via locus coeruleus (LC).
AGRIN INHIBITS SPINAL CORD INJURY INDUCED NEUROPATHIC PAIN

G. Tender, D. Erasso, R. Levitt, J.-G. Cui, USA

Spinal cord injury induced neuropathic pain (SCINP) occurs in up to 85% of patients with spinal cord injury (SCI) and current treatments for this disease are often ineffective. Agrin, a heparan-sulfate-proteoglycan functioning as a neuromuscular junction inducer, plays an important role in pain modulation and may prove useful for the treatment of neuropathic pain.

Male rats were subjected to a chronic constriction or photochemical sciatic nerve injury, or to an SCINP rat model made by quisqualic acid (QA) injection into the lumbar dorsal horn (DH). A non-pathogenic adeno-associated virus serum type 2 (AAV2) was then selected as a gene carrier, to deliver the agrin 50kD isoform (Ag50) by injection into the superficial spinal cord of neuropathic rats. Behavioral testing for allodynia and hyperalgesia was performed throughout the experimental period. The spinal cord was harvested for immunohistochemical and mRNA analysis.

In both sciatic nerve injury rat models, as well as the SCINP model, agrin decreased only in the DH of neuropathic rats. When the agrin gene was delivered into the DH via AAV2, increased Ag50 expression suppressed neuropathic pain. The underlying mechanism was that Ag50 specifically activated phosphorylation of NMDA receptor subunit NR1 at serine 896/897 residues in the GABA inhibitory interneurons, which in turn suppressed pain.

These results indicate that agrin is an inhibitory molecule in the DH, acting via the GABA inhibitory interneurons. These biological features may be useful not only for neuropathic pain treatment, but also for other neurological disorders involving hyperexcitability, such as tremor and spasticity.
METHYLGLYOXAL INFUSION IN NORMOGLYCEMIC WISTAR RATS - ITS IMPACT ON NEURAL FUNCTION

R. Elvert, A. Pfenninger, A. Kannt, Germany

Plasma methylglyoxal (MG) is elevated in patients with diabetes and correlates with susceptibility for painful neuropathy. Streptozotocin (STZ)-induced diabetes or MG infusion in mice caused hyperalgesia and tactile allodynia (Bierhaus et al. 2012, Nat Med). We performed a rat study to confirm the MG induced painful neuropathy. We analyzed MG concentrations in plasma, urine and several tissues and monitored the impact of chronic MG infusion on metabolic parameter.

Three groups of healthy Wistar rats (n=8 each) were included into the study: one served as healthy control, the second was treated with STZ (60mg/kg i.v.) and served as diabetic control. The third was infused via pumps with 60mg/kg/day MG for 7 weeks. Neuronal function was determined by measuring tail nerve conduction velocity (NCV) and von Frey filaments. Plasma, urine and tissue MG levels were measured using an LCMSMS system. An oGTT and ITT were performed for determination of glucose tolerance or insulin sensitivity.

MG treatment attenuates NCV already after two weeks which further decreases comparable to diabetic rats versus sham control (64.0±1.1m/sec vs. 76.7±2.1m/sec in controls) and leads to hyperalgesic perception. MG levels in plasma, urine, liver and sciatic nerve were significantly elevated. Even in kidney and heart we measured a 2 fold increase of MG protein modification. No impact on metabolic parameters could be observed.

This comprehensive study confirmed data obtained from mice and humans indicating the inducibility of neuropathic pain via elevated MG levels. It could be a promising therapeutic option to scavenge MG in patients with neuropathic pain.
LIDOCAINE TOPICAL PATCH 5% FOR THE TREATMENT OF CHRONIC REFRACTORY NEUROPATHIC PAIN IN CANCER PATIENTS: A PROSPECTIVE OPEN-LABEL STUDY

G.D. De La Cruz, F.O. Javier, A.B. Yap, L.S. Kwong, Philippines

Introduction: Cancer-related persistent neuropathic pain are often difficult to manage due to the complexity of the pain mechanisms involved in the disease process. Lidocaine topical patch is a first line treatment in peripheral neuropathic pain, but there still has limited studies done on the potential of Lidocaine patch in treating cancer-induced peripheral neuropathic pain.

Objective: To determine the effectiveness of Lidocaine topical patch 5% in the treatment of refractory peripheral neuropathic pain among cancer patients.

Method: This is a prospective, open-label, pilot study in 27 patients (mean age 66.7 years) with reported persistent inadequate pain relief (VAS 4 and above) and treated with combination of opioids, antidepressants and anticonvulsants. Patients were started on Lidocaine topical patch 5% on focal affected areas (maximum of 3 patches/day) changed every 24h. Other analgesic regimens were continued throughout the study. Patients were evaluated from baseline, at day 7 and day 30. Pain outcomes were measured using the Brief pain inventory and ID pain screening tool.

Results: Mean VAS scores were, at baseline (6.0±1.7), at day 7 (3.3±1.6), and at day 30 (2.4±1.6). There was a significant reduction in VAS scores (p< 0.01) after 7 and 30 days. Treatment with lidocaine topical patch helped relieve various characteristics of pain, including burning, electrical shock-like pain and allodynia. No adverse events were reported with lidocaine patch.

Conclusions: Lidocaine topical patch 5% have potential benefits for treatment of refractory neuropathic pain in cancer patients; controlled clinical trials is suggested to further evaluate the efficacy and also assessment in a larger study is recommended.
EPIGALLOCATECHIN GALLATE SUPPRESSES NFkB SIGNALING PATHWAY & APOPTOSIS IN THE EXPERIMENTAL MODEL OF DIABETIC NEUROPATHY

A. Kuhad, K. Chopra, India

Introduction: Diabetic neuropathic pain, an important microvascular complication in diabetes mellitus is recognised as one of the most difficult types of pain to treat. The development of tolerance, inadequate relief and potential toxicity of classical antinociceptives warrant the investigation of the newer agents to relieve this pain. Reactive oxygen species and cytokine induced activation of nuclear factor kappa-B signaling pathway and apoptosis in sciatic nerve are implicated in the pathogenesis of diabetic neuropathy.

Objectives: The aim of the present study was to explore the effect of epigallocatechin gallate on nerve functions, oxidative nitrosative stress, inflammation and apoptosis in streptozotocin induced experimental diabetes.

Methods: Streptozotocin-diabetic rats developed neuropathy which was evident from significant reduction in motor nerve conduction velocity, nerve blood flow, increased thermal hyperalgesia associated with enhanced oxidative-nitrosative stress, release of inflammatory mediators (TNF, IL-1beta, NFkB) and caspase 3.

Results: Chronic treatment with epigallocatechin gallate (25, 50 and 100 mg/kg body weight; p.o.) for 4 weeks starting from the 4th week of streptozotocin injection significantly suppressed behavioral, biochemical and molecular changes associated with diabetes. Epigallocatechin gallate offered better protection than tocopherol in this experimental model of diabetic neuropathy. Moreover, diabetic rats treated with insulin-epigallocatechin gallate combination produced robust effect on molecular parameters as compared to their per se groups.

Conclusions: Taken together, the data reveal that suppression of NFkB signaling pathway & caspase-3 by epigallocatechin gallate prevent diabetic neuropathy and point towards the therapeutic potential of epigallocatechin gallate in diabetic neuropathic pain.
Introduction: Mozambique is a country that has been experiencing profound political and social changes over the last 50 years. Within this context, in 1996 a Pain Unit was set up in the Central Hospital of Maputo.

Objectives: The objective of the present study was to describe the epidemiological and clinical aspects of patients with chronic pain in general and neuropathic pain attended at the Pain Unit.

Methods: The study was designed as a cross-sectional study. Inclusion criteria was presence of chronic pain.

Results: A total of 118 patients were interviewed over. Of these, 79 (66.9%) were women and 39 (33.1%) were men. Mean patient age was 52.4 years. Hundred seven (90,7%) were black. Forty patients (33,9%) had a diagnosis of neuropathic pain, 40 (33,9%) had musculoskeletal pain, 8 (6,8%) had pain related to SIDA, 17 (14,4%) had oncologic pain. Between neuropathic pain, 28 (23,7%) had radiculopathy and pain following lumbar spine surgery, 12 (10,1%) had neuropathic pain secondary to peripheral nerve damage (as diabetes, post herpetic syndrome, alcohol, drugs...) and 3 (2,5%) had amputation pain (as phantom pain). Mean of numeric scale for pain was 8.37 and chronic pain duration was 41,75 months. Regardless of their treatment at the Pain Unit, between the abortive medications for pain, paracetamol was the most used and prophylactic amitriptyline was the most widely used. Fifty eight patients (49.2%) also received some treatment from local healers.

Conclusion: Social and cultural causes influenced the epidemiology of pain in Mozambique.
HOW OFTEN DO PATIENTS UNDERGOING HIP JOINT REPLACEMENT EXPERIENCE IMPROVEMENTS THAT ARE MEANINGFUL TO THEM?

J.A. Singh1,2, D.G. Lewallen, USA

Background/purpose: To characterize clinically meaningful improvements in pain and limitation of key Activities of Daily Living (ADLs) after primary or revision total hip arthroplasty (THA).

Methods: We analyzed prospectively collected data from the Mayo Clinic Total Joint Registry to study clinically meaningful improvements in index hip pain severity and limitation in seven key ADLs related to hip joint function (walking, climbing stairs, putting on shoes/socks, picking up objects, getting in/out of car, rising from a chair and sitting), from preoperative to 2- and 5-year post-THA.

Results: The primary THA cohort consisted of 6,168 responders preoperatively, 5,707 at 2- and 3,289 at 5-years. Revision THA cohort consisted of 2,063 responders preoperatively, 2,682 at 2- and 1,627 at 5-years. In primary THA cohort, clinically meaningful pain reduction to mild or no hip pain at 2-years was reported by 94% with moderate and 91% with severe preoperative pain; respective proportions were 91% and 89% for 5-years follow-up. For revision THA, respective proportions were 84% and 77% at 2-years and 80% and 78% at 5-years. In primary THA cohort, up to 4% with moderate and 17% with severe preoperative ADL limitation reported severe limitation in the respective activity 2-years post-primary THA; at 5-years, the respective proportions were, up to 7% and 20%. Respective proportions for revision THA were up to 10% and 26% at 2-years and 13% and 30% at 5-years.

Conclusion: Knowledge of clinically meaningful improvements in pain and key 7 ADLs can help patients set realistic goals for improvements after THA.
EMPOWERMENT OF THE FAMILY - BASED ON ADHERENCE TO PHYSICAL ACTIVITY IN PATIENTS UNDERGOING CORONARY ARTERY BYPASS SURGERY

S.S. Nejati¹,², Iran

Aground: Denial of physical activity after surgery, one of the main problems is considered influential in the recovery of heart patients. This study examines the impact of family empowerment model - based on patients undergoing coronary bypass surgery, as a family-based intervention on patient adherence to physical activity and active cooperation of family members, was conducted.

Method: This clinical trial study, quasi-experimental control group was tested before and after, in 102 patients and 102 family members stay in cardiac surgery was performed in 89-90 years. Sampling study, a block and was based on random allocation, patients undergoing elective vascular surgery were literate and had a phone call after discharge from hospital, were studied. Pattern of group empowerment for families - the four dimensions of perceived threat (severity and susceptibility), self efficacy educational participation, and evaluation, control group were implemented for routine care. Research tools used include demographic information, adherence to physical activity during the 8 weeks.

Results: Adherence physical activity levels in all patients before the intervention was similar in both groups (p (0.05< after the intervention group had a statistically significant greater (p> 0.000). Adherence cooperation of family members in adherence to physical activity all values were similar in both groups before intervention (p (0.05< and after the intervention were statistically significant. ( P(0.000>.

Conclusion: Findings seem to be empowerment of model of family - oriented for patients undergoing coronary artery bypass is feasible and compliance with the improvement or modification of physical activity is associated with the patien.
CHRONIC NEUROPATHIC PAIN: ETIOLOGY, GENDER CHARACTERISTICS, SOCIO ECONOMIC STATUS AND QUALITY OF LIFE - STUDY IN INDIAN PATIENTS

A. Waheed, S. Bhat, V. Nabi, India

Background and aim: Chronic pain resulting from peripheral nerve damage is a frequent painful complication of diabetes, degenerative spine disease, cancer and infectious diseases. The problem is especially severe in developing countries where prevalence is high and a large number of patients actually seek medical help for these complications rather than the primary disease. Still not much work has been done to study various aspects of neuropathic pain in these countries. With this background we undertook this study of various aspects of neuropathic pain and its effect on the quality of life.

Methods: 100 patients aged 18-65 yrs suffering from neuropathic pain were studied for etiology, gender characteristics, socio economic class and level of education. The patients were also studied for the intensity of pain(VAS) and quality of life using EORTC qlq-30 questionnaire.

Results: Diabetic neuropathy was the most common diagnosis(39%) followed by herpetic neuralgia(34%). Lower Socio-economic Classes and illiterate population had significantly higher prevalence of neuropathic pain (p< 0.05). Females had a higher pain score at presentation although the difference was not significant(p>0.05). Impact on quality of life in such patients was severe with low global quality of life, decreased functional scores and increased symptom score according to EORTC qlq-30 questionnaire as compared to healthy controls(p< 0.05). The patients had significantly increased financial difficulties as compared to general population(p< 0.05).

Conclusions: Preventable diseases like diabetes account for a bulk of neuropathic pain. The disease has severe impact on the quality of life as well as economy of the affected population.
A RETROSPECTIVE QUESTIONNAIRE FOR PATIENTS USING BOTOX® TO TREAT CHRONIC MIGRAINE IN CLINICAL PRACTICE

R. Salt, A.J. Dowson, UK

Introduction: In the UK, Botulinum toxin type A (BOTOX®, Allergan, Marlow, UK) was licensed for use in Chronic Migraine (headaches on at least 15 days per month of which at least 8 days are with migraine) in July 2010 by the MHRA.

We questioned a group of patients using Botulinum toxin type A in clinical practice about some issues influencing their care-seeking behaviour.

Methods: An 18-item questionnaire was developed and sent by post to the last 50 patients treated with Botulinum toxin type A for Chronic Migraine by the Surrey Headache Service. The questions were developed to gain insight into efficacy, side effects and impact on patients' quality of life. In addition, the length of action of the treatment, the actual time to repeat treatment and other aspects concerning patient behaviour were addressed.

Results: An interim analysis suggested that 68% of patients found that Botulinum toxin type A reduced their illness burden and for 64% this was seen as improving quality of life. For most the benefits were lost between 10 and 12 weeks, but 32% waited longer than 12 weeks to repeat dosing. 46% reported using a reduced amount of other treatments. 39% reported side effects; in one this was drooping eyelids and in the remainder local reactions.

Conclusion: In clinical practice Botulinum toxin type A appears to be an effective and acceptable treatment for some Chronic Migraine patients. It appears that individualizing injection strategies and, in particular, dosing intervals maximizes outcomes.
"PLEASE LISTEN TO ME" - PATIENTS' EXPERIENCE OF SPINAL CORD INJURY NEUROPATHIC PAIN MANAGEMENT

C. Norrbrink, M. Löfgren, Sweden

Background and aims: In a study published in 2012, 18 informants with spinal cord injury (SCI) and neuropathic pain were interviewed. The aims of that study were to increase knowledge about strategies and treatments used by individuals with neuropathic pain following SCI for handling long-term pain, and of their experience, needs and expectations of SCI neuropathic pain management. A model with four categories emerged: "Pain is my main problem"; "Drugs - the health care solution"; "The gap in my meeting with health care" and "But...this works for me.

The present follow-up study sought to deepen our knowledge about how to design future health care for individuals with SCI and neuropathic pain. Sixteen of the former 18 informants participated. Physicians working with SCI neuropathic pain rehabilitation from nine hospitals were also invited as informants.

Methods: The study used focus group interviews, and individual interviews are being conducted with the physicians.

Results: Preliminary results indicate that great interest in and knowledge about SCI neuropathic pain are essential, as is a good dialogue with the treating physician. Further suggestions include an individual approach where complementary treatments are offered by health-care, information about neuropathic pain and how to live with it, the need for shorter waiting-lists, a possible neuropathic pain emergency facility, regular follow-ups of their pain problems and pain coaches/role models/peer groups.

Conclusion: Rehabilitation warrants improvements in order to meet the needs of individuals with SCI and neuropathic pain.
NOVEL PERIPHERALLY-RESTRICTED CANNABINOID RECEPTOR AGONISTS ALLEVIATE PERIPHERAL NEUROPATHY SYMPTOMS WITHOUT CENTRAL SIDE-EFFECTS


The widespread use of cannabinoids to alleviate neuropathic pain is limited by their CNS-mediated psychotropic side-effects. CB1 receptor (CB1R) agonists were engineered for high hCB1R affinity, peripheral selectivity, metabolic stability and in vivo efficacy without CNS effects. Introduction of charged (quaternary ammonium), actively exported (carboxylate), and subsequently other moieties evolved indoles and indenes with low nM hCB1R affinity in the best cases. Blood-brain barrier penetration modeled with the MDCK cell line assay identified candidates with < 1% permeation for in vivo testing and in vitro metabolic stability studies; subsequent modifications increased metabolic stability. Candidate compounds were examined for effectiveness against mechanical allodynia in a rat neuropathy model induced by unilateral sciatic nerve entrapment (SNE). The ipsilateral hindpaw withdrawal thresholds were reversibly increased to 50-100% of pre-SNE values, depending on the compound, after intraperitoneal injection. A tetrad assay modified for rats compared the effects of the brain penetrable CB1R agonist HU-210 at doses that alleviate neuropathy symptoms as a positive control to our novel ligands and to vehicle. While HU-210 exhibited strong CNS effects in the tetrad, at systemic doses that relieve neuropathy symptoms our novel CB1R agonists showed a complete lack of side-effects in catalepsy, hypothermia and motor incoordination assays. At the same doses, pharmacokinetic studies revealed a cerebrospinal fluid: plasma ratio of ~0.001, further supporting limited CNS penetration. The potency, peripheral selectivity, in vivo efficacy and absence of CNS side-effects of the indole and indene classes of CB1R agonists hold promise as a viable treatment for neuropathic pain.
EVIDENCE FOR CORRESPONDENCE BETWEEN NEUROPHYSIOLOGICAL AND CLINICAL MEASUREMENTS OF CHEMOTHERAPY-INDUCED PERIPHERAL NEUROPATHY


Introduction: Chemotherapy-induced peripheral neuropathy (CIPN) lacks standardized clinical measures.

Objectives: We examined associations between clinical examinations and abnormal sural nerve (SN) and common peroneal nerve (CPN) amplitudes obtained from neurophysiological testing (NCS) in cancer patients with self-reported CIPN.

Methods: Patients from an international, multi-site study received NCS of SN and CPN amplitudes and vibration, pin sensibility, and monofilament examinations. Moderately abnormal examinations were abnormal findings up to/including the wrist/ankle. Severely abnormal examinations were abnormal findings at/above the elbow/knee. General linear mixed models were used to calculate odds ratios (OR) of abnormal (< 100% of lower limit of normal for center norm) SN and CPN amplitudes, relative to those with a normal examination.

Results: Mean age of patients (N=202) was 62.6±9.5 years, and 45.5% were female. Cancer diagnoses included colorectal (45.5%), breast (14.9%), lung (8.4%) and multiple myeloma (7.4%). Patients received platinum compounds (59.4%), platinum/taxane combinations (14.4%), and taxanes (12.4%). After controlling for age, sex, chemotherapy type, and center, monotonic relationships were found between each examination type and SN amplitudes, with higher ORs as clinical examination revealed more severe impairment. For example, those with moderately abnormal upper and lower extremity monofilament examinations were 3.16 (95%CI: 1.33-7.47) and 3.49 (1.50-8.12) times more likely to have abnormal SN amplitudes, respectively. With a severely abnormal lower extremity monofilament examination, patients were 4.52 (1.26-16.25) times more likely to have abnormal SN amplitude.

Conclusions: Abnormalities detected with vibration, pin sensibility and monofilament examinations are associated with abnormal amplitudes, suggesting a role for clinical examinations in accurately identifying CIPN.
HONEY ALTERED THE SERUM CORITISOL AND FERRITIN LEVELS IN SCIATIC NERVE LIGATED NEUROPATHIC RATS

B.V. Owoyele, O.T. Adenekan, Nigeria

Background and aims: Neuropathy is associated with some endocrine and metabolic abnormalities which have led to concerted effort in its management. It has been previously reported that elevated serum cortisol is part of the findings in diabetic neuropathy and honey has been reported to have beneficial effect in reducing serum cortisol and ferritin levels in normal subjects. Therefore the present study was undertaken to determine the effects of honey on serum cortisol and ferritin in sciatic nerve legated rats.

Methods: Animals were grouped into five groups comprising of six rats each. Groups A and B received saline and 40 mg/Kg of imipramine respectively, groups C and D received honey at the doses of 200 and 600 mg/Kg respectively while group F were sham treated. All animals except group A had their left sciatic nerve partially ligated while all drugs/saline were administered orally for 14 days and blood samples were collected using cardiac puncture.

Results: The results showed that honey significantly reduced the serum cortisol from 6.77±0.83 to 2.50±0.18µg/dl compared with the control and sham treated groups, while the level of ferritin was decreased by honey (600mg/Kg) compared with the control and sham treated groups.

Conclusions: These results further demonstrate the usefulness of honey in the treatment of chronic inflammatory and painful conditions as well as its ability to modulate chemical imbalance in neuropathic animals.
ENDOCRINE DYSFUNCTION IN MALE PATIENTS WITH DIABETES AND CO-MORBIDITIES ON LONG TERM STRONG OPIOIDS FOR PAINFUL POLYNEUROPATHY

T. Ivanova-Stoilova, P.J. Evans, UK

Opioids have been found to be effective in reducing severity of symptoms in painful diabetic neuropathy when applied short term. There is evidence that opioids cause dysfunction of hypothalomo-pituitary-adrenal or gonadal axis when used for long term in chronic non-malignant pain.

Aim: We hypothesized that male patients with painful diabetic neuropathy are at risk of developing hypogonadism when treated with opioids long term. Worsening of clinical condition may therefore be a result of endocrine dysfunction and not disease progression.

Methods: We followed the symptom progression in 22 male patients with diabetes and painful polyneuropathy, autonomic neuropathy and co-morbid systemic diseases treated between 2008-2012. Strong opioid medication was prescribed in conjunction with anticonvulsants and antidepressants to better control intractable pain. We identified patients who developed tiredness, increased pain and reduced mobility at follow-up. We measured serum testosterone, cortisol, fasting glucose, glycated haemoglobin levels. We calculated free testosterone levels (Vermeulen equation).

Results: Patients' mean age - 56 years, mean duration of treatment with strong opioids - 18 months. 7/22 (31.6%) patients developed worsening of symptoms. Two (28.5%) had low cortisol mean 6nmol/l. All patients had low serum testosterone - mean 11.6 nmol/l, high glycated haemoglobin (HBACIC IFCC) - mean 72.8 mmol/ml and low free testosterone - mean 0.22 ng/dl.

Discussion: We found evidence of opioid induced endocrinopathy with worsening of clinical symptoms within the progress of the neuropathic disease.

Conclusion: Further studies are needed to elucidate the safety of long term opioids in treatment of painful diabetic neuropathy.
EVALUATION OF EFFICACY OF DULOXETINE AND PREGABALIN IN PATIENTS WITH PAINFUL DIABETIC PERIPHERAL NEUROPATHY

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Introduction: Diabetic polyneuropathy (DPNP) is a symmetrical peripheral neuropathy that results from nerve damage after prolonged periods of suboptimal glycemic control. Neuropathy is often associated with significant burning, stabbing or tingling pain and numbness, and can result in sleep interference and severe disability. The aim of this study was to compare the efficacy and safety of duloxetine (DLX), a balanced and potent dual reuptake inhibitor of serotonin and norepinephrine, with pregabalin (PGB), a calcium Channel blocker in the management of diabetic peripheral neuropathic pain.

Methods: We performed a double-blind 12-week RCT study of patients with diabetic peripheral neuropathic pain whom have been treated with pregabalin (150 mg/d) (n=55) or duloxetine (60 mg/d) (n=50) and had a daily pain score of ≥4 (VAS) in admission time. The primary objective was a comparison between DLX and PGB on improvement in the weekly mean of the daily pain score. Secondary efficacy measures included sleep interference score, Patient Global Impression of Change (PGIC), and Clinical Global Impression of Change (CGIC).

Results: A significant reduction in pain score (VAS), sleep interference score, PGIC, and CGIC was seen in all the two treatment groups across time with no statistically significant difference between the groups. The improvement in pain scores and sleep interference score was faster with PGB compared to DLX. (P< 0.05) Adverse drug reactions were mild in 4.5% of all cases.

Conclusions: DLX and PGB Produced a clinically and subjectively meaningful pain relief in patients with DPNP with onset of pain relief being faster with PGB.
DEMOGRAPHIC AND PAIN CHARACTERISTICS OF NEUROPATHIC PAIN (NP) PATIENTS ATTENDING A PUBLIC HOSPITAL PAIN MANAGEMENT CLINIC IN KARACHI, PAKISTAN


Introduction: Neuropathic Pain is an important health problem in adult populations around the world. However, it has been little studied in the developing world.

Objective: To describe the demographic and pain characteristics of NP patients attending a Pain Management Clinic at the Civil Hospital, Karachi, Pakistan.

Methods: A retrospective chart review from a consecutive series of 104 NP patients, representing approximately 11.8% of all new patients seen over one year period (2010-2011). Data extracted: demographics, body drawings, pain ratings on a 0-10 Numeric Rating Scale (NRS) and pain duration at the time of first consultation. Diagnostic classification was obtained via retrospective chart reviews (during the first or subsequent visits, if further investigations were needed).

Results: Female/male ratio was 1:0.96, mean age years 44.3±13.7; married/single 10.5:1. Married were older than single patients (mean 46.1±12.3 vs 24.7±2.04 years, p<0.0001). The mean pain duration was 1.64±1.6 years and mean NRS ratings were 6.6±1.3. About half (46.1%) of the patients were in severe pain category (>7/10). The commonest NP syndromes were NP due to multiple injuries, chronic lumbar and cervical radiculopathy, spinal cord injury, peripheral neuropathies including diabetic neuropathy. Coexisting musculoskeletal pathology was found in 24.03% of the women and 19.2% of men. Based on the body map, the most common complaint was low back pain (14%, n=193).

Conclusions: The study represents the preliminary results of first detailed information about demographics and pain characteristics of NP patients attending a public hospital pain management clinic in urban area of Pakistan.
CORRELATION OF ALCOHOL POLYNEUROPATHY PECULIARITIES AND PSYCHOTIC MANIFESTATIONS IN PATIENTS WITH ALCOHOLIC DELIRIUM

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In 1887 Russian psychoneurologists S.S. Korsakov paid attention to an internal interconnection between polyneurithis manifestations and psychoses.

We examined 502 patients in an acute period of alcoholic delirium. In 122 patients there were no signs of polyneuropathy (I group); 202 patients had a symmetric distal polyneuropathy with hyperesthesia of a superficial sensitivity (“a sensory positive variant”, II group); 141 patients had the same disorder with a decreasing of sensitivity (“a sensory negative variant”, III group); 37 patients had motor impairments and distal myooathrophies (“a motor variant”, IV group). Duration of the psychotic period in each variant of polyneuropathy was evaluated with a semi-quantitative scale developed by us.

It was pointed out that in patients of I and II group the duration of psychosis was the shortest and did not differ. This duration was significantly longer in III group. Patients of IV group had the significantly longest duration of psychotic period as compared with other groups. Besides, a gradual growth of patients' mortality was revealed from I to III group (2±1 %, 4±1.5 %, and 8±4 % correspondingly) with an acute increasing in patients of IV group (32±12 %). Among laboratory parameters a significant decreasing of a urea-creatinine index in persons with polyneuropathic signs as compared with I group should be emphasized. A regular decreasing of a leukocyte index of immune reactivity was also manifested from II group to IV one.

Thus peculiarities of polyneuropathy in patients with alcoholic delirium correlate clearly with fundamental clinical and several laboratory parameters.
NEUROPATHIC PAIN IN PRIMARY CARE. A MEDICAL RECORDS REVIEW

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The prevalence of chronic pain with neuropathic features is 7-8%. This has implications for healthcare use and primary care management. We explored relationships between reported chronic pain with neuropathic characteristics and documented diagnosis and treatment in primary care.

Data were collected from electronic records of patients from two general practices in Grampian, Scotland, UK and reviewed for diagnosis of neuropathic conditions, current and recent treatment, consultations and referrals. We matched these records to previously collected questionnaire data. Participants were classified into: ‘Chronic Pain with Neuropathic Characteristics’ ie S-LANSS positive (CP+NC); ‘Chronic Pain without Neuropathic Characteristics’(CP without NC); ‘No Chronic Pain’(No CP), and we compared these groups.

In total, 135 respondents participated: CP+NC, n=33; CP without NC, n=57 and No CP, n=57. There were no significant differences in most sociodemographic variables between groups. More of the CP+NC group had at least one neuropathic diagnosis, (54.5% vs 36.8% CP without NC; p=0.102). Those reporting CP+NC were more likely to have been prescribed at least one analgesic drug (CP+NC 90.9%; CP without NC 70.2%; p=0.023) and at least one neuropathic pain drug (CP+NC 42.4%; CP without NC 19.3%; p=0.018). Patients reporting any CP, were more likely to be referred to secondary care (CP+NC 75.8%; CP without NC 61.4%; No CP 24.4%; p< 0.001) and see their GP (CP+NC median=16 (range 2, 93); CP without NC, median =12 (0, 41); No CP, median=7 (0.35); p=0.023).

Neuropathic pain results in considerable use of healthcare services, placing a greater burden on primary care than non-neuropathic pain.
DOES A PATIENT’S PAIN CATEGORY INFLUENCE ANY IMPROVEMENT FROM ATTENDING A PAIN MANAGEMENT PROGRAMME? A PILOT STUDY

J. Watson, UK

Introduction: The Glasgow Pain Management Programme (GPMP) is a psychology-led outpatient programme consisting of 12 weekly half-day sessions for people with chronic pain. The programme consists of a multidisciplinary team of psychologists, nurse, consultant and physiotherapists.

Sessions consist of education advice on 'living better with pain', including information on pain neurophysiology, pacing, flare up management, cognitions, values and goal setting and mindfulness.

Objectives: To establish if there are differences in outcomes between patients categorised as having neuropathic, musculoskeletal (MSK) or mixed neuropathic and MSK pain following completion of a PMP.

Methods: Patients accepted for the GPMP from January 2011-October 2012 were categorised by pain type on information supplied by their Pain Consultant.

These categorised patient’s were asked to complete a series of questionnaires at assessment and on completion of the programme. These included Chronic Pain Acceptance Questionnaire, Hospital Anxiety and Depression Scale and Oswestry Disability Index.

Results: Significantly more patients who complete a PMP are in the MSK or Mixed Pain category, considerably less have a straight diagnosis of neuropathic pain.

Those categorised as having neuropathic pain have better pre-programme outcome scores in the areas reviewed than those in the other 2 categories.

Those in the neuropathic pain category show less improvement in all 3 outcome measures following completion of the programme.

Conclusions: Could we enhance the education and information we provide in a PMP to improve the outcomes of those patients with neuropathic pain?

We cannot look at these measures alone to establish improvement.
AN OPEN-LABEL LONG-TERM STUDY OF PREGABALIN FOR THE TREATMENT OF CENTRAL NEUROPATHIC PAIN

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Background and aims: Studies of pregabalin for the treatment of central neuropathic pain have been limited to double-blind studies and one previous 6-month open-label safety study (spinal cord injury [SCI]). The current study examines the long-term safety and efficacy of pregabalin for up to 1 year in patients with central neuropathic pain.

Methods: Data were from a 53-week, open-label trial of pregabalin in patients with central neuropathic pain due to SCI, multiple sclerosis, or cerebral stroke. Safety was assessed via adverse event reports, and efficacy was based on Short Form McGill Pain Questionnaire (SF-MPQ) and 10-item Modified Brief Pain Inventory (mBPI-10) scores.

Results: A total of 103 patients received pregabalin (post-stroke = 60; SCI = 38; multiple sclerosis = 5). A majority of patients (87.4%) experienced ≥1 treatment-related adverse event, most commonly somnolence, weight gain, dizziness, or peripheral edema. The adverse event profile is similar to that seen in other indications of pregabalin. Most treatment-related AEs were mild (89.1%) or moderate (9.2%) in intensity. Pregabalin treatment improved total score, sensory pain, affective pain, visual analogue scale (VAS), and present pain intensity on the SF-MPQ, and mBPI-10 total scores at endpoint. Improvements in SF-MPQ VAS and mBPI-10 total scores were evident in all patient populations. Mean change from baseline of SF-MPQ VAS is -20.1, and mean change from baseline of mBPI-10 is -1.4.

Conclusions: Pregabalin was well tolerated and demonstrated sustained efficacy in patients with chronic central neuropathic pain over a 53-week treatment period.

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DIODE LASER (DL) SELECTIVE QST IN PATIENTS WITH PAINFUL NEUROPATHY (PN)

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The stimulation of trpv1 positive A-delta and C-nociceptors by DL was recently proved in DRG/HEK cells, rodents and healthy volunteers. The protocols were safe and reliable for specific activation of A-delta (pin-prick pain) or C-fibers (burning pain) in humans with linear correlation between amplitude of vertex potentials and pain-rating. The DL provides homogenous/direct heating of entire skin depth and simultaneous specific activation of small nerve fibers regardless of the depth of their location and these effects were not published with other lasers and CHEP. The 60 ms@1 mm DL-stimuli were used for activation of A-delta and 1.5 s@5 mm for activation of C-nociceptors. The protocols were applied to the patients with diabetic painful neuropathy and healthy control.

This study demonstrated that this differential activation of peripheral small nerve fibers, which pointed to the impaired function of A-delta fibers while C-fiber function was unaffected in this patients with PN. Stimulation was safe without any dermal effect in HC/PN. Parameters used in this study were demonstrated in preclinical rodent study to be identical for differential activation of A-delta or C-fibers. DL is an ideal tool for translational pain research where specific activation of A-delta or C-fibers, or both, is required.
NEUROMODULATION FOR CHRONIC PAIN CONDITIONS

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**Background and aims:** In cases of severe localised pain, neuromodulation offers an alternative. In peripheral nerve field stimulation (PNFS), leads are subcutaneously placed to stimulate the affected cutaneous afferents, or the dermatomal distribution of the nerves, which converge back to the spinal cord. PNFS provides paresthesia to regions not previously reached with spinal cord stimulation. This study set out to investigate PNFS for the treatment of chronic pain.

**Methods:** We prospectively assessed 174 patients implanted with percutaneous leads within the major area of pain in their craniofacial, thoracic, lumbar/sacral or abdominal/pelvic regions. Outcome measures included pain, analgesic use, employment and disability. Statistical analysis was performed, significance set at $p \leq 0.05$. IRB approval obtained.

**Results:** An average pain reduction of 4.3±2.5, on an 11-point scale was reported ($p \leq 0.00$). Notably, 73% of patients reported good (>50%) to excellent (>75%) pain relief. Pain relief achieved after implantation was sustained for greater than 12 months. Overall, 74% of patients reduced their analgesic use, with reduced analgesic use correlating with improved pain relief $r=0.704$ ($p=0.00$). Disability was significantly reduced following PNFS. Where applicable, 48% of patients below the age of 60 years increased their capacity for paid employment. Of the 174 cases, 24 patients reported complications, of which 6 were rectified by explant. No long-term complications were reported. Overall, 85% of patients were satisfied with their outcome.

**Conclusions:** PNFS is a safe and effective treatment option for, otherwise, intractable chronic pain conditions and has the potential to fundamentally change the way we think about pain management.
POSSIBLE PROTECTIVE EFFECT OF CCL2 PROTEIN DURING MORPHINE TOLERANCE FORMATION PROCESS

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**Objects:** The present study was investigated the possible role of CCL-2 protein in morphine tolerance model formation process.

**Methods:** 15 µg of morphine were administrated intrathecally twice per day for consecutive 7 days on rats to establish morphine tolerance model. Tail-flick latency was measured to evaluate the antinociceptive effect of morphine. CCL2 neutralizing antibody were intrathecally injected 15 min before morphine administrated everyday.CCL2/GFAP expression were detected in the dorsal spinal cord on morphine-tolerant rats before or after CCL2 neutralizing antibody administrated.

**Results:** During the process of mophine tolerant model establishment, spinal dorsal horn CCL2 expression gradually increased, and CCL2 positive cells mainly express in spinal cord astrocytes. CCL2 neutralizing antibody administration could partially suppressed morphine-induced tolerance, and enhance morphine-induced analgesia.

**Conclusion:** CCL2 protein might involve in morphine tolerance formation process and improve morphine induced pain tolerance threshold.
COMPARISON OF ANALGESIC EFFICACY OF KETOROLAC VS TRAMADOL IN THE POSTOPERATIVE PAIN AFTER MAXILLOFACIAL SURGERY

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Background: The goal of this study is to assess analgesic efficacy of ketorolac and tramadol in treatment of postoperative pain, incidence of side effects and patient satisfaction.

Methods: After their informed consent, 64 patients ASA I-II, aged 18-65 years, undergoing maxillofacial surgery, were enrolled in this double blind, randomized clinical study. The patients were randomly allocated in two groups: KTRn=32 received ketorolac 30 mg IV and TMD n=32 tramadol 100 mg IV. The time of the first administration of both drugs was at the time of skin closure and every 8 hrs in first 24 hrs. Morphine 3-5 mg IV was used as a rescue analgesic. Analgesic efficacy was assessed using a visual analog scale VAS from 1-10. The side effects were assessed. Patient satisfaction was assessed through Satisfaction Rating Scale.

Results: There were no significant differences between the groups with respect to demographic data. Good postoperative analgesia was recorded in both groups. VAS score (KTR vs. TRD) were 4.1 vs 5.0 p=NS at T0, 2.8 vs. 5.9, p< 0.05 at T1, 2.2 vs. 2.6, p=NS at T2, 2.0 vs. 2.5, p=NS at T3, 2.7 vs. 2.4, p=NS at T4, 1.1 vs. 1.2, p=NS at T5. Only a 3 patients in TRD group at T3 required rescue analgesic. Nausea were reported in 23% of TRD group and in 4.0% of KTR group (p < 0.005). Treatment with ketorolac was considered satisfactory by patients with SRS > 3, whereas with tramadol SRS was < 2 (p < 0.05).
Inhibition of Neuropathic Manifestations by Dorsal Column Nuclei (DCN) Stimulation in Rats Sustaining Chronic Bilateral Dorsal Columns (DC) and Dorsolateral Funiculi (DLF) Lesions

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Aim of investigation: The DC and DLF are considered as the principal ascending and descending pathways, respectively, involved in pain modulation. It is likely that spinal cord stimulation (SCS)-induced orthodromic DC activation is relayed to brain stem centers resulting in pain modulation mediated by the DLF. This study examines the effects of lesion of both of these tracts on the inhibition of neuropathic manifestations by DCNS and SCS.

Methods: Rats were subjected to the spared nerve injury procedure and to chronic bilateral DC and DLF lesions at the C5-C7 level. Two sets of miniature electrodes were implanted in each animal, one at a low thoracic level and another over the DCN above the lesions. Stimulation was applied via either of the electrodes. A battery of behavioural sensitivity tests was applied to assess the effects of stimulation. Various receptor antagonists were administered prior to the application of stimulation.

Results: Rostral and caudal stimulations produced comparable decreases (80-90% of the control) of neuropathic manifestations in rats with intact spinal cords. In animals with DC- DLF lesions, the suppressive effects of both types of stimulation were attenuated. Pretreatment with receptor antagonists differentially counteracted the effects of rostral and caudal stimulation, being less potent, however, in rats with chronic spinal lesions.

Conclusion: Our findings give further support to the involvement of the brainstem pain modulating centers in the observed effects. A major component of the inhibitory effect of both types of stimulation is carried by the fibers running in the DC and DLF fibers.
ROTATION FROM WHO III OPIOIDS TO TAPENTADOL IN SEVERE LOW BACK PAIN: TAPENTADOL IMPROVES NEUROPATHIC SYMPTOMS

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Background and aims: Neuropathic back pain patients complain spontaneous pain and sensory abnormalities. Pain is assessed by spontaneous pain rating at certain time points or periods. Time-depended (brief attacks) or evoked (allodynia) phenomena are missed. Tapentadol has two mechanisms of action (m-agonistic, noradrenaline re-uptake inhibition). We aimed to compare the change in spontaneous pain with the change in neuropathic sensory abnormalities after rotation from standard opioids to tapentadol.

Methods: Retrospective analysis of a phase 3b study in which opioid-responsive back pain patients were rotated to tapentadol. The painDETECT questionnaire (>12 before rotation) indicated neuropathic elements. Outcome measures after rotation were average spontaneous pain ratings, the PainDETECT questionnaire (PD) and the Neuropathic Pain Symptom Inventory (NPSI) items.

Results: 65 neuropathic back pain patients were switched from WHOIII opioids to tapentadol. The average spontaneous pain decreased slightly (NRS -0.83). Tapentadol rotation had a pronounced effect on specific neuropathic symptoms: burning (PD -1.45/NPSI -1.32), prickling (PD -1.38), tingling (NPSI -1.19), allodynia (PD -1.51/NPSI -1.30), attacks (PD -1.78), electric shocks (NPSI -1.29), stabbing (NPSI -1.67), numbness (PD -1.11) and pressure induced pain (PD -1.57/NPSI -1.73). No additional improvement occurred in the items squeezing, pressure pain and pain increase by temperature.

Conclusions: Tapentadol is effective in spontaneous back pain and reduces neuropathic symptoms. After rotation from WHOIII opioids to tapentadol the changes in neuropathic symptoms are greater than the change in spontaneous pain. For typical nociceptive symptoms the change was similar. The additional NRI mechanism of tapentadol might explain these findings.

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PHARMACOLOGICAL MODULATION OF MITOCHONDRIAL-DERIVED REACTIVE OXYGEN SPECIES IN PACLITAXEL-INDUCED PAINFUL PERIPHERAL NEUROPATHY

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Introduction: Previous work suggests a causal role for reactive oxygen species (ROS) in paclitaxel-induced painful peripheral neuropathy.

Objectives: Here we modulate the major cellular ROS source in vivo, by pharmacologically inhibiting complexes I or III of the mitochondrial electron transport chain.

Methods: Effects of modulating mitochondrial ROS were investigated on established, and development of, paclitaxel-induced mechanical hypersensitivity. Adult male rats were administered with paclitaxel (2mg/kg i.p.) on four alternate days (0, 2, 4, 6), which typically causes peak mechanical hypersensitivity, assessed with von Frey filaments, at day 27-33.

To investigate effects of complex I or III inhibition on established pain, paclitaxel-treated rats displaying peak mechanical hypersensitivity received rotenone (3 or 5mg/kg i.p.) to inhibit complex I, antimycin A (0.4 or 0.6mg/kg i.p.) to inhibit complex III, or vehicle. Von Frey testing was performed 1, 3 and 24h post-injection of complex inhibitors.

In separate experiments, investigating effects of complex inhibition on development of paclitaxel-induced hypersensitivity, paclitaxel-treated rats also received antimycin A (0.2 or 0.4mg/kg i.p.), rotenone (1 or 2mg/kg i.p.), or vehicle, for seven consecutive days (days 7-13). Development of mechanical hypersensitivity was assessed using von Frey filaments until day 44.

Results: Both antimycin A and rotenone resulted in dose-related inhibition of established paclitaxel-induced mechanical hypersensitivity. Rotenone administered on day 7-13 had no effect on development of paclitaxel-induced mechanical hypersensitivity. The effect of prophylactic antimycin A on paclitaxel-induced pain is under assessment.

Conclusions: Direct modulation of the mitochondrial electron transport chain, and thus ROS production, attenuates established paclitaxel-induced mechanical hypersensitivity.
OROFACIAL SENSORY CHANGES AFTER STREPTOZOTOCIN-INDUCED DIABETES IN RATS


Background and aims: Peripheral neuropathy represents a common complication of diabetes and is often accompanied by pain episodes. There is evidence that diabetic neuropathy may also affect the trigeminal nerve, altering the transmission of orofacial sensory information. The current study evaluated the development of orofacial sensory changes after streptozotocin-induced diabetes in rats, and their sensitivity to pregabalin and morphine. Furthermore, stereological analysis of the trigeminal ganglia was performed.

Methods: Diabetes was induced by a single injection of streptozotocin (STZ, 50 mg/kg). Thermal and mechanical hyperalgesia was assessed once a week after diabetes induction. Five weeks after STZ, rats were treated with pregabalin or morphine and thermal hyperalgesia was evaluated (protocols approved by the UFPR’s Committee on the Ethical Use of Animals # 534).

Results: There was no change in the facial mechanical threshold of diabetic rats up to 5 weeks after STZ. In contrast, diabetic rats developed orofacial heat and cold hyperalgesia from 1 up to 5 weeks after STZ. Stereological analyses revealed significant neuronal loss (over 20%) in the trigeminal ganglia of diabetic compared to normoglycemic rats. Pregabalin treatment (30 mg/kg) of diabetic rats resulted in marked and prolonged (up to 6 h) reduction of heat and cold hyperalgesia. Likewise, morphine treatment (2.5 mg/kg) abolished orofacial heat and cold hyperalgesia, but its effect was significantly only up to 1 h after administration.

Conclusions: We demonstrated that streptozotocin-treated rats developed long-lasting orofacial heat and cold hyperalgesia, which is more amenable to reduction by pregabalin than morphine.

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A POLYAMINE-DEFICIENT DIET PREVENTS OXALIPLATIN-INDUCED ACUTE SENSORY DISORDERS IN RATS

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Background/aims: Oxaliplatin is a reference anticancer drug used for the treatment of advanced colorectal cancer. However, oxaliplatin is a neurotoxic drug responsible for painful peripheral neuropathies. The pathophysiology of these neuropathies has not been yet fully elucidated, but may involve spinal N-methyl-D-aspartate receptors (NMDAR), particularly the NR2B subunit. As polyamines are positive modulators of NMDAR-NR2B and mainly originate from dietary intake, the modulation of polyamine food intake could represent an interesting way to prevent neuropathic symptoms involving glutamatergic/NMDAR neuromediation.

Methods: In comparison to a normal polyamine-containing diet (PCD), we assessed the ability of a polyamine-deficient diet (PDD) to prevent nociceptive disorders (mechanical and thermal) induced by a single oxaliplatin (6 mg/kg) injection in rats and to interact with glutamatergic neuromediation.

Results: In PCD fed animals, oxaliplatin injection induced an acute mechanical allodynia and a cold hypersensitivity (day 2 to 4 post-injection). In the same condition, ¹H-NMR spectroscopy-based metabolomic analysis revealed an increase of glutamate concentration in the spinal cord dorsal horn of oxaliplatin-treated animals (day 3 post-injection). Inversely, in PDD fed animals, oxaliplatin didn't produce any thermal or mechanical hypersensitivity, and spinal glutamate concentration remained unchanged compared with control animals (vehicle). In PCD fed animals, oxaliplatin-induced pain hypersensitivity was not associated with an increase in NR2B subunit expression or its phosphorylation (day 3 post-injection). However, intrathecal administration of the NMDAR-NR2B antagonist, ifenprodil, reversed oxaliplatin-induced mechanical and cold hypersensitivity.

Conclusions: A PDD could represent a promising nutritional therapy to prevent oxaliplatin-induced neuropathic pain through a decrease of glutamatergic/NMDAR neuromediation.
SUCCESSFUL CAPSAICIN 8% PATCH TREATMENT OF A PREGABALIN-REFRACTORY PATIENT WITH PERIPHERAL NEUROPATHIC PAIN DUE TO SEVERE NERVE DAMAGE

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Background and aims: In the EU the capsaicin 8% patch is approved for the treatment of peripheral neuropathic pain (PNP) in nondiabetic adults. We describe the case of a patient with nerve damage to the hand and forearm, resulting in PNP responsive to capsaicin patch treatment.

Methods: Pain scores were determined using the Numerical Pain Rating Scale (NPRS).

Results: In May 2008, a 46-year-old male experienced a crush injury to his right hand and forearm, causing trauma to the radial and ulnar nerve area, resulting in PNP. In April 2010, the patient presented to our clinic reporting several symptoms including severe allodynia and pain-related sleep disorder. Prior treatments, including ibuprofen (1800 mg/day) and surgery, had been unsatisfactory and he had been unable to work since the accident. At our clinic, the patient received pregabalin (300 mg/day), resulting in a 50% reduction in pain, but no improvement in sleep. Due to adverse effects, however, it was necessary to reduce pregabalin, causing a consequent pain increase. In June 2010, the patient received capsaicin 8% patch treatment. NPRS scores reduced from 7 (baseline) to 3 (Day 1) and 0 (Week 8). The patient remains pain-free after 28 months. Pregabalin was discontinued by Week 8. The patient resumed work 1 week after capsaicin patch treatment and can use the injured hand without any pain increase.

Conclusions: Capsaicin 8% patch treatment provided rapid and effective relief from PNP in this patient. He stopped concomitant PNP medication use and resumed physical work 1 week after treatment.
Drug Effects and Placebo: Are They Additive?

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Background: Treatment effect sizes are calculated by subtracting the effect during placebo from the treatment effect. However, large meta-analyses of neuropathic pain RCTs suggest that the effects during active and placebo treatments are not additive.

Aim: The aim of the present study was to test whether the treatment effect and placebo effect are additive in an experimental pain model.

Methods: Healthy volunteers received injections with hypertonic saline (HS, 5%) in the masseter muscle. The subjects received one injection with HS at baseline, and their pain intensity was registered on a continuous VAS. 23 subjects were conditioned with lidocaine (1,2%). At a separate visit, the subjects received a total of 4 injections. Two of the injections included lidocaine (1%): one was open (the subjects were aware of the administration of an analgesic) and one was hidden. The two remaining injections were with HS alone: one open and one hidden. The investigator was blinded to whether the injection was with or without lidocaine.

Results: Forty-six subjects (50% men, mean age 23.4 (SD 6.2) years) were included. The mean peak pain intensity of HS at baseline was 53.4 (SD 19.9) and of HS with lidocaine 14.3 (SD 18.2). The last 5/46 subjects are expected to participate at the second visit within the next weeks.

Conclusions: Baseline registrations show that HS causes a stable pain that can be reduced by lidocaine. The final results will be presented at the congress.

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1Finnerup NB et al. Pain 2010;150:573-81
A RANDOMIZED, BLINDED, PLACEBO-CONTROLLED, MULTIPLE ASCENDING DOSE STUDY OF THE SAFETY, TOLERABILITY, PHARMACOKINETICS AND EFFICACY OF NEUBLASTIN IN SUBJECTS WITH SCIATICA


Introduction: Neublastin (artemin) is a protein in the glial cell line-derived neurotrophic factor (GDNF) family. It is a selective ligand for the GFRα3 co-receptor that normalizes cellular changes resulting from damage or disease, and potentially alleviates neuropathic pain.

Objectives: This study aimed to investigate the safety, tolerability, and pharmacokinetic (PK) profile of 3 intravenous (IV) injections of neublastin and to explore the potential of neublastin to reduce pain. This study was the second study of neublastin in humans.

Methods: This was a randomized, blinded, placebo-controlled study in subjects with sciatica. The study was divided in two parts that included two different dose regimens. In Part I, four IV dose levels were examined (50, 150, 400, 800 µg/kg) and in Part II, three dose levels were examined (400, 600 and 1200 µg/kg). Each group consisted of 4 subjects (3 on neublastin, 1 on placebo). Safety and efficacy assessments were used as endpoints.

Results: In total, 21 subjects were treated with neublastin. The most common adverse events reported by the subjects were pruritus and changes in temperature sensation. No clinically significant changes were found in vital signs, ECG, QST or safety laboratory tests. The 11-point Numeric Rating Scale (NRS) showed a decrease in numerical pain rating assessments in the higher dosing groups compared to the placebo group.

Conclusions: In this study, neublastin was well tolerated and a decrease in NRS at higher doses compared with placebo was observed. The results of this study support further development of neublastin.
THE INFLUENCE OF B VITAMINS COMBINATION ON THERMAL HYPERALGESIA INDUCED BY CONstriction OF THE INFRAORBITAL NERVE IN RATS

C.M. Kopruszinski, R.C. Reis, K.Y.S. Sato, J.G. Chichorro, Brazil

Background and aims: There is evidence that B vitamins can help to control neuropathic pain. We previously demonstrated that repeated treatment with B1, B6 and B12 vitamins individually ameliorate some aspects of experimental trigeminal neuropathic pain. Herein, we evaluated the influence of a combination of B vitamins in heat hyperalgesia induced by constriction of the infraorbital nerve (CION) and a possible synergistic effect of the association of the B vitamins with the anticonvulsant carbamazepine (CBZ).

Methods: CION was induced by placing two loose ligatures around the infraorbital nerve. Rats received the B vitamins combination or CBZ on day 4 after CION or the combination for 5 days. Heat hyperalgesia was estimated as a decrease in the response latency after approximation of a heat source to the vibrissal pad (protocols approved by the UFPR’s Committee on the Ethical Use of Animals # 471).

Results: A single administration of B1, B6 and B12 in combination (180, 180 and 18 mg/kg, respectively) significantly reduced heat hyperalgesia. In contrast, a single injection of the combination of B vitamins in doses 10 times lower failed to modify the response latency, but in association with CBZ (10 mg/kg) marked reduced the heat hyperalgesia. Additionally, repeated treatment of rats with the combination at lower doses promoted a slight reduction of thermal hyperalgesia, but when it was associated with CBZ (3 or 10 mg/kg) abolished the heat hyperalgesia.

Conclusion: We suggest that B vitamins might constitute a relevant adjuvant to control orofacial neuropathic pain.

Financial support: CAPES
Background and aims: This report demonstrates the utility of a pudendal nerve block by pulsed radiofrequency ablation (RFA) for the treatment of male pelvic pain, urinary urgency and hesitancy.

Methods: The patient is an 86-year-old gentleman with a 30-year history of urinary hesitancy and urgency. The patient also had pain in the area of the perineum but considered it a secondary issue. The patient was seen by a number of specialists, tried various medications, and underwent a variety of procedures to no avail. Therefore, the patient underwent a pulsed RFA of the pudendal nerve.

Results: The patient underwent a pulsed RFA of the pudendal nerve. He reported marked improvement in his pelvic pain as well as a drastic reduction in his urinary urgency and hesitancy.

Conclusion: Urinary urgency, hesitancy, and male pelvic pain are some of the most common symptoms affecting men. Pudendal nerve block by pulsed RFA is an effective treatment of pelvic pain. It may also hold some therapeutic value in the treatment of urinary urgency and hesitancy as our case demonstrated. Further studies are needed to help clarify both the anatomy of the pelvis as well as if pudendal blocks are effective in treating more than pelvic pain.
METALLOTHIONEIN DEFICIENCY IN THE INJURED PERIPHERAL NERVES OF COMPLEX REGIONAL PAIN SYNDROME AS REVEALED BY PROTEOMICS

S.-I. Imai, G. Oki¹, Y. Fujita¹, H. Sohma¹, N. Takei, T. Wada, T. Yamashita, Y. Kokai, Japan

Introduction: Complex regional pain syndrome (CRPS) is characterized by persistent and severe pain after trauma or surgery. However, its molecular mechanisms in the peripheral nervous system are poorly understood. We previously suggested that the injured nerve may express specific proteins, generating pain in CRPS.

Objectives: In this study, we aimed to identify specific proteins contributed to the pathogenesis of CRPS.

Methods: We obtained nerve samples from patients with CRPS-2 who underwent resection of part of an injured peripheral nerve. Sural nerves from fresh cadavers with no history of trauma or neuropathic pain served as controls. The analysis of protein profiles using a proteomic approach, Western blotting and immunohistochemistry of nerves from both CRPS-2 and control were performed.

Results: Proteomic analysis showed that the number and functional distribution of proteins expressed in CRPS-2 and control nerves was similar. Interestingly, metallothionein was absent in the injured nerves of CRPS-2, although it was readily detected in control nerves. Western blotting further confirmed the absence of metallothionein in CRPS-2 nerves, and immunohistochemistry corroborated the deficiency of metallothionein expression in injured nerves from 5 of 5 CRPS-2 patients and 2 of 2 patients with painful neuromas. In contrast, all control nerves, including 5 sural nerves from fresh cadavers and 41 nerves obtained from surgically resected tumors, expressed metallothionein. However, expression of S100 and neurofilament M was comparable in both CRPS-2 and controls.

Conclusions: Metallothionein deficiency from the injured nerves of patients with CRPS-2 suggests a potential pathogenic role in generating pain in the damaged nerves.
STUDIES OF THE PHYTOCHEMICAL COMPONENTS, ACUTE TOXICITY, ANALGESIC AND ANTI-PYRETIC PROPERTIES OF THE AQUEOUS LEAF EXTRACT OF PLECTRANTHUS BARBATUS (FAMILY-LAMIACEAE)

G.K. Nambirige, Uganda

Plectranthus barbatus is a popular tropical perennial plant traditionally used in Africa to treat pain. This study was done to investigate the phytochemical components, acute toxicity, analgesic and anti-pyretic activity of the aqueous leaf extract of Plectranthus barbatus locally known as ekizeera (Uganda), to ascertain its constituents, safety and acclaimed medicinal value scientifically. The plant leaves were identified, collected and extracted by decoction as used locally. Phytochemical screening was conducted using methods outlined by Trease and Evans to determine the components of the extract. Acute toxicity tests were conducted in rats using modified Lorke’s method to determine the safety of the plant material. Analgesic studies were carried out using both a mechanical method (thermal induced pain by tail-flick method) and a chemical method (formalin induced pain) in rats by administering extracts orally at 100, 200 and 400mg/kg of body weight. Decoction yielded a 9.93% extract. Phytochemical screening confirmed presence of saponins, tannins, alkaloids and essential oils. Acute toxicity tests revealed no deaths in any of the rats treated with the extract administered orally up to a dose of 10,000mg/kg. Analgesic studies (thermal induced pain-tail-flick method) tested insignificant with student t-test, and chemical induced pain (formalin) demonstrated appreciable activity. Anti pyretic studies showed no significant activity exhibited by the extract using the student t-test. These results suggest that the aqueous leaf extract of Plectranthus barbatus has potent dose dependent analgesic activity, but no anti-pyretic activity and can be generally regarded as safe for use as a medicinal herb traditionally.
NEUROTROPHIN-3 AND ANTI-NERVE GROWTH FACTOR AMELIORATES HEAT HYPERALGESIA IN A RAT MODEL OF TRIGEMINAL NEUROPATHIC PAIN

R. Reis, C.M. Kopruszinski, C.F.M. Nones, D.A. Aguiar, J.G. Chichorro, Brazil

Background and aims: There is evidence that the neurotrophic factors neurotrophin-3 (NT-3) and nerve growth factor (NGF) participate of the nociceptive process, but have opposite roles. While NGF has been described as pro-hyperalgesic, NT-3 inhibits hyperalgesia related to inflammation or neuropathic pain. Thus, this study aimed to investigate the role of NT-3 and NGF on thermal and mechanical hyperalgesia induced by constriction of the infraorbital nerve (CION), a model of trigeminal neuropathic pain.

Methods: CION was induced by placing two loose ligatures around the infraorbital nerve. In different time periods after CION, male Wistar rats received NT-3 or anti-NGF (0.3 - 3 µg/50 µL), subcutaneously into the upper lip, and orofacial thermal (to heat and cold) and mechanical hyperalgesia was assessed at 1 h-interval. All protocols were approved by the UFPR’s Committee on the Ethical Use of Animals (# 432).

Results: A single administration of NT-3 (1 µg/50 µL) or anti-NGF (3 µg/50 µL) promoted significant reduction of heat hyperalgesia, but both treatments, in all doses tested, failed to modify cold hyperalgesia. Additionally, NT-3 and anti-NGF administered into the upper lip at 1 µg and 3 µg /50 µL, respectively, also failed to influence the mechanical threshold of nerve-injured rats.

Conclusions: NT-3 and anti-NGF treatments affect heat, but not cold or mechanical hyperalgesia after CION. Further studies are necessary to explore the mechanisms underlying NT-3 and anti-NGF anti-hyperalgesic effects in this model.

Financial support: CNPq, CAPES/DS, CAPES/REUNI.
Neuropathic pain (NP) is chronic pain arising from nerve injury. A key mediator of NP pathogenesis is tumor necrosis factor-alpha (TNF). TNF increases during NP development, at injury sites, and also supraspinally. Inhibition of TNF along pain pathways results in transient decreases in pain perception. Specific enhancement of brain TNF produces hyperalgesia, or increased sensitivity/responsiveness to noxious stimuli. TNF has profound effects throughout the body, therefore it is imperative to specifically block TNF in the brain (site where integration of pain stimuli occurs). Introduction of a TNF silencer within the brain lowers TNF levels locally, but with short-term effectiveness.

This study objective was to inhibit TNF production solely in the hippocampus of rats experiencing NP, thereby alleviating pain perception by using TNF small inhibitory RNA complexed to gold nanorods (GNR-TNF siRNA; TNF nanoplexes).

Sprague-Dawley rats received chronic constriction injury (CCI) to right sciatic nerve. Withdrawal latencies to noxious thermal stimulus (hyperalgesia) and withdrawal to innocuous forces (allodynia) were recorded every other day for 10 days and compared to baseline values and sham-operated rats. Four days after CCI/sham, subgroups received stereotaxic injection of either GNR-TNF siRNA or GNR-scrambled siRNA into the contralateral (left) hippocampus. TNF levels (protein, mRNA, staining) were measured.

Thermal hyperalgesia and mechanical allodynia were significantly alleviated in CCI rats receiving hippocampal TNF nanoplexes. Bioactive TNF, TNF staining, and TNF mRNA in hippocampal tissue was decreased.

TNF nanoplex introduction directly into the hippocampus alleviates NP showing that TNF in the hippocampus is integral to modulation of pain perception.
NON-INTERVENTIONAL STUDY ON THE SAFETY AND EFFECTIVENESS OF A SINGLE APPLICATION OF THE CAPSAICIN 8% CUTANEOUS PATCH IN 1044 PATIENTS WITH PERIPHERAL NEUROPATHIC PAIN

C. Maihöfner, M.-L.S. Heskamp, Germany

Introduction: Defunctionalisation of nociceptors by the TRPV1 agonist capsaicin is a new concept for the treatment of peripheral neuropathic pain. The capsaicin 8% cutaneous patch is marketed in Germany since October 2010. The aim of this study was to monitor its usage and therapeutic performance in clinical practice.

Methods: Patients were treated with the patch and followed up after 1, 4, 8 and 12 weeks. At each visit average pain intensity (NPRS-11) pain attacks, neuropathic symptoms, sleep parameters and concomitant neuropathic medication were assessed.

Results: 509 females (48.8%; N=1044) and 531 males (50.9%) were included, mean age was 61.1 years. Postherpetic neuralgia was the most frequent diagnose (31.9%), followed by postoperative neuralgia (22.8%) and posttraumatic neuropathy (12.4%), polyneuropathy (14.3%) and mixed pain syndromes (16.6%). 30% and 50% responder rates were 42.7% and 23.7%, respectively, with a mean pain intensity reduction during weeks 1-12 of 24.7% and significant improvements of pain attacks, sleep duration and sleep quality, while the consumption opioids and antiepileptics decreased significantly. Short pre-existing pain was associated with significantly higher pain relief (< 6 months vs. 6-24 months: p< 0.01; vs. >2-10 years p< 0.001). In 106 patients (10%; N=1063) 146 adverse drug reactions (ADRs) were reported, almost all of which were application site reactions (erythema, pain). A total of 27 serious ADRs were documented in 17 patients (1.6%).

Conclusions: Analgesic treatment of peripheral neuropathic pain with the capsaicin 8% cutaneous patch is safe and effective. The duration of pre-existing pain is inversely correlated with the analgesic effect.
The aim of the study was to verify the effectiveness of two methods of introducing standard CIPN-treatment drugs into the therapy.

Group A included patients attending weekly appointments, while group B monthly. Standard treatment with amitriptyline, gabapentin (GAB), and oxycodone (OXY) was administered. In group A, the drugs were gradually introduced, while in group B within one week. After a month and six months of treatment, the therapy effectiveness was assessed by examination of pain intensity (VAS), symptoms of peripheral neuropathy (sNCI-CTC), occurrence of tactile and brush allodynia, and the daily dose of GAB and OXY.

Pain intensity during the study decreased from 5.59 to 2.9 and 2.76 in group A, and from 5.07 to 2.52 and 2.81 in group B. The sNCI-CTC values were, respectively, 1.9; 1.48; 1.34 in group A and 1.93; 1.52; 1.44 in group B. Tactile allodynia occurred in 15; 5; 5 group A patients and 18; 6; 5 group B patients. Brush allodynia decreased in group A (9; 5; 5) and B (11; 6; 5). The daily GAB dose was 0; 951.72; 927.41 in group A and 900.0; 900.0; 1000.0 in group B. The daily OXY dose was 0; 21.72; 22.07 in group A and 20.0; 20.0; 27.04 in group B; a statistically significant difference was found in the final stage.

The results do not allow recommendation of non-schematic treatment and they should be regarded as a preliminary study. Randomized trials are indispensable for assessment of advantages and drawbacks such treatment.
EFFECT OF VARIOUS ANALGESICS IN FORMALIN INDUCE NOCICEPTION - A NEUROPATHIC MODEL FOR PAIN

R. Nirogi, R. Abraham, V. Goura, R.B. Medapati, P. Jayarajan, India

Background and aims: The objective of the current study was to investigate the effect of various analgesics having different mechanism of action in the formalin induced nociception model.

Methods: Rats of 230-290 g were habituated to arenas for a period of 20 minutes. 50 mL of 2.5% v/v formalin was injected into the subplanatar region of the paw and duration of licks as well as number flinches noted. Mirrors were placed below the arena in order to observe the various pain behaviors as well. Various analgesic agents were administered and their effect during the phase-1 and phase-2 pain response was observed.

Results: Diclofenac showed a 45-48% reduction in the duration of licks during the second phase. Duloxetine showed a significant decrease in the duration of licks during the first and second phase of licks by 59% and 79% respectively. Gabapentin showed a reduction in the duration of licks during the second phase by 40-60%. Pregabalin significantly reduced the number of flinches during phase-1 and phase-2. The duration of licks were significantly reduced by 57-71% during phase-2.

Conclusions: Well known and widely used analgesics for neuropathic pain, duloxetine and pregabalin have a centrally acting component (morphine like) on pain transmission evident from decrease in the pain behavior in the first phase. In addition these agents also influence central sensitization. Gabapentin and cyclooxygenase inhibitor, diclofenac was found to have an effect solely by influencing central sensitization evident from a reduction in pain behaviour observed only in the second phase.
COMPARISON OF TWO SIMILAR MECHANICAL PRESSURE EVOKED STIMULI METHODS FOR EVALUATION OF NEUROPATHIC PAIN BEHAVIOR IN RATS

R. Nirogi, V. Goura, P. Jayarajan, R. Abraham, India

Background and aims: Subjective reports which are comparable to clinical research cannot be obtained in preclinical research. Our aim was to compare the different evaluation methods in various preclinical models of neuropathic pain.

Methods: An automatically (dynamic plantar aesthesiometer) and manually (Von Frey monofilaments) applied force was used to assess mechanical allodynia in three different etiological pain models (partial sciatic nerve ligation (PNL), chronic constriction injury (CCI) and spinal nerve ligation (SNL). Behavioral testing was performed on different post surgical period in PNL (day 14), CCI (day21) and SNL (day11), these time periods were chosen based on the maximal nociceptive response observed earlier. Time course comparisons of mechanical allodynia were performed on day of testing to mimic drug testing conditions.

Results: Consistent paw withdrawal thresholds were observed in three different models of neuropathic pain when evaluated with monofilaments, whereas variable paw withdrawal thresholds were noticed in PNL and CCI models but not in SNL model with dynamic plantar aesthesiometer.

Conclusions: The paw posture and deformity could play major role in the inconsistent results of PNL and CCI surgery models.
Introduction: Cannabinoids are effective in treating neuropathic pain, and FAAH inhibitors have the potential to enhance endocannabinoid tone without the psychoactive effects of CB1 agonists.

Objectives: To determine the PK/PD relationship for V158866, after single dose oral administration to man.

Methods: 18 healthy male volunteers in 2 alternating cohorts each received 2 single oral doses of V158866 and 1 dose of placebo, such that 6 dose levels (5, 15, 30, 70, 150 & 300 mg) were studied. Blood samples were collected at intervals up to 72 hours post-dose, to assay plasma V158866 and endocannabinoid levels.

Results: V158866 was rapidly absorbed with dose-proportional increases in Cmax and AUC. The 300 mg PK data fitted a 2 compartment model with α and β elimination half-lives of 1.6 ±0.2 and 22.0 ±5.0 h, respectively (N=5). The plasma EC data fitted a sigmoidal population dose-response model (Table 1). A time lag between the maximum PK and PD response occurred for AEA, OEA & PEA, resulting in a counter-clockwise hysteresis loop.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>AEA</th>
<th>LEA</th>
<th>OEA</th>
<th>PEA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Derived</td>
<td>ED50 (mg/kg)</td>
<td>1.05 ±0.93</td>
<td>2.32 ±5.67</td>
<td>0.23 ±0.07</td>
</tr>
<tr>
<td>from slope</td>
<td></td>
<td>0.75 ±0.21</td>
<td>0.52 ±0.20</td>
<td>0.80 ±0.17</td>
</tr>
<tr>
<td>Fit</td>
<td>Emax (ng/mL)</td>
<td>3.97 ±1.05</td>
<td>6.47 ±3.87</td>
<td>9.57 ±0.81</td>
</tr>
<tr>
<td>Measured</td>
<td>Baseline (ng/mL)</td>
<td>0.31 ±0.01</td>
<td>0.38 ±0.01</td>
<td>1.31 ±0.02</td>
</tr>
</tbody>
</table>

Conclusions: V158866 has predictable PK after oral dosing and causes dose-related increases in plasma endocannabinoids. This study identifies relevant V158866 doses and PD markers for further evaluation in patients with neuropathic pain.
PREVALENCE OF POST-THORACOTOMY PAIN IN CHILDREN

J. Chou1,2, C.W. Chan2,3, G. Chalkiadis, Australia

Background and aims: Post-thoracotomy pain, defined as persistent or recurring incisional pain ≥2 months after thoracotomy, is common and affects >50% of adults [1]. Studies suggest that children are at a lower risk of developing persistent post-surgical pain [2]. In this retrospective cross-sectional study, we sought to determine the prevalence of chronic post-thoracotomy pain in children.

Methods: Following IRB approval, patients who underwent a lateral thoracotomy from January 2005 to December 2007 at the Royal Children's Hospital, Melbourne, Australia were sent a questionnaire for telephonic completion with a researcher, with assistance from the parents if required.

Results: Of the 87 patients eligible to participate, 51 (59%) completed questionnaires. The majority of respondents were male (65%), underwent a single thoracotomy (84%; range 1-3), and were non-elective operations (71%). The median age at first thoracotomy was 5.7 (IQR 2-14.2) years. The median age at questionnaire completion was 9.0 (IQR 5.4-17.9) years; with 3.6 (IQR 2.8-4.1) years between thoracotomy and time of questionnaire completion.

Three patients (6%) scored >12 on self-report versions of the Leeds Assessment of Neuropathic Symptoms and Signs pain scale [3]. Of these, only one patient complained of current post-thoracotomy pain. All three patients had a single thoracotomy and were older (mean age 14.2 years) at the time of thoracotomy. The rate of post-thoracotomy pain calculated using the binomial exact method is 1.96% (95% CI 0-10.4%).

Conclusions: Our study reports a low prevalence of post-thoracotomy pain in childhood and adolescence, and stands in contrast to previously published adult data.
ANALGESIC EFFICACY PROFILING USING A RAT MODEL OF VARICELLA ZOSTER VIRUS (VZV) INDUCED NEUROPATHIC PAIN

V. Das1,2, A. Leen Lam, M.T. Smith1,2, Australia

Background and aims: Pain that persists for greater than 3 months after the shingles rash has healed is known as postherpetic neuralgia (PHN), a condition notoriously difficult to treat. Hence, the objective of this study was to establish a rat model of VZV-induced neuropathic pain for analgesic efficacy profiling of novel molecules.

Methods: VZV (Ellen strain) was propagated in vitro in cultured MRC-5 cells to ~80% confluence; infection of MRC-5 cells was confirmed by RT-PCR and Western blot using an antibody against the VZVgE protein. Adult male Wistar rats were randomized to one of three groups (n=4-12 per group) that received unilateral intraplantar injections (50 µL) of:

(i) Phosphate buffered saline (pH7.4, 1mM, control group),

(ii) MRC-5 cells (7x10^6 cells/ml; sham group) or

(iii) VZV-infected MRC-5 cells containing 10^4 plaque forming units.

Von Frey filaments were used to define the time course for development of mechanical allodynia in the hindpaws and for ‘blinded’ analgesic efficacy assessment. Rats with fully developed hindpaw hypersensitivity (day 7 until at least day 35), the ED_{50}'s for gabapentin and morphine were 25mg/kg and 1mg/kg respectively. EMA300 at 1 mg/kg was efficacious.

Conclusion: Using the VZV-induced rat model of neuropathic pain, EMA300 was shown to have analgesic efficacy.
SYNTHESIS AND BIOLOGICAL EVALUATION OF PYRROLIDINE DERIVATIVES AS NOVEL T-TYPE CALCIUM CHANNEL BLOCKERS FOR NEUROPATHIC PAIN THERAPY

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Introduction: Development of T-type Ca\textsuperscript{2+} channel blockers could lead to the treatment of hypertension, epilepsy, sleep disorders and neuropathic pain. T-type Ca\textsuperscript{2+} channels control muscle contraction, hormone release and cellular proliferation. Ca\textsubscript{v}3.2 is the predominate T-type channel subtype in the dorsal root ganglion with lower expression of both Ca\textsubscript{v}3.1 and Ca\textsubscript{v}3.3 detected. Ca\textsubscript{v}3.2, therefore, is strongly implicated as contributing to the development of neuropathic pain.

Objectives: The goal of this study was to identify compounds that block the Ca\textsubscript{v}3.2 channels and to evaluate their \textit{in vitro} and \textit{in vivo} efficacies.

Methods: Several pyrrolidine derivatives were designed using a 3D ligand based pharmacophore model. The synthesized compounds were evaluated \textit{in vitro} in HEK293 cells which stably express both Ca\textsubscript{v}3.1 and Ca\textsubscript{v}3.2 subunits using FDSS6000 assay and patch-clamp assay.

Results: Compound KKPG0001 was demonstrated to have good \textit{in vivo} efficacy in mechanical and cold allodynia that was comparable to gabapentin through the rat spinal nerve ligation model.

\begin{figure}
\centering
\includegraphics[width=\textwidth]{test_results}
\caption{Test results}
\end{figure}

[\textit{In vivo test results}]

\[\text{\textbf{Mechanical allodynia}}\]
\[\text{\textbf{Cold allodynia}}\]
Conclusions: We will optimize our compounds to get more positive values in cytochrome P450 inhibition and stability in human hepatic micosomes and to make more selective Ca,3.2 channel blockers.
THE PHARMACOLOGICAL EFFECTS OF TWO LIDOCAINE CONCENTRATIONS TESTED ON SPONTANEOUS AND EVOKED PAIN IN HUMAN PAINFUL NEUROMA. A NEW CLINICAL MODEL OF NEUROPATHIC PAIN

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Objective: To investigate the analgesic effects of lidocaine in two concentrations on several neuroma related pain modalities, spontaneous neuropathic pain and specifically stimulus-evoked allodynia and hyperalgesia.

Method: Sixteen patients with painful neuromas caused by traumatic nerve injury or after nerve surgery affecting the radial, ulnar or the median nerve, or branches of these nerves, participated in this randomized, double-blind experiment. All of the enrolled patients experienced spontaneous chronic neuropathic pain. Clinical examination revealed stimulus evoked allodynia and hyperalgesia in all patients. The patterns of sensory changes were compared before and after they received two solutions of Lidocaine 0.1% and 0.5% 1 ml with 1-2 weeks apart, close to the neuroma. Spontaneous and evoked pain was assessed using a visual analogue scale (VAS) and quantitative sensory testing. Levels of pain scores related to thermal and brush-induced allodynia, movement evoked pain and pinprick induced hyperalgesia were noted at baseline.

Results: Dose-dependent reductions in evoked pain scores were observed after lidocaine treatment. In addition, statistically significant differences in pain scores between evoked and spontaneous pain indicated different pain mechanisms that may provide a rationale for a mechanism-based classification of neuropathic pain. Both lidocaine concentrations produced a sensory loss within the area with hyperalgesia and allodynia, that was statistically significantly different between solutions (p=0.018).

Conclusions: This trial indicates that the painful neuroma, is a human model that elicits all the clinical features of neuropathic pain. The model may be used for testing new drugs systemically or locally administered, with lidocaine as the reference drug.
PAINFUL DIABETIC NEUROPATHY IN EARLY TYPE 2 DIABETES MELLITUS AND PREDIABETIC STATE AND ITS RELATION TO SMALL FIBER INVOLVEMENT

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Background and aim: To evaluate the prevalence of diabetic peripheral neuropathic pain (DPNP) in early (< 3 yrs) type 2 diabetes mellitus (DM2) and prediabetic states (impaired glucose tolerance [IGT] or impaired fasting glucose [IFG]), and its relation to clinical and laboratory signs of large and small nerve fibers.

Methods: A group of 47 patients with early DM2 and 14 patients with prediabetes (24 women, 37 men, median age of 59 yrs) and with no other cause of neuropathy was examined clinically (including evaluation of thermal, pain and tactile sensation) and with electromyography (EMG), thermal quantitative sensory testing (T-QST) and skin biopsy (using intraepidermal nerve fiber density - IENFD).

Results: DPNP was present in 15 (24.5%) patients: 25.5% in DM2, and 21.4% in prediabetic patients; other positive sensory symptoms were found in 27 (44.3%) patients. Objective signs of polyneuropathy were detected in 16 (26.2%) patients. EMG signs of sensory large fiber dysfunction were found in 21 (34.4%) patients, and dysfunction of sensory small fibers in 36 (59% using T-QST) and 41 (67.1% using IENFD) patients, respectively. Signs of small-fiber lesion were significantly more frequent in patients with DPNP compared to those without pain: abnormal T-QST in 86.7 vs. 50%; abnormal IENFD in 78.6 vs. 63.1% (p< 0.05). Altogether, signs of sensory small fiber dysfunction were detected in all but one prediabetic patient.

Conclusion: DPNP is an early symptom of peripheral nerve involvement in prediabetes or DM2 that is almost invariably associated with laboratory signs of sensory small nerve fibers.
INTRA VENOUS METHADONE TREATMENT FOR SEVERE NEUROPATHIC CANCER PAIN

D. Lossignol, I. Libert, B. Michel, C. Dumitrescu, C. Rousseau, M. Obiols-Portis, Belgium

Purpose: Methadone, a synthetic opioid agonist, is an effective alternative to antidepressants, anticonvulsants, local analgesic or strong opioids (morphine, hydromorphone, oxycodone, buprenorphine) in the neuropathic pain and is widely available as an oral formulation. Few data have been published so far on the use of intravenous (IV) methadone for the management of severe or refractory neuropathic cancer pain.

Methods: We followed 10 consecutives cancer patients with severe neuropathic pain, treated with IV methadone. All had advanced disease and were already received antidepressants, anticonvulsants, local analgesic and strong opioids, some in association with ketamine. Pain was assessed at T0, T24 hours, and at the end of treatment.

Results: All patients benefited from the switch to IV methadone with a reduction of pain on VAS after 24 hours (median: 4/10-range, 0-5) until the end of treatment (all cases < 3/10). The median starting dose was 100 mg/day (range, 20-400) and the final dose remained stable with a median of 100 mg/day (range, 27-700). The median duration of IV methadone was 11 days (range, 2-59). No cardiac toxicity had been observed.

Conclusions: IV methadone is an effective pain relieving alternative for the treatment of severe neuropathic cancer pain, especially in refractory pain syndrome. No cardiac or neurological toxicity was observed, nor any other major side effects and the treatment were overall well tolerated. More extensive comparative studies should be planned.
ENDOGENOUS SEROTONIN AND OPIOIDS MEDIATE THE ANTIINOCICEPTIVE EFFECT OF LOW-INTENSITY EXERCISE AFTER TRAUMATIC INJURY OF THE SCIATIC NERVE IN MICE


Background and aims: Physical exercise can activate pain control systems by inducing the release of neurotransmitters, like serotonin and opioids. The aim of this work was to investigate if low-intensity exercise would be able to modulate the descending pain control reducing the neuropathic pain.

Methods: Male Swiss mice (n=8) under anesthesia (ketamina, 80 mg/kg and xylazine, 10 mg/kg; i.p.) were submitted to sciatic nerve crushing for 30 s. Mice performed low-intensity exercise (10 m/min, 30 min daily) for 2 weeks, beginning on day 3 postoperative. To study whether the exercise activated the endogenous opioid or serotoninergic system, mice were pretreated with naloxone (5 mg/kg i.p.; 20 min. before each exercise session) or p-chlorophenylalanine methyl ester (PCPA) (100 mg/kg i.p., once daily for 4 consecutive days before exercise and again on days 11-14 postoperative) or saline, respectively. Mechanical hypersensitivity was measured using von Frey filaments. On the 15th postoperative day, spinal cord and brainstem were removed to measure the endogenous levels of serotonin (5-HT) and their metabolite 5-hydroxyindoleacetic acid (5-HIAA) by HPLC.

Results: Pre-administration of naloxone prevented the anti-hypersensitivity produced by exercise from 5-14th postoperative day (p< 0.001). The pretreatment with PCPA prevented the anti-hypersensitivity on Day 5, 7 (p< 0.01) and 14 (p< 0.001) postoperative. In addition, the PCPA significantly prevented the increase of 5-HT and 5-HIAA levels caused by exercise, mainly in the brainstem (p< 0.01).

Conclusions: Low-intensity exercise reversed mechanical hypersensitivity after traumatic injury of sciatic nerve through activation of the endogenous opioid and serotoninergic system.
REPETITIVE TRANSCRANIAL MAGNETIC STIMULATION OF THE LEFT PREFRONTAL DORSOLATERAL CORTEX DOES NOT HAVE ANTALGIC EFFECT IN CENTRAL POSTSTROKE PAIN PATIENTS

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Introduction: Central poststroke pain (CPSP) is commonly refractory to the current treatment options. It has been shown that repetitive transcranial magnetic stimulation (rTMS) of the left dorsolateral prefrontal cortex (DLPFC) has analgesic effects in healthy subjects, in acute post operatory pain and fibromyalgia patients but its effects in neuropathic pain patients have not been extensively studied.

Objectives: The aim of this prospective, placebo controlled study was to evaluate the analgesic action of rTMS of the left DLPFC in CPSP patients.

Methods: CPSP patients were randomized to either ten daily sessions of real_rTMS of the left DLPFC (10Hz, 1250 pulses/day) or sham_rTMS. Visual analogue scale (VAS), neuropathic pain scale (NPS), McGill pain questionnaire (MPQ), Hamilton Scale for Depression (HAMD), Hamilton Anxiety Scale (HAMA) and 36 Items Short Form Health Survey (SF-36) were assessed.

Results: After a predetermined interim analyses after inclusion of half the projected sample (n=21) the study was terminated due to lack of effect of real_rTMS. The mean baseline VAS for pain (0-10) were 6.86 +/- 1.7 (real_rTMS) and 6.8 +/- 2.2 (sham_rTMS), their respective variations, right after (0.069 and -0.1) the rTMS series, and after one (0.091 and -1.0), two (-0.681 and -1.55) and four (-0.454 and -1.3) weeks after the end of the sessions, were consistently non-significant. Secondarily, no changes in NPS, MPQ, HAMA, HAMD, and SF-36 were found.

Conclusions: rTMS of the left DLPFC does not improve pain in CPSP patients using the present parameters of stimulation.
PROTECTION OF NEUROPATHIC PAIN IN MICE BY NEUROPROTECTIN D1
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Introduction: Neuropathic pain is a debilitating syndrome associated with pathological changes in the peripheral and central nervous system. Current therapies only give transient pain relief. Neuroprotectin D1 or protectin D1 (NPD1/PD1) is a novel pro-resolving and anti-inflammatory lipid mediator biosynthesized from omega-3 fatty acid DHA that exhibits potent analgesic actions in inflammatory pain conditions.

Objectives: In this study, we investigated whether NPD1 could prevent and reverse nerve injury-induced neuropathic pain and address the mechanisms.

Methods: Neuropathic pain was induced by chronic constriction injury (CCI) of the sciatic nerve in CD1 mice. Mechanical allodynia was assessed by von-Frey filaments to measure evoked neuropathic pain, and two-chamber conditional place preference (CPP) was used to assess nerve injury-induced ongoing pain. Nerve injury-induced long-term potentiation (LTP) was recorded in the spinal cord in vivo. Patch clamp recordings in spinal cord slices were performed to determine nerve injury-induced synaptic plasticity.

Results: Treatment with NPD1 not only prevented evoked neuropathic pain symptom (mechanical allodynia) but also abrogated nerve injury-induced ongoing pain (CPP). Mechanistically, NPD1 pretreatment blocked nerve injury-induced LTP and glial responses in the spinal cord. Post-treatment of NPD1, via intrathecal route, also effectively reduced mechanical allodynia, and repeated injections of NPD1 produced no signs of analgesic tolerance. Furthermore, spinal NPD1 treatment reversed nerve injury-induced spinal cord synaptic plasticity.

Conclusions: NPD1 could effectively attenuate nerve injury-induced neuropathic pain by reducing glial activation and neuronal hyperactivity in the spinal cord. NPD1 and its mimetics might be used for preventing and treating neuropathic pain.
**HYDROGEN SULFIDE-MEDIATED GASTRIC HYPERSENSITIVITY IN DIABETIC RATS**

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**Introduction:** Patients with long-standing diabetes often demonstrate gastric hypersensitivity. Evidence suggest that gastric hypersensitivity is associated with altered function of visceral afferent pathways.

**Objective:** To determine the role for nuclear factor-kB (NF-kB)/hydrogen sulfide (H₂S) signaling pathways in diabetic gastric hyperalgesia.

**Methods:** Diabetes were induced by streptozotocin (STZ). Behavior responses was recorded by EMG. Patch clamp recordings, western blotting, real-time PCR analysis, methylation specific PCR, bisulfite sequencing, chromatin immunoprecipitation (ChIP) assays were used in the study.

**Results:**

1. Diabetic rats were more sensitive to graded gastric balloon distention 4 weeks after STZ treatment (P< 0.01). I.p. injection of CBS inhibitor could attenuate diabetic gastric hyperalgesia.

2. The excitability of gastric-specific DRG neurons from diabetic rats was increased. 1 week after i.p. injection of AOAA, the neurons’ excitability decreased. In addition, NaHS (donor of H₂S) could increase the excitability of the gastric-specific DRG neurons of normal rats.

3. CBS and CBS mRNA expression of gastric-specific DRGs in diabetic rats greatly enhanced (P< 0.05). And i.p. injection with NF-kB inhibitor for 1 week reduced upregulation of CBS expression.

4. Recognition sequence of NF-kB in cbs gene promoter was significantly demethylated in diabetic rats (P< 0.05). ChIP assay showed a dramatic increase in p65-binding to the CBS promoter region for NF-kB binding site.

5. DNMT mRNA expression of gastric-specific DRGs in diabetic rats greatly decreased (P < 0.05).

**Conclusions:** Our findings suggest that epigenetic regulation of CBS expression may contribute to gastric hyperalgesia in diabetic rats and that upregulation of CBS expression may be mediated by NF-kB.
INTERFERON-GAMMA PRODUCED BY T-LYMPHOCYTES INFILTRATING INTO THE SPINAL DORSAL HORN IS INVOLVED IN THE MAINTENANCE OF MURINE HERPETIC ALLODYnia

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Introduction: Patients with herpes zoster and postherpetic neuralgia suffer from tactile allodynia, pain due to gently stroking stimulation of the skin. Percutaneous inoculation of mice with human herpesvirus 1 (HHV1) induced zoster-like skin lesions and tactile allodynia.

Objectives: Since viral infection induces the infiltration and activation of T-lymphocytes, we investigated the involvement and role of T-lymphocytes infiltrating into the spinal dorsal horn in HHV1 infection-induced tactile allodynia.

Methods: C57BL/6j mice received percutaneous inoculation with HHV1. Tactile allodynia was assessed using an art paintbrush. Using MACS sorting systems, CD4- or CD8-positive T-lymphocytes were isolated from the spleen of herpetic mice and incubated in phosphate buffered-saline at 37°C for 1 h. The supernatant from each T-lymphocyte was administered intrathecally into naive mice.

Results: mRNA expressions of T-lymphocyte markers (CD3, CD4 and CD8) and interferon-gamma in the dorsal spinal cord were drastically increased in mice with HHV1 inoculation, especially at the herpetic phase. Immunoreactivity for interferon-gamma was localized in CD3 (a pan-T-lymphocyte marker)-immunoreactive cells. Repetitive intrathecal administration of interferon-gamma neutralizing antibody inhibited the maintenance of herpetic allodynia without significantly affecting the induction of herpetic and postherpetic allodynia. Intrathecal administration of cell supernatant of CD4-positive T-lymphocytes into naive mice induced tactile allodynia and this tactile allodynia was partially inhibited by intrathecal administration of interferon-gamma neutralizing antibody.

Conclusions: The present results suggest that interferon-gamma produced by T-lymphocytes infiltrating into the spinal dorsal horn is involved in the maintenance, but not induction, of tactile alldynia during herpes zoster.
CELLULAR SOURCES OF COX-1 AND COX-2 IN RAT SPINAL CORD AFTER SPINAL NERVE LIGATION

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Background and aims: Cyclooxygenase (COX) is involved in the development of neuropathic pain. Recent studies suggested that the development of allodynia associated with neural injury may be partly due to up-regulation of COX-1 as well as COX-2. However, the cellular source of COX-1 and COX-2 after nerve injury was not clear. In the present study, we examined the changes of COX-1 and COX-2 expression in spinal cord associated with pain perception, and the cellular sources of COX-1 and COX-2 in the development of allodynia following spinal nerve ligation.

Methods: Allodynia was induced by ligation of the left L5 spinal nerves in rats. Postoperative pain-related behavior was quantified by measuring the mechanical paw withdrawal thresholds (PWT) and thermal paw withdrawal latencies (PWL) 7 days following spinal injury. COX-1 and COX-2 immunohistochemistry, with collabeling for cell types, were performed on the spinal cord for cellular source determination.

Results: SNL rats displayed significant behavioral thermal and mechanical hypersensitivity (p< 0.05). There was an increase in both COX-1 and COX-2 immunoreactivity in the ipsilateral lumbar dorsal horn at 7 days post surgery. Double immunofluorescence labeling demonstrated that COX-1 immunoreactive cells co-localized with microglia and neurons, predominantly expressed in nucleus, whereas COX-2 was expressed in cytoplasm of neurons only.

Conclusions: Spinal dorsal horn neurons are important source of COX-2 as well as COX-1, but microglia also contribute to the COX-1 up-regulation for neuropathic pain after spinal nerve injuries.
POST LIMB AMPUTATION CHRONIC PAIN-2 YEAR REVIEW OF CASES IN A TRAUMA CENTRE

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Background and aims: Limb amputation due to various indications - trauma, diabetes, infections, and mismanagement of simple fractures by traditional bone setters (TBS) is a regular procedure in our theatre. Pain management is a vital aspect of the treatment. However little is seen for concern and treatment of phantom limb pain. This review intends to highlight and draw attention to the overlooked pain.

Methods: The operation register was searched for all cases of limb amputations performed in 2010/2011. Information extracted includes demographic details, numbers, indications for amputation and anaesthesia provided. Case notes were retrieved and studied for diagnosis of phantom limb pain - treatments, persistent, associated factors and other limb amputation pains.

Results: 98 amputations were registered, of which 68 case notes were retrieved and reviewed. This included 57 males and 11 females (5:1). 80%(52) had general anaesthesia and 20%(16) spinal block. Indications include trauma 40%, diabetic foot 20%, TBS 13%, infections 12%, others 15%. Amputation was seen across ages 5-90, highest in 20-40 years, least in extremes of the ages. 50%(35) of reviewed cases suffered amputation chronic pain - phantom pain 20%(15), stump pain 24%(18), neuroma 6%(2). All who suffered phantom pain had general anaesthesia for amputation. However, no statistically significant association between anaesthesia given and development of amputation chronic pain. (P=0.6099). 54%(19) amputees who suffered chronic pain received no form of treatment. Insomnia, depression, and fear were major associated factors.

Conclusions: Incidence of 50% post amputation chronic pain deserves greater attention for active treatment. Excellent perioperative analgesia as obtained in spinal nerve block may minimize this incidence.
LEARNING TO AVOID INJURY IN CONGENITAL INABILITY TO EXPERIENCE PAIN DUE TO SCN9A MUTATION


Background: Congenital inability to experience pain is due to loss of function mutations in the SCN9A gene encoding the voltage gated sodium channel NaV1.7. We describe a family with compound heterozygote mutations in SCN9A.

Methods: Assessment included neurological examination, quantitative sensory testing and genomic sequencing as part of the Painful Channelopathies Study (UK NRES No.: 12/LO/0017) with full informed consent.

Results: A 27 year old patient presented with history of painless injuries, self mutilatory behavior during childhood as well as decreased sense of smell. He had never perceived pain. In his late teens he had learnt to avoid injury by attending to a tingling sensation which was not unpleasant but he had noticed occurred in the context of tissue injury. His two siblings were affected by the same condition, leading to death in one as a consequence of sepsis. Physical examination revealed a short stature (149 cm) due to multiple epiphyseal fractures, and multiple surgical scars with joint deformities. He was anosmic, power was normal. Bedside sensory testing exhibited insensitivity to pinprick stimulation. Quantitative sensory testing revealed hyposensitivity to non-noxious thermal stimuli as well as inability to experience pain. With suprathreshold thermal stimuli he noticed what he described as a tingling sensation the intensity of which correlated to stimulus strength. Genetic testing demonstrated compound heterozygote mutations in the SCN9a gene (pArg830X, pGlu1773fs).

Conclusions: This case illustrates patients with SCN9a mutations can perceive a sensation that relates to potential tissue injury although this is not overtly painful.
RESPONSES OF COLD- OR HEAT-SENSITIVE INJURED AFFERENT FIBERS TO THE TRPV1 AND TRPM8 ION CHANNEL AGONISTS

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Background and aims: After a nerve lesion injured cutaneous and muscle afferent fibres develop ectopic thermo- and mechano-sensitivity along the affected nerve. This ectopic sensitivity may trigger in patients with nerve lesion burning pain and mechanical and/or thermal (cold or heat) hyperalgesia and/or allodynia. The mechanisms underling the enhanced thermo-sensitivity are poorly understood. Here we tested the hypothesis that heat- and cold-sensitive lesioned muscle and cutaneous axons are activated and de- or sensitized by the TRPV1 agonist capsaicin and TRPM8 agonist menthol, respectively.

Methods: In anesthetized rats capsaicin (0.05, 0.1, 1, 10mM) or menthol (0.05, 0.1, 1, 4mM) were applied to the gastrocnemius soleus or sural nerve injury site.

Results and conclusions:

1) Capsaicin dose-dependently activates most heat-sensitive muscle and cutaneous C- and some heat-sensitive muscle A-fibers, desensitizes almost all heat-sensitive afferents for heat stimuli without affecting cold- or mechanosensitivity. Thus heat-sensitivity of most C- and some A- muscle afferents is dependent on the TRPV1 channel.

2) Menthol dose-dependently activates and sensitizes all cold-sensitive muscle C-fibers. Most cold-sensitive muscle A-fibers are depressed in their activity by menthol and desensitized for cold stimuli.

3) Cold-sensitivity of injured unmyelinated muscle afferents is probably mediated by the TRPM8 channel. However, cold-sensitivity of injured muscle A-fibers is dependent on other channels (e.g., TRPA1).

4) Injured cutaneous cold-sensitive afferents consist of two types: low-threshold afferents which are menthol-sensitive and high-threshold afferents which are menthol-insensitive.
COMPARISON OF C-FOS IMMUNOREACTIVITY IN THE RAT AMYGDALA FOLLOWING PERIPHERAL NERVE INJURY OR URINARY BLADDER INFLAMMATION

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This study investigated the degree of correlation between complex, ethologically-relevant pain behaviour and activation of amygdala neurones as measured by c-Fos immunoreactivity in rat models of peripheral nerve injury and persistent urinary bladder inflammation. There is an association between pain conditions and affective comorbidities and therefore elucidating the neurobiological basis of such associations is vital to improving our understanding of pain and its consequences in patients. Recent studies have suggested a role for the amygdala both as a convergence point for pain and emotional circuits in the brain, and as a ‘relevance detector’; as such pain would alter this response to the environment.

A predator-avoidance behaviour (thigmotaxis) was measured in open field paradigm (100x100 cm, central zone: 40x40 cm; 12lux) in Wistar rat models of traumatic nerve injury (L5 spinal nerve transection; SNT), and persistent visceral inflammation (extended turpentine model). The associated neuronal activation in the central amygdala (CeA) and its three subdivisions was then measured by means of c-Fos immunoreactivity.

Both spinal nerve transection and persistent visceral inflammation increased thigmotactic behaviour (p<0.05). Analysis of the brains harvested from SNT rats showed a greater number of c-Fos immunoreactive cells in the CeA when compared to naive animals (p< 0.05). c-Fos expression in the amygdala will be compared between models and correlations with behavioural outcomes investigated.

The results suggest that pain of varying aetiologies induce changes in ethologically-relevant complex behaviour which are detectable by the open field paradigm, and that this correlates with increased c-Fos expression in the central amygdala.
NEUROPATHIC PAIN IN PATIENTS WITH RHEUMATOID ARTHRITIS

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Background: Chronic pain is the most typical clinical presentation of rheumatoid arthritis (RA). The exclusively nociceptive nature of RA pain is being reconsidered, and neuropathic and psychogenic aspects are increasingly discussed.

Aims: Study neuropathic pain (NP) in the RA patients.

Methods: We recruited 183 patients, aged 18-60 (average age 46.6±11.7 years) admitted to the Research Center for Rheumatology. RA duration ranged from 3 months to 30 years. Using the DN4 questionnaire, we divided patients into two groups: I - patients with no NP (0-3 points), II - NP (4-8 points). We performed clinical, neurological and rheumatologic examination.

Results: 43% of RA patients had symptoms of NP. Patients with NP were older than patients in the first group (49.4±9.9 vs. 44.5±12.5 years), had longer disease duration (10.7±8.2 years vs. 7.8±6.6 years), more often had clinical stage 3-4 (89.8% vs. 63.8%) and R-stage 3-4 (70.4% vs. 40.9%), and had higher functional disability (stage 2-3 94.9% and 68.6%, accordingly). We found no significant differences between the two groups in RA activity (DAS28 score) or quality of life.

Neurological examination in I group identified evoked and spontaneous sensations typical for NP - allodynia in 19.2%, hypoesthesia in 74.4%, hyperesthesia in 16.7%, and hyperalgesia in 15.4%, numbness 96.2%, tingling 87.1%, burning in 47.4% and creeping 69.2% (p< 0.05).

Conclusions: The pain syndrome in RA is complex, with the neuropathic component prevailing in a third of patients. Patient age, RA duration, clinical and radiological stages impact NP severity, while disease activity is not linked to NP.
GABAPENTIN REVERSES BILATERAL PAIN SENSITIZATION IN A RODENT MODEL OF CENTRAL PAIN INDUCED BY UNILATERAL INTRATHALAMIC HEMORRHAGE

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Background and aims: Central neuropathic pain treatment remains amongst the biggest challenges for pain specialists. The objective of this study was to assess gabapentin, amitriptylline and carbamazepine for the treatment of this condition using a central neuropathic pain rat model.

Methods: Male Sprague-Dawley rats were trained on the rotarod, Hargreaves and Von Frey behavioral tests, and baseline values were obtained prior to surgery. A stereotaxic injection of either collagenase solution (0.025UI) or saline was performed within the right ventral posterolateral thalamic nucleus (VPL). Rats were tested on days 2, 4, 8 and 11 post-surgery. They were re-tested at 2 days intervals from day 15 to day 25 post surgery following oral administrations of either the vehicle (7 collagenase controls, 8 saline animals) or the different therapeutic drugs (gabapentin, amitriptyline, carbamazepine) (n=8/drug).

Results: During the first 2 weeks, no significant change in motor coordination was observed following surgery however significant decreases in thermal and mechanical thresholds were observed in both hind limbs in animals that received collagenase. Reversal of thermal and mechanical hypersensitivity was achieved only with gabapentin (p< 0.05 compared to control). Amitriptylline and carbamazepine failed to show any effect on thermal and mechanical thresholds. Microscopic observation of brain sections (H&E and Cresyl violet stains and GFAP immunohistochemistry) revealed a well localized small lesion with loss of neurons and astrocytosis within the VPL following the collagenase injection.

Conclusion: Intrathalamic hemorrhaging in the ventrolateral thalamic nucleus induced bilateral thermal hyperalgesia and mechanical allodynia which is alleviated by gabapentin but not amitriptylline nor carbamazepine.
PAIN MODULATION BY NEGATIVE AND POSITIVE EMOTIONAL SOUNDS


Background and aims: Music has been frequently used to alleviate pain, although the exact mechanisms are not well understood. Previous studies have shown increases in experimental pain during induction of negative emotion. The goal of the present study was to clarify the correlation between the subjective pain intensity, autonomic response and positive or negative emotional sounds.

Methods: Negative, positive emotional sounds and silence of 90 seconds duration were presented while heat stimuli were administered to the left forearm in 16 healthy volunteers and 18 patients with chronic neuropathic pain. Participants performed the written informed consent. They received two levels of heat stimulation (44°C and 46°C) administered by PATHWAY (Medoc, Israel) in the three sound conditions; negative, positive and silence. During the experiments, they estimated the pain intensity using continuous evaluating systems of visual analogue scale (COVAS: Medoc, Israel). The perfusion index was analyzed using pulse oximeter (Masimo, Tokyo, Japan) throughout the experiments. Statistical analyses were performed using the Wilcoxon non-parametric test and P< 0.05 was significant.

