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Aims and Scope

The European Journal of Pain is the official journal of the European Federation of Chapters of the International Association for the Study of Pain (EFIC). It is a multi-disciplinary journal that aims to be a global forum on all aspects of pain and its management. The journal differs from existing pain journals in its clinical and educational emphasis. The journal publishes clinical and basic science research papers relevant to all aspects of pain and its management, including specialties such as anaesthesia, dentistry, neurology and neurosurgery, orthopaedics, palliative care, pharmacology, physiology, psychiatry, psychology and rehabilitation; socio-economic aspects of pain are also covered.

The journal publishes original clinical and basic science articles; reviews on pertinent topics not recently covered by other international journals; clinical and experimental notes, such as case reports of educational or scientific value, qualified and long-term clinical observations, technical advances in clinical practice and experimental research, therapeutic studies or experiments with negative results and pain-provoking procedures; short communications on clinical or basic science articles; and letters to the Editor.

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Chairman’s Letter

A glance into the Book of Abstracts – Second International Congress on Neuropathic Pain

Neuropathic pain, i.e. pain arising as a direct consequence of a lesion or disease affecting the somatosensory system, is common in clinical practice, in many cases very difficult to treat, greatly impairs the quality of life of patients and is, therefore, a major economical health problem. An impressive body of scientific work over the last two centuries has convincingly shown that the distinction of neuropathic pain from other chronic pain types is crucial. First, neuropathic pain expresses itself with different somatosensory signs and symptoms. Therefore, screening and diagnosing these specific phenotypes is of utmost importance for classification. Second, the underlying pathophysiological mechanisms of pain generation are most likely different from other pain types. Therefore, a deeper understanding of these mechanisms is necessary to design novel treatment strategies that target the specific mechanisms. Third, clinical studies show that neuropathic pain requires different therapeutic approaches than other pain types. Therefore, well designed clinical trials with new drugs are desperately needed. Only the holistic approach of translational research including animal research, genetic approaches, pathophysiological studies in patients and large, multicenter pharmacological trials will ultimately calm the cruel tormentor of neuropathic pain.

All the issues stated above are the goals of the Special Interest Group on Neuropathic Pain (NeuPSIG) of the IASP (International Association for the Study of Pain). NeuPSIG has the task to achieve these goals by joining the forces of many disciplines, from the bench to the clinic. NeuPSIG received a tremendous increase in recognition during the last years, clearly indicating that neuropathic pain is an important medical problem that combines the interest of many disciplines.

This special issue of the European Journal of Pain contains the abstracts of invited and volunteered contributions to be presented at the 2nd International Congress of NeuPSIG. Thus, this book of abstracts provides a snapshot of the status of research and clinical medicine in the field of neuropathic pain as of summer 2007.

A word about the topics covered. The focus of plenary lectures and topical seminars reflects the ideas collected from all members of NeuPSIG. The program includes 12 plenary lectures that are structured in three sessions on treatment of neuropathic pain from bench to bedside, neuropathic pain and inflammation and modulatory influences on neuropathic pain. Also 30 topical workshops that are structured in six main themes to discuss all aspects of neuropathic pain, i.e. basic sciences, epidemiology and health care, mechanisms and translational research, assessment and diagnosis, specific diagnosis, therapy. Beside this, the overlap between neuropathic pain and other chronic pain types like back pain, migraine and headache will be touched upon. The emphasis on cutting edge science and evidence-based medicine is a silver thread throughout the entire program.

A total of over 300 posters under 13 different categories have been selected for presentation at the meeting. We hope all participants take the opportunity to view these, and discuss them with the authors.

One of our most important visions within NeuPSIG is to encourage young investigators in many fields of medicine to share the enthusiasm of neuropathic pain research. There is much more to come in the future, be it in the field of basic science, clinical research or in the pipelines of pharmaceutical companies.

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Just read the book of abstracts or, even better, approach participants of the congress to get an impression of the fascinating world of neuropathic pain research. All this and much more you will experience at 2nd International Congress of the Special Interest Group on Neuropathic Pain in Berlin, June 7–10, 2007.

See you all there and enjoy the program.

Ralf Baron
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Division of Neurological Pain Research and Therapy,
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Invited Presentations

PLenary Lectures

Plenary Session: TREATMENT OF NEUROPATHIC PAIN FROM BENCH TO BEDSIDE

1 THE ROLE OF POTASSIUM AND OTHER CHANNELS IN THE PATHOPHYSIOLOGY AND TREATMENT OF NEUROPATHIC PAIN
A.H. Dickenson
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Electrical impulses are generated and shaped by sodium and potassium channels and increases in voltage will in turn open calcium channels that trigger the release of transmitter. Recent understanding of ion channels has shown important roles of particular sodium, potassium and calcium channels in the genesis and maintenance of neuropathic pain, both peripheral and central. Most knowledge and therapy is presently based on peripheral located sodium channels and calcium channels but potassium channels which will be featured here are key controllers of excitability and may provide a new approach to treatment.

Neuropathic pain arises from initiating changes in the damaged nerve which then alter function in the spinal cord and the brain and leads to plasticity in areas adjacent to those directly influenced by the neuropathy.

Both familial pain disorders and their roles as substrates for excitability blockers such as carbamazepine and lignocaine show the importance of sodium channels whereas both neuropathy induced changes and the effects of alpha-2 delta ligands such as pregabalin demonstrate the importance of calcium channels. Certain potassium channels such as KCNQ are strongly suggested to be key “brakes” on neuronal excitability and the potential for therapy will be discussed.

In addition to these peripheral mechanisms of hyperexcitability, spinal cells participate in a spinal–supraspinal loop that involves parts of the brain involved in affective responses to pain but also engages descending excitatory systems that become more active after nerve injury and are a major factor in the state-dependent actions of gabapentin and pregabalin.

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2 EVIDENCE-BASED MEDICAL TREATMENT OF NEUROPATHIC PAIN
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Within the past decades, basic research has shed light on several mechanisms of neuropathic pain, and drugs with different pharmacology have been tested in controlled trials in neuropathic pain. Some drugs were selected for clinical trial because they had a pharmacological action with a potential to interfere with one or more of the mechanisms of neuropathic pain and maybe also their ability to reduce pain in animal models of neuropathic pain. Other drugs entered a clinical trial programme via empiric observations of pain relief in patients with neuropathic pain. This process has led to evidence-based efficacious treatments of peripheral neuropathic pain such as the anticonvulsants gabapentin and pregabalin, and the dual uptake inhibitor antidepressants duloxetine and venlafaxine. Some drugs failed to show consistent and clinically meaningful efficacy despite a pharmacological action suited to interact with one or more pain mechanisms and positive results in the animal models of neuropathic pain. Examples of such drugs are the anticonvulsants oxcarbazepine, topiramate and lamotrigine, and the NMDA-receptor antagonist memantine. The new treatments like gabapentin/pregabalin and duloxetine appear less efficacious than tricyclic antidepressants when efficacy is measured by Numbers Needed to Treat (NNT). This may in part be caused by different data sources for NNT calculations, i.e. many small single-centre cross-over trials for tricyclic antidepressants versus large scale multi-centre, parallel-group trials for the new treatments. In order to improve treatment, there is a desperate need for large scale trials.

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3 EVIDENCE-BASED ASSESSMENT OF INTERVENTIONAL TREATMENTS FOR NEUROPATHIC PAIN
H.J. McQuay

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There is an obvious double standard when it comes to looking critically at how we treat neuropathic pain. On the one hand, we have the drug treatments, and on the other we have our reversible and irreversible interventions. The drug treatments are usually assessed with rigorous clinical trials, and it is possible to assess the evidence base professionally. This applies to both the conventional and the unconventional analgesics.

The interventional treatments are rarely subject to such rigorous trials, and yet we all use them, to greater or lesser extent, to manage those who have failed on medical treatment. The credibility of the evidence, because the trials are usually of lower quality, is thus questionable. The reversible interventions, using drugs with time-limited (and reversible) action, have perhaps a slightly better evidence base than the irreversible (cutting, burning, freezing, etc.). Some interventions do not quite fit this classification, and stimulation may be an obvious example.

Efficacy is not the whole story, however. The duration of efficacy may appear to be simple to measure, but a low morbidity short duration may be preferable to long duration at higher risk. Safety of the interventions may be very important, as the patient choice studies in arthritis show.

The lecture will attempt a sure-footed path through this minefield, in the certain knowledge that it will fail to please all those who attend.

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4 COMBINATION DRUG THERAPY FOR NEUROPATHIC PAIN
I. Gilron

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Current drugs reduce neuropathic pain and improve mood and quality of life. However, as single agents they are limited by incomplete efficacy and dose-limiting adverse effects. Recent experimental and clinical data support the potential of combination pharmacotherapy for neuropathic pain. Therapeutic benefits may include greater efficacy, lower doses and fewer adverse effects. Due to potential adverse, as well as beneficial, drug interactions, safety and efficacy of specific combinations must be empirically evaluated. Techniques such as isobolographic analysis, response-surface modeling and other model-free tests have been used in order to characterize analgesic interactions as antagonistic, additive or synergistic. Whether synergistic or not, a clinically useful combination could simply have additive or even subadditive analgesia, provided that there is less additivity for side effects. Despite widespread clinical use, there are surprisingly few published observations on combination therapy for neuropathic pain. Current and future efforts are underway to develop research strategies aimed at bridging current knowledge gaps, including safety, compliance and cost-effectiveness; discovering optimal drug combinations and dose ratios; comparing concurrent with sequential combination therapy; and combining more than two drugs. Continued close integration of basic and clinical sciences is crucial in further harnessing the potential of combination pharmacotherapy in neuropathic pain.

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Plenary Session: NEUROPATHIC PAIN AND INFLAMMATION

5 NEUROPATHIC PAIN AND INFLAMMATION: AN ANIMAL MODEL OF POST-HERPETIC NEURALGIA
S.M. Fleetwood-Walker

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Chronic pain arising from nerve injury is difficult to treat. New effective pain-killers are urgently needed. One such nerve injury is caused by varicella zoster virus (VZV) is a neurotropic human herpesvirus that remains latent in sensory ganglia following primary infection (chickenpox or varicella). Reactivation of latent varicella zoster virus (VZV) within sensory trigeminal and dorsal root ganglia (DRG) neurons produces shingles (zoster), often accompanied by a chronic neuropathic pain state, post-herpetic neuralgia (PHN). PHN persists despite latency of the virus within human sensory ganglia and is often poorly responsive to current analgesic or antiviral agents. To study the basis of varicella zoster-induced pain, we have recently developed a model of chronic VZV infection in rodents. Unilateral VZV infection induced
increased behavioral reflex responsiveness to both noxious thermal and mechanical stimuli ipsilateral to injection and characteristic phenotypic changes were found in sensory neurons in the DRG, broadly similar to those found in other nerve injury models. These changes were reversed by gabapentin, NMDA receptor or sodium channel blockers in agreement with clinical findings.

Molecular receptors for cooling have been identified in sensory nerves and we have identified how activation of one of these, the transient receptor potential TRPM8 cation channel, produces profound, mechanistically novel, analgesia in chronic pain states, including neuropathic pain. This can be achieved using selective activation of the TRPM8 channel by applying cooling chemicals such as menthol and icilin topically to the skin, pointing to a new, independent strategy for therapeutic analgesia in neuropathic pain.

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6 TOWARDS PREVENTION OF POSTHERPETIC NEURALGIA
R.W. Johnson

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Herpes zoster (HZ) and postherpetic neuralgia (PHN) most commonly affect older persons and individuals whose cell-mediated immunity (CMI) is compromised for other reasons. The age of the population is increasing and we may expect increased incidence of HZ resulting in a significant burden on individuals and the economy.

There has been no mechanism for prevention of HZ. Prevention of PHN has proved difficult with negative outcomes from trials of oral steroids combined with antiviral drugs and single epidural injections of local anaesthetic with steroid. Antiviral drugs reduce duration of zoster-associated pain but there is no unequivocal evidence that they reduce the burden of PHN. Effective analgesia from other medications during acute HZ as a PHN prevention strategy has yet to be tested adequately. PHN treatment has improved but about 50% of sufferers achieve 50% pain relief with significant side-effects.

A vaccine against varicella was introduced in the USA for children in 1995 and has had dramatic effects in reducing incidence of varicella. Older adults have reduced CMI responses compared with children making adult vaccination against HZ less certain.

A HZ vaccine using the Oka strain attenuated virus was developed and the Shingles Prevention Study investigated a population of 38,546 immunocompetent adults ≥ 60 years considered to be seropositive (thus susceptible to developing HZ), comparing active vaccine with placebo vaccine. Incidence of HZ was reduced by 51.3% and PHN by 66.5% with good safety outcomes. Ongoing surveillance will confirm duration of protection.

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7 PAIN IN HIV-ASSOCIATED NEUROPATHY
D.M. Simpson

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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 or myopathy. Risk factors for the development of HIV neuropathy include advancing age, white race, and other conditions that may also cause neuropathy, such as diabetes mellitus and alcoholism.

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), and possibly certain protease inhibitors, 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 will present data from clinical trials for the management of HIV-associated neuropathic pain, including recent and ongoing studies of pregabalin and high-concentration capsaicin patch.

References


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### Plenary Session: MODULATORY INFLUENCES ON NEUROPATHIC PAIN

#### 8 DESCENDING CONTROL OF NEUROPATHIC PAIN: INHIBITORY OR FACILITATORY?

**M.H. Ossipov**

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Enhanced abnormal pain associated with peripheral nerve injury depends in part on a sensitized spinal cord. Enhanced afferent drive immediately after injury may promote spinal sensitization. Spinal sensitization is associated with enhanced responsiveness of dorsal horn neurons to sensory stimuli, increased expression and internalization of NK1 receptors, increased release of PGE2 and upregulation of spinal dynorphin. We recently reported that dynorphin may promote nociception and transmitter release through an interaction with the bradykinin receptors. These pronociceptive changes lead to an increase in nociceptive signals that are transmitted to supraspinal pain processing sites. Converging evidence indicates that the sustained increased afferent inputs may provoke neuroplastic changes at medullary sites that serve to maintain a state of spinal sensitization and enhanced pain. Studies with animal models of neuropathic pain showed that the rostralventromedial medulla (RVM) shows evidence of increased activity of descending pain facilitatory pathways to the spinal cord. These projections from the RVM enhance the sensitivity of dorsal horn neurons to afferent input and also promote the release of excitatory neurotransmitters from primary afferent terminals. Pharmacologic and surgical manipulations that disrupt descending pain facilitatory systems also abolish the maintenance of the behavioral signs of enhanced abnormal pain as well as upregulation of spinal dynorphin, enhanced transmitter release and internalization of the NK1 receptor in the spinal cord. It is suggested that neuropathic pain may be maintained by a spinal-supraspinal-spinal loop that provides a “feed-back” to constantly maintain abnormal pain. These processes and how they relate to neuropathic pain will be discussed.

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### 9 THE PLACEBO EFFECT: FROM MECHANISMS TO CLINICAL IMPLICATIONS

**F. Benedetti**

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The placebo effect is a rapidly growing research field, whereby sophisticated neurobiological research tools have recently been applied, such as neuropharmacology, brain imaging, in vivo receptor binding, and single-neuron recording in awake humans. These techniques have allowed a better understanding of the mechanisms underlying the placebo effect, with the most secure and promising results in the field of pain and analgesia. Both placebo analgesia and nocebo hyperalgesia have been investigated and the underlying biochemical mechanisms have been identified. It is fundamental to understand that the study of placebo and nocebo effects is basically the study of the psychosocial context around the patient and the treatment, and has immediate clinical implications that embrace both clinical trials methodology and clinical practice. For example, as placebos induce opioid release in the brain, any drug may potentially interact with these placebo-activated endogenous opioids, thus confounding the interpretation of clinical trials. Likewise, nocebos may activate cholecystokinin through the induction of anticipatory anxiety. A key question is whether the loss of these placebo mechanisms may represent a point of vulnerability for the expression and maintenance of a pathological condition and for the response to its therapeutic intervention. To answer this question, the disruption of placebo-related mechanisms has recently been obtained experimentally by means of hidden administrations of treatments and has also
been described in dementia. Importantly, in both these cases, the effectiveness of analgesic therapies has been found to be reduced. These findings have important clinical implications in all painful conditions, including neuropathic pain.

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10
FUNCTIONAL IMAGING IN NEUROPATHIC PAIN
I. Tracey

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Neuroimaging tools have become widespread tools for the investigation of acute and chronic pain processing in humans. To date, most FMRI related work has focused on acute nociceptive processing in the healthy CNS under varying conditions (i.e. during psychological or pharmacological manipulation). The cerebral signature for such pain experiences is reasonably well defined, and areas commonly modulated to produce behavioural analgesia better understood (Schweinhardt P, Lee M, Tracey I. Imaging pain in patients: is it meaningful? Curr Opin Neurol 2006;19(4):392–400 [review]; Tracey I. Nociceptive processing in the human brain. Curr Opin Neurobiol 2005;15(4):478–87 [review]; Apkarian AV, Bushnell MC, Treede RD, Zubieta JK. Human brain mechanisms of pain perception and regulation in health and disease. Eur J Pain 2005;9(4):463–84 [Epub 2005 Jan 21, review]). From such normal subject studies, hypotheses have been generated to test in chronic pain patients as well as models of key neuropathic pain symptoms (i.e. the capsacain model for primary and secondary hyperalgesia) using FMRI. Areas found that seem critical for generating and maintaining central sensitization include the brainstem’s descending modulatory pathway. Both defects in descending inhibition and enhancement of descending facilitatory mechanisms have been separately identified in several patient cohorts. Furthermore, higher cortical regions such as the anterior insula, entorhinal/hippocampal complex and several separate regions of the prefrontal cortex (i.e. mPFC and DLPFC) seem to be involved in mediating how the more affective, cognitive aspects of a chronic pain state (i.e. catastrophising, depression, anxiety, hypervigilance) influence and exacerbate the pain experience. Some evidence further links these cortical and subcortical structures to areas of the brainstem’s descending pain modulatory.

Finally, recent work using structural imaging and sophisticated analysis methods shows significant atrophy in the brains of chronic pain patients (especially DLPFC and thalamus). This implies possible neurodegeneration. This talk will highlight the literature that supports the above statements. It will also discuss the exciting and current application of neuroimaging for clinical diagnosis and drug discovery.

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11
PLASTICITY OF INHIBITION THROUGH MICROGLIA TO NEURON SIGNALLING
M.W. Salter

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Over the past decade there has been a radical change in our understanding of the roles of glial cells in the function and dysfunction of the central nervous system (CNS). Historically, glial cells were considered to serve primarily housekeeping roles but these cells are now known to be critical for key aspects of development, plasticity and diseases. Microglia, which comprise about 10% of the glial cells in the CNS, were once considered to be dormant in the healthy nervous but it is now known that they continually scan the extracellular environment and react rapidly to various stimuli that threaten physiological homeostasis. Moreover, a growing body of evidence indicates that microglia in the dorsal horn of the spinal cord play a causal role in neuropathic pain behaviours resulting from peripheral nerve injury, and specific neuron–microglia–neuron signalling pathways have been elucidated. Within the dorsal horn microglia suppress neuronal inhibition, transforming the response properties of spinal nociceptive output neurons which may account for the symptoms of neuropathic pain. Thus, preventing or reversing microglia–neuron signalling may represent the basis for new forms of therapy for chronic pain following nerve injury, strategies not previously anticipated by a neuron-centric view of pain plasticity.

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TOPICAL WORKSHOPS

Workshop – Assessment And Diagnosis 1: DIAGNOSIS OF NEUROPATHIC PAIN – BRAIN EVOKED POTENTIALS

12 Workshop Summary: BRAIN EVOKED POTENTIALS AS A TOOL TO DIAGNOSE NEUROPATHIC PAIN
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This workshop will provide a state-of-the-art description of the usefulness of brain evoked potentials to explore the function of somatosensory pathways in patients with neuropathic pain and in experimental models of central sensitisation. The evidence for the sensitivity of laser-evoked potentials (LEPs) in assessing neuropathic pain of peripheral and central origin will be reviewed and discussed, and their recording technique will be detailed. Brain potentials evoked by noxious mechanical stimuli (pinprick-evoked potentials, PEPs) will be also described and discussed. PEPs are a novel measure to assess the function of the mechanical nociceptive sensory channel; these responses are increased in experimental models of central sensitisation and have the potential of providing an electrophysiological correlate of positive symptoms in neuropathic pain.

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13 LASER-EVOKED POTENTIALS IN PERIPHERAL NEUROPATHY
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Standard electrical stimulation covers 10–30% of the somatosensory pathways only, leaving the function of thinly myelinated or unmyelinated fibers and/or the spinothalamic tract untested. So far, three different types of stimulators have been used to activate nociceptive nerve endings: (1) specially designed electrodes delivering electrical stimuli to the superficial skin layers, (2) contact heat stimulators (fast thermodes), and (3) infrared lasers that activate nociceptors selectively without tactile co-activation. The first part of the talk will give a brief overview of these techniques and applications. In the past 20 years, the usefulness of laser evoked potentials (LEP) has been demonstrated in numerous clinical studies, and this method is recommended by the European Federation of Neurological Societies. Other than standard SEP, LEP are particularly powerful in the trigeminal system as well.

The second part will focus on the role of LEP in the diagnosis of peripheral neuropathies. Although it is still unclear, what distinguishes patients with peripheral neuropathy who exhibit spontaneous pain from patients who do not report pain, recent data suggest that either the lack of small fibers or the impaired balance between different fiber types may be crucial (“wrong composition of signals reaches the brain”). In this context, determination of the fibers involved becomes important. Combination of standard SEP and LEP enables the clinician to distinguish between large and small fiber neuropathy. Furthermore, it is possible to distinguish between involvement of A-delta and C-fibers by changing the laser output energy and/or the size of the irradiated skin area.

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14 DIAGNOSTIC ROLE OF LASER EVOKED POTENTIALS IN CENTRAL NEUROPATHIC PAIN
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Laser evoked potentials (LEPs) have proved reliable in assessing damage to the peripheral and central nociceptive system. In central conditions causing pain, such as syringomyelia, spinal injury, multiple sclerosis, brainstem syndromes and post-stroke pain, LEPs are diagnostically useful and – combined with SEPs to electric stimulation – more sensitive than any other neurophysiological test. LEP attenuation/suppression to stimulation of a painful territory substantiates the diagnosis of neuropathic pain. In central neuropathic pain LEP attenuation is observed even in case of hyperalgesia or allodynia; in this case, ultra-late components (800–900 ms) may appear concomitantly with the attenuation or disappearance of late responses. Emerging data suggest that the pattern of LEP abnormality (a) depends of lesion localisation and (b) may differ in patients with provoked pain (hyperalgesia, allodynia) and in patients with spontaneous pain exclusively. In pseudo-neuropathic syndromes such as fibromyalgia and myofascial or chronic fatigue syndromes, as well as in psychogenic pain, LEPs are normal or even facilitated, and never depressed. In selected patients, normal or enhanced LEPs to stimulation of a painful territory may reflect enhanced attention toward the laser stimulus, and increase the diagnostic probability of psychogenic pain. Analysis of single trials and assessment of inter-trial var-
iability is a powerful tool that may increase diagnostic and prognostic yield, and would deserve wide dissemination. Laser evoked potentials are currently the easiest and most reliable neurophysiological method of assessing function of nociceptive pathways. Their main limitation in clinical practice is that they are available in too few centres.

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15
BRAIN POTENTIALS EVOKED BY MECHANICAL STIMULI: A NEW TOOL FOR ASSESSING CENTRAL SENSITISATION?
G.D. Iannetti

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Brain potentials evoked by short laser pulses (laser-evoked potentials, LEPs) are the best available tool for the diagnosis of neuropathic pain. However, neither LEPs nor other electrophysiological methods are sensitive to the sensory plus signs of hyperalgesia (Crucce, 2004).

This lecture describes a novel measure of brain activity in response to short somatosensory stimuli delivered with a mechanical probe with a flat tip (diameter 0.2 mm, force 128 mN). These stimulators mostly activate type-I A-delta mechano-heat nociceptors (AMHs), the nerve fibre population that signals pain to punctate stimuli in normal skin as well as punctate hyperalgesia during capsaicin-induced central sensitisation (Magerl, 2001). Therefore, they are widely used to assess psychophysically this phenomenon both in normal subjects and in patients with neuropathic pain (Baumgaertner, 2002). When the timing of the stimulation is recorded by means of an optical detector inside the mechanical probe, reliable time-locked in the ongoing electroencephalogram can be reliably detected (pinprick-evoked potentials, PEPs). PEP amplitude is increased when an area of experimental secondary hyperalgesia is stimulated, thus providing a laboratory correlate of this psychophysical phenomenon. Although patient studies are still lacking, brain potentials evoked by the mechanical stimulation of A-delta nociceptors are a promising tool to assess instrumentally the positive sensory signs of hyperalgesia in patients with neuropathic pain.

References

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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. The fact that these different questionnaires, developed independently and in parallel in different countries, share a large number of items, strongly supports the validity of this approach. In this workshop we will address the potential applications of these new questionnaires both in daily practice and clinical research. The high diagnostic value of these questionnaires also suggests that they could be helpful for the definition of new operational diagnostic criteria for neuropathic pain.