Results: Pain intensity differences ΔV = VAS(negative sound)- VAS(positive sound) were higher when applying the 44°C stimuli in volunteers than in patients (P< 0.05). The perfusion index differences ΔPI = PI(negative sound)- PI(positive sound) were lower in volunteers than in patients (P< 0.05). There was no significant difference in pain intensity and perfusion index when applying 46°C stimuli.

Conclusions: Experimental heat pain was modulated by sound through the autonomic nervous response. The negative emotional sound effect was stronger in volunteers than in patients with chronic neuropathic pain.
Neuropathic pain in individuals with spinal cord injury is a frequent condition. However, diagnosis is doubtful in some cases, particularly in incomplete injuries. The aim of the present study was to evaluate the use of the DN4 questionnaire as an instrument to identify neuropathic pain in individuals with spinal cord injury.

**Methods:** A cross-sectional study with spinal cord injury patients residing in Brazil. The study subjects were 109 adult patients with spinal cord injury. The presence of pain was detected and, subsequently, its neuropathic component was identified with the administration of the DN4 questionnaire, a universal, properly validated instrument translated into the Portuguese language. The Visual Analogic Scale (VAS) was also used to assess pain intensity.

**Results:** Pain was present in 34 (31.2%) patients. Nine of these presented with musculoskeletal pain, four had visceral pain, and one, mixed pain. Regarding the neuropathic component, 20 of these patients (58.3%) had neuropathic pain fulfilling the DN4 criteria (scores higher than 4/10), with intensity of 8 to 10 according to the VAS. The patients with neuropathic pain were predominantly male, under 40 years of age, paraplegic with incomplete injury, and duration of injury between one and five years. The prevailing etiology was gunshot wound.

**Conclusions:** The DN4 questionnaire was shown to be an adequate tool for the identification of neuropathic pain in individuals with spinal cord injury, specifically in incomplete injuries. This instrument helps in establishing a specific diagnosis of pain in these patients, which enables adequate and targeted therapy planning.
OXALIPLATIN-INDUCED NEUROPATHIC PAIN INVOLVES CHOLINERGIC SYSTEM IN THE POSTERIOR INSULAR CORTEX: A HR-MAS PROTON NMR SPECTROSCOPY-BASED METABOLOMIC ANALYSIS

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Background and aims: Oxaliplatin-induced peripheral neuropathy is the major dose-limiting toxic effect of colorectal cancer chemotherapy but little is known about its pathophysiology. This study aimed at investigating the metabolic changes at the supraspinal level in a rat model of oxaliplatin-induced chronic painful neuropathy.

Methods: Pain behavior was assessed in male Sprague-Dawley rats exposed to oxaliplatin (9 injections twice a week, cumulated dose: 18 mg/kg) or to the vehicle using the electronic von Frey test. After 31 days, tissue samples from 8 brain structures involved in pain processing were collected and analyzed using the solid-state high resolution magic angle spinning nuclear magnetic resonance spectroscopy to assess metabolic variations between controls and oxaliplatin-treated animals. Metabolites were quantified using the jMRUI software. TaqMan low density arrays (TLDA) were applied to assess differential gene expression between controls and oxaliplatin-treated rats.

Results: Metabolomic analysis of brain structures revealed a marked metabolic response in oxaliplatin-treated animals. In particular, a significant increase of choline was observed in the posterior insular cortex (pIns) of oxaliplatin-treated rats (+22%, p=0.0046), which was significantly correlated with mechanical pain thresholds (p=0.0008). In addition, TLDA revealed an overexpression of the high affinity choline transporter (+56%, p=0.046) as well as an overexpression of muscarinic M2 receptor (+131%, p=0.016) and nicotinic subunit alpha2 (+118%, p=0.015) and beta4 (+63%, p=0.027) in the pIns of oxaliplatin-treated rats.

Conclusion: Our findings report supraspinal phenotypic variations in oxaliplatin-treated animal involving the cholinergic system in pIns, and might offer new insights into the treatment of oxaliplatin-induced neuropathic pain.
MACROPHAGES AND MICROGLIA PLAY DISTINCT ROLES IN NEUROPATHIC PAIN PERCEPTION

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Background and aims: The discovery that activation of non-neuronal CNS microglia plays a causal role in spinal processing of nociceptive signaling has shed new light on the processes underlying neuropathic pain facilitation. However, there remains much uncertainty as to the necessary contribution of microglia to enhanced pain states. We aim to define the particular role of microglia for the initiation of neuropathic pain and by answering this question also learn if the function of peripheral myeloid cells is distinct or redundant in this process.

Methods: To specifically investigate spinal microglia and peripheral macrophages in the pathogenesis of neuropathic pain, we model chronic pain by performing partial ligature of the sciatic nerve in CD11b-HSVTK mice engrafted with GFP bone marrow (GFP>CD11b-HSVTK). CD11b-HSVTK+/− mice allow the exchange with peripherally-derived, GFP+ macrophages upon central depletion of endogenous CD11b+ microglia. Following this depletion/repopulation paradigm, behavioral analyses of mechanical and thermal allodynia are conducted.

Results: We established a selective tool to exchange CNS parenchymal microglia with peripheral GFP+ myeloid cells. In chronic pain tests for mechanical and thermal hyperalgesia, GFP>CD11b-HSVTK+/− mice show considerable decreases in paw withdrawal thresholds in response to mechanical, but not thermal stimuli ipsilateral to the injury, indicating distinct roles of microglia and macrophages in the facilitation of thermal hyperalgesia.

Conclusions: We identified a differential contribution of resident spinal microglia vs. peripheral myeloid cells in the development of neuropathic pain in GFP>CD11b-HSVTK chimeras. Future studies aim to examine the exact mechanisms underlying the distinction between these two populations.
COMPARATIVE STUDY OF COLD ALLODYnia DEVELOPMENT IN ANIMAL MODELS OF NEUROPATHIC PAIN: DIFFERENT ETIOLOGIES, DISTINCT PATHOPHYSIOLOGIC MECHANISMS

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Background and aims: Despite of the importance of cold alldynia to early detection of polineuropathy, little has been explored about the mechanisms involved in this pain abnormality. So, this study aims to evaluate the development of cold alldynia in diabetic and injury nerve evoked-neuropathic pain (NP) in rats, as well as the role of TRPM8 and TRPA1 receptors.

Methods: NP was induced in male adult Wistar rats (n=8-10) by intraperitoneal injection of streptozotocin (STZ, 50mg/kg, diabetic-DBT) or by chronic constriction injury (CCI) of sciatic nerve. Normoglycemic (NGL), sham and naive groups were also conducted. Acetone drop, electronic aesthesiometer or mustard oil intraplantar injection (MO-0.1%; 50µL/paw) were used to assess cold (TRPM8 activation), mechanical allodynia or TRPA1 activation, respectively.

Results: Acetone-evoked flinches was significantly higher (37%) in DBT animals only at week 4 after STZ, while in the CCI-rats, this increase was observable from first (112%) to 4th (204%) week after surgery. The mechanical withdrawal threshold (MWT) was significantly reduced in DBT rats from week 2 (37%) while in the CCI rats, the MWT was significantly reduced since first week (30%). DBT animals exhibited significant reduction (53%) in the MO-evoked flinches, while this treatment induced a significant increase of flinches in the CCI-rats (108%).

Conclusion: Although the pathophysiological mechanisms involved in neuropathic pain development are distinct, clinical treatments are usually very similar and commonly ineffective. Considering the cold alldynia, the present study showed that both TRPM8 and TRPA1 receptors are sensitized differently depending on NP etiology.

CURATIVE-LIKE ANALGESIC EFFECT OF AS1069562, (+)-ISOMER OF INDELOXAZINE, IN RAT MODEL OF STREPTOZOTOCIN-INDUCED DIABETIC NEUROPATHY


Background and aims: Indeloxazine had been clinically used as a cerebral activator with 5-HT and NE reuptake inhibition for the treatment with cerebrovascular diseases. The aim of this study was to investigate the analgesic effect of chronic dosing of AS1069562, (+)-isomer of indeloxazine, compared with duloxetine on pain-related behavior in a rat model of streptozotocin (STZ)-induced diabetic neuropathy. Furthermore, expression levels of neurotrophic factors were determined in the rat spinal cord and DRG receiving chronic dosing of AS1069562.

Methods: Rat diabetic neuropathy was induced by an injection of STZ at 45 mg/kg, iv. AS1069562 or duloxetine was orally administered once daily at 3-30 mg/kg for 4 weeks. Mechanical allodynia was evaluated at both week 4 and a consecutive 1-week withdrawal point. Following behavioral evaluation, the expression levels of neurotrophic factors in spinal cord and DRG were analyzed with real time PCR.

Results: AS1069562 and duloxetine significantly ameliorated mechanical allodynia at week 4 after dosing in a rat model of STZ-induced diabetes. Interestingly, the analgesic effect of AS1069562 but not duloxetine continued after a consecutive 1-week withdrawal, even though the plasma levels of AS1069562 were completely disappeared. In expression analysis, AS1069562 treatment also significantly restored the decrease of IGF1 and FGF2 mRNA levels in this model.

Conclusions: Chronic dosing of AS1069562 but not duloxetine causes a persistent analgesia even after the treatment discontinuation. The restoration of IGF1 and FGF2 may well be involved in the curative-like effect. AS1069562 might offer a better treatment option for diabetic neuropathic pain than current agents.
A SYSTEMATIC REVIEW OF THE PREVALENCE OF NEUROPATHIC FEATURES OF LOW BACK PAIN IN CLINICAL POPULATIONS

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Background and aims: While the prevalence of neuropathic pain in the general population has recently been reviewed, data on clinical cohorts of patients with low back pain (LBP) have not yet been reviewed. The aim of this study was to conduct a review of the prevalence of neuropathic features of LBP in clinical populations.

Methods: We searched the following databases from their inception to 30 July 2011: EMBASE, CINAHL, Medline, and all EBM REVIEW databases. Studies were included if they reported any aspect of neuropathic pain from a clinical cohort of LBP of non-serious pathology. There was no restriction of study design. Pooled estimates of the point prevalence of neuropathic features of back pain were calculated for three clinical sub-groups using inverse variance and random effects analysis (RevMan 5.1).

Results: The search located 54 papers of which 10 were included. Each study used one of three screening instruments for neuropathic pain: painDETECT, the LANSS or the DN4. In primary care the prevalence estimate is 17% (95%CI: 14 to 21%); in mixed clinical settings the estimate is twice as high at 34% (95%CI: 31 to 37%), and in tertiary care higher still, at 53% (95%CI: 49 to 58%).

Conclusions: Neuropathic mechanisms may be involved in LBP more commonly than currently considered, particularly in primary care even in the absence of radicular signs and symptoms. Timely identification of neuropathic pain involvement may enable greater opportunity to select appropriate therapeutic targets.
AS1069562, (+)-ISOMER OF INDELOXAZINE, BROADLY AMELIORATES PAIN-RELATED BEHAVIORS IN RAT MODELS OF NEUROPATHIC PAIN WITH A MINIMAL ADVERSE GASTRIC EFFECT


Background and aims: Indeloxazine had been clinically used as a cerebral activator with serotonin (5-HT) and norepinephrine (NE) reuptake inhibition for the treatment of cerebrovascular disease. The purpose of this study is to investigate 1) the analgesic effects of AS1069562, (+)-isomer of indeloxazine, on various types of pain-related behaviors in a rat of neuropathic pain, and 2) the adverse effect on gastric function. These effects were compared with duloxetine which is one of standard clinical agents for neuropathic pain.

Methods: Rat model of neuropathic pain was induced by chronic constriction injury (CCI) of the sciatic nerve. Four types of pain-related behavior, mechanical, heat and cold hypersensitivity, spontaneous pain measure, were tested after oral dosing of AS1069562 and duloxetine. Adverse effect of compounds on gastric function was assessed with gastric emptying study in rats.

Results: In CCI model, AS1069562 and duloxetine ameliorated mechanical and cold hypersensitivity with the similar potency of 30mg/kg. It is notable that AS1069562 significantly ameliorated heat hypersensitivity at 30 mg/kg, but duloxetine did not. AS1069562 also significantly ameliorated spontaneous pain measure at ≥10mg/kg. however higher dose (30mg/kg) of duloxetine was required to recover this spontaneous pain measure. In gastric emptying study, AS1069562 significantly delayed gastric emptying by approximately 50%, however, duloxetine almost completely inhibited gastric emptying at 30 mg/kg.

Conclusion: AS1069562, (+)-isomer of indeloxazine, has broader analgesic effects in nerve injury induced neuropathic pain and wider safety window for adverse effect on gastric function than duloxetine. AS1069562 may offer a better treatment option in clinical neuropathic pain.
LOCAL TREATMENT FOR PERIPHERAL NEUROPATHIC PAIN: IS THERE ROOM FOR IMPROVEMENT? THE “LIFT” STUDY


Background and aims: Topical application of the high-concentration (8%) capsaicin patch (QUTENZA™) is an effective treatment for peripheral neuropathic pain (PNP), despite possible application-related discomfort. To improve tolerability, the affected area of the skin is treated with local-anaesthetic cream for an hour prior to patch application. Such a pre-emptive procedure could be ineffective in relieving application-related discomfort, unpleasant on allodynic skin, prolong overall treatment duration and is dependent on availability of topical anaesthetic creams. We performed the LIFT study to evaluate the tolerability of Qutenza™ following pre-administration of topical anaesthetic or oral tramadol.

Methods: This was a multicentre, randomised, assessor-blinded study. Qutenza-naïve PNP patients were randomised to receive either topical lidocaine 4% or oral tramadol 50mg, 60 or 30 minutes, respectively, prior to patch application. The intended duration of patch application was 60 minutes. The primary endpoint was the proportion of Qutenza™-tolerant patients (receiving at least 90% of intended duration of patch application). Main assessments included: patient-rated tolerability, dermal assessment of application area and adverse events. ‘Pain Now’ NPRS scores were collected before, during and after patch application. Descriptive statistics were used.

Results: 122 patients were enrolled and treated; 121 completed the study. Data were analysed for the treated population. Similar proportions of Qutenza™-tolerant patients in the lidocaine (98.4%) and tramadol (100%) arms were observed. Incidence of adverse events, mean tolerability and dermal assessment scores were comparable between groups.

Conclusions: Qutenza™ was well tolerated. Similar tolerability results were observed when Qutenza™ was applied after pre-treatment with topical lidocaine or tramadol.
Voltage dependent N-type calcium channel deficient mice exhibit markedly reduced symptoms of neuropathic pain after spinal nerve injury, suggesting a critical role of N-type calcium channel in the development and/or maintenance of neuropathic pain. We have searched for the downstream molecules of N-type calcium channel contributing to neuropathic pain. During this process, we found several molecules, whose blockers were verified to be effective for reducing neuropathic pain, were expressed not only in neurons but also in microglial cells. Furthermore, some molecules were only expressed in activated microglial cells. Then, we have tested whether N-type calcium channel is also expressed in microglial cells and found it is. It is generally believed that contribution of N-type calcium channel in neuropathic pain is through releasing nociceptive neurotransmitter from primary afferent terminals and/or enhancing excitability in the postsynaptic neurons. On the other hand, microglial accumulation, proliferation, and activation at the injured sites after spinal nerve injury have been implicated to be the cause of neuropathic pain. Actually, agents known to reduce microglial activation were shown to be effective for reducing neuropathic pain. Thus, a possibility emerged that N-type calcium channel expressed in microglial cells may activate and play a role in neuropathic pain. To test this hypothesis, we have constructed tamoxifen-controlled conditional transgenic mice in which expression of N-type calcium channel only in microglial cells can be down-regulated. The results obtained from this mouse suggested N-type calcium channel is actually activated in microglial cells and is involved in the mechanism inducing neuropathic pain.
NOVEL SULFONYLHYDRAZONE DERIVATIVE REDUCES DIABETIC NEUROPATHY IN STREPTOZOTOCIN-INJECTED RATS


Introduction: Diabetes is a metabolic disorder characterized by hyperglycemia. Along with hyperglycemia and abnormalities in serum lipids, diabetes is associated with cardiovascular diseases and neuropathy.

Objectives: We describe the beneficial effects of a novel sulfonylhydrazone derivative (LASSBio-1473) in neuropathic pain induced by diabetes in streptozotocin (STZ)-treated rats.

Methods: Male Wistar rats (180-220 g) received a single intravenous injection of STZ (60 mg/kg) to induce diabetes. After six weeks, STZ-treated rats with glucose levels >200 mg/dL were treated with either vehicle (dimethyl sulfoxide) or LASSBio-1473 (20 mg/kg, i.p.) for 14 days. Plasma glucose levels which were examined using the Accu-Check® Performa monitoring system, mechanical allodynia and thermal hyperalgesia were evaluated before and weekly. The Animal Care and Use Committee of Universidade Federal do Rio de Janeiro approved the protocols used.

Results: After 6 weeks of STZ injection: 1. blood glucose levels of diabetic rats increased from 126.0 ± 3.4 mg/dL to 555.9 ± 16.9 mg/dL (P < 0.05); 2. paw withdrawal threshold decreased from 41.1 ± 0.3 g to 17.6 ± 1.1 g (P < 0.05) and recovered to 34.0 ± 3.1 g after 15 days of treatment with LASSBio-1473 (P < 0.05); 3. paw withdrawal latency decreased from 10.5 ± 0.6 s to 7.1 ± 0.5 s (P < 0.05) and recovered to 10.3 ± 0.4 s after 15 days of treatment (P < 0.05) with the derivative.

Conclusions: LASSBio-1473 effectively reduced neuropathic pain, assessed by mechanical allodynia and thermal hyperalgesia in rats with STZ-induced diabetes.
PHα1β, A PEPTIDE ISOLATED FROM THE VENOM OF BRAZILIAN SPIDER PHONEUTRIA NIGRIVENTER, POSSESS ANTINOCICEPTIVE EFFECT AFTER CONTINUOUS INFUSION IN A NEUROPATHIC PAIN MODEL IN RATS

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Introduction: An option for refractory neuropathic pain management by intrathecal (i.t.) route is ziconotide, which block N-type voltage-sensitive Ca^{2+} channels (NVSCC). However, despite its analgesic efficacy ziconotide produced serious adverse effects. Phα1β is a peptide purified from the venom of Phoneutria nigriventer spider, which acts by blocking preferentially the NVSCC and possessed antinociceptive effect without related side effects.

Objectives: The aim of this study was to observe the antinociceptive and toxic potential of Phα1β after single i.t. injection or continuous i.t. infusion in a rat model of neuropathic pain.

Methods: We have observed the antihyperalgesic effect of Phα1β after single i.t. (10-100 pmol/site) injection or after continuous infusion (60 pmol/µL/h) in the neuropathic pain model of constriction of the sciatic nerve (CCI) in adult male Wistar rats (200-300 g).

Results: Phα1β (30 or 100 pmol/site) produced a remarkable antihyperalgesic effect after single i.t. injection from 1 to 6 hours (I_{max} of 100 %), without showing apparent toxicity. In addition, the continuous infusion of Phα1β by an osmotic pump (1 µL/h) for 7 days was also able to reduce the mechanical hyperalgesia from 1 to 7 days (100% inhibition from days 3 to 7). Moreover, the continuous Phα1β i.t. treatment did not evoked any behavior side effect or histopathological changes in spinal cord, brainstem and total encephalon.

Conclusions: Thus, we have shown for the first time that the continuous i.t. delivery of Phα1β produced analgesia disconnected to toxicity in a relevant model of neuropathic pain.
ANTINOCICEPTIVE EFFECTS OF HYDROALCHOHOLIC EXTRACT (ASE) FROM *EUTERPE OLERACEA* MART. (*AÇAÍ*) IN RODENT MODELS OF ACUTE AND NEUROPHATIC PAIN


**Introduction:** Treatment of acute and chronic pain is still an unsolved problem in medicine. Natural products have been used as source for new analgesics.

**Objectives:** We investigated the antinociceptive effect of *Euterpe oleracea* Mart. seeds, a native plant from Amazon region in acute and chronic pain.

**Methods:** The antinociceptive effect of ASE (p.o.) was investigated in acute and inflammatory pain in mice approved by Animal Care and Use Committee using the hot plate test and intra-paw injection of formalin (2.5%). Effect of administration of ASE for 7 days (p.o.) on thermal sensitization and mechanical allodynia induced by spinal nerve ligation (SNL) in rats was also investigated.

**Results:** **Hot plate:** the analgesic activity (%AA) induced by ASE (10, 30 and 100mg.kg⁻¹) was 24.6±5.9, 39.1±10.0 and 46.5±8.3%, respectively.

**Formalin test:** licking time of neurogenic phase was not changed; however, ASE was as effective as salicylic acid in inflammatory phase.

**SNL:** thermal threshold was reduced from 14.7±0.8 to 8.0±0.5s and from 13.6±0.5 to 7.4±0.9s after 7 days surgery, which was increased by ASE (30 and 100 mg.kg⁻¹ p.o.) to 10.6±0.5 (P< 0.05) and 13.2±0.4s (P< 0.05), respectively. Mechanical threshold was reduced from 41.9±1.9 to 17.9±0.5g and from 40.5±0.6 to 18.8±1.0g after 7 days surgery which was increased by ASE (30 and 100mg.kg⁻¹ p.o.) to 23.4±1.1g (P< 0.05) and 34.2±1.4g (P< 0.05), respectively.

**Conclusions:** Acute and inflammatory pain was effectively reduced by *Euterpe oleracea* Mart. (*Açai*) seeds. ASE also reduced chronic pain symptom, thermal sensitization and mechanical allodynia, induced by spinal nerve ligation.
A HUMAN EXPERIMENTAL MODEL FOR NEUROPATHIC PAIN INCLUDING IPSILATERAL POSITIVE AND NEGATIVE SIGNS AND INDUCING CONTRALATERAL SENSORY CHANGES

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A combination of both positive and negative sensory signs occurs in ~40% of the patients with neuropathic pain. Contralateral sensory changes have also been reported. To mimic these both constellations, we developed a human experimental model of concomitant c-fibre sensitization and block and analyzed the bilateral sensory changes by quantitative sensory testing (QST) according to the protocol of the German Research Network on Neuropathic Pain.

28 subjects were firstly randomized in 2 groups to receive either topical capsaicin (0.6%, 12cm²) or lidocaine/prilocaine patch (10cm², 25/25mg) unilateral on the right volar forearm. Secondly, 7-14 days later these subjects received in the same area a co-application of either first capsaicin then local anesthetics (Cap/LA) or in inversed order (LA/Cap). Before, after each intervention and 7-14 days later QST was performed bilaterally. Statistics: Wilcoxon-test, ANOVA, significance level p< 0.05.

The monoapplication of capsaicin induced thermal hypoesthesia, cold hypoalgesia, heat hyperalgesia and tactile allodynia. Lidocaine/prilocaine alone induced mainly thermal, tactile hypoesthesia and mechanical hypoalgesia. Ipsilaterally both co-applications induced a combination of the above mentioned changes. Significant contralateral sensory changes were observed only after co-application, with an increase of the cold (Cap/LA and LA/Cap) and mechanical detection as well as cold pain threshold (LA/Cap).

This model using co-application of capsaicin and local anesthetics imitates some of the characteristic patterns also observed in patients with neuropathic pain. Similar to a subgroup of patients, our model also induced contralateral sensory changes in the same directions as unilateral but to a lesser extent.
EFFICACY OF GABAPENTIN IN THALAMIC SYNDROME

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Introduction: Thalamic syndrome is a condition following a thalamic stroke with excruciating pain (spontaneous or evoked) and decreased pain and temperature in contralateral part of body. Despite the time last of about more than a century after the first report of this syndrome, in addition to the high frequency of this disorder, its severity and great impact on quality of life, little scientific evidence on treatment of this syndrome do exist.

Objectives: Regarding safety, no interaction with other drugs and relative tolerability of patients to gabapentin, response of patients with thalamic syndrome to gabapentin and effect of hypertension, hyperlipidemia, diabetes mellitus, gender, age and stroke type (ischemic or hemorrhagic) on this responsiveness were studied.

Method: Gabapentin was prescribed 600 mg/day in two divided dose for 84 patients with thalamic syndrome, for one month in a multicenter clinical trial. At the onset and the end of treatment, patients were asked about pain severity on basis of NRS. Pain decrease of ≥3 scales in NRS was considered as positive response to gabapentin.

Results: In this study, 59.5% of patients showed positive response to gabapentin. Noteworthy, demographic and mentioned indexes did not have significant effect on patients’ response.

Conclusion: Regarding the difficulty of pain release as the treatment of thalamic syndrome, pain reduction (rather than relief) is considered as the treatment of choice; therefore, patients’ response in this study may be considered promising. Results of this study suggest gabapentin to be considered and used at least as seconded-line or add-on therapy in treatment of thalamic syndrome. Further studies about efficacy of gabapentin on treatment of pain in patients with thalamic syndrome are necessary.
Severe acute diabetic polyneuropathy is a complication of suboptimal glycaemic control, which may not respond to conventional treatment.

**Aim:** We hypothesize that patients with acute diabetic polyneuropathy may manifest psychiatric co-morbidities and may require novel treatments.

**Methods:** A 24 year old female patient with type I diabetes, anorexia, depression and suboptimal glycaemic control, presented to secondary diabetes service with sudden onset of painful paraesthesia in both feet, which spread to involve thighs and upper limbs over a four month duration. She was severely depressed, suicidal and reported a reduced appetite. Trial of Gabapentin and Duloxetine had resulted in minimal clinical benefit. She was assessed and managed by a multidisciplinary team comprising a pain specialist, diabetologist, psychologist and dietician. Detailed evaluation involved sensory testing with VAS, BPI, HADS and BMI monitoring.

**Results:** Initial VAS 9/10, BPI score 78/90, HADS 16/14, BMI 16.2. She was not weight bearing and there was loss of vibration sensation to T4 dermatome and severe allodynia to touch over upper, lower limbs and torso.

She was treated with intravenous lidocaine infusion 2mg/kg 3 times in 12 weeks, Oxycontine/Naloxone 20/10mg bd, Pregabalin 500 mg daily and duloxetine 30 mg bd.

After three months of treatment VAS 6/10, BMI 18. She returned to university to complete her studies. 20 months later patient was discharged from Pain clinic with vax 1/10, HADS 3/2, BPI 6/90, BMI 20.

**Conclusion:** Acute polyneuropathy can be debilitating in patients with psychiatric co-morbidities. Multimodal and multi-professional approaches may be needed for good clinical outcome.
Ketamine has been used in high doses as a surgical anesthetic agent in humans as well as an anesthetic in veterinary medicine. Ketamine has also proven itself to be highly effective in treating patients diagnosed with chronic neuropathic pain conditions when given in low doses over prolonged intravenous infusions. Ketamine binds with the N-methyl-D-asparte (NMDA) and is a highly lipid soluble causing it to cross the blood-barrier rapidly. Due to desensitization of sensitized NMDA receptors, ketamine has a prolonged analgesic effect that makes it ideally effective for specific chronic pain syndromes. Ketamine, in spite of its benefits, can cause severe side effects which require close continuous monitoring throughout the infusion. As of this date there has been no formal clinical studies with definitive results. Our goal was to develop a systematic procedure/protocol that will assure safe, effective outcomes for treating our chronic pain patients with intravenous ketamine. Clinical considerations include but are not limited to a defined systematic monitoring, intervention, and documentation by an ACLS trained nurse for adverse side effects that may occur. Physician’s standing orders were strategically developed to treat adverse reactions allowing the nurse to act autonomously throughout treatment.

We required that a physician must always remain in-house and accessible. We have developed and utilized a patient centered protocol which has provided positive outcomes for many patients. Our hope is that our protocol can be used as a model for other clinicians who have an interest in treating chronic pain patients with intravenous ketamine.
HYPERBARIC OXYGEN (HBO₂) ANTINOCICEPTION IN CHRONIC PAIN IS BLOCKED BY NEURONAL NITRIC OXIDE SYNTHASE (NNOS) INHIBITOR

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Background and aims: HBO₂ can reduce acute pain; inhibiting nitric oxide (NO) production can reduce HBO₂ antinociception (Chung et al., J. Pain 11:847, 2010). It has been reported that HBO₂ can also relieve chronic pain (Thompson et al., Neurosci. Res. 66:279, 2010). Recently, we reported that paclitaxel (PAC)-induced neuropathic pain in rats can be suppressed by HBO₂ exposure at 3.5 ATA (Zhang et al., FASEB Journal 26:662.9, 2012). The aim of this study was to discover whether inhibiting nNOS can reduce HBO₂ antinociception in chronic pain.

Methods: Male Sprague Dawley rats were injected i.p. with PAC (1.0 mg/kg) on days 0, 2, 4 and 6 to produce neuropathic pain. Twenty-four hours after the last injection, rats were exposed to 3.5 ATA HBO₂ for 60 min. The selective nNOS inhibitor S-methyl-L-thiocitrulline (SMTC) was continuously infused i.c.v. at a rate of 0.50 nmol/hr starting on day 5 for seven days. Mechanical thresholds were assessed using an electronic von Frey anesthesiometer.

Results: PAC-treated rats showed an allodynia that lasted for about 30 days after the initial injection. Rats receiving 60-min HBO₂ treatment at 3.5 ATA on day 7 exhibited a recovery of the threshold after day 9. However, inhibiting the production of NO in the brain by SMTC reversed the recovery, which indicated that NO was involved in the antinociception produced by HBO₂.

Conclusions: HBO₂ antinociception in PAC-induced neuropathic pain in rats is NO-dependent. (This research was supported by NIH Grant AT-007222 and the Allen I. White Distinguished Professorship at Washington State University).
LIDOCAINE INFUSIONS FOR NEUROPATHIC PAIN RELIEF: A ONE YEAR EXPERIENCE
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Background and aims: Lidocaine infusion can relieve neuropathic pain and the beneficial effect could be maintained by regular treatments. The aim of this retrospective study is to audit the current departmental practice.

Methods: We have collected demographic and clinical data, and have analysed the outcome of 637 procedures carried out during the 12 month period, started in 01/07/2011.

Results: 287 patients received infusions: 121 started their treatment before and 166 within the observational year. In the former group 91 patients continued later with regular procedures, 15 dropped out and 15 were still in the trial.

In contrast, out of 166 newstarters only 26 eventually joined the group of repeated infusions, for 99 patients the lidocaine trial was unsuccessful. Of the rest 41 patients with still unclear outcome 24 reported a significant relief. That gives a 30% success rate for lidocaine trials over 1 year (26+24 out of 166).

Demographics showed a small age difference between responders and non-responders (54.58±1.2 versus 50.97±1.22 years), but more obvious gender ratio shift (M:F) from 1:1.8 to 1:3.0. It looks like men are less likely to benefit from lidocaine infusion.

A wide range of neuropathic painful conditions, both central and peripheral, demonstrated an equal distribution between successful and unsuccessful groups. Only low back pain with leg pain and visceral pain were less responsive to the treatment.

The lidocaine doses varied between 2 and 3 mg/kg over 1-3 hours in vast majority of the cases.

Conclusion: Our current practice is safe with 30% predictable outcome.
THE EFFECT OF KNEE AND HIP STRENGTHENING EXERCISES ON PAIN, FUNCTION AND ISOKINETIC MUSCLE FORCE IN FEMALES WITH PATELLOFEMORAL SYNDROME

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Objective: The aim of this study was to investigate the efficacy of strengthening exercise program of hip abductor and lateral rotator muscles in addition to strengthening exercise of quadriceps muscle on pain, functional status and isokinetic muscle strength in females with patellofemoral pain syndrome (PFPS).

Material and methods: Fifty-five female patients with PFPS were included the study. Patients were randomized into two groups. Group I received knee exercise and, group II received hip exercises in addition to knee exercises with green theraband five days per week for six weeks. Pain levels during nine different positions were evaluated with VAS, subjective and objective functional status was determined by Kujala questionnaire, and with step-down, squat and three limb hop tests. Peak torque values were assessed with isokinetic dynamometer. All the evaluations were recorded at baseline and at 6th. and 12th weeks of the therapies.

Results: The improvements in pain and functional scores of patients in group II were statistically significant than in patients of group I. Both groups had significant improvements in peak torque values of hip flexion, abduction, lateral rotation and knee extension but improvements in peak torque values for hip abduction and lateral rotation at 60º/sec in group II, were found to be greater than in the values of the other group.

Conclusion: The addition of strengthening exercises of hip abductor and lateral rotator muscles, to quadriceps muscle strengthening exercise leads to significant improvements in functional status, VAS-pain scores and isokinetic hip muscle strength in females with PFPS.
DIFFERENTIAL STAGED SACRAL REFLEXES: METHODOLOGY AND NORMAL VALUES FROM 51 HEALTHY SUBJECTS AND 134 PATIENTS WITH PUENDAL NEURALGIA

R. Nundlall, E. de Bisschop, France

Developing a reproducible method for electrophysiological study of pudendal nerves which can explore the different risk areas: sacral spinal, infrapiriformis area and ischiorectal fossa. This method is called “differential staged sacral reflexes (DSSR)”. 51 patients not suffering from pudendal neuralgia and 134 patients with pudendal neuralgia have been selected. The sacral reflexes (SR) are made at the ventral and dorsal quadrants of the anal sphincter and at the pubococcygeus muscle. Considering the values of the DSSR obtained on healthy subjects and on patients with pudendal neuralgia, maximum threshold values have been established: a significant difference between ventral and dorsal quadrant of the anal sphincter: damage orientation at the level of the ischiorectal fossa; significant difference between dorsal quadrant of the anal sphincter and pubococcygeus muscle: damage orientation at the level of the infrapiriformis area. SR delayed uniformly at the three aforementioned muscles: damage orientation at the level of the sacral spinal. The DSSR allow in a reproducible way to investigate the pudendal nerve in all areas suitable to entrap this nerve, which is impossible with the method of pudendal nerve terminal motor latency (PNTML).
SURGICAL DECOMPRESSION OF PUENDELAL NERVE BY TRANSPERINEAL APPROACH USING A BALLOON PROBE

E. de Bisschop, R. Nundlall, France

Since 2009 may to 31 January 2012, 512 patients (371 females, 141 males) have benefited from a pudendal nerve (PN) decompression by transperineal approach using a balloon probe. These patients had clinical symptoms of pudendal neuralgia. Neurophysiological tests based on the staged sacral reflexes, on ultrasound investigations of pudendal vessels and on a pelvic floor ultrasounds evoked a zone of compressive hyperpressure at the level of the axis infrapiriformis area-ischiorectal fossa. All of these 512 patients, injection block at the level of the infrapiriformis area appeared positive between 1 to 9 months. Patients were known for this pathology since many years. Among these 512 patients, 66 had already PN decompression, 27 by transgluteal approach, 36 by transvaginal (♀)/transischiorectal (♂) approach and 3 by transperineal approach (Shakik extended) but without clinical efficiency.

All of these 512 patients, surgical decompression was done by transperineal approach using a balloon probe.

Surgical methodology, post-op follow up and results are reported hereby, which appear quite successful with few risks to make worse the pathology and no risk on pelvic static.
A NORDIC PROSPECTIVE OBSERVATIONAL MULTICENTER STUDY EVALUATING EFFECT AND SAFETY IN PATIENTS WITH PERIPHERAL NEUROPATHIC PAIN RECEIVING QUTENZA TREATMENT

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Background and aims: The aim was to gather information about the effect and safety of an 8% capsaicin patch (Qutenza) in patients suffering from peripheral neuropathic pain.

Methods: Each patient was to receive up to two treatments and was followed-up over 12+12 weeks.

Parameters: PNRS, patient's pain intensity over the past 24 hours: usual, highest, lowest and right now PGIC.

Size of treated area Skin and pain reaction due to Qutenza application.

Patient’s willingness to undergo re-treatment.

Results: 412 patients were included, 382 patients completed first treatment period, 266 with partial peripheral nerve injury; 51 post herpetic neuralgia (PHN); 19 polyneuropathy and 46 other. 59 % were women, mean age was 53 years (range 18-88). 184 patients were given a re-treatment, and 181 patients completed the re-treatment period.

PNRS: Usual pain intensity over the past 24 hours (maximum pain reduction at any time point) decreased from 6.3 to 4.4 (p < 0.001) and at re-treatment from 6.3 to 5.0 (p < 0.001). PGIC: 57% reported improvement after first treatment and 85% after re-treatment. The area treated had at baseline a median size of 180 cm² and at re-treatment 160 cm².

53% received treatment for the pain due to patch application, 10% for skin reaction. At re-treatment the corresponding figures were 48% and 8%.

57% wanted re-treatment and 71% asked for a third treatment.

Conclusions: Qutenza seems to be a useful and tolerable treatment for subgroups of patients with PNP. The results support the clinical trials previously reported in patients with PHN and HIV-AN.
SUBANESTHETIC INTRAVENOUS KETAMINE INFUSION THERAPY: ASSESSMENT OF LONG-TERM EFFECTIVENESS IN THE MANAGEMENT OF CHRONIC REFRACTORY NON-CANCER PAIN

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Background: Ketamine is a non-competitive antagonist of N-Methyl-D-Aspartate (NMDA) receptors. Ketamine helps to minimise excessively painful responses. Antagonizing these receptors improves opioid receptors sensitivity, reduces opioid tolerance and suppresses opioid-induced hyperalgesia.

Objective: Currently, there is no evidence on the long-term effectiveness of ketamine infusions in the setting of chronic pain. We sought to determine whether ketamine provides long-term benefit to:

Ø Reduce pain levels.
Ø Reduce opioid requirements.

Methodology: This prospective study was designed to evaluate the long-term effect of a 3-7 day ketamine infusion in 100 sequential patients with refractory chronic, non-cancer attending the RPAH Pain Clinic between 2007 and 2012. The assessment was based on the evaluation of a questionnaire performed over a telephone conversation.

Results: Current preliminary data suggests that around 35% of patients are able to maintain their opioid dose reductions with similar or reduced VAS scores. Final results will be presented in the conference.

Conclusion: The preliminary results of this prospective study suggest that an inpatient subanesthetic infusion of ketamine may offer a promising therapeutic option for long-term relief of chronic refractory non-cancer pain. The study establishes the safety and efficacy of this novel approach and strongly supports ketamine being a useful and safe long-term analgesic option.
The aim of the present study was to determine if micronutrients supplementation can improve neuropathy indices in type 2 diabetes.

Materials and methods: In this randomized, double-blind, placebo-controlled clinical trial, 75 type 2 diabetes patients were assigned to three treatment groups, receiving one of the following daily supplement for 4 months: Group MV: zinc (20 mg), magnesium (250 mg), vitamin C (200 mg) and E (100 mg); Group MVB: both of the above mineral and vitamin supplements plus vitamin B1 (10 mg), B2 (10 mg), B6 (10 mg), biotin (200 µg), B12 (10 µg) and folic acid (1 mg); Group P: placebo.

Results: 67 patients completed the study. Neuropathic symptoms based on the MNSI questionnaire improved from 3.45 to 0.64 (p=0.001) in group MVB, from 3.96 to 1.0 (p=0.001) in group MV and from 2.54 to 1.95 in placebo group after 4 months. There was no significant difference between three treatment groups in MNSI examinations after 4 months supplementations. Over 4 months of treatment, patients showed no significant changes in glycemic control, capillary blood flow or electrophysiological measures in MV and MVB groups compared with placebo group.

Conclusions: These studies suggest that micronutrients supplementation might ameliorate diabetic neuropathy symptoms.
MOUSE MODELS OF CHEMOTHERAPY INDUCED POLYNEUROPATHY

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Background and aims: Neuropathic pain as a symptom of sensory nerve damage is a frequent and potentially severe side effect of clinical tumor chemotherapy. Despite intense research efforts, the underlying pathomechanisms of this phenomenon are still poorly understood and current therapeutic options only serve to alleviate the symptoms, rather than to prevent the damage. The goal of this study was to establish mouse models of chemotherapy induced neuropathy (CIPN) with a common genetic background and to characterize behavioral, electrophysiological and histological changes.

Methods: Adult male C57BL/6 mice were treated with paclitaxel, cisplatin, vincristine or bortezomib to induce neuropathy. The phenotype of the animals was assessed in vivo at 4 different time points with electrophysiology and behavioral tests including rotarod, von Frey hair as well as catwalk. At the end of the experiment we performed histological analysis of dorsal root ganglia and the sciatic nerve.

Results: Motor coordination was not impaired in any of our treatment paradigms, whereas all mice receiving verum treatment developed mechanical allodynia and distinct gait alterations. Behavioural results correlated with electrophysiological measurements, which showed a significant decrease of the sensory nerve action potential amplitude. This finding and the histological analysis of the sciatic nerve confirmed a predominantly axonal damage in animals suffering from CIPN.

Conclusions: This study describes functional and morphological alterations in the peripheral nervous system induced by an array of frequently used chemotherapeutic drugs, and provides reliable mouse models with a common genetic background to study pathomechanisms and prevention strategies of CIPN.
Aim: The present study aims to evaluate the effect of low intensity laser (LLLT) in animals with neuropathic pain.

Methods: The chronic constriction injury by (CCI) was performed on male Wistar rats underwent 10 sessions of laser therapy after 14 days of CCI. During treatment, animals were evaluated by behavioral tests to check the nociceptive behavior. At the end of the 10 sessions the animals were euthanized and the posterior root ganglion removed for analysis of immunofluorescence and immunohistochemistry to verify satellite cells (GFAP) and nerve growth factor (NGF).

Results: The results through behavioral tests showed a reversal of nociceptive behavior after treatment with Laser compared to the CCI group. We observed a decrease in immune reactivity for NGF and GFAP in animals with CCI and treated with LASER when compared with CCI group (without treatment). It is concluded that LLLT is effective for the treatment of neuropathic pain since there was reversal of nociception observed in the behavioral tests and reduced NGF and GFAP observed in immunohistochemical assays.
DIFFERENTIAL REGULATION OF MGLURS IN TRIGEMINAL GANGLIA FOLLOWING NERVE AVEOLAR INFERIOR INJURY AND LASER APPLICATION

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Aim of investigation: Nerve-related complications have been frequently reported in dental procedures, and a very frequent type of occurrence involves the inferior alveolar nerve (IAN). Numerous studies have described how peripheral nerve injury causes a variety of functional deficits in sensory processing and contribution of peripherally localized glutamate receptors in pain processing. We examined the effects of IAN injury following laser application in the modulation of mGluRs, to evaluate if laser stimulation changes the expression of mGluRs in trigeminal ganglia. Thus, our main goal is to better understand the mechanisms involved in laser therapy using the IAN injury model.

Methods: We used male Wistar rats, the IAN injury was induced by a Crile haemostatic clamp. The laser treatment was performed every two days, during 10 sessions, using the Ga-As laser (Gallium-Arsenide, Laserpulse - Ibramed) emitting a 904 nm.

Results: Our immunoblotting data demonstrated a decrease of mGluR1 expression after injury when compared to the control group and we observed an increase of mGluR1 expression in the group treated with laser when compared to the injured, non-laser treated, animals. On the other hand, mGluR2 expression increase after injury when compared to the control group and we observed a higher increase in the group treated with laser.

Conclusions: Our initial immunoblotting results indicate that laser therapy modulates the expression of mGluRs in the trigeminal ganglia. Our initial results about regulation of mGluRs in trigeminal ganglia indicate that the protocol of laser therapy, changes the expression of this receptors.
Neuropathic pain due to postsurgical and other lesions to the peripheral nerve is common and often debilitating. It is typically refractory to pharmacological, surgical, and other therapies. Cryoablation (cryoneurolysis) has been used to denature the targeted peripheral nerves. However, outcome data is limited to reports of small number of cases. The primary aim of this retrospective study was to determine the degree of pain relief after cryoablation among patients with painful neuropathies. Specifically, we sought to estimate the mean percent of pain relief achieved 1-3 months after the procedure. With IRB approval, data on 51 patients who underwent cryoablation between 2007 and 2011 in the Cleveland Clinic were extracted from electronic medical records. The cases involved the ilioinguinal (20), genitofemoral (8), intercostal (16), lateral femoral cutaneous (3), and other nerves (4), with an average pain score (numeric rating scale, NRS) of 5.9 (± 2.3) and a median duration of 24 months (Q1 12 months, Q3 36 months). In order to estimate the mean percent pain relief, we used a multivariable linear regression model, adjusting for the baseline NRS pain score as well as duration of pain. This mean percent relief was tested against zero using a standard model-based Wald test. Based on this model, the estimated mean reduction in NRS pain score 1-3 month after the procedure was 61.7% [95% CI: 23.2%, 100%], which was significantly different from zero (P=0.0025). We thus demonstrated that cryoablation is an effective treatment for reducing neuropathic pain in selected patients with no complications.
SUPPRESSION OF PAIN-RELATED BEHAVIOR IN TWO DISTINCT RODENT MODELS OF PERIPHERAL NEUROPATHY BY A HOMOPOLYARGININE-CONJUGATED CRMP2 PEPTIDE

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The N-type voltage-gated calcium channel (CaV2.2) is a clinically endorsed target in chronic pain treatments. As directly targeting the channel can lead to multiple adverse side effects, targeting modulators of CaV2.2 may prove better. We previously identified ST1-104, a short peptide from the collapsin response mediator protein 2 (CRMP2), which disrupted the CaV2.2-CRMP2 interaction and suppressed a model of HIV-related neuropathy induced by antiretroviral therapy but not traumatic neuropathy. Here, we report ST2-104 -a peptide wherein the cell-penetrating TAT motif has been supplanted with a homopolyarginine motif, which dose-dependently inhibits the CaV2.2-CRMP2 interaction and inhibits depolarization-evoked Ca\(^{2+}\) influx in sensory neurons. Ca\(^{2+}\) influx via activation of vanilloid receptors is not affected by either peptide. Systemic administration of ST2-104 does not affect thermal or tactile nociceptive behavioral changes. Importantly, ST2-104 transiently reduces persistent mechanical hypersensitivity induced by systemic administration of the antiretroviral drug 2’,3’-dideoxycytidine (ddC) and following tibial nerve injury (TNI). Possible mechanistic explanations for the broader efficacy of ST2-104 are discussed including investigations into the calcium channel target(s) of this novel peptide.
INHIBITION OF TRANSMITTER RELEASE AND ATTENUATION OF AIDS THERAPY-INDUCED AND TIBIAL NERVE INJURY-RELATED PAINFUL PERIPHERAL NEUROPATHY BY NOVEL SYNTHETIC Ca2+ CHANNEL PEPTIDES

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N-type Ca2+ channels (CaV2.2) are a nidus for neurotransmitter release and nociceptive transmission. However, use of CaV2.2 blockers in pain therapeutics is limited by side-effects resulting from inhibition of the physiological functions of CaV2.2 within the CNS. We identified an anti-nociceptive peptide derived from the axonal collapsin response mediator protein 2 (CRMP2), a protein known to bind and enhance CaV2.2 activity. Using a peptide tiling array, we identified novel peptides within the first intracellular loop (CaV2.2[388-402] ‘L1’) and the carboxyl terminus (CaV1.2[2014-2028] ‘Ct-dis’) that bound CRMP2. Microscale thermophoresis demonstrated micromolar and nanomolar binding affinities between recombinant CRMP2 and synthetic L1 and Ct-dis peptides, respectively. Co-immunoprecipitation experiments showed that CRMP2 association with CaV2.2 was inhibited by L1 and Ct-dis peptides. L1 and Ct-dis, rendered cell penetrant by fusion with the protein transduction domain of the HIV TAT protein, were tested in in vitro and in vivo experiments. Depolarization-induced calcium influx in dorsal root ganglion (DRG) neurons was inhibited by both peptides. Ct-dis, but not L1, peptide inhibited depolarization-stimulated release of the neuropeptide transmitter calcitonin gene-related peptide (CGRP) in mouse DRG neurons. Similar results were obtained in DRGs from mice with a heterozygous mutation of Nf1 linked to neurofibromatosis type 1. Ct-dis peptide, administered intraperitoneally, exhibited antinociception in Zalcitabine (2’-3’-dideoxycytidine (ddC)) model of AIDS therapy-induced or tibial nerve injury (TNI)-related peripheral neuropathy. This study suggests that CaV peptides, by perturbing interactions with the neuromodulator CRMP2, contribute to suppression of neuronal hypersensitivity and nociception.
DECREASE IN SYSTEMIC ANALGESIC USE RESULTING IN COST REDUCTIONS FOLLOWING CAPSAICIN 8% PATCH USE: A PRELIMINARY STUDY

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Background and aims: The capsaicin 8% patch is an effective therapy for peripheral neuropathic pain. It allows the delivery of capsaicin directly to the source of pain, namely skin small Aδ and C fibres. Here we present a preliminary retrospective study investigating changes in systemic analgesic use following treatment with the capsaicin 8% patch.

Methods: The use of systemic analgesics by patients receiving treatment with the capsaicin 8% patch between July and December 2011 was assessed pre- and post-treatment. During this period, calculations were carried out to quantify the cost of the capsaicin patch compared with the cost of daily pain medications.

Results: Thirty-one patients (aged 24 to 87 years) received treatment with the capsaicin 8% patch for neuropathic pain conditions including post-surgical pain, radio- and/or chemotherapy-induced neuropathy and post-herpetic neuralgia. At baseline, patients were receiving a range of pain medications, including gabapentin, pregabalin, tramadol, topiramate, oxcarbazepine, oxycodone and lidocaine plasters. Systemic analgesic use following capsaicin 8% treatment was completely stopped in 5 (16%) patients, decreased in 19 (61%) patients and modified or increased in 7 (23%) patients. This led to an estimated saving of €250-€340 per patient over 90 days (theoretical interval between 2 patch applications), equalling or exceeding the price of 1 patch.

Conclusions: Treatment with the capsaicin 8% patch resulted in an overall decrease in the use of systemic analgesics, potentially reducing systemic side effects in these patients, and in a reduction in the cost of treatment for patients with peripheral neuropathic pain.
SAFFRON EXTRACT AND ITS ACTIVE CONSTITUENT CROCIN DECREASES ALLODYNIA AND HYPERALGESIA IN A RAT MODEL OF NEUROPATHIC PAIN

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Inflammation at the site of nerve damage causes neuropathic pain. It has been shown that saffron acts as an anti-inflammatory agent. In this study, we investigated the effects of saffron and crocin, a major constitute of saffron, on behavioral responses of pain induced by chronic constriction injury (CCI).

Adult male Wistar rats (200 to 250 g n=50) were randomly assigned to 4 groups; CCI, CCI plus saline injection, CCI plus saffron (30mg/kg) and CCI plus Corocin (30 and 15mg/kg) injection. Method of Bennett & Zie (1988) was used to create CCI. Two weeks after nerve lesion, injections of saline, saffron and crocin were started and continued until day 26. Behavioral responses by the test mechanical allodynia (Von Frey) and thermal hyperalgesia (plantar test) were measured on days 14, 17, 20, 23, 26, and 40, post-CCI.

Results showed that CCI induced significant increases in behavioral responses. Crocin (30 mg/kg) decreased mechanical allodynia from the day 20 and Saffron (30 mg/kg) decreased thermal hyperalgesia from the day 23. Saffron and crocin (30 mg/kg), decreased thermal hyperalgesia and mechanical allodynia from the day 23, and this effect continued until the day 40. Crocin 15 mg/kg not affected in thermal hyperalgesia but decreased mechanical alodynia from day 23, post-CCI, and this effect continued until the day 40.

Our results demonstrate that saffron and crocin could be effective in reducing neuropathy pain resulting from CCI.
KETAMINE AND PHANTOM LIMB PAIN PREVENTION

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Background and aim: Phantom pain mostly occurs after limb amputation. Therefore we started with study in this field. Purpose was to determine the incidence of phantom pain three months and three years after surgery and necessity of analgesics during the first week after amputation.

Materials and methods: It was blind, prospective, placebo-controlled study. Patients with diabetic leg condition, who had undergone lower limb amputation surgery in general anesthesia were included (n=32). They were divided into 3 groups. After administration of anesthesia, a 0.5mg/kg bolus of i.v. ketamine was given before the operation was started (Group 1, n=12; Group 2, n=13). Patients with different medical conditions who were unable to receive ketamine were placed in Group 3 (n=7). Right after surgery, participants received a 48 hour post-operative intravenous infusion of 0.1mg/kg/h (Group 1),

or 0.05mg/kg/h (Group 2),

ketamine or magnesium (Group 3).

The patients' conditions were rechecked on day 2, 7 and at 3 months and 3 years after surgery.

Results: The necessity of analgesic treatment was highest in the control group. The incidence of phantom pain 3 months after surgery was 0% in Group 1, 15.4% in Group 2, 66.6% in Group 3. 3 years after surgery - 0% in Group 1, 14.3% in Group 2. The control group was not be evaluated, 6 of the 7 patients died.

Conclusions: Administration of pre-operative bolus of ketamine and continuous post-operative 48 hour intravenous ketamine infusion had significantly reduced incidence of the phantom pain and necessity of analgesic treatment after amputation.
SATELLITE CELLS AND NERVE GROWTH FACTOR IN DORSAL ROOT GANGLION AFTER NEURAL MOBILIZATION TREATMENT IN NEUROPATHIC PAIN MODEL

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Aim: The neural mobilization is efficient in improvement the life quality of patients with neuropathic pain. Glial cells and neurotrophins are directly involved in painful processes, under chronic pain conditions. We evaluated the glial fibrillary acidic protein (GFAP) of satellite cells and nerve growth factor (NGF) synthesis by immunofluorescence and immunoblotting methods in DRG after neuropathic pain and treatment with neural mobilization technique.

Methods: Wistar rats (170-190g) were submitted to the nerve sciatic surgery (CCI). Animals sham-operated (SHAM) without nerve ligation were used as controls. To evaluate the nociceptive threshold we used Randall & Selitto, Hargreaves test and Von Frey. After fourteenth day of surgery the animals received neural mobilization sessions each other day, during 10 sessions. After treatment, animals were perfused and DRG (L4) sections were incubated for performing immunofluorescence and immunoblotting to analyze GFAP and NGF.

Results: The animals CCI showed decrease of the nociceptive threshold, when compared with control and improvement after neural mobilization. The immunoblotting results demonstrated a decrease of GFAP and NGF in DRG after neural mobilization when compared with CCI animals. The immunofluorescence demonstrated a colocalization of GFAP and NGF and a decrease of those immunoreactivity after mobilization treatment.

Conclusion: Ours results suggest the involvement of satellite cells and NGF in neural mobilization, once were possible to observe change in their markers after treatment. In addition, we suggest that glial cell could produces neurotrophihs evidenced through the colocalization of GFAP and NGF in DRG cells. We also emphasize the neural mobilization technique importance and effectiveness as treatment.
ANTINOCICEPTIVE EFFECT OF NEW ANALOGS CHEMICALLY RELATED TO ZOLPIDEM FOR THE TREATMENT OF THERMAL HYPERALGESIA AND ALLODYNA IN STREPTOZOTOCIN-INDUCED DIABETES IN RATS


Introduction: Hyperalgesia and allodynia are neuropathy-related symptoms of diabetes mellitus.

Objective: We investigated the antinociceptive effect of new compounds chemically related to the benzodiazepine receptor agonist zolpidem (LASSBio-873 and LASSBio-981) in chronic pain associated to streptozotocin-induced diabetes in rats.

Methods: Protocols were approved by Institutional Animal Care and Use Committee. Experimental diabetes was induced by a single injection of streptozotocin (60 mg.kg⁻¹, i.v.) in Wistar rats (180-220 g) which were considered diabetic when blood glucose level was >240 mg.dl⁻¹ with loss of body weight. Thermal hyperalgesia and mechanical allodynia symptoms were observed 28 days after streptozotocin-induced diabetes. After confirmation of neuropathy, LASSBio-873, LASSBio-981 and amitriptyline were orally administrated in a dose of 100, 30 and 10 mg.kg⁻¹, respectively during 7 days.

Results: In the three tested groups, thermal threshold latency was reduced from 11.7±0.5 to 8.4±0.4 s; 13.3±1.1 to 8.4±0.5 s and 12.0±1.0 to 7.4±0.2 s, which returned to normal values (P< 0.05) to 12.0±0.4, 12.4±0.7 and 10.5±1.0 s after treatment with LASSBio-873, LASSBio-981 and amitriptyline, respectively. Mechanical threshold was reduced (P< 0.05) from 38.9±0.5 to 25.4±0.9 g, 38.9±0.8 to 24.2±2.0 g and 40.2±1.0 to 21.1±1.5 g after 28 days of streptozotocin injection. Paw withdrawal threshold recovered to 38.6±0.8, 38.9±0.7 and 29.3±1.1 g (P< 0.05) after 7 days of treatment with LASSBio-873, LASSBio-981 and amitriptyline, respectively.

Conclusion: Thermal hyperalgesia and mechanical allodynia observed in streptozotocin-induced diabetic rats were reverted by p.o. administration of LASSBio-873 and LASSBio-981. Amitriptyline significantly reduced thermal hyperalgesia but not able to reduce mechanical allodynia symptom.
THE EFFECT OF VENLAFAXINE ON NEUROPATHIC AND NON-NEUROPATHIC PAIN IN PERSONS WITH SPINAL CORD INJURY: RESULTS OF A RANDOMIZED CONTROLLED TRIAL

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Background and aims: Persons with spinal cord injury (SCI) often experience both neuropathic and non-neuropathic pain, the former being particularly difficult to treat. We hypothesized that neuropathic pain in particular might respond to venlafaxine XR, and examined this hypothesis as a secondary outcome of a multi-site trial investigating venlafaxine’s impact on major depression in persons with spinal cord injury.

Methods: 133 persons with SCI from six sites were enrolled in the depression trial of which 123 reported on 1-3 different pain sites. Pain sites were categorized as neuropathic or non-neuropathic. Outcomes included NRS and pain interference ratings at baseline and at 12 weeks (end of the trial). Participants were randomly assigned to treatment or placebo conditions. Change in depression scores (HAM-D) were used as a covariate.

Results: Contrary to our expectation, neuropathic pain sites did not respond to venlafaxine any better than to placebo. However, non-neuropathic pain sites did respond positively to venlafaxine with significantly better improvement on all pain outcome measures than was the case for placebo treated pain sites. Average NRS ratings for the treatment group improved from 5.7 to 3.4 compared to 5.5 and 4.8 for the placebo group. Half of the treatment group were 50% responders vs 24% of the placebo group. Controlling for changes in depression did not significantly affect the results.

Conclusions: We did not detect an hypothesized effect of venlafaxine on neuropathic pain in persons with SCI, but did see a substantial effect for non-neuropathic pain.
Pain is a frequent non-motor symptom of Parkinson’s Disease (PD). Studies strongly suggest that basal ganglia and dopaminergic system are involved in central pain processing. The aim of this study was evaluate pain characteristics in PD patients. Thirty-five patients with PD and chronic pain (mean age, 69.09 ± 8.6 years) were included in this study. Pain and allodynia were assessed by administering McGill Pain Questionnaire and the Leeds Assessment of Neuropathic Symptoms and Signs (LANSS) scale. Mechanical sensory and pain thresholds were assessed using von Frey monofilaments and a pressure analog algometer. Thermal sensory and pain thresholds were evaluated both in the clinical pain (CP) areas as well as in the thenar eminence (TE). Reported pain intensity was 3.6 in average (0-10 VAS). Allodynia as defined by the LANSS scale was found in 14 patients (40%). The legs were the most frequent location of pain (40%), followed by back (25%), arms and shoulders (8.6%), feet or neck (5.7%), and head or abdomen (2.9%). The CP foci showed a significant increase in warm but decrease in cool detection thresholds as compared to TE (P < 0.01). In the CP, heat pain thresholds were significantly higher (P< 0.01), but both cold and mechanical pain thresholds significantly lower (P< 0.01), than in the TE. PD patients present impaired heat perception but increased mechanical and cold pain perception in the clinical pain sites. The possibility of a peripheral sensory deficit involving small-calibre fibres should be considered in future studies in PD patients.
EQUINE HEADSHAKING: A NATURALLY OCCURRING ANIMAL MODEL OF TRIGEMINAL NEURALGIA?

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Introduction: Idiopathic headshaking is a spontaneously occurring nociceptive and potentially crippling disorder of mature horses. Trigeminal neuralgia has been proposed as the likely cause.

Objective: To compare sensory nerve conduction threshold and velocity of the trigeminal nerve using the infraorbital nerve in control and headshaking horses.

Methods: Control (n=6) and headshaking (n=6) horses were subject to general anesthesia. A Nicolet Viking evoked potential system was used. A pair of stimulating electrodes was placed at the gingival mucosa of the maxillary canine. Four pairs of recording electrodes were placed along the tract of the infraorbital nerve (point 1), maxillary nerve (point 2), spinal somatosensory (point 3 at C1), and cortical somatosensory evoked potentials (point 4 at fronto-parietal cerebral cortex). A reference electrode was placed between the stimulating and point 1 recording electrodes. Stimuli (0.1 ms) were applied at 2.5, 5, 10, 15, 20 mA.

Results: The threshold of sensory nerve action potential occurred at low stimuli (2.5 and 5 mA) in horses with headshaking; and at higher stimuli (10 mA in 3 horses, 15 mA in 1 horse, and 25 mA in 2 horses) in control horses. Conduction velocity was not significantly different between groups.

Conclusions: Headshaking horses have a low threshold for inducing sensory action potentials upon minimal stimulation compared to control horses; supporting involvement of the trigeminal nerve in the pathogenesis of affected horses. Further work validating equine headshaking as an animal model of human trigeminal neuralgia is warranted.
Auriculotemporal neuralgia (AN) is an uncommon disorder characterized by pain in the area supplied by the auriculotemporal nerve, which covers the temporal region, temporomandibular joint, and in the parotid, auricular and retro-orbital region. The lack of awareness of this head and facial pain may possibly be due to its rarity and problems with making the diagnosis. Herein, we report 4 cases of auriculotemporal neuralgia with the purpose of gathering and sharing information about this poorly discussed neuropathic pain. We analyzed 4 patients (2 women and 2 men) diagnosed with AN in a headache outpatient clinic. The pain was moderate to severe, daily in 75% of cases and lasting from 5 minutes to 3 hours, with burning, pressure or stabbing exacerbations. Palpation of the ipsilateral auriculotemporal nerve region elicited a sharp pain familiar to the patient which extended to the tenderness region. The pain remains confined to the same symptomatic area which does not change in shape or size with time. All cases were treated with an anesthetic blockade and achieved complete relief lasting from three to six months. One patient before blockade received amitriptyline 25 mg for four months without improvement. Since manual palpation of the auriculotemporal nerve region often triggers pain, and infiltration with local anesthetics abolishes the pain in all patients, we suggest that auriculotemporal neuralgia could be responsible for head and facial pains. Although local nerve blocks are often used for diagnostic reasons, herein we consider that they are also of therapeutic value.
CONTRIBUTION OF PERIPHERAL SENSORY INPUT IN MAINTAINING CHRONIC NEUROPATHIC PAIN AND PREDICTORS OF RESPONSE TO INTRAVENOUS LIDOCAINE

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Background and aims: Injured or disease-affected peripheral nociceptors frequently develop sodium-channel dependent membrane hyperexcitability, which may contribute to spontaneous pain.

Study aims: To investigate the magnitude of contribution of peripheral (vs. central) sensory input in maintaining chronic pain in two subsets of peripheral neuropathy; and to evaluate clinical biomarkers of peripheral nerve fiber dysfunction as predictors of response to systemic sodium channel blockade.

Methods: Patients with neuropathic pain secondary to peripheral nerve injury (PNI) to the foot or small fiber neuropathy (SFN) underwent quantitative sensory testing for thermal and mechanical thresholds, and assessment of pain and local flare response to topical 10% capsaicin cream. Subsequently, the patients were randomized to intravenous lidocaine (5mg/kg) infusion and an ultrasound-guided peripheral nerve block in a cross-over design.

Results: Ten patients (5 PNI, 5 SFN, mean age=60.5 years, spontaneous pain intensity=64 on 0-100 NRS) have completed the study so far. Peripheral nerve block completely abolished the pain in the ipsilateral foot (mean 15.5 minutes) in all patients. Mean±SD pain reduction following lidocaine infusion was 41.8±28.7% (22.8±15.9% in PNI vs. 60.7±26.7% in SFN, p< 0.05). More patients with SFN (4/5 vs. 0/5) achieved ≥50% pain reduction endpoint following lidocaine infusion (p< 0.05). Thermal detection and pain thresholds, mechanical detection threshold, or response to topical capsaicin did not predict the response to lidocaine infusion.

Conclusions: These preliminary results suggest that peripheral sensory input is crucial in maintaining chronic neuropathic pain following PNI or SFN. Pain etiology was likely to predict the response to lidocaine infusion.
HEMOPRESSIN (INVERSE AGONIST OF CB1R) INHIBITS NOCICEPTION ASSOCIATED TO DIABETES MELLITUS-INDUCED NEUROPATHY IN MICE

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Peripheral neuropathy is one of the most common complications of diabetes affecting about 50% of patients with the disease. The most prominent symptoms involve the extremities and occur as both an exaggerated response to noxious stimuli (hyperalgesia) and for mild or non-painful stimuli (alodynia). Hemopressin (Hp) is a nonapeptide first found in rat brain extracts, which selectively binds CB1 cannabinoid receptors (CB1R) and exerts antinociceptive actions in experimental inflammatory and neuropathic pain models. However there is no data about efficacy in metabolic-related neuropathy like diabetes mellitus. The aim of this study is investigate the role of Hp in a mouse model of type 1 diabetes mellitus-induced neuropathy, as well as the mechanisms involved in such effect.

Mechanical allodynia was assessed by Von Frey filaments 7 and 28 days after the injection of streptozotocine (intraperitoneal 200 mg/kg). Weight and blood glucose were monitored once a week. Hp was administered once a day for 7 or 28 days (oral, 2.5 mg/kg). CB1R-glia colocalization and activated CB1R expression were evaluated in the dorsal horn of spinal cord (DHSC) by fluorescence immunohistochemistry, respectively.

Hp reverses allodynia in diabetic-induced neuropathy in both acute and chronic treatments without changing blood glucose levels or animals weight. Hp increases microglia staining as well as CB1R/astrocytes colocalization after 7 days of treatment. However only chronic treatment with Hp, increased activated CB1R expression in the DHSC.

These results make hemopressin an attractive approach for the development of cannabinoid-based therapies for the treatment diabetic neuropathic pain.
TOPICAL HERBAL MEDICINE FOR TREATMENT OF DIABETIC PERIPHERAL NEUROPATHY: A SYSTEMATIC REVIEW OF RANDOMIZED CONTROLLED TRIALS

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Background and aims: Chinese herbal medicine (CHM) has been commonly used in China alone or in combination with conventional medicine to treat diabetic peripheral neuropathy (DPN). This review aims to assess the beneficial effects and harms of Chinese herbal medicine for people with diabetic peripheral neuropathy.

Methods: A systematic literature search of Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, AMED, Chinese BioMedical Literature Database, Chinese National Knowledge Infrastructure, and Chinese VIP information was conducted till October 2012. Randomized controlled trials were included if they compared topical CHM to conventional medicine, placebo, or no treatment on DPN patients.

Results: Fifty RCTs involving 3711 participants were included. Most of the trials were of low methodological quality. Thirty-nine different herbal medicines were tested including 4 single herbs (including extracts from a single herb), 8 Chinese traditional patent medicines, and 27 self-composed Chinese herbal compound prescriptions. The outcomes reported include global symptom improvement, pain relief, and changes in nerve conduction velocity. Most trial showed beneficial effect on global symptom improvement while only one self-composed Chinese herbal prescriptions (Tongluo Tangtai Decoction) demonstrated beneficial effect on pain relief specifically. There was inadequate reporting on adverse events in the included trials. Conclusions cannot be drawn from this review about the safety of herbal medicines due to inadequate reporting.

Conclusions: Due to weak evidence, the claimed benefits of topical CHM for DPN are inconclusive; more rigorous studies are warranted to support clinical practice. However, pain relief reported with Tongluo Tangtai Decoction should be further investigated.
CENTRAL HABITUATION TESTING WITH LASER EVOKED POTENTIALS: A NEW DIAGNOSTIC TOOL FOR NEUROPATHIC PAIN?

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Background and aims: Laser evoked potentials (LEP) are commonly used as diagnostic tool for the testing of the integrity of small nerve fibers (A-delta and C-fibers) in neuropathic pain patients. Under certain conditions repetitively applied painful laser stimuli lead to central habituation. Recent studies proposed altered habituation as an indicator for the dysfunction of central pain processing in patients with migraine or fibromyalgia. We hypothesized that neuropathic pain patients also show altered electrophysiological habituation. We used capsaicin as the surrogate model for neuropathic pain and tested central habituation with LEP.

Methods: 15 subjects received repetitive painful laser stimuli at the primary or the secondary area after topical capsaicin application. N1, N2, P2-latencies and N1-, N2P2-amplitudes were recorded with EEG. Quantitative sensory testing, Mc-Gill pain questionnaire and the Liewald Diary reaction time experiment were used as control testing. LEPs and test results from of the primary and secondary condition were compared. LEPs of capsaicin treated subjects were compared to a control group without capsaicin application.

Results: The N2P2-amplitude habituated significantly later in the primary area of the capsaicin application, compared to the secondary area and the control group. In the secondary area there was an early N2P2-amplitude habituation and a significant reduction of pain sensation, although, compared to the control group the effect was less pronounced.

Conclusions: Capsaicin induced central sensitization seems to delay physiological habituation of pain. Testing central habituation with LEP in neuropathic pain patients might be useful to prove or rule out dysfunction of central pain processing.
IMMUNISATION WITH MYELIN-DERIVED ALTERED PEPTIDE LIGAND INHIBITS NEUROPATHIC PAIN FOLLOWING PERIPHERAL NERVE INJURY

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Background and aims: A growing body of evidence indicates that neuroinflammation plays a pivotal role in the development and maintenance of neuropathic pain. Altered peptide ligands (APLs) are mutant peptides that shift the T helper 1 cell-mediated pro-inflammatory response to T helper 2 cell-mediated anti-inflammatory response. Therefore, we studied the effects of immunisation with a myelin-derived APL on pain hypersensitivity and immune cell reactivity in an animal model of peripheral neuropathic pain.

Methods: Chronic constriction injury (CCI) of the sciatic nerve was performed on Lewis rats, followed by a subcutaneous injection with complete Freund's adjuvant (CFA) (1mg/ml) as vehicle control, native myelin basic protein (MBP) (cyclo-MBP87-99, 250µg), or APL (cyclo(87-99)[A91,A96]MBP87-99, 250µg) in CFA. Animals were tested for mechanical pain hypersensitivity using a dynamic plantar aesthesiometer (n=6), immune cell reactivity by immunohistochemistry, and the prevalence of systemic regulatory T cells by flow cytometry (n=3-4).

Results: Rats immunised with APL had a significant reduction in mechanical pain hypersensitivity compared to rats immunised with cyclo-MBP87-99 and CFA only, on days 8, 10 (P< 0.01), 19 and 23 (P< 0.05) post-CCI. Furthermore, APL treatment resulted in a significant (P< 0.01) reduction in T cell numbers and macrophage density in the injured nerve on day 30 post-CCI. However, there was no significant difference in the percentage of regulatory T cells among the three groups.

Conclusions: Immunisation with non-encephalitogenic myelin-derived APL exerts an analgesic effect in neuropathic animals through neuroimmune modulation, suggesting immunotherapy as a novel approach for the treatment of peripheral neuropathic pain.
SUBQSTIM: A PROSPECTIVE, MULTICENTER, RANDOMIZED, PARALLEL-GROUP STUDY OF SUBCUTANEOUS NERVE STIMULATION (SQS) IN SUBJECTS WITH BACK PAIN DUE TO FAILED BACK SURGERY SYNDROME (FBSS)

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Background and aims: Chronic radicular pain can be effectively treated with spinal cord stimulation.[1] A number of case series report SQS to be a potential solution for FBSS patients with chronic, intractable back pain. However, there remains no large, randomized clinical trial (RCT) evidence for SQS. The aim of the SubQStim RCT is to compare the clinical effectiveness of SQS plus optimized medical management (OMM) versus OMM alone in patients suffering from back pain due to FBSS.

Methods: Up to 400 subjects with back pain due to FBSS will be recruited from approximately 30 European and Australian centers. Subjects will be evaluated pre-randomization and at 1, 3, 6, 9, 12, 18, 24, 30, and 36 months post-randomization. OMM subjects that fail to achieve \geq 50\% pain relief at 9 months will be allowed to receive SQS and vice versa. The primary outcome is the proportion of subjects at 9 months with a \geq 50\% reduction in back pain intensity compared to baseline. The secondary outcomes include: ODI, SF-36, EQ-5D-5L, subject satisfaction, Patient Global Impression of Change, pain medication and non-invasive pain treatment use, HCU costs, adverse events and device programming parameters.

Results: SubQStim is the first RCT designed specifically to provide evidence on SQS for the treatment of chronic, intractable back pain secondary to FBSS.

Conclusions: This poster describes the SubQStim study.

Aim: To compare the efficacy and safety of low-dose naltrexone (LDN) and amitriptyline in the control of pain of diabetic neuropathy.

Methods: A randomized, double-blind, active-control, crossover clinical trial with optional dose titration was conducted using LDN 1, 2 and 4 mg or amitriptyline 10, 25, and 50 mg tablets daily. Initially, the lowest dose of either drug was given for 2 weeks. Dose escalation was done if improvement was not satisfactory. A placebo washout of 2 weeks was given between the two drugs with paracetamol rescue. Pain relief, overall improvement and treatment emergent adverse events (TEAEs) were assessed at baseline, 2, 4 and 6 weeks of drug therapy. This planned interim-analysis was conducted in 27 completed cases.

Results: Pain relief was found to be good in 16 (59%) vs. 17 (63%), moderate in 4 (15%) vs. 3 (11%) and mild in 5 (19%) vs. 3 (11%) with LDN vs. amitriptyline by patient's global impression of change (VAS) showing similar efficacy. The SF-McGill pain questionnaire and Likert pain scale also showed similar findings. Eight (30%) and 20 (74%) adverse events were observed with LDN and amitriptyline respectively. The preferred daily effective dose was 2 mg for LDN and 25 mg for amitriptyline. Relatively more patients preferred LDN (63%) over amitriptyline (37%).

Conclusions: In this interim analysis, LDN showed similar analgesic efficacy and a lower potential of TEAEs compared to amitriptyline, thus indicating LDN may be a promising pharmacotherapeutic alternative in PDN pain management and requires further evaluation.
Background and objective: Since its introduction in 2005 the PD-Q has been widely used. Data from >225,000 patients have been collected in the painDETECT project register. The original validation did not include “test-retest” because of the necessity to suspend or interrupt pain treatment. Validation of the test-retest performance of the PD-Q items and the derived score is reported.

Methods: For the patients in the data base with stable disease, retrospective analysis of 2 consecutive visits was performed. To ensure stable disease, visits had to fulfill the following criteria: interval between visits, 7-21 days; time since first capture in database, \( \geq \) 6 months; indication, back pain; difference of average, maximum and current pain between visits each < 5 points on the 100-point NRS.

It was verified that the selected sub-population was representative of the whole study population.

Intra-class-correlation ICC, Pearson correlation and weighted kappa were used as statistical measures for ordinal scaled items. Bland-Altman plot and Passing-Bablok regression were also assessed for continuously scaled PD-Q score.

Results: Data from 94 patients fulfilled the narrow criteria; mean duration between visits was 15 days. There was no relevant deviation of mean PD-Q score or pain severity in comparison with the whole study population. The measures were in the range of typical results for pain questionnaires (e.g. VAS).

Conclusion: This validation has shown that the PD-Q is reliable and can be used for follow-up. Further investigations will be necessary to determine the clinical relevance of changes in PD-Q score.
TOPICAL HIGH-CONCENTRATION MENTHOL - REPRODUCIBILITY OF A HUMAN SURROGATE PAIN MODEL

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Introduction: The reproducibility of human pain models is a prerequisite for proof-of-concept trials which use pharmacological treatments.

Objectives: The aim of this study was to investigate the reproducibility of the topical high-concentration menthol pain model in human volunteers. Recent studies have shown that in this model cold and mechanical hyperalgesia can be studied.

Methods: In 10 healthy volunteers high-concentration (40%) menthol was applied to both ventral forearms twice daily, four hours apart, in a randomised order. The identical procedure was repeated 1 week later. Before and after application selected quantitative sensory testing parameters (QST) were assessed in the testing area using the standardized protocol of the German Research Network on Neuropathic Pain (DFNS). T-test was used to investigate differences before and after menthol application and the agreement between the two application days. Correlation analysis was performed by using Pearson’s product-moment correlation. P values < 0.05 were regarded as statistical significant.

Results: The application of 40% menthol led to a significantly reduced cold pain (CPT) and increased mechanical pain sensitivity (MPS), indicating cold and mechanical pin-prick hyperalgesia (p< 0.001 resp.). Correlation analysis revealed high correlation coefficients (r=0.96/0.89 (CPT); 0.93/0.87 (MPS)) and no significant differences (t-test; p= 0.21-0.74).

Conclusions: The menthol pain model is highly reproducible within the period of 1 week and therefore suitable for the investigation of menthol-evoked sensory symptoms and signs (cold hyperalgesia; mechanical pin-prick hyperalgesia), e.g. with pharmacological interventions.
NEW INSIGHTS INTO DISEASE-SPECIFIC PATTERNS OF NEUROPATHIC PAIN SYMPTOMS USING THE PAINDETECT-QUESTIONNAIRE (PD-Q) WITH A SIMPLE STANDARDIZATION PROCEDURE

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Background and objective: The PD-Q was originally developed for the screening of neuropathic components in patients with chronic pain. Nowadays it is widely used for documentation of pain in wilder range of indications. Since 2006, data >522,000 assessments have been collected in a project register.

A standardization allowing the comparison of patterns of neuropathic components in serval diseases causing pain has been developed.

Methods: Items of PD-Q are normalised by mean of all patients at their first visit, whereby each indication is considered with the same weight. Only indications for which N>1000 cases are considered in this standardization.

Within this PD-Q-disease standardization, a horizontal line, showing no deviation from the initial value, represents an "average patient".

Results: Patterns of neuropathic pain components for frequent pain conditions using PD-Q disease-standardization (disease-specific means per items of patients from the register) are shown in the figure.

Conclusion: The standardization allows comparison of neuropathic components in different pain diseases. Results of the cluster analysis (profiles/patterns) fit with physicians’ experience. In conclusion, the application of PD-Q together with this simple standardization allows one to compare populations between studies, as well as within studies, in a simple way.
A NETWORK META-ANALYSIS OF FOUR IN-HOUSE, RANDOMIZED, ACTIVE-CONTROL CLINICAL TRIALS IN PAINFUL DIABETIC NEUROPATHY

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Aim: To analyse the pooled data of four randomized double blind active comparison trials evaluating the efficacy and safety of lamotrigine, duloxetine, pregabalin and low dose naltrexone (LDN) compared against amitriptyline in patients of painful diabetic neuropathy (PDN). All 4 studies were conducted at the same center following similar protocol.

Methods: Amitriptyline, lamotrigine, pregabalin, duloxetine and LDN were administered to PDN patients with optional dose up-titration fortnightly for 6 weeks in randomized, double-blind, crossover trials conducted between 2005-2012. A network meta-analysis was conducted to compare the efficacy and safety using changes in the patient’s global impression of change by VAS and the occurrence of adverse events using open-source software developed by Canadian Agency for Drugs and Technologies in health for indirect treatment comparisons.

Results: Amitriptyline lamotrigine, pregabalin, duloxetine and LDN demonstrated similar efficacy in pain relief. In all trials, amitriptyline showed a higher probability of developing adverse events and the odds for developing an adverse event (95% C.I.) was 8.08 (3.18-20.54), 4.91 (1.94-20.54), 3.14 (1.42-6.94) and 6.25 (1.96 - 19.93) against lamotrigine, pregabalin, duloxetine and LDN respectively. However the odds for developing an adverse event with other 4 drugs were not significantly different.

Conclusions: In the present network meta-analysis, all the four drugs demonstrated equi-analgesic efficacy in neuropathic pain relief. Amitriptyline showed a relatively higher odds of developing adverse events when compared to other drugs. In addition to efficacy and safety, the overall cost of treatment must be considered in the long term management of chronic pain.
THE IMPACT OF SATISFACTION/DISSATISFACTION WITH CURRENT MEDICATIONS ON THE QUALITY OF LIFE OF PATIENTS WITH NEUROPATHIC PAIN

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Background and aims: Neuropathic pain (NP) can be a chronic disease that is difficult to manage and has a negative impact on health-related quality of life (HRQoL). We investigated the hypothesis that patient satisfaction with current NP medications is associated with improved HRQoL.

Methods: Data were drawn from the 2012 Adelphi NP Disease Specific Programme, a cross-sectional study involving 413 primary care physicians and specialists across France, Germany, Italy, Spain and the UK. Patients with NP (excluding diabetic peripheral neuropathy) were asked to complete a questionnaire to assess disease severity, concomitant conditions, satisfaction with current medications and HRQoL, measured using the EuroQol 5-Dimensions questionnaire (EQ-5D). Doubly robust regression analysis was used to assess the relationship between treatment satisfaction and HRQoL, while controlling for the confounding factors of age, body mass index, gender, pain severity and number of prescribed drugs.

Results: Of 1775 patients who completed a questionnaire, 1372 were satisfied (a little, very or extremely) and 403 were dissatisfied (a little, very or extremely) with their current NP medications. Satisfied and dissatisfied patient groups had similar mean ages (55.7 versus 55.0 years, respectively) and a similar gender split (47% versus 48% male, respectively). Dissatisfied patients had a significantly (p< 0.05) greater mean number of concomitant conditions (2.1) compared with satisfied patients (1.7) and were significantly more likely to have clinical depression (26% versus 16%, respectively; p< 0.001). Treatment satisfaction had a significantly positive association with HRQoL (p< 0.001).

Conclusions: In patients with NP, satisfaction with current medications is significantly positively associated with HRQoL.
ROLE OF PREEMPTIVE ORAL PREGABALIN IN REDUCING ACUTE NEUROPATHIC PAIN IN POST MASTECTOMY PATIENTS

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Preoperative gabapentinoids have a role in reducing intensity of postoperative pain and thereby have a significant role in preventing chronic postsurgical pain. This study of oral preoperative pregabalin shows a reduction of pain after breast surgery.

Background and aim: Post mastectomy pain syndrome occurs after axillary node dissection caused by the nerve injury. Severe intensity of pain may lead to chronic pain. This study evaluated the role of preoperative oral pregabalin 150 mg in preventing acute postmastectomy pain and onset of neuropathic pain following surgery.

Methods: Eighty women undergoing elective mastectomy/ breast conservation procedure with concomitant axillary node dissection under GA, were administered pregabalin one hour before surgery. Preoperatively patients were explained about the use of numerical rating scale (0-10) for pain assessment and neuropathic pain questionnaire ‘painDETECT’. Pain scores (NRS 0-10) were assessed at 2, 4, 8, 12, 24 hours in postoperative recovery. All patients responded painDETECT questionnaire on 10th P.O. day in English, Hindi or Marathi.

Results: Postoperatively mean pain scores (NRS: 0-10) at rest were 1.56, 1.32, 0.81, 0.7 and 0.45 and on movement 2.42, 2.2, 1.55, 1.35 and 0.91 at 2, 4, 6, 12 and 24 hours respectively. 12 out of 80 patients had a score on “PainDETECT” of > or equal to 19/35 which implies a 15% incidence of neuropathic pain.

Conclusion: Preoperative oral pregabalin led to reduction in the postoperative pain and the incidence of neuropathic pain.
PAIN IN SPINAL CORD INJURY

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Pain is one of the more disturbing sequelae of spinal cord injury, often interfering with the basic activities, effective rehabilitation, and quality of life of the patient. Pain after spinal cord injury can occur in parts of the body where there is normal sensation (feeling) as well as areas that have little or no feeling.

The purpose of this study was to investigate the development of neuropathic pain in spinal cord injury, and its relationship between the injury etiology, duration, vertebral level, the Functional Independence Measure (FIM) and the presence of spasticity.

In this study, 79 spinal cord patients who attended to our outpatient clinic between 2005-2008 years were followed. The pain was questioned in these spinal cord injured patient's.

29 of the patients stated that they have pain and the character of the pain was neuropathic in 62% of the patients. The development of neuropathic pain was not associated with the spinal cord injury etiology, duration, vertebral level and the presence of spasticity. Also there were no relationship was observed between the neuropathic pain and FIM.

For this reason studies are needed to examine the relationship between the development of neuropathic pain after spinal cord injury.
IN INVOLVEMENT OF THE MIDDLE SHORT GYRUS OF THE INSULA IN PAIN PROCESSING: STUDY BY ELECTRIC STIMULATION INTRACEREBRAL OF THE EPILEPTIC PATIENTS

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Objectives: The data of this study suggests the involvement of the upper middle short gyrus in the procedures of pain.

Materials and methods: We included 25 patients suffering from severe drug refractory partial epilepsy were investigated by stereo-electroencephalography (SEEG). At least one electrode was used to explore the insular cortex using an oblique approach (trans-frontal or trans-parietal) and who had a normal insular region. 313 stimulations were performed in 27 insula. 83 responses induced by insular electrical stimulation (ES), eight (9.6%) were reported by five patients as painful sensations. The stereotactic approach allows us to identify the stimulation sites within the insular cortex in terms of its gyri and sulci. The stimulation sites were anatomically localized via image fusion between pre-implantation 3D MRI and post-implantation 3D CT scans revealing the electrode contacts.

Results: We could obtain pain responses to direct ES of a small anatomical region. We discuss our results in terms of anatomical localization in gyral substructures of the insular cortex. The findings suggest that middle short gyrus is involved in the processing of pain producing stimuli. These sensations were evoked ipsilaterally or bilaterally to stimulation.

The data provide evidence of a highly restricted area of the insular cortex inducing painful sensation in response to direct ES. The region of the head is more posterior than the trunk and limbs.

Conclusion: The results of this study are the first to described painful responses in evoked by electrical stimulation of the human insular cortex classified in terms of its gyri and sulci.
A PHASE IIA STUDY OF BMS-954561 IN POST-HERPETIC NEURALGIA

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Background: BMS-954561 has exhibited efficacy in pre-clinical models of neuropathic pain. A Phase IIa study was conducted to evaluate BMS-954561 in patients with post-herpetic neuralgia (PHN).

Methods: This was a randomized, double-blind, placebo-controlled, two-period crossover study of BMS-954561 in patients with PHN. Patients received 4 weeks of treatment in each period followed by a weeklong placebo washout. Group 1: BMS-954561 40 or 80 mg (40 mg TID in Week 1, followed by 80 mg TID thereafter)/placebo; Group 2: BMS-954561 150 or 300 mg (150 mg TID in Week 1, followed by 300 mg TID thereafter)/placebo. The primary outcome was the within-patient difference between the fourth week of each period in average weekly pain score (11-point scale).

Results: 100 patients were randomized and 86 (n = 42 Group 1; n = 44 Group 2) were evaluable. BMS-954561 at up to 300 mg/day was associated with discontinuation rates similar to placebo, and with few serious adverse events. No statistically significant improvement in pain scores from placebo was observed in either BMS-954561 dose group (Group 1 = 0.194, p = 0.193; Group 2 = 0.350, p = 0.060). A similar lack of effect was observed in the analysis of the brief pain inventory-short form and the patient global impression of change.

Conclusions: BMS-954561 was not effective in this study for the treatment of PHN. The absence of an active control limits the interpretation of efficacy in the study. BMS-954561 was well tolerated with an acceptable safety profile.
CENTRAL ROLE OF THE DELTA OPIOID RECEPTOR IN ACUTE HEAT NOCICEPTION AND DIABETIC HEAT HYPERALGESIA

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Background and aims: µ-opioid receptor (MOR) agonists are standard analgesics in moderate to severe pain conditions. Their use is limited by side effects. Two other opioid receptors, δ (DOR) and κ (KOR) receptors have been cloned, and interactions between these receptors have been described. The aim of this study was a systematic analysis of these interactions in pain models using receptor knock-out mice.

Methods: Male MOR, DOR and KOR knock-out and congenic wild-type mice were tested for acute heat nociception and diabetic heat hyperalgesia in naïve and STZ-treated (200 mg/kg) animals, respectively. Reference agonists morphine (MOR), SNC-80 (DOR) and U50488H (KOR) or vehicle were administered i.p..

Results: In wild-type mice, 60-100% antinociceptive and antihyperalgesic efficacy was reached with similar (morphine: 10, 10) or different (SNC80: no effect at 10, 3.16; U50488: 21.5, 3.16) doses (mg/kg), respectively. While agonists showed complete lack of efficacy in the corresponding knock-out strains, efficacy was also reduced in the heterologous knock-out strains. Only morphine showed full efficacy in heterologous knock-out strains.

Conclusions: A clear interaction could be demonstrated between different combinations, being most prominent for DOR-KOR in heat hyperalgesia. Although the DOR agonist was ineffective in heat nociception, an interaction with KOR could be demonstrated by reduced KOR agonist efficacy in DOR knock-out mice. Thus, DOR seems to play a central role in both heat nociception and heat hyperalgesia. Furthermore, while morphine equipotently inhibited acute and chronic pain, all other agonists showed a preference towards heat hyperalgesia.
SOMATOSENSORY ABNORMALITIES IN ATYPICAL ODONTALGIA PATIENTS

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Objectives: The aim of the pilot study was to evaluate the somatosensory abnormalities of patients with atypical odontalgia (AO) through comprehensive quantitative sensory testing (QST).

Methods: Seventeen patients with AO were recruited from Bauru School of Dentistry, University of São Paulo, Brazil. Definitive Diagnosis was made by clinical and image examination ruling out any hypothesis of dental abnormality. Subjects with systemic conditions such as diabetes, uncontrolled hypertension, leprosy and/or neurological and psychological disorders were excluded. QST included mechanical detection threshold (MDT), mechanical pain threshold (PPT), dynamic mechanical allodynia with cotton swab (DMA1) and with toothbrush (DMA2), heat pain thermal detection (HPD), cold pain thermal detection (CPD), temporal summation (WUR) and controlled pain modulation (CPM). Stimuli were applied in the painful site and compared to the contralateral one. Results were analyzed with Mann-Whitney u test, with significance level of 5%.

Results: It was evaluated 11 women and 6 men, with mean age of 56.76 years (SD 14.06) and mean pain duration of 3.5 years (range 1-10 years). When the affected side was compared to the pain-free side significant higher values were found for DMA1 (p=0.002), DMA2 (p=0.004), CPD (p=0.04) and HPD (p=0.04).

Conclusion: In this pilot study, significant changes in intraoral somatosensory function were observed in AO patients with dynamical mechanical allodynia, cold and heat pain thermal detection tests. These results may reflect peripheral and central sensitization of trigeminal pathways. Further studies with larger sample are necessary to confirm the actual findings.
IMPAIRED QUANTITATIVE SUPERFICIAL, PROPRIOCEPTIVE AND CORTICAL SENSATION OF THE HANDS IN FEMALES WITH RHEUMATOID ARTHRITIS

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Background and aims: We aimed to assess the sensory and motor dysfunction in the hands of the patients with rheumatoid arthritis (RA) and relationship with disease activity parameters and radiographic damage.

Methods: Eighty-six females (46 patients with RA and 40 healthy controls) were included to the study. Disease activity assessed by DAS28 were recorded in patients. Hand x-rays and functional disability were assessed by Larsen index and HAQ respectively. Comprehensive hand evaluation including quantitative sensory thresholds of Semmes-Weinstein (SW) monofilament for superficial sensation, joint position sense for proprioceptive sensation, 2-point discrimination (2-PD) for cortical sensation, and pinchmetry for pinch strength were performed to all subjects.

Results: Forty-six female RA patients with a mean age of 56.4 years and 40 controls were recruited to the study. Joint position sense of both D2, 2-PD of the left D3, and tip-to-tip pinch strength of both hands were better in control group (p< 0.05). SW monofilament thresholds and classification of SW monofilaments (green=1.65-2.83, blue=3.22-3.61, purple=3.84-4.31, red=4.56-6.65) of the both hands were better in patients with RA. The hand deformities were positively correlated with disease activity and disability, while pinch strength, proprioception were correlated negatively with hand deformities.

Conclusion: We indicated not only the impaired proprioceptive and cortical sensation but also decreased superficial sensory threshold in rheumatoid hands which were related with structural damage. The latter may indicate the neuropathic component of hand pain in patients with RA. Future studies are needed to confirm the effect of neuropathic pain therapy in patients with this chronic condition.
MODULATION OF PRIMARY AFFERENT SPROUTING VIA GSK-3β ACTIVATION AS AN INTERVENTION FOR NEURONAL REMODELING ASSOCIATED WITH SPINAL CORD INJURY PAIN

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Introduction: Neuropathic pain is common in spinal cord injury (SCI) patients. Maladaptive primary afferent sprouting is gaining recognition for its role in creating dysesthesias. A potential mechanism of sensory sprouting involves GSK-3β.

Objectives: The purpose of this study was to administer a GSK-3β activator, LY-294002 (LY), to SCI animals in an effort to modulate sprouting of sensory neurons.

Methods: Long-Evans rats underwent SCI through intramedullary injection of quisqualic acid or saline (sham) followed by daily intrathecal delivery of LY or vehicle (veh) to the level of injury. After 3 and 6 days, DRGs ipsilateral to the site of injection were cultured and analyzed for sprouting and neurite length.

Results: SCI rats showed a significant (p< 0.05) increase in the percent of sprouting neurons and length of sprouts (41.9%, 160.7 ± 15.5 µm) versus sham animals (34.9%, 90.4 ± 13.0 µm). Treatment with LY for 3 days significantly decreased (p< 0.05) both the percent of neurons sprouting (20.5%) and the length of neurites (66.9 ± 7.5 µm) compared to SCI animals. Treatment with LY for 6 days also significantly (p< 0.0001) decreased the percent of neurons sprouting from 48.0% to 19.6% as well as decreasing neurite length (p< 0.05) from 294.2 ± 20.6 µm following SCI to 101.6 ± 20.8 µm.

Conclusions: We show that SCI results in enhanced DRG neuronal sprouting and that intrathecal delivery of a GSK-3β activator reduced DRG neuronal sprouting to non-injured levels, suggesting that GSK-3β may be a potential therapeutic target to prevent maladaptive sprouting associated with SCI pain.
A CLINICALLY RELEVANT RODENT MODEL OF HIV ANTIRETROVIRAL DRUG (INDINAVIR) INDUCED PERIPHERAL SENSORY NEUROPATHY

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Introduction: HIV-associated sensory neuropathy (HIV-SN) is the most frequent neurological manifestation of HIV disease. Recent studies show that HIV-SN prevalence does not decline in well-resourced settings where the neurotoxic antiretroviral drugs of the NRTI class are no longer being used, suggesting other factors may contribute to HIV-SN (1). Evidence suggests that exposure to indinavir, a protease inhibitor commonly used as a part of the antiretroviral therapy, may be a causal factor for the persisting high prevalence of HIV-SN (2).

Objectives: Therefore, our aim was to validate a rodent model of indinavir induced neuropathy for the purposes of mechanism and target identification and preclinical evaluation of novel agents.

Methods: We investigated simple reflex pain behaviours as well as complex ethologically relevant thigmotaxis behaviour following indinavir treatment (50mg/kg; 2 i.v. injections at 4 days apart) in adult rats. We also examined the neuropathological responses in the skin and dorsal root ganglion.

Results: Indinavir-treated rats developed hindpaw mechanical and cold, but not heat, hypersensitivity. Initial studies revealed increased thigmotaxis behaviour, reduced hindpaw intra-epidermal nerve fibers, and an infiltration of macrophage in the L4 DRG following indinavir treatment.

Conclusions: We have initially characterized a clinically relevant rodent model of indinavir induced painful peripheral neuropathy. Further experiments are needed to characterize the thigmotaxis behavioural and histological changes.

The study is part of the Europain Collaboration, which has received support from the IMI Joint Undertaking (No. 115007).


THE IMPACT OF ADHERENCE TO CURRENT MEDICATIONS ON QUALITY OF LIFE AND PAIN INTENSITY IN PATIENTS WITH PERIPHERAL NEUROPATHIC PAIN

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Background and aims: Many neuropathic pain (NP) treatments are associated with side effects and complex regimens that can negatively affect adherence to treatment. Poor patient adherence contributes to the difficult management of NP and the negative impact NP has on health-related quality of life (HRQoL). We investigated the hypothesis that patient adherence to current NP medications is associated with HRQoL and average pain.

Methods: Data were drawn from the 2012 Adelphi NP Disease Specific Programme, a cross-sectional study involving 413 primary care physicians and specialists across France, Germany, Italy, Spain and the UK. Patients with peripheral NP (excluding diabetic peripheral neuropathy) were asked to complete a questionnaire to assess disease severity, concomitant conditions, satisfaction with current medications and HRQoL, measured using the EuroQol 5-Dimensions questionnaire. Pain was measured using the Brief Pain Inventory current average severity score. Doubly robust regression analysis was used to assess the relationship between treatment adherence and HRQoL, as well as treatment adherence and current pain, while controlling for confounding factors.

Results: Of 951 patients who completed a questionnaire, 568 (60%) were fully adherent to their current NP medications (physician-reported 'full adherence' in agreement with patient-reported 'I follow instructions fully and give my medicine every chance to work'). Adherence had significantly positive associations with HRQoL (p< 0.009) and lower average pain severity (p< 0.017). Both results were independent of time since diagnosis, age, gender and each other.

Conclusions: In patients with NP, increased adherence to current medications is significantly positively associated with HRQoL and lower current pain.
Activation of CNS descending pain inhibitory circuits causes norepinephrine release in the spinal cord dorsal horn. Regulatory mechanisms involved in this descending pain inhibition are of both scientific and clinical importance. Here we introduce TIP39 modulation of the descending norepinephrine system. Glutamatergic fibers expressing parathyroid hormone receptor 2 (PTH2R) and its endogenous ligand TIP39 are abundant throughout the brainstem, including the noradrenergic locus coeruleus (LC). To test the hypothesis that TIP39 transmission regulates nociception during chronic pain we examined the effects of partial sciatic nerve ligation (PNL) in PTH2R and TIP39 knockout mice. Both knockout lines developed less tactile allodynia and thermal hypersensitivity, and returned to baseline sensory thresholds much faster, than controls. Injection of a lentivirus encoding a PTH2R antagonist into the LC area produced similar effects on pain, but the virus was not effective when injected into the amygdaloid nucleus. Injection of noradrenergic blockers yohimbine (intraperitoneal) and atipamezole (intrathecal) increased the tactile and thermal sensitivity of the injured knockout and viral antagonist injected mice, bringing their sensitivity to that of injured controls. PTH2R expressing fibers in LC coexpressed markers for glutamatergic neurons and closely apposed the noradrenergic neurons. These results suggest that TIP39 release modulates sensory thresholds. Very likely TIP39's role is to inhibit the release of analgesic amounts of norepinephrine into the spinal cord during chronic pain. In this way the neuropeptide may help maintain a certain level of central sensitization during a prolonged time period. A possible biological role of TIP39 is to enhance guarding behavior.
INTENSITY-DEPENDENT INHIBITION OF WDR NEURONAL WIND-UP BY PERIPHERAL NERVE STIMULATION IN AN ANIMAL MODEL OF NEUROPATHIC PAIN

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Introduction: Analgesia by peripheral nerve stimulation (PNS) relies on activation of large fibers with sufficient input to the spinal cord to inhibit pain signaling. Thus, it is assumed that therapy-intensity is an important parameter for success.

Objectives: We sought to understand the intensity-dependent mechanisms of PNS analgesia by means of in vivo extra-cellular single unit recordings, where we examined the stimulus-response functions of PNS on inhibiting spinal wide-dynamic-range (WDR) neuronal activities in rats after L5 spinal nerve injury.

Methods: To mimic therapeutic PNS, a pair of bi-polar platinum hook electrodes were used to stimulate the tibial nerve (TN). To calibrate TN stimulation, we measured the L4 compound action potential and determined the intensity that resulted in the first detectable Aα/β waveform (Ab0), followed by the peak Aα/β waveform without Aδ stimulation (Ab1).

Results: TN stimulation (50 Hz, 0.2 ms, biphasic, 5 min, Ab0, Ab1, 2Ab1 intensities) induced an intensity-dependent inhibition of WDR neuronal response to windup-inducing electrical stimulation (16 pulses, 0.5 Hz, supra-C threshold) applied to the skin receptive field. The total C-fiber components to windup stimulation were decreased to 93.7±3.8% (Ab0, n=28, p>0.05), 69.4±5.8% (Ab1, n=34, p< 0.01), and 65.0±6.3% (2Ab1, n=30, p< 0.01) of the pre-TN stimulation value at 0-15 min post-TN stimulation. However, the total C-fiber components of WDR neuronal responses to graded electrical stimuli (0.1-10 mA, 2 ms) were not significantly different from the pre-TN stimulation baseline levels.

Conclusions: We demonstrated that the modulation of spinal WDR windup by PNS stimulation is dependent on stimulus intensity.
EFFICACY OF SUCROSE FOR ANALGESIA IN MINOR PROCEDURES VERSUS INFLAMMATORY PAIN IN NEONATES AND YOUNG RATS

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The exposure of neonates to a repeated painful stimulus can develop long-term changes in the spinal cord that result in alterations in responses to a further painful stimulus. There is evidence that sucrose can alleviate pain in children and newborn animals. The aim of this study was to investigate the effect of sucrose intake on hyper-nociception caused by chronic treatment with PGE₂ in rodents. We also observed the long term effect of multiple injections of PGE₂ on skin sensitivity.

Inflammatory pain was induced by daily subcutaneous intra-plantar administrations of 100 ng PGE₂ over 14 days in P14-day-old rats (n=6) and in P28 young rats (n=6). Intra-plantar injection of phosphate buffered saline (PBS) was performed as a control in both groups. Animals from each experimental group were orally treated with tap water or 25% sucrose solution ad libitum as the only source of liquids. Mechanical thresholds were determined by measuring withdrawal responses to von Frey filaments before (baseline) and 3 hours after daily intra-plantar treatments. Adult animals were re-injected at P67 and P72. The investigator was blind to the injection protocol.

The present findings demonstrated that sucrose decreased hyper-nociception in control groups (P14 and P28 rats), however sucrose was not effective in the PGE₂ injected group. Re-injected adult animals treated with PGE₂ displayed no differences in baseline threshold or 3 hours after intra-plantar injection compared with control.

Sucrose provides pain relieve for minor events (needle stick) in rats P14 and P28 rats but not for inflammatory pain induced by PGE₂.
INVESTIGATIONS OF CENTRAL PAIN AMPLIFICATION IN THE HUMAN DORSAL HORN: AN FMRI STUDY

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Background and aims: Central pain amplification in neuropathic pain can be evaluated by assessment of the temporal summation of pain (TSSP). TSSP occurs when repetitive pain stimuli are presented at a high frequency (> 0.33Hz) and results from a C-fiber evoked enhancement (or “windup”) of the dorsal horn neurons. With advancement in spinal cord functional MRI, we can non-invasively probe the central mechanisms of the pain response in humans. The aim of this study is to characterize the fMRI BOLD responses in the healthy human spinal cord that correspond to TSSP.

Methods: Healthy female adults underwent training to confirm TSSP. Functional MRI studies of the spinal cord and brainstem were conducted at 3T. A thermode was placed on the right thenar eminence and TSSP (0.33 Hz) and non-TSSP (0.17 Hz) heat pain paradigms were employed. Data were analyzed by means of the general linear model.

Results: In the TSSP condition, all participants rated the pain intensity from the last stimulus (50/100) more painful than the first (35/100). No significant differences between first (40/100) and last (43/100) ratings were evident in the low frequency condition. Preliminary fMRI results indicate that the BOLD response to the TSSP condition was more robust and was sustained beyond the duration of the stimulation block, compared to the non-TSSP condition.

Conclusions: Results from this study confirm the TSSP and indicate the presence of wind-up in the dorsal horn. Future studies will assess the contribution of central sensitization to the pain phenotype in patients with neuropathic pain.
LOWER EXTREMITY SPLINTING TO MANAGE NEUROPATHIC PAIN AND SLEEP DISTURBANCES IN PEOPLE LIVING WITH HIV/AIDS

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Background: Distal symmetrical peripheral neuropathy (DSPN) and sleep disturbances are among the most common complications reported in people living with the human immunodeficiency virus infection and acquired immunodeficiency syndrome (PLWHA). DSPN-pain is predominantly managed by using systemic agents with little evidence supporting their analgesic efficacy. Animal models suggest the presence of analgesic effects associated with immobilization.

Aim: The purpose of this study is to evaluate the effect of nighttime lower extremity splinting application on DSPN-related pain and sleep disturbances compared to a parallel splint liner application.

Methods: Forty-six PLWHA and DSPN were randomized to night time wearing of bilateral lower extremity splints or the liners only. Pain and sleep outcomes were measured at baseline, week three and six. The pain outcome was measured using the Neuropathic Pain Scale and the sleep outcome using the Pittsburgh Sleep Quality Index.

Results: Pain and sleep scores improved in both groups over time. The median percentage pain reduction at week six was 8% in the liner group and 34% in the splint group. The change in pain scores in the splint group was found to be significant over time, p< 0.0005. The contrast between the splint and liner groups was underpowered (26%) and was not found to be significant, p>0.05. Sleep scores improved 20% from baseline to the end of the study in both groups; all participants were classified as poor sleepers.

Conclusion: The six-week use of nighttime splints reduces DSPN-pain. Future studies are needed to validate effective non-pharmacological interventions for DSPN.
GENETIC FACTORS ARE INVOLVED IN THE NOCICEPTIVE BEHAVIOUR, MEDULLARY DORSAL HORN (MDH) CENTRAL SENSITISATION AND GLIAL MORPHOLOGICAL CHANGES OCCURRING IN MICE FOLLOWING TRIGEMINAL NERVE INJURY

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Background and aims: A genetic predisposition to trigeminal neuropathic pain has been suggested, but the mechanisms are unclear. This study aimed to test for differences between 2 genetically different mouse strains in nociceptive behaviour, glial changes, and central sensitisation in MDH following trigeminal nerve injury.

Methods: Facial mechanical withdrawal thresholds (MWTs) were determined bilaterally with von Frey filaments pre-operatively and post-operatively in adult A/J and C57BL/6 male mice following left infraorbital nerve transection (IONX) and in control mice. In some mice on day 5, the MDH was either removed and immunohistochemically treated to label astroglia (GFAP) and microglia (Iba1), or single MDH neurons were recorded and mechanical stimuli applied to test for evidence of central sensitisation (increases in receptive field size and responses to noxious stimuli and reduced activation threshold) in functionally identified nociceptive-specific neurons in IONX and control mice (N=6/group).

Results: MWTs were significantly decreased bilaterally in both strains, with a peak at day 5 after IONX (p < 0.05, ANOVA) but the decrease was significantly longer in A/J mice, lasting up to day 49. At day 5, there were also significant strain differences in the increases that occurred ipsilaterally and/or contralaterally in MDH of both GFAP and Iba1 labelling post-IONX, and in the occurrence of MDH central sensitisation.

Conclusions: These findings suggest that genetic factors may be involved in the predisposition to nociceptive behaviour, glial changes and central sensitisation in MDH, and contribute to the individual variation in the manifestation of neuropathic pain following trigeminal nerve injury.
Background and aims: It has been hypothesised that central nervous system changes underpin the pain experienced by patients with carpal tunnel syndrome (CTS). This is largely inferred from studies using quantitative sensory testing. The aim of this study was to investigate changes in facilitatory and inhibitory central pain processing in patients with CTS by studying the efficacy of conditioned pain modulation (CPM, inhibitory) and pain hypersensitivity following hypertonic saline injection (facilitatory).

Methods: Twenty-five patients with mild to moderate CTS and 15 healthy participants volunteered to participate. CPM was determined by investigating the effect of cold water immersion of the contralateral foot (conditioning stimulus) on pressure pain threshold (PPT) (test stimulus) over the thenar and hypothenar eminence bilaterally, as well as over the tibialis anterior muscle. To determine the presence of facilitatory mechanisms, the duration, area and intensity of pain induced by injecting hypertonic saline (1ml, 5% saline) into the ipsilateral upper trapezius muscle were measured.

Results: There was an increase of 45kPa in PPT averaged across all sites during cold water immersion, but there was no difference between groups (p>0.46). This suggests no CPM deficit in patients with CTS. Saline injection into the upper trapezius resulted in a larger perceived area of pain (p=0.044). Consistent with this indication of facilitatory mechanisms, the numerical pain ratings during PPT testing were consistently higher in patients with CTS (p< 0.009).

Conclusions: Pain experienced in CTS is likely due to pain facilitatory mechanisms, rather than a lack of endogenous inhibition.
THE EFFECTS OF TWO DIFFERENT ORAL DOSES OF DOXEPIN ON POSTOPERATIVE PAIN IN LOWER LIMB ORTHOPEDIC SURGERY PATIENTS COMPARED TO A CONTROL GROUP

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Background: Postoperative pain is a usual phenomenon that can cause some problems such as increased blood pressure, increased oxygen use, an increased risk of myocardial infarction (MI). Like any other medical procedure, orthopedic surgery is associated with pain and complications. Recently, doxepin has been used as a tricyclic antidepressant (TCA) to decrease pain. Therefore, we designed this study to evaluate the effects of doxepin on the postoperative pain following lower limb orthopedic surgery.

Methods: This randomized double blind placebo controlled trial was performed on 102 lower limb orthopedic patients in three groups of 34. The first two group received 50 and 100 mg doxepin while the last group received placebo. Patients aged between 18 and 65 years. Data was collected by a standard questionnaire and analyzed by analysis of variance (ANOVA) and chi-square test in SPSS.

Findings: No significant differences were observed between the three groups in terms of pain intensity before or after surgery (P = 0.58). The only significant difference was seen between the first (50 mg doxepin) and placebo groups during the first 24 hours after surgery (P = 0.25). The groups were not different in demographic characteristics (age, gender, or education), either. In addition, received doses of morphine, and the frequency of nausea, vomiting, itchiness, and other side effects were not significantly different between groups.

Conclusion: According to our results, doxepin was not effective on pain reduction after lower limb orthopedic surgery. We therefore hypothesize doxepin to have more effects on chronic pains than acute pains.
POSSIBLE INVOLVEMENT OF BDNF IN NEUROMA FORMATION AFTER TRIGEMINAL NERVE INJURY

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Background and aims: Peripheral nerve injury can induce neuroma formation, followed by intractable dysesthesia. However, the mechanisms underlying neuroma formation remain unclear. Neurotrophic factors are known to promote regeneration of damaged nerves. This study investigated whether BDNF participates in neuroma formation after nerve injury.

Methods: The inferior alveolar nerves (IAN) of male Sprague-Dawley rats, 6-10 weeks of age, were severed under general anesthesia. One µg of antibody against BDNF (anti-BDNF group) or normal saline (vehicle group) was administered to the lesion immediately after severing the IAN. Withdrawal thresholds following mechanical touch to the mental area were measured for two weeks after surgery. BDNF mRNA expression in the trigeminal ganglion was measured by real-time quantitative PCR after the surgery.

Results: Resection of the IAN caused a significant increase in BDNF mRNA expression in the trigeminal nerve ganglion 24 hours post-injury (one-way ANOVA, p< 0.05). Withdrawal threshold increased just after surgery and decreased to pre-surgical levels within two weeks. Anti-BDNF administration inhibited this decrease compared with the vehicle group.

Conclusions: BDNF mRNA expression was increased in the ganglion early after peripheral nerve injury, and administration of neutralizing BDNF antibodies inhibited recovery of sensation. Combined with our recent morphological observation that these BDNF antibodies also inhibit neuroma formation, these results suggest that BDNF may affect recovery and/or neuroma formation in damaged peripheral nerves.

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ANTIDEPRESSANT DRUGS RELIEVE NEUROPATHIC ALLODYnia BY A PERIPHERAL BETA2 ADRENOCEPTOR MEDIATED ANTI-TNFALPHA MECHANISM


Background and aims: Antidepressant drugs (ADS) are clinically recommended as first-line drugs for chronic treatment of neuropathic pain. The noradrenaline recruited by ADs has been proposed to act through beta2-adrenoceptor (beta2-AR) to lead to their antiallodynic action. However, the precise downstream mechanism by which ADs relieve neuropathic pain remains poorly understood.

Methods: To mimic human neuropathy resulting from a trauma of peripheral nerves, we used chronic sciatic nerve cuffing in mice. To study AD mechanism, we combined behavioral pharmacology, KO mice, lesional approaches with guanethidine, immunohistochemistry, molecular approaches (qPCR, Western blot), and ex vivo calcium imaging.

Results: The cuff insertion induced a sprouting of noradrenergic fibers in lumbar dorsal root ganglia (DRG). We then investigated the possible source of endogenous noradrenaline which is used by ADs to alleviate neuropathic allodynia. We demonstrated with localized noradrenergic lesions that the antiallodynic effect of the nortriptyline is mediated through the peripheral nervous system. More particularly, ADs-recruited noradrenaline acts within DRG, on beta2-ARs which are expressed by non neuronal cells. These findings reveal a novel anatomomolecular substrate for the antiallodynic action of antidepressants. Our results also showed that both nortriptyline and the stimulation of beta2-ARs suppresses the overexpression of TNF-alpha induced by the neuropathy.

Conclusions: Our findings suggest that ADs act by a peripheral beta2-AR-dependent mechanism targeting TNF-alpha-containing non neuronal cells, which prevents maintenance of neuropathic pain and may offer novel opportunities for management of painful neuropathies.

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PHOSPHODIESTERASES AS TARGETS FOR THE TREATMENT OF NEUROPATHIC PAIN


Background and aims: Tricyclic antidepressants are a first-line treatment against neuropathic pain. Noradrenaline recruited by their action on reuptake transporters has been proposed to act through Beta2-adrenoceptors (Beta2-ARs) to lead to the antiallodynic effect. However, the precise downstream mechanism remains to be identified. Beta2-AR stimulation increases cyclic adenosine-monophosphate production, which is controlled by a molecular complex containing phosphodiesterases (PDE). More particularly, Beta2-ARs are coupled with type 4 phosphodiesterases (PDE4). At first, PDE4 inhibitors have been described for their antidepressant activity. Recently, studies have shown therapeutic potential of PDE4 inhibitors in different models of chronic pain. The present study was done to identify the action of different PDE inhibitors on neuropathic allodynia.

Methods: Neuropathy was induced by implanting a unilateral cuff around the main branch of the sciatic nerve. It induces mechanical allodynia, measured with von Frey's hairs. Behavioral pharmacology was used to test chronic treatment with various PDE inhibitors. KO for opioids receptors were used to assess opioid system contribution. Western blot and ex vivo calcium imaging allowed studying the mechanism.

Results: Pharmacological screening showed that PDE4 inhibitors (rolipram…) - but not PDE1, 2 or 3 inhibitors - had an antiallodynic effect after chronic treatment. This mechanism involves the recruitment of delta opioids receptors. The PDE4 inhibition also leads to a decrease in neuropathy-induced TNFalpha production, correlated to the measured antiallodynic effect.

Conclusion: Our results show the therapeutic potential of PDE4 inhibitors in the treatment of neuropathic pain.

This work was supported by CNRS (contract UPR3212) and Université de Strasbourg.
TESTOSTERONE REPLACEMENT THERAPY FOR NEUROPATHIC PAIN: CASE STUDY

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Introduction: Case report demonstrating reduced neuropathic pain with Testosterone replacement therapy.

Objectives: Clinical description with pre-post-outcome measures.

Methods: A 34-yr-old University residence manager was seen initially on 25-02-2009 with a chief complaint of burning thoracic pain following complicated Harrington rods scoliosis surgery 05-98 (titanium alloy reaction requiring surgical removal 11-99; rib fractures). Her symptoms were worse with cold, movement, exertion, prolonged walking, sitting, standing. Better with oxycocet and lorazepam SL. On extensive supplements including omega 3, multivitamins, oregano oil, digestive enzymes, probiotics. Height: 5'9 ¾'' Weight: 148lbs. BP 101/72 mmHg. HR 76 bpm. Marked brushed allodynia with wind-up phenomenon, dermatographism. 18/18 tePts. Neck flexion 44, extension 40, lateralflexion L30 R30, rotation L70 R60. Back flexion 80, extension 10, lateralflexion L10 R10. Started on pregabalin 75mg qhs. With titration upward, she could then tolerate intradermal OnabotulinumtoxinA injections. This provided temporary relief every 3 months with nociceptive muscular pain decreasing from 6-7/10 to 1-3/10 and neuropathic pain from 6/10 to 0/10. Did not tolerate trials of tramadol, SNRIs, TCAs, tizanidine, nabilone. Sativex SL spray was helpful. Bloodwork 06-2011 revealed low free/total testosterone (< 0.5 pmol/L) suggestive of opioid-cannabinoid-induced hypogonadism. She was started on topical testosterone 5mg qAM.

Results: She returned in 09-2011 with marked improvement in pain and energy. She was able to stop further Botox injections, reduce analgesic use and improve exercise rehabilitation and function.

Pre-treatment: NRS (Numerical Rating Scale) pain 7/10 (3-10/10); SF-McGill (Short-Form McGill Pain Questionnaire) 25/45; NRS fatigue 7/10; FIQ (Fibromyalgia Impact Questionnaire) 69/100.

Post-treatment: NRS pain 0-4/10; SF-McGill 6/45; fatigue 1/10; FIQ 28.5/100.

Conclusions: Topical testosterone replacement may help in neuropathic pain.
Changes in regional gray matter volume in patients with chronic neuropathic pain

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Background and aims: To compare changes in gray matter volume in patients with chronic neuropathic pain with changes in patients with acute neuropathic pain and in healthy controls.

Methods: We compared 15 patients with chronic postherpetic neuralgia (pain > 3 month evolution, VAS > 4) with 19 patients with acute pain due to herpes zoster (pain < 3 month, VAS > 4) and 17 controls (no pain). The samples were composed of men and women aged between 65 and 85 years old. Evaluation included clinical history, neurological and psychological examination (STAI, BDI, McGill, SF-36 questionnaires). Patients with neurological or psychiatric diseases were excluded. All participants underwent a 3-Tesla Magnetic Resonance whole brain analysis to map gray matter volume.

T1 3D MPRAGE images were processed using FS (FreeSurfer) software. Statistical analysis was performed comparing the 3 groups using a general linear model (QDEC).

Results: Gray matter volume analysis showed a decrease in volume in different regions of the frontal and parietal lobes in chronic pain patients when compared with acute pain patients. These changes were more significant both in volume and region extension when compared with the control group.

Increased volume was observed in the anterior insula and dorsolateral prefrontal cortex in acute pain patients compared to controls, findings that may suggest neuroplasticity compensatory processes.

Conclusions: Our findings suggest that chronic pain can behave as a neurodegenerative process, both from a functional and an anatomical perspective. This would imply that a maladaptive neuroplasticity can contribute to maintaining the sensation of pain, even in the absence of stimulus.
EPHRINB-EPHB RECEPTOR SIGNALING CONTRIBUTES TO BONE CANCER PAIN THROUGH GLIAL CELL TOLL-LIKE RECEPTOR 4-PROINFLAMMATORY CYTOKINES PATHWAY

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Background and aims: EphrinB-EphB receptor signaling is critical to the development of bone cancer pain. This study investigated activation of ephrinB-EphB signaling, glial cells and Toll-like receptor 4 (TLR4) and their interactions in the spinal cord in bone cancer pain animals.

Methods: Bone cancer pain was produced by tibia bone cavity tumor cell implantation (TCI) in adult rats. Changes of the molecules were detected by Western blot, ELISA and immunochemistry. Spontaneous and evoked pain in rats with bone cancer was measured and evaluated.

Results: TCI increases expression of ephrinB2, EphB1 and TLR4 proteins, activates astrocytes and microglial cells, and increases activity of TNF-α IL-1β, in addition to causes bone cancer pain. Spinal administration of an EphB1 receptor inhibitor EphB2-Fc (5 µg, 3 doses on 3 consecutive days) suppressed TCI-induced increased expression of TLR4, activation of astrocytes and microglial cells, TNF-α and IL-1β, as well as bone cancer pain. Meanwhile, TCI-induced activation of astrocyte and microglial cells and painful syndromes were inhibited by TLR4-targeting siRNA (i.t., 2 µg, 3 doses). In naïve rats, a single dose of an EphB receptor activating reagent ephrinB2-Fc (2 µg) induced a rapid increase in expression of TLR4, activation of astrocytes and microglial cells, and increased TNF-α and IL-1β. All of these alterations induced by ephrinB2-Fc were prevented or suppressed in rats that received repetitive pretreatment of TLR4-targeting siRNA.

Conclusions: EphrinB-EphB receptor signaling may contribute to bone cancer pain through regulating RLR4 activation and increasing activity of proinflammatory cytokines.

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"ENTHESES/ENTHESALGIA": ARE CLBP/FAILED BACK SURGERY SYNDROME DUE TO NEUROPATHIC MICRONEUROMAS ON DAMAGED A-DELTA AND C FIBRE RECEPTORS ASSOCIATED WITH TRPV1 ACTIVATION?

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Introduction: Primary care of Chronic Low Back Pain (CLBP) is difficult. Underlying pathophysiological mechanisms are unclear. Entheses are now defined as separate organs.

Objectives: Bogduk hypothesis that damaged peripheral receptors (electron microscopy) appear as ‘microneuromas’, thus musculoskeletal pain maybe neuropathic, underlying Dorsal Ramus Syndrome. Identified TRPV1 Receptors (burning sensation) in chronic neuropathic pain respond to subcutaneous dextrose 5% (D5%) injections (neuroprolotherapy).

Method: Since 2002, McKay treated over 3000 patients with CLBS/DRS by ‘peppering’ LA/methylprednisolone and recently D5% injections to the altered entheses and associated dorsal rami with immediate pain relief and restoration of back function. In 2004 a group of 33 single blinded patients in 3 groups (needle + LA + Steroid, Needle +LA or Needle only), have been followed-up over 9 years, and the results compiled and analysed. Neuroprolotherapy and ‘Sweet Caudal’ D5% epidural have been added and extra benefits observed.

Results: 9 year follow up data are detailed, 80% demonstrating 85% or better improvement in Quality of Life (N=1 methods) Some patients have pain free periods of 1 to 7 years before further injections. The added benefits of neuroprolotherapy and/or ‘Sweet Caudal Epidurals’ in CLBP/FBSS patients since 2012 are similarly detailed.

Conclusions: CLBP/FBSS is the main ‘bugbear’ for Primary Care Physicians. Few simple management options are readily available. Entheses with receptor damage become neuropathic. This simple injections protocol creates options for Primary Care doctors; the skills needed can be quickly taught, thus available for doctors who work in isolated or rural areas or away from specialist help.
DOES CURRENT PERCEPTION THRESHOLD TEST DIFFERENTIATE CATEGORIES OF MECHANICAL NECK DISORDER?

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Background and aims: Neurological signs exist under sub-classifications of neck pain. Current Perception Threshold (CPT) testing can help detect changes in sensory detection thresholds that may reflect neurological changes. The purpose of this study was to determine whether current perception can differentiate between subtypes of Mechanical Neck Disorders (MND).

Methods: Patients with MND (n=106) classified into three groups (MND-I=60, MND-II=29, and MND-III=17 patients) based on the Quebec Task Force on Spinal Disorders classification. A rapid protocol of CPT testing was performed at three frequencies (5, 250, 2000 Hz) using 3-dermatomal locations (in hand) in a cross-sectional study design. A one-way ANOVA with post-hoc comparison was done to compare the mean CPT score between the groups. A binary logistic regression model predicted probability of higher CPT in MND-III, where the CPT score counted as the risk factor for having neurological signs or symptoms. A Receiver Operating Characteristic (ROC) curve was created from predicted probability by binary covariate.

Results: Large CPT differences between MND groups indicated by the effect size (MND-I vs. MND-II, d=1.11 and MND-II vs. MND-III, d=2.06). CPT testing was able to distinguish between MND-II and MND-III by a cut-off (threshold value>11 in MND-III). The discriminative model determined an optimal cut-off of CPT test with correct classification being 64.7% sensitivity and 96.6% specificity. The area under the ROC curve (AUC) was 0.84 (95% CI=0.72-0.96, P<.001).

Conclusions: CPT-testing demonstrated moderate-higher sensitivity and specificity for classification of MND categories. AUC indicates a moderate discriminatory power of CPT in MND.
HIV-ASSOCIATED SENSORY NEUROPATHY AMONG A HOSPITAL-BASED COHORT IN NIGERIA: RESULT OF A PILOT STUDY

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Introduction: Sensory neuropathy is a significant cause of morbidity among patients living with the human immunodeficiency virus (HIV). However, there is a paucity of information on HIV-associated sensory neuropathy in Nigeria in spite of a large disease burden.

Objective: The objective of this pilot study was to determine the prevalence of HIV-associated sensory neuropathy among the cohort of patients attending our highly-active antiretroviral therapy (HAART) clinic.

Method: Consecutively consenting adults diagnosed with HIV and who were on follow up in our services were recruited. Information was obtained in a standardized manner using an interviewer administered questionnaire. Diagnosis of peripheral neuropathy was using the well-validated Brief Peripheral Neuropathy Screen which has been used in similar studies.

Results: In this pilot study, there were 49 respondents with a mean age of 39.6±10.4 years. Majority of the patients were females (77.6%). Peripheral neuropathy was found in 40.8% of the respondents. There was no significant relationship between presence of peripheral neuropathy and the age, gender, duration of HIV infection and CD4 cell count of the patients.

Conclusion: HIV-associated sensory neuropathy is present in a significant number of patients in this hospital-based cohort. However, we were unable to establish a relationship with such variables like age, duration of HIV and CD4 cell count possibly as a result of small sample size.
SPINAL AND SUPRASPINAL PROCESSING OF PAINFUL AND NON-PAINFUL THERMAL STIMULI - A FMRI STUDY

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The study investigated spinal and supraspinal activation patterns during painful and non-painful heat prior and after sensitization with capsaicin using functional spinal magnetic resonance imaging (spinal fMRI). Sixteen healthy subjects (6 female, 10 male, mean age 26.3 ± 2.3 years) were examined during spinal fMRI (3T, 10 sagittal slices, slice thickness 2mm, single-shot FSE, TR 9000 ms, TE 38 ms, FOV 288 x 144 x 20 mm, matrix 192 x 96, voxel size 1.5 x 1.5 x 2 mm) with noxious and innocuous heat stimuli applied to dermatome C6. Afterwards, capsaicin was applied topically in the test area and scanning was repeated using the same thermal stimuli which were then perceived as (more) painful.

Increased activity was observed in the spinal ipsi- and contralateral ventral and dorsal horn during noxious heat and heat hyperalgesia/allodynia. During heat hyperalgesia/allodynia, decreased activity was observed in the dorsolateral pontine tegmentum, periaqueductal grey and cuneiform nucleus compared to noxious heat as well as increased activity in bilateral ruber nuclei, rostral ventromedial medulla oblongata (RVM) and contralateral subnucleus reticularis dorsalis (SRD) compared to innocuous heat. Activations in RVM and SRD correlated to activations in the ipsilateral dorsal horn of the spinal cord.

Results show increased spinal activity and changes in activation of supraspinal centers involved in pain modulation after sensitization with capsaicin. The successful demonstration of activation in the spinal cord and supraspinal centers using a new method for spinal fMRI opens up perspectives for further in vivo studies on pain processing in humans.
INVASIVE NEUROMODULATION OF THE MOTOR CORTEX IN CHRONIC NEUROPATHIC PAIN

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Background and aims: Invasive treatment options are performed in specialized centers as an extended part of interdisciplinary or multimodal treatment settings. Patient selection and indication are investigated if long term treatment including psychological evaluation is ineffective. The authors present their single-center experience with motor cortex stimulation (MCS) including an up-to-date review of the literature.

Methods: The patient sample includes 55 patients (21 female, 34 male, life age: 28-73) with MCS for post-stroke pain (PSP, n=17), trigeminal neuropathic pain (TNP, n=23), brachial plexus injury (BPI, n=12) and other peripheral neuropathic pain syndromes (PNP, n=3). Placement of the leads was performed using intraoperative neuronavigation, neurophysiology and test stimulation. A standardized test trial for 8-16 days was conducted in all cases.

Results: In all patients accurate placement of the leads parallel to the precentral gyrus and central sulcus was achieved. Test trial was successful in 16/23 patients with TNP, 6/17 with PSP, 8/12 with BPL and 1/3 with PNP. Placebo and double-blinded stimulation during the test trial identified 9 false-positive responders and therefore leads were explanted. Complications were documented consisting of local wound infections (2) or epileptic seizures (2).

Conclusions: In patients with refractory neuropathic pain syndromes like TNP, BPI or phantom limb pain MCS should be offered as an individual treatment option. Operative risks and procedure related complications are very low in experienced neurosurgical pain centres. Placebo or double-blinded testing is mandatory. To achieve a level of evidence and clinical recommendation a prospective, randomized controlled multi-center study is urgently needed.
Background and aims: The level of survival in patients with malignant tumors of skull base depends on possible combined treatment modalities - chemo-radiotherapy and surgery. Therefore, early establishment of correct diagnosis is the main task the clinician should provide for the patient.

Case: Diagnosis of malignant skull based tumor takes 10 months for a 40 year aged woman. Complaints of pain started from the right ear region, gradually becoming more severe at night, additionally she had a feeling of fullness, stiffness, as well as, painful and limited mouth opening and deviation to contralateral side, without signs of bone damage on OPG. Patient undergo conservative treatment of ear, temporomandibular joint and multiple endodontic procedures. Signs of neuropathic pain, dysesthesia, numbness of lingual nerve, inferior alveolar nerve, mechanical hyperalgesia, allodynia leads to an appropriate diagnostic test, as single photon emission computed tomography of skull. Results were conclusive for secondary involvement of bone.

Conclusions: Retrospectively the incomplete basis of primary orofacial pain diagnosis, failed to respond to treatment, worsens of clinical picture leads to late reconsideration of diagnosis. Detailed neurological examination as diagnostic tools for identification of different kinds in cancer - related neuropathic pain seems to help early detection of paraneoplastic stage of malignancy.
SCRAMBLER THERAPY: AN INNOVATIVE NEUROMODULATION APPROACH TO COMPLEX REGIONAL PAIN SYNDROME

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Complex Regional Pain Syndrome has long been considered to be a pain disorder that is difficult to treat and is often treatment resistant. Aggressive therapies including Ketamine coma and Ketamine infusion have been applied with varying results and significant risk. The use of TENS has been an ineffective treatment for this neuropathic pain disorder. Scrambler Therapy (ST) was developed over 10 years ago in Italy and was recently introduced to the United States. Briefly, ST is an electrical neuromodulation treatment that passes a non-pain code (strings of action potential algorithms) through the skin to the dorsal horn and ultimately scrambles the pain signal thereby resulting in a subjective experience of significantly less pain or no pain. In essence, the ST device is an artificial neuron that changes the information within the nervous system that is projected to the brain. Additionally, chronic pain syndrome components such as: mood disorder, reduced activity, mobility limitations, impaired sleep, impaired interpersonal relations and lack of joy are also significantly improved. In this study 40 patients diagnosed with CRPS were evaluated and treated with ST. Each patient received ten consecutive ST sessions and pain ratings were recorded prior to and following each treatment. The Brief Pain Inventory and VAS was administered prior to ST and at six month follow-up. Statistical analysis (paired t-tests) demonstrated significant positive treatment effect on pain level session to session. Additionally, statistical analysis also indicated a significant improvement in pain level and BPI scores at six month follow-up.
A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, SINGLE ASCENDING DOSE OF XEN2174 PK/PD STUDY ADMINISTERED INTRATHECALLY IN HEALTHY SUBJECTS


Introduction: Xen2174 is a synthetic 13-amino acid peptide that specifically binds to the norepinephrine transporter, which results in inhibition of norepinephrine uptake. Xen2174 showed a strong anti-nociceptive and anti-allodynic effect in preclinical studies when administered intrathecally. However, at higher dose levels, Xen2174 was epileptogenic. Based on CSF PK studies in dogs and previous clinical studies, 2.5 mg Xen2174 IT was expected to lead to safe CSF concentrations.

Objectives: The current study was performed to assess the pharmacodynamics and the CSF pharmacokinetics of Xen2174 in healthy subjects.

Methods: This was a randomized, blinded, placebo-controlled study in healthy subjects. The study was divided in three treatment arms (0.5 mg, 1.0 mg and 2.5 mg Xen2174 intrathecal). Each group consisted of 8 subjects on active treatment and 2 or 3 subjects on placebo. CSF was sampled for 32h using an intrathecal catheter. Pharmacodynamic assessments were performed using a battery of nociceptive tasks.

Results: In total 25 subjects were administered Xen2174. CSF PK analysis showed a higher AUC of Xen2174 in the highest dose group than allowed by the predefined safety margin based on preclinical data. Pressure pain measurements showed an increased tolerability in the highest dose group. The most common adverse event was post lumbar puncture headache, with no increased incidence in the treatment groups.

Conclusions: In this study, Xen2174 was well tolerated. An increase in pain tolerance was seen in the 2.5 mg group. However, at this dose level, CSF concentrations exceeded the pre-specified exposure limit based on preclinical safety margin.
ANALGESIC EFFICACY AND PROBLEM SOLVING IN LONG TERM SPINAL CORD STIMULATION FOR COMPLEX, NEUROPATHIC PAIN SYNDROMES

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Introduction: Spinal Cord Stimulation (SCS) is an effective treatment of complex pain syndromes. Impulse generator (IPG) changes will be required, sometimes frequently.

Objectives: We describe twelve cases presenting with severe pain due to loss of function of long term SCS. Replacement with a rechargeable IPG was considered an attractive option in all patients.

Methods: Seven women and five men, mean age 57 (range 26-73) years, with long term SCS (mean 14.5, range 2-32 years), epidural electrodes (Medtronic, Resume, Symmix, Quad) and up to nine previous IPG-changes due to severe, neuropathic pain were scheduled for elective re-implantation of rechargeable IPG:s (Boston Scientific Precision Plus, Medtronic Restore Ultra).

Results: Individualized technical and surgical approaches were applied, as all SCS electrodes, extensions, connectors, remote controls and IPG:s, even from the same manufacturer, are not always compatible. All patients perceived stimulation in appropriate areas after implantation. Analgesic efficacy was equivalent or improved, compared to previous stimulation.

Conclusions: Successful long term spinal cord stimulation requires good compliance, easy access to the implanting centre for prompt problem solving as well as monitoring of efficacy and side effects.

Analgesic efficacy of long term SCS was maintained in 12 complex pain patients after change to rechargeable IPG:s using possible connectors and extensions.

Consideration of compatibility of components of different kinds and from different manufacturers may allow for improvement in long term analgesic efficacy of SCS and flexible choice of new IPG:s. Newer SCS components should preferably be compatible with previous equipment.
ANTINOCICEPTIVE EFFECTS OF THE FLAVONOID RUTIN IN TRAUMATIC INJURY OF THE SCIATIC NERVE IN MICE

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Background and aims: In a previous study, we described the rutin antinociceptive effect, in glutamate induced-liking in mice (Lapa et al., Basic Clin. Pharmacol Toxicol., 104:306-315, 2009). This study aim to extend our previous findings, investigating rutin effects in the model of traumatic injury of the sciatic nerve.

Methods: Male Swiss mice (n=8) were distributed in three groups: Sham-operated; Operated and Rutin. Animals were anesthetized (ketamin, 80 mg/kg and xylazin, 10 mg/kg; i.p.) and the right sciatic nerve (Operated and rutin group) was exposed and crushed for 30s. Rutin (30 mg/kg, i.p.) treatment began on 4th day and was given once a day, for 2 weeks. Mechanical hypersensitivity (MH) was measured using Von Frey filaments and the motor functional recovery degree, by grip-force test (GFT) and sciatic functional index (SFI), 30 min after treatment. On the 14th postoperative day the levels of serotonin (5-HT) and 5-hydroxyindoleacetic acid (5-HIAA) were measured in the brainstem by HPLC.

Results: The rutin time-course effect was performed on the 7th day and showed a significant antinociception 3h after treatment that remained up to 6h. On day 12 and 14, rutin reduced 68 ± 6 % and 63 ± 9 % the hypersensitivity. GFT and SFI showed an improvement of motor functional recovery when compared with operated group. The brainstem levels of 5-HT and 5-HIAA increased with rutin treatment (p< 0.01).

Conclusions: The results suggest that rutin reduced MH after sciatic nerve crush and improves motor function, an effect that might involve the serotonergic system.
PERIPHERAL SUBCUTANEOUS NERVE STIMULATION IN NEUROPATHIC PAIN - 7 YEARS OF EXPERIENCE

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Introduction: PNFS represents a promising addition to the array of neuromodulation techniques.

Patients and methods: Following convincing results, introduced by Barolat, we performed a so called “Periphere Nerve Field Stimulation” pilot study from May 2005 to February 2006 in 31 patients and due to the encouraged results in further 45 patients mainly with neuropathic pain, until January 2010.

Indication was a well described exactly localized area of pain, partly connected to Allodynia. After the exclusion of radicular pain, this method was considered the first step of invasive pain therapy on the neurosurgical pain scale, which was independent of medication. The patients suffered from different pain syndromes. Leads were implanted, allowing access to the outer border of the pain area.

After a one-week trial-phase, the trial electrodes were removed and replaced by permanent subcutaneous electrodes in the same location, which were later connected to a programmable generator.

The patients were assessed, both post-operatively and after a follow-up period of 6, 12, and 3 years, using the VAS scale, Drugs-reduction and improvement in QoL.

Eleven out of 31 patients in the pilot study (33%) and 33 out of 48 (68.8%) in the following time, received an implantation of a complete system.

Conclusion: PNFS is a simple, promising method, and can be considered as the first step of invasive pain therapy for treating well described pain emission. The operation technique is very simple and of low risk, however, long term results have to be awaited.
PRIMARRE ERYTROMELALGIA: HEREDITARY NEUROPATHIC PAIN

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Introduction: Primary Erythromelalgia is a rare condition characterized by intense symmetrical and bilateral neuropathic pain in response to small noxious stimuli, affecting primarily the lower extremities. This is the first human pain syndrome to be understood at a molecular level, having been linked to gain-of-function mutations of a particular sodium channel (Na\textsubscript{v}1.7).

Objectives: We report a case of Primary Erythromelalgia and the positive response to activity modification in daily living.

Methods: Case presentation.

Results: A 46 year old woman presented with a history of episodic bilateral burning pain in her lower limbs since birth. Small noxious stimuli applied to her legs would cause an intense burning sensation that lasted several hours accompanied by warmth and erythema. Sexual intercourse with inadequate lubrication and passing hard stools would also cause intense pain.

A thorough history and physical exam, along with diagnostic testing excluded secondary causes. Genetic testing confirmed the diagnosis: a gain-of-function missense mutation within SCN9A, the sodium channel gene that encodes Na\textsubscript{v}1.7, was found in this patient.

Modification of daily activity, avoiding noxious stimuli, using lactulose to avoid constipation and using lidocaine and prilocaine gel in the genital area before intercourse, improved the patient's quality of life with no pain episodes during one year. Tramadol 50 mg pro re nata was never used by the patient.

Conclusions: Despite multiple treatment options, Erythromelalgia is a challenging disease to effectively manage. Daily activity modification proved to be efficient and, above all, the patient was satisfied with the results.
PERCUTANEOUS OPERATIONS FOR TYPICAL TRIGEMINAL NEURALGIA. LONG-TERM RESULTS IN THE ADULTS ARE POOR THAN IN THE ELDERS

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Introduction: The results of percutaneous operations for typical trigeminal neuralgia (TTN) reported in the Literature series are referred to the general population.

Objectives: The aim of our study is to verify if long-term results in adults are different than in the elders.

Method: We followed-up prospectively:

- Group I: 198 adult patients (age 31-65 years);
- Group II: 368 elderly patients (age 66-94 years).

From 1980 to 2011 all underwent one or more percutaneous operations on the gasserian ganglion/trigeminal root (phenol/glycerol injection, cryolysis, thermorhizotomy, balloon microcompression) as a first or only one surgical treatment. All were affected by TTN, not related to multiple sclerosis/tumor. The mean follow-up was 7.2 (Group I) and 6.3 (Group II) years.

At the final follow-up the patients were classified as:

- cured: patients pain-free without medication and without significant sensory deficits in their face;
- partially cured: patients pain-free with a low dosage of drugs and/or with significant sensory deficit (extended hypo- or anaesthesia, tolerated paresthesias);
- not cured: patients not pain-free, requiring high/poor-tolerated dosage of drugs, and/or suffering because of disabling dysesthasias.

Results:

Group I (Adults): cured: 55 (28%); partially cured: 64 (32%); not cured: 79 (40%).

Group II (Elders): cured: 222 (60%); partially cured: 58 (16%); not cured: 88 (24%).

Conclusions: Long-term results of percutaneous procedures for TTN in adult patients are significantly poor than in the elders. Therefore percutaneous procedures should be the first choice operation only in the elders. In adults microvascular decompression, giving significantly better results, should be preferred.
INTRAPERITONEAL ONLAY MESH AUGMENTATION OF THE ABDOMINAL WALL - A NEW PROMISING THERAPEUTIC OPTION FOR TREATMENT OF ANTERIOR CUTANEOUS NERVE ENTRAPMENT SYNDROME

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Introduction: Treatment of anterior cutaneous nerve entrapment syndrome (ACNES) remains elusive and controversial. We report an unique series of 17 patients with ACNES who underwent intraperitoneal onlay mesh (IPOM) repair as a structural augmentation of the painful area.

Methods: In 17 patients with ACNES (10 F/7M, age 20-60 years, mean 49 years), visceral and hernia pathology were excluded by clinical and radiological examinations. All patients had sharply localized pain at the lateral margin of rectus abdominis muscle and a positive “hover” and Carnett's sign. Injection therapy provided temporary relief in 53%. Since debilitating symptoms were persisting, an IPOM repair was considered. Laparoscopy excluded occult herniation and repair was identical as for a ventral abdominal wall hernia; a mesh (Dualmesh, Gore), fixed with a double ring of tacks (Protack, Covidien), was tightly applied over the trigger point with an overlap of ≥4 cm. Procedures and postoperative course were uneventful. All patients were interviewed by using a verbal rating score (VRS) 3-75 months after surgery (mean 32 months; 13>1 year).

Results: Twelve patients had VRS 1 (completely pain-free), three VRS 2 (very satisfied, occasionally some pain), and two VRS 3 (better but regularly experiencing pain).

Conclusions: IPOM repair seems to be a very promising option for treatment of selected patients suffering from ACNES. The probable explanation for gratifying effect of IPOM repair on ACNES is that mesh prevents pushing of neurovascular bundle against the rectus fibrous structures.
Background and aims: As per current evidence, the diagnosis of CRPS following stroke is based on clinical features (IASP Criteria). A negative bone scan does not rule out diagnosis. Pain reduction with sympathetic blockade was once considered diagnostic; however, not all patients with CRPS exhibit sympathetically mediated pain. The objective was to confirm the clinical diagnosis with Triple Phase Bone Scan versus Stellate Ganglion Block.

Methods: This study was conducted by Pain Medicine and Neurorehabilitation Unit of a tertiary care hospital. The sample included patients with first episode of stroke with clinical diagnosis of CRPS. Triple phase bone scan and diagnostic Stellate ganglion block was done in all subjects.

Results: 20 stroke subjects (M:F:12:8) with ischemic (14) and hemorrhagic (6) stroke, with post stroke duration ranging from 2 - 24 months (mean 9.6 months) were evaluated. Motor recovery on Brunnstrom’s staging for involved upper extremity was Stage I (10), II (1), III (3), IV (3) and V (3 subjects) and 12/20 (60%) had shoulder subluxation. Triple Phase bone scan was positive in 13/20 (65%) subjects and remaining 7 (35%) subjects with negative bone scan revealed increased radiotracer uptake suggestive of inflammatory changes in wrist and hand. Stellate ganglion block was positive and hence diagnostic in all 20 (100%) subjects.

Conclusion: Stellate ganglion block is more sensitive than Triple phase bone scan as a diagnostic modality for CRPS following stroke with good concordance with clinical criteria. Large case series is recommended to confirm our findings.
ANTINOCICEPTIVE PROPERTY OF ST36 ACUPOINT STIMULATION BY LOW-LEVEL LIGHT THERAPY (LLLT) IN MICE

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Background and aims: LLLT is a modality of low-level light therapy used as an alternative to needling for the past three decades. The ST36 (Zusanli) acupoint is used to treat inflammatory processes, pain and gastrointestinal disturbances. For this reason, the aim of the present study was to evaluate the antinociceptive effect of LLLT on ST36 acupoint using models of acute and chronic nociception.

Methods: Male Swiss mice were treated with LLLT on ST36 thirty minutes before intraplantar injection of capsaicin (CAPS, 5.2 nmol/paw), bradykinin (BK, 3 nmol/paw) and prostaglandin E2 (PGE2, 3 nmol/paw). The mechanical allodynia (von Frey) was performed on the partial sciatic nerve ligation (PSNL) method. The experiments were approved by the Ethics Committee for the use of Animals (CEUA-UFSC).

Results: Our results demonstrated that application of LLLT on ST36 inhibited the CAPS-, PGE2- and BK-induced nociception in 53, 32 and 69%, respectively. A single application of LLLT on ST36 inhibited the mechanical allodynia response induced by PSNL, with total reversion at 0.5 h after application. Long-term treatment of animals LLLT on the same acupoint, once a day, also reduced the PSNL-induced mechanical allodynia response during 8 days of treatment.

Conclusion: Collectively, these results demonstrated that ST36 photonic stimulus with LLLT showed antinociceptive effect in acute and chronic models of nociception. These findings suggest that LLLT may constitute an interesting therapeutic alternative to control acute and chronic pain. However, further studies must be carried out to identify the mechanism of action of LLLT.
STUDY OF DIFFERENT PATIENT CONTROLLED ANALGESIA MODELS USING HYBRID SIMULATION TECHNIQUE

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Introduction: Patient Controlled Analgesia (PCA) is not used for the administration of ketamine and lidocaine because their pharmacokinetic profile precludes their safe use with this mode of delivery. If new algorithms of PCA operation could be proven safe, that would open new ways of neuropathic pain treatment. One of such possible algorithms might be based on the infusion on-demand.

Objectives and methods: PCA, infusion PCA (iPCA), and Target Controlled Infusion (TCI) drug delivery protocols were studied using Quantized State System model for the creation of hybrid aggregate models. We simulated fentanyl analgesia utilizing three-compartment pharmacokinetic/pharmacodynamic model. These three analgesia modes were compared by calculating of how close drug concentration in the effect compartment matches target of minimum effective analgesic concentration (MEAC) target using median performance error (MDPE) and median absolute performance error (MDAPE). Recovery from the drug overdose was estimated by the length of the context sensitive effect compartment 50% decrement time in the effect compartment, when analgesic delivery stops.

Results and conclusion: MEAC was approximated best when using target controlled infusion. iPCA was superior to the traditional PCA in terms of safety (had faster concentration 50% decrement time in the effect compartment) and ability to maintain concentration at MEAC as expressed by MDPE, MDAPE.
PRELIMINARY DEVELOPMENT OF A PEDIATRIC NEUROPATHIC PAIN INSTRUMENT: SYSTEMATIC REVIEW OF CURRENT INSTRUMENTS

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Background & aims: Chronic pain is a common problem affecting at least 25% of children and adolescents. It is not known what proportion of the pediatric population experiences neuropathic pain. Frequent causes of neuropathic pain in adults differ from those in pediatrics, yet data from adult trials is extrapolated to treat children. The lack of a pediatric neuropathic pain instrument makes it difficult to understand the burden of neuropathic pain in this population. We aim to develop an instrument to identify pediatric neuropathic pain.

Methods: The first phase involved a systematic review for current instruments to generate items for inclusion in an iterative Delphi survey (phase 2). Embase, Medline and PsychINFO databases were searched and relevant citations were screened by two independent investigators. The Delphi survey is currently under ethics review and iterative surveys are planned to refine the items in the tool using international experts in pediatric neuropathic pain.

Results: Our search yielded 1062 citations, of which 40 were retrieved in full-text. 5 screening and 2 measurement instruments have been validated for neuropathic pain in adults. Items comprising clinical history, clinical signs and symptoms were then generated.

Conclusions: Results of our literature search and Delphi survey will be presented. The next step will involve validation of this tool in children and adolescents with chronic pain. A pediatric neuropathic screening tool will help to ensure more timely detection of neuropathic pain and treatment to optimize health outcomes in this population, and serve as a useful measure for future research.
THE EFFECT OF OUTPATIENT KETAMINE INFUSIONS ON PATIENT HEMODYNAMICS, SEDATION AND LEVEL OF PAIN

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Background and aims: Ketamine, an NMDA receptor antagonist, helps reduce severe debilitating neuropathic pain in patients unresponsive to conventional treatment. Potential ketamine side effects include sedation, hallucinations, hypertension and tachycardia. Our goals are to examine the effect of outpatient ketamine infusions on patients' hemodynamics, sedation and pain level.

Methods: With IRB approval, we reviewed the vital signs, sedation assessment and pain scores of patients who underwent 3 consecutive days of 4 hour ketamine infusions with doses ranging from 0.2 mg/kg/hr to 1.2 mg/kg/hr for 4 hours. Vital signs and Sedation-Agitation Scale (SAS) scores were obtained at baseline and every 15 minutes during the infusion, and 1 hour after infusion completion. Pre and post infusion pain scores were obtained. We used chi square to evaluate the association between dose and the largest increase and decrease in the above variables and paired t-test to examine changes in pain scores.

Results: 46 patients received 138 ketamine infusions with ketamine dose ranging from 36 mg to 510 mg. Most patients had < 20% changes in hemodynamic, respiratory and oxygenation.. The lowest SAS score for all patients during the infusions was 3 (sedated, easily arousable). Pain scores decreased significantly from Day 1 pre-infusion to Day 3 post-infusion (p< 0.0001).

Conclusions: Outpatient ketamine infusions decrease pain level in sub anesthetic doses and may be safely administered to outpatients for management of severe chronic neuropathic pain.
DIAGNOSIS AND MANAGEMENT OF NEUROPATHIC PAIN IN A LARGE TURKISH FAMILY WITH FABRY DISEASE

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Fabry Disease is an X-linked lysosomal storage disease caused by the mutations in the GLA gene coding for the lysosomal enzyme α-galactosidase in chromosome Xq22.1. The disease leads to accumulation of neutral sphingolipids in tissues. Neuropathic pain episodes are common both in childhood and adulthood.

Our goal here was to investigate the diagnostic yield of Lanss and DN4 scores which have not been used in Fabry Disease until now, to our knowledge. We also kept track of these tests in the follow up.

The study group consisted of 18 patients aged 8-51 years. The diagnosis of Fabry was confirmed by mutation analysis (C.508 G> A on exon 3). Three of the patients were men, the rest were women and girls. Neurological examination, electroneuromyography, Lanss and DN4 tests, Beck Depression and Life Quality scores of each patient were performed. The tests were repeated after enzyme replacement and pregabalin therapies every month.

The most frequent symptom was itching. Seventeen of 18 patients had pain. All had scores higher than 12 in Lanss and more than 4 “yes” answers in DN4 which pointed out to a diagnosis of neuropathic pain. During six months of treatment, Lanss and DN4 scores regressed showing a direct correlation with the improvement in Beck Depression and Quality of Life scores.

Neuropathic pain diagnosis in Fabry patients deserves more attention especially in adolescents and women. Lanss and DN4 scores seem to be reliable both in diagnosis and monitoring of neuropathic pain in Fabry patients.
TRIGEMINAL NERVE INJURY INDUCES NEUROPLASTIC CHANGES IN FACE MOTOR CORTEX (FACE-MI) AS WELL AS FACIAL MECHANICAL HYPERSENSITIVITY IN RATS

D. Yao, B.J. Sessle, Denmark, Canada

Background and aims: Trigeminal nerve injury can induce motor disturbances as well as pain but whether neuroplastic changes in face-MI are involved is unclear. This study aimed to determine if infraorbital nerve transection (IONX) in rats induces face-MI neuroplasticity as well as nociceptive behaviour.

Methods: Right IONX was performed in adult male Sprague-Dawley rats (n=14) under general anaesthesia; sham-operated rats (n=11) served as controls. Facial mechanical sensitivity of awake animals was tested pre-operatively and post-operatively (1-28 days) with von Frey filaments. Intracortical microstimulation (ICMS; 35-ms train, 12 x 0.2 ms pulses, 333 Hz, 60 µA) was also applied at histologically verified sites in a series of microelectrode penetrations at post-operative days 7, 14 and 28 in anaesthetized animals to map the anterior digastric (AD) and genioglossus (GG) motor representations in face-MI by analyzing ICMS-evoked movements and AD and GG electromyographic activity.

Results: IONX induced a significant (2-way repeated-measures ANOVA, P< 0.001) decrease in mechanical threshold from days 4-28 (right face) and days 6-28 (left face). IONX also induced a significant bilateral decrease in the total number of AD plus GG sites in face-MI at post-operative days 14 and 28 compared to sham (t-test, P< 0.001) and in the number of AD sites at post-operative day 28 (P< 0.001).

Conclusions: These findings indicate that trigeminal nerve injury induces neuroplastic alterations in tongue and jaw motor representations in face-MI that are associated with facial mechanical allodynia and that may contribute to sensorimotor changes following trigeminal nerve injury. Supported by CIHR grant MOP-4918.
KETAMINE IV - FOR CRPS, TN/TMD AND OTHER NEUROPATHIC PAIN IN THE OUTPATIENT PAIN CLINIC

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Ketamine is an antagonist of NMDA-type glutamate receptors. These play a strong promoting role in pain transmission in the CNS, in sub-anesthetic doses. We have also used this for migraines and headaches. This is an ongoing study of this agent for treating pain flareups in neuropathic pain syndromes.

389 patients (264=f, 125=m) were treated for pain flareups. All had alldynia or hyperalgesia in the region of pain. Conditions treated were: CRPS (#126), cervical/ lumbar radiculopathy (#145), TN (#34), TMD (#47), pelvic/vulvodynia pain (n#37). 285 patients had co-existent headache/migraine.

Antecubital IV was placed; pulse oximetry was used in each patient. Patients rated their pain on a 0-10 VAS both before treatment and at 15 minute intervals during and after treatment. 0.25-0.30 mg ketamine/kg was administered by IV infusion over 120-180 minutes. Another 0.30 mg/kg, or slightly higher dose, was administered again over the same time. Up to 4 infusions were given, not necessarily on the same day. We defined success as greater than 50% reduction in pain VAS from baseline.

Beginning pain (8.45/10) reduced to 2.03/10 after treatment (p< .001, 2 tailed t test). Average ketamine infusion time was 149 min; average ketamine dose was 185.6mg. Time of pain reduction was 4.4 days (range = 26 hrs to 233 hrs). Side effects were transient spaciness/calm (#344). Allodynia was gone in all but 2 patients. 12 patients reported less than 25% reduction.

Our data supports NMDA-type glutamate receptor over-activity in neuropathic pain disorders, with great efficacy, safety and tolerability for the treatment.
INFLUENCE OF BETA2 AGONISTS ON THE INCIDENCE OF POST-THORACOTOMY NEUROPATHIC PAIN

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Introduction: Thoracic surgery is known to induce persistent neuropathic pain which can be severe. This neuropathic pain is a neurological syndrome which is associated with distress and a reduction of the quality of life. First line treatments recommended for neuropathic pains are drugs like tricyclic antidepressants. It has been demonstrated in a murine model of neuropathic pain that beta2 adrenoceptors are essential for the antiallodynic action of antidepressant drugs.

Objective: To investigate whether beta2 agonist treatments could influence the incidence of post-thoracotomy neuropathic pain.

Methods: We designed an epidemiological study, collecting data on clinical preoperative characteristics of patients who underwent thoracotomy. In this retrospective survey, realized over a period of 6 months in the service of Thoracic Surgery from the Hopitaux Universitaires of Strasbourg (HUS) in France, 189 patients operated by lateral thoracotomy were questioned and examined. Neuropathic characteristics of pain in the scar area were evaluated using the DN4 questionnaire, calibrated Von Frey filaments and a brush.

Results: A persisting thoracic pain with neuropathic characteristics at the operated side was reported in 30% patients. We found that beta2 agonist treatments were associated with a five-time decreased incidence of neuropathic pain, as assessed by odd-ratio analysis.

Conclusions: Chronic beta2 agonist treatments have a significant influence on post-thoracotomy neuropathic pain. These results suggest the interest of initiating clinical studies to assess the therapeutic effect of beta2 agonists on neuropathic pain.
MITOCHONDRIAL MODULATORS AND PERSISTENT OROFACIAL PAIN IN MICE

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Introduction: Mitochondrial modulators, like methylene blue (MB) - which increases mitochondrial complexes I-IV activity; Cobalt (CoCl₂) - that increases reactive oxygen species production in cells and inhibits many of the mitochondria-related functions, and Vitamin C (VitC) - a redox modulator, were used.

Objectives: The aim of this study was to investigate the effects of long term administration of mitochondrial modulators on persistent orofacial pain in mice.

Methods: Thirty-two Swiss male mice were divided into 4 groups that received daily intraperitoneal injections with MB - 5 mg/kg for 14 days; CoCl₂ - 12.5 mg/kg, VitC - 500 mg/kg, saline 0.2 ml/ mice for 21 days. At the end of the treatment, mice received 20 µL of 5% formalin into the whisker pad. The intensity of the pain was assessed by counting the time mice spent rubbing the injected area and the antinociceptive activity was expressed as the percentage of inhibition: [(control mean - treated mean)x100]/control mean. The results were analyzed using one-way ANOVA and unpaired Student's t-test.

Results: Two weeks after MB administration there was a significant analgesic effect on both phases of the trigeminal pain induced by formalin (p=0.034, p=0.019), with an antinociceptive effect of 42.32%. After 3 weeks of CoCl₂ or VitC administration, there were no significantly modifications, however an antinociceptive effect of 9.65%, respectively 3.95% has been noted.

Conclusion: Our results show that the mitochondrial modulators used in this study have different effects on orofacial pain and on the peripheral and central components of formalin-induced pain.
NTG IN DIABETIC NEUROPATHY
M.P. Hormillosa, P. Noble, Philippines

Objective: This meta-analysis is to assess the effects, efficacy, safety and tolerability of Nitroglycerin spray in the treatment of diabetic neuropathy.

Background: There are various medications available in the market today that are being used to treat diabetic neuropathy. Recent evidences showed that Nitroglycerin is effective in the treatment of painful diabetic neuropathy.

Method: The author searched MEDLINE/ PUBMED to identify the studies. Two evaluators independently reviewed and selected articles of randomized controlled trials on the basis of predetermined selection. Three randomized controlled trials with a total of 113 patients with diabetic neuropathy were included.

Results: The primary outcome which is the change in the mean pain score using the VAS, showed that in all the three trials, Nitroglycerin spray brought about a significant reduction in the pain scores of patients with diabetes mellitus relative to the placebo group. Overall results show that the intervention of Nitroglycerin spray is effective in reducing the pain among patients, with mean difference of 2.14, and 95% narrow confidence interval of 1.978, 2.317.

Conclusion: Nitroglycerin spray is a well-tolerated medication and efficacious among diabetic patients.
SYMPTOM PROFILE IN LEPROSY-RELATED NEUROPATHIC PAIN COMPARED TO NEUROPATHIC PAIN OF OTHER AETIOLOGIES

I. Raicher, P.R.N.A.G. Stump, R. Baccarelli, L.H.S.C. Marciano, S. Ura, M.C.L. Virmond, M.J. Teixeira, D.C. Andrade, Brazil

Introduction: Leprosy (Le) is a chronic infectious disease that usually affects the skin and peripheral nerves. It is an important aetiology of peripheral neuropathy worldwide, as well of neuropathic pain (NeP). The prevalence of Le-related NeP is being studied and so far there are no evidence based information on its pharmacological treatment. It is unknown whether Le-related NeP shares similar symptom profiles with other causes of NeP.

Objectives: NeP symptoms [(NeP Symptom Inventory (NPSI)] were compared between leprosy patients (n=87) and neuropathic pain patients of other aetiologies (n=94).

Methods: Leprosy patients with defined neuropathic pain (d-NeP) according to the new IASP definition were evaluated by trained health agents who filled out the Brazilian Version of Brief Pain Inventory (BPI) and the Brazilian version of the NPSI.

Results: NPSI scores showed not to be statistically significant between Le and neuropathic pain of other aetiologies, except for number of paroxysms during the last 24h and stabbing pain. Pain triggered by stabbing score was 5.95+/−4.1 in Le and 4.01+/−4.07 in NeP of other causes (p=0.001). Higher scores in the NPSI correlated with more severe interference of pain in activities of daily living (rho=0.53, p< 0.0001).

Conclusions: These results suggests that Leprosy related NeP showed similar symptom profile as NeP of other aetiologies, with a similar negative impact in daily activities. This information could be useful in the design of treatments trials for NeP in this population.
Background and aims: Spatial summation, the increase in pain intensity associated with increasing the size of the stimulation surface, is an important aspect of pain processing. Past literature has suggested that spatial summation of pain occurs centrally, involving regions of the spinal cord, brain stem and/or brain. Thus, the current study aims to use spinal cord fMRI to examine, non-invasively, the central mechanisms involved in spatial summation.

Methods: Twelve healthy female participants underwent functional MRI of the spinal cord using established methods for data acquisition and analysis. Each participant was exposed to two noxious stimulation conditions, different only in the size of the thermode used (12 x 12 mm and 30 x 30 mm). Participants rated the pain using a numerical scale that ranged from 0 to 100. The intensity that resulted in a rating of 60 (slightly strong pain) for the large contact probe was considered the participants’ heat-pain threshold and was used for all subsequent thermal stimulations.

Results: The size of the surface area exposed to noxious stimulation modulated the pain response. Participants perceived the stimulation from the larger thermode as more painful compared to the smaller probe, despite identical stimulation intensities. This was reflected in differences in neuronal activity in regions of the spinal cord and brain stem.

Conclusions: Spatial summation of thermally-induced pain can be detected centrally in healthy individuals and future studies will investigate how central processing is interrupted in individuals with neuropathic pain.
METHADONE IN POST-HERPETIC NEURALGIA PAIN: A PILOT PROOF OF CONCEPT STUDY


Aim: This was a pilot proof-of-principle study designed to evaluate the use of low-dose methadone in post-herpetic neuralgia patients who remained refractory after first and second line treatment for post-herpetic neuralgia (PHN) and had indication for the association of an opioid agent to their current drug regimen.

Methods: This was a cross-over, double blind, placebo controlled study. Ten opioid naïve PHN patients received either methadone (5mg bid) or placebo for three weeks, followed by a 15 day washout period and a second three-week treatment with either methadone or placebo accordingly. Clinical evaluation was performed four times, both before and after each three-week treatment period. It included the visual analogue scale, assessment of evoked pain, the Category Verbal Scale (CVS), the daily activities scale, the McGill pain questionnaire, and the adverse events profile.

Results: Methadone did not significantly affect spontaneous pain intensity as measured by the VAS when compared to placebo. Spontaneous pain intensity was significantly decreased after methadone compared to placebo on the Category Verbal Scale (50% improved after methadone, none after placebo, p=0.031). Evoked pain was reduced under methadone compared to placebo (50% improved after methadone, none after placebo, p=0.031). Allodynia reduction correlated with sleep improvement (r=0.67; p=0.030) during methadone treatment. The side effects profile was similar between both treatments.

Conclusions: Methadone seems to be safe and efficacious in PHN. It should be tried as an adjunctive treatment for PHN in larger prospective studies.
USING THE FUNCTIONAL MEDICAL MODEL IN THE ASSESSMENT AND TREATMENT OF CHRONIC, REFRACTIVE, NEUROPATHIC PAIN, A CASE SERIES

L. Arseneau, G. Ko, A. Hum, Canada

Introduction: Functional Medical is a personalized medical system that recognizes the importance of understanding and assessing underlying impairments and alterations in system’s biology that lead to disease diagnosis. Assessment of antecedents, triggers and mediators using the functional medical model leads to identification of each patient’s unique dysfunctions in neuropathic pain. Treatment strategies include the use of nutritional, botanical and hormonal approaches to restore function which may lead to improved therapeutic outcomes in patients with neuropathic pain.

Objectives: The purpose of this case series is assess the potential benefits of implementing a functional medical approach in patients refractive to standard medical treatment.

Methods: Four patients with different types of neuropathic pain were treated with a variety of therapies using the Functional Medical model. Outcome measures were obtained pretreatment and posttreatment. These included validated surveys (short-form McGill Pain questionnaire, DN4 neuropathic pain scale, Pain Detect Questionnaire, Medical Symptoms Questionnaire, objective clinical tools (appropriate lab markers such as serum steroid hormones levels, nutritional markers, liver enzymes, thyroid function, stress hormones, blood sugar, oxidatives stress markers, etc.)

Results: These patients had clinically significant pain reduction and improved function as documented with both subjective and objective outcome measures up to as much as 18 months after treatment initiation. No serious adverse effects were reported.

Conclusion: This reported case series suggests that the Functional Medical model may be of benefit in the management of patients with neuropathic pain. Further investigations with randomized controlled trials in a more specific neuropathic pain population would be warranted.
INJURY-INDUCED ACROLEIN EXACERBATES NEUROPATHIC PAIN BEHAVIOR FOLLOWING SPINAL CORD INJURY

J. Park, M. Due, L. Zheng, M. Walls, F. White, R. Shi1,2, Mechanisms and Treatment of Neuropathic Pain, USA

Background and aims: Chronic neuropathic pain drastically impairs the quality of life for spinal cord injury (SCI) victims. We propose that acrolein, an aldehyde produced by lipid peroxidation, a known secondary injury mechanism post-SCI, plays a critical role in the pathogenesis of neuropathic pain. Acrolein is a known agonist of electrophile-sensitive transient receptor potential ankyrin 1 receptor (TRPA1) present on a subpopulation of nociceptive sensory neurons.

Methods: Rodents were subjected to contusive SCI. Spinal cord tissue was assayed for the presence of acrolein post-SCI. Intracellular current clamp techniques were used to distinguish the effects of acrolein exposure on sensory neurons derived from injured animals. SCI animals were assayed for the presence of tactile and thermal hypersensitivity following administration of a known acrolein scavenger hydralazine.

Results: Acrolein is elevated in the spinal cord following injury from hours to at least two weeks post SCI, a time course which coincides with the onset of post-SCI neuropathic pain behavior. Increased excitation was evident in nociceptive sensory neurons derived from SCI rats following acrolein exposure. We further show that the SCI-induced hyperalgesia can be effectively attenuated with hydralazine, initiated either immediately or 2 weeks following injury.

Conclusions: We propose that the increased neural sensitivity to acrolein, and the elevation in acrolein concentration, work synergistically to contribute to allodynia post-SCI. The hydralazine-mediated analgesic effect supports the role of acrolein in post-SCI neuropathic pain, but also suggests a novel analgesic therapy improve the quality of life for SCI victims.
NEUROPATHIC PAIN CAN BE SUPPRESSED BY THE RECOMBINANT METALLOTHIONEIN

Y. Fujita¹,², T. Wada, K. Iba, G. Oki, S.-I. Imai, Y. Kokai, T. Yamashita, Japan

Background and aims: Complex regional pain syndrome (CRPS) is an intractable disease with intolerable neuropathic pain, though little is understood for molecular mechanisms. By using proteomic analysis of the human peripheral nerves derived from CRPS comparing to intact nerves, we found that metallothionein (MT) is lacked in the affected nerves of CRPS patients. We intend to evaluate dynamic state of MT and effect for neuropathic pain.

Methods: We evaluated 16 rat sciatic nerves by immunostaining method on 3, 7, 14, 28 days after partially ligating (PSL). And we assessed pain response after administration of recombinant MT-2A. We compared rat sciatic nerve between treated and control group by immunostaining method.

Results: From a morphological point of view, we found that neutrophil and macrophages infiltrated to sciatic nerves with inflammation on day 3. After day 7, wallerian degeneration and neuroma were appeared. MT-2A was decreased gradually. Administration of recombinant MT-2A induces an evident attenuation of PSL-induced tactile allodynia and thermal hyperalgesia as early as 5 days of treatment.

Conclusions: MT are proteins with low molecular weight (6-7 kDa) and an ability of heavy metal binding contained abundant cysteine residues with a percentage of cysteine residues in all amino acid components ranging from 25 to 30%. They have free radical scavenging properties so that can protect the organs from cytotoxicity induced by the reactive oxygen species (ROS). This strong antioxidant property of MT-2A may be a key role to suppress the development of a neuropathic pain.
DIRECT PROJECTIONS FROM THE PREFRONTAL CORTEX TO OROFACIAL PAIN-RELATED LOWER BRAINSTEM AREAS, ESPECIALLY TO THE TRIGEMINAL CAUDAL SUBNUCLEUS, IN RATS


Little is known about the orofacial pain-related neurons in the prefrontal cortex. Orofacial pain is conveyed to the second-order neurons in the trigeminal caudal subnucleus (Vc) and oral subnucleus (Vo) by the primary afferents. Tract tracing methods were used in anesthetized rats. First, to examine the distribution of neurons in the prefrontal cortex, which project to the Vc and Vo, we injected a retrograde tracer, Fluorogold (FG), into the Vc and Vo. A large number of FG-labeled neurons were found in the prefrontal cortex, especially in the granular insular cortex (GI) and dysgranular insular cortex (DI) bilaterally with a contralateral predominance to the injection site, but not in the agranular insular cortex. Next, to examine features of descending projections from the GI/DI to the brainstem, we injected an anterograde tracer, biotinylated dextranamine (BDA), into the GI/DI. A large number of BDA-labeled axon fibers and terminals were contralaterally found in the superficial layer of Vc and the Vo, but not in the deep layer of Vc. BDA-labeled axon fibers and terminals were also found in the periaqueductal gray (PAG), parabrachial nucleus (Pb), Kölliker and Fuse nucleus (KF), trigeminal mesencephalic nucleus, rostral ventromedial medulla (RVM), and nucleus of the solitary tract. The present results strongly suggest that the GI and DI are involved in the orofacial pain and that the orofacial nociceptive processing of Vc and Vo neurons may be regulated by GI/DI directly or indirectly through brainstem nuclei such as PAG, Pb, KF and RVM.
MAGNESIUM VIA TRANSFORAMINAL EPIDURAL INJECTION IN FAILED BACK SURGERY SYNDROME

S.H.R. Faiz, P. Rahimzadeh, Iran

Objectives: Failed back surgery syndromes cause neuropathic pain pattern in somehow. For this purpose we decided to inject Magnesium via transforaminal epidural way in patients suffering from low back pain with burning or dysesthetic sensation because Magnesium can antagonize NMDA receptor channels by blocking calcium influx in a voltage-gated manner. Previous studies have demonstrated the anti-allodynic effects of NMDA receptor antagonists in neuropathic pain disorders.

Material and methods: In a randomized clinical trial 24 patients with history of failed back surgery syndrome and low back pain with neuropathic pattern entered in this study. Group 1 received 4 cc Ropivacaine 0.2% +15 mg triamcinolone transforaminally and group 2 received 4cc Ropivacaine 0.2%+ 100 mg magnesium in the same way. Visual analogue scale, LANSS scale improvement and patient satisfaction was calculated after 2, 6 and 12 weeks.

Results: In 86% of Group 2 patients VAS and LANSS was lower compared with 62% of patients in group 1 in the 2 and 6 weeks after injection. (p value< 0.05) Patient global satisfaction score was higher in Group 2 in all measured times. (p< 0.05)

Discussion: Magnesim could be a suitable drug for patients suffering from neuropathic pain patterns.
TESTING A PATH-ANALYTIC MEDIATION MODEL OF HOW MOTIVATIONAL ENHANCEMENT PHYSIOTHERAPY IMPROVES PHYSICAL FUNCTIONING IN PEOPLE WITH CHRONIC LOW BACK PAIN

G.L.Y. Cheing, S.K.S. Vong, F. Chan, N. Ditchman, R.J. Gatchel, C.C.H. Chan, Hong Kong S.A.R., USA

Background and aims: Motivation has been shown to influence outcomes related to management of chronic pain. It plays an important role in pain treatment outcomes and how well an individual applies self-management skills and engages in behavior change. It is likely that patient outcome expectations as well as patient-provider relationship factors play a role in this process. Therefore, the aim of the present study was to examine whether psychosocial factors—specifically, working alliance, outcome expectancy, and perceived pain intensity—mediate the relationship between motivational enhancement physiotherapy and physical functioning for people with low back pain using path analysis.

Methods: Subjects were randomly divided into the motivational enhancement physiotherapy group or the physiotherapy only group. Pain Rehabilitation Expectancies Scale, Visual Analog Scale, and Lifting Capacity Test were measured before and after the intervention.

Results: The re-specified path-analytic model of motivational enhancement physiotherapy fits the data reasonably well, with $\chi^2(3, N = 76) = 3.86, p = .57$; the goodness-of-fit index = .98; comparative fit index = 1.00; and the root mean square error of approximation = 0.00. However, working alliance, outcome expectancy, and perceived pain intensity did not directly mediate the relationship between motivational enhancement therapy and improvement in physical functioning. Reduction in pain intensity also directly influenced improvement in physical functioning.

Conclusions: The use of motivational interviewing techniques to increase outcome expectancy of patients and improve the working relationship between physiotherapists and their patients could strengthen the effectiveness of physiotherapy for people with chronic low back pain.
ALTERED PREFRONTAL CORTEX ANATOMY IN NEUROPATHIC PAIN SUBJECTS; ASSOCIATION WITH NOVELTY SEEKING

S.M. Gustin, C.C. Peck, G.M. Murray, L.A. Henderson, Australia

Background and aims: Neuropathic pain is associated with altered cognitive function, including impaired emotional decision making and changes in temperament such as novelty-seeking. In an animal model of neuropathic pain, altered decision making ability was associated with subtle changes in medial prefrontal cortex (mPC) anatomy, such as changes in basal dendrite length and dendritic spine densities. The cognitive/temperamental changes reported to occur in individuals with neuropathic pain may also result from subtle changes in brain anatomy including changes in the mPC.

Methods: Three magnetic resonance imaging techniques were used to explore brain anatomy and chemistry in 22 subjects with painful trigeminal neuropathy (PTN) and in 43 age-and gender matched controls.

Results: Diffusion tensor and T2 relaxation imaging revealed significantly reduced free and bound proton movement in PTN subjects in the contralateral (to ongoing pain) mPC, anterior cingulate cortex (ACC) and in the mediodorsal thalamus. These alterations in proton movement are indicative of subtle changes in underlying brain anatomy. Furthermore in PTN subjects, spectroscopy revealed a significant increase in N-acetylaspartate in the contralateral mPC suggesting an increase in neural integrity. In addition, in PTN subjects, the anatomical/chemical changes within the mPC and ACC were significantly correlated to the temperament of novelty-seeking, which itself was significantly reduced in PTN subjects.

Conclusions: Since the association between personality and brain changes is only reflected in the contralateral side to ongoing pain, these data suggest that subtle changes in brain anatomy in the mPC and ACC can evoke changes in individual's novelty-seeking temperament.
THALAMIC BIOCHEMICAL CHANGES IN NERUOPATHIC AND NON-NEUROPATHIC CHRONIC PAIN

S. Wilcox, S. Gustin, C. Peck, G. Murray, L. Henderson, Australia

Background and aims: Trigeminal neuropathic pain (TNP) and temporomandibular disorders (TMD) are thought to have fundamentally different etiologies. It has been proposed that TNP arises through damage to, or pressure on, somatosensory afferents in the trigeminal nerve, whereas TMD results primarily from peripheral nociceptor activation. Because some reports suggest that neuropathic pain is associated with changes in thalamic anatomy and biochemistry, it is possible that TNP is maintained by changes in higher brain structures, whereas TMD is not. The aim of this investigation is to determine whether changes in thalamic biochemistry occur in both conditions.

Methods: Seven TNP patients, 11 TMD patients, and 13 control subjects underwent Magnetic Resonance Spectroscopy (MRS). $^1$H-spectra (echo time, 32 ms; repetition time, 2000 ms; 128 repeats; voxel volume, $1 \times 1.5 \times 1$ cm) were acquired with the point resolved spectroscopy sequence from a voxel located in the ventroposterior (VP) thalamus.

Results: MRS revealed a significant reduction in the N-acetylaspartate/Creatine ratio, a biochemical marker of neural viability, in the VP thalamus of TNP patients (NAA/Cr: TNP, 1.64; controls, 2.06; TNP vs controls, $t = -4.38$, df = 11; $p = 0.001$). In contrast TMD patients showed no change (NAA/Cr: TMD, 2.04; controls, 2.08; TMD vs controls, $t = -0.39$, df = 17; $p = 0.71$).

Conclusions: The data suggest that the pathogenesis underlying neuropathic and non-neuropathic pain conditions are fundamentally different and that neuropathic pain conditions that result from peripheral injuries may be generated and/or maintained by neuronal changes in the thalamus.
THE PERSISTENT RELEASE OF HMGB1 CONTRIBUTES TO TACTILE HYPERALGESIA IN A RODENT MODEL OF NEUROPATHIC PAIN

Y.M. Allette, P. Feldman, M. Ripsch, M. Due, F. White, USA

Background: High-mobility group box-1 protein (HMGB1) is a nuclear protein that regulates gene expression throughout the body. After tissue damage or injury, HMGB1 may function as a neuromodulatory cytokine and alter the state of sensory neurons. The present study investigated the degree to which HMGB1 signaling contributes to the maintenance of neuropathic pain behavior in the rodent.

Methods: Rodents were subjected to tibial-nerve injury (TNI) or sham control injury. Dorsal root ganglia (DRG) derived from injured rodents were characterized for changes in nuclear and cytoplasmic HMGB1 and the presence of the receptors TLR4 and RAGE. Some injured rodents were subjected to systemic injection of glycyrrhizin (50 mg/kg; i.p.), a known neutralizer of HMGB1 and assayed for changes in pain behavior.

Results: Redistribution of HMGB1 from the nucleus to the cytoplasm occurred in sensory neurons derived from TNI rats and F11 sensory neuron-like cells exposed to a depolarizing stimulus. In addition, acutely dissociated dorsal root ganglion (DRG) neurons derived from naive or TNI rodents exposed to HMGB1 exhibited increased excitability. Finally, glycyrrhizin reversed TNI-induced tactile hypersensitivity at fourteen days and three months.

Conclusions: Persistent cytoplasmic release of HMGB1 may be a potent and physiologically relevant modulator of neuronal excitability. More importantly, the use of the anti-inflammatory compound and known inhibitor of HMGB1, glycyrrhizin, has the ability to diminish persistent pain behavior in a model of peripheral neuropathy. The identification of HMGB1 as a potential therapeutic target may contribute to a better understanding of mechanisms associated with chronic pain syndromes.
IMPACT OF NEUPSIG NEUROPATHIC PAIN CRITERIA ON CLASSIFICATION OF CANCER PAIN MECHANISM

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Background and aims: In the Edmonton Classification System for Cancer Pain (ECS-CP), designation of nociceptive (Nc), neuropathic (Ne), or unknown (Nx) pain mechanism is based on clinical judgment. The aim of this study was to examine the impact of applying NeuPSIG neuropathic pain criteria on classification of cancer pain mechanism in the ECS-CP.

Methods: All palliative care consultations performed at a Canadian cancer center over one year were reviewed retrospectively. Consultants’ notes and patient charts were abstracted for the following NeuPSIG criteria: 1) neuroanatomically plausible description of pain distribution and history suggestive of relevant lesion; 2) corresponding sensory signs on physical examination; 3) confirmatory tests. Pain was classified as No, Unconfirmed, Probable or Definite neuropathic pain.

Results: 109/329 consultations (33%) were classified as Ne pain (ECS-CP), compared with 47/329 (14%) classified as Probable or Definite neuropathic pain (NeuPSIG). Excluding Unconfirmed (n=34) and Nx (n=19) cases, sensitivity, specificity, positive and negative predictive values of Ne were 89.4%, 82.2%, 49% and 97% , respectively, in comparison with NeuPSIG criteria (Table).

Conclusions: Application of NeuPSIG criteria resulted in a decreased number of cases designated as neuropathic pain. The use of more rigorous criteria for neuropathic pain may impact on cancer pain research outcomes.

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[NeuPSIG vs. ECS-CP]
ZDF RATS AS A MODEL FOR PAINFUL DIABETIC NEUROPATHY

N. Gorodetskaya, A. Pekcec, H. Doods, Germany

Introduction: Pain of evoked and spontaneous character is a severe complication of diabetic polyneuropathy (DPN). Preclinical evaluation of novel analgesics is based mostly on STZ-induced acute diabetes. There is a high need of a model which would also mimic chronic phase of DPN. This investigation is designed to identify the relevant read-outs/age for the pain measurement in Zucker Diabetic Fatty (ZDF) rats, a genetic model of spontaneously developed diabetes type2 and done as a Boehringer Ingelheim Pharma contribution to the “EUROPAIN” project within the European Consortium “Innovative Medicine Initiative”.

Methods: Twelve ZDF and 12 age matched control Zucker Lean (ZL) male rats were investigated. During the 22-week study period from 9 to 26 weeks of age the hind paw sensitivity (mechanical allodynia and hyperalgesia) were monitored regularly. As non-evoked read-out, burrowing behavior and locomotor activity were measured twice, at the middle and at the late phase of the study.

Results: All 12 ZDF rats had diabetes established at age of 9 weeks. Withdrawal thresholds to tactile and pressure mechanical stimuli were significantly greater in ZDF as in ZL rats from onset of diabetes till study termination. In diabetic rats severity of mechanical allodynia was stable, though mechanical hyperalgesia was constantly increasing upon period of investigation. Burrowing behavior and locomotor activity were significantly attenuated in diabetic rats compared to control group.

Conclusions: Both kind of read-outs, based on reflex-withdrawal reactions (allodynia, hyperalgesia) and on innate behavior (burrowing, locomotor activity) have revealed a significant difference between diabetic and age-matched lean rats.
EFFECTS OF ALKALINISATION OF BUPIVACAINE AND ADDITION OF FENTANYL ON BRACHIAL PLEXUS BLOCK

K.C. Pant, India

Regional block is well accepted for surgery and for providing postoperative and chronic pain relief. Brachial plexus block is a simple procedure, easily instituted and has well-identifiable landmarks. Bupivacaine, a commonly administered drug in brachial plexus block has slow onset of action and duration of anesthesia are limiting factors. Various drugs have been co-administered with bupivacaine to improve quality and duration of block. It is unclear whether freshly prepared alkalinised bupivacaine improves quality, onset and duration of brachial plexus block. This prospective randomized, controlled trial compares the onset, quality and duration of analgesia with alkalinised bupivacaine and bupivacaine-fentanyl in brachial plexus block.

Material and methods: After obtaining ethical committee approval and informed written consent from all the patients under going study. Drug solutions were prepared by an anesthetist not involved in the performance of the supraclavicular brachial block, in patient care, or in data collection.

Patients received drugs as under:-

Group I 30 ml of 0.25% bupivacaine

Group II 30ml of 0.25% alkalinised bupivacaine.

Group III 30 ml of 0.25% bupivacaine with 75µg fentanyl All necessary vital signs were monitored. Quality of block was assessed every 5 minutes for 30 minutes and then every 15 minutes till surgery and two hrs after surgery.

Results and conclusion: Global assessment showed more efficacy in II and III as compared to group I, which was statistically significant. Efficacy was higher in group II as compared to group III but the difference was not statistically significant.
EFFECT OF PREGABALIN THERAPY ON POST-HYSTERECTOMY CHRONIC PAIN

S. Bhat, F. Jabeen, A. Waheed, S. Taing, India

Background and aims: The prevalence of persistent chronic pain after abdominal hysterectomy and LSCS is 5-32% and 6-18% respectively. Recent studies have pointed towards neuropathic origin of pain in a large proportion of such cases. We compared with placebo the effect of pregabalin in decreasing pain and improving quality of life (QOL) in such patients.

Materials and methods: 120 patients who had undergone TAH and were having chronic pain were enrolled in the study and were divided into two groups. Chronic pain was considered as which persisted beyond 6 months after surgery. Initial VAS and SF 36 scores were noted for all patients at study entry. In group I patients were given pregabalin 75 mg BID for 6 weeks and in the control group patients were given placebo. Pain was evaluated after 6 weeks again by using visual analogue scale (VAS) and quality of life (QoL) was evaluated using SF-36 questionnaire.

Results: Pain scores were significantly higher in Group II versus Group I (P < 0.05). Additional analgesic requirements decreased significantly in patients who received pregabalin (P < 0.001). The quality of life parameters were significantly improved in pregabalin group at 6 weeks as compared to controls (P < 0.05). Incidence of sedation was higher in pregabalin group but the difference was not significant (P > 0.05).

Conclusions: Post Hysterectomy chronic pain is a common and underreported phenomenon. There was a significant improvement of pain symptoms and QoL scores with pregabalin treatment as compared to placebo pointing towards neuropathic etiology as a possibility.
DISCOVERY OF NOVEL ALLOSTERIC METABOTROPIC GLUTAMATE RECEPTOR 1 ANTAGONISTS FOR TREATING NEUROPATHIC PAIN

G.H. Cho, A.N. Pae, Neuro-Medicine Center, Republic of Korea

Glutamate is an excitatory amino acid that mediates most of the excitatory neurotransmission within the central nervous system (CNS) and their receptors are located in presynaptic and postsynaptic site in afferent nerve terminals. Metabotropic glutamate receptors have been implicated in numerous peripheral nervous system pathways and pathophysiological processes of the central nervous system. Particularly, Group I mGluRs, mGluR1 and mGluR5, play key roles in the central sensitization of pain, in addition to a variety of functions with potential implications in neurological and psychiatric disorders such as epilepsy, Parkinson’s disease, cognitive disorders, drug abuse, anxiety and schizophrenia. As modulating the mGluR subtype 1 of them, we have expected that it can help to treat neuropathic pain.

In addition, we have focused on the discovery of allosteric antagonists since it has more structural diversity, better selectivity and pharmacokinetic profile than competitive antagonists being too polar. Synthesis, structure-activity relationships (SAR), in vitro and in vivo profile of PCTC series will be described.

Of our library, PCTC20043 and PCTC20045 showed moderate and excellent in vivo efficacy at single dose of 100mg/kg in an animal model, which has similar activity with Gabapentin (approved by FDA in 1994). We have continued to study further modification on PCTC20043 and PCTC20045 and to discover mGluR1 antagonists for neuropathic pain.
Effect on neuropathic pain model

**Figure.** Effect on mechanical allostynia (A and B) and cold allostynia (C and D) after oral administration of gabapentin (●, 100 mg/kg, n = 5) and PCTC20045 (●, 100 mg/kg, n = 4) to neuropathic pain-induced rats. Experimental time expressed as D for days after neuropathic injury (N) and h for hours after gabapentin or PCTC20045 administration. *P<0.05 (gabapentin), **P<0.05 (PCTC20045) vs pre-administration value (paired t-test), &P<0.05 gabapentin vs PCTC20045 (unpaired t-test).
PREOPERATIVE SKIN MARKING OF POSTTRAUMATIC NEUROMAS

P.D. Symeonidis1,2, N. Daniilidis, P. Givissis, Greece

Background and aims: The operative treatment of posttraumatic neuromas may include open exploration with a combination of excision of adhesions, neurolysis and/or neurectomy. Apart from the anatomical variations of the peripheral nerves and their branches, nerves may be further deviated from their expected anatomical locations due to scar tissue formation. We describe a new method of preoperative skin marking for neuromas which guides the surgeon and minimizes the surgical exposure.

Material and methods: Skin marking is based on preoperative bed side clinical assessment. It consists of mapping the skin with a permanent marker with a combination of three simple symbols, namely √, o and x. These refer respectively to areas of normal sensation, numbness (decreased or no sensation without paraesthesiae) and pain / dysaesthesia. Points with a positive Tinel sign were marked with x (an x within a square).

Results: Twelve patients with posttraumatic neuromas were marked with the method. One patient gave inconsistent responses and was excluded. In the remaining eleven cases a total of 16 neuromas were successfully located in the upper and lower limbs. Planning the surgical approach according to the marking enabled limited operative exposures and corresponded to atypical locations and branching of the peripheral nerves. All patients were improved with a good to excellent clinical outcome. The method was easily reproduced by three operative surgeons.

Conclusions: Using a simple and reproducible method of detailed preoperative skin marking based on clinical symptoms has assisted in the accurate localization of posttraumatic peripheral neuromas and atypical nerve branches.
BI113823, A NOVEL B1 ANTAGONIST SHOWING ANALGESIC PROPERTIES WITHOUT AFFECTING BLOOD PRESSURE

H. Doods, N. Hauel, K. Arndt, L. Corradini, A. Ceci, Germany

Background and aims: Bradykinin B1-receptors have been implicated to play a role in various pain conditions. However, it has been postulated that the B1 receptor might mediate, at least partly, the hypotensive effects of angiotensin converting enzyme inhibitors. Such an interaction would of course limit the use of B1 antagonist as broadly used analgesics. In the present study we investigated the analgesic properties of a novel B1 antagonist, BI113823, in a model of inflammatory pain and whether this compound has an effect on blood pressure or interferes with the blood pressure lowering effect of the ACE-inhibitor lisinopril.

Methods: The analgesic property was examined in the complete freund's adjuvant model (50 µl, 0.5 mg/ml, intraplantar). Thermal hyperalgesic was measured 24h after the application of CFA. BI113823 was dosed orally 1h before testing the pain withdrawal threshold. Spontaneous hypertensive rats were implanted with mini-pump containing either vehicle or lisinopril (1.2 mg/kg/day). The effects on blood pressure were monitored for 12 days using the Data Science telemetry system. After 5 days BI113823 was applied orally twice daily for 7 days (30mg/kg, bid).

Results: Following oral administration BI113823 dose-dependantly reversed CFA induced thermal hyperalgesy with a minimal effective dose of 3 mg/kg. A dose of 30 mg/kg BI113823 given twice daily for 7 days had no effects on blood pressure in control animals. Moreover, it didn't interfere with the blood pressure lowering effect of lisinopril.

Conclusions: BI113823 is a B1 antagonist showing analgesic activity without having any effect on blood pressure.
INJURY OF THE TYMPANIC NERVE MODULATES PAIN PROCESSING VIA THE TRIGEMINAL NERVOUS SYSTEM

Y. Imamura1,2, N. Shiiki, M. Kiyomoto, K. Iwata, Japan

Purpose: Recently some studies have suggested the possible neuropathic mechanism in burning mouth syndrome (BMS) although its etiology has not been elucidated. This hypothesis is based on the finding that the mucous epithelial small fibers are damaged in BMS patients and this small-fiber damage may be related to dysgeusia and burning pain of the tongue. This study was conducted to investigate if tympanic nerve injury modulates pain processing via the trigeminal nervous system.

Methods: The left auricle of anesthetized rats was surgically removed and the tympanic nerve was transected (TNX rats). A sham operation was applied by injuring the tympanic membrane but not the tympanic nerve (Sham rats). Both TNX and sham rats were anesthetized and noxious mechanical stimulation was applied on the ipsilateral side of the tongue to the operation on the seventh day postoperatively. Rats were immediately euthanized with high dose of sodium pentobarbital and the medulla was removed with the upper cervical spine. Phosphorylated extracellular gene-regulated kinase (pERK) expression was observed in the subnucleus caudalis of the spinal nucleus of the trigeminal nerve (SpVc) and the nucleus of tractus solitarii (NTS). The tongue was also transected and was used for the observation of morphological changes.

Results: Lingual papillae were atrophied in the ipsilateral side to the operation in the TNX rats. pERK expression was facilitated both in the SpVc and the NTS in the TNX rats as compared to sham rats.

Conclusion: Damage of the tympanic nerve may modulate pain processing via the trigeminal nervous system.
ARTEMIN SIGNALING CONTRIBUTES TO THE TONGUE PAIN IN BURNING MOUTH SYNDROME MICE

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Background and aims: Burning mouth syndrome is well known as chronic tongue pain which is unaccompanied by mucosal lesions or other evident clinical signs. However, the exact mechanism of the tongue pain in BMS remains unclear. We examined the role of the artemin signaling in tongue thermal hypersensitivity following 2,4,6-trinitrobenzene sulfonic acid (TNBS) application to the tongue surface.

Methods: TNBS (10 mg/ml) was administrated 1 hour on the tongue surface. After the administration, mice were lightly anesthetized with isoflurane (2%) and the head-withdrawal latency by thermal stimulation on tongue was recorded. The head-withdrawal latency was determined before and after TNBS treatment. Tongue pathology and Artemin release in the tongue was assessed in parallel experiments. We evaluated the effect of transient receptor potential vanilloid 1 (TRPV1) antagonist, SB366791 or neutralizing anti-Artemin antibody administration on the tongue thermal hyperalgesia. The number of GFRα3- and TRPV1-positive trigeminal ganglion (TG) neurons innervating the tongue was counted on day 5 following TNBS administration.

Results: TNBS application on the tongue induced marked tongue-thermal hyperalgesia without tongue inflammation for 15 days, and significantly increased Artemin expression in the tongue mucosa. On day 5 following TNBS administration, the successive administration of SB366791 or neutralizing anti-Artemin antibody completely inhibited thermal hyperalgesia. The number of GFRα3- and TRPV1-positive TG neurons innervating the tongue significantly increased following TNBS administration.

Conclusions: These results suggest that overexpression of Artemin in the TNBS-treated tongue increases the expression of TRPV1 in trigeminal sensory neurons innervating the tongue, which causes thermal hyperalgesia in the tongue.
IN INVOLVEMENT OF DIFFERENT CORTICAL REGIONS IN THE SOMATOSENSORY COMPONENT AND THE AFFECTIVE CONSEQUENCES OF NEUROPATHIC PAIN IN MICE

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Introduction: Mood disorders are frequently observed in patients suffering from chronic pain. However, the mechanisms underlying this comorbidity remain unclear. Clinical and preclinical attention has focused on injury-induced changes in cortical brain regions, some involved in somatosensory component of pain, e.g. Insular Cortex (IC), others in the affective component of pain, e.g. Anterior Cingulate Cortex (ACC).

Objectives: Using a mouse model of neuropathic pain known to develop mood disorders, we aimed to understand the involvement of different cortical areas in the development of pain behavior and affective disorders.

Methods: Peripheral neuropathy is induced by inserting a polyethylene cuff around the main branch of the right sciatic nerve. Stereotaxic surgery was done before the cuff surgery to cause cortical excitotoxic lesions by injecting ibotenic acid. Using a battery of behavioral tests, we then investigated the development of pain behaviors and mood disorders in these animals.

Results: Our cuff model develops a long lasting mechanical allodynia and mood disorders in a time-dependent manner. Cuff mice with ACC lesion still present mechanical allodynia but failed to show anxi-depressive like behavior while other cortical lesions reverse the development of mechanical allodynia.

Conclusions: Neuropathic pain leads to affective disorders. We show in this study that several cortical regions are implicated separately in somatosensory component and the affective consequences of neuropathic pain.

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SEX DIFFERENCES AND MODULATORY EFFECT OF 17BETA-ESTRADIOL ON BEHAVIORAL AND IMMUNE RESPONSES IN NEUROPATHIC MICE

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Background and aims: There is considerable literature on the effect of gonadal hormones on pain sensitivity, but their effect on neuropathic pain has not been clarified. Sex differences play a role in pain sensitivity, efficacy of analgesic drugs and prevalence of neuropathic pain, even if the underlying mechanisms are complex and far from understood. The aim of the present study was to investigate sex-related differences in a mouse model of neuropathic pain, focusing on the role of estrogens.

Methods: Chronic Constriction Injury (CCI) was used as neuropathic pain model in male and female CD1 mice. Mechanical allodynia and functional recovery of the injured paw was followed for 121 days. Behavioural data of control and 17beta-estradiol-treated (s.c. 50 µg/kg/day for seven days) neuropathic mice were correlated with immunofluorescence staining of cells markers (GFAP: astrocytes; CD11b: microglia; NeuN: neurons) alone or colocalized with p-p38 at the spinal cord level.

Results: CCI-induced mechanical allodynia gradually decreased in male mice and a complete recovery occurred 81 days post surgery. CCI induced an enhanced expression of p-p38 in microglia and astrocytes that completely disappeared in male 121 days after CCI. On the contrary, in female mice both allodynia and gliosis were still present 121 days after CCI. In both male and female 17beta-estradiol induced analgesic effects, facilitated recovery and counteracted gliosis.

Conclusions: All the above observations demonstrate the relevance of sex differences and the beneficial effects of estrogen modulation in processing of neuropathic pain, reinforcing the importance of this aspect also in clinical studies.
DOES CARPAL TUNNEL SYNDROME HAVE NEUROPATHIC PAIN PATTERNS?

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We ran prospective clinical study of NeP on carpal tunnel syndrome using Pain Detect just before carpal tunnel release in 136 patients, all are female. The 67.65 per cent showed no NeP but only numbness and the remaining showed NeP with the Pain Detect score more than 20 and only 10 per cent showed mild degree of hyperalgesia and allodinia. The clinical relevance of this study is that in patients with NeP by Pain Detect should be treated with gabapentinoid druds before and after surgery and not all carpal tunnel syndromes show NeP component.
EXCESSIVE PEPTIDERIC SENSORY INNERVATION OF CUTANEOUS ARTERIOLE-VENULE SHUNTS IN PALMAR GLABROUS SKIN OF FIBROMYALGIA PATIENTS: IMPLICATIONS FOR WIDE SPREAD DEEP TISSUE PAIN AND FATIGUE

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Background and aims: To determine if a neuropathology exists among the innervation of cutaneous arterioles and arteriole-venule shunts (AVS) in fibromyalgia (FM) patients.

Methods: Multi-molecular immunocytochemistry of 3mm skin biopsies was used to assess the cutaneous innervation in glabrous hypothenar and trapezius regions of 24 FM female patients and 23 healthy female controls. Serotonergic/noradrenergic-reuptake inhibitors (SNRIs) provide therapeutic benefit to some FM patients. We hypothesized that a pathology might exist among the convergence of sympathetic and sensory innervation to cutaneous arterioles and/or AVS.

Results: Cutaneous arterioles and AVS receive a convergence of sympathetic innervation that mediates vasoconstriction by releasing noradrenalin and NPY, and small fiber sensory innervation that mediates vasodilatation through an effector release of CGRP and Substance P. Sensory fibers express α2C receptors which could mediate sympathetic inhibitory modulation of sensory activity. The AVS, unique to glabrous skin, have excessive innervation in FM patients, and abnormally far greater sensory to sympathetic proportions. Arteriole innervation in both biopsy sites was surprisingly normal.

Conclusions: This study identified excessive sensory innervation of the AVS in patients with FM which may contribute to chronic widespread pain and tenderness observed in FM patients. Widespread pain and fatigue may be due to dysregulation in the proper apportioning of blood flow between richly-vascularized glabrous skin of distal extremities and vasculature of skeletal muscle, which is essential for balancing thermoregulatory and metabolic demands. We are currently evaluating whether SNRIs may provide therapeutic benefit by enhancing the impact of sympathetically mediated inhibitory modulation of the excess sensory innervation.
PERIPHERAL GLUTAMATE RECEPTORS CONTRIBUTE COLD HYPERALGESIA VIA TRPA1 MECHANISMS

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Background and aims: Peripheral tissue inflammation or injury causes glutamate release from keratinocytes or Schwann cells, resulting in thermal hyperalgesia. We have reported that peripheral glutamate injection induces heat and cold hyperalgesia in the injection site. However, it is still not understood the mechanisms underlying cold hyperalgesia following peripheral glutamate injection. The aim is to clarify the involvement of peripheral transient receptor potential ankyrin 1 (TRPA1) and protein kinase C epsilon (PKCε) in glutamate-induced cold hyperalgesia.

Methods: We analyzed nocifensive behaviors to cold stimulation following (N-methyl-D-aspartate receptor) NMDAR antagonist APV, Metabotropic glutamate receptor 5 (mGlu5) antagonist 6-Methyl-2-(phenylethynyl)pyridine hydrochloride (MPEP), TRPA1 antagonist HC-030031 or PKCε translocation inhibitor administration 1 week after continuous subcutaneous injection of glutamate into the facial skin. Next, we examined the expression of TRPA1-, N-methyl-D-aspartate receptors (NMDAR) subunit NR1- and CGRP-immunoreactive (IR) and TRPA1-, PKCε- and CGRP-IR trigeminal ganglion (TG) neurons. Moreover, we performed a single unit recording from the TG neurons following glutamate injection into the facial skin.

Results: Head-withdrawal threshold to cold stimulation was significantly decreased compared to vehicle-injected rats, and the decreased head-withdrawal threshold was significantly recovered by APV, HC-030031 or PKCε translocation inhibitor administration 1 week after continuous injection of glutamate into the facial skin. TRPA1-, NR1- and CGRP-IR neurons and TRPA1-, PKCε- and CGRP-IR neurons were observed in the TG. Neuronal activity in TG neurons was significantly increased following glutamate treatment.

Conclusions: Present findings suggest that TRPA1 activation through glutamate receptors signaling via PKCε is involved in facial cold hyperalgesia.
THE EFFECT OF 8% CAPSAICIN PATCH APPLICATION ON ALLODYNIA

D. Vondrackova, Czech Republic

Background and aims: Clinical picture of neuropathic pain is rather varied and the therapy is difficult. Its symptoms are very unpleasant for patients. Allodynia and hyperesthesia belong among the worst tolerated and impair the quality of life very much. The altered sensitivity is poorly controlled with systemic therapy and often persists even after an effective treatment. Local application of capsaicin satisfactorily reduces various types of peripheral neuropathic pain. We used 8% capsaicin patches to treat allodynia and hyperesthesia.

Methods: In the course of one year we applied high-concentration 8% capsaicin patches to 6 neuropathic pain patients with allodynia as dominant symptom regardless of duration of the illness and its cause. Area of mechanical allodynia was determined by using brush stroke. Patients assessed separately the pain level and allodynia on numerical rating scale 0-10. The level of pain and allodynia was rated one week and one month after application and before any subsequent application. Systemic pharmacotherapy was used in accordance with EFNS guidelines. If changes in basic therapy were necessary we tried to make them preferentially when allodynia subsided or was mitigated.

Results: Case reports of 6 patients with neuropathic pain confirm that application of 8% capsaicin patches leads to significant reduction or even disappearance of allodynia and hyperesthesia while reducing the size of affected area.

Conclusions: High-concentration 8% capsaicin dermal patch reduces allodynia - mechanical hyperesthesia and also diminishes the size of affected area.
BURST SPINAL CORD STIMULATION EVALUATED IN PATIENTS WITH FAILED BACK SURGERY SYNDROME AND PAINFUL DIABETIC NEUROPATHY


Introduction: Burst spinal cord stimulation was introduced [De Ridder et al. Neurosurgery, 2010] as a new stimulation paradigm with good pain suppression effects without causing paresthesias. Good results were obtained in patients who were naive to spinal cord stimulation (SCS).

Objective: In this study we assess the effectiveness of burst stimulation in chronic pain patients who are already familiar with SCS.

Methods: Three groups of patients with at least 6 months of conventional, tonic stimulation tested burst stimulation for a period of two weeks. VAS scores for pain were assessed prior to implantation, with tonic spinal cord stimulation and after two weeks of burst stimulation.

Results: When compared to tonic stimulation, burst stimulation led on average to an additional pain reduction of 43% in patients with painful diabetic neuropathy and 29% in patients with failed back surgery syndrome. In addition, burst stimulation caused little or no paresthesia, whereas tonic stimulation did induce paresthesia. Patients who over time had become non-responders to tonic SCS benefitted on average less from burst stimulation.

Conclusion: Compared to tonic stimulation, burst stimulation further reduced pain for almost all patients. When given the choice, 54% of the patients would prefer burst stimulation over tonic stimulation.
UPREGULATION OF IL-6 AND ITS SIGNALING MOLECULES IN THE DORSAL ROOT GANGLIA OF LUMBAR AND CERVICAL SEGMENTS AND THEIR INVOLVEMENT IN NEUROPATHIC PAIN INDUCTION

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Background and aims: Interleukin-6 (IL-6) is a key component of the nervous system response to an injury with various effects. The aim of the present study was to investigate alterations of IL-6 and its signaling in both ipsilateral and contralateral L4-L5 as well as C7-C8 dorsal root ganglia (DRG) in rat neuropathic pain models.

Methods: Unilateral chronic constriction (CCI) and spared nerve injury (SNI) of the sciatic nerve was performed aseptically in sixty rats. Neuropathic pain induction was tested by measurement of mechanoallodynia and thermal hyperalgesia. Expression of IL-6, IL-6R, gp130, STAT3 and SOCS3 was investigated bilaterally in lumbar (L4-5) and cervical (C7-8) DRG 1, 3, 7 and 14 days after surgery. Some DRG sections were simultaneously immunostained for GAP43. To prove a pathway for neuroinflammatory propagation, FluoroRuby was injected intrathecally at the level of L4-L5 spinal segments in six CCI-operated rats.