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18 NEW SCREENING TOOLS FOR NEUROPATHIC PAIN: ARE THEY USEFUL FOR DAILY CLINICAL ROUTINE?
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Although it is undeniable that accurate diagnosis is a milestone in choosing appropriate therapy, the main problem beside the lack of a world wide accepted definition of NeP is still the lack of a diagnostic gold standard. To prevent patients from a long pain career it is an important goal to assist primary-care physicians and non-pain specialists to identify patients with a NeP component. They have a key diagnostic position since they guide the therapeutic management from early on and have a pivotal role in triaging patients for specific treatment approaches.

Much research has been undertaken in several countries to develop new tools for this purpose and surprisingly, although without any knowledge of each other, the different workinggroups chose a similar approach to identify NeP with simple tools based on verbal pain description and neurological symptoms and signs (e.g. DN4, LANSS, NPQ, NPS, ID-Pain, PD-Q).

In cooperation with the German Research Network on Neuropathic Pain we developed the painDETECT questionnaire, a reliable, simple and validated screening tool to predict the likelihood of a NeP component in chronic pain disorders. It can easily be applied fully by the patient and without any prior physical examination. It is the first tool to use unique pain patterns as a principal component and, while it incorporates radiation, it is particularly suitable for initial screening of mixed pain patients, such as low back pain. In this workshop we will exemplary address the use of the PD-Q as one of the several available new questionnaires.

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19 NEUROPATHIC PAIN: DEFINITION AND SCREENING
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Neuropathic pain can strictly be defined as pains due to a lesion or disease of the somatosensory system and accordingly a series of different conditions may give rise to a neuropathic pain picture. Common elements in neuropathic pain such as sensory deficit in the painful area, hypersensitivity phenomena in the painful area, afferent sensations, gradual increase of pain following repetitive stimulation, and paroxysms of pain have raised the question whether these pains represent a clinical entity. According to some studies, neuropathic pain can be identified by simple screening tools, but other studies have questioned this notion. A major problem in the classification and grading of neuropathic pain is the lack of a specific diagnostic tool to diagnose these conditions, and some screening tools are subject to bias if the diagnostic instrument is used to define the condition. In certain pain conditions the symptoms and their underlying mechanisms may interact in an unpredictable fashion and add to the complexity of the clinical picture. This is particularly evident in mixed pain states. Screening tools have been shown to be useful in identifying neuropathic pain as a symptom with a reasonably high sensitivity and specificity. However, these tools can usually not distinguish one neuropathic pain condition from another. The underlying pathology of pain, which is an important element in classifying neuropathic pains will most likely influence both the choice of treatment and the prognosis of the condition, so a clinical assessment is always an important step in the work-up of patients with neuropathic pain.

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Workshop Summary: ECTOPIC DISCHARGES IN C-NOCICEPTORS AS A CAUSE OF NEUROPATHIC PAIN

J. Serra
Patients with peripheral neuropathy commonly express positive sensory symptoms, such as tactile paresthesias, dysesthesias and pains. Most of these symptoms and signs are caused by membrane hyperexcitability leading to ectopic impulse generation. Conventional electrophysiological methods are unable to record these disperse, chaotic discharges in sensory axons. Therefore, the study of positive sensory phenomena has largely relied on quantitative physiological tests. In animals, possible electrophysiological correlates of positive sensory phenomena have been documented in traumatic neuromas and in demyelinated nerve fibers. In experimental human volunteers, ectopic nerve impulses generated in single myelinated sensory fibers have been correlated with post-ischemic and post-tetanic paresthesias. In patients, abnormal nerve impulse activity in afferent myelinated fibers has occasionally been recorded in polyneuropathy, amputation neuroma, and Spurling and Tinel's signs.

Ectopic discharges from C-nociceptors are probably the basis of spontaneous burning pain in cases of peripheral neuropathic pain. Surprisingly, ectopia from identified C-nociceptors has only been reported a few times from animals and humans. Recent microneurographic techniques permit recording from individual unmyelinated C fibers and allow their segregation into different functional classes having discrete electrophysiological properties of their membranes. Particularly important for the study of physiological and neuropathic pain is the recording from mechanosensitive as well as mechano-insensitive, or silent, nociceptors. Recent findings from animal experiments and from neuropathic pain patients that have added considerable knowledge on the pathophysiological mechanisms of spontaneous neuropathic pain will be reviewed in this presentation.

Jordi Serra will present recent findings from animal experiments and from neuropathic pain patients that have added considerable knowledge on the pathophysiological mechanisms of spontaneous neuropathic pain. Stephen Waxman will discuss the lessons learnt from recent genetic and electrophysiological findings in familial erythromelalgia, the first inherited syndrome of peripheral neuropathic pain where a mutation in a gene encoding voltage-dependent sodium channel (the Nav1.7 sodium channel in the case of this disorder) renders nociceptive neurons hyperexcitable. Marshall Devor will discuss possible intimate mechanisms that may eventually lead to spontaneous discharges in C fibers and theorize on the possible drug class that will need to be designed to control them.

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ECTOPIC DISCHARGES IN C-NOCICEPTORS AS A CAUSE OF NEUROPATHIC PAIN
J. Serra

Neuropathic pain is not a single concept, but a complex group of positive sensory phenomena due to abnormal function at different levels of the nervous system. Each of these abnormal sensory phenomena may be due to a discrete pathophysiological mechanism operating at a defined level. There exists well-established evidence for some of these mechanisms. However, for the vast majority of other symptoms/signs that form the “neuropathic pain complex” there are scarce, and sometimes, conflicting proposed mechanisms.

Although current emphasis is put on possible mechanisms of central hyperexcitability and sensitization, we believe that peripheral mechanisms operating at the level of the damaged axonal membrane are at the core of neuropathic pain symptoms. Ectopic discharges from C nociceptors are probably the basis of spontaneous burning pain in cases of peripheral neuropathic pain, although ectopia from identified C nociceptors has only been reported a few times from animals and humans.

Recent microneurographic techniques permit recording from individual unmyelinated C fibers and allow their segregation into different functional classes having discrete electrophysiological properties of their membranes. Particularly important for the study of physiological and neuropathic pain is the recording from mechanosensitive as well as mechano-insensitive, or silent, nociceptors. Recent findings from animal experiments and from neuropathic pain patients that have added considerable knowledge on the pathophysiological mechanisms of spontaneous neuropathic pain will be reviewed in this presentation.

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22
ERYTHROMELALGIA AS A HUMAN MODEL OF C-FIBER HYPEREXCITABILITY
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Studies in vitro and in subhuman models strongly suggest that sodium channels contribute to pain by producing hyperexcitability of nociceptive DRG neurons. However, evidence for a role of sodium channels in human pain has been more limited. Recent studies have
demonstrated that mutations of the Nav1.7 sodium channel, which is preferentially expressed in small DRG and sympathetic ganglion neurons, produce inherited erythromelalgia (erythermalgia), a disorder in which patients experience severe burning pain in their extremities in response to mild warmth. These mutations hyperpolarize the channel’s activation voltage-dependence, thus decreasing the threshold for channel opening; slow deactivation, thereby keeping the channel open longer once activated; and increase the “ramp response” to small, slow depolarizations, thereby amplifying small stimuli such as generator potentials to a greater degree than normal. Some of these mutations also depolarize resting potential via increased overlap between activation and steady-state inactivation. When introduced into small DRG neurons, these Nav1.7 mutations produce hyperexcitability, lowering the threshold for generation of single action potentials and increasing the firing rate in response to graded stimuli. One mutation, L858H, has been expressed and studied within both DRG and sympathetic ganglion neurons. This mutation depolarizes both cell types by approximately 5mV, but produces hyperexcitability in DRG neurons, and hypoexcitability in sympathetic ganglion neurons. This is due to the selective expression of Nav1.8 sodium channels within DRG neurons, and the participation of Nav1.8 in action potential electrogenesis following depolarization which inactivates other sodium channel isoforms.

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CELLULAR PROCESSES ASSOCIATED WITH ECTOPIA
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Accumulating evidence points to ectopic discharge originating in the peripheral nervous system as both: (1) the primary nociceptive signal underlying spontaneous neuropathic pain, and (2) a factor that triggers and dynamically maintains central sensitization, hence tactile allodynia. At the time of pain onset the bulk of the ectopia originates within the dorsal root ganglion (DRG) and is carried centrally in A-beta afferents. The resulting pain and central sensitization may be partially due to upregulation and abnormal release from these neurons of peptides normally associated with C-nociceptors, one of the consequences of axotomy-induced reorganization of gene expression in large diameter DRG neurons. Another consequence is altered expression of ion channels, and the resulting enhancement in affected DRG neurons of depolarizing afterpotentials (DAPs) and high-frequency subthreshold oscillatory potentials. The newly emergent resonance of these neurons enhances their fundamental electrogensis, and promotes abnormal repetitive firing. Numerical simulations show that oscillations enhance electrogensis primarily by overcoming membrane accommodation rather than by virtue of membrane depolarization. Identification of gene transcripts whose regulation correlates with pain phenotype over time, and across rodent strains, is a strategy for advancing the understanding the neural processes that underlie ectopia and resulting neuropathic pain.

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hyperalgesia, nociceptive LTP) including their pharmacology.

Gunnar Wasner will detail models for a hitherto unresolved problem of neuropathic pain, namely cold pain focussing on the discrimination of nociceptive and neuropathic cold pain and on cold hyperalgesia.

Boris Chizh shall pinpoint the utility of human surrogate models from the viewpoint of translational pharmaceutical pain research namely as a rational strategy to hand over knowledge from animal research (i.e. from animal surrogate models) into clinical studies on neuropathic pain.

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HUMAN SURROGATE MODELS OF PAIN MEMORY: IMPLICATIONS FOR MECHANISMS OF CENTRAL SENSITIZATION AND RELATED TREATMENT OPTIONS IN NEUROPATHIC PAIN PATIENTS
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During the last years evidences have accumulated that central sensitization of nociceptive pathways – which probably contribute to some neuropathic pain symptoms – shares mechanisms of memory formation (Treede et al. Proceedings 11th world congress on pain; 2006). Use-dependent synaptic plasticity underlies sensitization which constitutes a fundamental mechanism of non-associative implicit memory. However, plasticity at synapses in humans can not be studied directly but can be deduced from the combination of signs and symptoms. A human surrogate model of implicit pain memory, nociceptive long-term potentiation (LTP), allows contrasting long-lasting homo- and heterosynaptic forms of central sensitization in the nociceptive system (Klein et al. J Neurosci 2004). Using this model we have shown that heterosynaptic facilitation may be more relevant for sustained behavioural changes to natural somatosensory stimuli than homosynaptic events (Lang et al. Pain 2007; Hansen et al. J Neurophysiol 2007). Central sensitization may depend on local spinal processes (e.g. volume transmission) or may involve interactions by either descending facilitatory or inhibitory circuits resulting in a complex pharmacology. For example, although blockade of NMDA-receptors by ketamine resulted in an inhibition of the homosynaptic form of central sensitization, heterosynaptic facilitation (secondary hyperalgesia and dynamic allodynia) was unaffected (Klein et al. Neuropsychopharmacol 2007). Generally, mechanisms underlying behavioural relevant heterosynaptic types of facilitation appear to be redundant making them more robust against pharmacological single-drug interventions. Therefore a multi-drug strategy in the treatment of hyperalgesic neuropathic pain states may be more promising than a single-drug approach.

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SURROGATE MODELS: ADVANTAGES AND LIMITATIONS EXEMPLIFIED BY THE SYMPTOM OF COLD INDUCED PAIN
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Human surrogate models are important for the understanding of neuropathic pain symptoms in patients. Cold pain is an example for this. It can be induced by either topical application of menthol or the experimental blockade of cold-specific Aδ-fibre afferents. The workshop will illustrate the suggested underlying mechanisms of the two models and how they can be distinguished according to further symptoms and signs. The database of the German Research Network on Neuropathic Pain offers the opportunity to identify patient groups to which the models can be applied. The limitations of this approach and alternative mechanisms of cold-induced pain will be discussed.