Results: Ipsilateral hind paws of all rats operated on CCI/SNI displayed mechanoallodynia and thermal hyperalgesia while contralateral hind paws and forepaws of both sides exhibited no significant hypersensitivity. Bilateral elevation of IL-6 and its signal molecules was not limited to lumbar, but also extended to cervical DRG. FluoroRuby applied intrathecally diffused into both lumbar and cervical DRG.

Conclusions: The results suggest that up-regulation of IL-6 and its signaling is not only associated with neuropathic pain induction. Neuroinflammatory reaction to neuropathic stress is propagated alongside neuroaxis from lumbar to remote DRG related probably with conditioning of the cervical DRG neurons to injury.

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QUANTITATIVE SENSORY TESTING (QST) AND PAIN SYMPTOM PROFILES IN LEPROSY PATIENTS IN MUMBAI-INDIA

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Background and aims: Neuropathic pain is present in ~ 20% of leprosy patients in whom the *M. leprae* has been successfully treated with multidrug therapy (Hietaharju et al 2000, Lasry-Levy et al 2011, Haroun et al 2012). A mechanism based approach to neuropathic pain treatment guided by symptom and sensory profiles has been advocated. However, there is no robust data regarding the symptom and sensory profiles of treated leprosy patients with and without neuropathic pain. We describe the somatosensory and symptom profiles of patients with leprosy and normative data of non-Caucasian cohort of healthy control.

Methods: A case control study was conducted in a leprosy cohort of 60 patients recruited from the Bombay Leprosy Project, with and without neuropathic pain, and 30 healthy volunteers. QST was conducted according to the full DFNS QST protocol by a qualified investigator trained and validated by the DFNS (Rolke et al 2006). All leprosy patients were firstly screened for neuropathy using the standard conventional clinical approach of bedside evaluation of motor function and mechanosensation. Those who fulfilled the criteria for neuropathy were screened for neuropathic pain using DN4 and PainDetect questionnaires translated into Hindi and Marathi.

Results: From the QST data obtained to date the predominant findings are sensory loss to thermal and mechanical detection thresholds and paradoxical heat sensations. There was no evidence of sensory gain.

Funding: Homes and Hospitals of St. Giles
AN IMPROVISED INDIGENOUS TECHNIQUE FOR NERVE STIMULATOR ASSISTED PERIPHERAL NERVE BLOCKS

S. Singh, A. Jain, India

Introduction: Nerve stimulator guided peripheral nerve block greatly enhances the success rate of the block. Often the nerve stimulation needle becomes the limiting factor due to the cost and its unavailability.

Objective: We have proposed a simple innovation to create a nerve stimulation needle at point of care that would overcome the limitation associated with commercially available needle for nerve stimulation. This innovation may prove instrumental in training of anaesthesia residents at no extra cost to the patient.

Materials and methods: The improvised needle is a modified 20 swg IV cannula that can be converted into a nerve stimulator needle in four simple steps,

1. Diaphragm of the flashback chamber is perforated using a 14 swg hypodermic needle.
2. Negative electrode is inserted through the perforated diaphragm of flash-back chamber.
3. Flashback chamber is attached to the Luer chamber.
4. Nerve stimulator electrode is adjusted so as to touch the stylet in the Luer chamber.

This modified IV cannula is thus converted into a ready to use nerve stimulator needle. Positive electrode of the nerve stimulator is attached to a simple EKG electrode. This assembly is used to locate the nerve by the nerve stimulator. Local anaesthetic is then injected through the cannula after removing the needle.

Results and conclusions: Near 100% success has been achieved using this needle in upper and lower extremity blocks in normal Asian population. However, length of the needle may not be adequate for lower extremity blocks in obese patients.
REDUCED PAIN-RELATED BEHAVIOUR IN DIABETIC GALANIN OVER-EXPRESSING TRANSGENIC MICE

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Background and aims: The neuropeptide galanin is involved in pain modulation, having a well established inhibitory role in models of nerve-injury induced neuropathic pain (NINP), in which the neuropeptide is significantly up-regulated. Interestingly, galanin is also pivotal to the developmental survival of a population of C-type neurons which appear to be important for mediating NINP, such that mice which lack galanin (Gal-KO) fail to develop NINP. However, the role played by galanin in painful diabetic neuropathy (PDN) remains to be determined.

Methods: A streptozotocin (STZ)-induced model of PDN was established in CBA/Bl6 wild-type (WT) mice. Dorsal root ganglia tissue was taken at 5 weeks post STZ and assayed for galanin, galanin receptors 1 and 2 (GalR1 and GalR2) by real-time RT-PCR (Taqman). Transgenic mice which inducibly over-express galanin (Gal-OE, on the CBA/Bl6 strain) and strain-matched WT animals were injected with STZ and tested for pain-related behaviour over several weeks.

Results: WT mice show no significant change in galanin, GalR1 or GalR2 mRNA levels 5 weeks following STZ treatment. Gal-OE mice show an amelioration of mechanical allodynia compared to strain-matched WT mice. Results from Gal-KO mice will be presented at the meeting.

Conclusions: STZ-induced PDN does not appear to influence galanin or GalR levels in WT mice. Pain-related behaviour in Gal-OE mice is reduced compared to WT controls, comparable to that previously observed in direct nerve trauma models of neuropathic pain. This suggests that the neuropeptide plays similar anti-nociceptive roles in various models of neuropathic pain.
ACTIVITY OF NEW FORM OF MAGNESIUM SALT AND TRAMADOL IN A DIABETIC NEUROPATHIC PAIN MODEL

E. Gąsińska, M. Bujlaska-Zadrożny, Poland

Background and aims: Streptozotocin-induced hyperglycemia accompanied by a chronic decrease in the nociceptive threshold is considered a useful model of experimental hyperalgesia. We examined the effect of the opioid receptor agonists (tramadol) and the effect of the normal and new form of magnesium salt on the antinociceptive action of tramadol in a diabetic neuropathic pain model.

Materials and methods: The research has been conducted on a group of male Wistar rats weighting 250-350g. The model of researched diabetes was achieved by administering STZ (40mg/kg) in rats intramuscularly on the first day of the experiment. Tramadol (at a dose of 125 mg/kg), and a traditional or a newly-created form of magnesium salt (at a dose of 15 magnesium ions mg/kg) were administered per os in acute and chronic treatment of diabetes neuropathy. The pain threshold levels were determined by using mechanical stimuli (the Randall and Selitto test).

Results: Pretreatment with magnesium (II) salts markedly enhanced the analgesic activity of Tramadol. However, a new form of magnesium salt were significantly more effective in enhancing the analgesic activity of orally administered tramadol than traditional form of magnesium salt.

Conclusions: An oral co-administration of tramadol and a new form of magnesium salt in alleviating of neuropathic pain may be relevant clinically.
ASSESSMENT OF NEUROPATHIC MEDICATION AMONG DIABETIC PATIENTS IN CENTRAL PART OF IRAN (SELF-MEDICATION VS PRESCRIPTIONS)

N. Khorasani, S. Sarahroodi, Iran

Background and aims: Neuropathic pain is a common problem among chronic diabetic patients and usually controls by TCAs, SSRIs and AEDs.

Some patients try to control these pains by self-medication which has high prevalence world-wide and some use their physician suggestions.

In this study we evaluated the pattern of neuropathic pain controlling via medication among Iranian diabetic patients.

Methods: The target population was 150 diabetic patients attending two diabetic clinics affiliated to Qom University of medical sciences, central Iran, in fall 2012.

Results: 25.7% of diabetic patients who suffered of neuropathic pains used some medications for removing their pains. Among respondents who used medication for his/her pains about 45% used self-medication for their pains. The most preferred agent for self-medication was Ibuprophen which is an OTC agent in Iran, while the most prescribed medicine by physicians was Gabapantin. Furthermore, self-medicating patients used medicines once a week or less while about 80% of patients who used prescribed medications, consummated their medicines once day or even more. At last, none of respondents reported side effects of used medicines for her/his neuropathic pain.

Conclusion: As the patients were not aware of neuropathic pains and their proper medications we suggest the government to aware physicians by mail or even in CME courses to train their diabetic patients about this problem and problems of self-medication.
DEVELOPMENT OF INTERNET BASED ELECTRONIC MEDICAL RECORDS IN THE PAIN CLINIC: THE BRAZILIAN INITIATIVE TO RECORD DATA ON CHRONIC PAIN (BIRD-CP)


Present study was to build an BIRD-CP of quantifiable validated tools for pain assessment that would allow for the pooling and analyses of data from different centers with focus on epidemiology, pain syndrome prevalences and treatment profile, and more important, outcome and prognosis of routine care of pain patients. Methods An internet based PHP program was build to provide secure, cryptography password protected assess to a medical record of pain patients. Clinical evaluation included general medical history and physical examination, the Brazilian version of the McGill Pain Questionnaire, Douleur Neuropathique-4, Neuropathic Pain Symptom Inventory, Pain Catastrophizing Scale, Brief Pain Inventory, Functional evaluation Scales and Questionnaires and the Medication Quantification Scale. Results After the medical consultation two outputs were generated, one was a PDF summary of the consultation (average 2 pages) intended to be printed. Also, data from the consultation was fed into a data bank containing all data from all patients, from all medical visits. This data bank was protected by different sets of passwords, and stored in a different external server, only accessible from an IP. In a pilot phase 830 patients were evaluated by 10 pain specialists during regular consultations. Use of this tool is currently being tested in two academic centers and should set the pillars for its more widespread use in our country. CONCLUSION BIRD-CP will allow us to better define the profile of chronic pain patients and their response to treatment in different Centers and will set the base for future care policies in Brazil.
PERCEPTION OF PAIN PHYSICIANS ABOUT NEUROPATHIC PAIN IN INDIA

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Neuropathic pain and its management is very important during the pain practice. This study shows the awareness about the neuropathic pain amongst the Indian pain Physicians.

Background and aims: In India, the knowledge and awareness regarding neuropathic pain is very low, particularly the clinical picture, diagnostic tools and management choices. The aim was to explore these aspects in the Indian pain practitioners.

Methods: 150 pain physicians were given a questionnaire related to different aspects of the neuropathic pain during a pain conference held in Mumbai recently. Out of them, 102 pain physicians responded with the proper answers. These answers were analyzed in depth, so as to know about their awareness in neuropathic pain practices.

Results: It was found that almost 96% pain physicians were anesthesiologists. 25% pain physicians were not aware about the symptoms and different ways to diagnose the neuropathic pain, so also more than 80% were not aware about different neuropathic pain scales. Almost 60-75% physician were unaware about the role of opioids, SSRIs, SSNRIs, ketamine and lignocaine patch in neuropathic pain. However, majority of them were aware that chronic neuropathic pain can be caused by the surgery and that it can also affect the quality of life.

Conclusions: Awareness regarding the neuropathic pain needs to be dealt seriously amongst the pain physicians from India through different pain conferences, CMEs and workshops.
Objective: This study aims to observe the changes of mechanical and thermal pain thresholds and depression symptoms of type II Diabetes Mellitus rats after electroacupuncture (EA) on body acupoints (ST36, SP6) and auricular vagus nerve points.

Method: For induction of DM II, streptozotocin was injected. After 30 days, rats were stimulated by metal fibril and thermal source on the hindfoot, and the reaction time between the stimulation and the subsequent withdrawal of hindfoot were observed to the mechanical and thermal pain thresholds. An open field test was used to measure indexes of exploratory behavior which indicates depression. EA was given continuously for 14 days.

Results: The mechanical pain reaction time increased and the thermal pain reaction time dropped (P<0.05), which suggested hyperalgesia and allodynia in model rats. The score of exploratory behavior reduced (P<0.05), which suggested depression in model rats. After 14 days of EA, the mechanical pain reaction time in the body point group and the auricular point group dropped, thermal pain reaction time increased (P<0.05). The score of exploratory behavior also improved (P<0.05). The auricular point group had higher exploratory behavior scores than the body point group, but there were no statistical difference (P>0.05) in mechanical and thermal pain reaction time.

Conclusions: DM II leads to sensory neuropathies, but also causes depression symptoms. EA helps to improve sensory neuropathies and depression symptoms of DM II rats. EA on auricular vagus nerve points has better effects than body points in terms of improving depression symptoms.
INTRATHECAL TREATMENT (IT) FOR NEUROPATHIC AND NOCICEPTIVE PAIN: MORPHINE VS. ZICONOTIDE

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Introduction: We want to evaluate the efficacy and tolerability of IT administration of morphine vs ziconotide in patients with complex pain.

Materials and methods: 61 patients with complex pain received a mono drug/pharmacological IT treatment. 38 patients were treated with morphine and 23 with ziconotide. 65% of our sample were oncologic patients. 43 patients were implanted with Medtronic Synchromed II ® and 18 with Prometra Programmable pump®.

Results: Enrolled morphine-treated patients VAS pain score at baseline (T0) was 8.7 while ziconotide-treated was 8.9. Mean morphine dose at T0 was 0.54 mg/die and ziconotide was 0.67 mcg/die, after 1 month (T1) mean morphine dose was 2.1 mg/die and ziconotide was 2.7 mcg/die. Mean morphine dosage at 3 months (T2) was 3.8 mg/die and ziconotide was 3.6 mcg/die at six months (T3) after the implant was 5.3 mg/die and ziconotide was 4.8 mcg/die, 1 year after morphine dosage was 6.4 mg/die and ziconotide was 5.4 mcg/die. No significant differences were observed at T1 between morphine and ziconotide in analgesic effect. During the other follow-up ziconotide showed to be more effective than morphine (p < .001). Some adverse events (Aes) such as dysesthesia, burning throat, pyrosis and auditory hallucinations were observed in 9 ziconotide patients. Hallucinations, vomiting and unsteadiness when walking (dizziness) were observed in 11 morphine patients. 4 patients interrupted ziconotide and 2 interrupted morphine because of Aes. 7 oncologic patient died during the study due to their own pathology.

Conclusion: despite of side effects ziconotide resulted better than morphine
The objective of this study was to demonstrate the safety and efficacy of a percutaneous paddle lead for SCS. Percutaneous paddle lead (S8 series™ leads, St Jude Medical) was implanted using introduction system for percutaneous implantation (Epiducer™ lead delivery system, St. Jude Medical). Our case studies reports about 44 percutaneous leads in 42 patients. 4 patients suffered a negative trial and explanted the percutaneous paddle. After 24 months from the implant VAS and all dimensions of IPQ decreased in significant way (p< .001). At the last follow-up 65% stopped their pain medications. SCS improved quality of life the variation (ΔT) of all SF-36 dimensions is significant higher than the baseline (p< .001). Regarding the body area coverage, in the axial-lumbar area it was in a range of 90-100% and in the radicular and lower limbs was in a range of 80-90%. No perioperative complications occurred. The dislocation of the percutaneous paddle is a rare adverse event (1%). Our Cases reported only 1 dislocation after an accidental shock. In 3 cases we recorded a dislocation soon after the post operative period (3%). In all the cases has been possible to operate with positive outcome without explantation. Four patients explanted the paddle after 5 weeks with no adverse events. 1 patient explanted after 6 months without adverse events too. Our results confirmed that SCS continues to be a valuable tool in the treatment of chronic disabling pain. Paddle leads seemed to be an efficient alternative for patients with FBSS.
TRANSDURAL MOTOR CORTEX STIMULATION REVERSES NEUROPATHIC PAIN THROUGH ACTIVATION OF SEROTONERGIC DESCENDING INHIBITORY SYSTEM AND INHIBITION OF SPINAL GLIAL CELLS

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Background and aims: Motor cortex stimulation (MCS) has been used in to treat patients with refractory neuropathic pain. However, this technique failed to improve chronic pain in up to one third of the patients, which implies the necessity of continuous research in the field. Herein, we evaluated the participation of supraspinal serotonergic nuclei and the activation pattern of spinal glial cells in neuropathic rats submitted to MCS.

Methods: Male Wistar rats were submitted to chronic constriction injury (CCI) of the sciatic nerve. After one week, transdural electrodes were placed over the primary motor cortex in the area corresponding to right hind paw. One week later, animals received MCS (1.0 V; 60 Hz; 210 ms, 15 min) and the paw pressure test was conducted under stimulation. False-operated (FOP) rats were used as controls. Immunohistochemistry (IH) for serotonin (5HT) in the dorsal raphe (DRN) and raphe magnus (RMN) nuclei and for GFAP, OX-42 and interleukin-1β (IL-1β) in the dorsal horn of spinal cord (DHSC) were evaluated.

Results: Rats with neuropathic pain showed a decrease of 5HT-IH in the DRN and RMN, astrocyte and microglial hypertrophy and increase of IL-1β-IH in the DHSC, ipsilateral to CCI, when compared with FOP. MCS reversed the mechanical hyperalgesia, increasing 5HT-IH, in both DRN and RMN, and decreasing the glial hypertrophy and IL-1β-IH in the DHSC.

Conclusions: These results suggest that the MCS reverses the neuropathic pain through activation of serotonergic descending inhibitory system, probably resulting in attenuation of the spinal glial activation and consequent IL-1β release.
CSF FINDINGS AND FOLLOW UP MRI IMAGING FEATURES OF ACUTE TRANSVERSE MYELITIS WITH NEUROPATHIC PAIN

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Purpose: We investigated CSF findings and follow up imaging features of acute transverse myelitis (ATM) with neuropathic pain patients in order to look at prognosis of ATM with neuropathic pain.

Method: From January 2000 to December 2011, 21 patients were registered. The CSF findings on admission and follow up MRI imaging study were reviewed and analyzed.

Results: Among 21 neuropathic pain patients of ATM, Thirteen patients were male, the age is from 21 years old to 63 years old and average age was 48 years old. The location of lesions on MRI was cervical spine in 11 patients, thoracic spine in 9 patients and lumbar spine in 1 patient. The follow up period of MRI study was from 3 month to 48 month and average was 10 month. The WBC cell count of CSF study on admission was classified as follow: group A (≥ 5), B (1 and <4), C (0). Among 5 patients of group A, the MRI lesions of 1 patients were disappeared, 1 patients were much improved, 2 patients were some improved, and 1 patients whose WBC count was 35, was aggrevated. Among each 8 patients of group B and C, almost all patients were much or some improved.

Conclusion: We reviewed clinical features of ATM with neuropathic pain. About the prognosis of ATM, about 57% of patients showed very good prognosis and 33% moderately good prognosis, but about 10% of patients showed poor prognosis. The WBC count of CSF study may give some information about prognosis.
BILATERAL EFFECT OF PALMITOYLETHANOLAMIDE ON THE EXPRESSION OF TNF-ALPHA IN PRIMARY SENSORY NEURONS IN A RAT MODEL OF NEUROPATHIC PAIN: A PRELIMINARY STUDY

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Introduction: In neuropathic pain models, an increase of TNF-α expression at the dorsal root ganglion (DRG) has been described. Otherwise, the administration of palmitoylethanolamide (PEA) showed an analgesic effect on several models of neuropathic pain.

Objectives: We studied the relation between the analgesic effect of PEA and its effect on TNF-α expression at the DRG in neuropathic pain.

Methods: We used chronic constriction injury (CCI) model to induce neuropathic pain. Plantar test and Von Frey test were used to evaluate thermal hyperalgesia and mechanical allodynia, respectively. TNF-α expression was studied using immunohistochemistry.

Results: CCI induced concurrently neuropathic pain behaviors on ipsilateral paw and a bilateral increase of immunoreactivity (IR) to TNF-α in the L4 and L5 DRG neurons. Administration of PEA (10 mg/kg i.p.), reduced significantly both, thermal hyperalgesia and mechanical allodynia on CCI model. Difference scores (ipsilateral - contralateral) on days 5 and 7 post-CCI were -2.96 ± 0.31 s and -1.81 ± 0.30 s for hyperalgesia and -1 rank and -0.5 ranks for alldynia. These values are not statistically different from those of naive animals. Same dose of PEA also reversed the bilateral increase of TNF-α IR in L4 and L5 DRG neurons observed after CCI.

Conclusions: These findings confirm the regulatory role of PEA on the expression of TNF-α in primary sensory neurons, whereas the bilateral effect support the hypothesis that its analgesic properties are not directly related with its effect on the expression of TNF-α.
CONTRIBUTION OF THE VOLTAGE-GATED SODIUM CHANNEL BETA1-SUBUNIT IN BASAL SENSITIVITY, NOCICEPTIVE AND NEUROPATHIC PAIN MODEL

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Voltage-gated sodium channels (VGSCs) contribute to the generation of ectopic neuronal activity in primary sensory neurons following peripheral nerve injury. VGSCs are composed of alpha and beta-subunits that can regulate trafficking and gating properties of alpha counterparts. Dorsal root ganglia (DRG) sensory neurons of beta1-subunit knockout mice (Scn1b−/−) were demonstrated to be hyperexcitable.

Here, we used a nociceptor-specific conditional knockout mouse for beta1-subunit to study the physiological contribution of this gene in vivo and investigated whether alpha-subunit expression in DRGs would be consequently altered.

The strategy employed sensory testing in wild-type (wt) and conditional knockout mice (SNS-Scn1b−/−), in which Scn1b is deleted in Nav1.8 positive nociceptors. Sensory testing consisted of: mechanical non painful stimulation (Von Frey test), heat sensitivity (Hot plate, tail flick) and mechanical nociception (electronic pincher). Mechanical allodynia was evaluated after the spared nerve injury (SNI) neuropathic pain model. We evaluated Navs transcripts in DRGs using qRT-PCR.

SNS-Scn1b−/− have a higher frequency of withdrawal response to mechanical innocuous stimulus (p=0.0063), demonstrate a shorter latency (p=0.0053) to noxious heat stimulus at 55°C and the force inducing a tail withdrawal after noxious mechanical stimulus is reduced (p=0.049). The mechanical allodynia after SNI was exaggerated in SNS-Scn1b−/− compared to wt (p=0.0027). Except for Nav1.1, none of the Navs transcript is modified.

Our results clearly demonstrate an important role of Scn1b in basal sensitivity, nociceptive and neuropathic pain. Because their primary function is the stabilization of Navs at the membrane, it is likely that SNS-Scn1b−/− phenotype is due to an impaired Navs regulation.
THE IMPACT OF UNCERTAINTY IN THE THERAPEUTIC TARGET ON THE QUALITY OF GABAPENTIN INDIVIDUALIZED DOSING

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Introduction: Gabapentin is instrumental in the treatment of peripheral neuropathy. However, high pharmacokinetic (PK) variations may impact its efficacy and dose-related side effects. We constructed a population model based on known PKs from gabapentin-treated patients and successfully developed an individualized dosing chart (IDC) for each individual, assuming a deterministic therapeutic target for the concentration.

Objectives: The aim of this study is to assess the impact of relaxing the assumption of deterministic therapeutic target on the quality of the gabapentin IDCs.

Methods: Existing literature suggests the uncertainties in the lower limit of the target gabapentin concentration range from 10-25%. IDCs for individual patients were compared with and without the target 10-25% uncertainty assumption using the Bayesian approach.

Results: The uncertainty in the upper limit of gabapentin's therapeutic target is more sensitive than that of the lower limit. Uncertainties affect the shape of the IDCs, however the optimal gabapentin dosing are largely unaffected.

Conclusions: The success of an IDC relies on the precision of the target concentration prediction. We show that, the IDC of gabapentin remains optimal, even considering some uncertainty at both lower and upper limits. Our result supports using the IDCs of gabapentin in the clinic to maximize pain control while minimizing toxicity.
MEDICAL SELF-MANAGEMENT OF NEUROPATHIC VERSUS NOCICEPTIVE PAIN: IS THERE A DIFFERENCE?

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**Background and aim:** Individuals with neuropathic and nociceptive pain report unique pain experiences. This study explored the medical management strategies used by individuals with probable neuropathic (NeP) and nociceptive (NoP) chronic pain.

**Methods:** This analysis was based on a subset of participants in a recently completed cross-sectional survey on chronic pain in the general population of Canada. Respondents were identified as having (1) chronic pain if they reported pain for more than three months, and (2) NeP if they scored 12 or greater on the Self-Report Leeds Assessment of Neuropathic Signs and Symptoms Pain Scale. Data collection included the Health Care Utilization & Medication Use Questionnaire, and Level of Expressed Need Scale.

**Results:** Five hundred and twenty-two respondents reported NoP (73.5%) and 188 reported NeP (26.5%). Individuals in both groups most commonly identified family doctors as their most helpful pain management clinician, however individuals with NeP were more likely to report five or more visits in the past 12 months (Relative risk [RR] 1.7, 95% confidence interval [CI] 1.3-2.3). Individuals with NeP were less likely to both manage their pain solely with non-pharmacological interventions (RR 0.4, CI 0.2-0.8), and to report complete satisfaction with ability to control pain (RR 0.5, CI 0.3-0.9).

**Conclusions:** Differences exist in the medical self-management of NeP and NoP. Further research is necessary to identify and test pharmacological and non-pharmacological approaches specific to the management of NeP and NoP.
A CLINICAL AND NEUROPHYSIOLOGICAL STUDY OF PAIN IN PATIENTS WITH EHLERS DANLOS SYNDROME

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Ehlers-Danlos syndrome is an inherited connective tissue disorder, caused by a defect in the synthesis of collagen, causing joint hypermobility. Pain is a frequent complaint in patients with this rare condition, but its underlying mechanism is still debated, thus limiting the effectiveness of treatment. Although several reports have suggested that many patients with Ehlers Danlos syndrome suffer from neuropathic pain no studies have been dedicated at investigating the underlying pain mechanism in patients with this rare condition.

In this prospective study we aimed at assessing prevalence, clinical features and underlying mechanism of pain in twenty patients with Ehlers Danlos syndrome. All patients underwent a detailed clinical and neurological examination, including the DN4 questionnaires for diagnosing neuropathic pain, the fibromyalgia rapid screening tool and standard nerve conduction study for assessing the non-nociceptive afferent fibres. All patients also underwent a quantitative sensory testing (QST) and laser evoked potentials for assessing thermal-pain pathway function.

We found that clinical examination, DN4 questionnaire, quantitative sensory testing, standard nerve conduction study and laser evoked potentials disclosed no abnormalities consistent with a diagnosis of neuropathic pain. Conversely clinical examination showed that most patients suffered of widespread pain, with a positive fibromyalgia rapid screening tool.

Our data argue against the view that Ehlers Danlos syndrome-related pain is a neuropathic pain condition, rather our patients suffered of a widespread, fibromyalgia-like pain. Our data might be useful for designing treatment for pain in patients with this rare condition.
AN EXAMINATION OF TTX-RESISTANT ACTION POTENTIAL CONDUCTION IN CULTURED PORCINE DRG NEURONES USING CALCIUM IMAGING

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Background and aims: The specific contribution of voltage-gated sodium channel (NaV) isoforms to action potential conduction in peripheral sensory axons remains controversial. Recordings from DRG somata indicate that TTX-r NaVs deliver the majority of current during an action potential. However, for conduction in mature sensory axons evidence suggests that TTX-s NaVs alone are sufficient. To examine this discrepancy, the contribution of TTX-r NaVs to action potential conduction was examined in cultured porcine DRG neurites.

Methods: DRG neurones were isolated from 4-8 day old piglets and cultured in a central chamber from which neurite extension into a lateral chamber was promoted with either NGF or GDNF. Neurites were imaged after 5-10 days in culture using the calcium indicator Fluo-8. Images were acquired (1Hz or 5Hz) and ratio changes in fluorescence intensity were determined after correction for photobleaching.

Results: Constant current electrical stimulation (20Hz, 1ms, 40mA for 1s) applied in the central (somal) chamber evoked calcium signals in neurites in the lateral chamber. Electrically-evoked TTX-r calcium signals were recorded in 80% of neurites following a 10 minute exposure to TTX (500nM). In contrast, exposure to lidocaine (1mM) for 10 minutes abrogated responses to electrical stimulation. This effect was reversible with calcium responses returning after 20 minutes of washout.

Conclusions: Consistent with recent reports, functional TTX-r NaVs are shown to contribute to axonal conduction in cultured neurites. The physiological conditions under which TTX-r currents contribute to axonal conduction are more likely to be associated with injury and regeneration.
EXAMINING THE TIME-TO-IMPROVEMENT OF SLEEP DISTURBANCE IN PATIENTS WITH CHRONIC NEUROPATHIC PAIN DUE TO SPINAL CORD INJURY

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Background and aims: Patients with chronic neuropathic pain due to spinal cord injury (SCI) often report disturbed sleep. Two placebo-controlled trials, which comprise the largest clinical database for the pharmacologic treatment of SCI-related neuropathic pain, have demonstrated that pregabalin improves sleep disturbance in such patients. This post-hoc analysis examines the time-to-improvement in sleep during these two trials.

Methods: Daily sleep interference scores were based on an 11-point numeric rating scale, with higher scores indicating more disturbed sleep. Changes in sleep interference scores were analyzed using analysis of covariance in the intention-to-treat population (N= 343). The time-to-onset (TTO) for reduction in sleep interference scores was calculated for both trials. TTO was defined as the first day sleep interference scores for that particular day, and the following day, were significantly lower than placebo.

Results: In both trials, pregabalin treatment significantly reduced sleep interference scores at endpoint compared to placebo. Mean placebo-adjusted improvements in sleep interference scores at endpoint were -1.37 (LOCF; \( p < 0.001 \)) and -1.08 (LOCF; \( p < 0.001 \)) for the two trials. In both trials, the TTO for reduction in sleep interference scores occurred on day one following initiation of treatment. Mean placebo-adjusted improvements in sleep interference scores on day one were -0.93 (\( p < 0.001 \)) and -0.71 (\( p = 0.001 \)) for the two trials.

Conclusions: These findings demonstrate that, in patients with neuropathic pain due to SCI, statistically significant and sustained improvement in sleep disturbance occurs rapidly in response to treatment with pregabalin.

Funded by Pfizer Inc.
Background and aims: Atypical Odontalgia (AO) is a relatively rare chronic orofacial pain condition, which represents a diagnostic and therapeutic challenge for the dentist. The aim of this study was to carry out a systematic review about the quantitative methods for somatosensory evaluation in AO patients.

Methods: A computerized search from most relevant databases including MEDLINE, EMBASE and Cochrane Library was performed. Studies that included Quantitative Sensory Testing (QST) such as Mechanical Detection Threshold (MDT), Mechanical Pain Threshold (MPT) (pinprick), Pressure Pain Threshold (PPT), Dynamic Mechanical Allodynia with a cotton swab (DMA1) and with a brush (DMA2), Warm Detection Threshold (WDT), Cold Detection Threshold (CDT), Heat Pain Threshold (HPT), Cold Pain Detection (CPT) or Wind-up ratio (WUR) in AO patients were included.

Results: Four publications met the inclusion criteria. The review of these studies reveals that the results from mechanical allodynia tests (DMA1, DMA2, WUR) were significantly higher and pain threshold tests to heat stimulation (HPT) were significantly lower in AO patients, when the affected side was compared to the contralateral side, however for MDT, MPT, PPT, CDT, WDT results were not significant. These outcomes reflect the presence of central sensitization features, such as allodynia and temporal summation.

Conclusions: Our review suggests that there is an important role of central sensitization process in AO patients, which needs further analysis at the time of planning a management strategy.
INVESTIGATING THE INFLUENCE OF FAVORITE MUSIC ON THE PAIN RESPONSE IN THE ENTIRE NEUROAXIS USING FUNCTIONAL MAGNETIC RESONANCE IMAGING

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Background and aims: Music analgesia has been used to treat pain for thousands of years, because it is successful, accessible, without side-effects, and inexpensive. With brain and spinal fMRI, we can demonstrate changes in neural activity within structures of the pain analgesia system of the brain, brainstem and spinal cord which is necessary for understanding the entire process of pain modulation.

Methods: Healthy, female, non-musicians, adults underwent a thermal stimulation model specifically targeting C-pain fibers. Thermal stimulation was applied to the right hand, corresponding to the C6 dermatome. After the painful stimuli, participants rated their pain perception. Concurrently, participants listened to either their favorite pieces of music or no music as a control. After each piece of music, gave a music rating based on 4 criteria to provide further insight on the mood of the individual. Data was analyzed by means of a general linear model.

Results: Preliminary data in training sessions demonstrated that subjective pain ratings are reduced when listening to favorite music, as opposed to no music. During the imaging session, we expect reduced activity in the music condition (compared to no music) in areas known to be involved in pain processing. We also predict that brain regions thought to be involved with reward and emotion will be selectively active in the music condition.

Conclusions: This study will investigate the role of the descending analgesia system in music analgesia, which may improve our understanding of pain processing mechanisms.
NEUROPATHIC PAIN PREDICTS THE ONSET OF CHRONIC WIDESPREAD PAIN: RESULTS FROM A LARGE-SCALE POPULATION BASED SURVEY

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Aim: To determine whether neuropathic pain (NP) predicts the onset of CWP.

Methods: 1540 (63% participation rate) individuals returned questionnaires at baseline and 12 months later. Participants shaded any pain lasting one day or longer in the past month on a blank body manikin; indicated whether they had been aware of this pain for three months or longer; and were classified as “no pain”, “some pain” or CWP (ACR 1990 criteria). Among those free from CWP, those with new onset CWP at follow-up were identified. Presence/absence of NP was categorized using the Douleur Neuropathic 4 questionnaire. Multinomial logistic regression tested study hypotheses with results presented as relative risk ratios (RRR) with 95% confidence intervals (95% CI).

Results: Participant median age was 61 (IQR=52-67) years and 58% (n=889) were female. Of the 1181 participants free from CWP at baseline, 155 (13%) developed CWP. A total of 3.7% (n=20) of subjects with no pain, 19.2% (n=109) with some pain that was not neuropathic, and 32.9% (n=26) with some pain that was neuropathic developed new CWP. After adjusting for age, sex and depression, those with some pain that was not neuropathic were 6 times more likely (RRR = 5.7, (3.4, 9.5)) and those with some pain that was neuropathic 9 times (9.4 (4.7, 18.7)) more likely to develop CWP.

Conclusion: Having some pain increased the risk of developing CWP and this relationship was augmented by the presence of NP.
ESTABLISHING THE MAGNITUDE OF A CLINICALLY MEANINGFUL DIFFERENCE IN QUALITY OF LIFE FOR PATIENTS WITH NEUROPATHIC PAIN

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Background: Recent Guidelines for Neuropathic Pain (NeP) assessment (Haanpaa et al 2011) recommend that Quality of Life (QoL) is included as a patient reported outcome in treatment trials. The Neuropathic Pain Impact on QoL scale (NePIQoL) is a relatively new condition-specific QoL measure for NeP with good psychometric properties. Information on the NePIQoL’s ability to detect minimal clinically important differences (MCID) i.e. the smallest improvement patients perceive as beneficial is not yet established. This information is needed to evaluate its utility as a patient reported outcome measure.

Objectives: To define a MCID for the NePIQoL. To provide data on NePIQoL profiles for patients with different types of NeP.

Methods: Pragmatic, prospective cohort study with repeated measures. ~320 patients will complete NePIQoL, SF36, HADS, mBPI, NPSI and sleep scales before and after treatment. Following treatment a patient global impression of change score (PGIC) is used as the gold standard against which to compare NePIQoL scores and determine MCID.

Results: To date, 116 patients, 52% female, mean age 52.0, SD 12.85 years have been recruited from primary care and a specialist pain centre. NeP types include; peripheral neuropathy, posttraumatic neuropathic pain, neuropathic low back pain, trigeminal neuralgia and central pain. Interim analysis of baseline data shows impairment in QoL associated with NeP of different types on multiple measures. Current post treatment scores are consistent with PGIC reports.

Conclusions: Recruitment is ongoing. Greater numbers are required for analysis of MCID to provide a benchmark for use of the NePIQoL in future clinical trials.
PERIPHERAL NOCICEPTOR SENSITIZATION MEDIATES ALLODYNYA IN PATIENTS WITH DISTAL SYMMETRIC POLYNEUROPATHY

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Patients with painful neuropathy frequently suffer from dynamic mechanical alldynia, i.e. pain in response to normally non-painful brushing. Despite many animal studies suggesting that alldynia arises when the spontaneous firing in damaged nociceptive afferents sensitise second-order nociceptive neurons to Aβ-fibre input, no studies have sought to confirm this mechanism by investigating Aβ-fibre sparing in human patients with alldynia. In this study we compared data from Aβ-fibre-mediated nerve conduction studies and nociceptive-fibre-mediated laser-evoked potentials (LEPs) in 200 patients with distal symmetric polyneuropathy (114 with neuropathic pain, 86 without). Of the 114 patients with painful neuropathy studied, 44 suffered from alldynia. Whereas no statistical difference was found in nerve conduction study data between patients with and without alldynia, LEP amplitudes were larger in patients with alldynia than in those without (P < 0.01 by Mann-Whitney U test). The lack of difference in NCS data between patients with and without alldynia suggest that this type of pain, rather than arising through second-order nociceptive neuron sensitization to Aβ-fibre input, might reflect a reduced mechanical threshold in sensitised intraepidermal nociceptive nerve terminals.
EFFECT OF HIGH CONCENTRATION (8%) CAPSAICIN PATCH ON THE AREA OF PAIN: PRELIMINARY REPORT

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Background and aim: High concentration (8%) capsaicin patch (HCCP) is a new formulation of capsaicin that recently became available for the treatment of peripheral neuropathic pain. Denervation of outer layers of epidermis is commonly considered the most important skin effect of capsaicin but its correlation with pain relief is poor. In case of continuous firing of peripheral unmyelinated afferents, central sensitisation (CS) occurs and pain area increases. On the other hand, when CS subsides, the pain area consequently decreases.

Aim of the study was to measure the pain area before and after the HCCP application.

Methods: We studied ten consecutive patients with neuropathic pain treated with HCCP. Six patients had post-herpetic neuralgia and four post-surgical neuropathic pain. The area of pain was measured before the first (T0) and the second (T1) applications, according to procedure for HCCP application. Time interval between the two applications ranged between 80 and 176 days (mean 105.6). Ongoing pain therapies remained substantially unmodified between applications.

Results: The area of pain underwent a decrease after the HCCP application. The mean area changed from 384.9 cm$^2$ (T0) to 292.8 cm$^2$ (T1), with a mean decrease of 24.78%. In particular, in eight patients the area clearly decreased, in one it increased (+21.12%) and in one it did not change (+2.5%).

Conclusions: The decrease of pain area observed in these preliminary results suggests that the attenuation of CS could be one of the antalgic mechanism of HCCP. Further studies on larger population are warranted.
THE ANTINOCICEPTIVE EFFECT OF GLUCOMANNAN IN MODELS OF ACUTE AND NEUROPATHIC PAIN IN MICE: INVOLVEMENT OF THE GLUTAMATERGIC SYSTEM AND PRO-INFLAMMATORY CYTOKINE PATHWAYS


Background and aims: Glucomannan (GM) is a polysaccharide obtained from Heterodermia obscurata lichens. The present study was conducted to elucidate the antinociceptive effect of GM in behavioral models of acute and neuropathic pain in mice.

Methods: Male Swiss mice (n=6-10) were used to investigate the effects of daily treatment with GM (100 mg/kg, i.p.) on the mechanical allodynia associated with neuropathic pain (partial sciatic nerve ligation, PSNL), using von Frey filaments. On Day 21 after surgery pro-inflammatory cytokines levels, IL-1β and TNF-α, were measured by Elisa in spinal cord and sciatic nerve. The participation of the glutamatergic system and pro-inflammatory cytokines in the GM effect (10-100 mg/kg, i.p.) was evaluated against nociception induced by intraplantar injection (i.pl.) of glutamate and intrathecal injection (i.t.) of NMDA, kainate, trans-ACPD, TNF-α and IL-1β. Motor skills were evaluated using the rota-rod test to determine the potential sedative effects of GM.

Results: Daily treatment with GM reduced significantly mechanical allodynia and the IL-1β levels in spinal cord and sciatic nerve in the PSNL model. Systemic treatment with GM inhibited the nociception induced by glutamate (i.pl.) or NMDA, trans-ACPD, TNF-α and IL-1β (i.t.). However, it did not alter the nociceptive response caused by kainate. Conversely, sedative effects were not evident from the rota-rod test at antinociceptive doses.

Conclusions: Taken together, our data demonstrate that GM have significant antinociceptive effects in acute and neuropathic pain, suggesting that it might be of potential interest in the development of new clinically relevant drugs for the management of pain.
LINALOOL, A NATURALLY OCCURRING MONOTERPENE, REDUCES THE HEAT HYPERALGESIA IN MODEL OF PARKINSON DISEASE INDUCED BY MPTP IN MICE

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Background and aims: The prevalence of pain in Parkinson Disease (PD) is significantly greater than age-matched controls. In this work we evaluated the anti-hyperalgesic effect of the linalool in a PD model induced by MPTP.

Methods: Male C57BL/6 mice received MPTP (20 mg/kg, i.p.) four times at 2-h intervals within a day. Control mice received saline. The treatment with linalool (5 and 10 mg/kg, p.o., 12/12 h) or vehicle started on Day 1 after administration of MPTP or saline. The hotplate test (~50°C) was used to measure heat hyperalgesia. The time elapsed between placement and shaking or licking of the hindpaws was recorded as the latency to nociception. To evaluate bradykinesia, the pole test was used. The mice were placed head upward on the top of a rough-surfaced pole (8 mm/50 cm, wrapped with gauze). The time until it climbed down to the floor was examined. In this study, the test was performed on Day 1 before and on Day 1, 3 and 7 after administration of MPTP or saline. On Day 7 striatal was removed for measurement of dopamine and homovallic acid levels by HPLC.

Results: Treatment with linalool in both doses reduced heat hyperalgesia on Day 3 and 7 after administration of MPTP in relation to MPTP plus vehicle group. However, linalool did not improve bradykinesia or dopamine levels in striatal.

Conclusions: Linalool reduced heat hyperalgesia induced by PD model in mice, suggesting that it may be used in addition to antiparkinson medication in patients with neuropathic pain.
Changes in CD200 and CD200R Expression in Two Rat Models of Neuropathic Pain

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Background and aim: The existence of CD200 in glial cells and neurons of the central nervous system is well-known, but there is limited information on the distribution of CD200 and CD200R in the peripheral nervous system. Here, we investigate bilateral changes of CD200 and CD200R expression in L4-L5 dorsal root ganglia (DRG) after chronic constriction (CCI) or spare nerve (SNI) injury of the sciatic nerve used as neuropathic pain models.

Method: Rats undergoing unilateral CCI and SNI were left to survive for 3, 7 or 14 days, sham-operated rats for 3 or 14 days. Neuropathic pain induction was tested by measurement of mechanoallodynia and thermal hyperalgesia. After the survival time, L4-L5 DRG were removed bilaterally from naive, operated, and sham-operated rats and CD200 and CD200R proteins were detected by immunohistochemical staining.

Results: Unilateral SNI induced a transient bilateral increase of CD200 protein levels in satellite glial cells after 3 days while immunostaining was reduced following 14 days from operation. In contrast, CD200 immunofluorescence was elevated bilaterally in DRG mainly after 14 days from CCI operation. Furthermore, CD200R expression was enhanced in DRG after 7 days from SNI and CCI operations compared with naive animals.

Conclusion: Our results suggest that CD200/CD200R might play an inhibitory role of neuroinflammatory reactions in the DRG to keep homeostasis after neuropathic stress.

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EVALUATION OF SENSORY AND PAIN PERCEPTION AND MECHANISMS OF CENTRAL MODULATION OF PAIN PERCEPTION IN PATIENTS WITH MULTIPLE SCLEROSIS (A PILOT STUDY)

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Introduction: Multiple sclerosis (MS) is considered as a suitable model for central neuropathic pain (CNP). Knowledge of sensory profile and function of central modulation of pain perception in CNP patients may help to reveal underlying mechanisms of CNP, which are still not fully understood.

Patients and methods: A detailed evaluation of sensory and pain perception and of mechanisms of central modulation of pain perception using an extensive battery quantitative sensory testing (QST) methods was performed in 25 patients with MS (14 men, median age 33 years) and 20 healthy volunteers (8 men, median age 34 years). Seven of the MS patients fulfilled the current diagnostic criteria for central neuropathic pain (CNP-MS subgroup). Among others, magnitude of conditioned pain modulation and temporal summation using thermal stimuli were assessed.

Results: Comparing to healthy controls, MS patients (irrespectively to the presence of CNP) showed the decreased perception of most of the sensory modalities examined. The only difference found between CNP and non-CNP MS patients was the finding of „paradoxical cold sensation“, i.e. warm stimuli perceived as a cold sensation, which were reported in 2 CNP (and no non-CNP) MS patients, while „paradoxical heat sensation“, i.e. cold stimuli perceived as a burning hot painful sensation was found in almost a quarter of both the CNP and non-CNP MS patients.

Conclusion: Significant decrease of sensory and pain perception of most of the modalities examined was found in MS patients comparing to healthy controls, while only minor differences were observed between CNP and non-CNP MS patients.
EFFECTIVENESS, TOLERABILITY AND IMPACT ON QUALITY OF LIFE OF CT-GUIDED EPIDURAL STEROID INJECTIONS AND PHARMACOTHERAPY FOR THE TREATMENT OF PERSISTENT LOW BACK PAIN WITH RADICULOPATHY

D. Bansal, P. Vilok, B. Ghai, India

Background & aims: Substantial number of patients with persistent low back pain (LBP) are treated with multimodal spectrum of conservative and invasive therapies. Few have investigated the utility of pharmacotherapy and epidural steroid injections (ESI) in large practice setting. We sought to gather comprehensive data about the characteristics, efficacy, tolerability and quality of life (QoL) of patients with LBP with these therapies.

Methodology: Information was collected on a standardized form. Information included patient characteristics, type and duration of therapies, adverse events, pain relief using visual analogue scale (VAS) and QoL by measuring disability using modified ODQ at each month of follow-up.

Results: Consecutive 81 patients were recruited and followed for 6 months. Average baseline pain duration was found to be 45.5 months. Combination of drugs and ESI was given in 75 (92%) patients. Anticonvulsants (75%) and Antidepressants (57%) were most commonly prescribed medications. Efficacy, QoL and safety data presented in Table 1

<table>
<thead>
<tr>
<th>Duration (months)</th>
<th>VAS</th>
<th>Change from baseline</th>
<th>P value</th>
<th>ODQ*</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>70 (50-80)</td>
<td>-</td>
<td>-</td>
<td>25 (20-28)</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>55 (40-65)</td>
<td>-15</td>
<td>0.004</td>
<td>19.5 (15-25)</td>
<td>0.01</td>
</tr>
<tr>
<td>6</td>
<td>45 (30-65)</td>
<td>-25</td>
<td>0.06</td>
<td>16(12-20)</td>
<td>0.04</td>
</tr>
</tbody>
</table>

P value was calculated by Wilcoxon Signed rank test, *ODQ=Oswestry's disability questionnaire, values expressed as Median (IQR)

(Table 1: Pain intensity and functional disability)

and Figure 1.
Conclusions: Pregabalin and amitriptyline were most commonly used drugs with maximum pain relief and improved QoL. Desired pain relief fluctuated with time. ESI can be promising choice when desirable pain relief is not achieved with medications.
Stomatin-like protein 1 regulates mechanotransduction in nociceptors

C. Wetzel, E.S. Smith, A. Kozlenkov, G.R. Lewin, Molecular Physiology of Somatic Sensation, Germany

Stomatin-domain proteins are a family of integral membrane proteins that play an important role in sensory neuron mechanotransduction. Genetic deletion of the stomatin-like protein 3 gene (stoml3) leads to a substantial loss of mechanosensitivity amongst myelinated afferents in the skin. Interestingly, these animals are also protected from neuropathic pain (Wetzel, C. et al. Nature 445, 206-9, 2007). Here we have examined the function of stomatin-like protein 1 (STOML1) which is also closely related to C. elegans’ Unc-24. We have generated a STOML1 allele in which the open reading frame of the stoml1 gene has been replaced with a nuclear localized β-galactosidase reporter cassette. This mouse allowed us to identify the cells in which STOML1 is normally expressed. We found that STOML1 seems to be exclusively expressed in a subset of small nociceptors in the dorsal root ganglia (DRG). We also observed that STOML1, like its relative STOML3, can regulate the activity of acid sensing ion channels. Whole-cell patch-clamp recordings from acutely cultivated DRG neurons indicated changes in the density of proton-gated currents in a small subset of nociceptors in stoml1−/− mutant mice. We further employed the in vitro skin nerve preparation to characterize non-myelinated nociceptors and examined their receptive properties. Interestingly, C-mechanonociceptors that lack a response to noxious heat stimuli were substantially impaired in their response to suprathreshold mechanical stimulation in stoml1−/− mutant mice compared to controls. Next we will examine the consequences of stoml1 gene deletion on pain behaviors in models of inflammatory and neuropathic pain.
ACUTE COLONIC INFLAMMATION LEADS TO VISCERAL HYPERSENSITIVITY AND LONG-LASTING NEUROPLASTIC ALTERATIONS

T.K. Lapointe, K. Chapman, C. Altier, Canada

Inflammatory bowel disease (IBD) is associated with debilitating abdominal pain, which in some cases can persist throughout quiescent stages of the disease. During inflammation, activation of sensory dorsal root ganglia (DRG) neurons leads to the release of neuropeptides, such as substance P, at the nerve terminal. This process, known as neurogenic inflammation, exacerbates inflammatory responses and contributes to the establishment of visceral hypersensitivity. The signaling pathways regulating neuronal sensitization and pain during IBD remain elusive. Therefore, this study aimed to identify the mechanisms of peripheral and central neuroplasticity in the context of IBD using the Dextran Sulfate Sodium (DSS) murine model of colitis.

Results: Our results indicate that mice subjected to 2.5% DSS in drinking water for seven days exhibit nocifensive behaviors consistent with visceral pain. Notably, colon-innervating sensory DRG neurons isolated from these animals showed extensive neurite outgrowth and a significant increase in brain-derived neurotrophic factor expression. These changes correlated with an increase in substance P in the colonic mucosa of diseased animals. Importantly, these molecular changes appeared to persist after the resolution of inflammation. Indeed, elevated colonic substance P and c-Fos expression in spinal dorsal horn neurons could be observed as late as five weeks post-DSS treatment, at which time the colonic mucosa appeared histologically normal.

Conclusion: Taken together, these observations suggest that, during colitis, DRG neurons undergo neuroplastic changes that result in long-lasting sensitization and visceral pain. This could explain, at least in part, persistent pain in patients with quiescent IBD.
Background and aims: US health professional schools must provide interprofessional team education under new accreditation standards. Similarly, US health professionals must increasingly manage groups of patients in the context of the Triple Aim (lower costs, better care, better patient outcomes). We designed an interdisciplinary 1-credit hour classroom module in population based pain management including meaningful use of health information technology, transitions in care management, chronic disease management, health promotion and population-based behavior change and communication.

Methods: Blooms and Frank’s Taxonomies of Learning, respectively, framed instructional design through a series of problem-based learning exercises. Content validity was assessed by a panel including an anesthesiologist, pharmacist, nurse, a nurse practitioner, a chiropractor and an acupuncturist. Embedded assessment statistical methods will associate student performance on exams and assessments with specific activities and learning objectives.

Results: The module is now required in the curriculum of the Wegmans School of Pharmacy, St. John Fisher College, Rochester, New York. 72 pharmacy students will complete the module by March, 2013. Student characteristics are: Male (n=38, 52.8%), aged 18-24 (n=62, 77.5%), Caucasian (N=66, 82.5%).

Conclusions: This interdisciplinary population-based pain management module may be a useful model for health professional schools seeking to adopt interprofessional and/or population-based management curricula mapped to learning taxonomies and for which performance data (i.e., learning outcomes) are known. Data-based revisions are expected by May, 2013.
ANTI TUMOR NECROSIS FACTOR - ALPHA ADALIMUMAB (HUMIRA®) IN THE TREATMENT OF COMPLEX REGIONAL PAIN SYNDROME: A PILOT STUDY

E. Eisenberg, I. Sandler, R. Treister, E. Dolnikov, M. Haddad, Israel

Background and aims: Evidence suggest that tumor necrosis factor-alpha (TNF-α) can mediate symptoms and signs in complex regional pain syndrome (CRPS). The present pilot study was aimed to assess the potential efficacy of the anti TNF-α adalimumab in relieving symptoms and signs of CRPS.

Methods: Ten patients with CRPS 1 were assessments before and 1 week, 1, 3 and 6 months following 3 bi-weekly subcutaneous injections of 40mg/0.8ml adalimumab (Humira®) and included the followings: Pain intensity (0-10 cm VAS); the Short Form of the McGill Pain Questionnaire; the Beck Depression Inventory; and the SF-36 questionnaire for assessment of health related quality of life; mechanical and thermal thresholds (Von frey hair) and Thermal Sensory Analyzer, respectively. Both intention to treat (ITT) and per-protocol (PP) analyses were performed.

Results: Completed data was available from five patients. Both analyses have demonstrated only a trend towards improvement in mechanical pain thresholds following treatment (ITT $\chi^2=13.83$, p=0.008; PP $\chi^2=10.29$, p=0.036). No significant changes were found in any of the other parameters. However, a subgroup of three patients with robust improvement in almost all parameters could be demonstrated, "warm" type of CRPS was found in two of them.

Conclusion: These results suggest that anti TNF-α may not be the optimal treatment for all patients with CRPS. Yet, they may also suggest that some patients, perhaps those with "warm" CRPS, can benefit from this treatment. Growing body of evidence witch points to the involvement of TNF-α in the pathogenesis of CRPS justifies further studies in this area.
INTRANEURAL MICROSTIMULATION (INMS) OF LARGE MYELINATED MECHANOSENSORY AFFERENTS FIBERS IN HUMANS: REACTION TIME DEPENDS CRITICALLY ON FREQUENCY OF STIMULATION

B. Bourkiza, J. Serra, G. Iannetti, UK

Background and aims: INMS allows stimulating single afferent axons in humans. It is assumed that tactile sensations evoked with short reaction times (RT) indicate Aβ-fiber stimulation. However, there is scarce information on the relationship between frequency of stimulation and RTs. This information is relevant for neuropathic pain patients with sensory dysfunction.

Methods: We performed INMS of the superficial peroneal nerve of 14 healthy participants. Trains (3s) of electrical pulses (0.2 ms) were delivered at 110% of the perceptive threshold at different frequencies (1-5-10-20-50-100 Hz). We recorded RTs to the first elicited sensation.

Results: INMS of 23 intraneural sites elicited pure tactile sensations fulfilling criteria for Aβ single-unit stimulation. RTs segregated into two groups. In 9 sites RTs were always < 1s at every stimulation frequency ('Flat RT' group, probably Fast Adapting units). In 14 sites RTs were < 1s at high stimulation frequencies (>10Hz), but >1s at lower frequencies ('Decreasing RT' group, probably Slow Adapting units). Thus, RTs in the 'Flat RT' group were always compatible with conduction velocity (CV) of Aβ-fibers. In contrast, RTs in the 'Decreasing RT' group were only compatible with CV of Aβ-fibers at stimulation >10Hz, whereas RTs at frequencies < 10Hz yielded misleading CV, compatible with Aδ- or even C-fibers.

Conclusions: When a single Aβ afferent is stimulated, RTs can dramatically depend on stimulation frequency. This is particularly true for SA Aβ-afferents. Thus, the observation of long RTs to stimuli delivered at < 10Hz might generate incorrect conclusions about the population of activated fibres.
THE EXPRESSION OF GROWTH FACTORS IN THE DORSAL ROOT GANGLION FOLLOWING HERPES SIMPLEX VIRUS TYPE-1 INFECTION IN MICE

G. Lucas, F. Cadetti, R. Kusuda, C. Almeida, M.I. Ravanelli, D. Rassi, S. Zanon, Brazil

Background and aims: Propagation of herpes simplex virus type-1 (HSV-1) in the dorsal root ganglia (DRG) produces herpetic and post-herpetic sensory disorder in mice. Here we investigated the expression of nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), and glial-derived neurotrophic factor (GDNF) during virus replication and the latent phase of infection.

Methods: Adult male Balb/C mice were inoculated with HSV-1 on the skin of the left hind. The expression of NGF, BDNF and GDNF in the DRG extracts was investigated 3, 7, 14 and 21 days after virus inoculation. Growth factors were measured by ELISA. Data were analyzed by two-way ANOVA and Student's t-test. p-values less than 0.05 were considered statistically significant.

Results: Following HSV-1 inoculation allodynia and hyperalgesia became evident in the hind paw on the inoculated side on day 3 and persisted until day 28 (p < 0.05). The application of heat-inactivated HSV-1 induced no allodynia, hyperalgesia and skin lesion. NGF expression in the DRG was significantly increased from day 3 to 21 post-infection (p < 0.01). Conversely, HSV-1 inoculation increased BDNF on days 7 and 15 post-infection (p < 0.001) whereas GDNF was marked increased only on day 7 after virus inoculation (p < 0.01).

Conclusions: These data suggest that herpetic pain may be associated to the phenotypic switch induced by NGF, BDNF, and GDNF in dorsal root ganglion cells. Moreover, post-herpetic neuralgia may be associated with increased NGF activity which seems to be a prerequisite for the maintenance of viral latency.
ALTERED CORTICOMOTOR REPRESENTATION OF AFFECTED MUSCLES IN SUBJECTS WITH CHRONIC NEUROPATHIC PAIN STUDIED USING TRANSCRANIAL MAGNETIC STIMULATION MAPPING

P. Sacco, K. Maciver, R. Bresnahan, G. Thickbroom, T. Nurmikko, UK, Australia

Aims: Functional imaging studies have shown that chronic pain patients have altered motor cortical (M1) representation of their pain-affected region, signifying cortical reorganisation. We used transcranial magnetic stimulation (TMS) mapping to quantify the M1 reorganisation by comparing differences in corticospinal representation between affected (contralateral to pain) and unaffected (ipsilateral to pain) hemispheres.

Methods: 24 patients with unilateral neuropathic pain of the hand (13), face (7) or lower leg (4) were studied. Motor evoked potential (MEP) responses from stimulation of the affected and unaffected M1 (first dorsal interosseus, perioral and tibialis anterior, depending on the location of the pain) were recorded electromyographically using a 5x5mm visual grid superimposed on an MRI reconstructed head model. Maps were generated by applying a 3D-spherical spline function to the MEP responses to obtain measures of optimal scalp location, centre of gravity (COG), area, and volume.

Results: The scalp area over which MEP responses could be obtained was, on average, over 30% greater for the affected area (12.7±0.9cm² vs 8.8±0.8cm², p< 0.001; Wilcoxon signed rank test). COG in the anterior-posterior plane demonstrated an anterior shift in the affected M1 (p< 0.01). MEP characteristics were not significantly different between sides.

Conclusion: The dramatic enlargement in corticomotor representation and anterior shift are indicative of the extent of maladaptive cortical reorganisation associated with neuropathic pain. TMS mapping provides a means to accurately quantify such changes. It may have use in the planning of motor cortex stimulation treatment for neuropathic pain.
OXALIPLATIN-INDUCED NEUROPATHY IS MEDIATED BY NRSF TRANSCRIPTIONAL REPRESSION OF TREK/TRAAK POTASSIUM CHANNEL FAMILY

V. Pereira, W. Legha, M. Devilliers, E. Bourinet, A. Eschalier, J. Busserolles, France

Background and aims: Oxaliplatin is a platinum derivate that is used in the treatment of colorectal carcinoma. Administration of this drug produces cold-induced dysesthesia and paresthesia immediately following the first infusion in 90% of patients. In order to understand the pathophysiology of this neurotoxicity we used a mice model of acute oxaliplatin-induced neuropathy. We showed that oxaliplatin both exacerbates cold perception and causes ion channel expression remodeling in nociceptors. Interestingly, we found a downregulation of three potassium channels involved in cold and mechanical perception: TREK1, TREK2 and TRAAK. Using bioinformatics tools, we found response elements in TREK1, TREK2 and TRAAK genes for NRSF, a transcriptional repressor involved in neuropathic pain following nerve injury.

Methods: To investigate the involvement of NRSF in oxaliplatin-induced neuropathy, we used intrathecal administration of antisens oligonucleotide to induce NRSF knockdown in oxaliplatin-treated mice dorsal root ganglia (DRG). During the treatment, we performed several behavioral experiments to assess mice cold and mechanical perception. Four days after oxaliplatin administration, lumbar DRG and spinal cord were removed for molecular analysis.

Results: We showed that NRSF knockdown prevent oxaliplatin-induced neuropathy in mice. We also demonstrated that NRSF overexpression is required for oxaliplatin-induced TREK/TRAAK channels transcriptional repression.

Conclusions: NRSF upregulation occurring after oxaliplatin treatment enables the TREK/TRAAK channels transcriptional repression responsible of cold and mechanical hypersensitivity.
Chemotherapy-induced peripheral neuropathy (CIPN), a major dose-limiting toxic effect of several frontline chemotherapeutic drugs, can cause severe distress and severely impacts on the cancer treatment and life quality of thousands of cancer survivors. Unfortunately, the mechanisms of CIPN are not well understood, and CIPN is often refractory to currently used pain-relieving medications. To explore the contribution of chemokines in CIPN, we here use chemokine PCR array to examine the expression of chemokines/chemokine receptors in DRG and spinal dorsal horn from animals treated with oxaliplatin or paclitaxel chemotherapy. Adult male Sprague-Dawley rats were treated with oxaliplatin (3 mg/kg in PBS, one injection, intraperitoneal) or paclitaxel (2 mg/kg, once every other day for four injections in total, intraperitoneal). L4/L5 DRG and L4 - L6 spinal cord dorsal horn were collected when animals showed peak level of mechanical hypersensitivity assessed by von Frey filaments stimulation following chemotherapy (Day 5 for oxaliplatin and Day 7 for paclitaxel). With a cut-off value of 1.5 fold-change, we observed an increase in chemokines and chemokine receptors in both DRG and spinal dorsal horn following both oxaliplatin and paclitaxel chemotherapy. Although different profile of chemokine/chemokine receptor was induced following each chemotherapy, same chemokines/chemokine receptors, such as CCL2, CCL25, CCL28, CCR1L1, CCR2 and CXCL1 in DRG, and CCL9 and CCR9 in spinal dorsal horn, were induced by both chemotherapies, suggesting shared inflammatory events. Our data suggest the induction of chemokines/chemokine receptors may play important roles in CIPN and targeting the commonly-induced chemokines may be a novel therapeutic strategy.
INTRAOSSEOUS BLOCKADES FOR THE TREATMENT OF FACIAL PAIN

L. Kornilova, E. Sokov, Russia

During last 32 years we use for the treatment for low back pain intraosseous blockades (IOB). High efficiency of IOB proves an important role of intraosseous receptors in the pathogenesis of low back pain. Assuming that intraosseous receptors are involved in the pathogenesis of facial pain (FP), we decided to use IOB in the treatment of FP. We observed 60 patients with FP.

The patients average age was 64 years, average duration of FP was 9.8 years. In these patients, conservative treatment of FP was ineffective. All the patients were treated with IOB, which involved injection of a solution of 2-4 ml of 1% Lidocaine with 1-2 mg of Dexamethasone into the bone marrow of the zygomaticus and/or mandibular bone. The pain syndrome was assessed before and after treatment using the Visual Analogue Scale (VAS).

After the treatment with IOB, pain syndrome had decreased on an average from 7.8 to 2.1 (VAS). 23 (38%) patients reported about full regression of pain.

Intraosseous blockade - effective method of treatment of facial pain. The high effectiveness of intraosseous blockades confirms the important role of intraosseous receptors in the pathogenesis of facial pain.
COMPARATIVE EFFICACY AND SAFETY OF FIRST LINE ANTIDEPRESSANTS AND ANTICONVULSANTS IN PAINFUL DIABETIC NEUROPATHY: A NETWORK META-ANALYSIS

G. Kapil, T.S. Teja, R. Neelima, D. Bansal, India

Introduction & objectives: Clinical trials comparing active treatments in painful diabetic neuropathy (PDN) are scarce. Hence, we performed network meta-analysis for comparative evaluation of efficacy and safety of the first line drugs-pregabalin, gabapentin, valproate, amitriptyline, duloxetine and venlafaxine.

Methods: A comprehensive data search was done in databases (from 1987 to 2012) for the drugs or any of their combinations. We performed a random-effects multiple-treatments meta-analysis to rank treatments in terms of efficacy and safety and risk-benefit analysis taking primary efficacy and safety outcomes as benefit and risk respectively. We chose the number of patients showing ≥50% reduction in pain and number of patients experiencing adverse events as primary outcomes for efficacy and safety respectively.

Results: We had included 22 published RCTs. Gabapentin was significantly more efficacious than amitriptyline, duloxetine, duloxetine+gabapentin, placebo, pregabalin and venlafaxine (odds ratios [OR] 7.27, 5.57, 5.21, 11.51, 4.29 and 4.45 respectively)

![Rank Probability](image)

Rank 1 is best, rank N is worst.

[Efficacy ranking]

Duloxetine was significantly safer than amitriptyline ([OR]-0.13)

[Safety ranking]
The decreasing order of efficacy was gabapentin, pregabalin, venlafaxine, duloxetine+gabapentin, duloxetine, amitriptyline, placebo and that of safety was placebo, duloxetine+gabapentin, duloxetine, venlafaxine, pregabalin, gabapentin and amitriptyline. Better benefit-risk ratio was observed with Gabapentin followed by placebo, venlafaxine, duloxetine+gabapentin, duloxetine, pregabalin and amitriptyline.

**[Benefit-Risk analysis]**

**Conclusion:** Gabapentin was found to be most effective and amitriptyline to be least safe among the treatments. Gabapentin showed most favourable balance between efficacy and safety.
NEUROEXCITATORY EFFECTS OF MORPHINE-3-GLUCURONIDE ARE DEPENDENT ON TOLL-LIKE RECEPTOR 4 SIGNALING

M. Due, A. Piekars, N. Wilson, P. Feldman, M. Ripsch, S. Chavez, H. Yin, R. Khanna, F. White, USA

Background and aims: The morphine metabolite, morphine-3-glucuronide (M3G), exhibits limited affinity for opioid receptors and no apparent analgesic effect. Previous reports suggest that M3G can act via the Toll-like receptor 4 (TLR4)/myeloid differentiation protein-2 (MD-2) heterodimer in the nervous system to elicit pain behavior in rodents.

Methods: Acutely dissociated dorsal root ganglia (DRG) neurons derived from sham and tibial nerve-injured (TNI) animals were exposed to either lipopolysaccharide (LPS) or M3G and assayed using intracellular calcium or current clamp techniques. Adult rats were also intraperitoneally injected with M3G alone or in combination with a small molecule inhibitor of the MD-2/TLR4 complex followed by thermal and tactile behavioral testing. Whole cell voltage-clamp recordings using DRG neurons were used to determine the potential influence of M3G on tetrodotoxin-sensitive (TTX-S) and tetrodotoxin-resistant (TTX-R) voltage-gated sodium channels (NaVs).

Results: Numerous DRG neurons derived from sham and TNI animals exhibited a change in intracellular calcium following LPS administration. Both nociceptive and non-nociceptive neurons were observed to respond. Increased excitability observed in sensory neurons following LPS or M3G could be eliminated using Compound 15, a small molecule inhibitor of the TLR4/M2 complex. Likewise, systemic injection of M3G induced rapid tactile, but not thermal, nociceptive behavioral changes in the rats which were reversed with Compound 15. Additionally, M3G increases TTX-S (NaV1.6 and 1.7) and TTX-R (NaV1.9) current densities in sensory neurons.

Conclusions: These outcomes provide evidence that M3G may play a role in OIH via the TLR4/M2 heterodimer complex and biophysical properties of TTX-S and TTX-R NaV currents.
LACK OF FLUOXETINE EFFECT ON ALLODYNIA AND SPONTANEOUS PAIN IS AMELIORATED BY DISRUPTION OF 5-HT2A/PDZ PROTEIN INTERACTION IN TRAUMA-INDUCED NEUROPATHIC PAIN

A. Dupuis, A.M. Privat, A. Eschalier¹,², C. Courteix, France

Background and aims: Antidepressants represent one of the reference treatments for neuropathic pain. Although activation of serotonergic neurons from the RVM reduces pain via descending tracts to the spinal cord, selective serotonin reuptake inhibitors (SSRIs) which increase the availability of 5-HT, fail to relieve neuropathic pain. This lack of efficiency is, at least in part, due to 5-HT2A receptor interactions with intracellular PDZ proteins.

The aim of this study was to investigate the effect of fluoxetine, an SSRI, on alldynia and spontaneous pain in neuropathic rats with spinal nerve ligature, when given alone or associated with a peptide disrupting the 5-HT2A receptor-PDZ protein interaction.

Methods: Fourteen days after spinal nerve ligation, behavioral study is performed to assess evoked and spontaneous pain, using von Frey hair test and dynamic weight bearing (DWB). Repeated fluoxetine administrations (10 mg/kg i.p., one injection every half-life/12 hours) are performed during 3 (von Frey) to 15 days (DWB). Six hours after every sixth fluoxetine injection, TAT-2A (a peptidyl mimetic of the 5-HT2A receptor PDZ ligand) is administrated (100 ng/rat, i.t.) and tests are performed 30 min after.

Results: One repeated fluoxetine administration has a slight antiallodynic effect, which is enhanced by the acute co-administration of TAT-2A. An increase in the time of this treatment (5 repeated fluoxetine administrations co-administrated with TAT-2A) enables a slight amelioration of spontaneous pain behavior.

Conclusion: Repeated fluoxetine administration combined with acute TAT-2A can be efficient against tactile stimulation-evoked pain and, to a lesser extent, spontaneous pain.
RETROSPECTIVE ANALYSIS OF NEUROPATHIC PAIN MANAGEMENT IN AN IN-HOSPITAL SETTING IN CANCER PATIENTS

D. Lossignol, C. Dumitrescu, D. Schrijvers, Belgium

Background: This retrospective study evaluated the pharmacological treatment of neuropathic pain in hospitalized cancer patients.

Neuropathic cancer pain (NPC) is difficult to treat due to the physiological presentation and treatment resistance. It is caused by extrinsic tumor compression or nerve invasion, but also by chemotherapeutic, radio-therapeutic or surgical specific treatments. Single use or combination of different agents treatment is still in progress.

Methods: NPC has been evaluated using a general questionnaire, by each of the 32 participating centers, on 156 cancer patients. The data recorded contained the number of patients with chronic pain with and without NPC component and the pharmacological treatment used as single agent or combined therapy.

Results: 98% of patients suffered from chronic pain and 28% had a NPC component. Single agent treatment included antidepressants for 8.3% of patients, and anticonvulsants for 19% of patients. 3.85% of cancer patients used a combination therapy of anticonvulsants and opioids, while 4.49% of patients used a combination of anticonvulsants, non-opioids and non steroidal antiinflammatories. As rescue therapy anticonvulsants have been used for only 1.95% of subjects.

Conclusions: NPC remains a challenge in terms of treatment management. Single agent use or combination therapy needs more detailed studies to determine the efficacy, safety and tolerability. As soon as this goal has been reached, treating the NPC could reduce the number and the duration of hospitalization, the overall toxicity and improve the quality of life in cancer patients, most of the time terminal ill.
HIGH CONCENTRATION (8%) CAPSAICIN PATCH IN REAL CLINICAL PRACTICE: 6-MONTH DATA FROM CZECH REGISTRY

T. Dolezal, J. Klimes, M. Vocelka, D. Kupkova, Czech Republic

Background and aims: To assess effectiveness, impact on quality-of-life and concomitant care consumption of patients on high concentration (8%) capsaicin patch in real clinical practice.

Methods: Observational prospective multicenter study in patients with not-adequately controlled neuropathic pain of non-diabetic etiology. Four visits have been planned - at time 0, 3, 6 and 12 months from patients' inclusion. This abstract presents the interim analysis of the 6 months follow-up.

Results: 323 patients have already been included, 283 of those have undergone the 2nd visit and 157 the 3rd visit. Mean patients age was 61.0 years. Mean NPRS score and QoL were 6.8 and 0.51 (SD 0.18) at time 0 month.

After 3 months (2nd visit) of patch administration 48.4% of patients revealed pain relief on NPRS scale by at least 30%. At 6 months, the mean NPRS score decreased to 3.1 (i.e. by 54.4%) for responders and to 4.1 (by 39.7%) for all followed patients. The utility increased to 0.62 (SD 0.66, P<0.001) and 0.66 (SD 0.66, P<0.001) at 3 and 6 months, respectively. 96.9% of patients consumed concomitant medication prior to 8% capsaicin patch. This percentage was reduced over time to 77.0% and 63.1% after 3 and 6 months of patch administration.

Conclusions: This study has confirmed the effectiveness from clinical trials, and simultaneously improvement of QoL and lower consumption of other care after 6 months follow-up. Additional follow-up data from subsequent visit (12 months) will be provided.
PREDICTORS OF NEUROPATHIC PAIN 6 MONTHS AFTER BREAST CANCER SURGERY: A PRELIMINARY ANALYSIS

L.R. Gauthier1,2, A. Easson, V. Chan, G. Koren, M. Li, G. Rodin, L. Gagliese1,2,4, Canada

Chronic neuropathic pain (NeP) is common following breast cancer surgery (BCS), but studies that prospectively assess its biopsychosocial predictors are unavailable.

**Aim:** Identify predictors of NeP 6-months after BCS.

**Methods:** 86 women undergoing BCS completed measures of pain, symptom severity and psychological wellbeing preoperatively and 6-months postoperatively. Demographic, biomedical, and surgical factors were assessed. Three groups were formed: those ≥ cutoff on the Neuropathic Pain Questionnaire-Short-Form (NeP); those below the cutoff but with Brief Pain Inventory Average pain severity ≥3/10 (nonNeP); and those below both cutoffs (pain-free; PF). ANOVA and χ² identified preoperative predictors of NeP at 6-months.

**Results:** Participants were 52.7±10.4 years old. 45(52.3%) underwent lumpectomy and 41(47.7%) underwent mastectomy. Preoperatively, 4(4.7%) had NeP, 12(14.0%) had nonNeP and 70(81.4%) were PF. At 6-months, 14(16.3%) had NeP, 7(8.1%) had nonNeP and 65 (75.6%) were PF.

More NeP underwent mastectomy than nonNeP and PF (85.0% vs.14.3% vs.43.0%; p=.003). NonNeP had higher preoperative pain severity (2.30±2.10 vs. 0.60±1.20 vs. 0.40 vs. 0.90; p≤.004) and pain qualities than NeP and PF (2.00±3.90 vs. 0.50±1.10 vs. 0.34±0.73; p≤.05). NeP had higher preoperative pain anxiety (83.9±35.3 vs. 36.7±22.8 vs. 45.9±36.1; p≤.01) and catastrophizing than nonNeP and PF (37.9±12.5 vs. 22.2±7.1 vs. 25.2±10.1; p≤.009).

**Conclusions:** In this first study to identify biopsychosocial predictors of NeP 6-months after BCS, we found that its predictors included surgical procedure (mastectomy vs. lumpectomy), and higher preoperative pain anxiety and catastrophizing. Further large-scale investigations into NeP 6-months after BCS are necessary.
Sickle cell disease (SCD) is a genetic blood disorder that is characterized by recurrent vaso-occlusive events (VOE), of which pain is a large component. It is known that SCD pain can be acute or chronic with both an inflammatory and neuropathic component. The pain associated with VOEs have been modeled by our lab using endothelin-1 (ET-1), which is a potent vasoconstrictor that causes nociception in both humans and animals. In our previous studies, ET-1 in the plasma of pediatric SCD patients was related to baseline pain, suggesting a role for ET-1 in existing vaso-occlusive pain. In rodent models, ET-1 sensitization is associated with downregulation of the vaso-dilatory and analgesia-signaling Endothelin B receptor. Building upon these studies we have recently begun to explore the role of apelin, a potent vasodilator in both human sickle cell pain and in our model of ET-1 induced sensitization. Our hypothesis is that in sickle cell disease there is a decrease in vasodilatory apelin signaling. In this study, apelin was found in the plasma of children with SCD. In the rodent model of ET-1 induced sensitization, Western blot analysis showed that the apelin receptor is downregulated in hindpaw skin. These results suggest that in sickle cell disease, acute VOEs early in development increase vasoconstrictive ET-1 tone and decrease vasodilatory apelin tone. The net effect of this is both vascular and nociceptive sensitization.
Neuropathic pain is a serious health issue that is often times difficult to treat with standard pain medications. The use of opioids to treat neuropathic pain is limited by centrally mediated side effects. The development of peripherally restricted opioids has been explored as a therapeutic alternative. We have recently shown that as with centrally active opioids, peripherally restricted opioids also produce tolerance. We hypothesize that blocking heterodimerization of mu- and delta-opioid receptors will prevent and reverse peripheral tolerance. A novel small peptide to block heterodimerization was constructed and linked to a TAT carrier peptide for intracellular delivery. Specificity of the small peptide blocker for mu- and delta-heterodimers was demonstrated in transiently transfected cells. Using Ca2+ imaging in cultured dorsal root ganglion neurons the peptide attenuated [D-Ala², N-MePhe⁴, Gly-ol]-enkephalin (DAMGO) tolerance. In vivo, in a rodent L5 spinal nerve transaction model of neuropathic pain continuous administration of the peptide through a subcutaneous mini-osmotic pump during the induction of peripheral opioid tolerance prevented peripheral opioid tolerance. Furthermore, in this same model an acute subcutaneous administration of the small peptide reversed peripheral opioid tolerance. These results suggest that by blocking heterodimerization of the mu- and delta-opioid receptors, peripheral tolerance can be prevented and reversed.
ANTINOCICEPTIVE AND ANTIOXIDANT EFFECTS OF ETHANOLIC EXTRACT FROM POLYGALA SABULOSA IN CHRONIC POST-ISCHEMIA PAIN (CPIP) MODEL IN MICE

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Background and aims: Recently, it has been described that prolonged ischemia and reperfusion in hindpaw of rodents produces a neuropathic pain syndrome. This is characterized by hyperemia, edema/plasma extravasation and hyperalgesia to mechanical and thermal (cold) stimulation. In addition, the maintenance of chronic post-ischemia pain (CPIP) is consistent with oxidative stress and ischemic conditions resulting from lesions in muscle tissue. The present study investigates the possible antinociceptive effect of ethanolic extract (EE) of Polygala sabulosa in CPIP model.

Methods: Mice male Swiss (n=5-11) were anaesthetized (choral hydrate 0.7%/kg, i.p.) and submitted to CPIP. In the 2nd and 7th day after surgery, the animals received EE (30-300 mg/kg, p.o.) twice a day and the mechanical (Von Frey filaments, 0.4 g) and thermal (cold plate, 5±1 °C) hypersensitivity were evaluated until the 16th day post-surgery. In other sets of experiments (n=4-7), the involvement of enzymes of the glutathione system was evaluated at the 2nd and 7th day post CPIP, in paw skin/muscle of mice 1h after administration of EE (300 mg/kg, p.o.) by colorimetric assay.

Results: The EE was able to reduce mechanical hypersensitivity caused by CPIP in mice. In addition, EE also reduced the cold hypersensitivity in the 8th day of treatment at dose of 300 mg/kg. Finally, the acute administration of EE (300 mg/kg) reestablished the activity of enzyme glutathione redutase at the 2nd day post-surgery.

Conclusion: The EE of P. sabulosa reduces mechanical and cold hypersensitivity caused by CPIP, probably involving modulation of glutathione system.
TREATMENT OF PAINFUL HIV-ASSOCIATED SENSORY NEUROPATHY AT A PUBLIC TERTIARY HOSPITAL IN SOUTH AFRICA

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Background and aims: HIV-associated sensory neuropathy (HIV-SN) is a leading cause of chronic pain in HIV-infected individuals, but there are few proven treatments for the pain. In the context of the poor evidence-base and lack of clear guidelines on how to treat the pain we investigated treatments used in clinical practice to manage painful HIV-SN in patients attending a large public tertiary hospital.

Methods: 67 HIV-positive patients (69% female; mean (SD) age: 44.8 (9.3) years; median (IQR) CD4 T-cell count: 294 (157-415) cells.mm\(^{-3}\); 91% on antiretroviral therapy) with painful HIV-SN were recruited at the Chris-Hani Baragwanath Hospital, South Africa. Neuropathy was diagnosed using the ACTG Neuropathy Screening Tool, and was defined as the bilateral presence of at least one sign and one symptom of peripheral neuropathy. Data on analgesic medications and HIV-SN diagnosis by treating physicians were obtained from patients' medical records.

Results: On average, patients pain was severe [median (IQR): 8 (5-10)]. Only 22% of patients were diagnosed with HIV-SN by their physicians, but all of these patients received analgesic treatment for their pain. Overall, 81% of patients in the cohort received pharmacological treatment. Across all patients, amitriptyline was the most common analgesic prescribed either alone (39%), in combination with codeine-phosphate and paracetamol (37%), or in combination with the two latter medications plus ibuprofen (5.5%) or diclofenac (5.5%).

Conclusion: Painful HIV-SN was poorly recognized by treating physicians, but once recognized, treatment generally involving amitriptyline was instituted. Early detection of painful HIV-SN by physicians will contribute to the proper management of HIV-SN.
SENSORY PAIN PROFILES IN PRIMARY SJOGREN’S SYNDROME
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Background: Sjogren's syndrome (SS) is an autoimmune disorder characterized by inflammation of exocrine glands. Neuropathic pain and widespread musculoskeletal pain characteristic of fibromyalgia are both prevalent in patients with SS. Since both types of pain are common, Sjogren’s represents an excellent model for investigating neuropathic pain and fibromyalgia including the possible role of central sensitization. The aim of this study was to analyze typical patterns of sensory symptoms.

Methods: Using a cluster analysis (hierarchical Ward analysis) based on the items of the Neuropathic Pain Questionnaire (NPQ), we looked for subgroups with different pain profiles within the neuropathic pain group. Profiles were compared by t-test.

Results: 109 subjects (mean age 60, 92% female, 78% college educated) were classified into those with neuropathic pain symptoms (N+, N=40) and those without neuropathic symptoms (Non-NP, N=69). Average pain intensity (NP=5.4, Non-NP=3.3, was greater (p=< .0001) in the NP+ group. Two neuropathic pain subgroups with distinct sensory profiles could be detected. One profile occurred predominantly in neuropathy patients. One profile was found frequently in patients with both Fibromyalgia and Neuropathy.

Conclusions: Phenotypic similarities in SS between neuropathic pain and fibromyalgia are consistent with the hypothesis that both painful entities might share some pathophysiologic mechanisms of pain generation. It is likely that pattern of sensory symptoms closely reflects the underlying pain-generating mechanisms. Moreover, comorbidities which are frequently present in chronic pain might influence the intensity and quality of pain. Detailed phenotypic characterization could provide insight into mechanistic pathways and provide a framework for more rationale therapy.
THE TRAJECTORY OF NEUROPATHIC PAIN IN THE FIRST SIX MONTHS AFTER BREAST CANCER SURGERY

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Although neuropathic pain (NeP) following breast cancer surgery (BCS) is common, its trajectory is not well understood.

Aim: To document NeP from 6 weeks (6wk) to 6-months (6mo) following BCS

Procedure: 76 women (aged 52.9±10.7), who underwent lumpectomy (n=40) or mastectomy (n=36), completed measures of pain, symptomatology and psychological wellbeing preoperatively and 6wk, 3-months (3mo) and 6mo postoperatively. Demographic, biomedical and pain threshold (thermal, punctate, pressure) data were collected. The Neuropathic Pain Questionnaire-Short-Form (NeP) was completed at each assessment. Scores ≥cutoff were coded as NeP. Persistent NeP (NeP-P) was coded if scores were ≥cutoff on two consecutive assessments. Resolved NeP (NeP-R) was coded if scores were ≥cutoff on one assessment but below it on subsequent assessments.

Results: At 6wk, 14 women reported NeP. At 3mo, 13 women reported NeP (7 new NeP; 6 NeP-P) and 8 had NeP-R. By 6mo, 24 women (31.6%) had NeP at least once, with 13 (54.2%) reporting ongoing NeP (3 new NeP, 10 NeP-P) and 11 (45.8%) NeP-R. NeP-R at 6mo was associated with lower preoperative pain anxiety (49.0±43.6 vs. 84.2±36.8; p=0.04), higher pain expectations (45.6±27.1 vs. 25.3±17.9; p=0.04), more intense tingling sensations at 6wks (22.7±26.8 vs. 3.9±7.7; p=0.04) and higher surgical site cold pain threshold at 6mo (17.9±11.7 vs. 4.4±7.0; p=0.04) than ongoing NeP.

Conclusions: Almost half of women reporting NeP during the first 3mo following BCS experienced resolution by 6mo. They differed from those with ongoing NeP on psychological and somatosensory factors. Further research is needed to elucidate NeP's trajectory following BCS.
NORMATIVE DATA OF CORTICAL EXCITABILITY IN A BRAZILIAN POPULATION

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Background and aims: Measures of cortical excitability (CE) parameters by transcranial magnetic stimulation have gained increasing interest as a way to obtain information on the functional integrity of the cortico-spinal tract and interneuronal networks within the primary motor cortex (M1). Changes in CE parameters have been reported in fibromyalgia and neuropathic pain syndromes, showing correlation with the severity of different components of these pain syndromes, and seeming to change during treatment. Despite its potential use, there is lack of normative data for CE parameters. We aimed to obtain normative data for CE in healthy volunteers (HV).

Methods: A sample size of 100 men and 100 women were matched according to age. Rest motor threshold (RMT), motor evoked potentials (MEP), intracortical inhibition (ICI) and facilitation (ICF) were measured in the first dorsal interosseous muscle for both M1. The inter and intrainvestigator variability was assessed in a sample of 20 HV.

Results: Normative data for HV < and ≥ 50 years respectively (mean ± standard deviation):

1. RMT: 49 ± 9.39%; MEP120%: 587.63 ± 779.52 µV; MEP140%: 1413.08 ± 1343.18 µV; MEP120/140%: 3.83 ± 5.39 µV; ICI2ms: 0.40 ± 0.44; ICI4ms: 0.61 ± 0.84; ICI: 0.56 ± 0.63; ICF10ms: 1.95 ± 1.82; ICF15ms: 1.80 ± 1.73; ICF: 1.87 ± 1.64

2. RMT: 49.1 ± 9.58%; MEP120%: 467.71 ± 650.61 µV; MEP140%: 1172.43 ± 1158.47 µV; MEP120/140%: 4.04 ± 4.27 µV; ICI2ms: 0.73 ± 1.26; ICI4ms: 1.04 ± 1.67; ICI: 0.81 ± 1.03; ICF10ms: 2.46 ± 3.85; ICF15ms: 2.12 ± 3.05; ICF: 2.28 ± 3.32

There was no difference between left and right hemispheres. We found a good inter/intrainvestigator correlation for RMT and MEP. ICI and ICF had low correlations but an acceptable reliability.

Conclusions: We reported normative data for CE in adult individuals. We found no left-right asymmetries or differences related to gender. Age has a non linear effect on CE.
Diabetic neuropathy is a complication of diabetes that represents a major world health problem. Conventional drugs that relieve acute pain are not effective in neuropathic pain. This type of pain is characterized by hyperalgesia (increased pain to a painful stimulus) and allodynia (pain to innocuous stimuli). Some studies have reported that ketorolac and celecoxib reduced the nociception and allodynia in inflammatory and diabetic pain, respectively. On the other hand, a CCK antagonist decreases behavior in inflammatory pain. The aim of this study was to evaluate the effect of celecoxib, ketorolac or proglumide per se and its combinations. Experimental diabetes was induced in male Wistar rats (weight 280-320g), by intraperitoneal streptozotocin injection (60 mg/kg), the blood glucose level was measured three days after and allodynia was evaluated 4 weeks after by paw withdrawal threshold. The rats with threshold greater than 4 g were excluding. Celecoxib (0.3, 3, 10 and 30 mg/dl i.p.), ketorolac (0.3, 1, 3 and 10 mg/kg) or CCK antagonist (proglumide; 20, 40, 60 and 180 mg/kg) were administered intraperitoneally. Our results suggest that systemic administration of celecoxib, ketorolac or proglumide, as well as the combinations, reduced the neuropathic pain in rats.

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EVIDENCE FOR POSITIVE EFFECTS OF DATE EXTRACT THAT ATTENUATES THERMAL HYPERALGESIA IN A DIABETIC RAT MODEL OF NEUROPATHIC PAIN

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Introduction: Diabetic neuropathic pain is one of the pains which hardly respond to pharmaceutical treat. Today, various chemical and herbal compounds have been used to reduce pain. The aim of this study is to compare the effect of date extract and melatonin in preventing pain in diabetic rats by injecting single dose of streptozotocin.

Methods: To study hyperalgesia response and to compare the effect of date extract and melatonin in preventing pain, hot plate and tail flick tests were used. After prescribing single dose of streptozotocin (65mg/kg) to Sprague dawley rats and approving their diabetes, treatment rats received date extract (4ml/kg/day) or melatonin (10 mg/kg/day) for a period of 6 weeks. At the end of the sixth week, control and treated rats were examined by thermal pain response test.

Results: According to hot plate results, response time to thermal pain at the end of sixth week in treated group showed a significant decrease in comparison with the control group (P< 0.01). Prescription of date extract increased response time to thermal pain in comparison with treated group (P< 0.01), so that response time approximated to control group. In hot plate test, although melatonin approximated to the response time to control group, the significant difference was not observed among melatonin receivers and other groups.

Conclusion: Findings of this study showed that date extract decreased thermal hyperalgesia and can prevent pain resulted from diabetic neuropathy.
THE SLANSS AS AN ASSESSMENT AND PROGNOSTIC TOOL: A PSYCHOMETRIC EVALUATION

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**Rationale:** It has recently been suggested that whiplash-related signs and symptoms may have a predominant neuropathic component in some people, and when present is associated with a more complex clinical picture.

**Purpose:** To evaluate the validity of the self-report version of the Leeds Assessment for Neuropathic Signs and Symptoms (SLANSS) for use in evaluating people with whiplash associated disorder (WAD).

**Methods:** Data from two separate databases were combined. All subjects presented for physiotherapy treatment of WAD following motor vehicle accident. The SLANSS was part of a battery of tests performed on initial assessment. Pain threshold (PPT), neck disability index (NDI), pain intensity (NRS), age, sex and duration of symptoms were also extracted from the databases. A subset of patients were followed up 3 months later. Exploratory factor analysis was performed to evaluate the factor structure of the the SLANSS. Concurrent validity was evaluated through bivariate correlations with NDI, NRS and PPT. Moderators(age, sex and duration) were explored through tests of association. Linear regression was used to evaluate the predictive validity of the SLANSS on 3-month outcomes.

**Results:** Factor analysis revealed 3 unique domains (deep symptoms, superficial symptoms, active tests). Hypotheses for concurrent validity were satisfied for each subscale. No clinically-relevant moderators were identified. SLANSS explained 16% of unique variance in 3-month outcomes. The SLANSS appears to be a useful tool in clinical diagnosis and prognosis in acute WAD.
A FMRI STUDY OF PERIAQUEDUCTAL GREY ACTIVITY DURING EXPERIMENTAL PAIN IN NORMAL HUMANS

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The descending modulatory system abnormalities probably participate in the development of chronic idiopathic pain conditions such as fibromyalgia, persistent idiopathic facial pain, tension headaches. Although the periaqueductal grey (PAG) plays a pivotal role in the descending modulation of pain, little information is available on the relationship between the intensity of PAG activation and the severity of pain, and no studies have assessed the time course of PAG. In this study seeking information on PAG function we acquired functional MRI (fMRI) scans of PAG during cold pressor test (CPT) in 12 normal humans. We used a 3T (Siemens-Verio) to acquire fMRI data during CPT. For performing CPT subjects placed their left hand in the ice water bath for 1 minute. Subjects were instructed to indicate the exact point of time when the cold sensation began to elicit pain (pain threshold) and rated the maximal pain intensity they felt during the immersion, with the 0-10 numeric rating scale (NRS). fMRI data were analyzed using SPM5. Significant clusters of activation were observed in middle and superior frontal gyrus, insula and in the PAG (p < 0.05). The pain intensity had an inverse correlation with PAG signal (p < 0.05). The change of PAG signal intensity showed a greater increase after 45 sec of hand immersion.

Our study shows that the pain intensity is inversely related to the PAG activation. The time course analysis indicates that PAG signal follows a specific temporal profile, with a delayed activation. Our findings might be useful for neuroimaging studies dealing with PAG in chronic idiopathic conditions.
RELATIONSHIP BETWEEN SYMPTOMS AND SENSORY NERVE EXCITABILITY PROPERTIES IN INDIVIDUALS WITH PERIPHERAL NERVE INJURY AND NEUROPATHIC PAIN

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Background and aims: Neuropathic pain patients complain of positive sensory symptoms, such as spontaneous pain and paresthesia. The reason why some patients with apparently similar nerve lesions develop pain while others do not is unclear. One possibility is that a person's predisposition to develop pain after peripheral nerve lesions depends in part on the distribution and function of different ion channels and pumps. The present study aimed to determine whether axonal excitability studies (“excitability profiling”), which can assess ion channel activity in large fibers, can help to explain the differential responses to nerve injury.

Methods: Sensory nerve excitability studies were performed using the Trond protocol (Kiernan et al., 2000), on an unaffected nerve (median nerve, wrist level) of 23 adults (20M, 3F, age 29-65,) with focal chronic (>6 months) traumatic peripheral nerve injuries. Pain and other positive sensory symptoms were assessed by the NPSI questionnaire.

Results: Patient reports of “pins and needles” (NPSI Q11) and “tingling” (NPSI Q12) were strongly correlated with the excitability responses of large sensory fibers to subthreshold depolarizing currents (P<0.001). Weak correlations (P< 0.05) were also found between other patient complaints and several nerve excitability measures: “number of pain attacks” (NPSI Q7), and “cold sensitivity” (NPSI Q10) with HCN channel function.

Conclusion: Assessment of excitability properties of large myelinated fibers correlate with specific sensory complaints. This “excitability profiling” assessment may become a tool to predict predisposition to specific positive sensory symptoms following peripheral nerve injury or disease.
Introduction: Spinal Cord Stimulation (SCS) for chronic neuropathic pain has become a standard treatment option, however, it is often impossible to get the paraesthesia to some discreet anatomical locations. A recently approved alternative to traditional SCS is stimulation of the Dorsal Root Ganglion (DRG). We present two patients with failed conservative management who were successfully treated with the Axium Neurostimulator System for groin pain.

Methods: Two patients suffering with neuropathic pain in the groin area were treated with DRG stimulation. One of these was a lady with abdomino-cutaneous nerve entrapment syndrome with neuropathic pain for 12 years. The other was post-inguinal orchiectomy pain of 8 years duration. Patients underwent a trial of the therapy where the specifically designed leads were implanted at the target DRGs at T12, L1 and L2. Following a successful trial for 1 week the leads were connected to the implantable neurostimulator. Patients reported pain scores on a Visual Analogue Scale (VAS) and completed an EQ-5D quality of life questionnaire.

Results: With stimulation at a single lead, we could cover 95% of the painful area and achieved 85% pain relief. The overall VAS scores reduced from 66.5 mm preoperatively to 6 mm postoperatively over an average follow up period of 7.25 months. The average improvement on the EQ-5D was 0.769.

Conclusions: This small case series suggests that SCS of the DRG may be an effective treatment for chronic neuropathic pain conditions of the groin. We aim to present one year follow up data at the meeting.
NKTR-171: PRECLINICAL EFFICACY AND IMPROVED CENTRAL NERVOUS SYSTEM (CNS) SIDE EFFECT PROFILE OF A NOVEL SODIUM CHANNEL BLOCKER DESIGNED FOR THE TREATMENT OF NEUROPATHIC PAIN


The widespread utility of existing sodium channel (Nav) blockers for neuropathic pain is limited by their narrow therapeutic indices with respect to CNS side effects (SEs), and for some agents, their cardiovascular SEs. NKTR-171 is a novel Nav blocker designed using Nektar Therapeutics’ technology to regulate CNS entry of a validated scaffold with a low cardiovascular liability.

Methods: Nav block by NKTR-171 was characterized in vitro and analgesic efficacy was measured in rat models of persistent pain and neuropathic pain. Pharmacokinetic studies were conducted in dogs and rats.

Results: NKTR-171 shows low brain exposure in rats and oral bioavailability of ~35% in dogs. In the rat formalin model, acute oral administration of NKTR-171 (30-300 mg/kg) produces a dose-dependent suppression of flinching behavior. The in vivo exposures at efficacious doses of NKTR-171 correlate well with its potency for Nav block in vitro. NKTR-171 (200 mg/kg) produced a 70% reduction in the cumulative number of flinches in Phase II of the rat formalin model, comparable to that produced by pregabalin (65% reduction at 100 mg/kg), however NKTR-171 exhibited a favorable therapeutic window with respect to CNS SEs. The time spent on a rotarod was not impaired by a maximally analgesic dose of NKTR-171 whereas an equianalgesic dose of pregabalin reduced the time spent by 70%.

Conclusions: These results from preclinical studies show that NKTR-171 is a novel Nav blocker that demonstrates analgesic efficacy with an improved therapeutic index compared to existing standards of care through a separation of analgesia from CNS SEs.
TRIGEMINAL NERVE INJURY INDUCED VOLTAGE GATED CALCIUM CHANNEL A2Δ1 SUBUNIT INCREASE LEADS TO INCREASED EXCITATORY SYNAPSES THAT CORRELATE WITH NEURONAL SENSITIZATION AND BEHAVIORAL HYPERSENSITIVITY

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**Introduction:** Expression of α2δ1, an accessory subunit of voltage gated calcium channels, was greatly increased in the trigeminal ganglia (TG) and associated upper cervical spinal cord after nerve injury that correlated with development of orofacial behavioral hypersensitivity. Blocking this α2δ1 increase using antisense oligodeoxynucleotide treatment led to a reversal of established behavioral hypersensitivity.

**Objectives:** Since α2δ1 has been shown to play a role in CNS synaptogenesis, we hypothesize that nerve injury induced α2δ1 upregulation may lead to increased excitatory synapses in the spinal cord that contribute to orofacial neuropathic pain development.

**Methods:** α2δ1 expression in TG and synaptic changes in the subnucleus caudalis (Vc/C2) were examined with immunofluorescent staining and colocalization of α2δ1 and VGlut2 immunoreactivities, respectively, in infraorbital nerve (ION) ligated rats one- or three-weeks post injury, which correlated with the absence or presence of orofacial hypersensitivity and Vc/C2 neuron sensitization.

**Results:** ION ligation increased α2δ1 expression in the TG, and α2δ1 positive VGlut2 synapses in Vc/C2 superficial dorsal horn at three-weeks, but not one-week, post surgery, which correlated with orofacial hypersensitivity and Vc/C2 neuron sensitization.

**Conclusion:** We propose a mechanism by which α2δ1 mediated abnormal synaptogenesis post trigeminal nerve injury leads to dorsal horn neuron sensitization and development of orofacial hypersensitivity.
CAPSAICIN INDUCES GABAPENTINOID PERMEATION OF NEURONAL TRPV1 CHANNELS AND INCREASES THEIR EFFECTIVENESS BOTH IN VITRO AND IN VIVO

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Introduction: The use of gabapentin (GBP) and pregabalin (PGB) in management of neuropathic pain is limited by dose-dependent untoward effects. It was recently shown that local anaesthetics can pass through TRPV1 channels following their activation by capsaicin. We found previously that this may also be a viable route for facilitating access of gabapentinoids to their target protein; the α2δ subunit of voltage-gated Ca^{2+} channels.

Objectives, methods and results: To test whether capsaicin can increase gabapentinoid effectiveness, we exposed organotypic cultures of rat spinal cord to GBP or PGB for 5 days and examined changes in stimulation-evoked Ca^{2+} signals as an index of overall dorsal horn excitability. Whereas 100µM GBP or 1µM PGB (5-6 days) significantly reduced amplitude or area under the Ca^{2+} signal following electrical stimulation, 10µM GBP was only effective in the presence of 100nM capsaicin (1h exposure every 2 days). Application of BCH, an amino acid transport inhibitor that blocks GBP entry into neurons, did not reverse effects of GBP in the presence of capsaicin, as would be expected if GBP enters via TRPV1 channels. in vivo experiments showed that GBP (50-100mg/kg, IP, every 12h for 5d) increased paw withdrawal threshold following sciatic chronic constriction injury and that its effectiveness was increased by injection of capsaicin (1µg every 48h for 5d) into the dorsal side of the foot.

Conclusions: Potential improvements in the delivery of gabapentinoids to TRPV1 expressing neurons may lead to improved pharmacological management of neuropathic pain and limitation of their side effect profile.
INJURY-INDUCED CHANGES IN PRIMARY AFFERENT EXCITABILITY: CRITICALITY, DEGENERACY, AND THE IMPLICATIONS FOR NEUROPATHIC PAIN

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Introduction: Injury-induced changes in primary afferent excitability contribute to neuropathic pain. Computer simulations predict that qualitative changes in excitability arise through a switch in spike initiation dynamics when molecular pathologies reach a tipping point (criticality), and that this tipping point can be reached via several distinct molecular pathologies (degeneracy) (Rho and Prescott, PLoS Comput Biol 2012).

Objectives: We sought to test these predictions in real primary afferent neurons to demonstrate what types of ion conductance changes are sufficient, alone or together, to account for injury-induced changes in neuronal excitability.

Methods: We experimentally tested simulation predictions by pharmacologically blocking native conductances and/or inserting virtual conductances using the dynamic clamp technique. Using acutely dissociated primary sensory neurons from naïve rats, we applied different manipulations, each of which was predicted to reproduce neuropathic changes in excitability. Conversely, using hyperexcitable sensory neurons from nerve-injured rats, we applied manipulations predicted to reverse hyperexcitability.

Results: We successfully replicated or reversed a triad of qualitative excitability changes (altered spiking pattern, membrane potential oscillations, and bursting) in primary afferents from naïve or nerve-injured rats, respectively.

Conclusions: Our data confirm the predicted criticality and its degenerate basis. In other words, we show that there are multiple routes to a common tipping point. Degeneracy implies that several molecular pathologies are individually sufficient to cause hyperexcitability, and because several such pathologies co-occur after nerve injury, that no single pathology is uniquely necessary. These insights may help explain certain enigmatic features of neuropathic pain, including its unpredictable time course and intractability.
SPINAL CORD STIMULATION OF THE DORSAL ROOT GANGLION FOR COMPLEX REGIONAL PAIN SYNDROME (CRPS)

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Introduction: Spinal Cord Stimulation (SCS) for chronic neuropathic pain has become a standard treatment option, however, it is often impossible to get sustained paraesthesia coverage to some discreet anatomical locations such as foot. A recently approved alternative to traditional SCS is stimulation of the Dorsal Root Ganglion (DRG). We present four patients who were successfully treated with the Axium Neurostimulator System for CRPS Type I of the lower limb/foot.

Methods: Four patients with CRPS Type 1 of the lower extremity were treated with DRG stimulation. Patients underwent a trial of the therapy where specifically designed leads were implanted at the target DRGs at L3, L4 and L5. Following a successful trial the leads were connected to the implantable neurostimulator. Patients reported pain scores on a Visual Analogue Scale (VAS) and completed an EQ-5D quality of life questionnaire.

Results: With stimulation at two leads, we could cover 92.5% of the painful area and achieved 80% pain relief with DRG stimulation. The overall VAS scores reduced from 69.25 mm preoperatively to 16 mm postoperatively over an average follow up period of 5.75 months. The average improvement on the EQ-5D was 0.479. 50% patients were able to reduce their analgesic medication.

Conclusions: This small case series suggests that stimulation of the DRG may be an effective treatment for CRPS involving lower extremity and feet. As such SCS of the DRG offers a useful alternative to traditional SCS for neuropathic pain in the feet that does not always respond optimally to traditional SCS.
ANTIHYPERALGESIC EFFECT OF DIAZEPAM IN COMPLEX GABA<sub>A</sub> RECEPTOR POINT MUTATED MICE

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We have previously shown that spinal application of the classical benzodiazepine site agonist diazepam reverses pathological pain sensitization in rodents by potentiated activation of dorsal horn GABA<sub>A</sub> receptors. Work done in GABA<sub>A</sub> receptor point mutated mice in which benzodiazepine-sensitive subunits had been rendered diazepam-insensitive by a knock in mutation showed that most of this spinal antihyperalgesic effects could be attributed to α2-GABA<sub>A</sub> receptors and to a lesser degree to α3- and α5-GABA<sub>A</sub> receptors. α1-GABA<sub>A</sub> receptors, which mediate the sedative effects of diazepam, did not contribute.

Now, we extended this work and investigated
(i) whether a similar antihyperalgesic action can also be achieved with systemic treatment,
(ii) which subunit combinations would yield the strongest antihyperalgesic effect, and
(iii) whether the loss of effect seen in point mutated mice would correspond to the level of antihyperalgesia reached in mice with only this GABA<sub>A</sub> receptor subtype left diazepam sensitive.

For this, we bred double, triple and quadruple GABA<sub>A</sub> receptor point mutated mice, which all carried α1 point mutated GABA<sub>A</sub> receptors (to avoid sedation) in addition to all possible combinations of α2, α3 and α5 point mutated subunits. Baseline nociceptive (thermal and mechanical) sensitivities and neuropathic pain sensitization (by chronic constriction injury of one sciatic nerve) were indistinguishable in all mutant mice. Orally applied diazepam significantly reversed hyperalgesia in almost all genotypes tested but to different degrees. These experiments demonstrate that profound antihyperalgesia can be obtained with systemic benzodiazepine-site agonists in mice and that α2-GABA<sub>A</sub> receptors are the most important target of this action.
ASSESSMENT OF MEMANTINE’S EFFECTIVENESS ON MECHANICAL AND THERMAL HYPERALGESIA IN A NEUROPATHIC PAIN MODEL IN RATS

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Background and aims: The primary aim of this randomized preclinical study was to evaluate efficacy of memantine on mechanical and thermal hyperalgesia.

Methods: The principles outlined in the Declaration of Helsinki were strictly followed throughout all experiments. Male adult Wistar rats were randomly labeled in 2 groups (n:7) as control and memantine. Mechanical thresholds were measured by electronic von Frey (evF.) and thermal thresholds by hotplate (HP) (basal value) before undergoing surgery. Chronic constriction injury (CCI) of the right sciatic nerve was induced. Mechanical and thermal thresholds were re-measured on 21 th. day again. Saline 2 ml. (Group I), memantine 15 mg/kg (Group II) were administered intraperitoneally. The effects of drugs on mechanical hyperalgesia (MH) were measured at 30., 90., 150. min. on the right hind paw and on thermal hypersalgesia (TH) at 60., 120., 180. min. Mann-Whitney U Test and Kruskal-Wallis Test were used for statistical analysis.

Results: There were significant differences between Group I and Group II (p< 0.05) indicating that CCI was occurred. There was significant difference between groups at 30. min. on MH (p< 0.05) but there was no significant difference at 90. and 150. min. (p>0.05). We have found out no significant differences between two groups at any min. on TH (p>0.05).

Conclusions: As a conclusion, we have found out that, effect of memantine on TH was not superior to MH in rats with a neuropathic pain model.
Z160: A POTENT, STATE-DEPENDENT, N-TYPE CALCIUM CHANNEL BLOCKER EFFECTIVE IN ANIMAL MODELS OF NEUROPATHIC PAIN

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Background and aims: While indiscriminate block of N-type calcium channels by cone-snail derived peptides is known to be highly efficacious in alleviating a number of types of chronic and neuropathic pain, there remains a significant opportunity to develop orally available small organic molecule blockers of the N-type channel for the treatment of chronic pain conditions. To both minimize adverse effects and increase efficacy, we have sought to discover and develop potent, selective and state-dependent N-type channel blockers.

Methods: Structure-activity-relationship studies generated several new classes of compounds that were screened in cell-based assays for modulation of native and recombinant N-type channel function. The lead compound, Z160, was further characterized in nonclinical models of neuropathic pain.

Results: Z160 blocked the N-type channel in an irreversible, dose-dependent manner with sub-micromolar potency and 25- to 100-fold selectivity over P/Q- and L-type calcium channels. Z160 mediated a hyperpolarizing shift in the midpoint of the steady-state inactivation curve, consistent with a mechanism involving inactivated state blockade. Z160 also demonstrated use-dependent block of N-type channels. In the Chung and CCI rodent models of neuropathic pain, Z160 demonstrated dose-dependent reduction of thermal hyperalgesia and tactile allodynia at levels comparable to morphine, ω-conotoxin MVIIA and gabapentin.

Conclusions: These data demonstrate the discovery and nonclinical evaluation of Z160, a novel, potent, selective and state-dependent N-type calcium channel blocker with efficacy in animal models of neuropathic pain.
PRESENCE AND PATTERNS OF NEUROPATHIC PAIN IN CHRONIC RHEUMATIC PAIN PATIENTS

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Objectives: To estimate the rate, qualitative and quantitative characteristics of neuropathic pain for patients with chronic rheumatic diseases and evaluate influence pain duration in the generation of neuropathic pain.

Methods:

1. 69 patients with pain > 6 months from 2 Rheumatology departments from Kaunas city participated in the study.

2. Patients completed sociodemographic data, features of rheumatic diseases; in the 4 projection body scheme marked exact pain localisation, Lithuanian versions of DN4, McGill questionnaire (SF-MPQ-2) and number rating scale (NRS) were used for neuropathic pain screening and pain intensity measurement; HADS assessed patients mental state.

Results: 40 women (67.8%) and 19 men (32.2%), mean age 58±16.8 year. 59.4% participants diagnosed arthritis, 13.6% sistemic diseases, 27% other rheumatic diseases. 18.6% patients suffered pain < 1 year, 32.2 % - 1-5 years, 25.5 % - 6-10 years, 10.2 % - >10 years. Pain in NRS "now" - 5.6, strongest pain - 7.64, least pain - 4.19 (yesterday). According to DN4 - 78% patients detected having possible neuropathic pain component (value ≥3 points), in 37.3% cases pain was burning, 55.9% - like painful cold, 50.8% - felt tingling, 44.1% - pins and needles, 61 % - numbness in the pain area. According to SF-MPQ-2, in 72.9% cases pain had sharp quality, 66.1% - gnawing, 81.4% - tiring/exhausting pain. Higher depression scores had stronger relationship with DN4 scores (r=0.405, p< 0.01).

Conclusions: Our data support the hypothesis of secondary involment of peripheral nervous system and steady link between chronic rheumatic pain and depression.
PREVALENCE OF NEUROPATHIC COMPONENT IN ATYPICAL FORMS OF LOW BACK PAIN

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Introduction: Chronic low back pain (LBP) is one of the most difficult to treat medical problems. It is due to its etiological heterogeneity and variety of mechanisms of pathogenesis.

Objectives: In this work we tried to determine prevalence of neuropathic component in patients with chronic LBP.

Methods: Sixty seven patients (27 men, 40 women) with various chronic LBP conditions were examined. Pain score varied from 4 to 10 on VAS and duration of pain was more than 3 months. All patients were split into 3 groups: group #1 - LBP with no irradiation of pain to the leg, group #2 - LBP with irradiation of pain to the leg and no neurologic deficit, group #3 - LBP with radicular distribution of pain in the leg and presence of neurologic deficit. Complex neurologic and orthopedic examination was performed along with utilization of elements of quantitative sensory testing and DN4 questionnaire.

Results: Neuropathic component was found in 35% of patients in group #3, 22.2% of patients in group #2 and 10% of patients in group #1 on low back level and in 80% of patients in group #3 and in 26% of patients in group #2 on leg level.

Conclusions: Even though neuropathic component of pain is often seen in classic radiculopathy it may also be present in atypical forms of LBP. It makes sense to use DN4 questionnaire separately for different areas of the body. It is important to distinguish ratio between neuropathic and nociceptive components of LBP for adequate pharmacotherapy.
PERIPHERAL NOXIOUS INPUTS INDUCING TRIGEMINAL NEURALGIA

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Trigeminal neuralgia (TN) is classified as a neuropathic pain condition (IASP) with unclear etiology. This abstract discusses 2 cases with TN-like pain, induced by peripheral pain.

Case report 1: A female, age 49, presented with new-onset complaints of "electric pain" on upper right teeth, reproduced by light touch on gingiva of tooth numbers 3-8 and eliminated by local anesthetic infiltration. Was prescribed Trileptal 300mg bid and referred to neurologist. She returned in 2 weeks with similar symptoms triggered from infected tooth number 30, relieved by mandibular nerve block. Subsequent endodontic therapy and Oxcarbamazapine eliminated pain. At the 3/6 month follow-up, patient was pain-free.

Case report 2: Another female age 48, presented with new-onset, shock-like pain of right face subsequent to ENT cauterization in right nostril. Local anesthetic blockade of trigger zones decreased pain 50%. Prednisone prescribed, 4 weeks later reported 95% pain relief while on anti-epileptic medications. At 6 month- 1 year recall, patient is off of medication.

Discussion: Both patients presented signs and symptoms consistent with TN, following peripheral lesions. Diagnoses confirmed by board-certified neurologist, treated as TN and pain relief was complete with resolution of the peripheral entity causing the noxious input. Studies are needed to determine contribution of peripheral noxious inputs in triggering TN.
Currently, treatments available for neuropathic pain are limited making the development of therapies crucial. Evidence from our lab suggests that peripheral group III mGluRs have an anti-hyperalgesic role. We have demonstrated that peripheral group III mGluRs negatively modulate TRPV1 activity. To understand whether Group III mGluRs exert inhibitory control over other members of the TRP family, we examined the effects peripheral group III mGluR activation on TRPA1-induced activity. TRPA1 is expressed by nociceptors and is responsive to thermal (cold temperatures) and mechanical input. Currently, no studies have examined the effect of group III mGluR agonists on TRPA1 activation. In the present study, separate groups of rats received intraplantar injections of either PBS or 10µM L-AP-4, followed 10 min later by topical application of 10 mM mustard oil (MO) to the same hindpaw. Flinching was observed for 30 min post-MO. Results demonstrated that L-AP-4 reduced the average number of MO-induced flinches from 20 to 14 during the 30 min period. Calcium mobilization was measured as the change in the level of fluorescence under various conditions: 10 µM L-AP-4, 100 µM MO, and 100 µM MO + 10 µM L-AP-4. Behavioral findings suggest that peripheral group III mGluR activation can negatively modulate TRPA1 activity in the glabrous skin. Calcium imaging findings demonstrate localization of these two receptor families on the same cell. The findings demonstrate that peripheral group III mGluRs exert inhibitory control over a variety of TRP channels expressed by nociceptors, highlighting their potential as targets for neuropathic pain treatments.
THE NEUROCHEMICAL IDENTITY OF NEURONAL NITRIC OXIDE SYNTHASE (NNOS) CONTAINING NEURONS IN BRAIN AND SPINAL CORD REGIONS RESPONSIBLE FOR MODULATION OF NEUROPATHIC PAIN

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Background/aims: Nitric oxide (NO) in the spinal cord is released in models of peripheral neuropathy, and is believed to induce central sensitization responsible for chronic pain. Conversely, NO release in the brain is responsible for initiating analgesia of up to three-weeks duration, and shows benefit in models of neuropathic pain. This complex and opposing activity of NO is likely dependent on the site, concentration, and duration of exposure to NO. It is unknown, however, which neuronal populations are activated by NO and subsequently mediate pro- or anti-algesic effects. Because of the importance of NO in modulation of neuropathic pain, this study aims to determine the neurochemical identity of nitric oxide synthase expressing (nNOS+) neurons in the spinal cord, ARCN, PAG, NRMg, Gi/LPGi, and A5 regions of the pain modulatory pathways.

Methods: Standard fluorescence immunohistochemical co-labeling was performed on tissue taken from adult male NIH Swiss mice using antibodies against nNOS, TyrH, TrpH, ChAT, and B-End.

Results: These data indicate that nNOS+ neurons in the investigated brain regions are neither serotonergic, noradrenergic, beta-endorphinergic, nor cholinergic. nNOS+ neurons in the spinal cord are neither serotonergic, noradrenergic nor beta-endorphinergic. Studies continue to investigate co-labeling of nNOS with dynorphin, met-enkephalin, and GAD.

Conclusions: This study identifies populations of NO-producing neurons in spinal cord and pain modulatory regions, supporting evidence of NO influence on neuropathic pain. Absence of NO production within serotonergic and noradrenergic brainstem neurons suggests that the NO-mediated analgesic pathway is likely a multi-synaptic circuit, unlike the spinal NO-mediated hyperalgesic synapse.
Morphine is widely used to treat acute and chronic pain but with significant side effects after high doses or lengthy administration. Current studies aim to establish receptor groups and agonists that might potentiate analgesic efficacy of opioids, allowing treatment with lower doses in order to minimize side effects. One receptor family of interest is the metabotropic glutamate receptors (mGluRs). Specifically, central and systemic application of Group III agonists potentiates morphine analgesia in nerve injury models. We previously demonstrated that peripheral administration of a Group III-selective agonist synergistically potentiates morphine anti-hyperalgesia. Currently, we are employing the in vitro skin-nerve preparation to determine if potentiation occurs at the single fiber level. Fibers were sensitized to heat via application of inflammatory soup. Subsequently, morphine, L-AP-4, or a Group III mGluR8-selective agonist was applied. Dose response curves for each drug were used to identify individual IC50s and appropriate combination doses. Further study will involve applying the combination doses and assessing responses to thermal stimuli to determine if Group III potentiates morphine at the single fiber level. Additionally, we examined dorsal root ganglion (DRG) cells for co-expression of Group III mGluR8, the mu opioid receptor (µOR), and a nociceptor marker (TRPV1). Thus far, data indicate that the receptors are co-localized in 41% of nociceptors, suggesting that potentiation may occur via an intracellular mechanism. Overall, we expect that peripheral activation of Group III mGluRs will increase morphine-induced inhibition of inflamed peripheral fibers via modulation of an intracellular pathway.

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RESERPINE-INDUCED WIDESPREAD PAIN: MOVING TOWARDS THE UNDERSTANDING OF THE FIBROMYALGIA MODEL

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Neuropathic pain is the main symptom of some dysfunctional pain syndromes in which the nervous tissue is virtually absent of damage. Fibromyalgia is one member of this group and is mainly characterized by chronic widespread pain, and also by psychiatric comorbidities as well as non-painful sensory alterations. An animal model of Fibromyalgia was recently described using administration of reserpine which displays painful responses upon cold, heat and mechanical stimulation, as well as depressive signs observed in the forced swimming test.

Using a rat strain different from the original work, herein we evaluated sensorial alterations in different body locations (tail and paw) as well as anxiety/depressive status.

Reserpine was administered for three consecutive days (1mg/kg, s.c.). Measures were taken on days 1, 7, 14 and 21 after last injection. Tail sensitivity was measured by tail pinch test, heat sensitivity of the paw by plantar test and cold sensitivity of paw by acetone drop test. The anxiety/depressive related alterations were measured by open field test (vertical counts, vertical time and distance traveled).

Reserpine induced a transient increase in tail mechanical sensitivity and paw cold sensitivity only at the first day of evaluation. No alterations were observed on heat sensitivity. The open field revealed a decrease in all parameters in day 7 and a recovery to control levels in subsequent measures, with exception of vertical counts, which persisted decreased until day 14.

These results extend the knowledge about this model and reinforce its use for testing therapeutic approaches for Fibromyalgia.
ULTRA-LOW DOSE ALPHA-ADRENERGIC ANTAGONIST ATIPAMEZOLE ENHANCES MORPHINE ANALGESIA AND REDUCES THE DEVELOPMENT OF TOLERANCE FOLLOWING NERVE INJURY

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Introduction: Development of analgesic tolerance to opioids and decreased efficacy are significant problems in the treatment of chronic pain states. Previous studies have shown that administration of ultra-low dose (ULD) opioid antagonists paradoxically enhances morphine efficacy and attenuates the development of analgesic tolerance. This phenomenon has also been observed when opioids are co-administered with ULD alpha-adrenergic antagonists in pain naive animals, but this has not previously been investigated in a model of neuropathic (NP) pain.

Objective: To investigate the effects of chronic systemic ULD atipamezole (an alpha-2 adrenergic antagonist) on morphine analgesia following nerve injury.

Methods: NP pain was induced in male Sprague-Dawley rats through chronic constriction injury (CCI) of the sciatic nerve. Half the animals received once daily subcutaneous injections of morphine (5mg/kg), while the other half received morphine plus ULD atipamezole (5ng) for ten days following nerve injury. Behavioural responses were assessed at four, seven and ten days post-surgery through a thermal tail flick assay and by assessment of mechanical paw withdrawal thresholds with von Frey filaments.

Results: NP animals that had been chronically co-administered ULD atipamezole (5ng) along with morphine experienced enhanced and prolonged thermal and mechanical analgesia compared to those that had been treated chronically with morphine alone. Animals co-treated with ULD atipamezole were still experiencing significant analgesia two hours post-injection following ten days of chronic treatment while the morphine alone group were not.

Conclusion: ULD alpha-adrenergic antagonists like atipamezole may one day prove clinically effective in enhancing opioid analgesia and reducing development of tolerance.
TRESK TWO-PORE-DOMAIN K⁺ CHANNELS EXPRESSION HAVE A ROLE ON PAIN TRANSMISSION IN NEUROPATHIC RATS AFTER SPINAL NERVE LIGATION

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Introduction: Outward K⁺ current through the two-pore-domain potassium ion channels (K_{2p}) suppress cell excitability by hyperpolarizing the cell membrane. Recently reported TWIK-related spinal cord K+ channel(TRESK) is highly expressed in the neuronal tissue and is assumed to be associated with neuronal hyperexcitability, which is the basic mechanism of neuropathic pain. We have studied the relation between TRESK and neuropathic pain by examining the changes in the expression of TRESK in a pain model (lumbar spinal nerve ligation model, SNL model).

Method: Animals were divided into sham group (N=5) and spinal nerve ligation (SNL) group (N=5). The left L5 and L6 spinal nerves were isolated and tightly ligated with 3-0 silk thread. Mechanical allodynia (von Frey filament) was evaluated 0, 3, 7, 10 and 14 days after surgery. Immunohistochemistry was performed 14 days after surgery. All experiments followed the rules approved by the Medical School's animal Experiment Committee.

Result: Sustained mechanical allodynia was confirmed 3 days after lumbar spinal nerve ligation and TRESK expression was significantly increased in the spinal dorsal horn 14 days after SNL when compared with the sham group.

Conclusion: Our results strengthen the relation between TRESK and neuropathic pain.
RGS9-2 IN THE BRAIN REWARD CENTER MODULATES RESPONSES TO TRICYCLIC ANTIDEPRESSANTS IN A MOUSE MODEL OF NEUROPATHIC PAIN

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The signal transduction modulator RGS9-2 (Regulator of G protein signaling-9-2) plays a potent role in dopaminergic and opioidergic transmission in the striatum via actions as a GTPase accelerating protein or as effector antagonist for the G protein alpha subunit. Evidence so far points to RGS9-2 as a potent modulator of antiparkinsonian, antipsychotic, psychostimulant and opiate drug actions. In this study, we use a spared nerve injury (SNI) model and genetically modified mice to examine the role of RGS9-2 in the mechanical allodynia and thermal hyperalgesia associated with neuropathic pain. Although RGS9-2 does not affect the onset or intensity of neuropathic pain symptoms, it greatly affects responses to opioid and antidepressant drug actions. In particular, mice lacking the Rgs9 gene respond to much lower doses of tricyclic antidepressants (desipramine-DMI) in the Von Frey assay. To further understand the mechanism via which RGS9-2 controls responses to DMI we used viral mediated gene transfer and expressed RGS9-2 in the nucleus accumbens. Our data suggest RGS9-2 overexpression nucleus accumbens rescues the increased sensitivity to desipramine phenotype observed in RGS9 knockout mice, while it leads to reduced responses to DMI in C57Bl6 mice. At the cellular level, we identified RGS9-2 complexes associated with DMI actions, and monitored several signal transduction events affected by these complexes. Our findings provide new insights into the cellular mechanisms of antidepressant drug actions and point to RGS9-2 complexes as promising new pharmacological targets for the treatment of neuropathic pain.
ATYPICAL FACIAL PAIN (AFP): CHANGES IN CORTICAL EXCITABILITY AND PRESENCE OF NEUROPATHIC SYMPTOMS


AFP is diagnosed according to the exclusion of other primary causes of pain and in the absence of specific signs and symptoms.

It is believed that central and peripheral mechanisms are involved in its pathophysiology. The aim was to evaluate the profile of cortical excitability parameters in AFP compared with health subjects (HS) and its relationship with the presence of neuropathic symptoms.

Methods: 25 AFP patients and 25 healthy HS were enrolled in this study. Patients were evaluated by the McGill Pain Questionnaire, Douleur Neuropathique-4 (DN-4), Neuropathic Pain Symptom and Brief Pain Inventory.

Participants had CE parameters measured by TMS over the masseter muscle representation on M1 bilaterally (RMT, motor-evoked potentials, intracortical inhibition (ICI), and facilitation (ICF).

Results: AFP with neuropathic pain symptoms (DN4>=4) had similar scores in clinical pain CE results as those without (DN4<4).

ICF on the left M1 was increased 1.99±2.57;0.76±0.577 in the AFP group compared to HS(p<0.012).
IC on the left M1 was decreased in AFP compared to HS 1.93±1.98;0.86±0.67 (p<0.008). CE changes did not correlate with scores from clinical pain assessment tools.

Conclusions: The presence of neuropathic pain symptoms did not seem to impinge a more severe presentation of AFP or changes in CE. This profile (left increase in ICF and decrease in ICI) suggest a lateralized change in glutamatergic and GABAergic networks in M1 which was different from the pattern seen in neuropathic pain syndromes and fibromyalgia. A larger sample may be necessary to detect correlations with clinical pain symptoms in AFP patients.
ULTRASTRUCTURAL CHANGES IN SPINAL DORSAL HORN SYNAPTIC TYPES IN AN OROFACIAL NEUROPATHIC PAIN MODEL

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Background and aims: Trigeminal neuralgia is a debilitating chronic orofacial pain syndrome, which can occur after trigeminal nerve injuries. Its underlying mechanisms are still unclear. Emerging evidence suggest that synaptic alterations in the spinal cord can contribute to the development of chronic pain states. The aim of this study is to examine possible ultrastructural synaptic changes in the spinal cord from a chronic orofacial pain model.

Methods: Unilateral chronic constriction injury to the rat infraorbital nerve (CCI-ION) was used as a chronic orofacial pain model. Subnucleus caudalis/cervical C1-C2 (Vc/C2) spinal cord sections were collected 3-weeks post-CCI-ION injury, which correlates with peak orofacial hypersensitivity, and processed for electron microscopy analysis. Synaptic profiles with round vesicles (R-type), primary afferent synapses (C-type), and pleomorphic-flattened vesicles (F-type) were identified in superficial (I/II) and deep (III-IV) laminae of Vc/C2. Synaptic profiles were compared bilaterally within CCI-ION and sham rats.

Results: Our preliminary data suggested that CCI-ION injury caused an increase in R-type and F-type profiles in the superficial and deep dorsal horn on the injury side, respectively. In contrast, C-type profiles did not differ between the injury side and sham rats.

Conclusions: Synaptic changes in dorsal spinal cord after CCI-ION injury may contribute to the development of orofacial pain states.
Introduction: Malignant melanoma (MM) causes more than 75% of skin cancer deaths in USA. The treatment of MM is surgical: excision of the melanoma and sentinel lymph node biopsy (SLNB) and/or complete lymph node dissection (CLND). Since location and time of onset of the surgical lesion is well-defined SLNB and/or CLND may be a possible 'model' for how nerve injury pain develops.

Objectives: The study aim was to examine the development of pain and sensory changes in MM patients undergoing SLNB, with or without CLND.

Methods: The five study visits were before, and 1-4 hours, 10 days, three and six months after surgery. Visit assessments included ratings of average daily pain intensity, allodynia severity to stimulation with a foam brush and pin, and mapping of dysesthesia and pain in MM-excision-, SLNB- and CLND-sites.

Results: Preliminary analysis of thirty-six subjects enrolled to date demonstrate that of 27 subjects who underwent only SLNB, 14 subjects reported pain at 10 days, three subjects at 3 month visit (of 10; who completed follow-up visit to date), and one (of 2) reported pain 6 months after SLNB. Six underwent SLNB followed by CLND. Five reported pain 10 days after CLND, and one (of 2) reported pain 3 months after CLND. Full data-analysis will be presented at the meeting.

Conclusion: Preliminary results suggest that a subgroup of subjects develop neuropathic symptoms following surgery for MM. The most common symptoms being pain, numbness and tingling; with higher incidence amongst those who underwent SLNB and CLND.
NATURAL HISTORY OF PAIN FOLLOWING SURGICAL TREATMENT FOR MALIGNANT MELANOMA: SHORT-TERM

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Introduction: Surgical treatment of malignant melanoma includes sentinel lymph node biopsy (SLNB) followed by complete lymph node dissection (CLND) if malignancy is identified in the biopsy. The severity of acute post-operative pain may predict development of long-term post-operative pain.

Objective: Study the short-term post-operative pain and sensory changes in MM patients undergoing SLNB and/or CLND.

Methods: Five-visit observational study of MM patients undergoing SLNB with/without CLND. Clinical examination was performed pre-operatively and post-operatively (1-4 hours, 10 days, 3-months, 6-months) including medical history, VAS-rating (0-100mm), and sensory exam.

Results: Thirty-six subjects (22-89 yrs old; 75% male) have been enrolled to date. Twenty-seven subjects underwent only SLNB and six SLNB followed by CLND. In the SLNB-group, all subjects reported pain 1-4 hours post-surgery (VAS-rest: 13, VAS-cough: 26, VAS-movement: 15). Ten days post-surgery pain-ratings had declined (VAS-rest: 0; VAS-movement: 9). In the six subjects undergoing CLND after SLNB, pain ratings were higher immediately post-surgery (VAS-rest: 38, VAS-cough: 40, VAS-movement: 58) with minimal reduction over the next 10 days (VAS-rest: 38; VAS-movement: 49). The SLNB+CLND group reported more neuropathic pain symptoms at 10 days (≥60% reported pins/needles, numbness and altered skin sensitivity compared to ≥25% in SLNB-group). Twenty-one percent of the SLNB-group and all subjects in the SLNB+CLND-group were still using opioid-analgesics ten days after surgery. Full data-analysis will be presented at the meeting.

Conclusion: Subjects undergoing SLNB followed by CLND still reported moderate to severe pain and many neuropathic symptoms 10 days post-surgery despite opioid-analgesics.
IMAGING NEURONAL VOLTAGE GATED SODIUM CHANNEL DENSITY CHANGES IN VIVO IN A NEUROPATHIC PAIN MODEL USING $^{18}$F-SAXITOXIN POSITRON EMISSION TOMOGRAPHY-MAGNETIC RESONANCE IMAGING (PET-MRI)


Background and aims: Accurate identification of chronic pain generators is a significant clinical challenge. Voltage gated sodium channel (Nav) are critical in nociceptive activity. Our purpose is to image changes in Nav density using a novel radiolabeled Nav toxin derivative $^{18}$F-Saxitoxin ($^{18}$FSTX) and PET-MRI in a neuropathic pain model.

Methods: $^{18}$FSTX was prepared by conjugation of $^{18}$FSFB with 6-aminohexylcarbamoyl-saxitoxin. Measured IC$_{50}$ of $^{18}$FSTX showed nanomolar affinity against Nav (10.6±0.8 nM in PC12 cells). Spared-Nerve Injury (SNI) was performed in adult male Sprague-Dawley rats (n=6). For imaging, SNI and control rats received 500 µCi $^{18}$FSTX (IV) and then scanned with small animal PET-MRI.

Results: Counts were recorded from fused PET-MRI images based on ROIs defined by the MRI on the injured (white arrow) and uninjured (curved arrow) sciatic nerves. Additional $^{18}$FSTX uptake was visualized in surrounding soft tissues (red arrows), likely related to neuropathic changes. Increased $^{18}$FSTX uptake was seen in the SNI nerve (2.25±0.4) compared to control side (1.6±0.19) (p< 0.05). Autoradiography of harvested nerves confirmed radiotracer persistence in the neuroma.

Conclusions: $^{18}$FSTX shows potential as a specific radiotracer for visualizing Nav channels in vivo in the setting of neuropathic pain.

[[18FSTX PET-MRI in SNI]]
WHAT CAN SUBJECTS TELL US ABOUT MULTIPLE SCLEROSIS RELATED TRIGEMINAL NEURALGIA - TRIGEMINAL NEURALGIA SUPPORT GROUP SURVEY

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Background: TN is a severe chronic facial pain disorder about which there is limited knowledge and little high quality evidence.

Aim: To explore characteristics of a large cohort of subjects who have Trigeminal neuralgia (TN) and compare them to individuals with TN comorbid with multiple sclerosis (TN-MS) who answered a survey of the Trigeminal Neuralgia Association of the USA (TNA USA) support group.

Methods: In a survey of TNA USA members, a sample of individuals was evaluated to elicit key information regarding classic trigeminal neuralgia (TN) \((n=3989)\) compared to those with MS and TN \((n=465)\). Details of key characteristics including changes over time were determined. Their management was compared with classical TN.

Results: TN-MS tended to be more common among women and among older TN subjects \((P=0.09)\). The frequency of the four words used to express pain was not significantly different between groups \((P>0.05)\). Constant pain last year was more frequently reported by TN-MS subjects \((26.8\%)\) than TN subjects \((21.8\%, P=0.04)\). Pain was reported more frequently bilaterally among TN-MS \((11.6\%)\) than TN subjects \((5.2\%, P<0.0001)\). TN-MS subjects showed higher odds of bilateral pain than TN subjects \((OR=2.8, P=0.006)\). Baclofen, phenytoin, opioids, and amitriptyline were more frequently used by MS than TN subjects \((P<0.05)\). Hypertension, stroke and diabetes were also similarly distributed between TN than MS subjects.

Conclusion: Our results suggest few differences between TN and MS-TN.
DE NOVO SYNTHESIS OF GUANIDINIUM TOXIN DERIVATIVES THAT PREFERENTIALLY BLOCK THE PRIMATE NAV1.7 ISOFORM WHICH HAS BEEN IMPLICATED IN NEUROPATHIC PAIN

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Background and aims: Human Nav1.7, a target of significant interest for the development of anti-nociceptive agents, is blocked by low nanomolar concentrations of tetrodotoxin (TTX), but not saxitoxin (STX) or gonyautoxin-III (GTX-III). These findings question the long-accepted view that the 1.7 isoform is both 'TTX and STX-sensitive' (i.e., low nM IC50 values).

Methods: Single- and double-point amino acid mutagenesis studies along with whole-cell electrophysiology recordings establish two domain III residues, T1398 and I1399, which occur as methionine and aspartate in other Nav isoforms, as critical determinants of STX and GTX-III binding affinity. These two amino acids variants are unique to NaV1.7 found in primates (including humans) and do not appear in the rodent 1.7 isoform (which is blocked by low nM concentrations of both STX and TTX). Given this distinction, we used a highly advanced homology model of the channel pore to engineer and electrophysiologically test a number of STX-based inhibitors.

Results: Based on our detailed view of the molecular interactions that influence Site 1 binding, we were able to produce molecules with increasing selective affinity for the Nav1.7 channel isoform.

Conclusions: Identification of molecular variants for Site 1 of primate Nav1.7 may allow for the development of novel treatments for neuropathic pain.
MOTOR CORTEX STIMULATION IN THE COMPLEX TREATMENT OF CHRONIC NEUROPATHIC PAIN

E. Isagulyan, V. Shabalov, E. Salova, M. Khitj, Russia

Objectives: Motor cortex stimulation (MCS) is beneficial and promising technique that is increasingly being used for the treatment of chronic neurogenic pain syndromes. Our goal to present the outcomes of MCS in the complex treatment of deafferentation pain in our university clinic.

Material and methods: Since 2005 until 2011 22 patients (12 males and 10 females, aged 29 - 56 years) were undergone to implantation of epidural electrodes over the central sulcus region. In all patients repetitive transcranial magnetic stimulation (rTMS) of central cortex contralateral to the pain territory was performed as a trial preoperative test. In case of positive trial stimulation in 20 of them the neurostimulator was subcutaneously implanted. 15 patients achieved more than 50% pain relief, that lasted for 30 min to 36 h. Pain intensity was evaluated with Pain and Quality of Life Card (PQLC) based on 10-point Visual Analog Scale (VAS).

Results: Good outcomes were achieved in 17 patients both in immediate postoperative period and in long-term (up to 48 month) follow-up. Pain had improved by 35 to 70% in comparison with baseline. All 17 patients have stopped to use opiates.

Conclusions: Motor cortex stimulation is effective technique for the treatment of severe neurogenic pain. Efficacy of MCS can be improved by careful patient selection, advances in neuronavigation and electrophysiological control techniques, and also by upgrading of neurostimulation systems. Necessary to make more researches, that achieve more precise analyse of efficiency MCS in the treatment of different type of neuropathic pain.
PULSED RADIO-FREQUENCE AND TREATMENT OF TRIGEMINAL POST-HERPETIC NEURALGIA

J.S. Wang, X. Wei, J.J. Bao, China

Objective: Trigeminal post-herpetic neuralgia is one of typical painful diseases in human head or face. This paper report clinical effect of pulsed radio-frequency (PRF) on trigeminal post-herpetic neuralgia.

Methods: There are 60 cases with average history of 8 months, 30 cases of group A is in-patient and other 30 cases of group B is out-patient, of trigeminal post-herpetic neuralgia are investigated and index of pain types, sleeping condition and remain symptoms in zoster area are used. The amitriptyline 25-50mg /day and 3ml of neurotin intro-muscular injection are used in both groups. PRF is used in group A.

Results: Lightning pain, lancinating pain, burning pain are main complaint in clinical and average VAS score is 8.2. There are two sub-clinical types, irritable nociceptor group(42), deafferentation group(18), respectively. With PRF (2Hz, 40°C, 120s) treatment for two times (once every 3 days), VAS score is 3.3 in group A and 5.4 in group B. The therapeutic effect is stable after 14-18 months follow up in PRF group. The percent of recurrence is 20% in group A and 40% in group B, respectively.

Conclusion: After two times treatment of PRF, the quality of life of patient in group A markedly improve, the effect is better than the group B and therapeutic effect is stable during 14-18 months follow up.
SUB-TYPE CLINICAL INVESTIGATION OF POSTHERPETIC NEURALGIA

J.S. Wang, J.J. Bao, X. Wei, China

Objective: Postherpetic neuralgia (PHN) is one of typical painful diseases among that peripheral nerve injury pain after virus infection. The investigation data is reported from the department of pain medicine of Guangzhou Red Cross Hospital of Jinan University since 2004.

Methods: There are 686 cases, in-patient and out-patient, of PHN are investigated and index of pain types, clinical sub-type, comorbidities and remain symptoms in zoster area are used.

Results: Lightning pain, lancinating pain, burning pain and mixed type pain are main types in clinical and average VAS score is 6.8. There are four sub-clinical types, irritable nociceptor group(57.14%), normal nociceptor group (2.77%), deafferentation group(22.16%) and central reorganization group(17.93%), can be seen during the investigation, respectively.

Conclusion: The pain duration in this group is more than 3 months, even longer to 8 years, pain is middle to serious degree in clinic and the quality of life or/and working ability are significantly decreased for most of PHN patients.
EFFICACY AND SAFETY OF AN MGLUR5 ANTAGONIST IN NEUROPATHIC PAIN PATIENTS WITH MECHANICAL HYPERALGESIA: RESULTS OF A RANDOMISED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY

S. Butler, B. Jonzon, R. Karlsten, L. Stohle, B. Stacey, Sweden, USA

Background and aims: Neuropathic pain (NP) with mechanical hyperalgesia (MH) is difficult to treat. Several mechanisms are involved. Basic studies have shown that the NMDA/glutamate system is upregulated. The novel molecule, AZD2066, an mGluR5 antagonist, was shown to be effective in animal models of NP. After toxicity, PK/PD, receptor occupancy studies in animals and human volunteers, a Phase IIa study was undertaken to evaluate the efficacy and safety of 28 days oral treatment with AZD2066 compared to placebo in subjects with NP and MH.

Methods: This was a US-based, multicenter, 2-armed, double-blind, parallel group study. Male and non-fertile females 18-60 years of age with a variety of chronic neuropathic pain diagnoses and with MH (dynamic allodynia and/or punctate hyperalgesia) and average pain intensity 4-9 on an 11 point NRS at enrollment and randomization were studied. Planned sample size was 100 to achieve 40 evaluable subjects/group. The study was stopped after enrollment of 87 subjects due to a serious adverse event (SAE). Placebo or 12mg AZD2066 was given for four days followed by placebo or 18mg AZD2066. The primary endpoint was change in mean NRS average pain score from baseline to last five treatment days. Responder rates, PGIC, BPI-SF, SF-MPQ, pharmacokinetics, safety and tolerability were secondary endpoints.

Results: Reduction of mean pain scores from baseline to end of treatment was significantly greater (0.88, p=0.027) in the AZD2066 group. 71% versus 50% reported at least one adverse event (AE). The study was stopped after a psychotic SAE in an AZD2066 treated subject.
EARLY MARKERS OF PAINFUL BORTEZOMIB INDUCED POLYNEUROPATHY: A CASE REPORT STUDY

D. Naleschinski, A. Günther, R. Baron, F. Mahn, A. Binder, Germany

Aim of investigation: The proteasome inhibitor bortezomib has revolutionized the multiple myeloma therapy. However, under treatment the patients experienced excruciating neuropathic pain. Further studies have shown an impairment of A-beta, A-Delta and C-fibers during and after the bortezomib therapy. We hypothesized that quantified clinical assessment of neuropathic signs and symptoms might identify early markers of the bortezomib neurotoxicity and can so predict patients to develop neurological side effects.

Methods: We report about two multiple myeloma patients who started bortezomib therapy. We examined the patients using QST, autonomic tests and motor and sensory nerve conduction before starting therapy and repeated the examination at a four week interval to find predictors and create a prospective longitudinal study.

Results: Both patients had had to reduce the bortezomib therapy during their therapy; one patient had to end his therapy. We find a relationship between treatment duration and nerve fiber function.

Conclusions: The finding that hyperalgesia to cold and mechanical stimulus at the lower limb represent an early marker of a bortezomib neurotoxicity and this may help easily to identify patients with a higher risk to develop a bortezomib induced polyneuropathy. Peripheral and central sensitization processes and loss of small fiber function are thought to underlay bortezomib induced pain.
THE IMPACT OF A 12-PART ONLINE CME MULTIMEDIA CURRICULUM REGARDING CHRONIC PAIN ON PRACTICE PATTERNS IN PRIMARY CARE

A.C. Roc, S. Ullman, P.G. Fine, G. Salinas, S. Hwang, USA

Background and aims: Medscape survey data, literature review, and expert opinion suggest clinicians lack knowledge and competence in chronic pain management. To address this, 12 online CME-certified activities (15 to 25 minutes each) demonstrating best practices for assessment and management of chronic pain were developed, and the impact of education on practice patterns of participating primary care physicians (PCPs) was assessed.

Methods: Prior to curriculum launch, a 25-item survey including case vignettes and associated questions was developed, from which respondent data served as baseline. Questions linked to activities within the curriculum were posed to participating PCPs following activity completion; aggregate data from all activities serve as “participant” data. Chi square tests of baseline vs participant scores for each question determined overall effectiveness of the activities in the curriculum.

Results: Interim data from 7 of 12 activities (complete data to be presented at NeuPSIG 2013) indicate that following education, PCPs (baseline n=290, participants n=105 to 1776 depending on the question) are more likely to recognize postherpetic neuralgia when pain persists for 2 months beyond herpes zoster rash resolution (75% vs 59%, \( P < .001 \)); use the Brief Pain Inventory to assess the impact of persistent pain on physical functioning, emotional status, and sleep (43% vs 33%, \( P = .002 \)); and properly adjust pain medication for chronic low back pain (76% vs 56%, \( P < .001 \)).

Conclusions: The impact of online CME activities can be measured via case vignettes and associated questions and can demonstrate improvement in PCP knowledge and competency in assessing and managing chronic pain.
Introduction: Despite significant advances in knowledge regarding the multiple aspects of the experience of pain, and the development across the Western world of multiprofessional management of pain, few of these advances were evident in developing countries including Ethiopia. The extent of unrelieved pain globally, but in developing countries like Ethiopia in particular, is considerable.

Causes: The etiologies in developing countries range from a rising incidence of malignancies, rampant infectious causes and injuries. Childbirth is a widespread cause of untreated pain in Ethiopia and other developing countries.

Myth rejected: Palliative Care programs in other resource constraint settings have demonstrated the feasibility of providing pain and symptom relief. The correct diagnosis and proper treatment of pain should be an important public health concern, even in low resource settings.

Developments in Ethiopia: Summarized in the table attached

<table>
<thead>
<tr>
<th>Developments in Pain management in Ethiopia</th>
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<tr>
<td>1. Domestic production of oral morphine</td>
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<td>2. The training of few Palliative Medicine professionals</td>
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<tr>
<td>3. Recognition of Palliative Medicine as a medical specialty recently</td>
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<td>4. Conducive policy on availability of morphine for medical purposes</td>
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<td>5. The development of the National Pain Management Guideline</td>
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<td>6. Inclusion of opioids in essential drug list and issuance of 2 national guidelines on its use</td>
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<td>7. WORLD HOSPICE AND PALLIATIVE CARE DAY- an awareness campaign day</td>
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<tr>
<td>8. Panel of Physicians in essentials of pain management conducted and the outcome was submitted to government for review</td>
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<tr>
<td>9. Trial of introducing the pain management in medical curriculum is in swing in few public universities</td>
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Challenges: The effective relief of pain depends not only on the availability, accessibility or affordability of pain relieving drugs but also on the health sectors capacity to use those drugs efficiently. One of the biggest obstacles to provision of good pain treatment is the lack of training of health care workers. There is inadequate teaching of undergraduate doctors and nurses in pain management in Ethiopia.

Conclusion: Effective provider education on the policies, philosophy and intent of the use of analgesics, particularly opioids in treating pain, should help a lot. Work should also be diverted to enhance public awareness, particularly that of policymakers.
AMELIORATIVE POTENTIAL OF SILYMARIN ON STREPTOZOCIN-INDUCED NEUROPATHIC PAIN IN RATS

M.M. Al-Enazi, Saudi Arabia

Background and aims: The management of diabetic neuropathy is still a challenge for physicians. In the present study, we have targeted oxidative stress mediated nerve damage in diabetic neuropathy using silymarin, a potent antioxidant.

Methods: Diabetes was induced by single STZ (65 mg/kg i.p.) injection. Silymarin treatment was started after 21st day of diabetes induction and continued for 6 weeks. Pain-related behavior tests were performed including tail flick, paw-pressure analgesia and Rota-rod. In serum, tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6) and interleukin-1β (IL-1β) were estimated and in sciatic nerve, thiobarbituric acid reactive substances (TBARs), reduced glutathione (GSH), superoxide dismutase (SOD), catalase (CAT), glutathione-S-transferase (GST), glutathione-reductase (GR) and glutathione peroxidase (GSH-Px) activities were measured.

Results: Diabetic rats developed neuropathy which was apparent from decreased tail-flick latency (thermal hyperalgesia) and paw-withdrawal latency (pressure analgesia). This was escorted by decreased motor coordination as assessed by performance on Rota-rod treadmill. Silymarin (15 and 30 mg/kg/day) treatment for 6 consecutive weeks ameliorated hyperalgesia, analgesia and improved motor coordination. STZ significantly increased TBARs and decreased GSH levels in sciatic nerve where silymarin treatment significantly protected those changes. Pro-antioxidative enzyme activities: SOD, CAT, GST, GR and GSH-Px were reduced in sciatic nerve of diabetic rats. Silymarin treatment of both the doses showed significant ameliorated decrease in antioxidant defense respectively.

Conclusions: Present results clearly demonstrate protective effect of silymarin is mediated through attenuation of oxidative stress and proinflammatory process and suggest therapeutic potential of silymarin in attenuation of diabetic neuropathy.
INVOLVEMENT OF MICROGLIAL CD40 IN A MURINE RETROVIRUS-INDUCED PERIPHERAL NEUROPATHY

L. Cao, M.B. Butler, USA

Background and aims: Human immunodeficiency virus (HIV) associated peripheral neuropathy is the most common neurological complications associated with HIV infection, yet is still an under-studied area, in part due to the lack of appropriate animal model. C57BL/6 (B6) mice infected with LP-BM5 develop severe immunodeficiency (hence MAIDS), neurological deficits, and peripheral neuropathy. It is known that CD154-CD40 interaction between CD4+ T - B cells is required for the manifestation of MAIDS post-LP-BM5 infection and that HIV-1 encephalitis is associated with increased expression of CD40 on microglia. We aimed to determine whether spinal cord microglial CD40 signaling is involved in LP-BM5-induced peripheral neuropathy.

Methods: B6-CD40 KO mice were adoptively transferred with either total leukocytes or B cells and examined for mechanical sensitivity, tissue viral loads, and cytokine responses along with the development of MAIDS following LP-BM5 infection.

Results: CD40 KO mice with either types of cell transfer developed MAIDS and the severity of which was correlated with the peripheral cytokine responses. CD40 KO mice displayed transient and slightly increased mechanical sensitivity post-infection regardless of cell transfer. In all peripheral tissues examined, increased viral RNA was detected in all infected mice without significant group differences. However, in lumbar spinal cord, infected wild type B6 mice had the highest viral load and cytokine responses among all groups. Neither type of cell transfer further enhanced LP-BM5-induced increase in viral load and cytokine responses in CD40 KO mice.

Conclusions: Altogether, data support the involvement of microglial CD40 in LP-BM5-induced peripheral neuropathy.
IDENTIFICATION OF A NOVEL SIGNALLING PATHWAY OF [6]-S-GINGEROL IN HUH7 CELLS

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Background and aims: Calcium signals in hepatocyte regulate glucose, fatty acid and amino acid metabolism. They control cell growth, proliferation, and death. Members of the transient receptor potential (TRP) channel superfamily are candidate calcium influx channels. NFkB activation has been demonstrated to be strictly dependent on calcium influx and often induces genes favouring cell survival. We previously reported that [6]-S-gingerol is efficacious agonist of the TRPV1 channel in capsaicin-sensitive neurones. We now explore whether [6]-S-gingerol activates the TRPV1 channel and NFkB activation in liver cells.

Methods: The levels of intracellular calcium concentration ([Ca2+]i) were measured using Fluo-4 calcium assay. The mRNA levels of TRPV1 was measured using RT-qPCR. NFkB activity was identified using HuH7 cells transfected with NFkB luciferase reporter vector.

Results: [6]-S-gingerol rapidly increased [Ca2+]i in HuH7 cells in a dose-dependent manner; the increase was transient and blocked by EGTA. Induction of [Ca2+]i by the TRPV1 channel agonist capsaicin was consistent with activation of TRPV1 channel in HuH7 cells. Importantly, similarly to capsaicin, the [6]-S-gingerol induced [Ca2+]i was blocked by the TRPV1 channel antagonist capsazepine. NFkB activity was rapidly increased within 7.5 min of exposure to [6]-S-gingerol and reached a peak at the 15 min time point. After a longer incubation time point of 30 min, NFkB activity started to decline, and it switched off after 120 min.

Conclusions: The findings of this study suggest that [6]-S-gingerol acting as an TRPV1 agonist in liver cells that leads to transient activation of NFkB by calcium.
NEW TREATMENT FOR PAIN DUE TO LUMBAR STENOSIS WITH A PERCUTANEOUS 16POLAR LEAD: REDUCTION OF PAIN AND IMPROVEMENT IN QUALITY OF LIFE. - PRELIMINARY DATA

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Introduction: Lumbar Spinal Stenosis decreases the total area of the spinal canal, lateral recesses, or neural foramina. Pain management should be reserved for patients whose surgical risk is prohibitive. Whereas in FBSS and LB patients lower limb pain can be alleviated easily with SCS, it is more difficult to achieve sufficient pain relief in the low back region.

Material and methods: 7 patients with lumbar stenosis and indication for SCS have been implanted with a 16 polar lead (Infinion™ 16polar percutaneous lead, Boston Scientific Corp). A multidisciplinary assessment was conducted before implant.

Results: After 3 months pain intensity was -73.2% and all patients showed an improvement in quality of life (activity +62%, general health +58%, sleep +56%, anxiety -75% depression -50%). Percentage of disability (ODI) decreased from 58% to 40%. 5 patients had 100% coverage of body painful area and the other of 80%. During trial period all patients suspended drugs rescue dose and after 3 months all reduced pregabalin dose. Patients with psychiatric disorder maintained their therapy.

Conclusion: 16 polar lead is a good and safe alternative to treat pain due to lumbar stenosis. It guaranteed a good coverage of painful body area that lead a significant pain relief, an improvement in both mental and physical health conditions. Cylindrical shaped and the presence of 16 contacts allowed a safety surgical procedure in a reduced epidural space due to rachides stenosis. Further data and a larger sample and a longer follow-up period are required to confirm these data.
Introduction: Ethiopia's HIV prevalence stands at 0.1, 1.5 % in Rural and Urban setups respectively. Among HIV patients studies have revealed more than 34.6% in chronic care with-out Highly Active Anti Retroviral Treatment (HAART) & 48% on HAART suffer from Neuropathy in Ethiopia.

Despite significant advances in knowledge regarding the multiple aspects of the neuropathic pain, and the development across the Western world of multiprofessional management of pain, few of these advances are evident in developing countries including Ethiopia and remains a major challenge.

The following clinical types of Neuropathies were described in our setup:

a) AIDP & CIDP
b) AIDS-associated sensory axonal neuropathy
c) Mononeuropathy or mononeuropathy multiplex
d) Toxic Polyneuropathy

Challenges in management of Neurpathic pain:

- Lack of training for health care workers
- Serious problem with availability, accessibility or affordability of standard drugs
- Lack of standardized guideline for management.
- Inaccessibility of serologic, electrophysiologic, genetic diagnostic aids
- Lack of integration of care provision with psychiatry, surgery and radiology.

Developments in Pain management in Ethiopia:

Favorable developments for pain care will be given timeline.

Conclusion: In order to bridge the huge gap in resource limited settings all stake-holders should focus on:

1. Provision of standard drugs for treatment of Neuropathic pain as part of comprehensive HIV/AIDS care with the help of drug control authority and concerned stake holders.
2. Incorporation of Neuropathic pain course in medical/nursing national curriculum

Integration of palliative cares with psychiatric and surgical intervention whenever it is deemed necessary.
THE TIME DEPENDENT ROLE OF NEURONAL RAGE (RECEPTOR FOR ADVANCED GLYCATION END-PRODUCTS) IN A RAT MODEL OF NEUROPATHIC PAIN

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Background/aims: Persistent release of HMGB1 by injured sensory neurons can enhance sensory neuron hyperexcitability and contribute to neuropathic pain behavior. As cellular effects of HMGB1 can be mediated by either of two receptors, RAGE or TLR4, we sought to determine which receptor was responsible for the effects of this endogenous alarmin-mediated neuronal excitation and associated pain behavior.

Methods: Rodents were subjected to tibial-nerve injury (TNI) and lumbar dorsal root ganglia (DRG) were characterized for changes in RAGE and TLR4 mRNA/protein expression. The combination of intracellular current clamp techniques, humanized monoclonal antibody to RAGE (RAGE-Ab), and a small molecule inhibitor of TLR4/MD2 complex (Cmpd#15) were used to determine which receptor was responsible for HMGB1-induced neuronal excitation. Behavioral studies using injured rodents subjected to RAGE-Ab or Cmpd#15 were used to confirm in vitro observations.

Results: We observed that RAGE mRNA and protein expression in DRG significantly increased by 28 days post injury. In contrast, TLR4 mRNA and protein expression did not appreciably change following TNI. HMGB1 mediated increases in neural excitation were eliminated with RAGE-Ab, but not with small molecule inhibitors of TLR4 or TLR1/2. Systemic injection of RAGE-Ab completely reversed established pain hypersensitivity by day 28, while Cmpd#15 had no effect at days 14 or 28.

Conclusions: HMGB1 increases neural excitation in DRG neurons via RAGE, but the HMGB1/RAGE receptor interaction following TNI does not contribute to tactile hypersensitivity until day 28. These data suggest that RAGE may constitute a new target for the treatment of chronic, neuropathic pain.
USING AN EMDR - EYE MOVEMENT DESENSITIZATION AND REPROCESSING - THERAPY FOR THE TREATMENT OF NEUROPATHIC PAIN

M.-J. Brennstuhl, C. Tarquinio, France

Background and aims: The complex part of cognitive, behavioral and emotional in neuropathic pain make treatment complicated. Since few years, many authors have argued on a traumatic symptomatology who be responsible of chronic pain (reactionnal symptom of Post Traumatic Stress Disorder), or that chronic pain may induce a trauma (Beck & Clapp, 2011; Asmundson, Coons, Taylor & Klatz, 2002; Sharpey & Harvey, 2001).

This argumentation brought to us to envisage the EMDR - Eye Movement Desensitization and Reprocessing - therapy for the treatment of neuropathic pain.

The effectiveness of EMDR in the treatment of PTSD has been shown in five meta-analyses (Bisson & Andrew, 2007; Bradley, Greene, Russ, Dutra & Westen, 2005; Davidson & Parker, 2001; Maxfield & Hyer, 2002; Van Etten & Taylor, 1998).

One study about using EMDR on chronic pain, already shows interesting results (Mazzola, Calcagno, Goicochea, Pueyrredon, Leston & Salvat, 2009).

Methods: This research aims to test the effectiveness of treatment of neuropathic pain with a specific EMDR pain protocol (Grant & Threlfo, 2002) (n=15), compared to an EMDR standard protocol (Shapiro, 1995) (n=15), and eclectic therapy (control groupe) (n=15).

Results: After every session, and at the end of the treatment, the effects of EMDR protocol on neuropathic pain and traumatic symptomatology were evaluated and show significant improvement.

Conclusion: This presentation aims to show the effectiveness of using an EMDR therapy for the treatment of neuropathic pain, compared to eclectic therapy.
STUDIES OF SPINAL CHEMOTACTIC CYTOKINE LIGAND-1 (CCL-1) IN NEUROPATHIC PAIN IN MICE

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Neuropathic pain is a significant clinical problem and the current treatment is inadequate. Recently, neuroglia and cytokinines are involved in the development of neuropathic pain. However, little is known about functional roles of CCL-1, a well-characterized chemokine, in central nervous systems. In this study, therefore, we examined the functional role of chemokines in the neuropathic pain. The neuropathic pain model was produced by partially sciatic nerve ligation (PSNL) of a left hind paw in mice. Alldynia was evaluated using a von Frey filament. Chemokines in the spinal cord were measured by cytokine and chemokine array kits. Alldynia and activation of microglia occurred on the ipsilateral side after PSNL. Pre-emptive and chronic administrations of microglia inhibitor minocycline (20 mg/kg, i.p.) inhibited the alldynia. But post-chronic administrations of minocycline did not prevent the alldynia. Spinal CCL-1 was increased by PSNL and the increase in the CCL-1 was prevented by pre-emptive and chronic administrations of minocycline. Intrathecal (i.t.) injection of recombinant CCL-1 to naïve mice induced allodynia and hyperalgesia briefly. The CCL-1-induced alldynia was prevented by i.t. injection of the N-methyl-D-aspartate receptor antagonist MK-801. Pre-emptive and chronic i.t. injection of anti-CCL-1-neutralizing antibody prevented the PSNL-induced alldynia, but post-chronic i.t. injection of anti-CCL-1-neutralizing antibody did not. Moreover, CCR-8, the receptor for CCL-1, was detected in the spinal dorsal horn. These results strongly support that CCL-1 in the spinal cord contributes to the development of neuropathic pain.
THE MANAGEMENT OF NEUROPATHIC PAIN AND ITCH SYNDROMES IN PATIENTS WITH INSULIN-DEPENDENT DIABETES ON THE BASIS OF STRUCTURAL ANALYSIS OF ANTIDEPRESSANT AND ANTICONVULSANT MOLECULES

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Background and aims: To develop effective management of pain and itch syndromes in patients with insulin-dependent diabetes (IDD). The mental state of such patients is frequently complicated by depression or anxiety so the patients need psychotropic therapy. Earlier the structural criterion was formulated: the V-like group organization of aromatic rings in antidepressant and anticonvulsant molecules determines their analgesic and antipruritus action. 2 medicines having the group (antidepressants mianserin and anticonvulsant carbamazepine) and 2 medicines no having such group (antidepressant citalopram and anticonvulsant depakine) have been tested for treatment of 145 patients with IDD.

Methods: Pre-screening conformational analysis; standardized clinic studies, Hamilton scales of depression and anxiety, a pain scale (VAS), itch scale (Scorad-index). The study of 145 patients was open and randomized.

Results: Statuses of patients were estimated before and after 4 weeks from the beginning of the therapy. Daily doses of medicines were standard. After courses of mianserin and carbamazepine therapies the reducing of indexes had the following values: pain (VAS) 67.0%-67.0%; itch (Scorad-index) 73.6%-71.7%; depression level 73.6%-21.5%; anxiety index 71.4%-24.7%, respectively. Anti-itch effect of carbamazepine therapy was observed during the first week under lower doses but analgesic action of it was obtained 2-3 weeks later and under higher doses. On the contrary citalopram and depakine were noneffective. Both of them haven’t passed the structural selection while citalopram molecule has a system of two aromatic rings but their space orientation differs.

Conclusions: Mechanisms of pain and itch management have common targets that are complementary to the V-like group.
ASSESSMENT OF THE UTILITY OF CLINICAL INSTRUMENTS FOR DIAGNOSING HIV-ASSOCIATED SENSORY NEUROPATHY


Background and aims: HIV-associated sensory neuropathy (HIV-SN) afflicts ~40% of patients on antiretroviral therapy, and is usually associated with neuropathic pain. Simple accurate diagnostic instruments are required for both high- and low-resource-setting clinical use. This study explored the accuracy of three such tools commonly employed for diagnosing sensory neuropathy (SN) i.e. Brief Peripheral Neuropathy Screen (BPNS), Utah Early Neuropathy Score (UENS) and Toronto Clinical Scoring System (TCSS).

Methods: Data were extracted from detailed phenotyping study (HIV-PINS) conducted on 66 HIV+ve
patients attending Chelsea and Westminster Hospital. HIV-SN was diagnosed using criterion of ≥2 out of triumvirate: signs of distal SN, ≥2 abnormal DFNS QST findings or intra-epidermal-nerve-fibre-density of ≤7.63 fibres/mm. Diagnostic accuracy of BPNS, UENS and TCSS were analyzed using Receiver Operating Characteristic (ROC).

Results: Median values between those with and without HIV-SN showed statistical difference of $p < 0.0001$ both for UENS and TCSS, and 0.04 for BPNS. ROC analysis demonstrated UENS to have the highest accuracy with area-under-curve of 0.91.

Conclusion: Whilst all three instruments have validity for HIV-SN diagnosis, UENS has the highest validity.

Funding: Derek Butler Trust, IASP trainee fellowship - Scan|Design Foundation BY INGER & JENS BRUUN, Wellcome Trust strategic award to London Pain Consortium
Introduction: Patient presented with complaints of long standing bilateral hand numbness. Review of history revealed the numbness in her hands began approximately seven years prior. Despite undergoing bilateral carpal tunnel release, she continued to complain of numbness and pain in digits 1-5. Subsequently two years later, she continued with worsening hand numbness, but also developed extreme fatigue, dyspnea, and unrelenting nausea. Abdominal fat aspiration confirmed the diagnosis of Amyloidosis.

Objectives: Amyloid neuropathy can affects up to 20% of diagnosed Amyloidosis. Amyloid neuropathy presenting sign most often involve small fibers that affect the lower extremity (similar to Diabetes Mellitus) or isolated median neuropathy. In our case, the clinical and EMG findings were consistent with bilateral plexopathy secondary to Amyloidosis. To our knowledge, no previous reported case of bilateral brachial plexopathy has been reported. Clinicians and Electromyelographers evaluating EMG findings of bilateral brachial plexopathy could consider listing Amyloidosis in the differential diagnosis.

Methods: Electromyography, EMG, was ordered.

Results: EMG showed prolonged distal and significantly reduced amplitude of median motor studies. The ulnar motor amplitude was also reduced without focal conduction block or slowing. Needle exam showed florid fibrillation potentials and large complex motor unit potential in the first dorsal interossei, deltoid, triceps, and pronator teres. Clinical Interpretation concluded longstanding, smoldering patchy widespread bilateral brachial plexopathy.

Conclusions: Amyloidosis should be considered in the differential diagnosis when EMG and clinical symptoms correlate with bilateral brachial plexopathy.
SENSORY PROFILES AND EPIDERMAL INNERVATION IN PATIENTS WITH HIV-ASSOCIATED NEUROPATHY


Introduction & objectives: Approximately 40% of HIV +ve patients develop an HIV-associated sensory neuropathy (HIV-SN) a distal polyneuropathy causing neuropathic pain. We investigated whether quantitative sensory testing (QST) parameters enabled the ready differentiation of patients with and without HIV-SN and whether they correlated with intra-epidermal nerve fibre density (IENFD).

Methods: Symptom questionnaires, DFNS protocol QST, physical examination and skin and blood sample harvesting were performed on 66 HIV +ve patients and 36 healthy volunteers. Of the HIV +ve patients 21 had painful HIV-SN and 7 had non-painful HIV-SN. 38 patients did not meet the requirements of diagnosing HIV-SN, namely ≥ 2 of an IENFD of ≤ 7.63 fibres/mm, 2 or more abnormal QST findings, or signs of peripheral neuropathy on examination.

Results: Statistically significant differences in mean Z-scores (P< 0.05) were detected between HIV +ve patients with and without HIV-SN in Mechanical Detection Threshold (-2.17 vs -0.77) and Vibration Detection Threshold (-2.24 vs -0.84). Thermal QST parameters were non-discriminatory for HIV-SN. DFNS normal values were used to calculate Z scores. Mean IENFD was determined for HIV-SN and HIV without SN groups (6.4 vs 9.4 P=0.003). Strong correlation between Z-scores for Mechanical Pain Sensitivity (MPS) and IENFD (Pearson r = 0.58, P=0.019) was shown. There was no comparable correlation in HIV +ve patients without HIV-SN.

Conclusion: MDT and VDT are the most effective QST parameters in discriminating between HIV +ve patients with and without HIV-SN.

Funding:

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NIHR
Introduction: The efficacy and medico-economic value of spinal cord stimulation (SCS) for the treatment of failed back surgery syndrome (FBSS) is well established. However, the axial back pain (ABP) component of FBSS is poorly amenable to neurostimulation. Trials conducted by our team suggest that tripolar SCS is effective for treating back pain.

Objective: To demonstrate improved ABP control in FBSS patients with transverse tripolar SCS.

Method: A prospective, observational study of 76 patients with refractory FBSS, consecutively implanted with transverse tripolar SCS between 2008-2011 in 3 pain management centers (Poitiers, France, Montréal and Regina, Canada). The primary objectives were to assess the degree of pain relief and functional efficacy on the global and ABP component of these patients. The secondary objective was to analyze the effect of Specify® 565 electrode (Medtronic Inc, Minneapolis, MN) programming on the paraesthesia coverage of the ABP territory in these patients.

Results: Leg paraesthesia could be induced in all patients with at least one of the tested configurations. Bilateral low-back paraesthesia was induced in 53.5% of patients, while unilateral low-back paraesthesia was induced in 78.9%. Multi-column configurations were statistically more effective than single-column configurations for all zones considered. At 6 months, 75.4% of patients receiving multi-column stimulation (n=57) obtained ≥30% improvement of the ABP component on the visual analog scale (VAS), while 42.1% of patients obtained ≥50% improvement of ABP on VAS.

Conclusion: Multi-column SCS is effective in the management of FBSS. Therapeutic success is contingent on rigorous patient selection protocols and programming optimization.
DOES THE SPONTANEOUS PAIN RATING CORRELATE WITH DISTINCT QST PARAMETERS?

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Within the European research project “Neuropain” sensory profiles are assessed by quantitative sensory testing (QST), additionally clinical and questionnaire data (e.g. PainDETECT) is collected from patients with peripheral and central painful or painless neuropathies.

Preliminary data was taken to investigate if spontaneous pain correlates with any QST parameters, particularly if patients with high ratings of current, maximum or average pain of the last four weeks demonstrate decreased pain thresholds.

112 complete records from patients with painful polyneuropathy (n=49), peripheral nerve injury (n=21) or other neuropathies (n=43) were classified into patients with low (numeric rating scale, NRS 0-3), moderate (NRS 4-7) or high pain intensity (NRS 8-10). Pearson's correlation, t-Test, p< 0.05.

There’s a significant, but weak correlation for current pain intensity and pressure pain threshold (r=0.159). All other pain thresholds don’t show any correlation. Most z-values for detection thresholds (CDT, MDT, VDT) are lower in patients with medium and high average pain intensity, showing significance for the CDT (fig.1).
In patients with painful neuropathies, severe spontaneous pain isn’t accompanied by hyperalgesia in general; contrary hypoesthesia for cold, tactile and vibration stimuli occurs more often in this subgroup of patients. After further dataset collection also diagnoses-based analyses can be performed.

Supported by a grant from Pfizer Ltd
CHRONIC PAIN AND NEUROPATHY AFTER CHEMOTHERAPY


Introduction: Several patients develop peripheral neuropathy and pain due to neurotoxicity after adjuvant chemotherapy. Chemotherapeutics known to be neurotoxic include docetaxel, which is widely used in the treatment of high-risk breast cancer, and oxaliplatin, equally widely used in the treatment of high-risk colorectal cancer. The aim of the study was to characterize the chronic side-effects and look at the differences and similarities between these chemotherapy-induced neuropathies.

Methods: We examined 40 patients with pain and/or unpleasantness more than 6 months after ended treatment with either docetaxel or oxaliplatin. The patients filled in questionnaires. Quantitative Sensory Testing (QST) according to the protocol of the German Network on Neuropathic pain (DFNS), nerve conduction velocity, and intraepidermal nerve fiber density in distal skin biopsies were assessed on the dorsal hand and foot unilaterally.

Results: Preliminary results on 16 oxaliplatin-patients (8 female and 8 male, age (mean) 66.1 years) and 9 docetaxel-patients (age (mean) 56.6 years). There was no difference in number of patients with sensory gain (p=0.75) or loss (p=0.81) on the feet (mechanical and thermal stimuli). Furthermore there was no significant difference in percentage with paradoxical heat sensation (present in 75% and 56% respectively, p=0.39) or cold allodynia (12.5% vs 0%, p=0.52). Results from hands and feet on all 40 patients will be presented at the congress.

Conclusion: Despite differences in the acute symptoms of chemotherapy-induced neuropathy, there were less variation in pain and sensory phenotypes among patients with chronic symptoms.

This study is part of the Innovative Medicine Initiative EUROPAIN, www.imi.europa.eu.
The aim of the study was to evaluate the effectiveness of intraosseous blockades in the treatment of pain syndrome in distal symmetric diabetic polyneuropathy (DSDP).

We examined 78 patients (13 men and 65 women) with painful DSDP. The average age of patients was 62.0±8.8 years, mean duration of diabetes 9.7±7.5 years, duration of pain in legs and feet - 3.9 years. The diagnosis of painful DSDP was confirmed by neurological examination, from the data evaluated by the diagnosis of neuropathic pain DN4 and EMG investigation. Assessment of pain syndrome was carried out using a VAS before treatment, after treatment and 6 months after treatment.

40 patients (main group) received intraosseous blockades, 38 patients (control group) received 50 mg amitriptyline per day. The main and the control group were matched by sex, age, duration of diabetes, duration of neuropathic pain.

Intraosseous blockades (2-8 blockades) with 5 ml 1% Lidocaine were made into the bone marrow of the epiphysis of the tibia, head of fibula, posterior superior iliac spine.

Pain syndrome on VAS in the main group before treatment was 6.8±1.1, after treatment - 2.0±1.3 and 6 months after treatment - 4.2±1.2. Pain syndrome on VAS in the control group before treatment was 6.7±1.4, after treatment - 3.6±1.5 and 6 months after treatment - 6.2±1.4.

Intraosseous blockade is an effective method of treatment of pain syndrome in diabetic polyneuropathy. High efficacy of intraosseous blockades confirms the important role of intraosseous receptors in the pathogenesis of pain in diabetic polyneuropathy.
THE EPIDEMIOLOGY OF NEUROPATHIC PAIN IN CANADA

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Introduction: The prevalence of neuropathic pain ranges from 3%-17.9%, depending on the measurement tool used and the population surveyed.

Objectives: To estimate the prevalence of chronic pain with neuropathic characteristics (NC) in Canada, and to assess the agreement between two screening tools for neuropathic pain.

Methods: Questionnaires were mailed to a random sample of 8,000 Canadians aged 18 and over. Prevalence of NC was measured as the proportion of respondents with a score ≥3/7 on the Douleur Neuropathique en 4 Questions (DN4) and ≥12/24 on the self-report version of the Leeds Assessment of Neuropathic Symptoms and Signs (S-LANSS). Prevalence was weighted by age, sex and province using the 2011 Canadian Census data. Percent agreement and kappa were calculated between the screening tools.

Results: 1520 surveys were completed, representing a response rate of 33% after removing invalid addresses. The prevalence of NC was 19.1% with the DN4, 15.1% with the S-LANSS, and 11.0% on both tools combined. When individuals with fibromyalgia, chronic widespread pain, and arthritis were excluded, the prevalence dropped to 15.3% (DN4), 12.3% (S-LANSS) and 8.9% (both tools). The percent agreement between tools was 87.8% and Kappa was 0.57 (p< 0.01).

Conclusions: These findings are higher than international estimates, but similar to the 17.9% reported in Alberta, Canada. Both the S-LANSS and the DN4 appear to have captured conditions with a neuropathic component, e.g., fibromyalgia, arthritis. There was only fair to good agreement between the two tools. Both of these factors likely contribute to the high estimates of NC.
Prostaglandin E1 facilitates hyperpolarization-activated cyclic nucleotide-gated (HCN) channel through activation of prostaglandin E receptors of the EP2 subtype in somatosensory neurons

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Hyperpolarization-activated cyclic nucleotide-gated (HCN) ion channels and their current, I\textsubscript{h}, have been suggested to play an important role in neuropathic pain by involvement in ectopic discharges after peripheral nerve injury. Prostaglandin E\textsubscript{1} (PGE\textsubscript{1}), known as its powerful vasodilatory, antiplatelet and cytoprotective properties, has been well established as a therapeutic agent for lumbar spinal stenosis in clinical fields. We investigated the cellular action of PGE\textsubscript{1} on HCN 2 in primary dissociated neurons of trigeminal ganglia (TG) in rats.

Medium-size (DM 33 - 40 µm) TG neurons were prepared and whole-cell recordings were made using patch electrodes. The I\textsubscript{h} current was identified and the effects of PGE\textsubscript{1} on I\textsubscript{h} current were determined. To investigate the intracellular effect of PGE\textsubscript{1} on increasing I\textsubscript{h} current, we applied an adenylyl cyclase inhibitor (MDL-12,330A hydrochloride) and an analogue of cAMP (8-Br-cAMP), and observed the mechanisms of I\textsubscript{h} current and PGE\textsubscript{1}. We examined which subtype(s) of EP receptor was activated by PGE\textsubscript{1} to facilitate I\textsubscript{h} current in TG neurons. Finally, the frequency of action potential elicited by a current injection after exposure to PGE\textsubscript{1} was determined in I\textsubscript{h}-expressing TG neurons. I\textsubscript{h} was identified in the medium-sized TG neurons isolated from rats and increased by PGE\textsubscript{1} in a dose-dependent manner (ED\textsubscript{50} = 29 nM). Adenyl cyclase inhibitor and 8-Br-cAMP inhibited the facilitation of I\textsubscript{h} current by PGE\textsubscript{1}. EP\textsubscript{2} receptor antagonist inhibited the facilitation of I\textsubscript{h} current by PGE\textsubscript{1} and exposure to PGE\textsubscript{1} enhanced their excitability by an increase in action potential frequency in I\textsubscript{h}-expressing TG neurons.
GLUTAMATE ACTIVATED SPINAL ASTROCYTES ARE INVOLVED IN THE THERMAL HYPERALGESIA

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Background and aims: Pain is a serious public issue affecting millions of people worldwide. In addition to neuron, activated glia also plays an important role in chronic pain. But how did each stimulus activates glia still has no mechanisms. Glutamate is a significant excitatory transmitter and involved in the pain signal transmission. Whether glutamate could active astrocytes and participated in chronic pain is still not clear. This study explored whether glutamate can activate astrocytes and activated astrocytes are involved in the thermal hyperalgesia.

Methods:
1. Primary cultured spinal astrocytes were prepared from the spinal cord of 1-2 postnatal Wistar rats.
2. The morphologic changes of astrocytes were analyzed by IHC.
3. The mRNA and protein expression of IL-6 were determined by RT-PCR and ELISA assay respectively to observe the functional changes of astrocyte.
4. The glutamate activated spinal astrocytes were injected intrathecally into the lumber subarachnoid space of rats.

Paw withdrawal latency (PWL) in response to thermal stimuli was tested.

Results:
1. Glutamate stimulation could induce the morphologic change of astrocyte.
2. 6 hours after glutamate incubation, the IL-6 protein expression started to increase and reached the peak 24 hours after glutamate stimulation. The mRNA expression of IL-6 had the same tendency.
3. The intrathecally injection of glutamate-stimulated astrocytes induced a dramatic reduction in PWL. The PWL reduction started 2 h after astrocyte injection and lasted for 6 hours.

Conclusions:
1. Glutamate can activate astrocytes in vitro.
2. Glutamate activated astrocytes are involved in the thermal hyperalgesia.
3. IL-6 released from glutamate activated astrocytes may play an important role in the thermal hyperalgesia.
IMPAIRED SPATIAL LEARNING IN MONONEUROPATHIC B7-H1 KNOCKOUT MICE

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Introduction: Chronic pain is a multidimensional experience frequently associated with deficits in cognitive functions including memory, attention, and verbal performance. B7-H1 (PD-L1, CD274), a co-inhibitory molecule, attenuates T cell proliferation and cytokine production. Hence, B7-H1 knockout mice were selected as an appropriate model to elucidate the role of cytokines in pain-induced cognitive impairment.

Objectives: This work aims to establish an appropriate pain model leading to cognitive impairment and the role of cytokines in pain-induced cognitive impairment.

Methods: Chronic neuropathic pain was induced in B7-H1−/− and C57Bl/6 wild-type (WT) littermates by chronic constriction injury (CCI) of the right sciatic nerve. Morris water maze (MWM) to evaluate spatial memory and learning was performed between post-operative days 22 and 27. Serum and tissues were harvested on day 28.

Results: Mechanical withdrawal thresholds (von Frey test) were lowered in both B7-H1−/− and WT mice from day 7 post CCI with no intergroup difference. However, in the acquisition task performed in the MWM, the escape latency was increased in B7-H1−/− compared to WT nerve injured mice (Trail day 1,2: P < 0.05; Trail day 3,4: P < 0.01). The contribution of pro- and anti-inflammatory cytokines is being investigated.

Conclusions: The present findings demonstrate that B7-H1−/− CCI mice are impaired in their spatial cognitive abilities. The previously observed altered cytokine profile in nerve injured B7-H1 knockouts, with an increase in the pro-inflammatory and reduction in anti-inflammatory cytokines, makes this an ideal model to elucidate the link between cytokine dysregulation and pain induced cognitive impairment.
A STUDY OF THE METHODOLOGY FOR DETERMINING MINIMAL ERYTHEMIC DOSE FOR THE UVB PAIN MODEL

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Background: The UVB (sunburn) model evokes inflammation of the skin by exposing it to UVB light, thereby modelling acute inflammatory pain while also having some of the characteristics of chronic and neuropathic pain. Determination of the individual’s minimal erythemic dose (MED) is an important aspect of the model as it establishes the eventual UVB dose used.

Aims: The aim of this study was to determine the most objective and sensitive method for determining the minimum erythemic dose for subjects preceding UVB exposure.

Methods: 10 healthy, adult volunteers (5 women) were recruited. UVB sensitivity was determined by administering 6 ascending doses of UVB irradiation based on the subject’s Fitzpatrick skin type. The exposed area was assessed after 24 hours by visual inspection by two investigators for well-demarcated erythema, by colour meter measuring a* of the CIELAB colourspace, and by determining the erythemic index (EI) of a colour-corrected, digital photograph. Subsequently, subjects received a 3xMED UVB dose and nociceptive assessments 24 hours later.

Results: All subjects had an MED within the dose range used, in all but one subject the MED resulted from the third or fourth highest UVB dose. The visually assessed MED was either one dose higher or lower than the baseline +2.5 a* CIELAB value.

Conclusions: The three methods were equally effective. As visual inspection is a quick and accurate way of determining the MED and was less error-prone than the colourimetric and photographic assessments, we propose to use visual inspection for determination of MED in the UVB model.
THE ANTINOCICEPTIVE EFFECTS OF HYDROALCHOLIC EXTRACT OF GRAPE SEED USING HOT PLATE AND FORMALIN TEST IN MALE MICE

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Background and aim: The application of herbal plants instead of synthetic drugs is increasing in recent years because of their lower side-effects and high varieties of efficient components. The aim of the present study was to evaluate the antinociceptive effects of hydroalcholic extract of grape seed using hot plate and formalin test.

Methods: This study experimental has been done on 56 NMRI male mice (28±3 g) (n = 7 in each group) in weight. The hot plate and formalin test was used for acute and chronic pain. After preparation of extract, to evaluate the effect of pain related behaviors were monitored on antinociception, animals systemically received grape seed extract (75, 150, 300, mg/kg) and after 30 min pain related behaviors were monitored in formalin and for hotplate tests. The data were analyzed using SPSS software and ANOVA at significance level p < 0.05.

Results: Formalin injection into the plantar of right paw caused nociceptive behaviors in two phases. The first and the second phases were separated by a brief inter-phase where nociceptive behaviors decreased. The results showed that hydroalcholic Grape seed extract (75, 150, 300, mg/kg), significantly could induce antinociception in both phases of formalin test. Also, the Grape seed extract caused delay in painful behaviours (licking and jumping) in hot-plate test.

Conclusion: The present results show that hydroalcoholic extract of grape seed has analgesic properties and can be substituted for chemical analgesic drugs.
Background: Patients with gastroparesis (GP) often experience nausea, vomiting, early satiety, abdominal distension, and abdominal pain. We hypothesize some of these patients' pain is neuropathic in etiology.

Methods: 95 patients with known GP, treated with permanent gastric neurostimulator placement, underwent clinical evaluation for gastrointestinal (GI) symptoms on the Likert scale at baseline and during post-operative follow up. Operative serosal electrogastrograms (EGGs) were obtained. Intraoperative full thickness gastric biopsies were performed and the tissues were stained for nerve fibers (S-100). These biopsies were compared to autopsy normal controls. Patients were characterized according to gender, race, age, and the etiology of their GP (diabetes mellitus versus idiopathic).

Results: 81 of 95 patients reported moderate to severe abdominal pain preoperatively, in the absence of overt abdominal pathology (gallstones, obstruction, inflammation, infection, cancer). They had associated symptoms of nausea, vomiting, distension, and early satiety. The average EGG frequency of these 81 patients was 5.56 Hz compared to a normal range of 2.5-3.5 Hz. Biopsies showed an average S100 (nerve fiber) count of 7.79 for idiopathic GP ($p = 0.0013$) and 6.63 for diabetic GP ($p < 0.001$) compared to 19.16 for autopsy controls. Neurostimulation produced significant changes in the severity of nausea ($p = < 0.001$), vomiting ($p = 0.0024$), early satiety ($p = < 0.001$), and abdominal distension ($p = 0.0096$).

Conclusion: 81 patients with gastroparesis reported moderate to severe abdominal pain. Abnormal EGGs, abnormal nerve fiber counts, and improvement with electrical stimulation all indicate gastric neuropathy causes their abdominal pain.
PREVENTION OF ACUTE AND CHRONIC NEUROPATHIC POSTSURGICAL PAIN BY SINGLE-DOSE INTRATHECAL INJECTION OF AYX1, A TRANSCRIPTION FACTOR DNA DECOY

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Background and aims: Persistence of pain following surgery compromises recovery. Following an injury, particularly involving nerve trauma, the transcription factor EGR1 rapidly triggers broad and ongoing waves of pain-related gene regulation in the dorsal root ganglia and dorsal horn, leading to long-term sensitization and pain. AYX1 is an EGR1-decoy (an oligonucleotide-based, specific inhibitor of EGR1 activity) that mimicks the genomic EGR1-binding sequence. These studies evaluated AYX1 efficacy, pharmacokinetics, and safety across animal pain models and species.

Methods: AYX1 was delivered as a 0.02mL (rat, Sprague Dawley) or 1mL (dog, Beagle) bolus intrathecal injection. Efficacy was measured using von Frey hairs, weight bearing incapacitance or spontaneous rearing. Models of inflammatory (CFA), incisional, neuropathic injury or knee surgery-related pain in rats were performed as previously described. CSF and plasma were collected via catheter of percutaneously for pharmacokinetic measures.

Results: AYX1 dose-dependently prevented ongoing mechanical hypersensitivity with no evident effects upon motor function. AYX1 also accelerated recovery from spontaneous pain-related behaviors. AYX1 exposure was high in lumbar CSF but 3-5 orders of magnitude lower in plasma with half-lives of ~3 hours in CSF and < 10 min in plasma. There was an absence of toxicity up to maximum feasible dose.

Conclusion: These results illustrate the therapeutic potential of AYX1 for improving acute and preventing persistent neuropathic pain and accelerating recovery after surgery or trauma. Excellent safety results in a recent Phase 1 clinical study in healthy volunteers will allow the imminent initiation of a proof-of-concept Phase 2 study in surgical subjects.
SENSORY PHENOTYPES IN PATIENTS WITH PERIPHERAL NEUROPATHIC PAIN EVALUATED WITH QUANTITATIVE SENSORY TESTING


Background: Patients with neuropathic pain, quantitative sensory testing (QST) can define different sensory phenotypes thought to be related to different underlying mechanisms. One phenotype with abnormal sensitization of cutaneous nociceptors has been termed irritable nociceptors.

Methods: This study is part of a randomized, double-blind, placebo-controlled, crossover trial with the anticonvulsant oxcarbazepine. The study is ongoing. In this report, baseline QST measures from patients with peripheral neuropathic pain due to either peripheral nerve injury (PNI), polyneuropathy (PNP) or postherpetic neuralgia (PHN) were analyzed. QST was performed according to the protocol of the German Network on Neuropathic pain (DFNS). Patients with irritable nociceptors were defined as patients with normal cold and warm detection thresholds and either mechanical or thermal allodynia or hyperalgesia.

Results: November 2012, 41 patients with PNI, 33 with PNP, and 7 with PHN were included. There was no difference in mean pain duration (56.0 (SD 48.8), 70.4 (SD 51.5), and 53.4 (SD 40.8)) months, \(p = 0.42\) or pain intensity (NRS, 0-10) (6.3 (SD 1.7), 6.3 (1.6), and 6.3 (1.7) \(p = 1.0\)), but there were significant differences in age: PNI 52.0 (SD 14.7), PNP 62.6 (SD 9.1) and PHN 75.0 (SD 10.9) years, \(p < 0.001\). The percentage of irritable nociceptors in the PNI group was 39.0%, PNP group 30.3%, and PHN 42.9% (\(p = 0.68\)).

Conclusion: Preliminary results show that there was no significant difference in percentage of irritable nociceptors between the three groups.

Acknowledgements: This study is part of the Innovative Medicine Initiative project EUROPAIN, www.imi.europa.eu.
SWIMMING ANTINOCECEPTIVE EFFECT IN CHRONIC POST-ISCHEMIC PAIN (CPIP) MODEL IN MICE

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Background and aims: The chronic post-ischemia pain (CPIP) previously described as model for complex regional pain syndrome-type I (CRPS-I) consists in prolonged ischemia and reperfusion in hindpaw of rodents with hyperemia, edema, mechanical and cold hypersensitivity. The maintenance of this pain is a process consistent with oxidative stress and exercise is well known to produce an acute oxidative stress followed by a progressive adaptation. The aim of this study was to evaluate the effects of swimming exercise in this model.

Methods: CPIP was produced by ischemia, placing a tourniquet proximal to the ankle joint of anesthetized (chloral hydrate 7%, 0.6 ml/kg, i.p.) male Swiss mice (n=12) for 3 h and removing it to allow reperfusion. Mice swam (water temperature: 27°C, 30 min daily) for 5 days, before and/or after ischemia. To study whether the swimming exercise had or not positive effect in CPIP was measured: hyperemia (with thermometer Mallory Thermosensor Pro), edema (with vernier caliper), mechanical (with von Frey filaments) and cold hypersensitivity (with cold plate at 10°C). Six days after CPIP, thiol levels were measured.

Results: Only mice that swam after ischemia had edema reduced (p < 0.001) while all the mice that swam had hyperemia increased (p < 0.001). On the other hand, swimming exercise was able to reduce both mechanical and cold hypersensitivity (p < 0.001) but didn’t alter thiol levels.

Conclusion: Swimming exercise has antinociceptive properties in CPIP, reducing mechanical and thermal hypersensitivity, suggesting that it can be an effective approach to treat CRPS-I.
LERCANIDIPINE ALLEVIATES HYPERALGESIA AND ALLODYNIA IN RODENT MODEL OF PACLITAXEL INDUCED NEUROPATHY

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Objective: Abnormal activation of calcium channels has been implicated in the development of neuropathy induced by paclitaxel. The effect of Lercanidipine (L-type calcium channel blocker) on paclitaxel induced neuropathic pain was evaluated in rats.

Methods: Thirty Wistar rats were used (n=6 per group). Paclitaxel (2mg/kg) and graded doses of lercanidipine (0.5, 1 and 2.5mcg/kg) were administered to three groups of rats. Paclitaxel was administered i.p. on days 1,3,5 and 7 and lercanidipine was administered from day 1 to day 10. Animals were assessed for nociception at baseline, 7th and 14th day. Mechanical allodynia and hyperalgesia were assessed by the percentage withdrawal response to 4g and 15g von Frey monofilament respectively. Cold allodynia was assessed by tail withdrawal response to cold water at 40°C. Comparisons were made with the saline and paclitaxel control groups.

Results: Paclitaxel produced significant mechanical hyperalgesia and cold allodynia. The mean paw withdrawal response to 4g von Frey filament appeared from day 7 increasing to 29.1±13% on day 14 (p< 0.002) and to 15g von Frey filament, it increased from 15.2±6% at baseline to 68.1±16% on day 14. Paclitaxel produced a reduction in tail withdrawal response to cold water from 16.3±1.6s at baseline to 11.2±1.2s on day14. Lercanidipine treatment produced dose dependent inhibition of withdrawal response to both 4g and 15g von Frey filament (p< 0.05 for both), but could not abolish the pain perception completely. Lercanidipine protected all the animals from development of cold allodynia.

Conclusions: Lercanidipine ameliorates paclitaxel induced neuropathic pain in rats and needs further evaluation.
C-TACTILE FIBRES: A NOVEL SUBSTRATE OF MECHANICAL ALLODYNA IN HUMAN SKIN

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Background and aims: We recently showed that low-threshold unmyelinated mechanoreceptors, termed C-tactile (CT) fibres, in human hairy skin mediate allostynia during overt muscle pain (induced by hypertonic-saline, HS). In this project, we investigated whether the expression of CT-mediated alldynia is ubiquitously reproducible, or is limited to the hairy skin and/or a 'perceptual' level of deep somatic pain.

Methods: In experimental series I (n=28), we examined the effect of vibration on HS-pain arising from an adjacent skin region. In series II (n=42), the effect of vibration and brushing - applied to digital glabrous skin and forearm hairy skin - on HS-induced muscle pain was tested. In series III (n=30), vibration-evoked responses were recorded 24h after repeated eccentric contractions - an otherwise imperceptible pain-state termed delayed onset muscle soreness (DOMS). Furthermore, similar interactions were explored in a clinical subject with chronic heel-pain (and consequent pain-avoiding postural adjustment). In all experimental series, the peripheral substrate of allodynia was determined by employing conduction blocks of unmyelinated (intradermal anaesthesia) and myelinated (nerve compression) fibres.

Results: During HS-induced cutaneous (I) and muscle (II) pain, concurrent tactile stimulation produced generalized allodynia - an effect found to be comparable across skin types and spinal segments. In DOMS-state as-well-as pathological pain-state, although there was no resting pain, tactile allodynia elicited. In all experimental series, allodynia persisted during blockade of myelinated fibres, but was abolished following blockade of cutaneous C fibres.

Conclusions: These observations attest to a broader role of CTs in pain-processing. Further exploration of CT-fibre functionality is warranted.
CLINICAL AND FUNCTIONAL CHARACTERISTICS OF PAIN SYNDROME IN HAND-ARM VIBRATION SYNDROME

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For patients with Hand-Arm Vibration Syndrome (HAVS) the most common complaints are pain, tingling or numbness in fingers and chillness of hands and fingers alibration (white fingers).

The study of the relationship between qualitative and quantitative indicators of pain may contribute to the study of mechanisms of pain reception. The aim of this study was to examine correlations between quantitative sensory testing (QST) and pain questionnaires. (VAS, DN 4 и Pain Detect) in patients with HAVS. The group of 26 miners with upper extremities disorders was examined in clinic in order to study the character of the pain syndrome. Age: 35-57 years old, length of service: 10-33 years. These patients filled in the DN4 and PD questionnaires and were examined with EMG and QST.

On questionnaire DN4 all patients got more than 4 points, but on questionnaire PD the number of points PD (over 13) was observed in 19/26. It should be noted that the biggest number of experienced workers give positive answers to the questions as they have a motivation to get social benefits.

The examination revealed a decrease the CS, an increase of the WS and VS, decrease the CP, an increase of the HP (р< 0,05). Statistically significant Spearman correlation was revealed between the level of pain on the VAS and questionnaires on neuropathic pain, PD and CS, PD and WS, NCV- and DN4, NCV and WS, NCV and QST.

The received QST and ENMG data prove mainly sensory character of vibration neuropathy.
EVALUATION OF ANTINOCICEPTIVE ACTIVITY OF MELATONIN IN CPIP MODEL


Background and aims: Chronic post ischemic pain (CPIP) is an animal model of complex regional pain syndrome-Type I. This model is characterized by an inflammatory (2d) and neurophatic phase (7d) which promotes mechanical and cold hypersensitivity. Moreover, it is well known the key role of free radicals in ischemic/reperfusion (I/R) conditions, and that antioxidants dose dependently reduces the nociceptive behavior in this model. Thus, we aimed to evaluate antinociceptive and antioxidant effect of melatonin, as a possible mechanism of action in the CPIP model.

Methods: Male Swiss Mice (n= 5-7) were anaesthetized and submitted to ischemia induced by a tourniquet proximal to the ankle joint of the right hindlimb during 3h and then removing it to allow the reperfusion. 2 and 7 days after surgery, animals were pretreated with melatonin (10-100 mg/kg i.p.) and 30 min after, the evaluation of mechanical (Von Frey filaments) and thermal (cold plate, 4±1 °C) hypersensitivity were conducted. In other set of experiments, the activity of antioxidants enzymes (catalase, glutathione peroxidase and glutathione reductase) was measured at 2nd and 7th day post I/R, in paw (muscle/skin) of animals after administration of melatonin (100 mg/kg, i.p.).

Results: Melatonin significantly (P< 0.05) decreased the mechanical and thermal hypersensitivity 2 and 7 days after surgery. Moreover, CPIP promoted an increased in the activity of antioxidant enzymes witch was reduced (P< 0.05) at basal levels by pretreatment with melatonin.

Conclusions: The pretreatment with melatonin reduced the nociceptive behaviors in mice with CPIP, probably by modulation of redox balance.
QUALITY OF LIFE WITH TAPENTADOL PROLONGED RELEASE (PR) VERSUS TAPENTADOL PR/PREGABALIN COMBINATION THERAPY IN PATIENTS WITH SEVERE, CHRONIC LOW BACK PAIN WITH A NEUROPATHIC COMPONENT

I. Steigerwald, D. Falke, K.-U. Kern, G. Nuhr, R. Lange, S. Rehm, R. Baron, Germany, Austria

**Background and aims:** This phase 3b study (NCT01352741) evaluated effects of tapentadol PR versus tapentadol PR/pregabalin on quality-of-life measures (secondary endpoints) in patients with severe, chronic low back pain with a neuropathic component.

**Methods:** Patients with a painDETECT “unclear”/“positive” rating and pain intensity ≥6 (11-point NRS-3 [average 3-day pain intensity]) at baseline were titrated to tapentadol PR 300mg/day over 3 weeks; those with ≥1-point decrease from baseline and average pain intensity ≥4 were randomized (1:1) to tapentadol PR 500mg/day or tapentadol PR/pregabalin 300/300mg/day (8-week, double-blind comparative period).

**Results:** In both groups, pain intensity (NRS-3), EQ-5D health status index, and SF-12 composite scores improved significantly from baseline to final evaluation (Table). No significant between-group differences were observed in improvements from randomization to final evaluation in mean EQ-5D index or SF-12 composite scores. TEAEs (≥10%) during the comparative period included dizziness, somnolence, hyperhidrosis, nausea, and fatigue, with a higher incidence of CNS TEAEs with tapentadol PR/pregabalin.

**Conclusions:** Tapentadol PR 500mg/day or tapentadol PR/pregabalin 300/300mg/day treatment resulted in comparable pain intensity reductions and quality-of-life improvements.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean (SD) score at baseline</th>
<th>Mean (SD) score at randomization</th>
<th>Mean (SD) score at final evaluation</th>
<th>Mean (SD) change from Baseline to final evaluation</th>
<th>Randomization to final evaluation</th>
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<tbody>
<tr>
<td>Pain intensity (observed-case analysis)</td>
<td>Tapentadol PR 500 mg/day (n=150)</td>
<td>8.4 (1.11)</td>
<td>5.9 (1.41)</td>
<td>4.3 (2.49)=</td>
<td>Tapentadol: ~4.2 (2.52), &lt;i&gt;P&lt;/i&gt;</td>
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<td></td>
<td>Tapentadol PR/pregabalin 300/300 mg/day (n=157)</td>
<td>8.4 (1.07)</td>
<td>5.9 (1.28)</td>
<td>4.2 (2.50)</td>
<td>Tapentadol + pregabalin: ~4.2 (2.66), &lt;i&gt;P&lt;/i&gt;</td>
</tr>
<tr>
<td>EQ-5D health status index</td>
<td>0.28 (0.31)</td>
<td>0.18 (0.32)</td>
<td>0.54 (0.26)</td>
<td>0.61 (0.30)</td>
<td>Tapentadol: 0.36 (0.34), &lt;i&gt;P&lt;/i&gt;</td>
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</table>

Note: Significant differences are indicated with <i>P</i> values.
<table>
<thead>
<tr>
<th>SF-12 physical health composite score</th>
<th>28.4 (8.05)</th>
<th>28.5 (7.77)</th>
<th>34.2 (9.26)</th>
<th>33.9 (8.49)</th>
<th>40.4 (9.52)</th>
<th>39.8 (9.16)</th>
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<td>pregabalin:</td>
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<td>(0.39), P &lt; 0.0001</td>
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<td>Tapentadol:</td>
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<td>(12.59), P &lt; 0.0001</td>
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<td>Tapentadol + pregabalin:</td>
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<td>(11.3 (11.45), P &lt; 0.0001)</td>
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<tr>
<th>SF-12 mental health composite score</th>
<th>45.2 (12.47)</th>
<th>43.6 (13.31)</th>
<th>48.8 (11.81)</th>
<th>47.6 (11.85)</th>
<th>48.5 (10.41)</th>
<th>49.9 (11.32)</th>
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<tr>
<td>Tapentadol:</td>
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<td>(10.17), P &lt; 0.0001</td>
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<td>Tapentadol + pregabalin:</td>
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<tr>
<td>(11.59), P &lt; 0.0001</td>
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| Table | 0.09 (0.36), P < 0.0001 |
|       | Tapentadol: 6.6 (12.45), P < 0.0001 |
|       | Tapentadol + pregabalin: 6.1 (11.13), P < 0.0001 |
|       | Tapentadol: 0.3 (8.29), P = 0.6958 |
|       | Tapentadol + pregabalin: 2.1 (9.73), P = 0.0108 |
EPIDERMAL INNERVATION SYMMETRY RATIO (EISR) FOR THE DIAGNOSIS OF UNILATERAL NEUROPATHIC PAIN

M. Buonocore, A.M. Gatti, L. Demartini, Italy

Background and aim: Neurodiagnostic Skin Biopsy (NSB) permits to calculate the Epidermal Nerve Fibres Density (ENFD) which is an expression of the number of small fibres present in the nerve supplying the investigated skin.

In case of unilateral nerve lesion, the pathophysiological basis for Unilateral Neuropathic Pain (UNP), international guide-lines strongly recommend a comparative control sample from the contralateral, non-affected skin. Considering that, so far, side-to-side variability of epidermal innervation in normal subjects is largely unknown, aim of the study was to study the ENFD symmetry in a large group of normal subjects.

Methods: For each recruited subject two biopsies were performed in symmetrical parts of the body. Epidermal nerve fibres were identified using the immunofluorescence method. The side-to-side epidermal innervation symmetry was measured using the EISR (Epidermal Innervation Symmetry Ratio) calculated dividing the lower ENFD by the contralateral (higher) ENFD.

Results: In six years, we recruited 133 normal subjects (44 M, 89 F) with a mean age of 54.7 ±15.4 years. In the whole group of subjects the mean EISR was 0.84 ± 0.09. Superimposable results were obtained in the following four subgroups: head (15 subjects), trunk (48 subjects), lower limbs (56 subjects) and upper limbs (14 subjects).

Conclusions: EISR seems to be a good tool for studying the normal variability of the epidermal innervation in symmetrical parts of the body. It appears to remain quite constant in the investigated body sites. Normal values presented here could represent a valuable support for the use of NSB to diagnose UNP.
LASER-EVOKED EEG RESPONSES AND DEFENSIVE REACTIONS
M. Moayedi, G.D. Iannetti, UK

Transient and intense nociceptive stimuli elicit large-amplitude electroencephalographic (EEG) brain responses (laser-evoked potentials, LEPs). Although LEPs have been traditionally thought to represent “pain-related” potentials, we recently indicated that they largely reflect the arousal, detection and reaction to an intense and transient sensory stimulus, regardless of its sensory modality and perceptual quality.

The aim of this work is to test whether the main LEP peaks solely reflect neural activities related to arousal and attentional orientation, or whether they reflect neural activity important for the execution of purposeful, motor reactions, and thus for the defence of the body from external threats.

Participants agreed to methods approved by the local research ethics boards. We recorded the reaction times and the EEG responses elicited by laser stimulation of the dorsum of the right hand of healthy participants that were instructed to respond to the stimulus by moving the stimulated hand in different directions. Behavioural and electrophysiological data were analysed at single-trial level. We obtained within-subject, statistical correlation maps showing the temporal and spatial distribution of the neural activities related to different aspects of the motor reaction to the threatening stimulus. This approach allows identifying functionally-distinct spatial and temporal patterns of the cortical response elicited by a nociceptive stimulus.

We showed that the largest part of the LEP response related to the speed of the response triggered by the laser stimulus, regardless of the direction of the movement, which suggests that, in the time domain, the LEPs largely reflect arousal and/or non-purposeful motor preparation.
REPEATED QUANTITATIVE SENSORY TESTING IN PATIENTS WITH POSTHERPETIC NEURALGIA IN THE COURSE OF DISEASE

J. Hellriegel, O. Esau, A. Binder, S. Rehm, R. Baron, Germany

Background and aims: Postherpetic neuralgia (PHN) is known as a complication of shingles. Patients with PHN suffer from symptoms like mechanical allodynia or tactile hypoesthesia. These symptoms can be described and quantified by using quantitative sensory testing. This study questioned if there is a change in the sensory profile of PHN patients during the course of disease.

Methods: 14 patients underwent two QST for sensory profiling at a minimal inter-testing interval of six month. Additionally different pain questionnaires were given to the patients.

Results: The profiles were heterogeneous with different courses in the second testing period. Most frequently thermal and mechanical detection thresholds normalized and simultaneously the mechanical pain detection threshold decreases. Less common were profiles, which did not change or present a normalization of a profile characterized by positive symptoms.

Conclusion: The sensory profile of PHN patients changes during the course of disease. This may be due to regeneration, degeneration and sensitization processes. Knowing that sensory profiles change in PHN patients implicates that drug treatment should also be adapted to follow a mechanism based treatment approach.
TAPENTADOL PROLONGED RELEASE (PR) VERSUS TAPENTADOL PR/PREGABALIN COMBINATION THERAPY FOR SEVERE, CHRONIC LOW BACK PAIN WITH A NEUROPATHIC COMPONENT: RESULTS FROM AN OPEN-LABEL CONTINUATION ARM

R. Baron, D. Falke, A. Gyllensvärd, K.-U. Kern, G. Nuhr, I. Steigerwald, Germany, Austria

Background and aims: This phase 3b study (NCT01352741) evaluated the effectiveness and tolerability of tapentadol PR and tapentadol PR/pregabalin for severe, chronic low back pain with a neuropathic component.