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27
TRANSLATIONAL MEDICINE APPROACHES IN DEVELOPMENT OF NOVEL NEUROPATHIC PAIN TREATMENTS
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Despite a high unmet need, pharmaceutical industry has not been very successful in bringing new treatments for neuropathic pain to patients. The highest attrition appears to be at the preclinical–clinical interface. The potential reasons for this are species differences in pharmacology or pharmacokinetics, inadequate models or markers, failure to predict therapeutic index and incorrect dose selection. There are several potential ways to increase confidence in novel compounds before committing to large-scale patient studies. Demonstration of pharmacodynamic activity in humans could discharge the risk of species differences. Furthermore, human pain models could provide hints of efficacy, predict therapeutic index and help dose selection. Central sensitisation is a key mechanism of neuropathic pain and can be induced in humans by peripheral afferent stimulation (using capsaicin, heat, electrical current). Such models have mechanistic limitations (duration and types of induced plasticity, types of afferents involved, reliance on evoked measures); therefore, extensive pharmacological validation is required before they can be applied as efficacy filters. NMDA antagonists, sodium channel blockers, gabapentin and other drugs efficacious in neuropathic pain have all shown efficacy in human models of central sensitisation. NK1 antagonists have been discussed as a class that was efficacious in animal pain models, yet failed to alleviate pain in patients. The NK1 antagonist aprepitant was recently shown to lack efficacy in the human electrical hyperalgesia model; more such negative control data are needed. In summary, healthy volunteer models of pain and sensitisation could help bridge the gap between preclinical and patient stages of analgesic drug discovery.

The pathophysiology of central pain syndrome is still poorly understood and their treatment remains a major challenge. Despite the development of several animal models of spinal cord injury pain, human studies are necessary to better link mechanisms to neuropathic symptoms and signs. Over the past years, several significant clinical studies have been devoted specifically to the mechanisms of central pain, particularly with regards to allodynia, in humans. These studies have used psychophysics, functional or morphological neuroimaging and electrophysiology. This workshop will outline the recent advances in our understanding of central pain mechanisms from human studies.

Nanna Finnerup (Denmark) will present results of psychophysical and MRI studies obtained in spinal cord injury patients with at level and below level neuropathic pain, emphasizing the role of neuronal hyperexcitability at injury or higher level in spontaneous pain and allodynia.

Roland Peyron (France) will present the contribution of functional imagery in the understanding of the mechanisms of mechanical/cold allodynia and its relief after cortical stimulation in patients with central pain.

Jonathan Dostrovsky (Canada) will present clinical and electrophysiological evidence from human studies supporting the role of the thalamus in central pain.

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suggested that neuronal hyperexcitability in at the rostral end of the injury may be an important mechanism for pain below injury level.

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FUNCTIONAL IMAGING OF ALLODYNA IN NEUROPATHIC PAIN
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Brain areas involved in the alldynic phenomenon are still poorly identified in patients with neuropathic pain. To investigate this issue, we included prospectively a total of 46 patients with alldynic pain in a large fMRI and PET study. 27 and 19 patients were studied with fMRI and 15O2H PET, respectively. Study design was identical for both studies with a control (C) stimulation applied on the non-painful side of the body and an allodynic (A) stimulation applied on the painful side. While C stimulation was not painful, A stimulations induced a severe pain. As expected, C stimulation induced contralateral SI, SII, and insular activation while allodynic pain (A) conditions recruited additional/larger activations. The main finding was the contribution of the hemisphere ipsilateral to allodynic stimulation, in which SI, SII and anterior insula were recruited. Additional responses were also found (PET) in the anterior and medial portion of the thalamus, and in the motor system, including SMA, MI and cerebellum. These findings suggest primarily that activations in the hemisphere ipsilateral to allodynic stimulation, in brain regions that are participating physiologically to the pain matrix, may have some contribution to alldynic pain. Such a functional specialization may sustain the painful nature of the alldynic processes. Implications of these results will be discussed during the workshop.

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ROLE OF THALAMUS IN CENTRAL PAIN – A REVIEW OF FINDINGS FROM PATIENTS
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The thalamus has long been thought to play a key role in mediating central pain (CP) and in particular central post stroke pain (CPSP). Indeed the first detailed report of CPSP described the clinical findings in a group of patients who had sustained a stroke involving the thalamus. For many years this type of pain was referred to as thalamic pain or the thalamic pain syndrome, reflecting the view that the pain was due to thalamic dysfunction. It is now well known that damage anywhere along the spinothalamic tract and its relay onwards to insular cortex can result in the development of chronic CP although the thalamus probably plays a key role in the pathophysiology. My presentation will briefly review the main hypotheses regarding the role of thalamus in CP and then go on to summarize and discuss findings from my and several other labs obtained from CP patients. These studies took advantage of the opportunity afforded by functional stereotactic neurosurgery performed for implantation of deep brain stimulation electrodes to obtain neuronal recordings and examine the effects of microstimulation in CP patients. These studies have described the existence of abnormal low threshold calcium spike-mediated bursting and an increased incidence of stimulation-evoked pain in CP patients. The possible relevance of these findings to explaining the patient’s pain will be discussed.

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Workshop Summary: DEVELOPING CLINICALLY USEFUL CANNABINOIDS ANALGESICS
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There is strong evidence from laboratory studies demonstrating that cannabinoids have analgesic effects in a range of animal models of neuropathic pain and that they may have certain advantages over opioids in this context. This is supported by emerging evidence from clinical trials showing that cannabinoids are efficacious in central neuropathic pain, particularly in multiple sclerosis. However, currently available cannabinoids have a narrow therapeutic index and there are important concerns about the association between “recreational” cannabis use and psychosis and schizophrenia.

Andrew Rice will review the laboratory data supporting the analgesic actions of cannabinoids in models of neuropathic pain. He will also describe the mechanisms of analgesic actions of cannabinoids in both neurons and non-neuronal cells. He will then describe the various
strategies that are being employed to develop cannabinoids with minimal CNS adverse effects, such as targeting CB2 receptors on peripheral immune and glial cells and targeting CB1 receptors on primary afferent neurones.

Flemming Bach will review the clinical evidence base for the analgesic efficacy and adverse effects associated with cannabinoids in neuropathic pain. In particular, he will discuss some recent randomized controlled trials which have examined the analgesic efficacy of cannabinoids in neuropathic pain conditions, including multiple sclerosis.

Finally, Stephen Lawrie will describe the methodologies which have been employed to acquire the epidemiological data which suggest an association of cannabis use with psychosis. He will then discuss in depth the strength of this evidence and its implications for the development of cannabinoids as therapeutics.

The workshop will conclude with audience discussion and debate.

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33 CANNABIS CONCERNS AND CAUTIONS
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Psychiatrists are not renowned for reactionary views but see so many patients with psychoses apparently caused and/or exacerbated by the consumption of cannabis that the alternative interpretation of self-medication seems implausible. That clinical experience is increasingly supported by evidence from epidemiological surveys and prospective studies of subjects at high risk. Several recent large surveys suggest that cannabis causes psychotic symptoms and schizophrenia, and several systematic reviews and meta-analyses of these studies strongly suggest an overall 3-fold risk elevation and that the association is not artefactual. Our own study of young subjects at high risk of schizophrenia found a clear association between cannabis use and psychotic symptoms, with an apparent dose-response effect. There are also high quality reviews indicating that personality characteristics such as negative affect, emotionality, and unconventionality are at most weak predictors of subsequent cannabis abuse, and that the prescription of cannabinoids for chemotherapy induced nausea elevates the risk of hallucinations and delusions 6–9 times. Nevertheless, the baseline level of risk is low and there are effective antipsychotic drugs that can be used in such circumstances. The association between cannabis and psychosis does not therefore constitute a medical argument for criminalisation.

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34 Workshop Summary: QUANTITATIVE SENSORY TESTING IN RESEARCH AND CLINICAL TRIALS
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The increased knowledge of the pain-generating mechanisms and their translation into symptoms and signs may allow a dissection of the mechanisms that operate in neuropathic pain. If a systematic clinical examination of the neuropathic pain patient and 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. Such research can only be performed in large cohorts of patients, ideally on a Research Network level.

The workshop will present an overview of this technique, describe its strength and limitation. Major question that will be addressed include:

1. Is QST adequately validated to be used as a reimbursable diagnostic tool in the management of neuropathic pain?
2. Can we use QST to understand pathophysiological mechanisms in neuropathic pain?
3. Can we improve treatment outcome if we define QST results as primary outcomes in clinical trials?

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35 QUANTITATIVE SENSORY TESTING IN RESEARCH
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The nationwide multi-center German Research Network of Neuropathic Pain (GNNP) was founded to improve the diagnosis, understanding and management of neuropathic pain. The heart of this Network is a large data-base that includes epidemiological, clinical and history data. To translate the hypothetical concept of the mechanism-based classification theme into the clinical framework the GNNP has implemented a standardized QST protocol with 13 parameters including thermal as
well as mechanical testing procedures. To evaluate and compare somatosensory profiles of patients (plus or minus signs) an age- and gender-matched normative data-base of 180 healthy human subjects has been established. Furthermore, more than 1500 patients with a variety of different neuropathic pain states have been examined with these test procedures in a standardized fashion.

In etiologies as postherpetic neuralgia at least two different somatosensory patterns could be analyzed (sensitization type with cutaneous hypersensitivity in combination with little sensory loss, degeneration type with spontaneous pain and severe sensory loss). Other specific patterns in particular combined with cold hypersensitivity were detected in polyneuropathies and in patients with CRPS. Somatosensory patterns that are specific for human surrogate models of pain in which the underlying mechanisms are relatively well understood were searched in the data-base to identify patients with this particular pattern assuming that the underlying mechanisms are similar. As an example, the pattern that is characteristic for the menthol surrogate model (cold allodynia, pin-prick hyperalgesia) was detected in patients with oxaliplatin induced acute painful neuropathy.

The results of such multi-center network trials will ultimately substantiate the mechanism-based treatment concept in neuropathic pain.

Reference

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36 QUANTITATIVE SENSATION TESTING IN RESEARCH AND CLINICAL PRACTICE

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**Background.** The AMA CPT Committee has provided coding for quantitative sensation testing (QST) of touch pressure, vibration, cooling, warming, and heat-pain and as done per limb, face or axial region. This is a first step towards recognition of QSTs as reimbursable evaluation techniques in the USA. Regulatory committees have concerns that QST be properly defined, validated, and used with reference to adequate controls.

Standard procedures are being defined by the Quantitative Sensation Testing Society (www.qst-s.org) including description, quantitation, and reproducibility of stimuli. Stimuli should range over a broad range of magnitudes and should increase exponentially; algorithms should be pre-determined, efficient and accurate; and reports should relate to reference values and disease implications.

The special uses of quantitative sensation testing will be described and illustrated: diagnostic purposes; therapeutic trials; detection of hyperalgesia; and recognition of foot hypoalgesia and increased vulnerability to injury.

**Conclusion.** The neurologic community in the USA has a 3–4 year window in which to demonstrate the utility of QST approaches in diagnosis and management of metabolic, neurologic, and surgical disorders. Since psychophysical approaches have found a major place in hearing and vision studies, the time has come to use standard, calibrated, and appropriate approaches for the adequate study of human disorders of sensation.

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37 QST IN CLINICAL TRIALS – POTENTIALS AND CHALLENGES

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QST has been used in laboratory human research for more than a century, while application in human clinical practice and research, including clinical trials has been much more difficult to implement. The primary reason for that is the lack of widely accepted and implemented standards and procedures. Newly published databases and validation of procedures offer new methods that would require further efforts for standardization as well as for training and certification of examiners. The main effort in the development of QST methodology has been in the study of thresholds and to lesser degree analysis of suprathreshold stimuli, however complexity of neuropathic pain requires incorporation of negative sensory phenomena and study of special maps of positive and negative sensory phenomena. Limited experience with use of QST in clinical trials gives us a glimpse of what QST can offer. The ongoing challenge will be translation of information of QST findings into pain mechanisms.

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Workshop – Epidemiology And Health Care Systems 2: NEUPSIG GUIDELINES ON CLASSIFICATION, ASSESSMENT AND TREATMENT

38 Workshop Summary: NEUPSIG GUIDELINES ON CLASSIFICATION, ASSESSMENT AND TREATMENT OF NEUROPATHIC PAIN

R.-D. Treede
The Neuropathic Pain Special Interest Group (NeuP-SIG) of the International Association for the Study of Pain (IASP) has created several subcommittees that were charged with the task to develop and publish guidelines for practical clinical use. Rolf-Detlef Treede (Subcommittee on Classification and Taxonomy) will present the redefinition of neuropathic pain and a grading system for clinical use. Maija Haanpää (Subcommittee on Assessment) will outline a proposal how general practitioners can assess neuropathic pain. Robert Dworkin (Subcommittee on Treatment) will summarize the status of development of guidelines on pharmacological and non-pharmacological treatment of neuropathic pain. The aim of this workshop is to present these guidelines to a broader audience, and to discuss with the audience to what extent these guidelines meet the existing needs in clinical practice. The organizers of this workshop anticipate a lively discussion about classification of neuropathic pain and its distinction from other painful conditions, its assessment with current techniques and the need to develop additional tools, as well as the direction that improved treatment of neuropathic pain should take in the future.