Methods: Patients with painDETECT “unclear”/“positive” ratings and pain intensity ≥6 (11-point NRS-3 [average 3-day pain intensity]) were titrated to tapentadol PR 300mg/day over 3 weeks. Patients with ≥1-point decrease from baseline and pain intensity ≥4 were randomized to tapentadol PR 500mg/day or tapentadol PR/pregabalin 300/300mg/day (8-week, double-blind comparative period). Patients not qualifying for randomization with pain intensity < 4 continued receiving tapentadol PR 300mg/day (8-week, open-label continuation arm).

Results: Significant decreases in pain intensity were observed (Table), with greater improvements from baseline to end-of-titration in the open-label continuation arm (tapentadol PR 300mg/day) than double-blind comparative arms. Incidences of TEAEs (≥5%) in the continuation arm with a stable medium dose of tapentadol (constipation, nasopharyngitis, nausea, somnolence [all 5.1%]) were lower than in randomized arms.

Conclusions: A subpopulation of patients with low back pain with a neuropathic component responded very well to tapentadol PR 300mg/day. For patients who did not experience adequate pain relief at that dose, increasing the dose to tapentadol PR 500mg/day provided similar efficacy to tapentadol PR/pregabalin combination therapy (300/300mg/day).

<table>
<thead>
<tr>
<th>Study arm (treatment group)</th>
<th>Mean (SD) score at baseline visit</th>
<th>Mean (SD) score at randomization visit</th>
<th>Mean (SD) score at final evaluation visit</th>
<th>Mean (SD) change from baseline visit to final evaluation visit</th>
<th>Mean (SD) change from randomization visit to final evaluation visit</th>
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<tbody>
<tr>
<td>Continuation arm (tapentadol PR 300mg/day; n=57)</td>
<td>7.9 (1.23)</td>
<td>2.6 (1.27)</td>
<td>2.6 (2.09)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>−5.2 (2.39)</td>
<td>0.1 (1.88)</td>
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<td></td>
<td>&lt;i&gt;P&lt;/i&gt; = 0.0001</td>
<td>&lt;i&gt;P&lt;/i&gt; = 0.7758</td>
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<tr>
<td>Comparative arm (tapentadol PR 500mg/day; n=150)</td>
<td>8.4 (1.11)</td>
<td>5.9 (1.41)</td>
<td>4.3 (2.49)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>−4.2 (2.52)</td>
<td>−1.8 (2.43)</td>
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<td>&lt;i&gt;P&lt;/i&gt; = 0.0001</td>
<td>&lt;i&gt;P&lt;/i&gt; = 0.0001</td>
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<tr>
<td>Comparative arm (tapentadol PR/pregabalin 300/300mg/day; n=157)</td>
<td>8.4 (1.07)</td>
<td>5.9 (1.28)</td>
<td>4.2 (2.50)</td>
<td>−4.2 (2.66)</td>
<td>−1.8 (2.46)</td>
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<td>&lt;i&gt;P&lt;/i&gt; = 0.0001</td>
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<sup>a</sup>n=59; <sup>b</sup>n=152.

[Table. Pain Intensity Scores (Observed-case)]
Introduction: Spinal cord stimulation (SCS) is an alternative for patients with treatment-resistant neuropathic pain. More than 50% pain relief is obtained during SCS trial stimulation for 60-70% of the patients. Though successfully used since the 1960s, the SCS analgesic mechanism in neuropathic pain remains unknown. For responders, SCS is in many respects an ideal treatment. However, treatment is costly, not available to anyone and rather laborious since it includes trial stimulation, surgery, battery changes and in some cases lead migration correction. It is plausible that the cerebrospinal fluid (CSF) mirrors mechanism relevant molecular changes taking place in the CSN during stimulation.

Objectives: We aimed to elucidate the mechanism of pain relieving SCS in humans. Knowing the mechanism could improve patient selection, treatment parameters as well as generate completely novel ideas for pharmacological interventions against neuropathic pain.

Methods: CSF samples were collected from SCS-responsive neuropathic pain patients (n=12) at two separate occasions, first after the SCS had been turned off for 48 h, and then after the SCS had been used normally for three weeks. The off- and on-state proteomes for each patient were relatively quantified using mass spectrometry in a shotgun proteomic approach.

Results: A panel consisting of seven proteins, 5 up-regulated and 2 down-regulated, was found to be significantly altered by SCS (P≤0.01).

Conclusions: This is the first assumption-free longitudinal proteomic study of CSF from neuropathic pain patients using SCS. Our findings bring new insights into the therapeutic mechanism of spinal cord stimulation.
ROLE OF DEOXYSPHINGOLIPIDS IN PACLITAXEL-INDUCED PERIPHERAL NEUROPATHY IN BREAST CANCER PATIENTS

R. Kramer, J. Bielavski, D. Kornhauser, T. Hornemann, S. Spassieva, USA, Switzerland

Background: Paclitaxel is an effective chemotherapy agent against breast cancer. However, 40% of the patients develop a distal axonopathy with sensory neuropathic pain and abnormal sensations. Paclitaxel-induced neuropathy has clinical similarities to the hereditary sensory and autonomic neuropathy type 1, which is associated with increased levels of deoxysphingolipids. Deoxysphingolipids are an atypical class of sphingolipids produced when L-alanine is used as a substrate for the first step of sphingolipid biosynthesis rather than L-serine. Importantly, deoxysphingolipids been shown to be neurotoxic in vivo. In this work we are testing whether paclitaxel exposure alters sphingolipid metabolism resulting in increased levels of neurotoxic deoxysphingolipids in cells and in the plasma of breast cancer patients.

Methods: Deoxysphingolipids in cells treated with paclitaxel and in the plasma of breast cancer patients receiving standard adjuvant paclitaxel are measured by mass spectrometry. Patient samples are collected prior, during and at the end of therapy. The levels of deoxysphingolipids will be correlated with the development of neuropathic symptoms. 23 patients are currently enrolled in the study.

Results and conclusion: Our data in cells showed that paclitaxel treatment resulted in a significant increase of deoxysphingolipids (Figure 1), suggesting that deoxysphingolipids could be the underlying cause for paclitaxel-induced peripheral neuropathy.

![Figure 1](image)

[Figure 1]
OPIOID RECEPTOR TRAFFICKING IS ALTERED FOLLOWING PROLONGED MORPHINE TREATMENT

E. Ong, C. Cahill, Canada, USA

Aims: The post-internalisation trafficking of endogenous neuronal delta opioid receptors (DOR) was examined in dorsal root ganglia (DRG) neurons. This internalisation occurs both constitutively and in response to agonists. We investigated the effect of prolonged morphine treatment on DOR internalisation.

Methods: Primary DRG neuronal cultures were treated with morphine (10μM) or vehicle for 48 hours. Neurons were then acutely treated with one of: a peptide DOR agonist (Deltorphin II - DELT), a small molecule DOR agonist (SNC80), a mu opioid receptor (MOR) agonist (DAMGO), or vehicle (all 1 μM) for 60 minutes. DOR and markers of early endosomes (Rab5), recycling endosomes (Rab11), and lysosomes (LAMP1) were immunofluorescently double-labelled and imaged by confocal microscopy. Associations between DOR and each marker were assessed by colocalisation analysis.

Results and conclusions: Constitutive DOR post-internalisation trafficking is typically considered to proceed via early endosomes towards ultimate degradation in lysosomes. Following prolonged morphine treatment, we observed an augmentation of constitutive-pattern trafficking.

Acute treatment of neurons with two DOR agonists, DELT (peptide) and SNC80 (small molecule), revealed interesting differences. In prolonged vehicle treated neurons, DELT, but not SNC80, induced DOR recycling. Following prolonged morphine treatment, both induced DOR recycling.

As expected, in prolonged vehicle treated neurons DAMGO does not affect DOR trafficking. Following prolonged morphine treatment, however, DAMGO induced DOR internalisation and recycling. Prolonged morphine treatment appears to promote the availability of a DOR species upon which MOR agonists may act. This is consistent with the formation of MOR-DOR interactions.

Acknowledgements: CIHR MOP394808 and NSERC PGS-D
IMPACT OF NEUROPATHIC PAIN ON PATIENTS QUALITY OF LIFE AT FANN TEACHING HOSPITAL (A SMALL SERIES)

L.B. Seck, J. Kyelem, M. Ba, A.D. Sow, K. Touré, A.G. Diop, M.M. Ndiaye, Senegal

Background and aims: Chronic neuropathic pain impact on quality of life has to be taken into account during patient's management by practitioners. We aimed to assess the impact of some neuropathic pain on different parameters of quality of life, in pain complaining patients.

Methods: Prospective study on outpatients followed up for neuropathic pain complaint.

Results: Eight patients have been questioned. They were 42 to 67 years old, with mean age 53.25. There were 4 males and 4 females. Five patients suffered from painful radiculoneuropathy, and 3 from polyneuropathy. Functional impairment using Sheehan Disability Scale showed disruption of work or school work varying from 50 to 100%, that of social or leisure activities varying from 0 to 100% and the same for family life and home responsibility. Days lost was 2 to 5 and days unproductive 0 to 3. According to EQ-5D, mobility was reduced at 10-100%, self-care at 0-100%, usual activities at 0-100%. Using Hospital Anxiety and Depression Scale, we found that 2 patients were anxiety and depression free. Six had at least one of the 2 symptoms, of whom anxiety was missing for 1, doubtful for 1 patient and definite for 4, while depression was doubtful for 3 and definite 3. On Pittsburgh Sleep Quality Index, the global scoring varied from 3 to 14.

Conclusions: Impact of some neuropathic pain is a determining factor in patient distress. Thus it has to be assessed and included in patients care.
REDUCED BASAL GANGLIA M-OPIOID RECEPTOR AVAILABILITY IN TRIGEMINAL NEUROPATHIC PAIN

M.F. DosSantos, I.K. Martikainen, T.D. Nascimento, T.M. Love, M.D. Deboer, E.C. Maslowski, J.K. Zubieta, A.F. DaSilva, Brazil, USA

Aim of investigation: Although neuroimaging techniques have provided insights into some brain mechanisms of Trigeminal Neuropathic Pain (TNP) in humans, it is not completely understood how molecular mechanisms are affected in TNP. In this study we examined changes in the endogenous µ-opioid system in patients with TNP using positron emission tomography (PET) with $[^{11}\text{C}]$carfentanil, which measures regional µ-opioid receptor availability [Binding Potential (BP$_{ND}$)] in vivo.

Methods: Twelve subjects, including four patients with TNP and eight healthy controls were examined with PET. The comparisons between patients and controls were performed using two-sample t tests, on a voxel-by-voxel basis within SPM8. Significant effects were detected using a statistical threshold that controls an error rate at p < 0.001.

Results: Patients with TNP showed reduced µ-opioid receptor BP$_{ND}$ in the nucleus accumbens (NAc), a region known to be involved in the mechanisms of pain modulation and reward/aversive behaviors. Furthermore, the µ-opioid receptor BP$_{ND}$ in the NAc was negatively correlated with the McGill sensory score (MPQ sensory) and total pain ratings (MPQ PRI) in TNP patients.

Conclusions: Our findings give preliminary evidence that a reduction of the µ-opioid neurotransmission in the ventral striatal area of the basal ganglia is involved in clinical pain in TNP. Nonetheless, further studies will be necessary to confirm this hypothesis.
HIGH FREQUENCY SPINAL CORD STIMULATION IN PATIENTS WITH FAILED BACK SURGERY SYNDROME WITH PREDOMINANT AXIAL BACK PAIN

K. Koneti, A. Gulve, S. Eldabe, S. West, F. Garner, R. King, UK

Introduction: Spinal cord stimulation (SCS) is a well-established treatment for neuropathic pain in patients with failed back surgery syndrome (FBSS). With traditional SCS paraesthesia coverage is essential for pain relief. Coverage of thoraco-lumbar dermatomes for treatment of axial back pain is very difficult. We present our experience of high frequency stimulation in 11 patients.

Methods: 11 patients with previous back surgery with predominantly axial back pain were treated. Patients underwent a trial of the therapy where two octapolar, percutaneous leads were placed near the radiological midline, between T8-T11. After a successful trial over 1-2 weeks, the leads were then connected to a rechargeable implantable pulse generator (Nevro Senza™) System capable of delivering frequencies up to 10 kilohertz. Pain scores were captured on a visual analog scale (VAS) at baseline and at regular follow up visits.

Results: 9 patients (82%) had a successful trial over 1-2 weeks and went on to receive the fully implantable neurostimulators. The average follow up period for these patients was 8.8 months (range 3-20 months) and average pain reduction on a VAS was from 7.9 /10 to 2.3 /10 for back and leg pain. All the implanted patients experienced more than 50% reduction of their back as well as leg pain. 33% patients were able to significantly reduce or stop their analgesics. 33% patients required revision of leads.

Conclusion: These early findings suggest that high frequency SCS of the spinal cord may be an effective treatment for axial back pain in patients with FBSS.
INTRATHECAL SHRNA GENE THERAPEUTIC TREATMENT OF NEUROPATHIC PAIN

M. Graham, P. French, D. Yeomans, Australia, USA

Background and aims: We and others have demonstrated that PKC-gamma is critical in inducing central sensitization and ongoing neuropathic pain states after injury in rodents. Thus, long-term silencing of spinal PKC-gamma should prevent and/or reverse pain states induced by nerve injury. Small, hairpin RNAs (shRNA) have been demonstrated to produce highly-selective, long-term silencing of genes critical to pain and can be packaged in viral vectors. Thus, intrathecal application of a viral vector encoding shRNA should produce a persistent analgesic effect in animal models of neuropathic pain provided the vector is able to penetrate key spinal neurons.

Methods: ddRNAi (DNA-directed RNAi) is a unique technology for silencing unwanted or disease-causing genes wherein shRNA is produced inside the target cell from a DNA construct that has been delivered to the nucleus. In the context of therapy, ddRNAi avoids many of the drawbacks of other gene silencing technologies and produces much longer-lasting effects. A ddRNAi construct designed to silence neuronal expression of PKC-gamma was inserted into an equine immunodeficiency lentiviral vector and applied intrathecally in rats that had demonstrated allodynia following peripheral nerve damage. The delivery of the transgene and consequent effects on pain behaviors were assessed.

Results: Transgene was successfully delivered to spinal dorsal horn cells as assessed by effects on PKC-gamma levels and produced a consequent attenuation of pain behaviors.

Conclusion: These results illustrate the therapeutic potential of a gene therapeutic approach to chronic pain using intrathecal application of viral vectors encoding shRNA directed toward key mediators of neuropathic pain.
RELATIONSHIP BETWEEN PAIN SYMPTOMS, CUTANEOUS DENERVATION AND SENSORY ABNORMALITIES IN DIABETIC NEUROPATHY


Background and aims: peripheral neuropathy is common in diabetic patients. Our aim was to relate pain symptomatology and sensory dysfunction to cutaneous denervation.

Methods: The Pain in Neuropathy Study (PiNS) was approved by the National Research Ethics Service No.: 10/H07056/35. Patients were assessed by means of detailed interview, neurological examination, quantitative sensory testing (QST) and skin biopsy unless contraindicated. Patients were recruited from primary and secondary care clinics within the London area. Neuropathy was defined as having 2 out of 3 of the following items: 1) Symmetrical sign of neuropathy 2) Two abnormalities on QST 3) Evidence of small or large fiber involvement (abnormal IENFD or abnormal NCS when available). Patients with a score of 4 or more in a 11-point Likert rating scale were allocated to the pain group.

Results: 49 out of 59 recruited patients (83%) met the study definition of neuropathy. 35 (59%) of them rated pain as being higher than 4 of whom 91% had neuropathic pain as defined by DN4. IENFD was reduced in both groups but not significantly different between the NeuP (+) and NeuP (-) patients (p = 0.64015). Quantitative sensory testing parameters showed global hypofunction and did not differ between the NeuP (+) and NeuP (-) groups other than a trend for increased dynamic mechanical allodynia in the NeuP (+) group.

Conclusions: Neuropathic pain was common in diabetic neuropathy patients; interestingly there was no simple correlation between the degree of cutaneous denervation or QST abnormalities and the patients reported ongoing pain.
Efforts to treat prolonged and neuropathic pain without the development of tolerance and the other toxic side effects of our current analgesics including opiates are urgently needed. Based on the changes in the expressed genome which accompanies the development of prolonged and neuropathic pain, we have been developing a novel approach to treatment of these pain states which involves the design, synthesis and biological evaluation of novel peptide and peptidomimetic ligands which are multivalent (have more than one pharmacophore). These (novel ligands) include ligands with potent mu and delta opioid agonist activities; or mu and delta opioid agonist and neurokinin 1 antagonist activities; or mu and delta opioid agonist and cholecystokinin antagonist activities; or mu and delta agonist and melanocortin 1 or 4 receptor antagonist activities. Several of these designed compounds are highly potent in vivo as analgesics in neuropathic animal pain models, and show minimal or no development of tolerance and none of the toxicities of current opioid drugs. Several of these compounds cross the blood brain barrier and may be orally active.
Objective: Evaluate pain, physical function, and quality of life (QoL) for CRPS patients after use of transcutaneous electrical nerve stimulation (TENS).

Study design: Prospective observational study. 6 months followup.

Methods: 13 CRPS-patients used TENS 2-8 hours daily for 1 month, thereafter as needed. Outcome measures: Pain (BPI), physical function (DASH; Disability Arm Shoulder Hand), QoL SF-36, patient's general impression of change (PGIC) at baseline, after one month of TENS use, and after 6 months followup.

Results: N=13; 11 women, 2 men. Eleven of 13 patients chose to continue TENS after the first month. There was a reduction in bodily pain (SF-36) after one month, median 12(range 0-52) to 22(range 0-51); (p= 0.012), but not after six months. BPI-median pain decreased from 5(range 4-8) to 4(range 3-6) (p= 0.02). BPI-worst pain was reduced after one month: Median from 8(range 5-10) to 6(range 5-8) (p= 0.03) but not after six months. DASH-score reduced after one month from median 70(range 55-100) to 53(range 20-83) (p= 0.001) and increase in activity after one month 57(range 27-85) to 46(range 14-73) (p= 0.005). PGIC was moderate to much better for seven (54%) of 13 patients after one month, and for four (36%) of 11 patients after six months.

Conclusion: The results indicate improvement in function and pain after daily TENS use in patients with CRPS in one upper extremity. The effect was less after 6 months. There was no increase in HQoL, except for a short term painreduction. The patients' PGIC were positive.11/13 patients continued TENS.
This presentation will focus on the effects of botulinum neurotoxin A (BoNT/A) in neuropathic pain induced by sciatic nerve ligature (CCI) in mice. We found that a single intraplantar injection of BoNT/A (15 pg/paw) was able to counteract the CCI-induced alldynia/hyperalgesia. Parallel, BoNT/A-injected mice showed a quicker recovery of the injured limb. Behavioral improvements were accompanied by structural modifications in the sciatic nerve, as revealed by immunofluorescence and western blot analysis of the expression of Cdc2 and GAP-43 regeneration proteins and of S100b and GFAP Schwann cells (SC) proteins. In vitro experiments confirmed that BoNT/A influences regenerative processes by direct interaction with the proliferative state of SC. We also evaluated immunostaining of cleaved-SNAP-25 (cl-SNAP-25) in the peripheral nerve endings, along the sciatic nerve, in DRG and in spinal dorsal horns, alone or colocalized with either glial fibrillary acidic protein, GFAP, or complement receptor 3/cluster of differentiation 11b, CD11b, or neuronal nuclei, NeuN. We detected cl-SNAP-25 in all tissues examined, from the peripheral endings to the spinal cord, suggesting a retrograde transport of BoNT/A along axonal processes. Finally, we demonstrated a beneficial effect of the pharmacological combination BoNT/A-morphine and the ability of BoNT/A to inhibit morphine-induced tolerance. The enhanced expression of glial cells, in particular astrocytes, induced by neuropathic pain was also counteracted by BoNT/A. Alltogether our findings strongly encourage further studies on the use of BoNT/A as therapy of pathological pain conditions difficult to treat in clinical practice and dramatically impairing patients' quality of life.
PAIN PREVALENCE IN PRIMARY BRAIN AND SPINAL CORD TUMOURS

R. Gupta, J.E. Williams, UK

Aims: This study aimed to evaluate the prevalence of pain amongst brain and spinal cord outpatients, and to determine the adequacy of analgesic treatment.

Method: After ethics approval patients were recruited from neuro-oncology clinics. If the patients had pain in the last seven days, they were asked to complete the Brief Pain Inventory and S-LANSS score. Pain Management Index (PMI) was used to assess adequacy of pain management.

Results: Out of 45 patients who consented to the study, twenty three patients (51%) reported pain due to any cause in the previous seven days, while 21 patients (46%) rated their pain as moderate to severe (VAS >4). 86% of patients with pain had it for more than 3 months. Pain secondary to anticancer treatments was present in 30% of those with pain, while 21% had tumour-related pain, and 49% had non-cancer related pain. 82% of patients who reported pain had negative PMI scores indicating inadequate analgesia, and 26% had neuropathic pain according to the S-LANSS.

Discussion: This study demonstrated a prevalence figure (51%) of pain, which is similar to the results of Antoniouk et al (1993). 82% of patients with pain had inadequate analgesia, which is higher than 43%, as reported in the general cancer population by Deandrea et al (2008). 60% had non-cancer related pain as compared to 25% found in general oncology clinics by Valeberg et al (2008).

Conclusion: This study has highlighted the significant problem of pain and its inadequate control in brain and spinal cord tumour population.
PAINFUL DIABETIC PERIPHERAL NEUROPATHY: RESULTS OF A SURVEY CHARACTERIZING PERSPECTIVES AND MISPERCEPTIONS OF PATIENTS AND HEALTHCARE PRACTITIONERS

A. Sadosky, B. Parsons, J. Hopper, USA

Background and aims: Little information exists on patient and healthcare practitioner (HCP) perceptions of painful diabetic peripheral neuropathy (pDPN). This survey aimed to identify gaps between patient and HCP perceptions of pDPN.

Methods: An online survey of patients with Type 1 or 2 diabetes and HCPs who treat diabetes was conducted in 2012 in the United States from national research panels. Questions focused on the impact, understanding, and management of pDPN, and interactions between patients and HCPs.

Results: Respondents included 1,004 patients (53% female, average age 55 years) and 500 HCPs (250 generalists, 150 specialists, 100 nurses/physician assistants). While 83% of patients reported pDPN symptoms and 77% reported it impacts daily activities, only 41% of those with painful symptoms were diagnosed with pDPN. In contrast, HCPs estimated that 41% of their nerve-damaged diabetes patients experienced pain, and 38% had daily activity limitations. Only 36% of HCPs had patients complete a DPN assessment questionnaire and 41% performed specific diagnostic tests on patients reporting symptoms. Patients and HCPs demonstrated clinical misperceptions: 92% of HCPs told patients that blood-sugar control would help manage pain, and 43% of patients were not sure if pDPN was reversible. Only 49% of patients with pDPN spoke about it regularly with their HCP. Among those who were reluctant to talk about pDPN, 38% worried the HCP would think they were not controlling their diabetes.

Conclusions: These data suggest a need to broaden pDPN educational initiatives and improve patient/HCP dialogue to encourage discussion of pDPN distinct from underlying diabetes.
INNOVATIVE CHRONIC PAIN EDUCATION THROUGH PROJECT ECHO

J. Boyle, USA

Background and aims: The Extension for Community Healthcare Outcomes Project (Project ECHO®) at the University of New Mexico developed a technology based program in 2009 to address and fill a gap in pain expertise through an educational, case-based learning opportunity for clinicians treating chronic pain in rural, under-served primary care practices.

Methods: By video or phone, clinicians connect to an interdisciplinary pain team at the academic health center for a weekly 2 hour Pain TeleECHO clinic. The Hub/Spoke design incorporates adult learning principles into formal didactics and demonstrations, and learning is multiplied during case presentations whether or not a participant presents a case. No cost continuing education credits are provided. Although a program of this nature is difficult to study, it has been examined to understand its impact on clinician knowledge, skills and practice, curricular quality, program growth and theoretical implications of the model.

Results: Increased self-efficacy, relevance to practice, and curricular quality are demonstrated. Program growth is significant. Adult learning theory, diffusion of innovation, social cognitive theory and others prove foundational to success. Replications of the ECHO Pain Program are underway across a variety of systems and organizations. Costs related to this program are considered and presented.

Conclusions: The ECHO Pain Program has become a successful, easily replicatable model for high quality inter-professional pain education. International expansion of this highly successful program has the potential to bring chronic pain expertise at low cost to many hundreds of patients in their own community through their primary or other local clinician.
POSTROKE PAIN, AGE, DEPRESSION AND ANXIETY

M. Zaletel, A. Praznikar, J. Pretnar Oblak, B. Zvan, Slovenia

Background and aims: Post-stroke pain (PSP) is a clinical syndrome characterized by sensory disturbances and neuropathic pain. Functional disturbances such as depression, anxiety and sleep disturbances may significantly have an influence on neuropathic pain expression. The contribution of age in PSP is not clear.

Methods: We randomly investigated 431 patients (mean age 71±4.4 years) with first-time stroke over a 2-year period. Patients were evaluated 6 months, 12 months and 24 months after stroke onset. Pain was evaluated using a visual analogue scale extending from zero mm (no pain) to 100 mm. Using the scale, zero was defined as no pain, 10 to 30 as mild pain, and 40 to 100 as moderate to severe pain. Depression was evaluated on a depression scale. Anxiety was assessed using Hamilton Anxiety Rating Scale (HAM-A). Logistic regression was used to analyse the relationships.

Results: 37 (8.5%) pts developed PSP. Factors significantly associated with an increased likelihood of having moderate to severe pain included younger age and higher scores on a depression and HAM-A scale (p < 0.01). Pain was reported as constantly present in 37% pts, and disturbed sleep in 67% pts. Sleep disturbances significantly related to PSP. Multivariate analysis showed that age is independent factor for PSP (p< 0.05).

Conclusions: We concluded that PSP was associated with younger age stroke patients. Depression as well as anxiety are important factors in developing of PSP.
MECHANISMS AND ASSESSMENT OF MIXED NEUROPATHIC PAIN?

R. Baron, Germany

Different pathophysiological mechanisms are thought to operate in chronic back pain. Nociceptive and neuropathic pain components can be distinguished. Neuropathic pain may be caused by lesions of nociceptive sprouts within the degenerated disc (local-neuropathic), mechanical compression of the nerve root (mechanical-neuropathic root pain) or by action of inflammatory mediators (inflammatory-neuropathic root pain) originating from the degenerative disc even without any mechanical compression. Since different pain-generating mechanisms possibly underlie chronic back pain the term mixed pain syndrome was established.

It is a diagnostic challenge to identify which components are prominent and to estimate the Impact of the different paintypes. This knowledge is essential for tailoring treatment to the individual patient. The Pain Detect Questionnaire is a reliable screening tool to detect the neuropathic pain component in patients with chronic back pain with a high sensitivity and specificity. In a cohort of 8000 patients with chronic back pain a prevalence of 37% of a predominant neuropathic component was found. Furthermore, an immense impact of existing neuropathic pain on the occurrence and severity of different co-morbid symptoms such as depression, panic/anxiety- and sleep disorders, functionality or even on pain intensity was demonstrated. Patients with a neuropathic pain component suffer more and more severe than those without, seriously affecting their quality of life. The data provide further evidence for the impact of neuropathic pain on health care source utilisation.

A sub-group analysis of Pain Detect symptom patterns in patients with painful radiculopathy revealed many similarities but also subtle differences in sensory phenotype types as compared with classical neuropathic pain states. These findings point to some unique pathophysiological mechanisms operating in radiculopathy.

References:


Complex regional pain syndrome (CRPS) is clinically characterized by pain, abnormal regulation of blood flow and sweating, edema, movement disorders, and trophic and bone changes. CRPS cannot be reduced to one system or to one mechanism only. In the past decades, there has been absolutely no doubt that complex regional pain syndromes have to be classified as neuropathic pain disorders. This situation changed when a proposal to redefine neuropathic pain states was recently published, which resulted in an exclusion of CRPS from neuropathic pain disorders.

Can we combine central nervous system changes with neuropathic mechanisms in the periphery and in particular with the inflammatory processes? How does the autoimmune hypothesis fit into this picture? Do different patient subgroups exist who are characterized by a predominant neuropathic component or by a predominant inflammatory component? Do we have to treat these subgroups differently? Can we identify these patient groups in clinical practice?

As long as we do not have a clearer pathophysiological picture of these patients and because of the obvious heterogeneity of signs, symptoms and mechanisms it would be wise to study CRPS patients separately from other classical neuropathic pain syndromes. Thus, the new redefinition is likely to be useful for clinical trials. It remains to be seen, however, whether this redefinition will be as useful for the clinician. It is very important to reinforce the authors’ statement that the "grading system is for communication among clinicians and researchers and not for medico-legal purposes."
STRATIFICATION OF NEUROPATHIC PAIN PATIENTS BASED ON SENSORY CHANGES

R. Baron, Germany

A new hypothetical concept was proposed in which pain is analyzed on the basis of underlying mechanisms rather than on the basis of the etiology. If a precise phenotypic characterization is combined with a selection of drugs acting at those particular mechanisms, it should ultimately be possible to design optimal treatments for the individual patient.

The question is whether an individual somatosensory phenotype really mirrors distinct pain mechanisms or is associated with genetic variability? For this purpose the technique of somatosensory pattern recognition was used in combination with genetic profiling. One polymorphism in the 5-HT2A receptor contributes significantly to the development of mechanical hyperalgesia. This finding indicates that genetic variants in the 5-HT2A receptors can facilitate the development of central sensitization in patients with neuropathic pain.

Sensory profiling can also unravel subgroups with altered endogeneous pain modulation and can help to predict treatment outcome of a drug that interferes with this mechanism. Physiologically pain is modulated by monaminergic descending pathways originating in the brainstem and projecting to the spinal nociceptive transmission centers. Drugs that interfere with serotonin and noradrenaline, i.e. antidepressants can activate inhibitory control and reduce pain. The descending modulation capacity is individually variable and can be assessed experimentally by measuring a reduction in pain perception with QST during simultaneous administration of a conditioning painful stimulus at a distant body site. In diabetic painful neuropathy individuals with a malfunctioning pain modulation benefit more from duloxetine treatment than patients with a normal modulation pattern.
PHARMACOLOGICAL ACTIVATION OF NTS2 RECEPTORS REDUCES BEHAVIORAL HYPERSENSITIVITY AFTER PERIPHERAL NERVE INJURY

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Introduction: Neuropathic pain is a severe clinical issue facing a major unmet medical need. Although opioid receptor agonists are the most widely used therapeutic agents for neuropathic pain, their analgesic effectiveness is controversial. Central administrations of NTS2 agonists have been shown to produce dose-dependent non-opioid antinociception in a variety of acute and persistent pain tests.

Objectives: We investigated whether acute injections of NTS2-selective agonists in rats were effective in reducing pain behaviors observed following chronic constriction injury (CCI) of the sciatic nerve.

Methods: Mechanical allodynia and incidental pain onset was measured at days 0, 3, 7, 14, 21 and 28 post-surgery.

Results: Injection of the selective and stable NTS2 agonist JMV431 reduced tactile allodynia, achieving 70% pain relief. Similar analgesia levels were observed after intrathecal injection of levocabastine and beta-lactotensin. Furthermore, JMV-431 and levocabastine both reversed CCI-induced ipsilateral paw weight bearing deficit, reaching up to 25-30% weight recovery. Both NTS2 analogs also significantly improved the time of ambulation spent on injured paw, producing 75 to 85% of functional rehabilitation. Comparatively, the reference marketed drug, amitriptyline, administered intraperitoneally provokes nearly 60% reversal of allodynia, 15% of weight recovery, and 80% of ipsilateral limb use. Both pregabalin and morphine significantly attenuated CCI-induced mechanical allodynia, inducing 20-30% inhibition, but were without significant effect on CCI-induced weight bearing deficit and spontaneous pain behaviors.

Conclusions: Altogether, these results suggest that central NTS2 activation is relevant for relieving neuropathic pain, either for treating mechanical hypersensitive states or spontaneous ongoing pain manifestations, without apparent adverse effects.
DEFINING AND ASCERTAINING A NEUROPATHIC PAIN PHENOTYPE FOR POPULATION-BASED GENETIC STUDIES

B.H. Smith, UK

Genetic research on neuropathic pain will shed light on its biological processes and facilitate new treatments. While animal and small human studies can identify candidate genes, larger human studies are required to assess their relevance and effect size. Furthermore, any candidates identified in potential GWAS studies will require further investigation in smaller, focused human or animal models. Relevant SNPs have been identified but few-none have been replicated in large human samples, partly because no common phenotype exists.

There is no “gold standard” for assessing neuropathic pain, for clinical or research purposes, though considerable consensus exists. Agreed phenotyping would allow future research to:

1. be consistent with other research
2. collaborate between institutions, potentially achieving large samples
3. undertake replication studies
4. contribute to meta-analyses

The ideal phenotype is both valid and feasible to apply in practice. Generally, feasibility sacrifices validity, and vice-versa, so the optimal compromise must be sought.

The main considerations for Validity are: Accuracy; Reproducibility; Precision. Those for Feasibility are: Simplicity and time required; Materials, equipment, and expertise required; Ethical to apply. A single phenotype cannot meet all requirements, so a mutually consistent graduated range is required for:

1. Brief study questionnaires (large/very large samples)
2. Detailed questionnaires (smaller, intensively phenotyped cohorts)
3. Brief clinical examination (large samples with clinical component)
4. Detailed clinical examination (smaller cohorts with clinical component)
5. Animal models

This presentation will consider the issues involved in phenotyping for the range of neuropathic pain studies, suggesting an approach towards achieving an agreed phenotype.
CORRELATION BETWEEN SENSORY SYMPTOMS AND ELECTROPHYSIOLOGICAL FINDINGS IN MERALGIA PARESTHETICA

I.S. Joo, M.H. Choi, Republic of Korea

Background and aims: Meralgia paresthetica (MP) is a compressive mononeuropathy of the lateral femoral cutaneous nerve (LFCN) presenting annoying neuropathic sensory symptoms on the anterolateral aspect of the thigh. Although the electrophysiological studies including nerve conduction study (NCS) seem to provide little additional information for the diagnosis of MP, the correlation between sensory symptoms and NCS findings has not been fully evaluated.

Methods: Sixty-five consecutive patients were collected. The diagnosis of MP was made on the basis of the presence of the characteristic symptoms and signs. General demographics, sensory symptoms and NCS findings were retrospectively analyzed. To compare between normal and abnormal NCS groups in terms of sensory symptoms, independent t-tests and chi-square test were performed.

Results: Mean age of the patients was 48.4±13.4 years with a slight male predominance (56.9%). Symptom duration was quiet variable and long (31.9±71.1 months). Sixty-two patients (95.4%) had unilateral symptom. The right thigh was more frequently involved in the left (56.5 % vs. 43.5%). The most common symptom was numbness (63.1%), and then paresthesia (41.5%) and pain (21.5%). Of fifty-five patients performing NCS, thirty-nine patients (70.9%) showed abnormal sensory NCS. Symptom duration, pattern and severity did not show any significant differences between normal and abnormal sensory NCS groups.

Conclusions: Sensory symptoms were not correlated with NCS findings, suggesting that NCS could not be a parameter to evaluate symptom pattern or severity, or to decide treatment response in MP.
EFFECTS OF PREGABALIN IN MIGRAINE: DATA FROM ANIMAL MODEL INDUCED BY NITROGLYCERIN

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Induction of c-Fos immunoreactive neurons in trigeminal nucleus caudalis (TNC) is regarded as a better maker of neuronal activation and central sensitization. The calcitonin gene-related peptide (CGRP) released by trigeminal nucleus caudalis could modulate second-order sensory neurons in TNC and thus evoke central sensitization, which is likely involved in pathophysiological mechanism in facial allodynia or cutaneous hyperalgesia occurred in migraine. Antiepileptic drugs are commonly used in migraine treatment and prevention. This study investigated whether pregabalin (PGB), an antiepileptic drug, could modulate the expression of c-Fos immunoreactivity in TNC and decrease the serum concentration of CGRP, and thus relieve cutaneous hyperalgesia symptoms in nitroglycerin (NTG) induced migraine rats. We found that the number of c-Fos immunoreactive neurons, the protein level of c-Fos in TNC and serum CGRP concentration in jugular vein serum increased significantly at 4h after injection of NTG. Meanwhile, NTG significantly reduced the mechanical nociceptive thresholds of migraine rats, and this effect developed within 30min, peaked at 60min, and persisted until 4h after injection of NTG. Interestingly, pretreating NTG-induced migraine rats with PGB marked alleviated cutaneous hyperalgesia, reduced c-Fos immunoreactive neurons and c-Fos expression in TNC as well as serum CGRP level in jugular vein serum in a dose-dependent. These results have suggested that PGB might be a promising candidate for the prophylaxis or treatment of migraine.
ANTINOCICEPTIVE EFFECTS OF SPINAL GLUTAMATE TRANSPORTER INHIBITORS AND MEMBRANE PERMEABLE METABOTROPIC GLUTAMATE ANTAGONISTS IN RATS WITH PERIPHERAL NERVE INJURY

K. Vincent, V. Cornea, T. Coderre, Canada

Introduction: Group I metabotropic glutamate receptors (mGluRs) are a class of excitatory G-protein coupled receptors present in the spinal cord dorsal horn (SCDH) where they have a well-established role in pain. In addition to their known location on the cytoplasmic membrane, our lab has found evidence of these receptors intracellularly on the nuclear membrane in the SCDH of rats with spared nerve injury (SNI), a model of neuropathic pain. As of yet, the functional role of these receptors in the spinal cord is unknown.

Objectives: To determine the effect of selective neuronal GT inhibitors, as well as cell permeable vs cell impermeable group I mGluR antagonists, on nociception induced by mGluR agonists in rats with spared nerve injury of the sciatic nerve.

Methods: Nociception induced by intrathecal (i.t.) injection of monosodium glutamate in rats 7 days post SNI/sham surgery was examined. Nociceptive behavioural responses were measured as time spent licking the affected area during the post-injection observation phase. Effects of i.t. pretreatment with vehicle, selective EAAC1 inhibitor (L-βthreо-benzyl-aspartate), permeable mGluR antagonists (CPCCOEt and fenobam), and impermeable mGluR antagonist (LY395053) were measured.

Results: Pretreatment with neuronal GT inhibitors and cell permeable group I mGluR antagonists, but not cell non-permeable mGluR antagonist, attenuates glutamate-induced licking behaviours in SNI rats.

Conclusions: Blocking glutamate transport into neurons using EAAC1 inhibitors as well as blocking intracellular mGluR activation using cell permeable mGluR antagonists attenuates glutamate-induced pain behaviours in SNI rats, providing preliminary empirical support for the role of SCDH nuclear mGluRs in neuropathic pain.
PROSPECTIVE, RANDOMIZED, EFFICACY OF CORTICOSTEROIDS INFILTRATIONS VERSUS CONTROL ARM IN 201 PATIENTS WITH PUDENDAL NEURALGIA BY ENTRAPMENT

J.-J. Labat, T. Riant, A. Lassaux, B. Rioult, M. Khalfallah, B. Rabischong, R. Robert, France

**Background and aims:** Compare the evolution of the pain of patients with pudendal neuralgia for more than 6 months, 3 months after injection of local anesthetic alone (control arm A) or with anesthetic and corticosteroids (group B) or with an anesthetic corticosteroids and a large volume of saline (group C). Pudendal neuralgia by entrapment were defined by four clinical criteria (Nantes criteria: 1) Pain in the anatomical territory of the pudendal nerve. 2) Worsened by sitting. 3) The patient is not woken at night by the pain. 4) No objective sensory loss on clinical examination).

**Methods:** Multicenter study, randomized control arm, double-blind for the patient and physician controlled evaluator. Injection performed under CT scan systematically at the sacrospinous ligament and the Alcock's canal, according to randomization into 3 equal groups (A, B or C). Pain averaged over a maximum period of 15 days should be higher at baseline to 40/100. Primary endpoint: success when 3month, gain of more than 30 points out of 100, comparison of the results in the groups with and without corticosteroids.

**Results:** There is no significant difference between the groups with or without corticosteroids at 1, 2 or 3 months. For all patients at 3 months, only 13% of 201 patients improved by more than 30% with no difference between groups. 82% of patients had a positive anesthetic block.

**Conclusions.** Corticosteroids do not provide therapeutic gain in pudendal nerve entrapment. The benchmark treatment is decompression surgery, nevertheless obtaining a positive anesthetic block remains essential for this indication.
EFFECT OF TAPENTADOL ON LOCUS COERULEUS NEURONS IN THE STREPTOZOTOCIN MODEL OF POLYNEUROPATHIC PAIN: AN ELECTROPHYSIOLOGICAL STUDY IN ANESTHETIZED RATS

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Background and aims: Tapentadol is an analgesic that combines mu-opioid receptor (MOR) agonism and noradrenaline reuptake inhibition. Previous data in healthy rats showed that tapentadol inhibited the neuronal activity of locus coeruleus (LC), a nucleus regulated by both noradrenergic and opioid systems, critical in pain modulation. This inhibitory effect was due to the activation of alpha2-adrenoceptors and MOR. Therefore, our aim was to investigate the effect of tapentadol on LC activity in diabetic polyneuropathic pain.

Methods: Single-unit extracellular recordings of LC neurons were performed 4 weeks after the induction of diabetes (streptozotocin). Tapentadol dose-effect curves were performed without pre-treatment or after RX821002 or naloxone (alpha2-adrenoceptors and MOR antagonists, respectively) administration.

Results: In diabetic polyneuropathic rats, the spontaneous activity of LC neurons was decreased (0.9±0.1 vs 1.5±0.1 Hz) and tapentadol dose-response curve shifted to the right compared to naive (ED50=1.8±0.3 vs 0.8±0.1 mg/kg). RX821002 pre-treatment increased the spontaneous activity (1.6±0.3 vs 0.9±0.1 Hz) and shifted to the right the tapentadol curve (ED50=2.9±0.3 vs 1.8±0.3 mg/kg) while naloxone did not modify them (0.8±0.2 Hz and ED50=1.0±0.3 mg/kg).

Conclusions: Tapentadol inhibitory effect was decreased on LC neurons in diabetic polyneuropathic pain. Although the relation between the effects of analgesics on LC neuronal activity and in vivo analgesia is complex and remains to be determined, the observation that this effect had a predominant noradrenergic mediation might indicate an advantage of tapentadol treatment in diabetic pain with mild opioidergic side-effects.

INFLUENCE OF STIMULATION TIME ON THE ATTENUATING EFFECTS OF SUBCUTANEOUS ELECTRICAL STIMULATION IN A RODENT MODEL OF NEUROPATHIC PAIN

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Background and aims: Our lab has established a rodent model of subcutaneous electrical stimulation (SQS). We used this model to assess the influence of varying stimulation times on effectiveness outcomes. We hypothesized that longer stimulation duration would produce more robust antihyperalgesia.

Methods: Rats were implanted with a subcutaneous lead and received a spared nerve injury (SNI). Rats were tested for signs of pain behaviors and received stimulation for 5 consecutive days. Stimulation was given for either a period of 30, 60 or 120 minutes. Rats were classified as responders if their withdrawal thresholds came back to 50% of their baseline withdrawal threshold after stimulation. A carry-over effect was defined as a significant reduction in mechanical hypersensitivity persisting after stimulation is turned OFF.

Results: On day 1, all 3 stimulation times had a non-significant effect on mechanical hypersensitivity and the number of responders was only 2-3 rats out of n=8. Similar results were obtained on day 3. On day 5, 30 and 60 minutes of stimulation produced a carry-over effect (3 and 24 hours respectively) while 120 minutes of stimulation did not produce a carry-over effect. All three stimulation lengths produced similar levels of inhibition of hypersensitivity and number of responders while stimulation was ON.

Conclusions: These results suggest that SQS in this rodent model requires several days of stimulation to reach a peak effect. Additionally, at this intensity and frequency, 60 minutes of stimulation per day might be an optimal length of stimulation to obtain a longer carry-over effect.
Objective: To study the correlation between radicular/low back pain and herniation type in lumbar disc hernia.

Method: One hundred and fifty consecutive candidates for lumbar microdiscectomy were examined. The initial assessments, including location and duration of pain, neurological examination and straight-leg-raising (SLR) tests were performed by an independent observer who was unaware of final diagnosis. Intraoperatively, all patients were assessed by a single neurosurgeon for the presence of disc protrusion or extrusion.

Results: Patients with radicular pain alone and those who experienced a resolution of low back pain followed by increased severity of radicular pain were 6.5 (p< 0.002) and 10.2 (p< 0.000) times more likely to have an extruded disc respectively. The mean preoperative duration among the group of patients with extruded disc (11 weeks) was significantly shorter than protruded ones (18.6 weeks) (p< 0.005). Among all subjects, 103 patients showed neurological abnormalities. There was no association between presence of neurological deficits and the type of herniation (p>0.005). The positive crossed SLR test correlated significantly with the type of herniation (Relative Risk=2.56 p< 0.000 Chi2=27.4).

Conclusion: In lumbar disc disease, there were three groups of patients with a) radicular pain alone, b) those who experienced increase severity of radicular pain followed by resolution of back pain and c) patients with positive crossed SLR test who had a high probability of harboring an extruded disc. There was no significant association found between neurological abnormalities and the type of herniation.
ALTERATIONS IN THE MESOLIMBIC DOPAMINE SYSTEM IN A CHRONIC PAIN STATE

A. Taylor, C. Evans, C. Cahill, USA

Introduction: Opioids are among the most potent analgesics available for acute pain, but less effective for neuropathic pain. In addition to their analgesic properties, opioids possess rewarding properties that contribute to analgesia. Alterations in the reward system in chronic pain are a logical hypothesis for the sub-optimal analgesic effects in treating neuropathic pain. How chronic pain modifies opioid reward and analgesia remain poorly explored.

Objectives: We examine how the reinforcing properties of opioids change in chronic pain and the effect these changes have on the analgesic efficacy of these drugs.

Methods: We use an animal model of chronic pain whereby the left sciatic nerve was loosely constricted with a polyethylene cuff, a chronic constriction injury (CCI). The reinforcing properties of opioids were tested using the conditioned place preference test (CPP).

Results: CCI led to significant microglial activation in the ventral tegmental area (VTA). Microglial activation was correlated with significant increase in expression of BDNF, and blocking microglial activation reversed BDNF levels to normal levels. CCI also led to significant dysregulation of chloride homeostasis in GABAergic interneurons of the VTA, an effect that could be reversed by a TrkB antagonist. Under basal conditions, morphine CPP was similar in sham and neuropathic animals. However, concomitant treatment with a dopamine antagonist blocked morphine CPP in neuropathic, but not sham animals.

Conclusions: These results point to a dysregulation in reward systems of the chronic pain brain, and show an altered motivation for morphine. These results implicate microglial activation in mediating some of these changes.
NEW INSIGHTS IN ROLES OF DESCENDING INHIBITION IN EFFECTS OF SPINAL CORD STIMULATION ON NEUROPATHIC PAIN: INVOLVEMENT OF THE ROSTROVENTROMEDIAL MEDULLA AND LOCUS COERULEUS

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Introduction: During the last decades research on the mode of action of spinal cord stimulation (SCS) has mainly focused on segmental spinal mechanisms activated antidromically by SCS applied to the dorsal columns. Lately, however, studies of supraspinal circuitries activated by SCS have progressed considerably.

Methods: Using animal models of neuropathic pain (rats) the effects of SCS on manifestations of neuropathy, mostly hypersensitivity to tactile stimuli, have been examined. Different brain stem areas have been explored by microelectrode recordings as well as by modifying the cellular activity by administration of different drugs to the intrathecal spinal space or into the brain stem via indwelling cannulas. These methods have been applied during SCS in both SCS responding and non-responding animals.

Results: The studies indicate that there is participation in the SCS effect of both the rostroventromedial medulla (RVM), via descending serotonergic axons to the spinal cord, and the locus coeruleus (LC) area. These brain stem regions display different local activation patterns during SCS, and the analyses further demonstrate a complex participation of both spinal and brainstem circuitries in the effects of SCS. The prominent activation of the LC by SCS does not appear, contrary our expectations, directly associated with a descending medullo-spinal noradrenergic inhibitory control.

Conclusions: SCS activates both segmental and suprasegmental mechanisms. The activated circuitries in the brain stem presumably interact with segmental spinal interneurons exerting inhibitory effects on hypersensitive second-order neurons and primary afferents in the dorsal horns.
SORCS2 IN GLIAL SATELLITE CELLS - INVOLVEMENT IN NEUROPATHIC PAIN?

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CNS glial cells (astrocytes and microglia) are crucially involved in the initiation and maintenance of chronic pain. Much less is known about glial cells in peripheral sensory ganglia, however it is increasingly clear that Satellite Glial Cells (SGCs) are activated in response to peripheral nerve injury and play an important role in chronic pain mechanisms: SGCs show upregulation of GFAP and a dramatic increase in gap junctions between SGCs in newly formed processes. This increased coupling of SGCs is observed in several pain models, and blocking the gap junctions decrease spontaneous neuronal electrical activity and hyperexcitability. Further, gap junction blockers relieve pain symptoms in animal pain models without affecting control animals. The mechanisms by which nerve injury induce these changes remains speculative, however the involvement of NGF and its two receptors, TrkA and p75NTR, has been proposed. These receptors are both expressed in SGC (as well as in subpopulations of sensory neurons) and might be involved in the outgrowth of SGC processes and SGC-neuron communication following injury. We have previously demonstrated the involvement of the receptor sortilin in NGF signaling in sensory neurons by regulating Trk trafficking. Unpublished data show that the sortilin-related receptor SorCS2 also modulates neutrophin signaling. Interestingly, in the sensory ganglia SorCS2 is exclusively expressed in SGC, and SorCS2-/- mice display altered pain phenotype following sciatic injury. This project investigates the function of SorCS2 in SGC, and specifically if SorCS2 may be involved in SGC neurotrophin signaling and pain development following nerve injury.
SORTILIN IN NEUROPATHIC PAIN

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The molecular mechanisms underlying neuropathic pain are incompletely understood, but recent data suggest that down-regulation of the chloride extruding co-transporter KCC2 in spinal cord sensory neurons is critical: Following peripheral nerve injury, activated microglia in the spinal cord release BDNF, which stimulates neuronal TrkB receptors and ultimately results in the reduction of KCC2 levels. Consequently, neuronal intracellular chloride ion concentration increases, impairing GABA_\alpha-receptor mediated inhibition. We have previously described how the receptor sortilin modulates neurotrophin signaling by facilitating anterograde transport of Trk receptors. The purpose of this study is to explore the involvement of sortilin in neuropathic pain. Wild-type (wt) and sortilin knockout (Sort1\textsuperscript{-/-}) mice were subjected to the Spared Nerve Injury (SNI) model of peripheral nerve injury and mechanical allodynia measured by von Frey test. As previously described by several groups, wt mice developed significant mechanical allodynia following SNI. Interestingly however, mice lacking sortilin were fully protected from development of allodynia and did not display KCC2 down-regulation following injury. In addition, a single intrathecal injection of antibodies against sortilin could delay or rescue mechanical allodynia in wt SNI mice for 2-3 days. Finally, sortilin deficient mice were unresponsive to intrathecal injection of BDNF, in contrast to wt mice, which developed transient mechanical allodynia. We hypothesize that sortilin is involved in neuropathic pain development by regulating TrkB signaling.
POSSIBLE ROLE OF GLIAL CELLS AND BDNF IN SPINAL CORD AFTER CHRONIC CONSTICTIN INJURY AND NEURAL MOBILIZATION TECHNIQUE

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Aim of Investigation: The neural mobilization (NM) is a technique used to control the pain induced by injury which reflect on the peripheral nervous system. This technique it is able to restore the mobility and the elasticity of the peripheral nervous system. The present study examined the effects of the NM in response to the pain induced by the chronic constriction injury (CCI) and the participation of the glial cells and brain-derived neurotrophic factor (BDNF).

Methods: We used male Wistar rats, submitted to the CCI of the sciatic nerve, 14 days after injury we started sessions the NM, every other day, with a total of 10 sessions. Sham animals were submitted by the same procedures, but left unaffected the sciatic nerve and served as a control. Before and after each mobilization session, the animals were submitted to behavioral tests for evaluate the nociceptive threshold.

Results: Our behavioral tests showed a decrease of pain related behavior in the group treated with NM when compared to the injured, non-NM treated, animals. Our immunoblotting data demonstrated that after the CCI there was an increase of BDNF (148%), OX-42 (80%) and GFAP (140%) in spinal cord when compared to the control group. After NM treatment there was a decrease of the BDNF (56%), OX-42 (92%) and GFAP (77%) when compared to the increase after CCI.

Conclusions: We suggest that neural mobilization is efficient in improve behavioral response and suggest the involvement of glial cells and BDNF in such on effect.
INTRATHECAL DELIVERY OF AAV SEROTYPE 9-MEDIATED SHRNA AGAINST TRPV1 ATTENUATES THERMAL ALLODYNA IN A MOUSE MODEL OF PERIPHERAL NERVE INJURY

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Background and aims: Gene therapy for neuropathic pain requires efficient gene delivery to both central and peripheral nervous systems. Previously we have shown intrathecal injection of an adeno-associated virus serotype 9 (AAV9) vector expressing short-hairpin RNA (shRNA) is able to suppress target molecule expression in dorsal root ganglia (DRG) and spinal cord. An AAV9 vector encoding shRNA against vanilloid receptor 1 (TRPV1) was developed and administered intrathecally to a mouse model of neuropathic pain to evaluate therapeutic potential of this approach.

Methods: Spared nerve injury (SNI) was used to model neuropathic pain. AAV9 vectors targeting TRPV1 (AAV9-shTRPV1), superoxide dismutase 1 (AAV9-shSOD1), or PBS were injected intrathecally to mice 3 weeks after SNI. Behavioral analysis including mechanical, acetone test, and two thermal hot plate temperature tests (50°C and 55°C) were investigated chronologically in order to confirm the putative analgesic effect of the viral vector.

Results: Quantitative RT-PCR and western blotting showed significant suppression of TRPV1 mRNA and protein in the DRG and spinal cord of AAV9-shTRPV1 treated group. Treatment produced no statistically significant difference between treatment groups for paw withdrawal thresholds in response to mechanical, acetone, and 55°C thermal stimuli. However, latency to withdrawal in the 50°C thermal hot plate test was significantly increased in the AAV9-shTRPV1 treated group as compared to the two other treatment groups.

Conclusion: Our study provides important evidence for the contribution of TRPV1 to thermal hypersensitivity in neuropathic pain. Our data also establishes a potential therapeutic role for intrathecal AAV9-mediated gene delivery for nervous system treatment.
Predictors of Placebo Response in Clinical Trials of Pregabalin in Diabetic Peripheral Neuropathy and Postherpetic Neuralgia

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Background and aims: A number of recent clinical trials in neuropathic pain have failed to demonstrate a significant treatment effect versus placebo, despite previous positive results. Many of these trials had high placebo response rates; identifying the associated factors could help design trials with lower placebo responses to improve sensitivity and accuracy. This analysis investigated placebo response and its predictors in pregabalin trials in patients with diabetic peripheral neuropathy (DPN) and postherpetic neuralgia (PHN).

Methods: Data were pooled from 16 randomized, placebo-controlled, double-blind trials of pregabalin: 9 in DPN, 5 in PHN, and 2 in both DPN/PHN. High-placebo-response (>2-point mean reduction in pain score at endpoint with placebo) and low-placebo-response trials were compared with respect to patient and study characteristics. Univariate analysis was performed to identify predictors of change in pain score.

Results: This analysis included 4513 patients (2999 pregabalin, 1514 placebo). Three studies were designated high-placebo-response. All were in DPN and conducted post-approval of pregabalin. Univariate analysis of placebo treated patients across all 16 trials indicated that lower age, shorter duration of PHN, higher baseline pain score, longer study duration, higher site recruitment, lower treatment:placebo ratio and post-approval studies were all significantly associated with a higher placebo response. In all studies there was a trend towards an increased placebo response over time with no corresponding change in pregabalin response.

Conclusions: A greater understanding of factors contributing to a higher placebo response, such as those identified here, could help improve the sensitivity and accuracy of clinical trials in neuropathic pain.
LUMBAR STENOSIS OUTCOMES RESEARCH (LUSTOR II): OPIANA IR VERSUS PLACEBO AND ACTIVE PLACEBO FOR THE TREATMENT OF WALKING IMPAIRMENT IN LUMBAR SPINAL STENOSIS

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Background and aims: To determine the efficacy of oxymorphone hydrochloride (Opana) and propoxyphene/acetaminophen (active placebo) in prolonging the time to onset of pain and reducing the severity of pain associated with walking in patients with neurogenic claudication (NC).

Methods: This was a randomized, double-blind, placebo-controlled, cross-over study comparing the treatment effects of Opana, placebo and active placebo in subjects with NC due to lumbar spinal stenosis. The primary endpoint was time to first symptoms of moderate intensity (numeric rating scale (NRS) ≥ 4/10) during treadmill ambulation. Secondary outcome measures included area under the curve, final pain intensity with walking, walking tolerance, and time to return to baseline pain level after ambulation.

Results: The distribution of the primary endpoint, time to first symptoms of moderate intensity was not significantly different between Opana IR and active placebo for the 21 subjects enrolled.

There were no significant differences between Opana IR, and active placebo for NRS at rest (1.95 vs. 1.81 p=0.73), final NRS pain (6.20 vs. 6.22, p=0.95), distance walked (256.56 meters vs. 256.72 meters, p=0.99), recovery time (1.56 minutes vs. 1.67 minutes, p=0.74), or area under the curve (76.71 vs. 78.99, p=0.63).

Study was terminated early due to removal of active placebo from the U.S. market.

Conclusions: The primary and secondary measures efficacy measures did in not differ when subjects received Opana or active placebo. Opana was found to be safe and well-tolerated. Treadmill testing is shown to be a feasible, well tolerated, and safe method for testing oral opioid analgesics.
PREVALENCE OF NEUROPATHIC PAIN IN GENERAL POPULATION AT PARAKOU, IN THE NORTH OF BENIN

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Introduction: The frequency of neuropathic pain in general population is not well known in Africa.

Objective: We aimed to assess the prevalence of neuropathic pain and its associated factors in general population in Benin.

Methods: It was a cross-sectional study carried out from the 1st April to 31 May 2012 and included 2314 people selected by multistage sample (cluster sampling) in door-to-door survey. The diagnosis of neuropathic pain was based on DN4 criteria. The questionnaire was translated and back translated by the neurologists in local language with a good accuracy. Multivariate analysis was performed to determine the associated factors.

Results: The male represented 49.7%. The mean age was 32.3+/-13.1 years. The frequency of chronic pain was 31.9% The overall prevalence of neuropathic pain was 6.3% (CI95%: 5.0-7.9).

The associated factors were:

- Age (>50/<50 years): OR:2.2 (CI95%:1.2-3.8)
- Matrimonial status (widowed/married): OR:3.1 (CI95%:1.6-635)
- Body mass index (obese/normal): OR:2.8 (CI95%:1.5-5.1)
- Diabetes (Yes/no): OR: 36.1 (CI95%: 12.7-103.0)
- History of zoster (yes/no): OR: 13.6 (CI95%: 1.5-126.7)
- History of any surgery (yes/no): OR: 2.2 (CI95%:1.2-4.0)
- Brain Trauma injury (yes/no): OR: 6.0 (CI95%: 2.8-13.1)

Conclusions: Those results suggested the high prevalence of neuropathic pain at Parakou in the North Benin
AUDIT TO EVALUATE THE QUALITY OF POSTOPERATIVE PAIN RELIEF AND INCIDENCE OF CHRONIC POST-TORACOTOMY PAIN (CPTP)

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Introduction: Thoracotomy is among the surgical procedures that have the greatest incidence of persistent pain termed Chronic Post-Thoracotomy Pain (CPTP). The incidence of CPTP is approximately between 30-60%. The pain is neuropathic in 35-80% cases and causes significant long-term morbidity.

Objective: The aim of the audit was to evaluate the quality of postoperative pain relief during the first three days after surgery and to determine the incidence of persistent pain at six months after surgery.

Methods: We evaluated adult patients who underwent open thoracotomy at Glenfield Hospital, Leicester over a two-year period (May 2010 to April 2012) as part of a joint departmental (Pain Medicine and Thoracic Surgery) audit. A research nurse and two advanced pain trainees performed the telephone review. After obtaining verbal consent, the patients were asked to complete a questionnaire with 16 questions.

Results: This is an ongoing audit. A total of 504 adult patients underwent open thoracotomy over the two-year period. There were 364 survivors who were contacted over phone. Preliminary analysis was performed in 293 patients. The overall incidence of chronic pain at six months after surgery was 57% (36% mild, 15% moderate, 6% severe). 38% of patients with persistent pain had multiple episodes of severe pain during the first three days after surgery. Quality of life was impaired in 34% of patients with CPTP. There was a decrease in chronic pain over time in 75% of patients.

Conclusion: Our audit confirms that CPTP is a common problem that can significantly impair quality of life.
CSF2RB, THE BETA RECEPTOR OF GM-CSF, IL3 AND IL5, IS EXPRESSED BY SPECIALIZED SPINAL GLIA CELLS AND CONTROLS NEUROPATHIC PAIN LEVELS IN MICE

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Background and aims: We reported that PAIN1, a locus on mouse chromosome-15, controls autotomy, a neuropathic pain (NP)-related behavior produced by hindpaw denervation. Some evidence implicated Cacng2 as the autotomy gene in PAIN1. But comparing gene expression in spinal cords of high-autotomy A/J to low-autotomy C57BL6/J mice identified Csf2rb in PAIN1 as the most robustly up-regulated gene post-denervation. Here we validate Csf2rb as another NP gene in PAIN1, and identify cells expressing it.

Methods: A/J and C57BL6/J mice were perfused 14-days post-sciatic/saphenous neurectomy or sham operation. L3-L5 spinal cord segments were removed, cryo-sectioned and immuno-labeled with CSF2RB and Vimentin (reactive-glia marker). RNA was extracted, reverse-transcribed and underwent qPCR to quantify Csf2rb transcript abundance.

Results: Csf2rb mRNA levels were up-regulated in autotomizing A/J mice compared to non-autotomizing or sham A/J mice, and denervated C57BL6/J mice [2.47±0.33sem vs. 1.20±0.09(p< 0.002), 1.07±0.06(p< 0.008), 1.19±0.05(p< 0.004)]. CSF2RB immunoreactivity, co-localizing with Vimentin, was found in radial glia surrounding the central canal (CC), sending mid-sagittal processes to white matter, more in hindpaw-denervated autotomizing A/J than C57BL6/J mice [30.23±1.51 vs. 18.13±1.43/50µm section (p=0.04)], and in glia in dorsal columns sending processes to the pia and the dorsal horn.

Conclusions: Csf2rb mRNA up-regulation in the spinal cord by autotomy suggests that it is an additional candidate NP gene in PAIN1. Future research should elucidate how peripheral injury leads to spinal release of GM-CSF, IL3 and/or IL5, and how binding of these cytokines to CSF2RB receptors on glia cells around the CC and in dorsal columns produces NP.
ANALGESIC EFFICACY OF SMALL MOLECULE ANGIOTENSIN TYPE 2 RECEPTOR ANTAGONISTS IN A RAT MODEL OF ANTIRETROVIRAL DRUG INDUCED NEUROPATHIC PAIN

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Introduction: Small molecule angiotensin type 2 receptor (AT₂R) antagonists with >1000-fold selectivity over the angiotensin type 1 receptor, evoke dose-dependent relief of mechanical allodynia in several rodent neuropathic pain models¹.

Objectives: To investigate the efficacy of two selective AT₂R antagonists, PD123,319 and EMA300 (also known as PD-121,981), in a rat model of antiretroviral drug induced neuropathic pain (ATN).

Methods: Rats received single intraperitoneal (i.p.) bolus doses of zalcitabine at 50mg/kg three times per week for three weeks². Rats with fully developed hindpaw hypersensitivity received single i.p. bolus doses of PD123,319 (0.3-10 mg/kg) or vehicle. Anti-allodynia was assessed using von Frey filaments by a 'blinded' tester. The ~ED₅₀ was estimated using nonlinear regression. Other rats received i.p. bolus doses of EMA300 (1, 10 or 30 mg/kg), gabapentin (30 mg/kg) or vehicle twice daily for three days. Relief of hindpaw hypersensitivity was assessed using an electronic “von Frey” device at 45 min post-dosing in a 'blinded' manner.

Results: The mean ED₅₀ for PD123,319 was 3.2 (95% CI: 1.4 to 7.0) mg/kg. EMA300 at 30 mg/kg attenuated mechanical hypersensitivity on days 2 and 3 c.f. vehicle. The effect of EMA300 at 30mg/kg did not differ significantly from that of gabapentin at 30 mg/kg.

Conclusion: Small molecule AT₂R antagonists were efficacious in a rat model of ATN.


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KNOCK OUT OF THE CANNABINOID 1 RECEPTOR PROMOTES RECOVERY FROM MECHANICAL BUT NOT FROM COLD ALLODYnia FOLLOWING SURAL SPARED NERVE INJURY IN MICE

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Background and aims: Cannabinoid 1 receptor knock mice generated by Zimmer et al. 1999 are hypoalgesic in the hotplate assay and formalin test. We hypothesized that the hypoalgesic phenotype extends to cold and mechanical stimuli. Mechanical thresholds and responses to acetone were measured in cannabinoid 1 receptor (CB1) wild type (WT), heterozygous (HTZ) and knock-out mice (KO) before and after sural spared nerve injury (Sural-SNI).

Methods: Baseline mechanical thresholds in male CB1 WT, HTZ and KO mice were determined at approximately 4 months of age by stimulating the sural area on the plantar surface of both paws. Responses to acetone were quantified by measuring the time the paws were held in the air in the 30 seconds following acetone application. For the Sural-SNI model, the common peroneal and tibial branches of the sciatic nerve were ligated and severed, leaving the sural branch intact. Behavioral responses were assessed for 28 days following the injury.

Results: Baseline mechanical thresholds did not differ in the CB1 WT, HTZ and KO mice; however, post-Sural-SNI WT mice maintained a 50% reduction in mechanical threshold from 14 to 28 days, while KO and HTZ mice recovered to a 25% reduction in mechanical threshold relative to baseline. Both the baseline and post-Sural-SNI acetone responses were higher in the CB1 KO mice relative to the WT and HTZ animals.

Conclusions: Genetic deletion of the CB1 receptor results in hyperalgesia to cold stimuli, while it promotes recovery from peripheral nerve injury-induced mechanical allodynia.
INTRODUCTION OF A SPECIFIC AND SENSITIVE SIGN TO EVALUATE NERVE ROOT INVOLVEMENT IN PATIENTS WITH LOW BACK PAIN

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Background and aims: Almost 80% of the people suffer from low back pain (LBP) at least once in their lives. By means of clinical evaluation, clinicians consider the likelihood of the cause of the LBP. Differentiating between radicular versus non radicular LBP is a challenge since it affects plan for further evaluations like MRI and referral for surgery. We inferred from our clinical experience that many patients with radicular LBP have a trigger point on the upper outer quadrant of their gluteal area. We coined it Gluteal sign. The aim of this study was to evaluate the sensitivity and specificity of Gluteal sign to detect nerve root involvement amongst patients with LBP.

Methods: Two hundred forty one patients with LBP were evaluated by history, physical examination and MRI. Based on findings in history, physical examination and MRI (Gold standard) patients were categorized into two groups; with and without radiculopathy. The existence of Gluteal sign was evaluated by trained examiners in all patients at first stage of the physical examination while the examiner was blind to patient's history.

Results: The specificity of the sign was 97.2% and the sensitivity was 74.8%. The area under the ROC curve (AUC) was 0.860 (0.811-0.909). Positive and negative predictive values were 97% and 75.1% respectively.

Conclusions: The Gluteal sign is a highly specific and sensitive sign to pick up patients with nerve root involvement amongst patients with LBP.
A CONTROLLED TRIAL OF INTERMITTENT LUMBAR TRACTION AND EXERCISES FOR CHRONIC LOW BACK ACHE WITH RADIATING PAIN

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Introduction: We examined the effectiveness of Intermittent Lumbar Traction (ILT), a program of stretching exercises and combination of both for chronic low back ache patients.

Methods: 108 subjects with chronic low back ache with radiating pain in either/both legs (onset of pain = 4.1±1.2 years) were randomly selected to receive daily treatment (5 days/week) for 4 weeks. They were divided into 3 groups, group 1 (n=36) was treated with ILT, group 2 (n=36) with stretching exercise program and group 3 (n=36) was combination of both. Appropriate statistical analysis was done.

Results: After four weeks of planned treatment group 1 (56%) and group 3 (72%) showed significant improvement in low back ache and radiating pains in either/both legs of the subjects, while in group 2 (33%) there was not much significant results as after discontinuing the exercise program the radiating pain again started. The 95% confidence intervals for group differences excluded a major clinical benefit of ILT for most outcomes. By contrast, patients in group 3 had significant improvement in self-rated pain scores, reduction in frequency of pain and greater levels of activity as compared with patients in group 1 and 2.

Conclusion: Results strongly suggests that often complete protocol i.e. Intermittent Lumbar Traction in combination with stretching exercises is not given to the patients so the rehabilitation time and the frequency of recurrence is more prevalent. When ILT is given in combination with stretching exercise it reduces neuropathic pains more effectively then given alone.
EMERGENCY DEPARTMENT MANAGEMENT OF ACUTE NERVE INJURY PAIN: A LITERATURE REVIEW.

G. Watkins, Australia

Background and aims: Pain is a common presenting complaint in Emergency Departments, and about one fifth of these patients have neuropathic pain. This includes patients with disc related sciatic pain and traumatic nerve injury. Animal experiments have shown anticonvulsants (pregabalin and gabapentin) and antidepressants (venlafaxine and duloxetine) to be effective in reducing pain following peripheral nerve injury. The aim of this review was to look for evidence regarding the use of these agents in the emergency management of acute nerve injury pain.

Method: A literature review was conducted using Embase and PubMed with the keywords ‘peripheral nerve injury’, ‘neuropathic pain’ ‘antidepressant’ ‘anticonvulsant’ and ‘emergency ward’. 529 articles were assessed. The level of evidence provided by each article was evaluated.

Results: No randomized controlled trials (RCTs) regarding emergency department management of acute nerve injury pain were found. There was clinical evidence to support the use of gabapentin and pregabalin in chronic nerve injury pain. One study showed lower pain levels in patients treated with Venlafaxine who had both chronic pain and depression.

Conclusions: There are drugs on the market that experimental and clinical evidence suggests are likely to be effective for acute nerve injury pain, but they are not either not licenced for this indication or not available on the Prescription Benefit Scheme for first line therapy in Australia. There is an urgent need to conduct trials of these drugs for acute nerve injury pain in the Emergency Department setting.
SENSORY MODULATION DISORDER AND QUALITY OF LIFE IN CRPS

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Introduction: Central sensitization is a primordial mechanism in the development of Complex Regional Pain Syndrome (CRPS). Sensory Modulation Disorder (SMD) is a diagnostic referring to individuals who demonstrate exaggerated or inappropriate responses to non-harmful sensory input. Individuals with SMD are characterized by an inability to normally grade the degree, intensity and nature of their responses to sensory input.

Objectives: To characterize the sensory modulation pattern of people who suffer from CRPS and to investigate the correlation between the sensory modulation pattern and quality of life in CRPS.

Methods: Thirty CRPS adults (20 men, 10 women; 31.1 ± 12.36 years old; Range 19-61) filled in The Sensory Responsiveness Questionnaire (SRQ) and the Health-related quality of life SF-36 questionnaire.

Results: Among the CRPS patients 53% (n=16) were diagnosed as suffering from SMD. Exploring the type of SMD revealed that within the CRPS group 46% (N=14) showed the Over-Responsivity type (OR). Significant correlations were found between the SRQ profile and quality of life (SF-36) sub-scores (General health r=.46; p=0.01). Further, when testing these correlations within the OR sub-group correlations were enhanced (Physical role r=.65; p=0.01, General health r=.54; p=0.04, Physical function r=.58; p=0.03).

Conclusions: The high incidence of SMD-OR in CRPS patients may point to a pre-morbid or acquired central hyper sensitivity that affects modulation of sensory input across different modalities and not only touch and pain. The enhanced diminution of Health related QOL score in these patients, as compared to CRPS-non-SMD, may suggest variance in QOL SMD dependent in CRPS.
PKA-RIIβ EXPRESSION AND ACTIVITY DEFINES SENSORY NEURONS RESPONSIVE TO SENSITIZING INFLAMMATORY MEDIATORS

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Background and aims: Nociceptive neurons become sensitized by various inflammatory mediators including agonists of stimulatory G protein-coupled receptors resulting in increased cAMP levels. The effects of cAMP on nociception are partially mediated by protein kinase A (PKA), which represents a family of tetrameric kinases composed of catalytic (Cα, Cβ, Cγ, PRKX) and regulatory (RIα, RIβ, RIIα, RIIβ) subunits.

Methods: We analyzed the expression pattern and activation of PKA in over one million rat dorsal root ganglion neurons by high content screening microscopy. To monitor the activity of PKA-II in intact neurons, we developed a novel isoforms-specific approach based on antibodies detecting phosphorylation of RII subunits.

Results: We found that the regulatory subunit RIIβ is selectively expressed in »60% of neurons co-expressing classical nociceptive markers such as TRPV1, NaV1.8, IB4, and CGRP. Monitoring RII phosphorylation allowed the analysis of subgroup-specific responses to inflammatory mediators (e.g. PGE₂, PGI₂, 5-HT, and epinephrine), identification of the involved receptor subtypes, and quantification of dose-response or kinetic relationships. PGE₂ induced PKA-II activity in most DRG neurons while the responses to PGI₂, 5-HT, and epinephrine were restricted to subpopulations. Of note, activation of PKA-II by PGI₂ occurred exclusively in all RIIβ-positive neurons. PGE₂ responses involved EP₂ as well as EP₄ receptor subtypes while 5-HT responses were exclusively mediated by 5-HT₄ receptors. Moreover, PKA-II activity and phosphorylation of its substrate CREB were strongly enhanced in RIIβ-positive neurons at baseline and after stimulation with inflammatory mediators.

Conclusions: Our data reveal a novel subgroup-specific mechanism involved in sensitization signaling.
DIABETIC NEUROPATHIC PAIN IN TYPE 2 DIABETIC MOUSE MODEL AND THE MECHANISM OF COENZYME Q10 (COQ10) TREATMENT

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**Background and aims:** Chronic hyperglycemia in diabetes (DM) causes oxidative stress which renders them prone to neuropathic pain. Our study demonstrated the role of CoQ10 in treatment of diabetic neuropathic pain (DNP). Overexpression of NF-Kb, cytokines and mitogen-activated protein kinase (MAPK) is considered a universal factor contributing to the development of neuropathic pain. We evaluated the expression of these factors and the inhibitory effects of CoQ10 treatment in a DM mice model.

**Methods:** IRB approval was obtained and IACUC standards were followed. NZO/HILtJ mice, normal and type 2 DM with neuropathic pain, were used. Spinal cord and dorsal root ganglia (DRG) from mice treated by CoQ10 or vehicle were harvested. Immunohistochemistry, reverse transcription and polymerase chain reaction (RT-PCR) were performed. Statistic t-test was applied.

**Results:** The percentage of positive neurons of p65 (the activated marker of NF-KB) and MAPK in DRG were significantly higher in DM mice compared to controls (p65: normal vs. DM, p< 0.01; MAPK: normal vs. DM, p< 0.05). However, in the DRG of DM mice treated with CoQ10, p65 and MAPK positive neurons decreased significantly (p65 and MAPK: DM vs. DM+CoQ10, p< 0.05). RT-PCR demonstrated that elevated levels of mRNA of CCL2, CXCL10 or TLR4 in the spinal cord in DM mice decreased significantly in DM mice treated with CoQ10 (p< 0.05 for all factors).

**Conclusion:** The antioxidant effect of CoQ10 may result in down regulation of risk factors involved in DNP. These results suggest that CoQ10 may be useful in the treatment of DNP.
RESTING BRAIN ACTIVITY IN SUBJECTS WITH CHRONIC NEUROPATHIC AND NON-NEUROPATHIC PAIN


Introduction: Although brain areas activated by acute noxious stimuli have been well described, i.e. the pain neuromatrix (thalamus, insula, somatosensory cortices), brain activation patterns in subjects with chronic pain remain relatively unexplored. Some studies have found that chronic neuropathic pain is not associated with activation of the pain neuromatrix but instead is associated with decreased ongoing activity within the contralateral (to pain) thalamus.

Objectives: The aim of this investigation is to use quantitative arterial spin labelling (QASL) to determine brain activation patterns in individuals with chronic neuropathic and non-neuropathic orofacial pain.

Methods: In 15 subjects with neuropathic orofacial pain (trigeminal neuropathy), 15 subjects with non-neuropathic pain (painful temporomandibular disorder), and 30 pain-free controls, a QASL scan covering the entire brain was collected. Both pain groups had similar on-going pain intensities and pain distributions. Cerebral blood flow (CBF) maps were generated and normalized to a standard template using SPM8. The normalized CBF maps were smoothed and entered into second level analysis to determine significant changes in regional CBF compared with controls.

Results: Chronic non-neuropathic pain was associated with significant (p< 0.05) CBF increases within the pain neuromatrix. In contrast, chronic neuropathic pain was associated with significant CBF decreases in the contralateral thalamus, in the region of the reticular nucleus and in the primary somatosensory cortex.

Conclusions: These data suggest that chronic neuropathic and non-neuropathic pain are differentially represented within the brain. Whereas non-neuropathic pain is associated with activation of the pain neuromatrix, neuropathic pain is associated with discrete CBF decreases.
THALAMOCORTICAL CONNECTIVITY DURING ACUTE AND CHRONIC PAIN: EVIDENCE OF A VMPO-INSULA CONNECTION


Introduction: It is proposed that the posterior portion of the ventromedial thalamic nucleus (VMpo) relays nociceptive and temperature specific information to the dorsal posterior insula (dpInsula). Furthermore, it has been hypothesized that this thalamic nucleus is involved in the development of post-stroke neuropathic pain.

Objectives: Using functional connectivity procedures, this study aims to determine if signal intensity within the VMpo and dpInsula co-vary during innocuous warming, acute muscle pain and chronic neuropathic pain.

Methods: Two series of 180 whole brain functional magnetic resonance imaging (fMRI) volumes were collected in 15 healthy subjects (11 females) during sustained right masseter muscle pain (12 minute 5% hypertonic saline infusion; mean visual analogue scale [VAS] score: 5/10) and warm stimuli (38°C applied to right lip) and in 15 painful trigeminal neuropathy patients (9 females; mean VAS: 4.7/10). Functional connectivity maps of the ventroposterior (VP) and VMpo thalamic nuclei were generated by extracting signal intensities from 3mm 'seed' spheres and comparing them to signal fluctuations within the dpInsula.

Results: During innocuous heat, acute pain and chronic pain, signal within the VMpo co-varied significantly (p< 0.05) with signal in the dpInsula. In striking contrast, signal within the VP thalamus did co-vary with the dpInsula.

Conclusions: These data provide strong evidence for a functional connection between the VMpo and dpInsula during innocuous heat, acute and chronic pain. These findings provide insight into the neural pathways involved in acute and chronic pain perception and support the hypothesis that the VMpo transmits pain and temperature information to the dpInsula.
NON-PHARMACOLOGICAL TREATMENTS FOR NEUROPATHIC PAIN: EFFICACY AND MECHANISMS

M.P. Jensen, USA

Although neuropathic pain is defined as “pain cause by a lesion or disease of the somatosensory system”, many CNS structures unrelated to the somatosensory system influence pain. There is growing evidence for the efficacy of a number of non-pharmacological pain treatments that target CNS activity. The strongest evidence exists for hypnosis and meditation, but other promising non-pharmacological treatments include EEG biofeedback (also known as “neurofeedback”) and transcranial direct current stimulation (tDCS). However, little is known regarding the mechanisms of these treatments. To begin to address this knowledge gap, a sample of individuals with spinal cord injury and chronic pain were administered a single session of four procedures (hypnosis, meditation, neurofeedback, and tDCS) and one control procedure (sham tDCS), and measures of pain and brain oscillation activity (EEG) were administered before and after each procedure. The results indicated that each procedure had different effects on EEG. Although changes in EEG bandwidths were not strongly associated with changes in pain in the participants as a whole, stronger associations emerged in the neuropathic pain sample. Specifically, for those with neuropathic pain, any change in brain oscillation activity as measured from the T3 electrode (near the left sensory cortex) was associated with a decrease in pain, and global increases in alpha oscillations were associated with pain relief. Finally, pre-session brain oscillation activity predicted response to each procedure. The findings suggest that (1) different non-pharmacological interventions operate via different mechanisms and (2) knowing baseline patient brain activity may allow for better treatment matching.
GENERALIZED CHEMICAL, MECHANICAL, AND THERMAL HYPERALGESIA AND REDUCED HEART RATE VARIABILITY IN COMPLEX REGIONAL PAIN SYNDROME

A. Terkelsen, Denmark

Introduction: Complex Regional Pain Syndrome (CRPS) is a condition with continuing pain disproportionate to any inciting event. In most cases the involvement is unilateral and caused by trauma or immobilization of a limb. However, signs and symptoms may spread proximally or extend past the injured limb in a hemisensory distribution or affect all four limbs. At present it is unclear whether peripheral, systemic, and/or central neuronal mechanisms are the main mechanism in CRPS.

Objectives: Is CRPS a regional disorder?

Methods: Patients were required to fulfill the research criteria (the "Budapest Criteria") for CRPS. Healthy controls matched the patients with respect to age, gender, and body mass index. In two separate studies, participants underwent autonomic and sensory testing.

Results: Heart rate was increased and heart rate variability was reduced in CRPS patients compared with controls. Bilateral hypersensitivity to capsaicin, thermal, and mechanical stimuli was present in CRPS patients with unilateral symptoms compared to controls. The patients had normal thermal detection thresholds, quantitative sudomotor axon reflex test, and vasoconstrictor responses, suggesting preserved small fiber function.

Conclusions: The present clinical data show bilateral hypersensitivity to capsaicin, thermal, and mechanical stimulation in unilateral CRPS together with reduced heart rate variability. These changes are either due to generalized peripheral, systemic, or central changes and suggest that CRPS is not a pure regional disorder. The increased heart rate and decreased heart rate variability in CRPS suggest a general autonomic imbalance, which is an independent predictor for increased mortality and sudden death.
ROLE OF VOLTAGE-GATED CALCIUM CHANNEL ALPHA2DELTA-1 SUBUNIT IN SENSORY NEURON FUNCTION AND EXPERIMENTAL MODELS OF NEUROPATHIC PAIN

A.C. Dolphin, UK

The α2δ auxiliary subunits of voltage-gated calcium channels enhance calcium currents and affect their properties, but their mechanism of action is not well understood. The anti-epileptic and anti-nociceptive drugs gabapentin (GBP) and pregabalin (PGB) are known to bind to α2δ-1 and α2δ-2, and the α2δ-1 target is essential for the antihyperalgesic action of this. We have found that acute application of GBP does not affect calcium currents in several different systems. However, chronic application of GBP to cultured cells reduces both calcium currents and cell-surface expression of heterologously expressed α2δ and α1 subunits, and PGB also affects α2δ trafficking in vivo.

Evidence from numerous studies has identified an important role for α2δ-1 in neuropathic pain. The mRNA and protein for α2δ-1 are up-regulated in dorsal root ganglion (DRG) neurons following spinal nerve ligation (SNL), a model of neuropathic pain, an increase which correlates with the onset of mechanical hypersensitivity. In a recent study, we have examined the role of α2δ-1 in sensory neuron function by examining sensory processing and the development of experimental neuropathic pain in α2δ-1 knockout mice. Our results point to deficits in specific sensory modalities and that α2δ-1 is essential for the rapid development of behavioural hypersensitivity following nerve damage.
TOWARDS A NEW VIEW ON POST-STROKE SHOULDER PAIN

M. Roosink, The Netherlands

Shoulder pain is the most commonly reported type of pain after stroke. Traditionally, post-stroke shoulder pain (PSSP), is considered as nociceptive pain. However, treatment success is unsatisfactory, evidence for interventions is lacking, and a significant number of patients develop chronic pain. Diagnostic criteria for neuropathic pain are of limited use in patients with PSSP, who often present with mixed and/or pre-stroke pain complaints. Therefore, a better understanding of PSSP and its underlying mechanisms is needed.

So far, only a handful of PSSP studies have systematically assessed somatosensory abnormalities (e.g. using quantitative sensory testing and conditioned pain modulation) and their relationship to the presence and characteristics of PSSP and stroke. Although the individual studies used somewhat different approaches, importantly, they all showed a relationship between the presence and characteristics of pain and central nervous system abnormalities, including both sensory loss and sensitization. Moreover, an exploratory longitudinal study showed that central sensitization may develop within the first 6 months after stroke, and may be part of a vicious cycle of shoulder pain, limited range of motion and re-injury.

These results suggest that the mechanisms underlying PSSP are complex and may involve both nociceptive and neuropathic components. However, to infer causation, more in depth longitudinal assessment of somatosensory abnormalities after stroke is warranted. In addition, future research should feed the discussion on how to interpret sensory abnormalities in stroke patients presenting with pain in lesion-affected dermatomes, and on the subsequent differentiation between PSSP and other types of post-stroke pain.
Neuropathic pain, a chronic debilitating disease characterized by mechanical allodynia and spontaneous pain, is often unresponsive to conventional methods of treatment. Given that a loss of spinal cord dorsal horn inhibitory circuits is one of the major contributors to persistent neuropathic pain, a potentially disease-modifying therapeutic approach that restores inhibitory tone in the spinal cord should ameliorate the symptoms of neuropathic pain. Indeed, transplantation of precursors of GABAergic interneurons derived from the mouse medial ganglionic eminence (MGE) into the adult mouse spinal cord completely reverses the mechanical hypersensitivity produced by peripheral nerve injury, without altering baseline thresholds. Underlying this improvement is a remarkable integration of the MGE transplants into the host spinal cord circuitry and a normalization of the nerve injury-induced reduction of GABA signaling. By contrast, MGE transplants were not effective against inflammatory pain. Clearly, MGE-derived GABAergic interneurons have the essential properties for a cell-based therapy, particularly when loss of inhibitory control is a major contributor to the clinical condition.
GALLIUM MALTOLATE: A NEW TOPICAL ANALGESIC AGENT

L. Bernstein, USA

Introduction: Preclinical and clinical studies have shown that gallium can exert antiproliferative and anti-inflammatory activity. Gallium’s anti-inflammatory activity is due largely to its ability to inhibit activation and proliferation of Th1 cells and secretion of inflammatory cytokines by macrophages. Gallium’s analgesic properties likely relate to its anti-inflammatory activities and its actions on certain metalloproteinases and neuropeptides.

Objectives: Investigate the analgesic activity of topical gallium maltolate (GaM) in a pilot clinical study.

Methods: A formulation of 0.5wt% GaM in a hydrophilic petrolatum emulsion was applied to the skin at sites of neuropathic pain in six subjects: three with refractory postherpetic neuralgia, one with neuropathic pain following nerve damage to the hand, one with CRPS, and one with refractory trigeminal neuralgia. In addition, an aqueous solution of 1 wt% GaM was used to rinse the mouth of a patient with oral squamous cell carcinoma accompanied by severe mouth pain. For the subjects using the topical cream, pain was recorded over periods of weeks to years; for the subject using the mouth rinse, pain was recorded for seven days.

Results: All seven patients experienced significant, rapid pain relief. The subject with severe refractory postherpetic neuralgia experienced almost complete pain relief within 10 minutes of topical GaM administration, and used the formulation daily for more than five years. The patient with severe trigeminal neuralgia also experienced rapid relief of pain and edema.

Conclusions: Controlled, systematic research is warranted to further investigate the analgesic properties of GaM and to investigate GaM’s mechanisms of action.
CAN CONTACT HEAT EVOKED POTENTIALS BE USED TO ASSESS THE ROLE OF TRPV1 RECEPTOR IN NEUROPATHIC PAIN STATES?

J. Haefeli, J.L.K. Kramer, A. Curt, Switzerland, USA

Background and aim: Changes in the property of TRPV1 receptors are thought to be involved in the development of neuropathic pain. The present study addressed the value of a contact heat stimulation paradigm to disclose changes in TRPV1 receptor activities. To address this, different baseline temperatures of contact heat stimulation were examined before and after pharmacological TRPV1 sensitization.

Methods: In 19 healthy individuals three different baseline stimulation temperatures ranging from 35°C, 38.5°C to 42°C were applied to the hand. The target stimulation intensity was set to 52°C. In 7 healthy subjects the same paradigm was conditioned by topical capsaicin sensitization (0.075%) lasting for 30 minutes.

Results: The pain rating to contact heat stimulation increased linearly with increasing baseline temperatures. In contrast, N2P2 amplitudes significantly increased after stimulation with 42°C baseline temperature compared to 35°C and 38.5°C, but remained unchanged between 35°C and 38.5°C. This effect was enhanced when sensitizing the TRPV1 receptor by capsaicin.

Conclusion: The findings reveal that a specific stimulation of TRPV1 receptor can be achieved by using higher baseline temperatures. This effect can be attributed to effectively stimulating at TRPV1 receptors level. Contact heat stimulation therefore may allow for assessing modulation of the TRPV1 receptor in different neuropathic pain states, but may require higher baseline temperatures be applied.
MIDDLE EAST REGION GUIDELINES FOR THE TREATMENT OF NEUROPATHIC PAIN

A. Salti, United Arab Emirates

IASP defines (NeP) as "pain arising as a direct consequence of a lesion or disease affecting the somatosensory system". Confidence in the diagnosis of NeP depends on the history and examination of the patient presenting with a complaint of pain. In the treatment guideline literature, the most notable gap appears to be the exclusive focus on recommendations for managing NeP patients in Europe and North America. No similar NeP guideline is available for the Middle East Region. Guidelines are a crucial mechanism for translating the results of RCTs into standardized and optimized clinical practice. Guidelines must be region-specific to ensure they are tailored to the needs of a given region. This is especially important for the treatment of pain conditions since significant ethnic and cross-cultural differences have been identified in the perception of pain. Furthermore, the types of diseases and injuries that cause NeP exhibit a high-degree of cross-national variance. Rates of diabetes in the MER are among the highest of any region in the world. The MER was defined to include countries with an aggregate population of more than 300,000,000. Pregabalin was the consensus recommendation for first line treatment of peripheral NeP. Gabapentin was also a first line recommendation, but pregabalin was preferred due to its greater potency, and its more favorable pharmacokinetics, ease of use and speed of onset of action. Furthermore, two separate studies found pregabalin to be a more cost-effective treatment than generic gabapentin. Patients should typically be treated for 2-8 weeks, with at least 1-2 weeks at maximum tolerated dosage.
DRUG MANAGEMENT OF TRIGEMINAL NEUROPATHIC PAIN

J. Zakrzewska, UK

Introduction: Trigeminal neuralgia is the most recognised neuropathic pain of the face and has a distinct care pathway. However other orofacial pains that are thought to be neuropathic include short unilateral neuralgiform pain with autonomic symptoms SUNA, post herpetic neuralgia, traumatically induced neuralgia, atypical odontalgia and burning mouth syndrome.

Objective: Review the evidence for drug therapy of this group of conditions

Methods: Systematic reviews, guidelines, RCTs and cohort studies will be used to inform on drug therapy.

Results: The first line drugs for trigeminal neuralgia remain carbamazepine and oxcarbazepine. Current guidelines suggest that lamotrigine and baclofen may be other useful drugs. There is some evidence for the use of gabapentin and pregablin. There is a new sodium channel blocker that is currently undergoing trials. There are currently no trials and only small case reports on management of SUNA which responds better to lamotrigine with or without oxcarbazepine than carbamazepine. Post herpetic neuralgia is managed as in other parts of the body and there may be some value in use of lidocaine patches at night. Trigeminal neuropathic pain due to trauma often responds to treatment with tricyclic antidepressants but there is little specific evidence. Burning mouth syndrome has been the subject of a Cochrane systematic review and several randomised controlled trials. Both topical and systemic drugs have been used including clonazepam, alphalipoic acid and SSRI.

Conclusions: Apart from trigeminal neuralgia which can be well controlled other trigeminal neuropathic pains remain difficult to manage.
CHEMOTHERAPY-INDUCED NEUROPATHY

N.B. Finnerup, Denmark

Neurotoxic chemotherapeutic agents such as the taxane docetaxel and the platinum agent oxaliplatin may cause a chronic dose-dependent sensory axonal polyneuropathy. Oxaliplatin is unique in also causing an acute reversible neurotoxicity in nearly all patients, with cold allodynia and pins and needles sensations particularly in the hands. Despite the different symptoms and signs in the acute phase, the chronic neuropathy, which is seen in only a subset of patients, is similar between the two patient groups. This is mainly a length-dependent sensory polyneuropathy. Using the QST protocol and normal material developed by the German Neuropathic Pain Network, we found that patients with chronic polyneuropathy following docetaxel and oxaliplatin treatment have similar sensory profiles, characterized in particular by large fiber loss as indicated by increased vibration detection threshold. Sensory loss was seen in 80-85% and sensory gain in 35% in lower limbs. In upper limbs sensory gain was more common in docetaxel-treated patients. These data will be compared to neurophysiological data including laser evoked potentials, and pain symptoms in the acute and chronic phase will be compared between the two patient groups. This talk will also discuss predictors of neuropathy and pain based on prospective data and will discuss whether preventing acute cold allodynia will be expected to prevent chronic polyneuropathy in oxaliplatin-treated patients.

The workshop will devote time at the end to discuss and compare sensory abnormalities and symptom clusters in post-traumatic, HIV, leprosy, and chemotherapy-induced neuropathies.

The studies are part of the Innovative Medicine Initiative EUROPAIN, www.imi.europa.eu
The diagnosis of TNPs relies largely on the results of the patient interview (historical evidence) and clinical examination. Diagnostic criteria for TNPs are therefore largely devoid of objective evidence. I will present the International Headache Society's proposed changes to TNP classification. This will focus on trigeminal neuralgia, burning mouth syndrome and painful traumatic trigeminal neuropathies. For these current pathophysiologic concepts and theories will be presented.
PAIN EVALUATION IN A RAT MODEL OF METASTATIC SPINE MAMMARY CANCER

R. Sarabia-Estrada, P. Zadnik, A.M. Ampuero, M. Groves, D. Sciubba, Spine Oncology, USA

Metastatic spinal cord compression (MSCC) is derived from kidney, lung, prostate and breast cancer. Patients suffer from pain, fractures and paralysis. A key obstacle in the study of this disease is the lack of reliable, practical and reproducible animal models of MSCC. Behavioral evaluation was conducted in a group of 12 naïve and in 7 tumor-implanted (rat mammary adenocarcinoma, L5 vertebral body). At D12 von Frey monofilaments (VF) were applied in both groups. The rats that were able to use both hindlimbs were used for this evaluation. A total of 15 VF stimulus applications were performed on each paw, beginning with the 0.4 g and ending with the 74g. We observed differences with the 0.4; 0.8; 7.5 g; 11; and 12 gram VF. To evaluate sensation with a second test, we performed a pinching test between the rat toes to see if the rat responded with a withdrawal or vocalization. All rats evaluated responded in both groups. There was a delay in the response of tumor-implanted rats was different from control rats. Tactile sensory deficits were observed more frequently in the tumor implanted rats than in the control group. Positive paw withdrawal response to tactile stimuli were often accompanied by hypervigilant behaviors including licking the stimulated paw as well as turning and looking at the stimulus, and occasionally moving away from the stimulus. Further evaluations are needed to test different anatomical areas that correspond to the lumbar dermatomes.
MECHANISMS UNDERLYING EXTRATERRITORIAL NEUROPATHIC PAIN ASSOCIATED WITH TRIGEMINAL NERVE INJURY

K. Iwata, M. Shinoda, K. Honda, A. Katagiri, B.J. Sessle, Japan, USA, Canada

Trigeminal nerve injury may be associated with severe pain in orofacial regions innervated by uninjured nerves as well as the injured nerve. The presence of such extraterritorial neuropathic pain may complicate diagnosis and management. Although neuroplastic changes in the central nervous system and/or sensitization of afferents in the peripheral nervous system are thought to be involved in neuropathic pain, the mechanisms underlying extraterritorial spread in orofacial neuropathic pain states are not fully understood. To clarify the mechanisms, we have developed rat models of trigeminal neuropathic pain involving unilateral injury of infraorbital, inferior alveolar or lingual nerve. Using behavioral, electrophysiological, biochemical and immunohistochemical techniques, we have found that these models show behavioral evidence of neuropathic pain and spread to extraterritorial sites beyond those innervated by the injured nerve, plus wide spread and marked hyperexcitability of trigeminal ganglion (TG) neurons and trigeminal subnucleus caudalis (Vc) and upper cervical spinal cord (C1-C2) nociceptive neurons, as well as widespread activation of TG and Vc/C1-C2 glial cells. These changes are associated with up- or down-regulation of various molecules in these neurons and glia, most notably phosphorylated ERK, NGF, fractalkine, P2Y receptor and nitric oxide. The presentation will discuss how these various changes may contribute to the development and maintenance of extraterritorial pain following trigeminal nerve injury.

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ROLE OF NON-NEURAL AS WELL AS NEURAL PROCESSES IN ANIMAL MODELS OF OROFACIAL NEUROPATHIC PAIN

K. Iwata, M. Shinoda, K. Honda, A. Katagiri, B.J. Sessle, Japan, USA, Canada

The hyperactivity of glia and neurons in the trigeminal ganglion (TG), trigeminal spinal subnucleus caudalis (Vc) and upper cervical spinal cord (C1-C2) appears to play a pivotal role in the orofacial neuropathic pain state. Recently, we have documented that following lingual nerve crush, satellite glial cells are activated in the TG, and the accompanying mechanical and heat hypersensitivity in the tongue can be significantly reversed by P2Y12 receptor antagonist injection into the TG, suggesting the involvement of satellite cell activation in the TG via P2Y12 receptors in lingual neuropathic pain states. We have also documented that inferior alveolar nerve transection or chronic constriction injury of infraorbital nerve causes a significant enhancement of nocifensive behavior to mechanical stimulation of orofacial areas innervated by uninjured as well as injured nerves, accompanied by widespread TG satellite glial cell and neuronal activation. Furthermore, trigeminal nerve injury produces nociceptive neuronal central sensitization and astroglial and microglial activation in Vc and C1-C2, and phosphorylation of extracellular signal-regulated kinase (ERK) in Vc and C1-C2 neurons. The central sensitization, glial activation and associated nocifensive behavior can be significantly reversed following administration (i.t. or i.p.) of astroglial or microglial inhibitors, and i.t. administration of MEK1 inhibitor causes significant reduction of ERK phosphorylation in Vc and C1-C2 neurons and the nocifensive behavior. These findings suggest that satellite cell-neuron interactions in the TG, and astroglial-neuron and microglial-neuron interactions in Vc and C1-C2 have important roles in trigeminal neuropathic pain mechanisms.

Supported by NIH and CIHR grants and KAKENHI
Botulinum neurotoxin type A (BoNTA) has been studied for analgesic properties in painful conditions such as headaches and neuropathic conditions. Mechanisms underlying analgesic effects of BoNTA are partly elucidated. Human experimental pain models can act as a translational bridge between animal and clinical research. Short-term painful conditions produced in healthy volunteers are not identical to chronic pain conditions, but information from these studies may help in understanding of chronic pain and analgesic effects of potential pain killers. We performed two randomized, double-blinded; placebo-controlled studies and demonstrated that BoNTA (subcutaneous or intramuscular) was effective at decreasing capsaicin-induced pain. BoNTA also decreased flare area, skin temperature, cutaneous blood flow, secondary hyperalgesia, and increased pressure pain threshold. Other studies demonstrated conflicting results in capsaicin pain model. We have also shown onset and time course of BoNTA effect in a human experimental model of glutamate-induced pain and vasomotor reactions. BoNTA has also reduced blood flow and produced marginal decrease in an experimental model of electrically-induced pain. In an ultraviolet B-induced pain model, however, no effect of decreasing pain or cutaneous blood flow with BoNTA was observed. This mixed effect could be due to the type of pain model, method of delivery of noxious stimulus, and timing of BoNTA administration and show the importance of careful choices of such parameters. To overcome some limitations of psychophysical studies, we have recently performed a microdialysis study in humans to demonstrate BoNTA effect on pattern of release of several substances potentially involved in the transmission of pain.
BACK TO BASICS: AVOID COMMON FUMBLES IN GENETIC ASSOCIATION STUDIES

H. Kim, USA

This presentation will cover the issues related to the principles of genetic association studies from study design to data analysis. These include selection between candidate gene and genome-wide approaches including comparative genomic hybridization array and next generation sequencing technologies, appropriate sample size, correction for multiple comparisons, study replication, and etc. To avoid false findings and misinterpretation which induce inconsistent conclusions in genetic association studies, these principles should be strictly followed. Each principle will be discussed along with common errors and examples followed by suggestions for improving genetic association studies in neuropathic pain conditions.
EXPOSURE THERAPY FOR CHRONIC NEUROPATHIC PAIN

R.V. Dongen, J.P. Frolke, H.V.D. Meent, F. Klomp, H. Samwel, J.V. Egmond, The Netherlands

Aims: Complex regional pain syndrome type 1 (CRPS-1) is caused by a variety of injuries of a limb. Pain, functional disturbances and vaso-vegetative changes are the classical symptoms. Since the exact pathophysiological mechanism is unknown, therapy is mainly empirical. Pain complaints are severe and do not respond to conventional therapy. Therapists are reluctant to cause further pain complaints since we think that this leads to irreversible harm of the tissues. A new approach was studied in order to regain function while the pain during treatment was neglected. The new approach was given the acronym PEPT (Pain Exposure Physical Therapy).

Methods: First, using a functional approach neglecting the pain complaints, a series of chronic "end-stage" CRPS-1 patients was studied. In 106 patients, 49 reached full functional recovery while pain decreased in 75. This was followed by a safety, n=1 design, study of 20 newly diagnosed cases. Pain, pain intensity, muscle strength and functional improvement changed significantly as well as the QOL. No persistent increase of symptoms occurred. Finally, a single-blinded RCT was performed comparing PEPT with conventional treatment in 58 patients. The diagnosis CRPS-1 was also according to "Budapest" criteria. The CRPS-1 Impairment level Sum Score as primary end-point improved more in the PEPT group. Secondary endpoints (VAS, PDI, active range of joint motion, muscle strength and QOL) all improved more in the PEPT group.