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CONSENSUS STATEMENT ON REDEFINITION OF NEUROPATHIC PAIN AND A PROPOSAL FOR A GRADING SYSTEM
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Following an injury or in inflammatory conditions, pain results from activation of nociceptive afferents by actually or potentially tissue-damaging stimuli. In neuropathic pain, however, pain arises by activity generated within the nervous system without adequate stimulation of its peripheral sensory endings. According to the International Association for the Study of Pain (IASP), neuropathic pain has been defined as "pain initiated or caused by a primary lesion or dysfunction in the nervous system". While this definition has been useful in distinguishing some characteristics of neuropathic and nociceptive types of pain, it lacks both diagnostic specificity and anatomical precision. Two issues need to be resolved in a revised definition of neuropathic pain: (1) neuropathic pain needs to be distinguished from pain due to secondary changes in the nociceptive system resulting from its inherent plasticity resulting from sufficiently strong nociceptive stimulation; (2) neuropathic pain needs to be distinguished from musculoskeletal and other nociceptive pain that arises in the course of neurological disorders. A group of experts from the neurological and pain community developed the following more precise definition: Pain arising as a direct consequence of a lesion or disease affecting the somatosensory system. This revised definition fits into the nosology of neurological disorders and solves both issues mentioned above. Because of the lack of a specific diagnostic tool for neuropathic pain, we also propose to introduce a grading system of "definite", "probable", and "possible" neuropathic pain. The grade "possible" can only be regarded as a working hypothesis. The grades "probable" and "definite" require confirmatory evidence from a neurological examination. This grading system is proposed for use in clinical practice, clinical trials, and epidemiological studies.

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40 WHAT IS EXPECTED FROM GENERAL PRACTITIONERS IN THE DIAGNOSIS AND TREATMENT OF NEUROPATHIC PAIN?
M. Haanpää
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Neuropathic pain is prevalent, under-diagnosed and under-treated. Primary care physicians have a key diagnostic position since they guide therapeutic management of pain from early on and have a pivotal role in triaging pain patients for specific treatment approaches.

The examination of a patient with pain is aimed at identifying the underlying disease and understanding whether the pain is nociceptive, neuropathic, a combination of these or neither. A pain drawing is helpful in assessing weather the location of pain is neuroanatomically logical. Neurological examination is aimed at finding possible abnormalities relating to a neurological lesion. Sensory testing, which is crucial in the recognition of neuropathic pain, is directed by the patient’s history and pain drawing. Possible need of a referral to a specialist consultation for differential diagnosis of the pain is considered on the basis of the clinical findings.

As time is the limiting factor in general practice, screening tools (i.e. questionnaires helping to recognize neuropathic pain) have developed. They can alert the physician to carefully examine the patient in search of neuropathic pain, but they cannot replace clinical examination.

The treatment of neuropathic pain consists of patient counselling, psychosocial support, curative treatment if possible, and pharmacological treatment if needed.
Guidelines from the Neupsig Treatment Committee

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The Treatment Committee of the IASP Neuropathic Pain Special Interest Group has sponsored two treatment guidelines for patients with neuropathic pain. The objective of “Recommendations for the Management of Herpes Zoster” (Dworkin RH, et al., Clin Infect Dis 2007;44(suppl 1):S1–S26) is to provide evidence-based recommendations for the management of patients with herpes zoster. On the basis of the results of controlled trials and the authors’ clinical experience, acyclovir, brivudin (where available), famciclovir, and valacyclovir are recommended as first-line antiviral therapy for herpes zoster. Specific recommendations for the use of these medications are provided, and suggestions are made for treatments that might further reduce pain and other complications of herpes zoster when used in combination with antiviral therapy. A manuscript presenting the second guidelines prepared by the Treatment Committee, “Pharmacologic management of neuropathic pain: evidence-based recommendations,” has now been submitted for publication. On the basis of systematic literature reviews and randomized clinical trials, medications recommended as first-line treatments for patients with chronic neuropathic pain include certain antidepressants (i.e., tricyclic antidepressants and dual reuptake inhibitors of both serotonin and norepinephrine), calcium channel α2-δ ligands (i.e., gabapentin and pregabalin), and topical lidocaine. Opioid analgesics and tramadol are also recommended for first-line treatment of moderate-to-severe pain on a short-term basis, but are recommended for long-term treatment only in patients refractory to other first-line medications. Long-term studies, head-to-head comparisons between medications, studies involving combinations of medications, and clinical trials examining treatment of central neuropathic pain should be a priority for future research.
There is compelling evidence indicating that not only injured primary afferents, but also their spared neighbors, show an alteration of excitability and gene expression and that these changes have functional roles in neuropathic pain. A number of studies reported that mitogen-activated protein kinases (MAPKs) play an important role in the induction and maintenance of neuropathic pain. In mammals, four major MAPK pathways have been discovered. They are the extracellular signal-regulated protein kinases 1/2 (ERK1/2), c-Jun N-terminal kinase (JNK), and ERK5.

Here we report that activation of extracellular signal-regulated protein kinases 5 (ERK5), also known as big MAPK 1, participates in pain hypersensitivity caused by nerve injury. Nerve injury induced the activation of ERK5 in microglia, but not in neurons and astrocytes, in the spinal dorsal horn, and microglial activation through the ERK5 pathway contributed to the development of pain hypersensitivity. We also found that ERK5 was also activated in both damaged and undamaged dorsal root ganglion (DRG) neurons. Antisense knockdown of ERK5 suppressed nerve injury-induced neuropathic pain and decreased microglial activation. Furthermore, inhibition of ERK5 blocked the induction of transient receptor potential channels (TRPV1 and TRPA1) and brain-derived neurotrophic factor expression in DRG neurons.

Our results show that ERK5 activated in spinal microglia and DRG neurons contributes to the development of neuropathic pain. Thus, blocking ERK5 signaling in the spinal cord and primary afferents has potential for preventing pain after nerve damage.

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ACTIVATION OF C-JUN N-TERMINAL KINASE (JNK) IN SPINAL ASTROCYTES FOR THE MAINTENANCE OF NEUROPATHIC PAIN
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Although pain is regarded traditionally as neuronally mediated, recent progress shows an important role of spinal glial cells in persistent pain sensitization. Mounting evidence has implicated microglia cells in the development of neuropathic pain. Although astrocyte activation is more persistent than microglia activation in chronic pain conditions, little is known about the role of astrocytes in pain regulation. We will provide evidence to support a role of spinal astrocytes in maintaining chronic pain. After spinal nerve ligation, the MAP kinase family member JNK is activated persistently in GFAP-expressing astrocytes in the spinal cord. This activation is required for the maintenance of neuropathic pain because spinal infusion of JNK inhibitors can reverse mechanical allodynia. Further study reveals that JNK is activated strongly in astrocytes by basic fibroblast growth factor (bFGF), a well-known astrocyte activator that is up-regulated in primary sensory neurons and spinal astrocytes after nerve injury. Further, the transcription factor c-Jun, the best-known substrate of JNK, is also activated in spinal astrocytes after nerve ligation. Therefore, JNK pathway is an important signaling pathway in spinal astrocytes for maintaining neuropathic pain sensitization. Investigation of signaling mechanisms of JNK pathways in spinal astrocytes will identify new molecular targets for the management of neuropathic pain.

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ENDOTHELIN-A AND -B RECEPTORS ACTIVATE ERK IN DORSAL HORN NEURONS
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Peripheral nerve injury causing neuropathic pain rapidly activates extracellular receptor activated kinase (ERK) in spinal cord dorsal horn (DH) neurons. Endothelin-1 (ET-1), an endogenous peptide, can cause both pain and analgesia when injected in skin, via ETA and ETB receptors, respectively. ET-1 is present in peripheral nerves and in keratinocytes, and is released both peripherally and centrally upon injury or noxious stimulation. Intrathecal ET-1 administration causes thermal antinociception and depresses the second phase of paw flinching after formalin, via ETA receptors. We sought a link between the analgesia related to ET receptor stimulation and changes in ERK activation, in isolated spinal cord.

Exposure of rat spinal cord slices to ET-1 (10 nM–1 µM) elevated activated ERK (pERK), in individual DH neurons (EC50 ~10 nM). Antagonists of both ETA and ETB receptors suppressed ET-1-induced pERK; the limiting inhibition by each alone (at 1 µM) was ~60%, but combining both antagonists (at 1 µM) fully abolished ERK activation. Stimulation of ETA receptors alone elevated pERK, which was prevented by inhibition of PKC but not of PKA; the same selective effects occurred for ETB receptor stimulation. Remark-
ably, when both receptors were activated, by ET-1 alone, the separate inhibitors of PKA and of PKC suppressed pERK, by ~50% and 100%, respectively. Blockade of post-synaptic neurotransmitter receptors, or inhibition of TRPV1, did not lower ET-1-elevated pERK; the relevant ET receptors are thus post-synaptic. There appears to be a contradiction between antinociceptive effects of i.t. ET-1 in vivo and its activation of pro-nociceptive spinal pERK in vitro.

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46 PHOSPHORYLATION OF SODIUM CHANNEL NAV1.8 BY P38 MAPK INCREASES CURRENT DENSITY IN DRG NEURONS

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Sensory neuron-specific sodium channel Nav1.8 and p38 mitogen-activated protein kinase are well-recognized targets in inflammatory and neuropathic pain. Nav1.8 channels produce the slowly inactivating, tetrodotoxin-resistant (TTX-R) current in dorsal root ganglia (DRG) neurons which contribute most of the inward current underlying the depolarizing phase of action potentials. Nerve injury or inflammation of peripheral tissues activates p38 in DRG neurons which acutely impact nociceptive neuron excitability. We investigated the potential association and modulation of Nav1.8 by activated p38 in DRG neurons.

We used molecular, cellular and electrophysiological methods to investigate co-localization of Nav1.8 and p38, and the effect of activation of p38 on Nav1.8 current, in DRG neurons.

We demonstrate that Nav1.8 and p38 are co-localized in DRG neurons and more importantly, that activated p38 increases Nav1.8 current density in these neurons. The increase in current density is not accompanied by changes in gating properties of the channel. We now establish for the first time that Nav1.8 is directly phosphorylated by p38, and show that alanine substitution of two p38 phospho-acceptor serine residues on the loop joining domains I and II of Nav1.8 prevents p38-mediated increase in current density in transfected DRG neurons.

Our study shows that the effect of p38 MAPK on Nav1.8 is direct and suggests that one mechanism by which inhibitors of p38 reduce inflammatory and neuropathic pain may be through preventing p38-mediated increase of Nav1.8 current density.

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47 Workshop Summary: COLD PAIN – FROM SKIN TO BRAIN

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Evoked pain is known to be a striking symptom of neuropathic pain. However, the importance of cold hyperalgesia and cold hypersensitivity has been recognized just recently. Multiple underlying mechanisms are suspected to explain the variety of clinical pictures presenting pathological cold sensation and cold (evoked) pain. Thus, the aims of this workshop are to highlight: the molecular logic for the perception of cold-evoked pain, the current understanding of cold thermoreceptors, the controversy regarding TRPA1 and cold signaling, the human surrogate models of cold hyperalgesia, the phenomenology of cold hyperalgesia in clinical pain states, the brain mechanisms implicated in acute and chronic physiological and pathophysiological cold sensation and pain.

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48 THE MOLECULAR BASIS OF COLD SENSATION AND COLD PAIN

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The perception of temperature is a fundamental part of sensory perception and allows us to evaluate both our
external and internal environments. Thermosensitive nerves can be segregated into those that detect either innocuous or noxious (painful) temperatures; the latter being nociceptors. Over the last decade, ion channels of the transient receptor potential (TRP) family have been identified and shown to respond at distinct temperature thresholds, thus establishing the molecular basis for thermosensation. While much is known of those channels mediating the perception of noxious heat, those proposed to be involved in cool to noxious cold sensation, TRPM8 and TRPA1, have only recently been described. The former channel is a receptor for menthol, and links the sensations provided by this and other cooling compounds to temperature perception. While TRPM8 almost certainly performs a critical role in cold signaling, its part in nociception is still at issue. The latter channel, TRPA1, is activated by many pungent compounds, but has also been postulated to mediate our perception of noxious cold temperatures. However, a number of studies of the thermosensory properties of TRPA1 both in vitro and in vivo have been contradictory. Thus, the molecular logic for the perception of cold-evoked pain remains enigmatic and this part of the workshop will summarize our current understanding of these cold thermoreceptors, as well as address the current controversy regarding TRPA1 and cold signaling.

References


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BRAIN MECHANISMS OF COLD-PAIN AND COLD HYPERALGESIA
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Brain-imaging techniques using functional MRI, PET and magnetencephalography (MEG) have opened new emerging insights in exploring brain mechanisms implicated in the processing of acute and chronic cold-pain and cold-evoked pain. Furthermore, translational research, i.e. implementing human surrogate models of cold-pain and cold allodynia/hyperalgesia into functional imaging studies and the comparison with results derived from studies in clinical pain states, have enriched the knowledge. Using two different surrogate models of cold allodynia in healthy volunteers, i.e. topical application of menthol or the peripheral A-fiber block, experimental cold allodynia was shown to be processed in different cerebral areas depending on the underlying mechanism of generation. Peripheral sensitization favoured a preferential activation of the thermoreceptive spinothalamic pathway in the menthol model that did not differ from the activation matrix of physiological cold-pain. A-fiber block attenuated the thermoreceptive input through the lateral pain pathway and produced a consistent increase in cold-induced activity within the medial pain system pointing to a pathological disinhibition of activity in the ascending polymodal nociceptive channel following A-fiber block. These results will be compared with the different patterns of brain activity associated with cold-pain and cold-evoked pain studied in patients suffering from chronic neuropathic pain, e.g. syringomyelia.

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TOWARDS SURROGATE MODELS OF COLD HYPERALGESIA
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Cold hyperalgesia is a clinically important phenomenon and is observed in a number of peripheral or central nervous system lesions, particularly complex regional pain syndrome, oxaliplatin induced neuropathies and central post-stroke pain. In a prospective cohort of patients treated with chemotherapy, we have shown that cold hyperalgesia may be the unique expression of oxaliplatin-induced neurotoxicity. The mechanisms of cold hyperalgesia due to a nerve lesion are not clearly elucidated and have been suggested to involve a central lack of inhibition exerted by cold-specific afferents on nociceptors, a central sensitization to non-nociceptive cold-fiber input or a peripheral sensitization of cold-sensitive C nociceptors. One possible model for studying cold hyperalgesia in humans is represented by topical menthol. We will present the results of recent psychophysical studies in healthy subjects indicating, that topical menthol modulates selectively the responses to noxious cold (Hatem et al., 2006; Wasner et al., 2004). These models may be suitable for use in painful patients and their possible applications for the study of cold hyperalgesia in humans will be discussed.

References


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Workshop Summary: PHANTOM LIMB PAIN – MECHANISMS AND THERAPY
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Phantom limb pain provides important insights into the neural mechanisms that underlie most chronic pains. It highlights the persistence of severe chronic pain after several major peripheral and spinal contributions are eliminated, and forces us to focus on brain mechanisms. The speakers will examine the contributions of genetic, autonomic and cortical mechanisms. Available therapies for phantom limb pain will be discussed.

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NEURAL MECHANISMS OF PHANTOM LIMB PAIN
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Limb amputation severs the axon of all primary sensory neurons that innervate the limb. It is well known that stump neuromas become hypersensitive and generate abnormal afferent discharge. Diagnostic block of major nerve trunks to the stump eliminates phantom pain in ~50% of patients. The impulses giving rise to the phantom in these cases presumably arise in the stump. But when nerve block fails, is it logical to presume that the impulses underlying the phantom sensation must originate in the CNS (cortex or psyche)? Evidence from animal models indicates that sensory cell somata in segmental dorsal root ganglia (DRGs) become hyperexcitable after peripheral axotomy and a second source of ectopic afferent discharge. This is a consequence of emergent resonant properties in the DRG soma membrane. Sensory effects of afferent discharge originating in neuromas and DRGs are likely augmented by central sensitization. Map distortions do occur in the spinal cord after major nerve injury, and hence also in the somatosensory cortex. But evidence of a causal role of cortical activity in the perception of phantom limb pain, or of cortical remapping, is equivocal. Percepts, including phantoms, reflect neural activity in a conscious brain. Before assuming that this activity is generated in the cerebrum rather than being due to peripheral afferent drive, logic demands a trial of DRG (or spinal) block… does the phantom pain persist during times of confirmed absence of ectopic afferent input?

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TREATMENT OF PHANTOM LIMB PAIN
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Phantom limb pain (PLP) affects large numbers of patients who have undergone amputation. It varies considerably in its characteristics and is commonly intermittent. A body of sound research offering an evidence base for treatment is largely lacking. Potentially harmful invasive neurodestructive techniques are unsupported by satisfactory reproducible evidence. The frequently intermittent nature of PLP may make assessment of outcome of treatment difficult.

Thorough assessment of the patient is mandatory and should include a detailed history and examination to ascertain physical, psychological and behavioural factors. Peripheral and central mechanisms of pain may be identified and may suggest mechanism based treatment.

Simple physical measures such as prosthesis revision for best comfort are worthwhile and increased use of a prosthesis tend to reduce PLP. Regional block techniques may abolish or worsen PLP or have no effect. Sympathetic blocks appear to provide benefit for weeks or months for some patients with a clear burning component to their pain. TENS and biofeedback are considered useful by some patients. It would seem logical to prescribe drugs shown to be effective in other neuropathic pain conditions such as tricyclic antidepressants, gabapentin/pregabalin or opioids but there is little good evidence for their benefit.

It has been shown that motor and sensory cortical reorganisation occurs in response to loss of sensory input from the missing limb. Mental imagery of movement of the missing limb, possibly augmented by visualisation in a mirror of movement in the contralateral limb, shows promise as a means of reducing the burden of PLP.

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CENTRAL MECHANISMS OF PHANTOM PAIN: TREATMENT IMPLICATIONS
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Phantom limb pain is a frequent sequel of an amputation occurring in up to 80% of the amputee population. Peripheral factors such as local changes at the residual limb, alterations in severed nerves and associated dorsal root ganglia have been discussed as causal factors. More recently, spinal and supraspinal plastic changes have been examined with cortical reorganization and somatosensory pain memories as a major factor documented in humans. New insights about central changes have also come from studies on somatosensory illusions and altered body perception. These hypotheses have led to new behavioral and pharmacological treatment options that target maladaptive plasticity and learning and sensory incongruence phenomena. We will discuss these methods and the central and pain-related changes associated with these interventions.

Workshop – Therapy 2: SPINAL CORD TREATMENT FOR NEUROPATHIC PAIN – WHERE IS THE EVIDENCE?

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Workshop Summary: SPINAL CORD TREATMENT FOR NEUROPATHIC PAIN: WHERE IS THE EVIDENCE?

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The workshop is about neuropathic pain. The pain signal may be generated in absence of ongoing noxious events by pathologic processes in the peripheral or central nervous system. Non-steroidal anti-inflammatory drugs, opioids, and their association with anti-convulsant and anti-depressant drugs are the most common treatment. Unfortunately, the efficacy maybe very poor. Peripheral or central nervous system injuries may produce neuroanatomic, neurophysiologic, and neurochemical changes. Central sensitization at a dorsal horn level is the best characterized change involved in the generation of pain. As a consequence, invasive treatments, such as neuromodulatory therapy, influencing pain pathways, may significantly help to control the symptoms. Neurostimulation therapy efficacy has been assessed by the European Federation of Neurological Societies (EFNS). A Task Force evaluated its utility for many neuropathic pain syndromes. Giorgio Crucucc presenting EFNS guidelines on spinal cord stimulation for neuropathic pain, will summarize the EBM results on different neurostimulation techniques. Jean-Pierre Van Buyten will especially focus on the most difficult and frequent neuropathic syndromes, such as FBSS and CRPS. These represent a very hard challenge for the algologist. Radiofrequency (RF) and pulsed radio-frequency (PRF) are new and alternative therapies evaluated for neuropathic pain, with neurobiological effects, different from SCS. They could help the algologist where other techniques have failed. Jan Van Zundert will examine the influences of dorsal root ganglion pulsed radiofrequency on spinal cord.

EFNS GUIDELINES ON SPINAL CORD STIMULATION FOR NEUROPATHIC PAIN

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The European Federation of Neurological Societies (EFNS) launched a Task Force to assess the efficacy of neurostimulation therapy in neuropathic pain. After a systematic review of the literature complying with EFNS rules for evidence-based documents, the Task Force came to a series of recommendations regarding spinal cord stimulation (SCS).

The majority of systematic reviews, as well as primary studies, have focused on patients with failed back surgery syndrome (FBSS) or complex regional pain syndrome (CRPS). In FBSS there are two Class-II RCTs and several case series for a total of 3307 patients. The proportion of responders (pain relief >50%) to SCS was 62%. In CRPS, results and evidence level are also good, with one Class-II RCT in CRPS I and several cases series, for a total of 561 patients with CRPS I or II. The proportion of responders was 67%. The effect of SCS has also been studied in many other conditions. We found positive case series evidence for peripheral nerve injury, diabetic neuropathy, postherpetic neuralgia, brachial plexus damage, amputation (stump and phantom pains), and partial spinal cord injury, and negative evidence for central pain of brain origin, nerve root complete avulsion, and complete spinal cord transection.

In a pooled safety analysis of SCS, the undesired events were mostly dysfunction in the stimulating apparatus such as lead migration or lead breakage. Medical complications were minor and never life threatening and were usually solved, like the hardware problems, by removing the device.
Radiofrequency (RF) treatment consists of the application of high frequency current adjacent to the nerve, thus increasing the temperature in the tissue surrounding the electrode tip. The alternative use of RF, called pulsed radiofrequency (PRF), consists in its application in short pulses followed by a silent period allowing for the heat to wash-out. It has been shown that PRF and RF have differential neurobiological effects aside from heat-induced morphological changes. Because pain transmission is modulated in the dorsal gray matter, the early (3 h) and late (7 days) effect in the rat dorsal horn of continuous and PRF current adjacent to the cervical DRG versus sham intervention was investigated. A significant increase of c-Fos expression in the dorsal horn of animals that underwent active intervention compared to the sham-operated controls was observed: both an early increase in c-Fos immunoreactive cells in lamina I and II of the dorsal horn after PRF as well as a late bilateral increase in c-Fos activity in the dorsal horn 7 days after intervention (Van Zundert et al., 2005).

The first RCT on pulsed radiofrequency adjacent to the cervical DRG in patients with chronic cervical radicular pain was recently published. At 3 months the pulsed radiofrequency group showed a significantly better outcome with regard to the global perceived effect (>50% improvement) and visual analogue scale (20 point pain reduction). The need for pain medication was significantly reduced in the pulsed radiofrequency group after six months. No complications were observed during the study period (Van Zundert et al., 2007).

References


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INFLUENCES OF DORSAL ROOT GANGLION PULSED RADIOFREQUENCY ON SPINAL CORD

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Influences of dorsal root ganglion pulsed radiofrequency on spinal cord

Chronic neuropathic pain can be difficult to treat, especially when patients become refractory to pharmacotherapy. Despite the availability of new drugs, less than 50% of patients achieve significant benefit with medical treatment, while 70% of patients with failed back surgery syndrome (FBSS) receive inadequate pain relief after repeated back surgery. Finding a solution for such patients presents a therapeutic challenge.

Other treatment options are available. Radiofrequency is a target-selective neurolytic technique that has been used clinically for many years, often with good results. However, its success has not been adequately reproduced in good quality, randomized controlled trials (RCTs). The same is true for neural blockade, a diverse group of procedures that can provide localized pain relief. Although clinical experience advocates its use, there is little controlled evidence to confirm its efficacy in neuropathic pain. Intrathecal drug delivery using implantable, programmable pumps is often used to control intractable pain, but uncertainty surrounds its use in pain with a neuropathic component.

Neurostimulation can offer an effective alternative. Spinal cord stimulation (SCS) has been used successfully in several neurological disorders, including FBSS and complex regional pain syndrome, where RCTs have demonstrated that SCS is effective compared with reoperation, physical therapy and conventional medical management. Technological developments have also enabled the use of SCS in more difficult indications such as axial low pain. Recently, occipital neurostimulation has shown much promise in the treatment of intractable occipital neuralgia and cervicogenic headache and is has shown much promise in the treatment of intractable pain with a neuropathic component. This treatment option, in combination with other treatment modalities, allows for the use of SCS in more difficult indications such as axial low pain.

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References


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Neuroimaging methods have become widely used by researchers and clinicians interested in better understanding the functioning of the human brain in health and disease. For the field of pain advances have been made in understanding how nociceptive processing within the healthy human central nervous system generates a conscious perception of pain. The focus has recently shifted towards patient-related research, harnessing earlier developments to test specific hypotheses in a broad range of chronic pain disorders including neuropathic. Results to date strongly support the notion that neuroimaging will aid our understanding of basic mechanisms contributing to the generation of chronic pain states. Furthermore, these techniques might help diagnose a patient’s pain condition in a more objective and robust way. This could enable better targeting of therapies and more rapid development of compounds to alleviate pain. The timing is therefore ideal to assess the utility of data generated from studies utilising different methodological approaches to assess human CNS structure and function in neuropathic pain states: (1) brain morphometry, (2) functional MRI, and (3) neuroreceptor imaging for acute and chronic pain, and for neuropathic pain. What is fact rather than fiction?