Conclusions: Pain exposure physical therapy is a safe, non-pharmacological and effective treatment of CRPS-1 superior to the current evidence based conventional treatment.
CLASSIFICATION OF PAIN AFTER SCI

T. Bryce, USA

Although it is clear that pain after spinal cord injury (SCI) is common with an approximate prevalence of 80% of which a significant percentage is neuropathic (NP), it has not always been clear how to define the specific subtypes of pain after SCI including NP ones.

Over the years, over 30 classification systems have been described of varying subtype nomenclature and definitions. This has led to variance in reported prevalences, difficulty in comparing study outcomes, and at a basic level, confusion on how to define a specific subtype.

In order to bring clarity to the classification process needed to define the problem and to come up with an appropriate treatment, an international group of SCI and pain experts developed a consensus classification that was subsequently reviewed by several professional organizations and validated in an international study.

This talk describes the development, content, and how to apply the International SCI pain (ISCIP) Classification.
CHRONIC PAIN AFTER SURGERY: EPIDEMIOLOGY AND RISK FACTORS

A. Stubhaug, Norway

Chronic post-surgical pain (CPSP) has received tremendous interest the last years. Surgery may be looked upon as the most invasive experimental pain model that is ethically acceptable in humans. If we can understand and prevent the transition from acute post-surgical pain to CPSP, we may have found the key also to prevent other chronic pain syndromes. Good knowledge on epidemiology including reliable estimates of the prevalence is an important first step. However, huge differences in prevalence has been reported even when only one type of surgery is studied. CPSP prevalence after hernia repair is reported to be 0-43 % and after total hip or knee replacement between 6- 44% just to mention two examples. One reason for these discrepancies is the lack of an accurate definition. Critical issues are duration of postsurgical pain to qualify as CPSP, severeness of pain, and discrimination from simple continuation of presurgical pain. In a recent epidemiological study we found that most subjects reporting pain more than 3 months after surgery had mild pain. Only 51% of subjects reporting chronic postsurgical pain considered themselves having chronic pain when questioned without specific reference to the surgery. Definition, prevalence and risk-factors for CPSP will be reviewed in light of the most recent literature.

References:

Neuropathic pain, i.e., pain due to lesion or dysfunction of the somatosensory system is paralleled by somatosensory abnormalities (Treede et al. 2008). If afferent channels from the skin are affected sensory aberrations can be detected using simple bedside tools for suprathreshold stimulation (Haanpää et al. 2011). A brush/cotton bud/tuning fork is used to probe the sensitivity to touch and vibration, i.e., activating large A-beta fibres, the dorsal columns and their thalamo-cortical extension. Cold- and warm metallic rollers (“Lindblom rollers”) as well as a pin could be used to test temperature or pain sensation and hence activate different types of A-delta- and C-fibres and the spino-thalamo-cortical system. Importantly, pain in an area with sensory dysfunction is not to be equated with neuropathic pain since other types of pain may be expressed in such an area. Characteristics of the pain need further surveying to allow for its classification. Quantitative sensory testing (QST) of perception thresholds in the aforementioned somatosensory channels could be used to complement the search for somatosensory aberrations at bedside examination since it may not necessarily arrive at comparable results in one or several sensory channels (Leffler & Hansson, 2008). This insight is of outmost importance when QST outcomes are used in conjunction with results of bedside examination in the diagnostic situation. The reason for potential discrepant outcomes may be related to differences in categorization criteria for pathology, differences in physical properties of the employed stimuli as well as the way the stimuli are applied.
HYPERSENSITIVITY IN NEUROPATHIC AND NON-NEUROPATHIC PAIN CONDITIONS

P. Hansson, Sweden

Central sensitization, a wording derived from the animal neurophysiological literature, is undoubtedly in fashion in the field of pain medicine and is frequently articulated by clinical researchers when referring to any spread of pain-related sensitivity and is used by clinicians to explain strange clinical phenomenologies. In more strict neurophysiological terms central sensitization is a form of activity-dependent neuronal plasticity and has recently been described regarding it’s highly complex cellular and molecular mechanisms (Latremoliere & Woolf, 2009) and potential implications for the diagnosis and treatment of pain (Woolf 2011).

The pre-clinical literature on the subject offers insights into use-dependent synaptic plasticity in dorsal horn neurons in or near the segment receiving challenging peripheral nociceptive input. The clinical literature demonstrates local and remote widespread hypersensitivity in conditions with a fairly well understood pathophysiology (and in less well understood conditions) which frequently and indiscriminately is interpreted in terms of central sensitization.

The presentation will draw attention to clinical data interpreted as central sensitization and discuss alternative explanations and nomenclature for widespread increased sensitivity. Currently, central sensitization lacks diagnostic criteria in the clinical scenario and should hence be employed warily, if at all, in such a setting. Repeated use of an unproven concept has caught on in the pain community and may leave translational aspects of pain trivialized and us ridiculed by those who know better.
A PERIPHERAL BETA2-ADRENERGIC MECHANISM FOR ANTIDEPRESSANT ANTIALLODYNIC ACTION.

M. Barrot, France

Background and aims: Tricyclic antidepressants (TCA) and serotonin and noradrenaline reuptake inhibitors (SNRI) are among the first-line treatments for neuropathic pain. However, their therapeutic mechanism remains poorly understood. During the past 7 years, we developed researches to decipher this mechanism, identify required receptors, neuroanatomical and cellular substrate, and molecular actors.

Methods: We used models of neuropathic pain in mice, in which long-lasting mechanical allodynia is totally reversed after 10-14 days of antidepressant treatment. Various TCAs and SNRIs were studied. KO mice for beta2-adrenoceptors (beta2-AR) and for opioid receptors were used. Behavioral pharmacology, lesional approaches, immunohistochemistry, qPCR and Western blot analyses were also used to study TCA/SNRI mechanism. Clinical approaches on a new therapeutic target based on the mechanistic findings are completing this translational work.

Results: With preclinical pharmacological and genetic approaches, we show that antidepressant-recruited noradrenaline acts through beta2-adrenoceptors (beta2-AR) to relieve neuropathic allodynia. We show that this mechanism is shared by TCAs and SNRIs and requires delta-opioid receptors. Using anatomically targeted noradrenergic lesions, we demonstrate that the antiallodynic mechanism is mediated through the peripheral nervous system, via noradrenergic fibers issued from neuropathy-induced sprouting. More particularly, antidepressant-recruited noradrenaline acts within dorsal root ganglia, on beta2-ARs which are expressed by non-neuronal satellite cells. This beta2-AR mediated mechanism decreases the production of TNFα in dorsal root ganglia.

Conclusions: Our results revealed a peripheral beta2-AR-dependent mechanism, shared by TCAs and SNRIs, that prevents the maintenance of neuropathic alldynia.
EMOTIONS MATTER: A NOVEL EMOTIONAL AWARENESS AND PROCESSING PROGRAM FOR CHRONIC NEUROPATHIC PAIN


Introduction and Objectives: Current treatments for chronic neuropathic pain have limited effectiveness. We evaluated treatment outcomes and predictors of outcomes of a novel emotion-oriented intervention for chronic pain.

Methods: The research team conducted a baseline evaluation. A medical evaluation assessed medical conditions, reviewed psychosocial stressors, and identified linkages between the two. Treatment consisted of 4, weekly, small group, 2-hour sessions. Components included techniques to help people identify, understand, and express emotions related to stress and pain. Homework (e.g., expressive writing, meditative exercises) was assigned daily. Patients were assessed at baseline and again at post-treatment and 6-month follow-up with the Brief Pain Inventory (BPI) and the McGill Pain Questionnaire (MPQ).

Results: 75 adults with chronic neuropathic pain, primarily headaches, neck, back, and widespread pain (fibromyalgia). Individuals with significant structural disease processes were excluded. 80% women; mean age = 49.6 years; 90% Caucasian; mean duration of pain 8.6 years. Post-treatment: 68% had ≥ 30% improvement and 46% had ≥ 50% improvement; at 6-months: 61% had ≥ 30% improvement and 55% had ≥ 50% improvement. Mean BPI scores (0-10) were 5.03, 2.97, and 2.89 (baseline, post-treatment and 6-months; p< 0.001, d= -1.27). The MPQ showed similar reductions.

Conclusions: This high rate of improvement may surpass that of cognitive-behavioral interventions for chronic pain. An approach that helps patients understand and confront emotional contributions to their pain may prove beneficial. Randomized, controlled studies are underway to determine if targeting unresolved stress and emotions in chronic pain patients offers an advance in treatment.
NEW AVENUES IN THE DEVELOPMENT OF SUBTYPE-SELECTIVE MODULATORS OF GABA<sub>A</sub> RECEPTORS

H.U. Zeilhofer, Switzerland

Plenty of evidence indicates that diminished synaptic inhibition is a major contributor to inflammatory and neuropathic pain states. Activation or potentiation of spinal GABA<sub>A</sub> receptors has been shown to reverse exaggerated pain sensitivity in different models of inflammatory and neuropathic pain. Work in GABA<sub>A</sub> receptor mutated mice demonstrated that this antihyperalgesia depends on the activation of GABA<sub>A</sub> receptors containing alpha 2 subunits, while GABA<sub>A</sub> receptors containing the alpha1 subunit do not contribute. This finding suggests that GABA<sub>A</sub> receptor modulators that specifically target alpha 2-GABA<sub>A</sub> receptors should be well suited to reverse pathological pain hypersensitivity without evoking the typical unwanted effects of classical GABA<sub>A</sub> receptor modulators such as sedation, addiction or memory impairment. We have recently generated additional GABA<sub>A</sub> receptor mutant mouse lines to study the role of the different GABA<sub>A</sub> receptor subtypes in GABA-mediated antihyperalgesia more detail. Using mice that lack alpha 2-GABA<sub>A</sub> receptors specifically from the spinal cord we could demonstrate that the antihyperalgesic action of alpha 2-GABA<sub>A</sub> receptors is solely of spinal origin and does not involve supraspinal actions such as a reversal of anxiety-induced hyperalgesia. With the use of triple point-mutated mice in which only one GABA<sub>A</sub> receptor remains benzodiazepine-sensitive we could show that the alpha 2 subtype of GABA<sub>A</sub> receptors is the single most effective GABA<sub>A</sub> receptor subtype for antihyperalgesia. Receptor occupancy studies performed in these mice further allowed us to estimate the degree of subtype selectivity required for novel GABA<sub>A</sub> receptor ligands to be antihyperalgesic but not sedative.
Orofacial neuropathic pain may develop as a consequence of various types of dental procedures such as insertion of oral implants, wisdom-tooth surgery, orthognathic surgery in addition to accidental trauma to orofacial tissues. Although the anatomy and neural organization of the trigeminal system is distinct from the spinal system, lesions or diseases of the somatosensory trigeminal pathways may share many of the same clinical presentations, i.e., pain location in the neuroanatomical relevant distribution of the involved nerves and changes in somatosensory sensitivity with either gain or loss of afferent fiber function. These features stress the importance of a systematic approach to documenting patient reports of pain location and testing of somatosensory function. Recent studies in our laboratory have shown relationships between perceived area of nerve-evoked pain and distortions of the face using paper-and-pencil anatomical maps and warped photos of individual faces. A series of studies have tested the variability of quantitative sensory tests applied to the orofacial region and attempted to develop easy-to-use chair-side qualitative tests as well. Furthermore, mapping of somatosensory function in response to experimental manipulation of oral mucosal sensitivity using capsaicin and menthol has indicated the clinical applicability of QST techniques. The need for specific neurophysiological measures and imaging studies will be discussed. Finally, management strategies including a neuro-cognitive aspects will be presented.
AN IMPROVED APPROACH TO CATHETERIZATION OF THE SPINAL SUBARACHNOID SPACE IN RATS

R. Chen, H. Wang, Q. Zhou, W. Jiang, China

Chronic catheterization of the spinal subarachnoid space of the rat is a useful technique in the research of neuroscience and anesthesiology. The original technique is to insert a catheter through atlanto-occipital membrane, which is associated with high mortality and neurological deficits. The later method -- catheterization from lumbar interspaces into subarachnoid space, achieves a higher post-surgical success rate, but the catheters may easily be damaged or displaced. In this paper, Using the special anatomical features of rodents, we discovered a new subarachnoid catheterization approach through atlanto-axial intervertebral space, which encompasses the benefits of existing methods and circumvents their known shortcomings. With less surgical trauma, minimal mortality and morbidity, and firmer anchorage of the catheter, the new method of intrathecal catheterization compared favorably to both cisternal and lumbosacral approaches and easy to be employed by novice. Radiographs were taken to define the insertion points and the successful subarachnoid catheterization at day 14 after surgery. The other two commonly used catheterization methods were performed for comparison. Pharmacological validation was assessed by acute morphine administration.
ALTERNATIVE ENDPOINTS AND NOVEL BEHAVIORAL PARADIGMS FOR ASSESSMENT OF NEUROPATHIC PAIN AND COMPLEX BEHAVIORAL CHANGES IN RODENTS WITH NEUROPATHIC PAIN

K. Rutten, I.A. Lefevre, J.-P. Terranova, W. Huang, A.S. Rice, Germany, France, UK

Preclinical development of novel analgesic drugs requires robust assays to assess pain-like behavior and the efficacy of drug treatment. To be useful in predicting analgesic efficacy, an assay needs to demonstrate both sensitivity (the ability to predict efficacy) and specificity (the ability to predict negative outcomes). Traditional tests based on evoked responses, such as reflex-withdrawal tests, have poor face validity, because they use settings that are of little ethological relevance to the animal and because they translate poorly to the human disease setting in which spontaneous pain is usually the predominant symptom (Rice et al., 2008). In contrast, models that rely on innate animal behavior have the potential to improve the predictive validity of preclinical pain assays.

This presentation will focus on three novel behavioral readouts driven by complex natural rodent behavior that have been developed and validated as a collaborative effort of work package 2 of Europain (Innovative Medicines Initiative, IMI). Three alternative approaches to study spontaneous pain will be discussed which are based on pain driven changes in complex natural and ethologically relevant rodent behavior.

The first approach involves neuropathic pain-induced changes in social discrimination behavior. The second focuses on natural burrowing behavior in rodents which is disturbed by pain-like states and can be pharmacologically manipulated. Finally the use of models of predator/risk avoidance behavior for the assessment of spontaneous pain will be addressed.

The relevance, validity and reproducibility of these methods will be discussed and pharmacological validation of these novel approaches will be provided.

Funding: IMI-EUROPAIN
NEW INSIGHTS INTO PROCESSES THAT MODULATE TRIGEMINAL CENTRAL SENSITIZATION FOLLOWING OROFACIAL NERVE INJURY

B.J. Sessle, Canada

This presentation will review recent findings of processes that modulate trigeminal central sensitization following trigeminal nerve injury and that relate to clinical features of orofacial neuropathic pain states and their management. Rodent models of trigeminal neuropathic pain may display mechanical and thermal hypersensitivities within or adjacent to the site innervated by the injured nerve as well as extraterritorially in other body sites innervated by other trigeminal nerves or by spinal nerves. These nociceptive behavioural changes reflecting allodynia, hyperalgesia and extraterritorial spread are accompanied by enhanced glutamate release in trigeminal subnucleus caudalis (Vc, the “medullary dorsal horn”) and an increased excitability of Vc nociceptive neurons. This central sensitization appears to be a fundamental facilitatory process in the development and maintenance of chronic neuropathic pain states manifesting allodynia, hyperalgesia and pain spread. The expression of nociceptive behaviour and trigeminal central sensitization is modulated by several influences operating through a number of chemical mediators and receptor mechanisms (e.g. NMDA, purinergic, GABA), and is also dependent on the functional integrity of non-neural cells (e.g. Vc astroglia and microglia). Recent findings of variability in the expression across genetically diverse rodent strains/lines suggest that genetic factors contribute significantly to the variation between patients in the clinical expression of neuropathic pain following trigeminal nerve injury. Recent findings will also be presented that show that the Vc central sensitization and associated nociceptive behaviour can also be attenuated by recently introduced drugs to manage orofacial neuropathic pain states. Supported by NIH, CIHR, Pfizer Canada.
A TIME-DEPENDENT HISTORY AND NEUROANATOMICAL BASIS FOR NEUROSAPTHIC PAIN-INDUCED MOOD DISORDERS

M. Barrot, I. Yalcin, France

Background and aims: Mood disorders such as depression and anxiety are frequently observed in patients suffering from chronic pain. However, the mechanisms underlying this comorbidity remain unclear. Using a mouse model of neuropathic pain, we analyzed the time-dependent development of the affective consequences of chronic pain, and we studied the involvement of different cortical areas in the development of pain behavior and affective disorders.

Methods: We induced neuropathy by implanting a polyethylene cuff around the main branch of the right sciatic nerve in mice. This procedure induces an ipsilateral mechanical allodynia which starts a day after the surgery and lasts for 3 months. We assessed anxiety-related behaviors using elevated plus-maze, light/dark box, novelty suppressed feeding and marble test and depression-related behaviors using the splash/grooming test and the forced swimming test. Stereotaxic surgery was done before the cuff surgery to induce cortical excitotoxic lesions. Using a battery of behavioral tests, we then investigated the development of pain behaviors and mood disorders in these animals.

Results: Four weeks after induction of the neuropathy, mice develop mood disorders in a time-dependent manner. Neuropathic mice with lesion of the anterior cingulate cortex still present mechanical allodynia but failed to show anxio-depressive like behavior while other cortical lesions reverse the development of mechanical allodynia without blocking the affective consequences of chronic pain.

Conclusion: Neuropathic pain leads to affective disorders in a time-dependent manner. We also show that different cortical regions are implicated separately in the somatosensory component and in the affective consequences of neuropathic pain.
Peripheral sensory neuropathy is a common neurological complication of HIV infection, and with Africa being disproportionately affected by the HIV/AIDS epidemic (accounting for approximately 66% of the global HIV-infected population), infection with the virus is a major cause of peripheral neuropathy on the continent. Indeed, depending on factors such as HIV disease stage, the age of patients and the antiretroviral treatment regimens being used, the prevalence of peripheral neuropathy has been reported to be between 20 and 60% in ambulatory African HIV-positive populations. In most cases the neuropathy was reported to be symptomatic, with pain being the primary symptom. In my presentation I will provide an overview of the latest epidemiological data from Africa on HIV-associated sensory neuropathy, focusing on risk factors for developing the neuropathy in the Africa context, and regional differences in neuropathy rate. I will also discuss the neuropathy in the context of changing antiretroviral treatment regimens in Africa, which see the neurotoxic drug stavudine increasingly being phased out as a first-line treatment agent.
POST TRAUMATIC NEUROPATHY

E. Aasvang, Denmark

Traumatic injury including surgical procedures results in persistent sensory disturbances in the majority of patients. Clinically relevant pain is reported by 5-40% of patients depending on the type of surgical procedure, but without a clear relationship to the observed neuropathy. As such sensory disturbances are found in both pain and pain-free operated individuals, with positive phenomena such as allodynia and increased pain from repetitive stimulation mainly occurring in pain-patients. Data from healthy individuals are therefore not appropriate for identifying specific sensory profiles in the understanding of pathogenic mechanisms and treatment. Furthermore, QST studies and sensory mapping show that unilateral traumatic injury results in bilateral sensory changes, suggesting central nervous system neuroplastic changes and questioning the use of the contralateral side as a proper control area when interpreting the role of sensory function in pain. The need for describing sensory disturbances in pain-free individuals will be discussed, and how comparing normative QST data from pain-free operated patients with persistent postsurgical pain patients reveals heterogenic sensory profiles, despite a uniform surgical trauma. This later finding may form the basis for a mechanism based treatment approach.

The discrepancy between the QST focus mainly on cutaneous sensory changes and the patients complaints of pain from deeper structures than skin will be discussed, including the need to develop investigative tools for assessing the role of deep tissue hyperalgesia.
CANNABIS FOR NEUROPATHIC PAIN: ‘CON’

A.S. Rice¹,², UK

Cannabis use for neuropathic pain is unjustified:

- Clinical trials reveal efficacy in neuropathic pain, but specifically only in HIV-associated neuropathy and multiple sclerosis. Cannabis is ineffective in other neuropathic pain conditions (brachial plexus avulsion). Therefore, generic use of cannabis for neuropathic pain cannot be justified.

- Evidence from multiple large studies exists linking a dose-dependent cannabis use and long-term risk of psychosis and schizophrenia, especially in individuals with genetic and other risk factors. The current data supporting efficacy comes from trials which were too short, too small and with insufficiently long follow up to detect such effects. Risk of harm cannot be ignored.

- Cannabis is a widely misused drug. The societal and health dangers of prescribed drug misuse are concerning, especially when the misuse of prescription opioids is considered. The wisdom of marketing a potent, easily administered, form of cannabis is questionable.

- Much medicinal cannabis is taken in the form of smoked cannabis. The health risks of smoking are well known.

Pre-clinical clinical data support the case for cannabinoid analgesia. However, cannabis with its variable multiplicity of psychoactive constituents is not the solution - opium or laudanum are not prescribed for opioid analgesia. We cannot afford another group of potentially useful drugs to be discarded (eg COX2 and CB2) because of insufficient attention to adverse effects. A number of drug development avenues are being pursued, which are intended to divorce the analgesic and psychoactive effects of cannabinoids and thus deliver cannabinoids with an acceptable therapeutic index.
WORKSHOP: SENSORY TESTING IN THE DIAGNOSIS AND CLASSIFICATION OF NEUROPATHIC PAIN NEUROPATHY ASSOCIATED WITH HIV AND LEPROSY

A.S. Rice¹,², UK

About 40% of people living with HIV, whose infection is suppressed by antiretroviral therapy (ART), have a length-dependent distal symmetrical sensory polyneuropathy, in most cases is associated with neuropathic pain. This makes sensory neuropathy one of the most prevalent clinical manifestations of HIV in the current era of combined ART. Sensory neuropathy is usually attributable to either viral-neuronal interactions and/or ART neurotoxicity. We have conducted sensory profiling in HIV+ve patients with and without sensory neuropathy by assessing epidermal innervation density in skin biopsies and using the QST protocol and normal values developed by the German Neuropathic Pain Network (DFNS). These measures distinguished between patients with and without neuropathy, but not between pain and pain-free conditions. The predominant sensory features associated with a sensory neuropathy were loss of epidermal innervation and loss of mechanical and vibration detection thresholds. Sensory gain phenomena were rarely observed. An additional QST measure employed was a temperature-pain intensity response function for heat stimuli, but this did not distinguish between neuropathy from no neuropathy groups.

About 25% of patients with leprosy who have undergone multi-drug therapy are left with neuropathic pain from nerve damage. We have been QST profiling such patients in Mumbai using the German Neuropathic Pain Network protocol. The preliminary analyses to date suggest that loss of thermal and mechanical sensation are the predominant features which distinguished those with and without neuropathy. This study is the first to demonstrate the utility of the DFNS QST protocol in a resource restricted setting.
VALIDITY OF „NEW“ ANIMAL MODELS FOR CHRONIC PAIN

H. Doods, Germany

An important aim of Europain is to refine existing pre-clinical pain models and to establish new models which reflect the clinical disease conditions better. These models should provide a better link to clinical pain states in comparison to the more widely used settings, such as sciatic nerve ligation models of neuropathic pain or complete Freund's adjuvant (CFA)-induced inflammatory pain. Those indeed have only a “symptomatic” but not a “disease” link to important indications, such as diabetic neuropathy and osteoarthritis.

This presentation will focus on three animal models that have been developed and validated as part of Europain Initiative. We compared the pharmacological profile of the traditional Streptozotocin-induced diabetes type 1 model (STZ) to that of bio-breeding/Worcester (BB/WOR) and Zucker diabetes fatty (ZDF) rats where diabetic type 1 and 2, respectively, develop spontaneously. In addition, the anti-retroviral and chemotherapy-induced neuropathy models will be discussed. The development of pain behaviour, drug efficacy as well as initial electrophysiological characterization of these models will be presented.

Acknowledgements

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Currently there is no effective therapy for the prevention or treatment of chemotherapy-induced painful peripheral neuropathies (CIPPN). Furthermore, several analgesics with established efficacy in other painful neuropathies have failed to show any efficacy in double-blind, placebo-controlled RCTs of patients with CIPPN. Therefore understanding the causal mechanisms for CIPPN is essential to enable analgesic development in this area of substantial unmet clinical need. Several reports using rodent models of CIPPN have indicated evidence for mitochondrial dysfunction and reactive oxygen species (ROS) to be contributory factors to this pain syndrome. Our research team at King's College London, is examining the contribution of mitochondrial function before, during and at the resolution of paclitaxel-induced painful peripheral neuropathy to correlate cellular mechanisms to whole animal behaviour. During this talk, I will discuss our latest data on ROS, oxidative phosphorylation and mitochondrial DNA during paclitaxel-induced painful peripheral neuropathy.
HIV-associated sensory neuropathy (HIV-SN) is the most frequent manifestation of HIV disease, affecting about 40% of patients. It is consistently associated with previous exposure to nucleoside reverse transcriptase inhibitors (NRTIs) including stavudine (d4T), which is widely used in resource-limited settings. We investigated complex pain-related behaviours associated with d4T treatment using ethologically relevant thigmotaxis and burrowing behaviours in adult rats. We also examined neuropathological response to d4T treatment. We found complex behavioural changes and a distinctive neuropathology including injury to the central terminals of L5 dorsal root ganglion neurons and a lack of immune response. In summary, we have characterized a clinically relevant rat model of d4T-induced sensory neuropathy that is suitable for further pathophysiological investigation and preclinical evaluation of novel analgesics.

Recent studies show that HIV-SN prevalence does not decline in well-resourced settings where the neurotoxic NRTIs are no longer being used, suggesting other factors may contribute to HIV-SN. Evidence suggests that exposure to indinavir, a protease inhibitor commonly used as a part of the antiretroviral therapy, may be a causal factor for the persisting high prevalence of HIV-SN. We investigated simple reflex pain behaviours and thigmotaxis behaviour following indinavir treatment in adult rats. Indinavir-treated rats developed hindpaw mechanical and cold, but not heat, hypersensitivity, a sensory profile different to that seen in d4T-treated rats. Initial studies revealed increased thigmotaxis behavior following indinavir treatment. Further studies are being carried out to fully characterize the indinavir model.

This study has received support from the IMI Joint Undertaking (No. 115007)
A ROLE FOR ATYPICAL PKCζ/PKMζ IN NMDA-DEPENDENT PERSISTENT SPINAL NOCICEPTIVE PROCESSING?

F. Marchand, R. D'Mello, P.K. Yip, M. Calvo, S. Pezet, A.H. Dickenson, S.B. McMahon, France, UK

Binding of NMDA receptor subunits by the scaffolding protein PSD-95 facilitates downstream intracellular signalling, contributing to synaptic plasticity, which could participate to the manifestation of chronic pain states at spinal level. However, the activation of these various intracellular signalling pathways is not completely understood. Our aim was to study the effect of perturbing the interaction between PSD-95 and NR2B subunits, using a disrupting peptide, Tat-NR2B9c in inflammatory and neuropathic pain models and to better understand the intracellular pathways involved especially the role of the atypical protein kinase, PKCζ/PKMζ. First, we show that perturbing the interaction between PSD-95 and spinal NR2B subunits, using the disrupting peptide, Tat-NR2B9c, reduces wind-up of spinal sensory neurons, as well as formalin-induced neuronal activity and pain-related behaviours. Furthermore, a single intrathecal injection of Tat-NR2B9c in rats with established nerve injury-induced pain attenuates behavioural signs of mechanical and cold hypersensitivity, with no effect on locomotor performance. Importantly, we revealed a novel interaction of NR2B subunits and PSD-95 with atypical PKCζ/PKMζ by immunoprecipitation. Intraplantar formalin caused an increase in phosphorylated PKCζ/PKMζ in dorsal horn neurons which could be prevented by Tat-NR2B9c. In addition, direct inhibition of PKCζ/PKMζ activity reduced formalin-induced pain behaviours, the activity of deep dorsal horn wide dynamic range neurons (WDRs) and upregulation of spinal c-Fos. Thus, we suggest that atypical PKCζ/PKMζ could be a novel pathway of NMDA-dependent persistent spinal nociceptive processing following, at least, an inflammatory injury.
POPULATION STRUCTURE AND GENETIC ASSOCIATION STUDIES IN AFRICAN POPULATIONS

P. Kamerman, South Africa

Population-based designs, using unrelated cases and controls, account for the majority of studies investigating genetic associations in complex diseases. The main advantage population-based designs have over family-based designs is the relative ease of recruiting unrelated participants for the study. However, recruiting unrelated individuals increases the risk of inadvertent population stratification and the reporting of spurious findings (positive and negative). The need to account for population stratification is particularly acute when recruitment takes place in multi-ethnic societies, at multiple study sites, and when meta-analyses are performed.

The problem of population structure has important implications for genetic association studies in Africa. Genetic diversity and population structure are greatest in Africa, and the resulting difference in allele frequency and linkage disequilibrium patterns across African populations provide significant challenges to study design.

In this presentation, I shall cover the problem of population stratification in genetic association studies on pain, and provide an overview of how population stratification can be controlled for. I will also cover issues related to genetic diversity that are pertinent to conducting genetic association studies in populations with African populations.
Amygdala and Prefrontal Cortex Interactions - Emotional and Cognitive Aspects of Pain

V. Neugebauer, USA

The amygdala is generally considered a brain center for emotions. In pain models, synaptic plasticity develops in a network of lateral (LA), basolateral (BLA) and central (CeA) nuclei. The resulting hyperactivity of CeA neurons drives amygdala-dependent pain behaviors such as emotional-affective responses (vocalizations) and anxiety. Hyperactivity of BLA neurons inhibits processing in the medial prefrontal cortex (mPFC) through “feedforward inhibition”, resulting in cognitive deficits such as impaired decision-making. Counteracting abnormal inhibition of mPFC output neurons mitigates cognitive deficits and also inhibits pain behaviors. At least part of this beneficial effect involves cortical inhibition of amygdala neurons, suggesting that strategies to restore cortical control may have therapeutic value.
Although PKMzeta contributes to spinal nociceptive plasticity, the effects of PKMzeta inhibitors in various pain models are inconsistent. We propose that the ability to reduce allodynia by PKMzeta inhibition depends on the degree of peripheral inputs associated with the pain model. We show that intrathecal administration of a PKMzeta inhibitor, (ZIP), is unable to relieve allodynia in animal models of neuropathic pain (CCI; SNI), inflammatory pain (hind paw CFA) or early CRPS-I (CPIP). Conversely, ZIP is able to completely relieve late CPIP allodynia, after peripheral pathology has resolved, as well as referred hind paw allodynia observed after two acidic saline injections to the gastrocnemius muscle in the rat thigh. The prolonged (4-week) referred allodynia normally observed in this latter model is completely reversed by intrathecal ZIP treatment, given 1 day or 1 week after injury. The effects of ZIP are not replicated by intrathecal injection of scrambled-ZIP, or a PKC inhibitor. We also examined the role of the protein interacting with NIMA 1 (PIN-1), a peptidyl-prolyl isomerase that normally inhibits synaptic protein synthesis induced by glutamatergic signaling, in the regulation of PKMzeta. Juglone, an inhibitor of PIN-1, enhances intrathecal NMDA-induced mechanical allodynia, by increasing the activity of PKMzeta. We also examined whether the nociceptive role of spinal PKMzeta depends on enhanced plasma membrane trafficking of AMPA (GluR2) receptors in spinal neurons. Nociceptive stimuli which produce prolonged increases in spinal PKMzeta, also increase membrane-associated GluR2 in spinal cord dorsal horn, and these increases are blocked by spinal intrathecal treatment with ZIP.
BASIC SCI PAIN RESEARCH - WHERE ARE WE?

C. Baastrup, Denmark

Despite advances in our knowledge of mechanisms involved in neuropathic spinal cord injury (SCI) pain, patients continue to suffer from this chronic and disabling type of pain. In our search for new analgesic compounds and for the underlying mechanisms of SCI pain the task of establishing validity of animal models of SCI is essential. This talk will briefly summarize similarities and differences between the available experimental models of rodent SCI and their applicability to study specific SCI pain types.

The practical and methodological challenges related to working with SCI models will be discussed. They include problems in measuring spontaneous pain and the impact of pain on behaviour as well as the relevance of measuring evoked responses and its translation into human SCI pain. One important limitation in the interpretation of results of preclinical SCI pain assessment is related to the use evoked below-level reflex-withdrawals. Since spinal reflexes can be greatly increased, as part of the spastic syndrome, without concomitant pain, the use of thresholds based on evoked withdrawal reflexes of the hindlimb is particularly problematic following SCI. Furthermore, SCI may result in varying degree of motor impairment and a wide range of other injury-related problems that can influence both the performance in pain assessment method and on the interpretations of results (ranging from possible bias due to incomplete blinding to reservation in the interpretation of causality). Progress obtained using SCI models will be highlighted including results with the conditioned place preference, burrowing, and predator avoidance paradigms.
BOTULINUM TOXIN FOR MUSCLE CRAMPS ASSOCIATED WITH DIABETIC NEUROPATHY: A DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY

D.A. Restivo, A. Casabona, R. Spidalieri, D. Gullo, S. Squatrito, R. Vigneri, Italy

Background and aim: muscle cramp is a painful, involuntary, paroxysmal muscle contraction observed in several neurological and metabolic diseases other than in a number of physiological conditions including muscle fatigue, pregnancy, and in elderly. The association of muscle cramps with diabetes mellitus (DM), as well as with diabetic peripheral neuropathy, has been known for several years.

No pharmacological treatment has shown to provide adequate relief in reducing cramp-associated pain. Botulinum toxin type A (BoNT/A) has demonstrated to be effective in reducing cramp frequency and severity in patients with benign cramp-fasciculations syndrome.

The aim of the present study was to evaluate the effect of BoNT/A in reducing the severity and the frequency of occurrences of cramps in patients with diabetic neuropathy.

Patients and methods: In this double-blind, randomized trial, thirty patients with diabetic neuropathy and frequent leg cramps underwent BoNT/A injections (N=15) or normal saline (N=15).

Primary outcome: variation in the mean intensity of cramping pain (on a scale from 0 to 10). Secondary outcomes: variations in the number of occurrences; variations in the electrophysiologically measured Cramp Threshold Frequency (CTF); variations in the Cramp Severity Scale (CSS). Patients were evaluated before, and at week 1, 4, 8, 12, 16, 20 after injections.

Results: all the outcome measures showed significant changes in the treated group as compared with placebo. The effect appeared at week 1, and persisted until week 16, disappearing at week 20.

Conclusions: BoNT/A can be a safe and promising treatment for painful cramps associated with diabetic neuropathy.
The locus coeruleus (LC) is a relevant structure in both ascending and descending pain transmission but it is also regarded as part of central "stress circuitry" involved in the pathophysiology of depression and anxiety disorders, as the primary source of noradrenaline to the prefrontal cortex. Our studies, in rats subjected to chronic constriction injury (CCI), have shown that neuropathic pain at early stages does not modify tonic electrophysiological LC activity but disrupts LC-evoked responses to noxious stimuli. Furthermore, antidepressants with antineuropathic effects restored LC-evoked activity in parallel with their behavioral analgesic effects. On the other hand, we have shown that long-term neuropathic pain lead to anxio-depressive-like behaviors. Interestingly, the onset of these behavioral changes coincided with the irruption of noradrenergic tonic dysfunction, evident as: an increase in LC bursting activity; in tyrosine hydroxylase expression and that of the noradrenaline transporter; and enhanced expression and sensitivity of alpha2-adrenoceptors in the LC. Antidepressant treatment produced an increase in sensory pain threshold and reduced the depressive-like behaviours. However, the onset of antidepressant treatment was critical to alleviate anxiety. Antidepressants-mediated behavioural changes coincided with a recovery of noradrenergic dysfunction of LC. These results suggest that LC is involved in sensorial modulation at the beginning of the neuropathy but after a period, it is also involved in mood disorders related with pain. Antidepressants promoted an improvement of sensory but also affective dimensions of neuropathic pain acting through the LC.
CENTRAL POST STROKE PAIN: EPIDEMIOLOGY, CLINICAL CHARACTERISTICS AND DIAGNOSTIC CHALLENGES

H. Klit, Denmark

Approximately one third of stroke survivors develop post stroke pain. Post stroke pain can be of either musculoskeletal or neuropathic origin, e.g. shoulder pain and central post stroke pain (CPSP). In some patients, several pain conditions may be present concomitantly.

CPSP is a central neuropathic pain condition caused by a vascular lesion of the central nervous system. There are no pathognomonic symptoms or signs of CPSP, but CPSP is characterized by pain within the area of sensory abnormalities in the parts of the body that correspond to the brain territory that was injured by the stroke. In population-based studies, the prevalence of CPSP is 7-8%. The reported intensity of pain varies, and pain may be either constant or intermittent, and spontaneous or evoked. Findings of hyperalgesia, allodynia and dysesthesia are common on clinical sensory examination of CPSP patients. Lesions in any part of the somatosensory pathways can cause CPSP. The underlying pathophysiological mechanisms behind CPSP are not known, but there is indication of a central role of the thalamus. Other possible mechanisms include altered activity in the spinothalamic tracts, deafferentiation, disinhibition, sensitization, and plastic changes.

Since there are no defining symptoms or signs that can identify CPSP, it can sometimes be difficult to delineate CPSP from other post stroke pain conditions. At present, the diagnosis is based on the history and clinical sensory findings. Body charts indicating painful areas, QST, and screening tools for neuropathic pain may also be useful.
The analgesic efficacy of antidepressants comes from their ability to inhibit pre-synaptic monoamine reuptake. The monoamine hypothesis is based on the presence of descending pathways originating in midbrain and brainstem areas capable to modulate spinal pain processing, and on the presence of adrenoceptors and serotonin receptors within the spinal cord. Additional actions of antidepressants coming from preclinical studies have been proposed: blockade of sodium channels, adenosine receptor activation, opioid system activation, enhanced GABAergic neurotransmission.

We focus on the facilitatory/inhibitory effects of spinal serotonin (5-HT) receptor activation and the involvement of the opioidergic system in the analgesic effect of antidepressants. The activation of multiple 5-HT receptors in the central nervous system and/or the decreased responsiveness of some of them and/or an opioidergic mechanism could be responsible for the unpredictable analgesic effect of antidepressants and their limited effectiveness in neuropathic pain.

We report that a differential involvement of the opioidergic system could account for a differential efficacy between antidepressants. We tackle the controversial effects of spinal 5-HT₁A/5-HT₂A/5-HT₃ receptors involved in the action of dual noradrenaline serotonin antidepressants. In addition, we summarize a series of experiments aimed to understand the resistance to SSRI-mediated analgesic action in painful neuropathy and particularly how can the increase responsiveness of 5-HT₂A receptors enhance the analgesic efficacy of SSRI but also NSRI.

These data support the need for criteria mechanism-based choice of antidepressants for neuropathic pain, and the interest of combining antidepressants and drugs increasing the inhibitory aspect of 5-HT to enhance their analgesic effect.
Placebo analgesia effects have primarily been investigated in relation to experimental pain, acute pain or chronic pain such as irritable bowel syndrome where the underlying pathology is unclear. Recently, however, it has been shown that placebo analgesia effects can be obtained in relation to neuropathic pain conditions with a known nerve injury. In patients developing chronic pain following thoracotomy, placebo manipulations of open versus hidden administrations of lidocaine reduced the area of pin-prick hyperalgesia (P=0.027) and this placebo effect was significantly related to low levels of negative affect (P= 0.008, R² = 0.362). Factors contributing to placebo effects in hyperalgesic states will be reviewed and possible similarities and differences in the underlying mechanisms of anti-nociceptive and anti-hyperalgesic placebo effects will be discussed. Based on these studies it will be illustrated how knowledge from experimental placebo studies may be used to improve the understanding of the pain relief following placebo administration in clinical trials. Finally, it will be touched upon to which extent placebo effects and drug effects are additive in clinical trials.
RELIABILITY INDICES, LIMITS OF AGREEMENT AND CONSTRUCT VALIDITY OF CURRENT PERCEPTION THRESHOLD TEST IN NONSPECIFIC NECK PAIN

Z. Uddin, J. MacDermid, V. Galea, A. Gross, M. Pierrynowski, *Canada*

**Background and aims:** Nonspecific Neck Pain (NSNP) is a common musculoskeletal disorder, and neurological impairments may exist in a subset of patients. These may be detected by sensory detection responses like Current Perception Threshold (CPT) testing, but there is inadequate evidence on the clinical measurement properties of CPT testing in NSNP. Aims are to evaluate the reliability and validity of CPT tests in patients with NSNP.

**Methods:** Patients with NSNP (N=106) were recruited after a standardized physical assessment. The rapid-CPT protocol was performed at three frequencies (5, 250, 2000 Hz) using 3 dermatomal locations on the hand. A subset of patients (N=34) was reassessed at a second visit to determine the test-retest reliability. For inter-trial reliability the fingertip of both hands were assessed. Internal consistencies of CPT between frequencies were calculated from CPT test scores in the most affected hand. Construct validity of CPT was evaluated by correlating the 3 composite scores derived from the CPT tests with the Neck Disability Index (NDI) and Cervical Spine Outcomes Questionnaire (COSQ).

**Results:** Inter-trial reliability was good to excellent (ICC=0.73-0.82, p< 0.001). Internal consistency was satisfactory (α =0.84-0.90, p< 0.001). Test-retest reliability of CPT scores was excellent (ICC =0.76-0.84, p< 0.001). The mean retest difference and the 95% limits of agreement were: -0.3±3 (in 2000Hz and 250Hz), and 0.1±3.9 (in 5Hz). A small to medium-sized correlation was found between CPT and NDI or COSQ (r =0.21-0.37).

**Conclusions:** CPT was consistent across occasions; and was associated with neck disability.
The prevalence of neuropathic pain among leprosy patients is probably underestimated; so far only a few studies have addressed it. In a cross-sectional study from Ethiopia, neuropathic pain was found in 29% of a cohort of patients who had completed multi-drug therapy more than 10 years earlier. In an Indian study, 21% of treated leprosy patients had pain with neuropathic characteristics, indicating that it is almost as prevalent as painful diabetic neuropathy in India. A Brazilian cross-sectional study reported a 56% prevalence of neuropathic pain in a cohort of 358 newly presenting patients from a referral centre. According to a study from Ethiopia, in recently treated leprosy patients pure nociceptive pain seems to be more common than neuropathic pain and the pain profile seems to change to dominance of neuropathic pain in the long run.

Pathogenesis of neuropathic pain in leprosy is still unclear. Previous history of immune-mediated reactions and chronic inflammation induced hyperexcitability are clearly significant risk factors for the development of chronic neuropathic pain. An association with nerve tenderness and neuropathic pain has been shown, indicating that in some patients inflammation may still be ongoing in nerves despite the treatment. It is possible that neuropathic pain could be prevented if the nerve damage were diagnosed at an early stage and appropriate treatment started. Correlation has also been shown between neuropathic pain and psychological morbidity, especially depression, in patients with leprosy.
COLD AND MECHANICAL PINPRICK EVOKED POTENTIALS AS CLINICAL TOOLS TO STUDY SPECIFIC SUBTYPES OF THERMORECEPTIVE / NOCICEPTIVE PATHWAYS
U. Baumgärtner, Germany

Perception of pricking pain and of non-painful cold stimuli plays an important role in quantitative sensory testing (QST). Since QST depends on active participation of the patient, objective tests for A-delta-fiber function are also needed. Whereas laser-evoked potentials (LEP) have been validated as objective test to assess the pathways mediating pricking pain, typically indicating a lesion by findings of delayed responses and/or reduced amplitudes, no such test exists for the thermoreceptive pathways for cooling. Changes in cool- and cold detection are sensitive signs in the detection of radicular involvement in the context of low-back pain. Furthermore, cold-evoked pain and cold allodynia are frequent signs in patients suffering from peripheral or central neuropathic pain. Another well-known example for induction of pain sensations by non-noxious cooling stimulation are the paradoxical heat sensations that are frequently observed in multiple-sclerosis patients. Further, an objective test for plus-symptoms like mechanical hyperalgesia and allodynia that may accompany ongoing neuropathic pain has not been available so far. In a preliminary report, the type of pinprick stimulation, which is part of the standardized QST protocol, yielded reproducible vertex responses (pinprick-EP) in healthy volunteers that were increased in amplitude after experimental induction of secondary hyperalgesia. In this presentation, methodology and first experimental findings using cool-EP and pinprick-EP in healthy volunteers as well as in patients will be demonstrated and discussed.
**K-431, A NOVEL α2Δ LIGAND, AMELIORATED EXPERIMENTAL NEUROPATHIC PAIN WITHOUT CNS SIDE EFFECTS**

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**Background and aims:** Gabapentinoids (gabapentin and pregabalin) known as α2δ ligands, are first line drugs for the treatment of neuropathic pain, but their efficacy is partial and they have various CNS side effects (dizziness, somnolence, etc) that could not be fully avoided by dosage titration. K-431, a novel α2δ ligand, originally synthesized in our laboratory, and the chemical structure of K-431 is quiet different from gabapentinoids. The aim of this study is to investigate the analgesic efficacy and CNS side effects of K-431.

**Method:** The affinity of K-431 for α2δ subunit in rat and human was determined in a radioligand (3H-gabapentin) binding assay. K-431 was assessed in the models of neuropathic pain (sciatic nerve injury, diabetes, capsaicin models). The CNS side effects in vivo were examined by rotarod and pentobarbital-induced sleep time tests.

**Results:** K-431 and gabapentin indicated the binding affinity for α2δ subunits and the affinity of K-431 was higher than that of gabapentin. Gabapentin (30-300 mg/kg p.o.) partially ameliorated mechanical allodynia in sciatic nerve injury model and induced CNS side effects (rotarod impairment and increase of pentobarbital-induced sleep time) at the anti-allodynic doses. In contrast, oral administration of K-431 at doses of 0.3-1 mg/kg fully ameliorated mechanical allodynia in various models of neuropathic pain (sciatic nerve injury, diabetic neuropathy and capsacin models) without CNS side effects at doses up to 100 mg/kg.

**Conclusion:** K-431 may be a candidate of the novel therapeutic agent for treatment of neuropathic pain.
NOVEL MECHANISM OF AMITRIPTYLINE: BLOCKADE OF NA\textsubscript{v}1.8 CURRENTS IN NOCICEPTIVE TRIGEMINAL NEURONS AND INHIBITION OF TRIGEMINOVASCULAR NOCICEPTION

S. Yu, China

Amitriptyline (AMI), a tricyclic antidepressant, has been widely used to prevent the attack of migraine and alleviate other various chronic pain, but its exact mechanism of action remains unclear. Accumulated evidence suggested that such efficacy may due to blockade of voltage-gated sodium channels (VGSCs). The aim of the present study was to investigate the effect of AMI on tetrodotoxin-resistant (TTX-r) sodium channel Na\textsubscript{v}1.8 currents in nociceptive trigeminal neurons and trigeminovascular nociception induced by electrical stimulation of the dura mater surrounding the superior sagittal sinus (SSS) in rat, used as an animal model of vascular headaches such as migraine. Using whole-cell voltage recording technique, this study showed that Na\textsubscript{v}1.8 currents were blocked by AMI in a concentration-dependent manner with IC\textsubscript{50} value of 6.82 µM (holding potential of −50 mV) in cultured trigeminal ganglion (TG) neurons of the rats. AMI (5 µM) also caused a hyperpolarizing shift in voltage-dependence of activation and steady-state inactivation, and significantly blocked in use-dependent manner (60 pulses at 1 Hz) and slowed the recovery from inactivation of Na\textsubscript{v}1.8 currents. In addition, systemic administration of AMI and A-803467 (a selective blocker of the Na\textsubscript{v}1.8 sodium channel) potently alleviated nociceptive behaviors (head flicks and grooming) induced by electrical stimulation of the dura mater surrounding the SSS, respectively. Taken together, the results suggested that Na\textsubscript{v}1.8 currents in nociceptive trigeminal neurons were blocked by AMI through modulating activation and inactivation kinetics and these actions may be contribute to its anti-nociceptive effect in animal model of migraine.
GUGGULIPID OF COMMIPHORA MUKUL, WITH ANTIALLODYNIC AND ANTIHYPERTHERALSIC ACTIVITIES IN BOTH SCIATIC NERVE AND SPINAL NERVE LIGATION MODELS OF NEUROPATHIC PAIN

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Background and aim: Treatment of neuropathic pain, triggered by multiple insults to the nervous system, is a clinical challenge because the underlying mechanisms of neuropathic pain development remain poorly understood. The present study was undertaken to assess the antiallodynic and antihyperalgesic activities of guggulipid in rats.

Methods: The screening study included chronic constriction injury (CCI) and L5-L6 spinal nerve ligation (SNL) models of neuropathic pain. Guggulipid (100 & 50 mg/kg) or saline was administered intraperitoneally in a blinded, randomized manner from postoperative day (POD) 7 to 13. Paw withdrawal duration (PWD) to spontaneous pain, chemical allodynia and mechanical hyperalgesia and paw withdrawal latency (PWL) to mechanical allodynia and thermal hyperalgesia were tested before surgery, before and after guggulipid or saline administration (from POD7 to 13) and after withdrawal of treatment (from PODs14 to 20).

Results: The activity profiles of the different doses of guggulipid were found to vary with time. In CCI rats, both doses of guggulipid (100 & 50 mg/kg) were found to be effective in reversing the spontaneous pain, mechanical allodynia and mechanical and thermal hyperalgesia responses. In SNL rats, both doses of guggulipid (100 & 50 mg/kg) were found to be ineffective in reversing the spontaneous pain but showing antiallodynic and antihyperalgesic activity.

Conclusion: The results demonstrated that the guggulipid produce antinociception in the peripheral nerve injury (CCI and SNL) models of neuropathic pain. The underlying mechanisms are expected to be modulating the microglial activation occurs due to the peripheral nerve injury.
WHICH QST ASSESSMENTS ARE MOST USEFUL FOR CLINICAL PRACTICE?

R. Rolke, Germany

A neuropathic pain component can be suggested, if damage to the somatosensory system occurs with pain as a direct result of that lesion. Depending on the neurobiological pain mechanisms in action different sensory symptoms may develop. Peripheral sensitization of the nociceptive system, e.g. due to an inflammatory reaction will be indirectly reflected by localized hyperalgesia to heat and blunt pressure. In contrast, central sensitization leads to pinprick hyperalgesia and/or dynamic mechanical allodynia in the affected area. Deafferentation due to neuronal damage is reflected by a decreased sensitivity to all types of thermal or mechanical non-painful or painful stimuli.

Using the IASP grading system for neuropathic pain (Treede et al., 2008) it is possible to define a neuropathic pain syndrome. According to IASP criterion 3 quantitative sensory testing can be used as a confirmatory test to assess positive and negative sensory signs. An overlap of the spatial distribution of these signs and a neuroanatomically plausible painful area needs to be demonstrated to diagnose a neuropathic pain syndrome. Thermal and mechanical detection thresholds followed by mechanical pain thresholds are the most useful QST parameters here.

According to IASP criterion 4 other objective testing procedures such as MRI, CT, neuropgraphy or SEPs, LEPs may lead to the diagnosis of a definite neuropathic pain syndrome.

Quantitative sensory testing (QST) may allow testing for the presence of positive and negative sensory signs such as hypoesthesia, hyperalgesia and allodynia. Especially, the cold and warm detection thresholds can be used to non-invasively investigate small fiber sensory function. However, it remains unclear, whether the increase of these thermal detection thresholds corresponds with a decreased small fiber performance or even loss of these fibers. In selected cases skin punch biopsies may be obtained in order to validate the presence and density of intraepidermal nerve fibers against QST thermal detection thresholds.

While QST can be applied easily in larger patient cohorts across all possible types of peripheral neuropathic pain, skin biopsies should be considered more carefully. For example, the investigation of patients with diabetic painful neuropathy using skin biopsies at foot level are at higher risk for the development of skin ulcers or infections compared to other neuropathy syndromes. Hence, sensory phenotyping using QST is more feasible in larger patient cohorts. Skin biopsies play a major role in objectively testing small fiber function, where more sophisticated measures such as laser evoked potentials are not available.
A STEM CELL TREATMENT FOR DIABETIC PERIPHERAL NEUROPATHY (DPN)

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Background: DPN is the most frequently observed serious and chronic complication of diabetes. A decrease in the level of neurotrophic factors (eg. IGF-I) contributes to the pathogenesis of DPN. Insulin activity loss produces a secondary partial decrease in IGF-I activity, contributing to DPN. Gene expression levels of both IGF-I and IGF-II are reduced in diabetic nerves with associated neuropathy. Systemic IGF-I injections in animal models of diabetes with associated DPN minimize the effects of DPN and provide neuroprotection. We recently isolated a unique pluripotent stem cell from the neural crest (NCSC). Aim: Characterize our novel stem cell population for the expression, production, and secretion of IGF-I.

Methods: Quantitative PCR was used to compare IGF-I levels in NCSC vs. commercially available mesenchymal stem cells (MSCs) over a time series of 7 days. Immunohistochemistry was used to determine NCSC IGF-I production. ELISA assays were used to quantify IGF-I secretion from NCSC and MSCs.

Results: Our novel NCSC express much higher levels of IGF-I than commercially available MSCs. Immunohistochemistry confirmed IGF-I production by NCSC. The ELISA assay demonstrated IGF-I secretion of MSCs and NCSC at about the same level which may be due to the concentration reaching a limit in the culture media.

Conclusion: NCSC express, produce, and secrete IGF-I, a key neurotrophic factor in the maintenance of nerve structural integrity and protection against DPN. Inherently possessing characteristics of neural cells, NCSC are an excellent cell source to treat diabetic peripheral neuropathy.
PREVALENCE AND CHARACTERIZATION OF PAIN IN DIABETIC PATIENTS

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Background and aims: Pain is an unpleasant experience that can be an unfortunate reality in a diabetic patient’s daily life. A study conducted in 2012 by Dr. Maria Clara Kreling and student nurses Ligyana Candido and Natanna Leal provided new knowledge on pain in diabetes mellitus patients. The objective of this study was to first identify the prevalence of pain in the diabetic patient, characterize the pain (neuropathic or non-neuropathic), explore the impact of pain on daily life and identify health promotion and prevention strategies for the control of pain.

Methods: This is a mixed method study that utilized a cross-sectional, descriptive approach involving 50 diabetes mellitus patients who were seen in the Ambulatory Centre of the Clinical Hospital in the State University of Londrina, Brazil. All participants were interviewed once and asked to complete a validated Questionnaire for Neuropathic Pain Diagnosis (DN4) instrument.

Results: The study findings revealed that 42% of persons with diabetes mellitus experienced pain. Of the population experiencing pain, 76.1% rated their pain as non-neuropathic pain and 23.8% as neuropathic pain. It was observed that pain did impact the patient’s daily life and that non-pharmacological treatments were the most prevalent strategies used by persons with diabetes in treating their own pain.

Conclusions: The results from this study reinforce the importance of early, ongoing pain assessment in diabetic patients that will inform the creation of both a systematic and individualized plan of care that will minimize a person living with diabetes’ suffering that is the result of pain.
EXPLORING THE BIOMEDICAL WORLD OF NEUROPATHIC PAIN THROUGH MOLECULAR INTERACTIONS

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Background: Research into the underlying molecular mechanisms involved in chronic neuropathic pain remains a top priority for enabling novel therapeutics for a disease that affects up to 8% of the European population. However, there are no databases of pain specific molecular interactions to facilitate this. We have recently reported the first extensive database of pain related molecular interactions semi-automatically extracted from the entire pain literature collection (wiki-pain.org). The database was constructed to explore all molecular interactions associated with pain as well as explicit contexts (anatomy, mutations, diseases etc.) and sub-categories within pain. Here we explore the molecular interactions associated specifically with neuropathic pain.

Methods: From our database of pain related molecular interactions we found 1,407 that were associated with neuropathic pain, involved human, mouse or rat proteins and were non self-interactions. In previous studies we had already checked 271 of these for accuracy and we curated a further 229 to create a dataset of 500 molecular interactions.

Results: We have built a network of molecular interactions specifically associated with neuropathic pain. We highlight the most connected proteins and have compared the key proteins involved in these molecular interactions with other pain-related diseases. We have also analyzed the distinct anatomical regions associated and highlighted any significant variations in interactions between different regions.

Conclusions: We have created the first neuropathic pain specific dataset of molecular interactions derived from all of the available literature. Our analysis of these provides new insights into the overall molecular mechanisms involved in neuropathic pain.
ENDOGENOUS INHIBITORY RESPONSES IN RATS CHANGE WHEN CHRONIC PAIN SETS IN: EVIDENCE OF INITIAL COMPENSATION AND SUBSEQUENT EXTINCTION

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Background and aim: As chronic pain sets in, physiological responses to persistent pain challenges, such as the formalin test, might be altered, providing important clues to the development of chronic pain and to its neurobiological underpinnings. In order to better understand the pathological changes associated with the development of chronic neuropathic pain in male SD rats, the formalin test was performed 12, 28 and 90 days after induction of chronic pain.

Methods: The chronic constriction injury (CCI) model was used to induce chronic neuropathic pain. To confirm the presence of pain, mechanical allodynia was measured at fixed intervals with the dynamic von Frey filament. At each endpoint (12, 28 or 90 days post-pain induction), responses to persistent pain were evaluated by injecting 50 µl of formalin 5% in the plantar surface of the contralateral hind paw in sham and CCI animals.

Results: We observed a 21% decrease (in overall AUC, p< 0.05) in pain-associated behaviors during the 60-min testing period (acute phase, interphase and inflammatory phase), 12 days after pain induction. In addition, a surprising 55% decrease (p< 0.001) in these behaviors was highlighted on day 28. However, this trend seems to be reversed on day 90, since an increase in pain-associated behaviors is observed when compared to day 28.

Conclusions: Our data reinforce the idea that development of chronic neuropathic pain is triggered by pathological changes in central nociceptive processing, such as an early but transitory hyperactivation of endogenous pain inhibitory mechanisms and/or by a temporary central desensitization.
A SELECTIVE NAV1.7 CHANNEL ANTAGONIST ATTENUATES NEUROTRANSMISSION IN SENSORY NERVES AND SUPPRESSES NOCIFENSIVE BEHAVIORS IN PRECLINICAL MODELS OF PAIN

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Background: The discovery that gain- and loss-of-function mutations in the voltage-gated sodium channel subtype Nav1.7 (SCN9A) give rise to inherited painful neuropathies and insensitivity to pain, respectively, has suggested that selective blockers of this channel may be a novel therapeutic approach for chronic pain. The present studies explored this hypothesis using a recently disclosed Nav1.7 antagonist (Patent#WO2010079443, example#801, Compound A) in several preclinical models of pain.

Results: Electrophysiology studies demonstrated that Compound A is a potent, voltage-dependent antagonist of recombinant human (IC\textsubscript{50}=1.3nM), mouse (IC\textsubscript{50}=3.1nM) and rat (IC\textsubscript{50}=90nM) Nav1.7 channels, and selective vs hNav1.5 (IC\textsubscript{50}=6.5uM) and mouse/rat DRG TTXr channels (IC\textsubscript{50}>10uM) (though hNav1.2 IC\textsubscript{50}=5.7nM). The potency of Compound A was not changed by mutations in the local anesthetic binding site of hNav1.7, suggesting a novel site of action that may confer its favorable selectivity profile. Compound A blocked native mouse Nav1.7 in DRG neurons (IC\textsubscript{50}=1.7nM), reduced compound action potentials in mouse sciatic nerve (IC\textsubscript{50}=8nM), suppressed veratridine-evoked CGRP release from rat spinal cord slices (IC\textsubscript{50}=78nM) and attenuated rat spinal WDR neuron “wind-up” when applied locally (0.1-10uM) in vivo. Pharmacokinetic studies in mice (10mg/kg, s.c.) revealed low unbound plasma (88nM) and sciatic nerve (5nM) concentrations and undetectable levels in spinal cord. Compound A reversed nocifensive behavior in mouse veratridine-induced paw flinching and formalin models of acute sensitization pain, and tactile hypersensitivity in the CCI model of neuropathic pain in the absence of motor impairment.

Conclusions: Collectively, these results demonstrate that a Nav1.7 antagonist can attenuate nociceptive neurotransmission and behavior in preclinical studies.
A PRECLINICAL MODEL OF ADVANCED OSTEOARTHRITIS PAIN: POSSIBLE NEUROPATHIC COMPONENTS

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Background and aims: We recently developed a rat model of advanced OA pain wherein a high dose of monoiodoacetate (MIA) is injected into the knee joint. Ongoing pain was revealed by conditioned place preference (CPP) to intra-articular lidocaine. Systemic diclofenac did not affect lidocaine-induced CPP suggesting advanced, NSAID resistant OA pain that may have a neuropathic component. We assessed whether duloxetine, an SNRI used to manage neuropathic pain, blocks MIA-induced ongoing pain, weight asymmetry and evoked hypersensitivity.

Methods: Rats received intra-articular injection of a high dose (4.8 mg) of MIA. After 14 days, systemic duloxetine (30 mg/kg, i.p.) or saline was given followed 30 min later by intra-articular lidocaine to establish CPP; effects of systemic duloxetine on weight bearing asymmetry were also determined. Non-noxious palpation induced spinal c-FOS expression was measured in low (3.0 mg) and high (4.8 mg)-dose MIA treated rats.

Results: Systemic pretreatment with duloxetine prevented CPP from intra-articular lidocaine in MIA rats. Duloxetine additionally normalized weight-bearing asymmetry. Non-noxious palpation selectively induced the expression of spinal FOS in rats with high, but not low, dose MIA.

Conclusions: Duloxetine blocked NSAID-resistant, MIA-induced ongoing joint pain. This result supports a potential neuropathic pain component underlying persistent, ongoing OA pain and may be relevant to OA patients with severe NSAID-resistant OA pain. These data also support the hypothesis that central sensitization develops in rats with advanced OA pain.
SENSORY ASSESSMENT OF POST-DENTAL IMPLANT NEUROPATHY

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Background and aims: One of the more common complications related to dental implant placement is neuropathy; this can occur due to direct trauma to the branches to the Trigeminal nerve, however, often, neuropathy develops without detectable direct trauma to the nerve. The underlying mechanisms are not clear, and little is known about diagnosis and treatment of dental implant neuropathy. The aim of this study was to evaluate the sensory changes in patients suffering from dental implant neuropathy and healthy controls employing quantitative sensory testing.

Methods: Electrical (Nervscan NS3000) and heat stimuli (Medoc TSA -2001) were used for extra oral testing. Cold and mechanical stimuli were used for intraoral testing. A cooled cotton swab was placed in contact with the gingiva in the affected and contralateral areas for 3 seconds; the stimulus intensity and duration were recorded. The mechanical detection threshold was assessed with a von Frey monofilament.

Results: Eleven neuropathy patients and eighteen healthy controls were included in the study. The extra oral thermal and electrical thresholds of the neuropathy group were not different from the controls. Hypersensitivity to mechanical and cold stimulation was detected in the affected area. The cold sensation duration following the cold stimulus application (after sensation) was significantly increased in the neuropathy group (68.3 ±17.1 seconds), compared to the control group (30.6±4.8 seconds).

Conclusions: Dental implant neuropathy patients demonstrate localized sensory alteration. The prolonged cold after sensation, suggests central involvement. Cold test may be used clinically for intra oral dental implant neuropathy.
NEUROPATHIC PAIN AND DEPRESSION CAUSES SIMILAR BRAIN CHANGES IN ANIMAL MODELS

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Background: Many patients with neuropathic pain show depressive symptoms and many depressive patients end up suffering chronic pain. However, little is known about the anatomical and molecular basis linking both pathologies.

Methods: In the present study, we have used a rat model of neuropathic pain (chronic constriction injury, CCI) and a rat like-depression model (chronic mild stress, CMS) to test volume changes in brain structures by MRI. In addition, Bromodeoxyuridine (BrdU) incorporation and immunohistochemistry were performed to determine changes in the neurogenesis of these animals.

Results: The analysis of varianza (ANOVA) of ROIs revealed that the volume of frontal cortex and hippocampus was significantly lower in CCI and CMS groups compared to controls (p< 0.001). The number of doublecortin positive cells (neuroblasts) and BrdU + cells (proliferative cells) were significantly lower in CCI and CMS groups.

Conclusions: Rat models of neuropathic pain and depression caused similar structural changes in specific brain regions (hippocampus). Both models produce an inhibitory effect on the proliferation of new neurons in these areas.

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SEPARABLE MECHANISMS OF MECHANICAL AND THERMAL HYPERALGESIA IN A HIGH CONCENTRATION CAPSAICIN HEAT PAIN MODEL

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Introduction: Topical capsaicin application evokes spontaneous pain, hyperalgesia and allodynia, resembling phenomena observed in neuropathic pain patients. The theory that different neural mechanisms underlie different types of hyperalgesia prompted this study's hypotheses that mechanical and thermal hyperalgesia would have minimal correlation using a capsaicin pain model.

Methods: Thirty-eight participants received a 10% capsaicin cream on the calf, with subsequently applied heat (37° to 42°C) for 20 minutes. Participants rated pain on a 0-100 numerical rating scale (NRS) every minute during this capsaicin+heat pain exposure, generating our measure of heat hyperalgesia (HPhyper). Mechanical hyperalgesia was measured as 1) ratings (0-100 NRS) of pin prick pain using a 256 mN probe 10 and 25 minutes after capsaicin removal (MP256@10 and MP256@25), and 2) the area of pain sensation evoked by a 128 mN probe surrounding the capsaicin exposure site at the same time points (AreaPPH@10 and AreaPPH@25).

Results: There was a marginally significant correlation between HPhyper and MP256@10 ($r^2=0.362$, $p=0.03$), but not between HPhyper and any other mechanical hyperalgesia measure (all $p>0.15$). While the magnitude of mechanical hyperalgesia at 25 minutes was significantly correlated with the area of hyperalgesia at both time points (PPHArea@10: $r^2=0.454$, $p=0.009$; PPHArea@25: $r^2=0.478$, $p=0.007$), the magnitude of mechanical hyperalgesia at 10 minutes was not (both $p>0.15$).

Conclusions: The pattern of correlations suggests largely separate mechanisms underlying heat and mechanical hyperalgesia. Differences in the magnitude and the area of mechanical hyperalgesia correlations suggest different mechanisms operate for these two aspects of mechanical hyperalgesia at different times.
PREVIOUS PHARMACOLOGICAL TREATMENT IN PATIENTS RANDOMIZED IN A CLINICAL TRIAL ON COMBINATION THERAPY IN NEUROPATHIC PAIN

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Background and aims: Patients recruited for pharmacological trials in neuropathic pain have often been treated with drugs previously. The extent and impact on current pain intensity is unknown and was analysed in current trial.

Methods: Before randomizations in combination trial of tricyclic antidepressant and gabapentinoid for painful polyneuropathy the patients were asked to recall previous treatments and rated their off treatment average daily pain on a 0-10 point numeric rating scale.

Results: 73 patients qualified for the analysis. Aetiology of polyneuropathy was diabetes 22%, alcohol overuse 17%, neurotoxic drugs 10% and other known causes 13 %, whereas cause was unknown in the remainder. Mean age was 59 years and mean duration of pain 63 months.

12 patients had never had pharmacological treatment. The 61 patients with prior treatment had tried 1 drug (n = 31), 2 drugs (n = 22), or 3 or more drugs (n = 8). The off treatment average daily pain score was higher in previously treated (mean = 6.65) than in drug naive (mean = 5.36) patients (p< 0.011).

The drug previously used were tricyclic antidepressants (n = 37), selective serotonin reuptake-inhibitors (n = 5), serotonin noradrenaline reuptake-inhibitors (n = 4), gabapentinoid (n = 37), other anticonvulsants (n = 7), opioids or tramadol (n = 11), NSAIDs (n = 5), and paracetamol (n = 7).

Conclusions: Most patients randomized in a trial of neuropathic pain medication had tried one or more drugs prior to participation, and previously treated patients had more pain than drug naive patients.
Background: The cutaneus trunci muscle (CTM) reflex produces a “skin shrug” in response to pinch on a rat's back, and is mediated by a three neuron circuit: 1) A-delta and C fiber afferents in segmental dorsal cutaneous nerves (DCNs), 2) ascending propriospinal interneurons, and 3) the CTM motoneuron pool. The reflex is bilateral but asymmetric with a larger reflex response with ipsilateral stimulation.

Methods: Electrophysiological recordings were made in 4 groups (n=8) of female Long Evans rats: uninjured controls and animals 1, 3, and 6 weeks after T10 spinal cord hemisection contralateral to the CTM neurogram recording site. The reflex was recorded from a CTM nerve branch in response to electrical stimulation of individual DCNs (L01, T12, T08, and T06) ipsilateral and contralateral to the recording site (contralateral and ipsilateral to the hemisection) with 5mA at 1Hz for 20s and 5Hz for 10s. Both early (A-delta) and late (C fiber) responses were analyzed.

Results: Changes, most often increases, in DCN stimulation evoked CTM reflexes were observed on both the side of the hemisection and on the uninjured side as well as from both above and below the level of injury. This was true for both A-delta and C fiber evoked responses.

Conclusions: Complex nociceptive hypereflexia can be demonstrated in this intersegmental cutaneous reflex after spinal cord injury, raising the possibility that it could serve as an animal model for aspects of human neuropathic pain after SCI, at least the altered processing of noxious stimuli by the injured spinal cord.
CHLORIDE DYSREGULATION COMPROMISES THE ABILITY OF FEEDFORWARD INHIBITION TO REGULATE SPIKE TIMING

A. Khubieh¹², S. Prescott³⁴, Canada, Switzerland

Introduction: Disinhibition through chloride dysregulation occurs in many disease states including neuropathic pain. It is often caused by reduced expression or function of the potassium-chloride co-transporter KCC2. Inhibition plays a crucial role in many aspects of neural coding; for example, feedforward inhibition (FFI) restricts the time window over which excitatory input is integrated, thereby regulating spike timing and the transmission of synchronous spiking.

Objectives: We sought to test how different levels of chloride dysregulation affects FFI, specifically with respect to its role in regulating spiking timing and synchrony transfer.

Methods: Using computer simulations, model neurons were subjected to noisy background input plus an excitatory signal followed by inhibition, consistent with FFI. We measured the probability and timing of signal-evoked spiking under a range of stimulus conditions that included varying degrees of input synchrony, delays to the onset of inhibition, and chloride dysregulation.

Results: A depolarizing shift in the GABA A reversal potential predictably caused an increase in background spiking. We also found that neurons that behave as coincidence detectors under normal conditions behave more like integrators under pathological conditions insofar as they respond more vigorously to less synchronized inputs. This shift in operating mode is reflected in less precise spiking timing, which translates into less precise synchrony transfer.

Conclusions: Beyond chloride dysregulation affecting spike rate, our computer simulations of temporally coordinated excitation and inhibition showed that regulation of spiking timing is also compromised. This results in the impaired processing of synchrony-based signals that could be essential for neural coding.
MAPPING QUANTITATIVE TRAIT LOCI (QTLs) IN THE MOUSE GENOME FOR HEAT PAIN
SENSITIVITY AND THE EFFECT OF STRESS

M. Mashregi, D. Froimovitch, D. Tichauer, E. Soleimannejad, Z. Seltzer, Canada

Background: Naïve male and female mice of the A/J strain are less sensitive to noxious heat than C57BL/6J mice, justifying use of the AXB-BXA recombinant inbred (RI) panel of 25 mouse strains for genetic mapping of QTLs controlling heat nociception.

Objective: To map the mouse genome for QTLs controlling for (i) heat nociception, and (ii) modification of pain responses by repetitive noxious heat stimulation.

Methods: 5-10 mice/strain/gender, n=1300; age=8-12 weeks were tested for their behavioural response to noxious heat and tactile stimulation. Group#1 mice received noxious heat on days 1 and 2; Group#2 received tactile stimulation on days 1 and 3, then noxious heat on days 2 and 4. Three noxious heat pulses were applied to the ears and tail (dorsal and ventral) and quantified on a scale of 0-4. Stimulation of the hind-paws was measured with a stopwatch and quantified as the response duration (sec). A von Frey monofilament (0.2gr bending force) was applied 7 times to the ears, hind-paws and ventral tail and graded from 0-2.

Results: Repeated noxious heat stimulation did not cause sensitisation and/or adaptation. Noxious tactile stimulation 1 day prior to noxious heat increased heat nociception in some strains, but decreased it in others. A significant QTL was mapped on chromosome 10 for the behavioural response to noxious heat at the ears (both genders). Several candidate genes of interest were found, e.g. Tac2.

Conclusions: The behavioural response to noxious heat and the effects of stress depend on the tested body site, gender, and genetics.
COGNITIVE IMPAIRMENT IN EXPERIMENTAL NEUROPATHY

H. Leite-Almeida, Portugal

Chronic pain is frequently accompanied by anxiety, depression and cognitive deficits in both humans and experimental rodent models. The pathophysiological basis and the underlying mechanisms of this phenomenon are presently being scrutinized. While pain was originally suggested as a distractor, accumulating experimental evidence of the past decade supports a novel working hypothesis in which critical brain areas involved in executive function are plasticly modified as a detrimental consequence of pain resulting in cognitive and/or mood deficits. Furthermore, the contribution of different parameters such as duration and anatomical location of pain, age of the experimental subject, genetic background, also needs to be equated for dissecting the complex puzzle of this pain-cognition interplay. In this presentation, previous and current findings about the role and intersignificance of these factors will be discussed.
THE SPECIFIC DISEASE BURDEN OF NEUROPATHIC PAIN

N. Attal, France

Chronic pain is associated with a substantial disease burden, due to its severity and duration. In this presentation, we will discuss about the results of two large cross sectional studies of the impact of neuropathic pain on quality of life and on the psychiatric comorbidities associated with neuropathic pain. The first study shows that the impact of pain on quality of life clearly depends on the neuropathic nature of the pain (1). The second study indicates that the lifetime and point prevalence of anxiety and mood disorders is particularly high in neuropathic pain and outlasts that observed in chronic pain in general (2). These studies converge to indicate that neuropathic pain has a specific impact in terms of quality of life and psychiatric comorbidities probably because of its distinctive clinical characteristics and mechanisms.


Diabetic neuropathy is a progressive distal degenerative condition that most commonly presents as sensory loss in the extremities. In a sub-fraction of patients, loss of sensation is accompanied by pain. The cause(s) of pain in the setting of sensory loss and ongoing degeneration are not understood but recent clinical data has prompted re-evaluation of the suggestion that local consequences of nerve fiber degeneration may contribute. Therapies that halt or reverse degenerative neuropathy therefore have the potential to prevent or ameliorate pain. This approach contrasts with the majority of current interventions that acutely alleviate pain by suppressing nociceptive pathways or axonal dysfunction but which do not address the underlying degenerative neuropathy.

Diabetic rodents develop thermal hypoalgesia and epidermal nerve fibers loss accompanied by concurrent tactile allodynia, making them viable models to study co-incident sensory loss and pain. Many aspects of peripheral neuropathy modeled in diabetic rodents stem from a reduction in the function of axonal mitochondria. In recent studies we have demonstrated that agents that enhance mitochondrial function also prevent or reverse diverse indices of peripheral neuropathy, including sensory loss and epidermal fiber depletion. Efficacy is accompanied by prevention or reversal of indices of painful neuropathy. This is not an acute intervention but rather a gradual restoration of normal phenotype and function. Acute, transient alleviation of painful diabetic neuropathy combined with a chronic neuroprotective adjuvant may provide a sustainable approach to treating the diverse manifestations of diabetic neuropathy.
EXPERIMENTAL STUDIES: PATIENTS ARE ANOTHER MATTER!

U. Baumgärtner, Germany

The relatively simple LEP setup with nociceptive specific stimulation of a skin site and the sensor (eeg electrode) on the scalp puts the investigator/clinician into the role of an electrician who can test, whether the “nociceptive cable” is damaged by means of latency delay or amplitude reduction, or both. Since functional damage of the nociceptive pathway (peripheral or central) may be the cause of neuropathic pain, LEP are recommended as diagnostic test in this context. In contrast to studies in healthy volunteers, recordings in patients are often complicated both by technical difficulties as well as problems with the interpretation of the result that leads to the diagnosis “normal” or “pathologic”. Attentional state, different expectations and, of course, medication may have impact both on psychophysiology and LEP amplitudes. For these reasons and due to the variability of amplitudes in controls, the loss of amplitude has to be dramatic to be categorized as “pathologic” in absolute terms (in the inter-individual comparison). Consequently, the relative difference of amplitude within one patient (for example, in spinal lesions above/below level) is often the more sensitive and specific criterion. For the identification of C-fiber responses, which are extremely variable at distant skin sites (like hand and feet), novel analysis methods independent of the phase of the response may bring advantages in the future.
CRMPs CURB CALCIUM CHANNELS FOR CESSION OF CHRONIC PAIN

R. Khanna, USA

Chronic neuropathic pain management is a worldwide concern. Pharmaceutical companies globally have historically targeted ion channels as the therapeutic catechism with many blockbuster successes. The N-type voltage-gated calcium channel (CaV2.2) is an important target but blockers against CaV2.2 are typically limited by numerous physiological side-effects. Suppression of inflammatory and neuropathic hypersensitivity by inhibiting binding of collapsin response mediator protein 2 (CRMP-2) to CaV2.2, thus curbing channel function. A peptide of CRMP-2 fused to the HIV TAT protein (TAT-CBD3) decreases neuropeptide release from sensory neurons and excitatory synaptic transmission in dorsal horn neurons, reduces meningeal blood flow, reduces nocifensive behavior induced by formalin injection or corneal capsaicin application, and reverses neuropathic hypersensitivity produced by an antiretroviral drug. TAT-CBD3 was mildly anxiolytic without affecting memory retrieval, sensorimotor function, or depression. At doses 10-fold higher than that required to reduce hypersensitivity in vivo, a transient episode of tail kinking and body contortion was observed. By preventing CRMP-2-mediated enhancement of CaV2.2 function, TAT-CBD3 alleviates inflammatory and neuropathic hypersensitivity, an approach that may prove useful in managing chronic pain. Remarkably, sympathetic-associated cardiovascular activity is not affected by TAT-CBD3. Peptide analgesics, such as TAT-CBD3 and its derivatives, with restricted access to the CNS represent a completely novel approach to the treatment of severe pain with an improved safety profile. As peptides represent one of the fastest growing classes of new drugs, it is expected that peptide targeting of protein interactions within the CaV complex may be a paradigm shift in ion channel drug discovery.
Visceral pain has traditionally been interpreted as a typical example of nociceptive pain: i.e. driven by a peripheral lesion (injury or inflammatory process) and caused by a sequential activation of peripheral nociceptors or other visceral sensory receptors, spinal neurons and pathways and supraspinal structures. Although much of this interpretation is correct (supported by the fact that many forms of visceral pain are treated as symptoms of organ disease by the appropriate specialist - gastroenterologist, urologist, gynecologist etc) there are a number of conditions characterized by pain of internal origin not attributable to a clear peripheral cause (i.e. irritable bowel syndrome, painful bladder syndrome, chronic pelvic pain). These conditions are thought to be the result of central or peripheral hypersensitivity of visceral sensory pathways and therefore could be classified as neuropathic. The aim of this talk is to discuss visceral pain in the context of its clinical characteristics and debate whether or not some forms of visceral pain could be interpreted as neuropathic - which will have important consequences relative to potential therapeutic approaches.
MITOCHONDRIA - NOVEL THERAPEUTIC TARGETS FOR THE CONTROL OF NEUROPATHIC PAIN

G. Bennett, Canada

Chemotherapeutics in the vinca alkaloid, taxane, platinum-agent, and proteasome-inhibitor classes all produce a chronic distal symmetrical sensory neuropathy that is often accompanied by neuropathic pain. Clinical experience suggests that these chronic neuropathies are very similar, even though these drugs have distinctly different anti-cancer mechanisms of action.

Work with rat models of paclitaxel-, oxaliplatin-, and bortezomib-induced CIPN suggest that the chronic sensory neuropathies are nearly identical. Experimental data show that each of these agents causes an increase in the incidence of swollen and vacuolated mitochondria in peripheral nerve A-fiber and C-fiber primary afferent axons, but not in their Schwann cells. Direct measurements of mitochondrial function in peripheral nerve preparations from rats with confirmed CIPN and neuropathic pain show chronic dysfunction in mitochondrial respiratory Complexes I and II and in ATP production. The neuropathic pain and the mitochondrial dysfunction are prevented by prophylactic administration of acetyl-L-carnitine, a known mito-protective drug.

This work suggests that mitotoxicity is the fundamental cause of CIPN. A chronic drug-induced mitochondrial injury results in an energy deficiency that results in spontaneous afferent discharge and degeneration of intraepidermal nerve fibers (IENFs), i.e., the sensory axon's terminal receptor arbor.
Ankylosing spondylitis (AS) is a form of spondyloarthritis that causes joint inflammation, often in the sacroiliac region and is an important contributor to chronic low back pain in young adults. The mechanisms underlying AS pain has been attributed to inflammation although patients can describe their pain with neuropathic pain-like descriptors. Therefore, we investigated whether there is a neuropathic component in AS pain and assessed gray matter (GM) brain abnormalities in AS 17 patients compared to age/sex-matched controls (all consented to the approved study). The patients' mean BASDAI was 6.6 +/− 2.1 and total back pain was 6.1 ± 1.7. Most patients described their pain with words in the McGill Pain Questionnaire associated with neuropathic pain. Furthermore, PainDETECT scores were >12 for over half the patients, indicating a neuropathic pain component. Quantitative sensory testing revealed that compared to controls, the patients had decreased mechanical and cold sensitivity on their dorsal feet but had normal pain thresholds. An MRI-based GM analysis revealed that compared to controls, the AS patients had reduced GM in the primary sensory (S1), insular, anterior/mid cingulate (A/MCC) cortices and supplemental motor area, but increased thalamic and putamen GM. Also, painDETECT scores negatively correlated with S1 GM and positively correlated with GM in the motor cortex, ACC, prefrontal cortex, thalamus and striatum. These GM findings are concordant with the clinical picture of sensorimotor deficits and pain in AS and our data indicate that AS may be a mixed pain condition including a neuropathic pain component.
GENETICS OF PAIN IN RODENT MODELS OF NEUROPATHY

J. Mogil, Canada

A small minority of patients receiving major peripheral nerve injuries go on to develop chronic neuropathic pain; in most, the injury resolves quickly with no lasting effects. Why is this? Is it because some injuries are different than others, or because some injury recipients are different than others? We propose that this variability may hold the key to understanding and treating neuropathic pain. The purpose of this talk will be, therefore, to consider what is known at the present time about genetic and environmental factors contributing to neuropathic pain. I will focus on studies in laboratory animals, especially the mouse, from whom the bulk of the relevant data have been obtained. We have demonstrated that the “symptom” produced by the neuropathy (i.e., mechanical vs. thermal hypersensitivity) appears to be the inherited unit. Some progress is being made towards identifying responsible genes and variants within them. The recent discovery of the role of $P2RX7$ polymorphisms will be highlighted.
Some of the most dramatic aspects of the presentation of CRPS suggest peripheral inflammation. Indeed the erythema and swelling of CRPS sometimes cause confusion in establishing the diagnosis. Over the past several years studies in humans and animal models have begun to identify the mechanisms and mediators responsible for CRPS-related peripheral inflammation. At the neuronal level, results suggest that both peripheral neuropeptide containing afferent fibers as well as sympathetic neurons may control edema, warmth and pain sensitization. Looking more deeply, progress has been made in identifying cytokines such as IL-1β, IL-6 and TNFα as well as neurotrophins such as NGF as contributing to one or more of the peripheral manifestations of CRPS. The expression of these mediators appears to be under the control of the SP-NK1, CGRP-CRLR and norepinephrine-β2 adrenergic receptor systems. Complementing these results are studies showing that mast cells are recruited to CRPS limbs and degranulate supporting pain sensitization. The range of neuronal fiber types, immune cells, receptors and mediators suggests a complex collection of processes work together to support the diverse manifestations of CRPS. Adding to the complexity of the situation, recent results suggest autoimmune processes involving peripheral targets may support pain and other facets of CRPS in some patients. While none of these observations detracts from the importance of central contributions, it is becoming clear that a range of peripheral mechanisms support the diverse manifestations of CRPS, and that these mechanisms may evolve over time.
The brain mechanisms associated with neuropathic pain are not well understood. Human brain imaging can be used to studying the structural and functional features of brain networks underlying pain. This talk will provide an overview of these brain imaging technologies and how they are being used to study neuropathic type pains. Examples will be drawn from functional MRI studies that can be used to delineate the brain areas that signal different qualities of pain (“percept-related fMRI”) and thus identify those responses related to the pain qualities that signify neuropathic pain. An overview will also describe two types of connectivity methods that can be used to determine how such brain areas implicated in neuropathic pain are linked into a network: structural connectivity based on diffusion-tensor imaging, and functional connectivity based on synchronous oscillatory activity. Structural MRI can also be used to assess how neuropathic pain impacts cortical and subcortical gray matter. Finally, the ability of brain imaging to address pre-existing vulnerability to develop neuropathic pain after injury will be discussed.
REPEITIVE TRANSCRANIAL MAGNETIC STIMULATION FOR THE TREATMENT OF CHRONIC NEUROPATHIC PAIN

D. Bouhassira, France

Repetitive Transcranial Magnetic Stimulation (rTMS) is a non invasive brain stimulation technique which has raised an increasing interest in recent years for the treatment of various pain conditions, including not only peripheral and central neuropathic pain syndromes, but also non neuropathic pain syndromes such as fibromyalgia.

A large number of randomized sham-controlled trials have confirmed that it is possible to induce analgesic effects lasting up to several days after a single session of stimulation of the primary motor cortex or dorsolateral prefrontal cortex. More recently, it has been shown that it is possible to maintain the analgesic effects of rTMS of the primary motor cortex in patients with chronic pain over more than 6 months, strengthening the idea that rTMS could represent a valid option for the treatment of patients with chronic neuropathic pain.

Although the mechanisms of the analgesic action of rTMS are still poorly understood, recent studies have suggested that they depend on endogenous opioid system and changes in cortical excitability.
CHRONIC PAIN IN LEPROSY: NEW ASPECTS TO BE CONSIDERED

F. Reis, M.K. Gomes, L. Saadi, A. Gosling, A.J.L. Cunha, Brazil

Leprosy is still considered endemic in several developing countries. Infection with *M leprae* leads to chronic granulomatous inflammation in skin and peripheral nerves that can lead to sensory, motor and autonomic impairments. Since leprosy causes severe sensory loss, scant attention has been given to pain in leprosy, assuming that neuropathic pain (NP) could not occur in those patients. However, pain in leprosy arises as a disabling condition after multidrug therapy discharge. This condition could be caused by leprosy-induced neuritis, whether spontaneous or upon palpation of a nerve trunk, which may be associated with an impairment of function or could be influenced by others aspects of pain. This session presents the prevalence of NP among leprosy patient, the diagnosis of NP including screening tools, medical history and physical examination, as well as pain aspects. We also highlighted that not all pain in leprosy is neuropathic. Besides, we present an overview about chronic pain mechanisms and interaction with the central nervous system and also anatomical and functional reorganization of the brain. At the end, we suggest an approach to rehabilitation focus on activating components of the pain matrix, decreasing pain focus and promoting cortical changes. We suggest that pain is influenced by different aspects as defined by the neuromatrix theory and should be treated as a multimodal condition. This session presents promising treatments that focus on the brain's plasticity including educational sensory, and motor strategies.
Virtually all patients with central NP have lesions affecting the pathways for pain and temperature; hence, assessment of spino-thalamo-cortical (STT) function is an essential step to identify CNP and improve its management. Spinothalamic activation is obtained using infrared laser pulses, which excite thermo-TRP receptors (TRPV1-TRPV4) in peripheral A-delta and C-fibres. Laser-evoked potentials (LEPs) detect abnormal STT transmission and are widely used as electrophysiological method to assess patients with suspected CNP. Abnormal LEPs to stimulation of a painful territory is an electrophysiological signature of NP, while preserved LEPs argues against such diagnosis, and may suggest psychogenically-enhanced pain. Optimal use of LEPs requires combination with responses to non-noxious stimuli, since dorsal-column system lesions may be a rare cause of CNP. Behavioural and vegetative responses are useful adjuvants to LEPs, and may uncover crucial discordances between objective and subjective responses, suggesting a psychogenic factor. The type of LEP abnormality depends on (i) the size of the lesion; (ii) the anatomical distribution of lesioned fibres/neurons, and (iii) the induced pathophysiological changes (e.g. axonal/neuronal loss vs desynchronised transmission). Thus, lesions of similar size at different levels (cord, brainstem, thalamus, cortex) give rise to different LEP abnormalities, and the precise type of LEP dysfunction can inform on the type of CNP most likely to appear. For instance, remnant STT transmission is associated with enhanced probability of provoked pain (alldynia, hyperalgesia), and time-frequency LEP analysis may provide information as to the probability of developing CNP after a brainstem or thalamic lesion.
Despite a large number of etiologies and the heterogeneity of their clinical expression, neuropathic pain syndromes present with some commonalities, suggesting that they represent a specific clinical entity. Over the last few years, a series of studies have demonstrated that some symptoms (i.e. pain descriptors) can discriminate between neuropathic and non neuropathic pain. This finding allowed the development and validation of a series of simple clinical tools, in the form of questionnaires, based on the analysis of pain descriptors and neurological signs. Although none of the pain descriptor was specific by itself, these studies showed consistently that the combination of a relatively small number of items was sufficient to discriminate pain due to a definite neurological lesion. Because of their ease of use, these questionnaires can be used both in daily practice and clinical research. The advantages and limitations of these clinical tools for clinical practice will be addressed in this presentation.
Quantitative sensory testing (QST) is based on the measurements of responses to calibrated, graded mechanical and thermal stimuli. This method derived from psychophysics can be regarded as an extension of the routine bedside sensory examination that can be used to quantify somatosensory function in patients. Thus, in principles, QST could be useful for the diagnosis, assessment and monitoring and for the characterization of the somatosensory profile in patients with neuropathic pain.

However, despite its theoretical advantages QST has not gained large acceptance in clinical practice. The limitations of QST for clinical practice will be discussed during this presentation.
The credibility of ‘evidence-based medicine’ depends on access to information. Trial registration on a public database is now nearly universal, especially for pivotal phase 3 trials. More than 120,000 trials are registered on ClinicalTrials.gov. Unfortunately, reporting of study results lags behind. Only 39-44% of completed studies in the RReACT database were published in peer-reviewed journals. Even including the so-called “grey literature” (publicly-available meeting abstracts, posters, press releases and sponsor summaries), results could be found for only 63-68% of all completed trials in the RReACT database. The most worrisome explanation for the unavailability of trial results would be publication bias. Public-access resources from the FDA and European Medicines Agency are available to investigate such a possibility. Literature analyses indicate positive results and full publication are strongly correlated. Furthermore, journal publication of negative trials may incorrectly convey a ‘positive’ outcome. A Cochrane review of the “grey” literature found that published trials reported a 9% greater treatment effect, suggesting that negative trials were less likely to progress to full journal publication. The public has little ability to crosscheck results or determine whether a results source is reliable. Independent FDA assessments are publicly available for few trials. The grey literature is not reliably indexed and archived the way peer-reviewed journals are; results may be posted and then taken down, or a URL may no longer work. Websites can change from being freely accessible to a paid or subscription model. Efforts to further facilitate universal reporting of full results of completed trials are needed.
CLINICAL USEFULNESS OF AN AUTOMATED ANALYSIS OF LASER-EVOKED POTENTIALS TO ASSESS NOCICEPTIVE PATHWAYS

S.M. Hatem¹,², Belgium

Studying the neural activity related to the activation of nociceptors and the conduction of nociceptive input within somatosensory pathways constitutes a real challenge in the sense that only few external stimuli have the ability to activate nociceptors selectively. At present, laser-evoked potentials (LEPs) are considered the best available method to explore the nociceptive system in humans in a large variety of clinical conditions. The visual inspection of LEP waveforms is regarded as the generally agreed-on method to identify the different waves of LEPs. However, there are several important limitations underlying the identification of LEPs using visual inspection for its use in clinical research. Recently, Mayhew et al. (2006) and Hu et al. (2010) developed an automated, observer-independent method to estimate reliably the N1, N2 and P2 peaks of LEPs in healthy controls. Their most current approach is based on a combination of methods to enhance the signal-to-noise ratio of LEPs using a time-frequency filter based on the wavelet transform, and a multiple linear regression analysis to estimate peak amplitudes and latencies at the level of single trials. The usefulness of implementing this automated approach in the context of clinical research, will be discussed in the light of this automated approach’s ability to recognize pathological LEP waveforms in patients.
One challenge facing the patient with neuropathic pain is how to make sense of it. The dominant understanding of pain is that it is a measure of tissue damage so the very idea of pain generated erroneously can be difficult to grasp. However, that pain is fundamentally dependent on what it means strongly infers that if we can reconceptualise neuropathic pain to exclude tissue damage as a cause, then we should change the pain itself. Simply telling people they have a problem in their nerves that causes the pain is unlikely to shift the deeply held schema that pain equals tissue damage. I will describe a large body of data that show we can teach people about neuropathic pain by using established strategies of conceptual change and packaging sometimes complex material into appropriate ‘conceptual chunks’. It is possible to change not only their knowledge level, but also catastrophising, attitudes and beliefs about pain and, critically, their pain and disability.
Somatosensory stimuli are processed not only according to where they are in the body, but also where they are in relation to the body midline. People with unilateral spatial neglect after stroke, have a clear impairment in processing that is dependent on the midline of the body - they draw half a clock for example, omitting the numbers from 7 - 11. People with CRPS sometimes behave as though they have a type of neglect. I will present research that investigates this idea, from questionnaire and behavioural data to explicit interrogation of spatial processing. I will also present recent data that show a clear link between spatial perception and thermoregulation and pain.
There is now a large amount of evidence that persistent neuropathic pain is associated with changes in cortical function. It is not known whether these changes contribute to the pain or not. However, several rehabilitative strategies have been developed that directly target those brain changes and, so far, some of them appear to be clinically helpful. I will present the physiological rationale that underpins the most tested strategies and evaluate the evidence as it currently stands for their effects on neuropathic pain and related disability.
The broad spectrum of effect of steroids such as methylprednisolone on inflammatory cascades and the apparent role of these cascades in pain states secondary to nerve compression and injury makes them important agents for epidural and intrathecal delivery. In spite of their wide spread use there are surprisingly few efforts to assess their safety with neuraxial delivery. We have undertaken ongoing investigations with the depot formulation (methylprednisolone acetate: MPA separated from its commercial formulation and resuspended in saline) to address this issue. In an intrathecally catheterized canine model, we examined effects of intrathecal delivery of: vehicle + lidocaine, MPA 20 mg/ml + lidocaine (typical human dose), or MPA 80 mg/ml + lidocaine (maximum deliverable dose). In parallel with human protocols, four injections were given at 7-day intervals. Other than a brief motor block, no adverse clinical event occurred. Vehicle showed minimal histologic changes. MPA (20 mg/ml) had a diffuse inflammatory reaction and MPA (80 mg/ml) animals displayed a more severe inflammatory response, with inflammatory masses. No neuronal injury, demyelination, or gliosis was seen in any animal. Local deposits of white material (MPA) were noted proximal to the injection sites. These results thus revealed an unexpected dose-dependent intrathecal inflammatory reactions at MPA doses and concentrations comparable to those used in humans. The origin of these intrathecal reactions is not known. The possibility of a specific steroid effect vs an intrathecal space response to the particulate nature of the injectate requires consideration.
THE EVIDENCE ON THE COMPARATIVE COST-EFFECTIVENESS OF SCS VERSUS ALTERNATIVE TREATMENTS IN THE TREATMENT OF CHRONIC PAIN

K. Kumar, Canada

Introduction: The technology of spinal cord stimulation (SCS) is rapidly advancing, leading to higher costs without clear evidence of cost-effectiveness. We present the cost-impact of SCS compared with optimal medical management (OMM) as projected for the year 2020 for failed back surgery syndrome (FBSS), complex regional pain syndrome (CRPS), peripheral arterial disease (PAD), and refractory angina pectoris (RAP).

Methods: A Markov model was developed to evaluate the cost-effectiveness of SCS with OMM (SCS) versus OMM alone. Model inputs derived from chart reviews of 313 patients. Costs (Canadian dollars) and outcomes followed in six-month cycle. Health effects expressed as quality-adjusted life years (QALYs) gained. Costs and effects were evaluated over a seven year time horizon (2013-2020) and discounted at 3.5% per annum. Cost-effectiveness was identified by deterministic and probabilistic sensitivity analysis (50,000 Monte-Carlo iterations).

Results: The incremental cost-effectiveness ratio (ICER) for SCS was: $7,318 (FBSS), $9,618 (CRPS), $7,294 (PAD), $8,143 (RAP) per QALY gained, respectively. The probability of cost-effectiveness compared with OMM was 74-95% depending on pathology and willingness to pay (WTP) threshold per QALY. In all 4 pathologies, SCS provided a positive INMB over OMM at WTP thresholds ≥ $7,000 per QALY, which strongly suggests that SCS is a treatment strategy worth funding (figure 1). Sensitivity analyses demonstrated that results were robust to plausible variations in model costs and effectiveness inputs.

Conclusions: The ICER for SCS is below the WTP threshold of $50,000/QALY. SCS remains cost-effective compared with OMM.

[Incremental Net Monetary Benefit of SCS versus OMM]
ROLE OF ADVANCED GLYCATION END PRODUCTS IN NEURAL DAMAGE

S. Sauer, Germany

Typical AGEs result from periodic hyperglycemia due to muscle and fat cells being unable to utilize the blood glucose. Insulin independent neurons, however, over-utilize the surplus glucose by glycolysis and, thereby, generate excess amounts of reactive discarbonyls, methylglyoxal (MG) in the first place. These metabolites glycate proteins forming glycosamines, hemithioacetals etc., “early” AGEs in a way, that rapidly cause major functional disorders as found in painful diabetic neuropathy.

High MG plasma levels correlate closely with pain and hyperalgesia in human patients and experimental animals. Lowering these levels by various means effectively reduces the hyperalgesia which is entirely absent in mouse mutants devoid of the TTX-resistant, nociceptor specific, sodium channel Na\textsubscript{v}1.8 and reduced in other mutants lacking the universal chemoreceptor-channel TRPA1. MG stably binds to Na\textsubscript{v}1.8 protein, depolarizes sensory neurons and increases their electrical excitability, effects that are absent in Na\textsubscript{v}1.8\textsuperscript{-/-} neurons. In the TRPA1 protein, MG induces disulfide bridge formations involving the critical N-terminal cysteines which results in a sustained activation and a substantial calcium influx in sensory neurons, evoking CGRP release. On the other hand, MG also binds to the TTX-sensitive Na\textsubscript{v}1.7, essential for action potential generation in postganglionic sympathetic neurons, promoting its slow inactivation. This and a slowing of nerve conduction by MG suggests differential effects of MG on various ion channels, possibly accounting for the intriguing coexistence of positive and negative symptoms of diabetic neuropathy, e.g. pain and gastroparesis. Thus, methylglyoxal emerges as a validated target of medicinal chemistry to fight this debilitating complication.
AMYGDALA IN THE CONTROL OF NEUROPATHIC PAIN
L. Goncalves, N. Bourbia, H. Viisanen, O.B. Ansah, A. Almeida, A. Pertovaara, UK, Finland, Portugal

Amygdala has a key role in the processing of primary emotions, such as fear. Additionally, a subdivision of the central nucleus of the amygdala is particularly involved in processing of nociceptive signals. The amygdala may also contribute to regulation of pain through its reciprocal connections with other brain areas. Here we briefly review recent findings on neural plasticity of the amygdala in peripheral neuropathy. Peripheral nerve injury may induce neurogenesis in the amygdala of adult animals and this is accompanied by changes in synaptic functions and response characteristics of amygdaloid neurons. Moreover, the pain-regulatory action of amygdaloid neurotransmitters and neurotransmitter receptors (such as glutamate acting on the metabotropic glutamate receptor 1 or corticotropin-releasing factor, CRF, acting on the CRF₁ receptor) may change following peripheral nerve injury. It is proposed that these plastic changes of the amygdala following peripheral nerve injury contribute to the sensory and affective aspects of pain in neuropathy and to the comorbidity of neuropathic pain and mood disorders.
A NOVEL AND ROBUST APPROACH TO CHARACTERIZE C-FIBER LASER-EVOKED POTENTIALS IN HUMANS

A. Mouraux, A. Jankovski, L. Plaghki, Belgium

Brief high-power laser pulses applied onto the hairy skin of the distal end of a limb generate a double sensation related to the concomitant activation of Aδ- and C-fibers, often referred to as first and second pain. However, neurophysiological (e.g. laser-evoked brain potentials, LEPs) and behavioral responses related to the activation of C-fibers can be studied reliably only if the concomitant activation of Aδ-fibers is avoided. Methods to activate C-fibers selectively have been proposed, but are considered unreliable or difficult to implement. Here, we will (1) critically review the different approaches that can be used to elicit neurophysiological and behavioral responses related to the activation of C-fiber input in humans, (2) present an approach combining a laser stimulator able to generate constant-temperature heat pulses with an adaptive paradigm to maintain stimulus temperature above the threshold of C-fibers but below that of Aδ-fibers, (3) examine using a Receiver Operating Characteristics analysis whether this approach can be used to record reliable EEG responses related to the selective activation of C-fibers, (4) explore whether time-frequency analysis can improve the signal-to-noise ratio of the elicited responses because it enhances both phase-locked and non phase-locked EEG responses and (5) discuss the clinical usefulness of this approach for the diagnostic workup of small-fiber neuropathies and neuropathic pain.
HOW NEUROPATHIC IS LOW BACK PAIN?

N. Attal, France

Both neuropathic and nociceptive mechanisms are thought to contribute to the pain experienced by many patients with low back and leg pain (1). However, the current definition of "neuropathic LBP" remains vague, with no consensus concerning its best clinical determinants. It is difficult to resolve these issues through complementary investigations only, and it is therefore essential to improve the clinical identification and characterization of neuropathic components of LBP. This has recently been attempted through the use of screening tools, physical examination and quantitative sensory testing. Thus a large multicentre study has shown that almost one third of patients with LBP have a combination of neuropathic and non-neuropathic features (2). Another study has shown that up to 40 % of LBP patients have a neuropathic component even in the lack of typical radiculopathy (3). The therapeutic implications of these results will be discussed.