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60 WHAT TO LEARN FROM LIGAND-PET IMAGING STUDIES?
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Over the last decades, functional imaging studies have fostered our knowledge about cerebral pain processing in humans. Great interest has focussed on possible opioidergic mechanism of pain transmission and modulation. Today, reliable knowledge about in vivo distribution of opioid receptors in healthy human subjects is available from PET studies of opioidergic neurotransmission. Gender dependent differences in receptor distribution and ligand metabolism have been documented. Moreover, an increasing number of studies are reporting alterations of receptor distribution patterns in painful disease states. Various acute painful challenges have also been shown to induce measurable changes in receptor availability in multiple brain areas. The perigenual anterior cingulate cortex (ACC) has been identified as one brain region of major impact in opioidergic pain modulation. Thereby, the ACC apparently executes cortical top-down control on brainstem structures in (exogenous) pharmacological opioid analgesia. In addition, accumulating evidence suggests that also non-pharmacological treatment approaches utilize similar endogenous opioid dependent pathways to exert pain modulation. Moreover, it was recently shown that opioids modulate neurotransmission in the nigrostriatal dopaminergic pathway and that in turn dopaminergic changes such as increases or decreases in COMT enzyme activity affect opioidergic neurotransmission.

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61 FUNCTIONAL MRI AS A TOOL FOR DIAGNOSIS IN NEUROPATHIC PAIN
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Most functional MRI studies have focussed on acute nociceptive processing in normal, healthy subjects. The cerebral signature that reflects the painful experience is reasonably well identified and brain regions that are modulated during manipulations of the pain experience in differing circumstances increasingly understood. Only recently have laboratories started to translate these findings and hypotheses generated to chronic pain patients. The cerebral pattern that reflects central processing in such patients, particularly those of a neuropathic classification, is now emerging. Furthermore, the use of capsaicin as a model of key neuropathic pain symptoms combined with FMRI in healthy controls is contributing to a greater knowledge regarding signals that possibly reflect central sensitisation. Pharmacological studies using gold-standard agents in the treatment of neuropathic pain are further helping understand what regions are key in both the generation and maintenance of this pain state. The prefrontal cortex, thalamus, insula and brainstem seem to play particularly important roles in the context of chronic, neuropathic pain, however, the field is still emerging. Combined, these studies provide strong evidence that our knowledge regarding this condition is moving towards a point where the information available might enable a better diagnosis of an individual patient’s pain condition in the years to come. In this talk examples will be given to illustrate all the points discussed above.

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62 WHAT CAN BRAIN MORPHOMETRY TELL US ABOUT CHRONIC PAIN?
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There is accumulating evidence that chronic pain is associated with changes in brain anatomy, most commonly a decrease in gray-matter. Gray-matter decreases have been described for chronic low back pain and headache, and we now have similar results for fibromyalgia (FM). The decreases in gray-matter are related to duration and intensity of symptoms, suggesting that the structural changes may be an important component of the chronification of pain. Similar neuroanatomical abnormalities are found in stress-related disorders, including chronic fatigue syndrome and posttraumatic stress disorder (PTSD). In contrast to the decreased gray-matter observed in the older patients examined in most of these studies, we found that a group of young women with a chronic pain condition (vulvovestibulitis) had greater gray-matter density than controls. Similarly, our youngest FM patients had more gray-matter than age-matched controls. This biphasic effect is consistent with other disorders. Whereas adults with PTSD have reduced gray-matter volume, children and adolescents with PTSD have increased gray-matter volume. Similarly, adults with bipolar disorder have decreased gray-matter in the orbitofrontal cortex, whereas adolescent girls with bipolar disorder show the opposite effect. Thus, there is accumulating evidence that abnormal gray-matter density at a young age may be predictive of various disorders, including chronic pain. Although this idea is speculative, the available data suggest that the examination of differences in brain anatomy might provide a useful tool for predicting and diagnosing chronic pain states, including neuropathic pain.

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neuropathic component. Evidence supporting the performance of these tools in this context will be reviewed, and the strengths and limitations of this approach will be discussed.

Until consensus is agreed on a diagnostic approach to neuropathic pain, screening tools will serve to identify potential patients with neuropathic pain, particularly by non-specialists and this is probably their chief clinical strength. Their ease of use make these tools attractive because they provide immediately available information. Screening tools fail to identify about 10–20% of patients with clinician diagnosed neuropathic pain indicating that they may offer guidance for further diagnostic evaluation and pain management but clearly, they do not replace clinical judgment.

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QUANTITATIVE SENSORY TESTING: ASSESSMENT OF THE NEUROPATHIC COMPONENT IN LOW BACK PAIN
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Background and aims. In order to assess an impaired sensory function in neuropathic back pain the QST protocol of the German Research Network on Neuropathic Pain (DFNS) was used.

Methods. The QST protocol of the DFNS consists of seven tests measuring 13 parameters: thermal detection thresholds for the perception of cold, warm and paradoxical heat sensations, thermal pain thresholds for cold and hot stimuli, mechanical detection thresholds for touch and vibration, mechanical pain sensitivity including thresholds for pinprick and blunt pressure, a stimulus/response-function for pinprick sensitivity and dynamic mechanical allodynia, and pain summation to repetitive pinprick stimuli.

Results. Patients with different back pain syndromes were assessed: Facet joint arthropathy, and other radicular or pseudoradicular back pains. Back pain patients presented different sensory plus signs, i.e. pinprick-hyperalgesia, hyperalgesia to cold or blunt pressure, dynamic mechanical allodynia. Many patients showed sensory minus signs as well, i.e. hypoesthesia or hypoaesthesia to thermal and mechanical stimuli. In the case of a radicular lesion A-fiber function was gradually reduced following the rule “A-beta > A-delta”, while C-fiber function was almost preserved.

Conclusions. QST data from back pain patients show similar somatosensory phenotypes. Sensory plus signs indicate that peripheral or central sensitization of nociceptive pathways contributes to the back pain. Sensory minus signs most likely reflect a nerve damage pointing to the presence of a neuropathic pain component. The mixture of both sensory plus and minus signs is consistent with the mixed pain concept of nociceptive and neuropathic components in many back pain syndromes.

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TREATMENT OF NEUROPATHIC PAIN: INTERVENTIONAL TREATMENT OPTIONS
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Treatment of chronic, neuropathic low back pain continues to pose a burden for patients, although significant scientific advances in delineating pathophysiologic mechanisms have facilitated the development of targeted pharmacological and interventional treatments. 7% of low back pain patients experience associated neuropathic pain and although the exact numbers are unknown, it is believed that an estimated 5–10% of patients will be refractory to the majority of modalities used to treat chronic low back pain. The treatment algorithm for interventional therapies for neuropathic pain should be; failure of refractory treatments and combination therapy.

Interventional therapies considered for neuropathic low back pain are:
- Neuroablative procedures
- Nerve blocks.
- Percutaneous RF techniques.
- Neuromodulation
- Spinal infusion.
- Stimulation of the CNS or PNS.
- Pulsed radiofrequency
- Local anesthetic peripheral and sympathetic blocks provide useful diagnostic information but tend to afford only temporary therapeutic benefits in patients with peripheral neuropathy.

Despite the wide use of sympathetic nerve blocks in different pain syndromes, no substantive review in the literature on their role in pain treatment; a degree of multimodal therapy is inherent in most studies which may be beneficial for the patient but masks the outcome assessment measures.

Percutaneous radiofrequency techniques like dorsal root ganglion rhizotomy are also used for the palliation of pain in several neuropathic pain syndromes. A systematic review within the framework of the Cochrane...
Collaboration Back review group shows that there is limited evidence that RF-DRG is more effective than placebo, conflicting evidence for RF of lumbar facet pain, limited evidence suggesting that intradiscal RF may not be effective in relieving discogenic pain.

Recently a new mode of radiofrequency, pulsed radiofrequency have been appearing in the literature. PRF was conceived as a novel, potentially safer mode of administration of RF energy. In order to further elucidate the mode of action of PRF and to define its true value in the management of chronic pain, more research on this promising technique is justified.

When these techniques do not sustain adequate pain relief, spinal cord stimulation (SCS) or intrathecal therapy represent reasonable options. The level of evidence supporting this modality remains moderate. Pooled results of a recent systematic review of the SCS literature (one RCT, one cohort, 72 case studies) suggest significant benefit, with 50% or greater improvement in pain relief, in roughly 62.5% of patients.

A final option is intrathecal therapy. An important challenge posed by intrathecal delivery of medications is an inability, thus far, to address the correct target in the spinal cord. The only drug approved for use in intrathecal therapy is morphine and ziconitide (although hydromorphone and fentanyl, and the alpha-2 agonist clonidine are routinely used in clinical practice). While there is evidence for long-term analgesic efficacy, patient selection is critical and should be based on objective evidence of nonreversible pathology, coupled with a failure to achieve adequate results from oral upload therapy and/or an inability to tolerate the side-effects of oral opioids. In a recent review of 297 articles related to intrathecal drug therapy, investigators concluded that the scientific evidence for efficacy is incomplete.

In this lecture all efficacy of all techniques mentioned will be presented on the basis of evidence based medicine.

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Workshop Summary: TRANSIENT RECEPTOR POTENTIAL CHANNELS – AN UPDATE

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The transient receptor potential (TRP) channels constitute a large and diverse family of channel proteins that are expressed in many tissues and cell types in both vertebrates and invertebrates. Recently, TRP channels have collected much attention as molecular gateways in sensory systems, an interface between the environment and the nervous system. Several TRP channels transduce thermal, chemical, and mechanical stimuli into inward currents, an essential first step for eliciting thermal and pain sensations. Precise regulation of the expression, localization, and function of the TRP channels is crucial for their sensory role in nociceptor terminals, particularly after tissue damage or inflammation. In this workshop, three speakers will talk about recent findings about TRP channels. Dr. Tominaga will have a short review of TRP channels and also his new findings of warm sensitive TRP channels. Dr. Reeh will talk about his findings about inflammation-mediated changes in single-fiber activity using TRPV1 knockout mice. Dr. Koltzenburg will talk about cold sensitivity of sensory neurons, especially other cation channels in addition to TRPM8.

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THERMOSENSITIVE TRP CHANNELS AND NOCICEPTION

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TRP (transient receptor potential) channels were first described in Drosophila in 1989, and in mammals, TRP channels comprise six related protein families (TRPC, TRPV, TRPM, TRPA, TRPML, TRPP). TRP channels are best recognized for their contributions to sensory transduction, responding to temperature, nociceptive stimuli, touch, osmolarity, pheromones and other stimuli from both within and outside the cell. Among the huge TRP super family of ion channels, some have been proven to be involved in thermosensation detecting ambient temperatures from cold to hot. There are now nice thermosensitive TRP channels (TRPV1, TRPV2, TRPV3, TRPV4, TRPM2, TRPM4, TRPM5, TRPM8 and TRPA1) with distinct temperature thresholds for their activation. Interestingly, some of the thermosensitive TRP channels are expressed specifically in sensory neurons and involved in nociception. Involvement of TRPV1, TRPV3, TRPV4 and TRPA1 in nociception has been confirmed at an animal level using mice lacking the TRP channels. I will summaries the recent progress in the research of thermosensitive TRP channels and nociception especially by focusing on TRPV1 and TRPA1. In addition, I will discuss about the physiological significance of warmth sensitive TRP channels (TRPV3, TRPV4, TRPM2, TRPM4 and TRPM5).
Especially, the molecular mechanism of transferring temperature information to sensory neurons from skin keratinocytes, where TRPV3 and TRPV4 are strongly expressed, would be discussed.

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SENSITIVITY AND SENSITIZATION OF PERIPHERAL NERVE AXONS INVOLVE THE CAPSAICIN RECEPTOR TRPV1
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In painful neuropathies ectopic discharge activity originating from peripheral nerve axons is thought to contribute to paresthesias and to spinal sensitization leading to allodynia and hyperalgesia. Pathologically increased electrical excitability is one cause for ectopic impulse generation, but exaggerated sensitivity of axons to tissue temperature and proton concentration may be another essential mechanism. Normal unmyelinated axons have recently been shown to be well equipped with functional capsaicin receptor-channels TRPV1 that respond to noxious heat as well as tissue acidosis and induce, by virtue of their calcium conductance, a graded vesicular exocytosis of the pro-inflammatory neuropeptide CGRP. Recent single-fiber recordings demonstrate that axons also present with heat-induced discharge activity closely resembling the stimulus-response characteristics of their individual cutaneous nerve endings. The heat-induced axonal CGRP release can markedly be facilitated by treating the desheathed nerve with inflammatory mediators bradykinin and prostaglandin E2. The latter is also very effective in sensitizing the axonal proton response which was found to be missing in TRPV1 knockout mice, while the basal heat response was fully retained and, thus, probably due to other heat-operated ion channels. The inflammatory sensitization to heat, however, was lost in TRPV1−/− axons. These results show that peptidergic axons possess the complete stimulus and signal transduction machinery capable of inducing primary nociceptive sensitization. Lowering the heat threshold by just 3–4 °C would suffice to generate ongoing ectopic discharge in an inflamed neuropathic nerve.