References:


SPINAL CORD STIMULATION IN NEUROPATHIC PAIN: MODULATION AT THE SPINAL GATE

E. Joosten, M. van Kleef, The Netherlands

Although Spinal Cord Stimulation (SCS) of the dorsal columns is an established method for chronic neuropathic pain, patients still suffer from a substantial level of pain. From a clinical perspective it is known that the location of SCS is of pivotal importance thereby suggesting a segmental spinal mode of action. However, experimental studies suggest that SCS acts also through the modulation of supraspinal mechanisms, which might suggest that the location is unimportant. Data will be presented which show that SCS of the dorsal columns at the level where the injured fibers enter the spinal cord dorsal horn (i.e. the spinal gate) result in a much better pain relieving effect than SCS at more rostral levels. SCS-induced modulation of the pain transmission at the segmental spinal level was further substantiated by pharmacological experiments. Within the spinal gate the process of central sensitization plays a pivotal role in the induction and maintenance of (chronic) neuropathic pain and is thought to be the resultant of the activation of the N-Methyl-D-Aspartate (NMDA) receptor. The intrathecal administration of a single sub-effective dose of the non-competitive NMDA-receptor blocker ketamine was shown to enhance the pain relieving effect of SCS, thereby converting all non-responders to SCS into responders. Furthermore, the duration of the anti-allodynic effect of SCS was extended in the responders and non-responders to SCS after the combination with a sub-effective dose of ketamine. In conclusion: SCS induced modulation at the spinal gate is needed for an optimal pain relief in treatment of chronic neuropathic pain.
THE ROLE OF MCP-1/CCR IN CIPN

P.M. Dougherty, Y. Li, H. Zhang, USA

The use of paclitaxel or oxaliplatin is often limited by an associated peripheral neuropathy (chemotherapy-induced peripheral neuropathy, CIPN). CIPN results in sensory dysfunction including chronic pain and sensory motor function. In this symposium it will be shown that paclitaxel and oxaliplatin CIPN is associated with an induction of chemokine monocyte chemoattractant protein-1 (MCP-1) and its cognate receptor CCR2 in primary sensory neurons of the dorsal root ganglia (DRG). The patterns of expression between these therapeutics are unique. Whereas MCP-1 was mainly expressed in small nociceptive neurons and CCR2 was expressed in large and medium-sized myelinated neurons following paclitaxel treatment, MCP-1 and CCR are expressed only in small presumably nociceptive DRG neurons. Direct application of MCP-1 consistently induced intracellular calcium increases in DRG large and medium-sized but not small neurons mainly dissociated from paclitaxel- but not vehicle-treated animals. Paclitaxel also induced increased expression of MCP-1 in spinal astrocytes but no CCR2 signal was detected in spinal cord. Local blockade of MCP-1/CCR2 signaling by anti-MCP-1 antibody or CCR2 antisense oligodeoxynucleotides significantly attenuated paclitaxel CIPN phenotypes including mechanical hypersensitivity and loss of intraepidermal nerve fibers (IENFs) in hindpaw glabrous skin. Similar findings were found in oxaliplatin-treated animals. These results suggest that activation of paracrine MCP-1/CCR2 signaling between DRG neurons plays a critical role in the development of paclitaxel whereas autocrine signaling may occur in oxaliplatin CIPN. The activation of MCP-1/CCR in both models may depend on the activation of innate immunity via Toll-like receptor signaling.
NEUROPATHIC PAIN IN CANCER PATIENTS
M. Bennett, UK
This lecture will explore the epidemiology, assessment and management of neuropathic pain in cancer patients. Using systematic reviews and recent clinical studies, I will focus on terminology and population characteristics, the reliability of assessment in published studies and propose a more systematic approach based in IASP criteria. I will finish with an evidence based approach to prescribing including the role of combination analgesic therapy.
Neuropathic pain in cancer patients results in poorer quality of life and greater need for analgesia than non-neuropathic pain. This suggests that improvements in clinical management are only likely once earlier and more accurate identification of neuropathic mechanisms is made. This session will review the reliability of current diagnostic approaches in neuropathic cancer pain based on published prevalence and intervention studies. These data suggest that assessment is inconsistent and not systematic, and highlights the need for a consensus on a more rigorous standard of assessment.
Detecting neuropathic mechanisms in patients with cancer is important because alternative or adjunctive treatment strategies are required to optimise pain control. The IASP grading system for neuropathic pain does not include the use of specific screening tools for neuropathic pain though NeuPSIG assessment guidance suggests that they may be helpful in identifying patients with possible NP. The evidence to support their use in cancer patients is less strong than in non-cancer chronic pain. For example several studies suggest that they are less sensitive in this context. Explanations for this will be discussed including whether neuroapthic pain in cancer is phenotypically different from non-cancer, and whether modified tools are needed that contain a different range of symptom descriptors.
INTRODUCTION TO BEDSIDE SENSORY EXAM AND QST IN DIAGNOSIS OF NEUROPATHIC PAIN

M. Backonja¹,², USA

Sensory examination is critical step in attaining information necessary for the diagnosis of neuropathic pain (NP). Sensory examination is performed with the goal to determine presence of the suspected neurological disorders that lead to NP and at the same time to document presence of positive sensory phenomena, such as allodynia and hyperalgesia as hallmarks of NP. Quantitative Sensory Testing (QST) with its property of quantification is used to for documenting severity of sensory abnormalities and then those abnormalities could be monitored for status of the NP and for its response to treatments. Akin to other neurological investigations bedside sensory exam leads to where QST is applied and when it is repeated. Since standards for conduct of QST are recently publicized it is necessary to have healthy discussion about the role of each, bedside sensory exam and the QST, is invited.
TREATMENT OF NEUROPATHIC PAIN IN SCI

D.D. Cardenas, USA

The diagnosis of neuropathic pain attributed to the spinal cord lesion itself is essentially a diagnosis of exclusion; thus, the clinician seeks potentially treatable causes of pain first such as post-traumatic syringomyelia, Charcot arthropathy, or intra-abdominal pathology. Once other etiologies are excluded, the treatment of neuropathic pain is largely empirical and should include a comprehensive approach to the patient. The general treatment approaches of neuropathic pain may include behavioral interventions, pharmacological agents, alternative medical approaches, or rarely surgical approaches. The objective of this presentation is to discuss some of the evidence on the degree of pain relief provided by specific pain treatments that use a pharmacological approach and describe some of the alternative therapies that are sometimes tried as additional treatment options in this population. A recent large randomized placebo-controlled trial of pregabalin that demonstrated that pregabalin is effective and well tolerated in patients with neuropathic pain in persons with SCI will be summarized.
MECHANISMS OF DISTAL AXONAL DEGENERATION IN PAINFUL HIV-ASSOCIATED SENSORY NEUROPATHY

A. Hoke, USA

HIV-associated sensory neuropathy (HIV-SN) is characterized by slowly progressive distal axonal degeneration that affects predominantly the unmyelinated sensory fiber populations. Although HIV-SN is characterized by both direct and indirect neurotoxicity of the HIV itself, there is also a component of neurotoxicity of many of the antiretroviral drugs. What undermines the selective vulnerability of the unmyelinated fibers in HIV-SN is unknown, but unique properties of mitochondrial turnover in long unmyelinated axon populations may offer a unifying hypothesis. Mitochondria in long sensory axons “age” as they are transported down the axon and develop functional deficits that hinders the most distal portions of the axons more vulnerable to local stress (oxidative or metabolic) and may not need the local energy needs of the axon. In a study examining the mitochondrial mutations in matched samples of sural nerves and dorsal root ganglia in HIV-SN and control patients, we showed that the mitochondria in distal nerves have 30 fold higher incidence of a common deletion mutation associated with aging and result in increased oxidative stress markers in distal nerves in HIV-SN patients. These findings are replicated in a non-human primate model of HIV-SN and a transgenic mouse model of HIV-SN. Therapies aimed at improving mitochondrial turnover and transport in long axons may offer a potential therapeutic target for HIV-SN.
LONG-TERM OPIOID THERAPY: ETHICAL CHALLENGES

J. Ballantyne, USA

If opioids were not addictive, and through improper use potentially lethal, opioid decisions would be fairly straightforward. In fact, using the principles of best evidence - the randomized controlled trial being at the top in the evidence hierarchy - existing guidelines for the treatment of neuropathic pain recommend that “opioid analgesics are recommended as generally second-line treatment that can be considered for first-line use in select clinical circumstances”. This recommendation is based principally on efficacy studies, which to date have been conducted only over short periods of time, usually weeks. Yet as any clinician knows who treats patients with opioids over the long-term, concerns arise about gradual loss of efficacy coupled with declines in safety. Furthermore, there can be a multitude of concerns about misuse and diversion. This means that opioid decisions are not, in fact, straightforward. This presentation explores some of the ethical conflicts that arise in opioid decision making, including the age-old conflicts that arise concerning the use of addictive drugs to relieve suffering, the conflicts that arise concerning safety, issues of patient autonomy and competence to make decisions regarding use of addictive drugs, whether promoting of addictive drugs is ethical, and how to reconcile medical decisions that are driven by the need to bolster patient satisfaction ratings.
Chemotherapy induced peripheral neuropathy (CIPN) is often a dose-limiting side effect of most chemotherapy regimens. Clinical presentations of CIPN differ among many classes of cancer drugs but most cause length-dependent sensory-predominant peripheral neuropathy characterized by distal axonal degeneration. Using paclitaxel induced peripheral neuropathy as a model we showed that paclitaxel causes distal axonal degeneration by inhibiting the ubiquitin proteasome system and activating the caspase pathway locally in axons. This mode of neurotoxicity differs from the prevailing hypothesis about mechanism of neurotoxicity of paclitaxel (increased microtubule stabilization) and offers a potential for neuroprotective drug development that does not interfere with anti-tumor activity of paclitaxel. Using a phenotypic drug screening approach we identified ethoxyquin as a potential therapy for paclitaxel induced peripheral neuropathy. After confirming the findings in vitro and validating in animal models we showed that ethoxyquin does not block paclitaxel's ability to kill tumor cells. Furthermore, we showed that ethoxyquin mediates its neuroprotective activity by inhibiting the chaperone activity of heat shock protein 90 (Hsp90).
LOW BACK PAIN WITH OR WITHOUT RADICULAR PAIN: DIFFICULT MANAGEMENT
“BRIDGING THE GAP BETWEEN NEURONES AND VERTEBRA, BETWEEN BRAIN AND SPINE”

S. Perrot, France

In low back pain, two main approaches have been developed in parallel for pathophysiology and assessment:

- **The “Neurological” approach**: looking for neuropathic pain component, pain descriptors, psychological impact. This approach has demonstrated that low back pain with or without radiculopathy are the same diseases, with different stages. This approach has demonstrated the potent effect of anticonvulsants and antidepressants in low back pain and radiculopathy.

- **The “Spinal” approach**: looking for intervertebral disc abnormalities, spinal deformations, and functional impairment. In this approach, spine imaging, and especially MRI, is leading the management. This approach has demonstrated that intervertebral disc inflammation (Modic 1 grade) is associated with better outcome and better efficacy of anti-inflammatory agents, like NSAIDs or spinal steroids injections.

The management is still challenging because of several phenomenon that should be assessed and managed concomitantly:

- **work interactions**: low back pain is the condition that can be aggravated by many kinds of occupations.
- **functional impairment**: impact on daily life is important, and especially on work
- **litigations**: an important number of cases are associated with litigations with employers, healthcare system and companies…

In all cases, psycho-social approaches are mandatory, especially in the workplace.

Stepped and combined approaches, based on severity assessment and scoring system, are emerging for a better management of the most frequent painful condition.

In conclusion, low back pain is a difficult condition, with complex pathophysiology. Future research on patient-reported outcome may help to establish relevant and more adapted management.
MECHANISMS OF ACTION OF RTMS IN CHRONIC PAIN

D. Ciampi de Andrade¹,², Brazil

Non-Invasive Brain Stimulation (NIBS) techniques have been tested to control chronic pain in the last fifteen years. Among the different NIBS techniques, repetitive Transcranial Magnetic Stimulation (rTMS) has been the one more extensively studied. A large number of randomized, sham-controlled studies have evaluated its analgesic effect in different pain syndromes. Despite the different stimulation parameters and types of chronic pain syndromes evaluated, positive results have been found in fibromyalgia and in both central and peripheral neuropathic pain. Recently, new studies have broadened our current knowledge on the mechanisms of action of rTMS. In particular, animal studies on transdural cortical stimulation have deepened our understanding on the effects of motor cortex stimulation in distant brain areas such as the periaqueductal grey matter and the descending pain modulatory pathways. Experiments in healthy subjects have provided insights on the role of the endogenous opioid system and NMDA receptors in the analgesic effects of rTMS. Studies in chronic pain patients have shown that changes in cortical excitability present in these patients can be restored by rTMS. New targets are currently being explored with special coils that allow for the stimulation of deeper cortical structures and might provide new mechanism-based targeting of specific brain areas. These data may help to further improve the current clinical effects of NIBS techniques.
Glucocorticoids are known to influence the inflammatory process through fast non-genomic effects and slower genomic effects by transcriptionally activating (transactivation) or repressing (transrepression) genes. These actions jointly have been shown to impact upon the expression of over 6500 genes. The changes in transcription activity and protein expression cascades are likely involved in the events leading to changes in sensory processing following peripheral and/or spinal nerve injury. From animal studies there is evidence that after nerve injury, there is an increased expression in the spinal dorsal horn, of glucocorticoid receptors ipsilateral to nerve injury with a time course parallel to that of the development of neuropathic pain behaviors. Glucocorticoids could impact upon pro-inflammatory product secretion and cell migration. The effects upon cytokine secretion and the reduction in the upregulation of pro-inflammatory elements such as COX 2 and iNOS are evident regulatory targets which would control the evolution of the facilitated state and the development of neuropathic pain. During the presentation I will further elaborate on the mechanisms whereby glucocorticoids exert their action on the inflammatory and neuropathic pain cascade.
Chronic orofacial pain can have a devastating effect upon a patient’s quality of life. Virtually all life areas (mood, social and occupational function, close relationships, sleep, leisure activities, eating) can be negatively affected, and hence expectations of pain treatment are often very high. Given that medical treatments for persistent orofacial pains are often not curative, clinicians need to explore a wider set of options in order to maximize their treatment effectiveness. Recent reviews (e.g. Vowles & Thompson, 2012) have pointed to the significance of the patient-provider relationship in chronic pain treatment outcomes. In the broader psychological literature, effect sizes of $r = 0.23$ to $r = 0.34$ have been reported for treatments specifically relating to the so called non-specific elements of the intervention. In the persistent pain literature, these non-specific effects have been acknowledged (Newton-John & Geddes, 2008) but are often seen as a kind of “error” in the integrity of the treatment. However, this presentation will argue that quite to the contrary, psychological variables can and should be systematically utilized in order to improve treatment outcomes of patients presenting with intractable orofacial pain complaints. The key areas for clinical focus include expectation management, goal setting and active collaboration in treatment, progress monitoring and the use of empathy. While not especially time consuming, effective use of these strategies can greatly enhance treatment outcome.
A predominantly sensory neuropathy (SN) was among the earliest recognized complications of HIV infection. Advanced HIV disease was the main SN risk factor in early descriptions, but the neurotoxicity of some antiretroviral medications dominates in many recent cohorts. Thirty years on from the initial descriptions of AIDS in the USA, HIV has become a chronic, manageable condition for those with access to medical care. Most guidelines recommend early HIV treatment and neurotoxic antiretrovirals are being phased out, even in resource-limited settings. Despite these advances, the available data suggest SN remains extremely common in the era of “safer” HIV management, with high rates of pain among those affected and substantial impact on quality of life and function. Despite this, there is a relative lack of proven, effective analgesic strategies. This presentation will cover current knowledge of the pathogenesis and evolving epidemiology of HIV-SN. The available data regarding treatment options will also be reviewed, along with some personal insights into managing patients affected by painful HIV-SN. The presentation will conclude by mentioning some of the ongoing and future work needed to inform the optimal management of this common and difficult condition.
Transcriptional profiling using RNA seq was performed in the L5 spinal nerve transection (SNT) model of neuropathic pain using RNAseq. Pathway analysis showed significant dys-regulation of multiple inflammatory processes within both the injured dorsal root ganglion and spinal cord. mRNAs encoding multiple inflammasome components were up-regulated following SNT. The inflammasome is a multi-protein complex consisting of a central scaffold protein (such as NLRP 3), an adaptor protein (ASC) and the enzyme caspase-1. Endogenous or exogenous danger signals trigger assembly of this complex the end result of which is autolysis and activation of pro-caspase-1 which cleaves pro-IL-1b and pro IL-18 (cytokines with known algogenic potential) into their active forms.

Following L5 spinal nerve transection, inflammasome components NLRP3, ASC, and caspase-1 are up-regulated in the injured DRG and the ipsilateral lumbar dorsal horn. Immunohistochemical analysis reveals that ASC and caspase-1 are both highly expressed in macrophages and microglia. Application of LPS to these cell types in vitro results in activation of the NLRP3 inflammasome and caspase-1 dependent release of IL-1b into extracellular media. Inhibition of caspase-1 significantly reduced pain related hypersensitivity associated with intrathecal application of LPS and following nerve injury. Mice lacking the key adaptor protein ASC demonstrate reduced mechanical hypersensitivity induced by LPS however the hypersensitivity induced by nerve injury was unchanged. These findings emphasise the engagement of the innate immune system in neuropathic pain states and the fact that there are multiple mechanisms regulating IL-1β processing which are context dependent.
It has long been clear that psychosocial factors strongly impact the experience of persistent pain, shaping the transition from acute to chronic pain, quality of life, the degree of pain-related disability, and many other features of an individual's functioning. Processes that reflect pain-specific aspects of negative affect, such as catastrophizing, appear to play a particularly important role. Catastrophizing incorporates magnification of pain-related symptoms, rumination about pain, feelings of helplessness when in pain, and pessimism about pain-related events. Abundant evidence identifies high levels of catastrophizing as a critically-important risk factor for the development of neuropathic pain (for example, after surgery), and for poor adjustment to chronic pain. Moreover, functional neuroimaging studies indicate that negative cognitive and emotional processes such as catastrophizing can amplify pain processing in the central nervous system. Not surprisingly, there is a great deal of interest in the potential for behavioral and psychosocial strategies to decrease acute pain and forestall the development of chronic pain. To date, a number of meta-analyses have confirmed that treatments such as Cognitive-Behavioral Therapy (CBT) reduce pain intensity, negative affect, and pain-related disability. Several studies also hint that CBT may have the potential to diminish the likelihood of developing chronic neuropathic pain in those at high risk. This presentation will focus on the importance of cognitive and emotional processes in shaping the experience of neuropathic pain, and interventions that may change the "meaning" of pain in adaptive ways among individuals living with persistent pain.
Recent evidence suggests that patients with CRPS often have serum antibodies directed against bacterial/viral surface epitopes, or autonomic receptors. Serum-IgG from patients, when transferred to mice cause abnormal behavior, and some patients respond to treatment with polyvalent immunoglobulin or plasmapheresis. These results point towards a new understanding of CRPS as an autoantibody-mediated regional, posttraumatic, largely non-destructive autoimmune condition. The described abnormalities have been found in both early and late CRPS. It is unknown whether those described autoantibodies are by themselves pathogenic; alternatively they may be sentinels, which indicate an autoimmune pathophysiology while other antibodies, directed against other, yet to be discovered epitopes are involved in causing CRPS.

Recent discussions have focused on the possibility that CRPS is a neuropathic pain syndrome, because of its association with reduced epidermal nerve fibre numbers in some studies. However the above-described results suggest the possibility of an alternative mechanism. Perhaps trauma-induced regional inflammation in CRPS allows binding of autoantibodies, and in consequence regional changes in sensory nerve function. This disease process may thus directly affect the somatosensory system, albeit not necessarily with causing a lesion, and CRPS should then be defined as neuropathic pain in line with recent redefinitions.
Emerging evidence suggests that certain psychological variables might impact negatively on health and mental health outcomes associated with neuropathic pain. Variables such as catastrophic thinking, anxiety and depression have been associated with increased susceptibility to developing neuropathic pain, and with heightened pain experience in individuals with neuropathic pain. These variables have also been shown to compromise the effectiveness of interventions used in the treatment of neuropathic pain. This presentation will review current research on the influence of pain-related psychological variables on neuropathic pain. Discussion will address the mechanisms by which psychological variables might impact on neuropathic pain. Discussion will also address interventions that might reduce the negative impact of pain-related psychological variables on treatment outcomes.
PHASE 2-4 CLINICAL TRIALS
R. Dworkin, USA

In an increasing number of Phase 2 and 3 randomized clinical trials, the medications being evaluated have failed to provide significantly greater pain relief than placebo. Unfortunately, it cannot be determined in most cases whether these studies are “negative” trials of medications that truly lack efficacy or whether they were “failed” trials that were unable to demonstrate the benefits of truly efficacious medications. This uncertainty not only impedes the identification of treatments that could help patients who are refractory to existing therapies but exposes patients to investigational treatments that might have significant safety risks and also causes substantial expenditure of scientific and financial resources and. Several explanations for such neuropathic pain trial results have been proposed, including (1) preclinical animal models and methods have identified drugs with limited or no analgesic efficacy in human pain conditions; (2) these negative recent studies are falsely negative trials because of various methodologic factors that limited their assay sensitivity; (3) the optimal pain “phenotypes” were not studied; and (4) changes over the past two decades in the approaches used for conducting clinical trials and in the patients enrolled have adversely affected the validity of clinical trial outcomes. It is critically important that these and other factors that might have adverse impacts on the outcomes of neuropathic pain trials be determined and then addressed in future studies. Such research has the potential to provide the foundation for an evidence-based approach to the design of analgesic trials.
A fundamental assumption of placebo-controlled randomized clinical trials (RCTs) is that the effects of active treatment and placebo are additive and that the effects of the active treatment are determined by subtracting the placebo group response from the active treatment group response. If this assumption is correct, then modifications to clinical trial design intended to decrease placebo group responses will not increase assay sensitivity because such modifications would be expected to decrease responses in the active treatment group to the same extent as observed in the placebo group. However, the results of some studies suggest that “sub-additivity” of placebo effects in placebo vs. active treatment groups might occur in certain circumstances, potentially reflecting differences in the mechanisms of pain relief from placebo effects and from pharmacologic and other active treatments. Assuming that responses to active and placebo treatments are not necessarily additive, various methodologic aspects of RCTs could have differential effects on patients administered placebo and analgesic treatments. For example, Wise and colleagues [J Allergy Clin Immunol 2009;124:436-44] found that when treatments were presented with a neutral message about drug effectiveness, treatment efficacy vs. placebo was demonstrated, but that when treatments were presented with an optimistic bias, “the placebo group improved so much that there was no measurable benefit” of a leukotriene antagonist in patients with asthma. This presentation will review associations between placebo group responses and various patient, study design, and study site factors and discuss their implications for assay sensitivity.
Several signs and symptoms of Complex Regional Pain Syndrome (CRPS) are classically seen in inflammation. Sudeck was the first to suggest inflammation as a pathophysiological phenomenon playing a role in CRPS. During a long time this was not generally accepted by the scientific world mainly due to the fact that there is no fever and not a cell-mediated immune response. Sedimentation rates, autoimmune antibody levels, lymphocyte populations, activated T cells, and blood cell counts are all normal.

Evidence for a sterile inflammation has been demonstrated by increased levels of pro-inflammatory cytokines, such as interleukin 6 (IL-6) and tumor necrosis factor alpha (TNF-alpha) in artificially made skin blisters.

Neurogenic inflammation seems to be caused by excretion of neuropeptides from nociceptive C-fibers, which was demonstrated by elevated levels of substance P, bradykinin, and calcitonin gene-related peptide.

An inflammatory process is a normal physiological response after trauma, this immune response is meant to get restoration of damaged tissue. Typically in CRPS is the fact that this immune response seems to run out of control. Also typical is the strong cross talk of this inflammation with the nervous system. In a part of the patients this inflammatory response diminishes in time. It is unclear what is underlying the development of CRPS. There is evidence that genetic or immune derived factors are playing a role.

There is limited evidence for a role of immuno modulating therapies in CRPS.
In contrast to traditional thinking, opioid receptors are expressed, functionally coupled and effective in relieving pain throughout the neuronal pain pathway, i.e. at the level of the brain, spinal cord as well as peripheral sensory neurons (Khalefa et al., 2012). While in inflammatory pain peripheral opioid agonist efficacy is enhanced due to an NGF dependent opioid receptor up-regulation (Mousa et al., 2007), in diabetic neuropathic pain peripheral application of opioids, although effective, seem to be constrained most likely due to enhanced Rab7-mediated lysosomal targeting and degradation of sensory neuron mu-opioid receptors (Mousa et al., 2012). Peripheral opioid effects have the advantage of being devoid of life-threatening central side effects, however, they are hampered by the limitations of topical opioid treatment. Up to now, the systemic administration still is the main route of opioid delivery. Systemic administration of peripherally restricted opioids that do not cross the blood-brain barrier have been developed, however up to now, they have not been very successful in relieving pain in the clinical setting (Seghal & Smith, 2011). The question of the relative contributions of supraspinal, spinal and peripheral mu-opioid receptors to the overall antinociceptive effects of systemically applied centrally acting versus peripherally selective opioids will be discussed.

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PHENOTYPE VARIATION IN DIABETIC POLYNEUROPATHY

J. Scholz, USA

Patients with painful diabetic polyneuropathy (DPN) are often recruited into randomized controlled trials of analgesic drugs. The findings from these trials inform therapeutic guidelines for painful DPN specifically and peripheral neuropathic pain in general. However, DPN is inherently diverse, producing pain only in approximately half of the patients and different manifestations of pain, which may require adjustments in its management. To better understand phenotype variation in DPN, we recently enrolled 116 subjects with diabetes mellitus and 20 healthy control subjects in a prospective noninterventional study. We investigated somatosensory function including paresthesia and symptoms and signs related to pain by using a structured interview (47 items) and a standardized bedside examination (39 items). Ninety-seven of the subjects with diabetes mellitus had DPN with either a loss of sensory function, predominantly pain or a mixture of sensory loss and pain. The constellation of sensory symptoms and signs differed markedly within these subgroups, revealing distinct phenotypes of painful and nonpainful DPN. Dysfunction in different types of peripheral nerve fibers and activity of different pain mechanisms are likely to be responsible for this diversity. A standardized bedside assessment is capable of providing valuable information about differences in the clinical presentation of DPN. If applied in clinical trials, variation in the phenotype of DPN may be taken into account for evaluating the response to analgesic drugs or the efficacy of neuroprotective therapy to obtain more precise treatment recommendations.
An atypical PKC (aPKC) isoform, called PKMzeta, is thought to play a key role in the maintenance of synaptic plasticity in the adult CNS. Recently a potential role for PKMzeta, and possibly other aPKCs in chronic pain has been elucidated. We have utilized models of hyperalgesic priming to demonstrate that spinal administration of aPKC inhibitors at the time of priming leads to a failure of consolidation of maintenance as revealed by a peripherally or centrally administered stimulus. Importantly, during the maintenance phase of hyperalgesic priming, spinal inhibition of aPKCs is capable of completely reversing the pain-promoting consequences of priming, whereas other kinase inhibitors are ineffective. Hence, inhibition of aPKC may represent a mechanism to reverse a chronic pain state. To understand how aPKC is regulated in the spinal nociceptive system, we have investigated potential modulators of aPKC activity. We find that BDNF regulates aPKC activity at spinal synapses. Moreover, inhibition of BDNF/trkB signaling during initiation or maintenance of hyperalgesic priming also reverse the consequences of priming. Hence, BDNF signaling through spinal aPKCs tonically regulates the maintenance of hyperalgesic priming and blockade of this newly identified signaling axis may be advantageously manipulated to resolve a chronic pain state.
Targeting spinal GABA-A receptors is a potential strategy for alleviating chronic neuropathic pain. However, it is widely accepted that changes in K-Cl cotransporter, specifically KCC2, expression and function modifies GABAergic responses in the spinal dorsal horn after peripheral nerve injury. Although these changes alter responses to endogenous GABA, it is also clear that GABAergic modulation can still achieve antinociception after peripheral nerve injury. Using the tail-flick test in mice we have shown that blockade of KCC2 leads to a loss of analgesic efficacy of certain GABA-A modulators. Moreover, even under normal conditions, GABA-A agonists and positive allosteric modulators fail to maintain full analgesic effects at a broad dose range presumably due to deficiencies in Cl extrusion capacity. Here we will show that these dose-limiting effects of GABA-A agonists and allosteric modulators can be mitigated by inhibition of carbonic anhydrases. We hypothesize that this occurs due to a loss of depolarizing bicarbonate currents through GABA-A receptors when Cl extrusion is compromised. Moreover, we demonstrate that peripheral nerve injury recapitulates KCC2 inhibition-mediated losses in GABA-A-dependent analgesic efficacy in the tail flick test and that this can also be mitigated by blockade of carbonic anhydrase activity. Hence, even in the presence of peripheral nerve injury, the analgesic efficacy and effective dose range of GABA-A agonists and allosteric modulators can be advantageously manipulated by carbonic anhydrase inhibition at the spinal level. We propose that carbonic anhydrase inhibition may represent an effective adjuvant for GABA-A-dependent analgesics for the treatment of nerve injury-induced pain.
PROPOSAL FOR A CONSENSUS ON ASSESSMENT OF CANCER NEUROPATHIC PAIN

A. Caraceni¹ ², C. Brunelli¹ ², Italy, Norway

The diagnosis of neuropathic pain (NP) due to cancer is still debated. NP due to cancer is associated with worse analgesic response to standard treatment and require more complex analgesic regimens. The lack of homogeneous definition has compromised research and clinical understanding in this field as documented in recent literature reviews. The application of IASP NeuPSIG criteria for NP diagnosis to cancer pain presents specific issues; in particular the complex pathophysiology of cancer pain has to be considered. The aim of this project is to reach consensus on the development of a step-wise approach in diagnosing neuropathic pain in cancer patients at different levels: screening, first level evaluation for non-pain specialists and second level evaluation for pain or palliative care specialists.

A modified three-round Delphi survey was coordinated by a multidisciplinary restricted board of experts, not participating in the Delphi consultation; the board of experts identified the initial set of relevant issues and drafted the first proposal of algorithm for NP assessment and diagnosis.

Relevant topics dealt with by the survey are: peculiarities of NP in patients with cancer, IASP NeuPSIG diagnostic criteria adaptation in patients with cancer, standardized patient self assessment for NP screening, scoring of different items and their combination into a diagnostic algorithm.
Evidence from functional neuroimaging indicates that placebo analgesia involves a top-down activation of endogenous analgesic activity via the descending pain modulatory system. Functional connectivity analyses demonstrate that placebo analgesia depends on an enhanced functional coupling of the dorsolateral prefrontal cortex, the rostral anterior cingulate cortex and distinct subcortical structures such as the amygdala and the periaqueductal grey.

The majority of neuroimaging studies of placebo analgesia indicate that the reduced pain ratings during placebo analgesia are paralleled by decreased activity in classical pain processing areas including the thalamus, insula and somatosensory cortices. This supports the notion that the altered pain experience during placebo analgesia results from active inhibition of nociceptive input and not simply from re-appraisal or report bias. Indeed, recent evidence from spinal cord imaging reveals that pain-related activity in the ipsilateral dorsal horn, corresponding to painful stimulation, is strongly reduced under placebo. These results provided direct evidence for spinal inhibition as one mechanism of placebo analgesia and highlighted the fact that psychological factors can act on the earliest stages of pain processing in the central nervous system. Taken together, current evidence supports the notion that placebo analgesia involves a top-down activation of endogenous analgesic activity via the descending modulatory system. The additional contribution of emotional regulation processes and areas such as the limbic system is a fundamental step that needs to be further addressed. Importantly, these placebo-related mechanisms also modulate the efficacy of active analgesic treatments, as has recently been shown for remifentanil analgesia.
Spinal cord stimulation (SCS) involves placing leads or paddles into the epidural space to deliver electrical energy to the dorsal aspect of the spinal cord thereby resulting in pain relief. Systems currently in use have multiple contacts (commonly 16 or more) and allow programming via different contacts with many programming parameters. The technology has evolved dramatically in recent years possibly making older studies less relevant. The most studied conditions for SCS are failed back surgery syndrome (FBSS) and complex regional pain syndrome (CRPS), type 1; both with prospective, randomized studies. For these two conditions with positive prospective trials, a weak recommendation is given assuming less invasive treatment options have not resulted in a satisfactory result. There are less robust data for other neuropathic pain conditions (peripheral neuropathy, post herpetic neuralgia, CRPS type 2, spinal cord injury) resulting in an inconclusive recommendation. Finally, for central post-stroke pain SCS is not recommended.
CORNEAL CONFOCAL MICROSCOPY V PUNCH SKIN BIOPSY
R. Malik, UK

We currently lack highly sensitive and specific tests for the early diagnosis, and the assessment of progression or regression following therapeutic intervention in diabetic patients with small fibre neuropathy. Skin biopsies represent a minimally invasive technique to quantify Intra-epidermal nerve fiber density (IENFD) and have been shown to be reduced in subjects with IGT and in diabetic patients with no apparent evidence of neuropathy based on normal electrophysiology and quantitative sensory testing, suggesting that it detects early subclinical small fibre damage. However, such biopsies are invasive and demand experienced laboratory assessment. Corneal confocal microscopy is a rapid (2-minute) non-invasive ophthalmic technique, which directly visualizes corneal nerve fibres. A number of centres have now confirmed the utility of CCM for the assessment of primarily diabetic neuropathy, but also a range of other peripheral neuropathies including idiopathic small fibre neuropathy (ISFN), Fabry disease, Chemotherapy induced peripheral neuropathy (CIPN) and CMT1A. Abnormalities in CCM have been related to a loss of IENFD and severity of diabetic neuropathy. Furthermore, CCM has been shown to detect an improvement in corneal nerve morphology following pancreas transplantation in patients with Type 1 diabetes, providing persuasive support for its use as a surrogate endpoint in clinical trials of diabetic neuropathy.
QUANTIFYING PAIN IN HUMANS: A NEED AND A CHALLENGE
R.-D. Treede, Germany

Treatment of neuropathic pain is still a major unmet medical need. Although neuropathic pain is no longer considered a "chronic intractable pain", current treatments provide only partial pain relief to only a subgroup of patients (Sindrup et al. 2012). On the clinical side, the prospective identification of responders will therefore be an important step towards improved patient care. For this purpose, more complex clinical profiles of patients must be obtained than currently done. These profiles should include intensity, quality, time profile and spatial extent of ongoing pain, measures of somatosensory functions, quality of life parameters and biomarkers as they become available. Furthermore, the drug development process needs improvements to make new treatments with better efficacy and/or fewer side effects available. Here, the mismatch in readouts and disease pathophysiology are major hurdles. Since animal data mostly stem from reflex and other responses to external stimuli ("evoked pain") in models of peripheral nerve injury, early phase clinical trials should include evoked pain measures in humans and nerve injury should be one of the clinical conditions that are assessed. This presentation will focus on techniques for patient stratification and evoked pain assessment in humans.
ROLES OF QST IN NEUROPATHIC PAIN DIAGNOSIS

R.-D. Treede, Germany

The definition of neuropathic pain applies to individual patients, not to diseases. Therefore, assessment techniques are required that allow clinical judgement of the probability that a given patient with a given diagnosis and pain suffers from pain of neuropathic nature (Haanpää et al. 2011). The initial two steps of this clinical judgement require evidence form patient history that a) pain distribution is neuroanatomically plausible, b) a lesion or disease of the somatosensory system is plausible. It is important to reiterate that Quantitative Sensory Testing (QST) has no role in these initial steps, since it does not provide spatial data. These data can only come from a comparison of a patient's pain drawing and mapping of his/her sensory findings in bedside sensory testing. The diagnostic process then continues by looking for supporting evidence for a and b, leading to a probable neuropathic pain diagnosis when one of them is supported by clinical evidence, and to definite neuropathic pain when both are supported. QST can provide indirect evidence for a, by quantifying the pattern of sensory losses and gains within the painful area. For this purpose, QST is usually done within the most painful region and data are compared with published reference values (Magerl et al. 2010). This presentation will focus on the typical patterns of sensory losses for nociceptive and non-nociceptive modalities, hyperalgesias to thermal and mechanical stimuli and dynamic mechanical allodynia. Somatosensory profiling by QST is an important step towards a mechanism-based classification of (neuropathic) pain.
Accumulating evidence indicates that activation of spinal cord microglial cells plays a critical role in the pathogenesis of neuropathic pain. We and others have shown that activation of p38 MAPK in spinal cord microglia drives neuropathic pain by producing proinflammatory cytokines such as TNF-a and IL-1b and the neurophin BDNF. We have also demonstrated that TNF-a and IL-1b can directly and powerfully modulate excitatory and inhibitory synaptic transmission in the spinal cord. To indentify novel inhibitors for microglial activation and neuropathic pain, we tested the effects of resolvins and protectins, derived from omega-3 polyunsaturated fatty acids (fish oil), in mouse model of neuropathic pain produced by chronic constriction injury (CCI) of the sciatic nerve. Intrathecal injection of resolvin-E1 (RvE1) or neuroprotectin/protectin-D1 (NPD1/PD1) not only reduced neuropathic symptoms (mechanical allodynia and heat hyperalgesia) but also inhibited microglial activation (e.g., p38 phosphorylation). Direct application of NPD1 and RvE1 to microglial cultures also suppressed LPS-induced TNF-a release. Interestingly, peri-sciatic application of NPD1 effectively prevented nerve injury-induced microglial activation, long-term potentiation, and neuropathic pain. Our data suggest that resolvins and protectins may attenuate neuropathic pain in part via inhibiting microglial signaling in the spinal cord. The anti-inflammatory and pro-resolution lipid mediators may offer new options for preventing and treating neuropathic pain.
Multidisciplinary, multimodal treatment of neuropathic pain included pharmacotherapy with drugs from different classes. Current agents - as monotherapy - are limited by incomplete efficacy and dose limiting side effects such that less than one third of patients benefit. Knowledge of pain processing implicates multiple, concurrent mechanisms of nociceptive transmission and modulation. This suggests that synergistic drug interactions may provide superior analgesia and/or fewer side effects compared to monotherapy. This presentation will review evidence supporting the rationale and practice of combination pharmacotherapy for pain. Since escalating global efforts have not yet produced novel analgesics that surpass the efficacy of current treatments, combination therapy remains an important strategy. Recommendations for future research efforts will be made to harness the maximal potential of combination pharmacotherapy for pain.
Central sensitization represents a clear intersection between changes in the systems properties of nociceptive neural circuits and the clinical pain phenotype. To fully understand the meaning of this intersection we need to ask what operationally exactly is central sensitization, how is it initiated and maintained, how does it manifest, and is it a reasonable target for therapeutic intervention? This requires critical analysis both of what model organisms can tell us about how pain in humans is generated and of the utility of a comprehensive measurement of the pain phenotype in patients to provide information on neurobiological mechanisms. Such analyses should provide mechanistic insight into the well established but perplexing clinical finding that after damage to the nervous system, normally innocuous stimuli can begin to elicit severe pain.


TREATMENT OF PAINFUL DIABETIC NEUROPATHY

V. Bril, Canada

The management of painful diabetic neuropathy (PDN) has witnessed exciting developments in the last 10 years. Novel treatments for treating PDN have been accepted by regulatory agencies; the first time treatments for PDN have this indication. A critical evaluation of the evidence base for common treatments now helps guide caregivers in providing the best care possible. Although much work remains to be done, advances in the field have improved our treatment of patients with PDN.
ANIMAL MODELS

A. Rice, UK

Animal models of peripheral nerve trauma have played an important role in elucidating responses to the processes that may underlie the generation of neuropathic pain. Although such models are conventionally used in the drug development process, they have historically enjoyed limited success: whilst animal models are generally predictive for drugs which do have known efficacy in the clinic, they are less useful in predicting which drugs will not be shown to be efficacious in subsequent clinical trials - this limits the usefulness of such models to industry. There are multiple reasons, and therefore solutions, for this translational failure, the following of which will be discussed:

• Improved replication of the lesion/disease underlying pain in animal models. In particular the importance of creating a portfolio of models which properly reflects the spectrum of clinical conditions associated with neuropathic pain.

• The conventionally used outcome measures of hypersensitivity of limb withdrawal responses evoked by sensory stimuli have limited clinical relevance. The importance will be emphasised of creating a portfolio of outcome measures which are ethologically relevant to a social and prey species and which are validated by appropriate pharmacological responses.

• Adoption of robust “Good Laboratory Practice” experimental design and conduct standards aimed at bias reduction will be discussed.
Neuropathic pain (NP) is often inadequately relieved by pharmacologic and non-interventional therapies. Recently, a panel of experts from NeuPSIG evaluated the evidence for the role of interventional therapies in the management of NP (Dworkin et al, 2013). Two NP indications were identified where weak recommendations for epidural steroid injections could be made: (1) acute herpes zoster; (2) radiculopathy.

**Herpes zoster (HZ):** Epidural and paravertebral blocks local anesthetic and steroid injections have been shown in RCTs to decrease the pain associated with acute herpes zoster. Paravertebral injections q48 hours for 1 week resulted in a larger benefit than standard therapy and a lower incidence of PHN up to 12 months [Ji et al. 2009]. A weak recommendation was made for epidural or paravertebral local anesthetic and steroid injections for symptomatic treatment of acute HZ.

**Postherpetic neuralgia (PHN):** The efficacy of intrathecal methylprednisolone has been reported in two RCTs [Kikuchi et al., 1999; Kotani et al., 2000]. These reports have been criticized as it has the potential risk of adhesive arachnoiditis.

**Lumbosacral and cervical radiculopathy:** Based on recent systematic reviews and guidelines, a weak recommendation as made for the use of epidural injection for short-term benefits (up to 12 weeks), while the evidence for pain relief beyond 12 weeks or for prevention of future spine surgery was considered as insufficient. No clear recommendation could be made on the optimal frequency, timing, and number of epidural steroid injections for the treatment of radicular neuropathic pain in the extremities.
HYPNOSIS FOR CHRONIC PAIN: FACILITATING CHANGE IN MEANING AND MOOD

M. Jensen, USA

Research confirms that training in self-hypnosis can reduce the severity of chronic pain and that the benefits associated with hypnosis treatment can maintain for at least 12 months. Cognitive therapy is an alternative treatment for chronic pain, and focuses on teaching patients how to identify maladaptive thoughts that contribute to pain and distress, and use logic to develop more adaptive thoughts, which can contribute to improvements in functioning. Preliminary research supports the possibility that hypnosis can enhance the efficacy of cognitive therapy. However, the potential facilitating effects of hypnosis on cognitive therapy (i.e., “hypnotic cognitive therapy”) for pain has not yet been examined. This pilot study sought to test for these potential benefits. 15 individuals with MS and chronic pain were given four sessions of four treatment conditions: education control (ED), self-hypnosis training for pain (HYP), cognitive therapy (CT), and a hybrid intervention that uses hypnosis to alter pain-related beliefs (HYP-CT). The findings support a greater beneficial effect of HYP, relative to ED or CT, on average pain intensity. Moreover, the HYP-CT appeared to have greater beneficial effects than either CT or HYP alone. The findings support the potential for hypnosis to enhance the efficacy of cognitive therapy in pain treatment, and provide a model for how these interventions could be combined.
THE CHALLENGES OF ASSESSING THE COST-EFFECTIVENESS OF DEVICE-RELATED TECHNOLOGY

R.S. Taylor, UK

Faced with ever rising health care costs, payers are turning to economic evaluation as a means of controlling their budgets. As a result in many international jurisdictions, coverage for a new therapy depends not only on evidence of clinical benefit but also cost benefit. For example, in the United Kingdom, new medical technologies are only funded if they can demonstrate their cost-effectiveness falls below £20,000 to £30,000 per quality adjusted life year (QALY).

Most international guidelines for economic evaluation, although appearing to be generic, have been written with drugs in mind and may thus disregard the potential difficulties arising from evaluating other types of health technologies, in particular medical devices.1,2

Drawing on the experience of previous economic evaluations of spinal cord stimulation for chronic back pain, this workshop presentation will discuss some of specific challenges of assessing the cost-effectiveness of medical device based technologies, including the device-operator learning curve and the incremental innovation of medical devices over time. The particular role of modelling in aiding the reliable and informative evaluations of devices will be discussed.

References:


MECHANISMS OF NEUROPATHIC PAIN - A FOCUS ON DESCENDING MODULATION

S. Sikandar, F. Porreca, R. Baron, UK, USA, Germany

Nerve injury or trauma can produce sustained activity in peripheral afferents that results in significantly increased excitability of spinal cord neurones and higher centres, producing central sensitisation. There is increasing evidence for a significant role of supraspinal influences in the development and maintenance of abnormal sensitivity in neuropathic pain - in particular the brainstem rostral ventromedial medulla. The brainstem mediates the bulbar relay of descending modulatory projections to facilitate or inhibit spinal neurotransmission, and animal data suggest a key influence of enhanced excitatory events and/or reduced inhibitory controls. In addition, this brainstem-spinal pathway provides multiple pharmacological targets for analgesia, including those for antidepressant drugs, opioids and gabapentinoids. Pharmacological manipulations in animal models of neuropathy and imaging studies in humans have revealed an essential role of the brainstem in mediating pro-nociceptive changes in central excitability. The associated changes in various neurotransmitter systems are key to setting the scene for long-term sensory changes that promote a pain phenotype.

This workshop will provide a clear understanding of the role of these spino-bulbar interactions in producing and maintaining neuropathic pain. Recent preclinical and clinical data will be used to discuss changes that occur and the neurotransmitters involved within the spinal-brainstem loop of descending modulation, which ultimately leads to enhanced central excitability that underlies the altered sensory and pain phenotypes of neuropathic patient.
LASER EVOKED POTENTIALS: FROM DISTAL POLYNEUROPATHY TO TRIGEMINAL PAIN
A. Truini, Italy

Standard neurophysiological responses to electrical stimuli, such as nerve conduction studies and somatosensory evoked potentials, are useful to demonstrate, locate and quantify damage along the peripheral and central pathways, but they do not assess the function of nociceptive pathways. Laser evoked potentials are the easiest and most reliable neurophysiological technique for assessing nociceptive pathway function. Laser-generated radiant heat pulses selectively excite free nerve endings in the superficial skin layers and activate Aδ and C nociceptors. In peripheral neuropathic pains LEPs are more sensitive than any other neurophysiological test and the finding of LEP suppression helps to diagnose neuropathic pain. The trigeminal territory is particularly advantageous for LEP recording because of the short conduction distance and high receptor density. Trigeminal LEPs are of higher amplitude and are recorded more easily than LEPs after limb stimulation. Trigeminal LEPs have been studied in classical and symptomatic trigeminal neuralgia, trigeminal sensory neuropathy, postherpetic neuralgia, temporomandibular disorders, and headache. In general, in conditions that engender structural damage, such as herpes zoster, compression by tumours, or multiple sclerosis, LEPs are abnormal. In temporomandibular disorders, tension-type headache, or migraine, the LEP latency-though other types of abnormalities may be found-is always normal.
RISK FACTORS FOR CHRONIC NEUROPATHIC PAIN AFTER SURGERY

A. Stubhaug, Norway

Chronic postsurgical pain is common, and reported to be present in 5-85% of patients. The proportion of these being neuropathic has not been in focus in the literature so far. A recent meta-analysis found that the prevalence of neuropathic post-surgical pain differs in various types of surgery, probably depending on the likelihood of surgical iatrogenic nerve injury. Obviously, perioperative nerve injury is a risk factor for neuropathic pain. Perioperative chemotherapy and radiation therapy may also add to the nerve trauma. In addition, a number of pre-operative and postoperative risk factors have been found. This includes other preoperative chronic pain, preoperative pain in the area of surgery, high body mass index, previous smoking, older age and psychological factors. Poorly controlled post-operative pain may also be a risk factor. Altogether, current knowledge can guide clinicians to identify risk subjects and test preventive strategies.

References:


Epidural steroids are widely used for a variety of pain syndromes, such as sciatica and herpes zoster. About intrathecal use the literature is scarce. Glucocorticosteroids were intrathecally used for sciatica, arachnoiditis, multiple sclerosis, complex regional pain syndrome and postherpetic neuralgia (PHN). Although many adverse effects including cerebral hemorrhage, meningitis, conus syndrome, progressive weakness, reversible bladder dysfunction and paresthesia may occur, positive effects were described in patients with arachnoiditis and acute exacerbation of multiple sclerosis. For PHN, the results are contradictory. In a randomized clinical trial, 82 of 89 PHN patients treated with a series of 4 intrathecal injections of lidocaine and methylprednisolone acetate had good or excellent pain relief. Recently, a study with comparable methods was stopped early because of an increase in pain in PHN patients treated with intrathecal methylprednisolone acetate. During the presentation, possible explanations of the contradictory results will be discussed.
Botulinum neurotoxin (BoNT) has emerged as a major therapeutic advance in the treatment of many disorders, affecting motor and non-motor systems. It has applications in numerous medical specialties, including neurology, rehabilitation medicine, ophthalmology, otolaryngology, gastroenterology, orthopedics, dermatology, and urology. While the safety and efficacy of BoNT in the treatment of spasticity is well-established, its use for pain disorders is an emerging and active area of interest.

A task force of the Technology and Therapeutics Assessment Committee of the American Academy of Neurology performed a literature search for relevant, fully published, peer-reviewed articles related to clinical use of BoNT for neurological disorders. The panel was comprised of specialists with experience in the therapeutic use of BoNT for the indications under consideration or with expertise in guideline methodology. Authors reviewed, abstracted, and classified papers based on AAN criteria (Class I - IV). This lecture summarizes the evidence supporting the use of BoNT in neurological disorders, with a focus on spasticity and neuropathic pain.
Neuromuscular disorders are the most frequent of the neurological complications that occur in association with HIV infection and AIDS. Over one third of patients with AIDS have clinical evidence of peripheral neuropathy. The prevalence of neuropathy appears to have increased, due in part to increased lifespan of HIV-infected patients. However, non-neurological clinicians frequently misdiagnose neuromuscular disorders. Systemic disease or central nervous system (CNS) abnormalities may mask the symptoms and signs of peripheral neuropathy. The type, frequency, and mechanisms of peripheral neuropathies in HIV infection vary with the stage of immunosuppression. While distal sensory polyneuropathy is the most common form of HIV neuropathy, other patterns include mononeuropathy multiplex, demyelinating polyneuropathy and polyradiculopathy. The use of certain nucleoside analogue antiretroviral agents, specifically didanosine (ddI), zalcitabine (ddC) and stavudine (d4T), common in the developing world, may be limited by peripheral nervous system (PNS) toxicity. It is speculated that nucleoside-related toxic neuropathy is caused by mitochondrial toxicity. Therapeutic strategies for peripheral neuropathy include symptomatic therapy, primarily for pain, and pathogenesis-based treatment to reverse the underlying mechanism. This talk reviews the spectrum of neuropathic manifestations associated with HIV-infection, neurotoxicity of antiretroviral agents, treatment strategies and clinical trials available for these complications. New directions in research will be presented.
SMALL FIBER NEUROPATHY: DO WE NEED SKIN BIOPSIES IN CLINICAL TRIALS OR TO DIAGNOSE PATIENTS?

M. Polydefkis¹,², USA

Historically, small fiber neuropathy has been an elusive diagnosis that was ‘invisible’ to neurologists’ standard toolbox. As tests such as skin biopsy with intraepidermal nerve fiber density (IENFD) and quantitative sensory testing have emerged, Small Fiber Neuropathy (SFN) has garnered more attention clinically as well as from a clinical trial perspective. SFN is now appreciated to be a common clinical disorder and measures of small unmyelinated fibers are increasingly used in clinical trials.

This presentation will review historical developments central to the emergence of SFN as a clinical entity. In addition, questions such as the following will be addressed: Does ‘pure’ small fiber neuropathy exist? How do different measures of unmyelinated nerve fibers perform as a diagnostic test? Is any testing needed to make a diagnosis of SFN? Is there a relationship between IENFD and pain severity?

Finally, data from several recent clinical trials that used skin biopsies will be reviewed and contrasted to other peripheral nerve measures.
MICROGLIAL PURINERGIC SIGNALING IN NEUROPATHIC PAIN

S. Beggs, Canada

There is now a considerable canon of literature detailing interactions between the nervous and immune systems that are critical for the pathogenesis of pain sensitivity following peripheral nerve injury. In particular microglia, the cellular component of the immune system in the central nervous system, have been shown to have be key. Microglia are dynamic cells and are responsive to a range of stimuli in injury or disease. The modality of that response is signified by the adoption of a reactive phenotype. Here, a microglial phenotype characterized by the expression of the P2X4 purinergic receptor is proposed as a critical stage in the establishment of neuropathic pain. Activation of microglial P2X4 receptors initiates a signaling pathway with the synthesis and release of BDNF as the necessary intercellular signaling molecule between microglia and second order neurons in the sensory dorsal horn of the spinal cord. BDNF-trkB signaling in central neurons results in a disinhibitory increase in intracellular chloride and subsequent transformation of the output characteristics of spinal projection neurons. Activation of this pathway can account for the symptoms displayed in neuropathic pain and evidence is presented that targeted disruption of the microglial-neuronal signaling component of this pathway abolishes the pain behaviours elicited by peripheral nerve injury.
GENE THERAPY FOR TREATING CHRONIC NEUROPATHIC PAIN

S. Sweitzer, S.P. Wilson, S.N. Raja, USA

Herpes simplex virus mediated gene therapy approaches serve a dual purpose, to enhance peripheral opioid analgesia in neuropathic pain and to provide a better understanding of the complex interplay between endogenous opioid mediators in painful peripheral neuropathy. Ultimately, the main goal is to introduce a safe, efficient, and mechanism-based therapeutic strategy for neuropathic pain. Our laboratory has used gene therapy to over-express mu opioid receptor, preproenkephalin, or a combination of both receptor and ligand in preclinical acute nociceptive and persistent neuropathic pain models. Virus specific expression patterns have been found in the skin, dorsal root ganglia, and lumbar spinal cord. Similarly, we have observed virus-specific modulation of thermal hyperalgesia and mechanical allodynia in acute nociceptive versus persistent neuropathic pain models. In addition, we have observed virus specific enhancement of peripheral and systemic opioid analgesia in naive versus neuropathic models. These results suggest that increasing primary afferent expression of the mu opioid receptor or enkephalin or a combination of the two can have dramatically different effects on acute nociceptive versus neuropathic pain-associated behaviors, systemic opioid analgesia, and peripheral opioid analgesia.
This talk will suggest reducing, for practical purposes, the multi-dimensional pain experience into an unpretentious model of a one-dimensional spectrum ranging between pain inhibition and facilitation. Placing of individuals along this inhibitory-facilitatory continuum, based on their scores in simple dynamic psychophysical test paradigms, will reflect the interpersonal variability in pain modulation, stemming from environmental and genetic factors. Such placing is associated with the diagnosis of several pain syndromes, is of predictive value for acquisition of future pain, and is seemingly helpful for the choice of efficacious analgesics for the individual. Such placing seems to be dynamic; during painful times people are likely to shift toward the facilitatory end, expressing a 'pro-nociceptive' pain modulation state, while alleviation of pain is likely to be paralleled by return to the basic trait. The evidence supporting and disagreeing with this concept will be reviewed, with special emphasis on the utilization of the experimental-pain testing paradigms of conditioned pain modulation and temporal summation.
EXPLORING NEURAL CIRCUITS MODULATING AFFECTIVE DIMENSIONS OF PAIN: ENHANCING TRANSLATION FOR PAIN THERAPEUTICS

F. Porreca, J. Xie, E. Navratilova, USA

Preclinical studies of pain have been criticized as lacking translational relevance and failing to predict new mechanisms that might alleviate chronic pain in humans. Measuring relevant dimensions of pain in rodents is a challenge. Pain-induced aversiveness might be inferred in rodents through motivated behavior to seek relief. Drugs that are clinically useful in the treatment of acute and chronic pain states produce effects on brain reward circuits. Such information provides a basis for comparison with mechanistically novel therapeutic strategies in appropriate models of acute or chronic pain. A potential outcome is increased confidence in specific targets for potential translation. Circuits that underlie pain-induced motivated behavior appear to be highly conserved across species and offer an approach with likely high translational relevance with which to discover new therapies for treatment of pain.
An ongoing issue in the neurosurgical treatment of pain is the lack of objective methods of pain assessment, or study of the effect of treatment. Neuropathic pain can be the result of white matter injury, both in the peripheral (PNS) and central (CNS) nervous systems. We have used neuroimaging tools as *in vivo* correlates of pathophysiological processes involved in neuropathic pain. To do this, we use chronic facial neuropathic pain as a model. Important facial neuropathic pains include trigeminal neuralgia (TN) and multiple sclerosis-related trigeminal neuralgia (MS-TN). These two disorders share common clinical elements but differ in pathophysiology. Metrics derived from MR based diffusion tensor imaging (DTI)/tractography techniques can identify signature microstructural changes in each condition. These imaging modalities demonstrate that DTI diffusivity changes in TN are localized to the nerve entry zone, while in MS-TN, diffusivity changes are located in the brainstem fibers of the trigeminal nerve. DTI metrics can further help study the effect of treatment. Gamma Knife radiosurgery, a common method of TN treatment, results in marked focal changes in diffusivity in the trigeminal nerve and correlate with treatment effect, such that return of the diffusivities towards baseline with time is associated with return of pain.

The identification of microstructural changes in the trigeminal nerve in TN and MS-TN suggest that objective neuroimaging methods are crucial to the understanding of fundamental and clinical questions about neuropathic pain, study of treatment effect and variability in response.
The common emphasis of pain research is on potential mechanisms that can drive pain, and particularly, the transition from acute to chronic pain. However, little is known about the mechanisms that prevent chronic pain from developing following an injury. Nerve injuries can produce chronic pain in humans but this does not happen in the great majority of cases. In preclinical studies, however, nerve injuries almost always result in apparent “chronic” pain. Careful examination of data gathered over a period of years reveals, however, that some animals do not develop chronic pain. The potential contribution of descending pain modulatory mechanisms was explored in nerve injured rats following classification of the animals as “pain" and “pain-free”. Inactivation of the rostral ventromedial medulla (RVM) in injured animals with low sensory threshold transiently normalized “pain”. In contrast, inactivation of the RVM in animals that were classified as “pain-free” resulted in a time-dependent and transient evoked hypersensitivity suggesting the precipitation of pain. The data suggest that engagement of descending inhibition serves to “protect” from the development of neuropathic pain in some, but not animals. Why descending modulation may be differentially engaged following peripheral nerve injury remains to be elucidated.
When detected with traditional analysis approaches, most of the neural activity measured using currently available functional neuroimaging techniques (like EEG and fMRI) in response to a transient nociceptive stimulus does not reflect pain perception *per se*, but the unspecific detection of novel salient events, irrespective of the sensory modality of the stimulus. Hence, despite the importance of having an biomarker of pain perception, the neural correlates of the actual pain experience remain elusive. However, the application of recent methodological advances in the analysis of functional neuroimaging data is yielding spectacular advances towards capturing nociceptive-specific cortical activities in humans.
REACTIVE OXYGEN SPECIES IN DIABETIC NEUROPATHY

J.W. Russell\textsuperscript{1,2}, J. Choi\textsuperscript{1,2}, K. Chandrasekaran\textsuperscript{1,2}, USA

One potential mechanism of injury to the peripheral nervous system (PNS) is by oxidative stress. In the diabetic rat, levels of oxidative stress and reduced antioxidant defense parallel neuropathy; while blocking oxidative stress in diabetic animals restores normal blood flow and nerve conduction velocities. Increased metabolic mitochondrial flux due to high glucose results in increased formation of reactive oxygen species (ROS) and deficits in mitochondrial respiratory function. Generation of ROS is associated with mitochondrial permeability transition and mitochondrial swelling that disrupts the integrity of the outer membrane. In addition, there is membrane lipid peroxidation and degradation of DNA, all of which are associated with neuronal or axonal injury. Upregulation of antioxidant defense systems or regulation of mitochondrial function reduce the generation of ROS and may ameliorate neuropathy. For example, overexpression of SOD2 or uncoupling proteins (UCPs), which stabilize the mitochondrial membrane, can prevent generation of ROS. Medications which increase reduced glutathione (GSH) levels may reduce the severity of diabetic neuropathy. Alpha-lipoic acid (ALA), which reduces generation of ROS, has a disease modifying effect and in several studies has been shown to improve symptoms in diabetic neuropathy. ALA reduces pathological fluxes of nitric oxide (NO), decreases peroxinitrite mediated damage, prevents reduced endothelial NO production, and regenerates other antioxidants such GSH through redox cycling. Despite considerable promise, ALA has at best a limited therapeutic role in diabetic neuropathy. Transcription factors that regulate mitochondrial function may also play an important role in ameliorating diabetic neuropathy.
CANNABIS FOR NEUROPATHIC PAIN: DEBATING THE MERITS OF CANNABIS AS MEDICINE: PRO

M.A. Ware, Canada

There are few topics in medicine now that are as hotly debated as the use of cannabis (“marijuana”) for therapeutic purposes. The debate takes place mainly in the public domain, and while basic scientists continue to unravel the workings of the endocannabinoid system and its role in pain modulation and other neurological and immunological mechanisms, clinicians grapple with a limited evidence base and political and legal pressures to act as ‘gatekeepers’ to a drug that does not meet standard criteria for prescription medicines.

In putting forward the ‘pro’ side of this debate, I propose the argument that the clinical need is real and urgent, that biological plausibility for cannabinoid analgesia is solid, that clinical evidence is robust, and that there are indeed safe and legal ways for clinicians to address the question of cannabis for neuropathic pain.
LOST IN TRANSLATION: DRUG DEVELOPMENT LESSONS LEARNED FROM STROKE

M. Macleod, UK

If translational research is the taking of a set of research findings from one domain and using them to inform research or practice in another domain, then translational research in the neurosciences is in some difficulty. The reasons for translational failure can be studied, and much of this research has focussed on problems with drug development for stroke. Taking this example I will explore issues of risk of bias in individual animal studies; external validity of commonly used in vivo models and in vivo approaches; and the problem of publication bias. Then, I will briefly discuss the extent to which these concerns may hold more generally in the neurosciences. I will conclude by describing measures which might increase the prospects for translational success including good laboratory practice guidelines; use of publically available study protocols; registries of animal experiments; multicentre animal studies; and evidence based clinical trial design.
Using direct and indirect evidence drawn from datasets describing many thousands of in vivo experiments I will show that (1) there is an astonishingly low prevalence of measures to reduce the risk of bias; (2) that experiments at risk of bias give inflated estimates of drug effects; and (3) that publication in a journal of high impact is no guarantee of study quality. While much of this evidence comes from areas other than the modelling of neuropathic pain the effects are robust and highly prevalent. Either there is something very special about the tools used in the development of novel pain therapeutics (that is, unless they are intrinsically at low risk of bias), or the same holds here. What evidence we have suggests that this is indeed the case.
Allodynia is by IASP (2011) defined as “pain due to a stimulus that does not normally provoke pain”. While allodynia is considered to be mainly a manifestation of neuropathic pain it can also be seen in patients with inflammatory pain such as neck sprains, migraine arthrosis and idiopathic types of pain. The distribution of spontaneous and evoked sensory phenomena incl. allodynia may correspond to the innervation territory of the damaged nervous system structure, but it may also be seen both in peripheral nerve injury and in central lesions extending beyond the innervation territories.

The clinical expression and distribution of allodynia has provided information of some of the mechanism underlying this sensory phenomenon. There is ample experimental evidence from studies by e.g. LaMotte and Torebjörk that allodynia depends on activity in A fibers that express their non-noxious activity on a background of central sensitization. This central sensitization can be demonstrated both at the level of the spinal cord, but also in central brain structures. The evocation of allodynia by an external stimulus implies that a complete block of afferent input should lead to the abolition of allodynia. However, abnormal sensations similar to those seen in allodynia can also develop despite a complete loss of afferent input (anesthesia dolorosa) suggesting that the sensory characteristics of allodynia not always require a peripheral input.

The dynamic plasticity of allodynia is demonstrated by the ease with which this phenomenon can be altered by pharmacological and non-pharmacological manipulations. Examples of this will be illustrated.
COMBINATION TREATMENT OF NEUROPATHIC PAIN

T.S. Jensen, Denmark

Neuropathic pain is not a single condition but a syndrome caused by different etiologies and involving multiple mechanisms. Neuropathic pains have irrespective of underlying pathology certain essential characteristics which includes sensory deficit in the painful area, allodynia or hyperalgesia in the painful area, after sensations, abnormal temporal summation and sometimes a characteristic set of symptoms. Loss of sensation and increased sensation in the damaged nerve territory is a particular characteristic feature, which reflect damage to somatosensory structures and neuronal hyperexcitability as a consequence of loss of input.

Treatment should be directed at underlying mechanisms, but is in fact mainly symptomatic. This symptomatic treatment means in general a reduction of neuronal hyperexcitability, which is an essential part of neuropathic pains. Because of the multiple mechanisms involved in this hyperexcitability, there is a need to address this by compounds that act on multiple mechanisms. Also because of the adverse effects - mainly CNS related - combination therapy provides an opportunity to reduce dose of each compound and thereby possibly also reduce the magnitude of adverse effects. The classical targets for neuropathic pain are sodium channels, calcium channels, monoaminergic transporters, NMDA antagonists and in some cases also mu opioid receptor systems. The current status for the treatment of neuropathic pain will be presented.
NEUROPATHIC PAIN FOLLOWING INJURY: A MATTER OF LOSS OR GAIN?

N. Finnerup, Denmark

Trauma and surgery affecting the somatosensory nervous system are associated with a risk for development of neuropathic pain. There is a close relationship between the likelihood of injury to major nerves and the incidence of neuropathic pain. Thus more than 50% of patients develop chronic neuropathic pain following spinal cord injury and amputation, about 30% after lymph node excision, 5% following excision of malignant melanoma and 2 per 100,000 following blood donation. Consistent with this, we have found sensory loss to be a main predictor for persistent postoperative pain. Recent studies have also found early sensory hypersensitivity to predict the later development of central pain after stroke and spinal cord injury and chronic pain following certain types of surgery such as augmentation mammoplasty. However, early sensory hypersensitivity is not a predictor for e.g. as at-level spinal cord injury pain and certain types of polyneuropathy. It is likely that information about onset of pain and early sensory changes may help identifying different phenotypes of neuropathic pain.
A ROLE FOR NOVEL, ORALLY AVAILABLE MU-OPIOID AGONISTS WITH BOTH CENTRALLY AND PERIPHERALLY MEDIATED ANALGESIA IN THE TREATMENT OF NEUROPATHIC PAIN

L. Webster, USA

Introduction: Current pharmacologic treatments for neuropathic pain target both mechanisms. Opioid agonists are clinically efficacious in acute and chronic pain states, but may not be well suited to the chronic treatment of neuropathic pain due to adverse centrally mediated side-effects (such as sedation and abuse potential). Peripherally acting opioids should avoid these side-effects and previous work has suggested that peripheral opioids, such as morphine-6-glucuronide, have activity in human pain states. However, the properties that confer peripheral restriction on these previous compounds limit their oral bioavailability. A class of novel, orally bioavailable, mu-opioid agonists have been identified that are effective in animal models of both centrally and peripherally mediated pain. These opioids have been engineered to have a significantly reduced rate and extent of CNS exposure relative to standard opioids.

Results: Novel opioid compounds with slow brain entry have shown analgesic efficacy in animal models of pain that have both central (hot-plate) and peripheral components (formalin-paw, carrageenan). These compounds have comparable efficacy to standard opioids in these models. In animal models of abuse potential (self-administration and drug discrimination) and CNS-mediated side effects (rotarod), these compounds show substantially less adverse effects than the standard comparator opioids.

Conclusion: Novel, orally available, mu-opioid analgesics have been identified that appear to be as efficacious as standard opioids in animal models but exhibit lower abuse liability and CNS side-effects, giving them a markedly improved therapeutic window. These data suggest analgesic effect is mediated both centrally and peripherally and that NKTR-181 is effective in reducing human experimental pain.
We have published randomized controlled trial data comparing the cost-effectiveness of spinal cord stimulation (SCS) versus reoperation in treating failed back surgery syndrome.

**Materials and methods:** A disinterested third party collected charge data for the first 42 patients in our randomized controlled crossover trial. We computed the difference in cost with regard to success (cost-effectiveness) and mean quality-adjusted life years (cost-utility). We analyzed the patient-charge data with respect to intention to treat (costs and outcomes as a randomized group), treated as intended (costs as randomized; crossover failure assigned to a randomized group), and final treatment costs and outcomes.

**Results:** By our mean 3.1-year follow-up, 13 of 21 patients (62%) crossed from reoperation versus 5 of 19 (26%) from SCS (P 0.025). The mean cost per success was US $117,901 for crossovers to SCS. No crossovers to reoperation achieved success despite a mean per-patient expenditure of US $260,584. SCS was dominant (more effective and less expensive) in the incremental cost-effectiveness ratios and incremental costutility ratios. A bootstrapped simulation for incremental costs and quality-adjusted life years confirmed SCS’s dominance, with approximately 72% of the cost results occurring below US policymakers’ “maximum willingness to pay” threshold.

**Conclusion:** SCS was less expensive and more effective than reoperation in selected failed back-surgery syndrome patients, and should be the initial therapy of choice. SCS is most cost-effective when patients forego repeat operation. Should SCS fail, reoperation is unlikely to succeed.
In this presentation we will evaluate brain changes in patients with CRPS. Pediatric CRPS is a condition that normally resolves with time or with intensive treatments. Here we present data on alterations in brain networks in patients who have recovered or recovering and provide insights into functional systems that are involved in recovery from chronic pain.
At the beginning of the disease, CRPS is clinically characterized by an affection of peripheral tissues and nerves (edema, activation of osteoblasts, hyperalgesia to blunt pressure). These signs are the result of a dysbalance of pro- and anti-inflammatory cytokines, which normalizes six months after the beginning of the disease, independent from clinical outcome. At the same time, clinical signs such as allodynia (20%) cold hyperalgesia, reduced tactile acuity or symptoms of disrupted body representation (e.g. neglect-like syndrome, disrupted hand laterality recognition or shift of the body midline) suggest a crucial role of the central nervous system in the pathophysiology of this pain syndrome. In contrast to peripheral nerve injuries (PNI), imaging studies have found a severe but reversible reduction of the cortical hand representation (SI, SII and MI/II). Interestingly however, complex multi-sensory integration in central association areas are unaffected in CRPS, as patients are capable of integrating artificial body parts or recognize 2D forms despite tactile dysfunction. What is more, despite its unilateral clinical manifestation, it was shown that in CRPS but not in other unilateral peripheral nerve injuries, alterations in cortical excitability occur bilaterally, both in sensory and motor regions. In conclusion, a specific pattern of CNS reorganization appears to characterize CRPS, which can be assumed to be related to dysfunctions in the basal ganglia or in thalamo-cortical structures. Consequently, after having treated the inflammatory component of the disease, primary and secondary therapy should integrate neuro-rehabilitative training programs.
Many of the pain signalling and modulatory mechanisms in the CNS are changed following physiopathological events such as neuropathic pain and consequently, many of the drugs that can be effective in patients interact with this altered neural signalling systems. Many analgesic agents work on the principle of restoring balance between excitation and inhibition in chronic pain by increasing inhibitions (for example morphine) or decreasing excitatory input (for example anti-convulsant agents) to restore the physiological status of gates in the spinal cord, brain stem and higher centres.

This lecture will examine the peripheral and central targets, considering if drug actions can be used to probe mechanisms and attempt to provide principles for combinations of drugs, logical given that multiple mechanisms are likely to be at play in patients. Overall, targeting different mechanisms simultaneously has the potential to improve pain control.
VISUOSPATIAL ILLUSIONS IN POST-STROKE PAIN

S. Hatem$^{1,2}$, Belgium

Central post stroke pain (CPSP) is characterized by pain and sensory abnormalities due to a cerebrovascular insult in corresponding brain areas. CPSP may be difficult to recognize when occurring simultaneously with other stroke-related pain (e.g., shoulder pain, painful spasticity, musculoskeletal pain). It may develop following lesions at any level of the somatosensory pathways of the brain, including the medulla, thalamus and cerebral cortex and is a challenging condition to treat. Visuospatial rehabilitation treatments such as mirror therapy, biofeedback and prism adaptation are increasingly used to enhance motor and sensory recovery after a brain lesion. These approaches aim at gradually providing visual and proprioceptive input to influence cortical reorganization. Some of these rehabilitation therapies hold excellent promise as an adjuvant therapy for central neuropathic pain.
RTMS TO PREDICT THE EFFICACY OF IMPLANTED CORTICAL STIMULATION

J.-P. Lefaucheur, France

Chronic epidural motor cortex stimulation (EMCS) induces significant pain relief in patients suffering from chronic neuropathic pain. Repetitive transcranial magnetic stimulation (rTMS) allowed several questions to be addressed. We performed various experiments based on the assessment of rTMS-induced pain relief with respect to stimulus frequency, stimulation site, time course of the effects, clinical pain level, quantified sensory testing, or cortical excitability studies. We found that pain can be transiently relieved in patients with chronic neuropathic pain by applying rTMS at 10-20 Hz over the motor cortex corresponding to the painful zone. The targeting within the precentral gyrus influenced the results, justifying the use of an image-guided navigated approach. Pain relief was associated with changes in sensory discrimination within the painful zone and with the restoration of intracortical inhibitory processes. Cortical stimulation over the precentral motor area can produce analgesic effects. Regarding rTMS, the parameters of stimulation and the way of managing rTMS therapy remained to be optimized before considering this technique as a therapeutic tool. Conversely, motor cortex rTMS could be used to select good candidates for the surgical implantation of a cortical stimulator. A positive outcome of EMCS can be predicted by a real response to rTMS, but not on clinical grounds. Therefore, single sessions of sham-controlled preoperative rTMS tests can be used to confirm the indication of EMCS therapy but have no value to exclude patients from this therapy. New rTMS protocols remain to be assessed to improve the predictive value of preoperative rTMS in EMCS practice.
MULTIMODAL INTEGRATION OF NOCICEPTION AND PAIN IN THE PERIPERSONAL REPRESENTATION OF THE BODY

V. Legrain, Belgium

Being able to detect and react against stimuli that represent potential threats for the physical integrity of the body is a major function for survival. A nociceptive stimulus is an archetype of physical threat because it has the potential to afflict tissue damage to the body. Nociceptive processing involves spatial localization in order to detect what part of the body is potentially being damaged and to focus actions to the defense of that body part. The ability to localize nociceptive stimuli on the body depends partially on a direct relationship between the spatial organization of the skin receptors and the spatial organization of the neurons in the cortex. However, such a pure somatotopic representation of the bodily space might be insufficient to localize in external world what object is damaging the body. In most situations, at least in normal conditions, physical threats represent complex objects that also provide information to our other senses. Therefore, an adaptive control of behavior against potentially damaging objects requires the integration of information conveyed through nociceptive afferents and inputs originating from other sensory systems. The peripersonal frame of reference corresponds to an egocentric frame for spatial perception that codes both the position of somatosensory stimuli on the body surface, and the position of stimuli in external space (e.g., visual stimuli), when they occur close to the body. This talk will present the first data in favor of the use of peripersonal frames of reference for coding the spatial location of nociceptive inputs.
T-TYPE CALCIUM CHANNELS AND PAIN

G.W. Zamponi, Canada

T-type calcium channels are important players in afferent pain signalling. Inhibition or knockout of the Cav3.2 T-type calcium channels subtype mediates analgesia, whereas chronic pain conditions such as nerve injury, diabetes, or chronic inflammation up-regulate T-type channel activity. The cellular and molecular basis for this T-type current enhancement is not known. Here, we show that T-type calcium channel membrane expression is regulated by ubiquitination by the actions of specific ubiquitinating and deubiquitinating enzymes. The latter mechanism appears to be altered in chronic pain states, thus enhancing T-type channel expression. Interfering with de-ubiquitination in vivo via shRNA or disruptor TAT peptides combats neuropathic and inflammatory pain. Thus targeting aberrant channel regulation may serve as a novel therapeutic approach for pain.
CON: DOES EXPERIMENTAL BIAS CONTRIBUTE TO POOR BENCH TO BEDSIDE TRANSLATION OF NOVEL PAIN THERAPEUTIC AGENTS?

F. Porreca, USA

This debate will explore the question of whether experimental bias plays a role in the failure to translate novel pain biology to new therapies. This speaker will argue that there are many factors that need to be considered regarding the question of “translation”. These hurdles are likely to be much more significant than experimental bias.
ALTERATIONS OF THE SPINAL GABA\textsubscript{A} AND GLYCINERGIC SYSTEMS FOLLOWING NERVE INJURY AND THE IMPLICATION OF MICROGLIA IN THE HYPERSENSITIVITY CHARACTERISTIC OF NEUROPATHIC PAIN

Y. De Koninck, Canada

Inhibitory control by GABA\textsubscript{A} and glycine receptor-mediated neurotransmission determines how sensory information is integrated in the spinal dorsal horn and relayed via nociceptive output pathways to the brain. Weakened inhibition enables a cross-talk between sensory pathways allowing the aberrant relay of innocuous input through normally nociceptive specific pathways, which appears to be a substrate of allodynia characteristic of neuropathic pain. The mechanisms by which inhibitory control is modulated have remained elusive. We found that spinal inflammatory mechanisms which are triggered secondary to peripheral nerve injury can modulate GABA\textsubscript{A} and glycine receptor-mediated inhibition via the release of brain derived neurotrophic factor (BDNF) from activated microglia. We found that BDNF affects GABA\textsubscript{A}-mediated signalling in multiple ways. Yet, one final end-point is the disruption of Cl\textsuperscript{-} homeostasis, additively impairing the efficacy of both GABA\textsubscript{A} and glycine-receptor-mediated inhibition. This appears to be the main substrate of spinal disinhibition affecting sensory integration in spinal nociceptive relay pathways after nerve injury. Through this signalling mechanism, microglia alter the excitability of neurons, and thus appear to be the architect of pain hypersensitivity, opening new perspectives on how to understand and treat chronic pain. In addition, we have recently discovered that this sequence of events is also involved in morphine-induced hyperalgesia. The latter finding may explain the refractoriness of some neuropathic pain patients to opiate therapy. Targeting the microglia-BDNF-Cl\textsuperscript{-} pathway may thus not only be an avenue for chronic pain treatment, it may be key to develop adjuvant therapies against deleterious side effects of opiates.
POTENTIATORS OF THE POTASSIUM-CHLORIDE CO-TRANSPORTER KCC2 AS NOVEL THERAPEUTICS FOR NEUROPATHIC PAIN

Y. De Koninck, Canada

The K⁺-Cl⁻ cotransporter KCC2 is responsible for maintaining low Cl⁻ concentration in neurons of the central nervous system (CNS), essential for postsynaptic inhibition through GABAₐ and glycine receptors. Loss of activity of KCC2 has emerged as a key mechanism underlying several pathological pain syndromes. Recent studies have shown that enhancing KCC2 activity may be the favoured therapeutic strategy to restore inhibition and normal function in pathological conditions involving impaired Cl⁻ transport. We designed an assay for high throughput screening which led to the identification of KCC2 activators that reduce intracellular Cl⁻. Optimization of a first-in-class series of compounds resulted in KCC2-selective analogs that lower intracellular Cl⁻. These compounds restored impaired Cl⁻ transport in neurons with diminished KCC2 activity. The compound also re-normalised stimulus-evoked responses in spinal nociceptive pathways sensitized after nerve injury and alleviated hypersensitivity in a rat model of neuropathic pain. Oral efficacy equivalent to that of Pregabalin was achievable with no apparent motor impairment, validating KCC2 as a target for neuropathic pain.
Injury to the spinal cord occurs more commonly in the younger population (mean age 33yrs) [5] and has lifetime consequences for health and productivity [1]. Neuropathic pain remains one of the most difficult consequences of SCI to manage. It is a major cause of suffering and adds to the physical, emotional and societal impact of the injury. Despite the use of best available treatments, two thirds of people experiencing neuropathic pain following SCI do not achieve satisfactory pain relief.

Several types of pain occur following SCI, however neuropathic pain, which occurs in almost 50% of people, is one of the most intractable [3]. Interest in SCI neuropathic pain has been stimulated recently by a surge of translational research aimed at neuroprotection and regeneration [4]. This interest has been based on concerns that novel techniques aimed at neural regeneration also result in complications, including neuropathic pain [2].

Clinical examination has a limited capacity to detect partial fibre tract preservation following SCI. While neurophysiological tests are more sensitive, none are routinely available that assess temperature and pain transmission. A consensus approach for the assessment of sensory preservation following SCI, particularly subclinical spinothalamic tract preservation is yet to be achieved. Improved sensory assessment tools are desperately needed for ongoing SCI pain research.

Recent research has highlighted the profound changes that occur within the central nervous system in people who report ongoing pain. These changes will be reviewed and a number of novel treatment approaches and assessment measures discussed.

References available on request
WHAT DO STUDIES OF ANIMAL MODELS/DORSAL HORN TELL US ABOUT HUMAN NEUROPATHIC PAIN PATHOGENESIS?

M.W. Salter, Canada

Major advances in understanding are regularly reported about the pathobiology of pain hypersensitivity after injury to a peripheral nerve in non-human animals. Various means to produce peripheral nerve injury and to measure the behavioural consequences in animals have been developed to serve as more-or-less tractable models of human neuropathic pain. With knowledge from these models, we are in the midst of developing a ‘new biology of pain’ at increasingly fine detail in terms of the genetic, epigenetic, molecular, cellular and neural systems mechanisms. Neuron-neuron, neuron-immune and neuron-glia signaling interactions are viewed in increasingly complex ways to contribute to pain hypersensitivity in animals. Indeed, given the many diverse approaches developed - each of which appears to dramatically reduce pain hypersensitivity behaviours - one may argue that the outlook for neuropathic pain therapy is very good, if you are a rat or mouse that is. To bridge the species gap one may take advantage of the high interindividual variability that occurs in human neuropathic pain, and that can be produced in animal models. As pain variability is partially genetic, genes identified in animals can be interrogated in humans. For example, the purinergic receptor, P2X7, was identified as a prominent pain variability gene in mice and then in humans. Cross-species comparisons of pain variability not only give insight into common processes but are expected to lead to new strategies for diagnosing and managing pain that are personalized to each individual.

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QUANTIFICATION OF NOCICEPTOR DISCHARGES IN ANIMALS AND HUMANS

J. Serra, Spain

Treatment of peripheral neuropathic pain is still unsatisfactory, with only a few oral and topical available medications giving partial relief in most patients. This may in part reflect the fact that current preclinical models of neuropathic pain do not use appropriate surrogate markers for spontaneous pain, therefore having poor predictive validity.

If hyperexcitable peripheral nociceptors engage in spontaneous abnormal activity, which is a direct cause of spontaneous pain and central sensitization, why we do not record and quantify spontaneous impulse generation directly from peripheral nociceptors? This is what microneurography can offer, and it can do so both in humans and animals, providing a direct translational approach to drug development in neuropathic pain.

Spontaneous activity in the peripheral nociceptor system may also trigger central nervous system changes, such as central sensitization. The crucial question is to understand how many of these central changes are dependent on a continued peripheral input. Although there have been claims that central sensitization can become “independent” of a sustained peripheral input, the general view is now that altered sensitization in the CNS depends on peripheral input. The common outcome of local anesthetic blocks of isolated peripheral nerve neuromas strongly supports this view. If this is true, stopping spontaneous activity from peripheral nociceptors could be of important therapeutic value.

Microneurography can record and quantify spontaneous impulse generation directly from peripheral nociceptors in animals and humans, therefore providing a robust method that could be used in drug development for neuropathic pain.
The quest to find an objective biomarker for spontaneous pain has been long, and unsuccessful. Claims that measures such as patient somatosensory phenotyping, intraepithelial nerve fiber counts, electrophysiological recording of noxious stimulus-evoked cortical potentials, functional imaging, or genetic studies could offer an objective biomarker of spontaneous pain have all been disappointing. Radically, one might rightly argue that, in humans, the only possible true biomarker of spontaneous pain is the verbal report by the sentient patient of the conscious experience of pain.

Having an objective measure of pain would bring unquestionable advantages. It has been extensively demonstrated that hyperexcitable peripheral nociceptors may engage in spontaneous abnormal activity, which is a direct cause of spontaneous pain and central sensitization.

Microneurography can record and quantify spontaneous impulse generation directly from peripheral nociceptors in animals and humans. Microneurography probably has perfect face validity, as the measurements recorded in animals and humans are exactly the same, and the methods to obtain them are also identical. It also has good construct validity, as most probably the causes of spontaneous discharges in animals and humans are the same, although this point still needs further verification. Finally, we are convinced microneurography will have potent predictive validity, demonstrating that the same agents work in animals at the similar exposures that they do in humans. It is important to engage in human studies to test these assumptions as microneurography could provide an opportunity to test the efficacy of different compounds in stopping abnormal ongoing activity in peripheral nociceptors.
Pain from peripheral nerve injury is characterized by ongoing pain, hyperalgesia and allodynia that arise from an interplay between peripheral and central processes. The latter can be located at spinal levels and at higher centres and descending controls from the brainstem can link these processes.

There is clear evidence from both preclinical, human imaging and clinical studies that both peripheral changes and central hyperexcitability play important roles in determining the level of pain perceived.

This presentation will cover these processes and emphasize the interplay between very different peripheral events in the processes of persistent pain states and the more similar central mechanisms. Since neuronal communication relies on transmitter release the roles of events at spinal levels will be used as an example of convergence of the various processes of pain onto these key substrates.

Rightly, much emphasis has been put on spinal cord mechanisms in central excitability but it now becoming clear that spinal excitability can be regulated by descending inhibitory and excitatory pathways from the brain. These originate from predominantly monoamine systems which are additionally implicated in control of emotions, fear, anxiety and the sleep cycle and so may mediate these pain induced co-morbidities. Furthermore, dysfunctional processing at these higher levels of the CNS has the potential to produce maladaptive activation of descending pathways to elicit diffuse pain states that may include fibromyalgia.
Approximately one of three diabetic patients is affected by distal symmetric polyneuropathy (DSPN) which represents a major health problem due to clinical manifestations such as excruciating neuropathic pain, diabetic foot ulceration, and amputations which are associated with substantial morbidity, reduced quality of life, and increased mortality. The prevalence of painful DSPN is 13-26%. Recent evidence suggests that even prediabetes is associated with an increased risk of neuropathy. Treatment of DSPN is based on three cornerstones: 1.) multifactorial intervention aimed at (near)-normoglycemia and reduction of cardiovascular risk factors, 2.) treatment based on pathogenetic mechanisms; 3.) symptomatic treatment. Symptomatic treatment of chronic diabetic painful neuropathy remains a challenge for the physician. Non-pharmacologic options should always be given consideration. Pain treatment includes administration of antidepressants such as duloxetine and amitriptyline, calcium channel α2δ modulators such as pregabalin and opioids as drugs of second choice or for combination therapy. Pain reduction of at least 50% by monotherapy using these drugs can be achieved in around 50% of the patients, resulting in a number needed to treat (NNT) at around 4-5. Analgesic combinations have to be tried to optimize efficacy, and potential drug interactions have to be considered. Individual tolerability, quality of life, and the various comorbidities of diabetes such as obesity, coronary artery disease, or depression remain important aspects in any treatment decision. Recent advances in understanding the neurobiology of neuropathic pain should help to improve our armamentarium against this sequel of diabetes associated with substantial morbidity in the future.
INTENSITY AND FREQUENCY-DEPENDENT FEATURES OF SPINAL CORD STIMULATION-INDUCED ANALGESIA: BEHAVIORAL AND ELECTROPHYSIOLOGICAL EVIDENCE IN NEUROPATHIC RATS

Y. Guan, USA

Spinal cord stimulation (SCS) is a useful neuromodulatory technique for treatment of certain neuropathic pain conditions. The optimal stimulus parameters and mechanisms by which SCS produces analgesia are unclear. We sought to delineate intensity- and frequency-dependent mechanisms of SCS analgesia by behavioral testing and in vivo extracellular recordings in rats after L5 spinal nerve ligation (SNL). Three consecutive daily SCS at different frequencies (50-Hz, 1-kHz, and 10-kHz) progressively inhibited neuropathic mechanical hypersensitivity in an intensity-dependent manner (20%, 40%, 80% motor threshold). At 80% motor threshold, the ipsilateral paw withdrawal threshold increased significantly from pre-SCS measures, beginning with the first day of SCS at the frequencies of 1-kHz and 10-kHz, while it was significantly increased beginning on the second day in the conventional SCS (50-Hz) group. In electrophysiological study, 50 Hz dorsal column stimulation inhibited the C-component response of spinal wide-dynamic-range (WDR) neurons to graded intracutaneous electrical stimuli and windup (a short form of neuronal sensitization) in an intensity-dependent manner. Both 1-kHz and 50-Hz dorsal column stimulation reduced sciatic Aα/β-compound action potential size at high intensity, but only 1-kHz stimulation was partially effective at the lower intensity. In a separate study, windup in WDR neurons was significantly decreased after 50-Hz, but not 1-kHz, dorsal column stimulation. Thus, kilohertz SCS attenuated mechanical hypersensitivity in a time course and amplitude that differed from conventional SCS, and may involve different peripheral and spinal segmental neuronal mechanisms. Future studies are needed to examine whether different frequencies of SCS may activate different neurochemical and network mechanisms.
EFFECTIVENESS OF OPIOIDS IN THE MANAGEMENT OF NEUROPATHIC PAIN

C.F. Stannard, UK

Use of opioids for the management of acute and cancer-related pain was established in the 1980s and led to discussion of the role of opioids in the management of chronic non-cancer pain (CNCP). Early studies suggested that opioids may be poorly effective for the management of CNCP in general and neuropathic pain (NP) in particular.

Subsequently, controlled trials were conducted which suggested that opioids may have a role in CNCP management (including NP). This coincided with a sharp increase in prescribing of this class of drugs. More recent systematic review of evidence suggests that we must be cautious in concluding that opioids are effective for NP, and, set in the context of what we know of long term harms, we need to reappraise their role.

NP remains refractory to treatment. The new challenges that face us therapeutically are how to predict who may be helped by which drugs. Patients who fail to gain useful relief of symptoms with one drug or class of drug should be offered alternative treatment and opioids may have a role in properly sequenced therapy. Additionally, it is common clinical practice (with scientific rationale) to prescribe different drug classes in combination for the management of neuropathic pain but there is currently little in the literature to guide practice.

The presentation will discuss evidence for efficacy of opioids in the management of NP and explore the challenges posed by safe and sustainable use of opioids as part of the pain management plan.
SYMPATHETIC BLOCK FOR NEUROPATHIC PAIN

J.C.D. Wells, UK

Complex Regional Pain Syndrome

The potential benefits of sympathetic blockade with local anesthetics in patients with CRPS have been studied only in small randomized crossover studies. The quality of evidence is low, justifying an “inconclusive” recommendation, the treatment options for CRPS refractory to other management strategies are limited. Given ease of application, relative safety, and their clinical experience, the authors consider sympathetic blocks a reasonable treatment option to consider for patients refractory to pharmacologic and non-pharmacologic non-interventional treatments.

Favorable responses associated with local anesthetic sympathetic blockade have led some clinicians to perform destructive procedures targeting the autonomic nervous system in an effort to produce a permanent interruption in the transmission of sympathetically-maintained pain. Multiple techniques have been employed to accomplish this, including chemical neurolysis (usually performed with phenol or alcohol), and radiofrequency or surgical ablation. Available literature describing these techniques consists of either uncontrolled case series or poorly controlled comparison studies. Furthermore, there is a significant risk of patients developing post-ablation pain conditions that are often worse than the original pain. The authors believe that ablative procedures of autonomic structures for NP should be avoided given the weak evidence and potential for serious sequelae associated with these interventions.
Incidence of chronic pain after nerve injury is reported in up to 30% of patients. In many cases the extent and time of onset of nerve injury is unknown. The lecture will discuss how incidence of chronic pain is highly dependent on how nerve injury pain is defined and the time since injury occurred and in many cases the incidence is based on retrospective studies. Melanoma surgery is an example of acute nerve injury in human subjects where onset and to some degree extent of injury was known. Herpes Zoster is another condition where the onset of nerve injury is known. Longitudinal studies will be discussed to help us understand the process of resolution of pain and sensory signs and symptoms after nerve injury. The lecture will also include a discussion of the presence of itch during recovery after nerve injury.
HUMAN MODELS IN PHASE ONE

K. Petersen, USA

Early demonstration of analgesic efficacy in Phase 1 trials in healthy volunteers using experimental pain models is an alluring proposition, both from a financial and ethical perspective. Using relatively simple and inexpensive study designs we can study analgesic effect on pain thresholds, subjective ratings of evoked pain, and primary and secondary hyperalgesia following reversible cutaneous sensitization. Models are safe, reproducible and well-characterized mechanistically. Yet, since models induce some, but not all the changes that occur following actual nerve injury, not all compounds will show a signal in such models. In such cases, one may consider small "proof-of-concept" studies in patients with a well-defined neuropathic condition prior to undertaking large clinical trials. This workshop will provide examples studies where the model study predicted positive and negative outcome in the clinical setting and examples where the model study did not correlate with clinical results. Alternate strategies for detecting early analgesic signals will be discussed.
SCREENING INSTRUMENTS IN RESEARCH

N. Torrance, UK

A number of screening tools for identifying pain with neuropathic characteristics have been developed in recent years, and there is a growing body of published literature on their use in clinical practice and in research studies. This presentation will explore the use of screening tools used in a number of different study designs, including RCTs but focusing mainly on epidemiological studies of the general population. I will also present some new and interesting comparisons of the similarities and differences found when two screening tools, the S-LANSS and the DN4, are administered to a large random sample of the general population of the UK. What are the implications for future research? Should we think about combining/modifying some components of existing screening tools to generate a new consensus driven instrument?
A wide range of non-surgical and non-pharmacological treatment modalities are commonly used in physical medicine and rehabilitation in the management of neuropathies. Recent practice surveys revealed that typical management strategies for neuropathies include explanation and education, postural and ergonomic advice, joint mobilization, soft tissue techniques, neural mobilization and exercise. Due to the lack of high-level evidence, only weak recommendations can be made for any treatment modality. There is however an increased interest to evaluate which treatment modalities, especially those directed to the nervous system, can reverse various pathobiological processes typically observed in neuropathies, both locally and centrally, before embarking on large clinical trials. A recent MRI study in patients with carpal tunnel syndrome revealed a decrease of intraneural edema following one week of nerve and tendon gliding exercises. Preliminary results also indicate that similar exercises may be able to reduce extraneural edema in approximately half of the patients with carpal tunnel syndrome. A decrease in excitability of spinal dorsal horn neurons was observed (reduced temporal summation) following neural mobilization and a normalization of the satellite glial cell and astrocyte response in the dorsal root ganglia and spinal cord. A recent clinical trial illustrated the potential benefit of neural tissue management in patients with nerve related neck and arm pain. Treatment outcomes in most clinical trials are however still suboptimal, indicating that novel treatment modalities that have shown promising results in other persistent pain states, will need to be evaluated in patients with neuropathies.
A number of neurosurgical procedures, including Deep Brain Stimulation in the thalamus, are being used to treat serious treatment resistant pain conditions. The thalamic regions that have been used most often include the ventrocaudal nucleus as well as the periaqueductal gray. In the course of conducting the mapping that is necessary to localize these targets, it is possible to record from thalamic neurons to look at their spontaneous or provoked activity, and to use stimulation to map functions. In so doing, a number of observations are possible including changes in neurophysiologic function, plasticity and reorganization. The probing of such neurons in awake humans provides a unique opportunity to develop insights into thalamic neurophysiology and pain.
DYNAMICS OF INTRACELLULAR CHLORIDE REGULATION: INSIGHTS FROM COMPUTER SIMULATIONS

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Disinhibition caused by chloride dysregulation is implicated in several neurological disorders including neuropathic pain. This form of disinhibition stems primarily from impaired chloride extrusion through the potassium-chloride co-transporter KCC2 and is normally evidenced by a depolarizing shifts in GABA reversal potential ($E_{\text{GABA}}$) secondary to increased intracellular chloride concentration ($[\text{Cl}^-]$). We have reproduced conditions of KCC2 hypofunction in computer models in order to decipher precisely how chloride dysregulation arises and how it impacts neural coding. Our simulations highlight the importance of considering the influx, efflux, and intracellular diffusion not only of chloride, but also of other ions; indeed, a number of feedback loops involving multiple ion species exist. These feedback loops directly impact $[\text{Cl}^-]$ and can manifest highly nonlinear behaviors such as bursting. Computer simulations also reveal that even mild KCC2 hypofunction (i) allows non-constant chloride loads to produce exaggerated fluctuations in $[\text{Cl}^-]$ and (ii) slows the rate at which $[\text{Cl}^-]$ stabilizes at new steady-state values. Together, these two effects create an ionic memory of past inputs that degrades neural coding. Importantly, both effects manifest after less KCC2 reduction than required to produce gross changes in $E_{\text{GABA}}$ measured under low chloride load conditions. From a therapeutic perspective, it is notable that compensatory increase of GABAergic input fails to correct and instead exacerbates the disruption. Overall, the mechanistically detailed understanding of chloride regulation revealed by computer simulations is crucial for strategically developing interventions aimed at restoring normal synaptic inhibition.
Opioids have been recognized to have significant impact on the endocrine system for hundreds of years if not longer. Effects occur with single doses and become more profound with chronic use; the majority of individuals utilizing opioids chronically, whether in the context of addiction or pain, develop endocrinopathy. The major effects are on sex hormones, leading to alterations in libido, sex drive, mood, fatigue, fertility, and ultimately osteopenia and fractures. Additional effects have been reported including on corticosteroids. Because of the high prevalence and clinical importance of opioid induced endocrinopathy, routine screening and management is a mandatory part of clinical practice when using chronic opioid therapy.
PAIN-RELATED CATASTROPHIZING AND PERSISTENT NEUROPATHIC PAIN

J. Haythornthwaite, USA

While the literature is more extensive in other chronically painful conditions, there remains substantial support for the role of pain-related catastrophizing as a cognitive-emotional response to pain that contributes to the persistence of neuropathic pain and poor adaptation over time. Recent work suggests that pain-related catastrophizing in healthy subjects is associated with central sensitization and a neurophysiological response to pain that is indicative of an enhanced stress response. These individual differences in neurophysiological response to pain may provide the mechanisms linking catastrophizing to increased post-operative and chronic postsurgical pain. In the context of persistent pain, these processes may contribute to longer-term problems with adaptation and inhibit treatment responsivity.
NEUROPATHIC, STUMP AND PHANTOM PAIN IN AMPUTEES : ACCURACY OF GUIDELINES FOR USING HIGH CONCENTRATION 8% CAPSAICINE PATCHES

E.J. Viel, France

A 64-yr old man was treated for neuropathic (NP) and phantom pain on 3 fingers stumpsof the left hand after failure of conventional treatments including systemic drugs and lidocaine plasters. First application lead to phantom pain relief while NP was persisting. Early re-application one month after and again 3 months after allowed 50% reduction of NP and phantom pain relief and reduction by 2/3rd of systemic medication daily consumption (pregabaline, duloxetine). Six months later, no recurrence of phantom pain was seen while NP recurred on finger stumps. Two applications of capsaicin patches were done at one month-interval allowing total pain relief while the patient was able to quit systemic drugs daily intake. This conclusive case is linked to several other clinical cases where various stump NP (amputations above and below knee, fingers, toes, forearm...) conditions were treated the same way allowing to obtain progressively reduction in the intensity and surface of localized NP. Two questions arise as to the accuracy of current guidelines for 8% capsaicine patches use (mainly period between two applications) and also as to the place of such a local treatment in the current international guidelines for the treatment of NP : should we use capsaicine patches as a first-line treatment ?
QST: USEFUL FOR DIAGNOSTICS IN AN INDIVIDUAL CASE? YES!

C. Maier, Germany

QST was developed for group comparison. However, the European database including > 500 healthies and approx. 3500 patients with neuropathic pain allows us today to discriminate between normal and abnormal QST profiles also in an individual subject. QST results are influenced by proband's motivation. However, using a standardized protocol feigning or over-reporting patients are detectable. The risk of false positive QST results in case of hypoesthesia is < 10%. Therefore, QST is the first line technique to detect small fiber neuropathy with a higher specificity than sensitivity. Anecdotal evidence shows that the sensitivity of QST to detect peripheral nerve lesion better as of traditional procedures. However, QST is improper to ensure other clinical diagnoses, not for methodical reasons but rather because there are actually different underlying mechanisms in the same patient and within a group suffering of the same clinical entity. But new data demonstrate the discrimination between CRPS and PNI may be alleviated by QST with a specificity >90% if joint-associated blunt pressure pain threshold is measured instead of muscle PPT. QST may also be valuable to predict no response for example in patients treated with topical capsaicin and allows a differentiation of reason of treatment failure after lidocaine/capsaicin treatment (no sensitive pain versus too less pharmacological effect). In conclusion, step by step there is a growing knowledge to use QST also for individual diagnostic and monitoring. However, it has to be assured that QST is used with a standardized protocol for assessment and findings are critically evaluated.
THE DIABETIC EPIDEMIC: IMPLICATIONS FOR NEUROPATHIC PAIN

R. Freeman, USA

Epidemiologic studies estimate the worldwide prevalence of diabetes as 366 million persons in 2011 and 566 million persons in 2030. There is evidence that 50% of individuals with diabetes have a peripheral neuropathy. Neuropathic pain is present in up to 25% of these individuals. Neuropathic pain is present even in the earliest stages of diabetes, impaired glucose tolerance and impaired fasting glucose. Individuals with painful diabetic neuropathy have a substantially diminished quality of life. Painful diabetic neuropathy also imposes a significant individual and societal financial burden.

There are several neuropathies associated with diabetes. These include the generalized polyneuropathy, focal peripheral neuropathies due to compression, entrapment, ischemia and vasculitis; treatment induced peripheral neuropathy (insulin neuritis); and the neuropathy associated with impaired fasting glucose and impaired glucose tolerance. Each has a unique clinical phenotype and underlying pathophysiological mechanism. Therapeutic interventions differ among the different neuropathies.

Set against the background of the growing prevalence of diabetes, this talk will cover the pain phenotype, pathophysiological mechanisms and therapeutic interventions for the different painful peripheral neuropathies associated with diabetes.