Cold hypersensitivity is a symptom of many painful neuropathies. Several lines of evidence indicate that changes in the thermosensitivity of sensory neurons are contributing. In this lecture, I will discuss the cellular mechanisms of cold-sensitivity in sensory neurons and how they could contribute to cold hypersensitivity.

Several TRP channels are implicated in the normal cold-sensitivity of sensory neurons. The menthol and cold-sensitive TRPM8 is found on both non-nociceptive as well as nociceptive cutaneous afferents. However, in animal models of nerve injury presenting with cold hypersensitivity there appears to be little change of TRPM8 expression. Several lines of evidence argue against TRPA1 being an important cold transducer under normal circumstances, but it could contribute to cold hypersensitivity after injury. A significant proportion of sensory neurons that do not express TRPM8 or TRPA1 are cold-sensitive, but the cellular transduction pathways have remained obscure. One possible mechanism is a reduced conductance of voltage gated potassium channels (VGKCs). The expression of many VGKCs decreases after nerve injury and their pharmacological blockade induces a novel cold-sensitivity in many neurons. Cold also alters the kinetics of voltage gated sodium channels (VGSCs). The chemotherapeutic agent oxaliplatin which elicits cold-induced dysesthesias in humans activates myelinated primary afferents possibly by acting on VGSCs.

Thus, several mechanisms induce cold-sensitivity in sensory neurons. TRPM8 is involved in cold transduction of normal nociceptive and non-nociceptive neurons whereas changes in the properties of VGKCs and VGSCs may become more important after nerve injury.

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COLD-SENSITIVITY OF SENSORY NEURONS
M. Koltzenburg

UCL Institute of Child Health, London, UK

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Workshop Summary: SMALL FIBER NEUROPATHY – FROM BASIC SCIENCE TO THE CLINIC
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Small fiber neuropathy is an increasingly recognized syndrome. The main symptom is distally accentuated burning pain. Although many underlying conditions of small fiber neuropathy have been described, the pathophysiology of ‘idiopathic’ small fiber neuropathy is unclear. Furthermore, it is incompletely understood how the loss of skin innervation can lead to pain. In this
workshop, we will give an update on new developments in our understanding of small fiber neuropathy from basic science to the clinic. Susan Fleetwood–Walker will report on some neuropathic pain models and subgroups of sensory nerve fibers with specific receptors, which may be able to modulate sensitized nociceptive input. One such receptor is the TRPM8 cool receptor, which may be a target for new analgesic drugs. John Griffin will talk about the diagnostic value of intraepidermal nerve fiber measurements in small fiber neuropathies of different etiologies, for example prediabetic and autonomic neuropathies. He will also report on follow-up and measures of regeneration in these diseases. Claudia Sommer will relate findings on painful small fiber neuropathies, in particular how systemic and local cytokine production may contribute to pain.

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LABORATORY MODELS OF NEUROPATHIC PAIN AND THEIR APPLICATION IN DEVELOPING NEW ANALGESICS
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Chronic pain states resulting from injury to primary sensory afferents are maintained by hypersensitivity of spinal neurons. Thermal hyperalgesia, mechanical and cold allodynia ensue and are difficult to treat with current analgesics at doses that do not cause side effects. We work extensively with the sciatic nerve chronic constriction injury (CCI) model of clinical nerve damage which produces an outcome of both injured and uninjured afferents with the same sensory ganglia. Nerve injury produces characteristic phenotypic changes in both small and large afferents and consequent changes in the central processing of afferent inputs. The CCI pain state is dependent on spinal NMDA receptors and their assembly with receptor-interacting proteins such as PSD-95, AMPA receptors and their protein:protein interactions as well as receptors for phenotypically induced afferent mediators like vasoactive intestinal polypeptide (VIP) and their intracellular signalling pathways. Small fibre neuropathy with therapeutically intransigent pain is commonly found after varicella zoster infection, so we generated a laboratory rodent model of this in which we have demonstrated the analgesic effectiveness of Na+ channel blockers, NMDA receptor blockers and gabapentin. We have taken a quite novel approach to analgesic design for neuropathic pain, considering whether sub-groups of non-nociceptive afferents may be able to gate out sensitised nociceptive inputs. Striking analgesic effects (limited to the sensitised state) were observed following activation of the TRPM8 cool receptor (also selectively activated by chemicals such as menthol and icilin), pointing to a new, independent strategy for therapeutic analgesia in neuropathic pain.

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CUTANEOUS INNERVATION IN SMALL FIBER NEUROPATHIES
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Disease of small sensory fibers, including C fiber nociceptors innervating the epidermis, is implicated in some painful neuropathies. In man several lines of evidence have found that most patients with painful sensory neuropathies have reduced intraepidermal nerve fiber densities in distal sites. Even in more proximal sites, where IENF density may be normal, the work of Polydefkis and others has identified defective regenerative and collateral regeneration. To make clinical trials of agents that protect axons or promote regeneration more realistic, we have defined features that are associated with rapid progression and that should favor measurable regeneration. The dermal and epidermal nociceptors include a group that express the Ret receptor and respond to artemin or GDNF and an NGF-responsive group that express TrkA. We have found that impairment or blockade of TrkA function in TrkAF592A knockin mice markedly reduces inflammatory and neuropathic pain behaviors, providing further evidence for a role for NGF-responsive fibers in these settings.

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PAIN IN SMALL FIBER NEUROPATHIES: SKIN BIOPSY FINDINGS AND MEASURES OF INFLAMMATION
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b Department of Neurology, University Hospital Brno, Czech Republic
The complaint of burning feet may point to a number of underlying conditions. A small fiber neuropathy is often found, but the pathomechanism of pain associated with a decrease in dermal innervation is still unclear. We are presently investigating additional factors that may determine painfullness in patients with small fiber neuropathy. In a first prospective study, we characterized patients with burning feet through quantitative sensory testing and skin biopsy evaluation. Intra- and subepidermal nerve fiber densities were reduced by 50% compared to controls. Elevated warm detection thresholds were found to correlate with intra- but not with subepidermal nerve fiber density. Intraepidermal nerve fiber density and pain intensity had a weak inverse correlation. Furthermore, specific painful symptoms as detected from standardized questionnaires were associated with low IENFD values. In a further group of patients with proven small fiber neuropathy, we measured cytokine mRNA in blood samples and in skin biopsy samples from painful and painless areas. Preliminary data point to altered systemic and local cytokine profiles in these patients. In peripheral blood, patients with small fiber neuropathy had a mildly pro-inflammatory profile with increased pro-inflammatory and decreased anti-inflammatory cytokines compared to controls. In some patients, local cytokine mRNA levels in painful skin were dramatically increased compared to those from a non-painful area. We hypothesize that the symptom of “burning feet” may result from a combination of intraepidermal nerve fiber damage and sensitization by pro-inflammatory cytokines. This will be discussed in the context of new cytokine-modifying therapies.

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Workshop – Specific Diseases 3: CRPS – A DISEASE WITH MANY FACES

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Workshop Summary: CRPS – A DISEASE WITH MANY FACES

S.N. Raja

The Johns Hopkins University, Department of Anesthesiology and Critical Care Medicine, Baltimore, MD, USA

Aims:

(1) To discuss challenges in the clinical diagnosis of CRPS and examine the role of objective diagnostic tools for CRPS.

(2) To understand the pathophysiologic mechanisms of pain, hyperalgesia and motor disturbances in CRPS, particularly the changes in the central nervous system.

(3) To examine the available clinical evidence for therapeutic strategies that are effective in the management of CRPS.

Complex regional pain syndrome (CRPS) is characterized by varying combinations of a constellation of symptoms and signs: sensory, vasomotor, sudomotor/edema and motor/trophic changes. Studies in patients with CRPS have shown anatomical and functional abnormalities, e.g., changes in cutaneous innervation, alterations in sympathetic, somatosensory and somatomotor systems. How these peripheral and central changes are involved in the generation and/or maintenance of pain and hyperalgesia in CRPS is still not well understood. Not all patients with traumatic injuries to soft tissues or nerves develop CRPS and the factors that predispose a patient to CRPS are not known. Moreover, little is known of the natural course of the disease and why some patients with CRPS have a remission of the disease, while others have a progressive worsening of their symptoms with marked functional limitations.

Dr. Christoph Maier will discuss challenges in the clinical diagnosis of CRPS. Patients with long-term limb immobilization, limb disuse or gait abnormalities associated with a severe psychiatric/psychosomatic disorder may develop a clinical picture that mimics CRPS. This necessitates a thorough clinical and psychological examination of the patient. The potential usefulness of bone scintigraphy, comprehensive evaluation of skin temperature changes in the affected and unaffected extremities during activity, joint range of movements under anesthesia in improving the specificity of the diagnosis will be discussed.

Dr. Christian Maihöfner will review the evidence that CRPS may involve changes within the CNS. Studies, using magnetoencephalography (MEG), suggest a dynamic cortical reorganization within the primary somatosensory cortex (S1) the extent of which correlates with the magnitude of CRPS pain and mechanical hyperalgesia. In addition, functional imaging studies indicate that activations of the posterior parietal cortices, SMA and primary motor cortex correlated with the extent of motor dysfunction suggesting that adaptive changes within the central nervous system may contribute to motor symptoms in CRPS.

The lack of a clear understanding of the epidemiology of CRPS, predictive factors, and the pathophysiologic mechanisms has significantly hampered the development of rational therapies for CRPS. In addition, few randomized controlled studies have examined the long-term efficacy of specific treatment strategies for CRPS. Dr. Srinivasa Raja will review the available evidence for the effectiveness of pharmacological and interventional therapies for CRPS, and potential future therapies based on our understanding of the mechanisms of pain and hyperalgesia in CRPS. He will discuss the need
for better preventive strategies since the success of available therapies have been less than promising.

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EXTENDED DIAGNOSTIC PROCEDURES IN PATIENTS WITH COMPLEX REGIONAL PAIN SYNDROME
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Within the last decade in Germany the number of patients referred with the diagnosis of “CRPS” to the comprehensive pain centers has been escalated. Most of them suffer from painful limb pain, associated with more or less edema and movement/gait disorder. To our experiences, CRPS is the right (or the only one) diagnosis only in 50–60% (in children <10%) of these patients. Some patients suffer from poor diagnosed post-traumatic sequels (for example arthrosis of the wrist/ankle) and the diagnosis “CRPS” was made notwithstanding the IASP and the recent published criteria was not fulfilled overall. However, in two other groups of patients all typical CRPS symptoms and signs are present: (i) pain mostly after nerve (or joint) injury with distal spread of pain often in combination with vasoconstriction leading leg temperature differences (e.g. sympathetically maintained pain-SMP) or (ii) in patients with long-term immobilisation, limb disuse or gait abnormalities due to severe psychiatric/psychosomatic disorder (for example: adjustment disorder, self-inflicted injury or other psychiatric disorder). The clinical diagnosis is a great challenge, not at least because some of these patients develop a CRPS additionally (some primary), other do not. Many of these are treated without any effect with invasive and potential threatening measures like intrathecal opioid treatment, spinal cord stimulation or neurolytic blocks or are opioid dependent. Therefore extended diagnostic procedures are obviously important. Nevertheless, the accurate clinical (including the analysis of neglect-like syndrome), but also psychological examination remain the most important steps. In some cases with severe, but confusing findings we perform an advanced protocol, including the examination of joint range of motion in general narcosis. Its characteristic figures in 3rd phase provide the highest specificity (> as X-ray > MR1) and adequate sensitivity for the diagnosis of CRPS, unfortunately only within the first 6–9 month after onset of CRPS. Another new diagnostic approach is the comprehensive PC -assisted 6–8 h evaluation of skin temperature changes of the affected and the contra lateral limb during daily activities. Side temperature differences >2–3 °C allow no discrimination of CRPS from SMP and immobilized patients. The most striking issue is the number of short-time changes at both sides (decreased in CRPS) and the frequency of non-synchronous temperature changes (increased only CRPS ).

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COMPLEX REGIONAL PAIN SYNDROME: NO BRAIN – NO PAIN?
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Complex regional pain syndromes (CRPS) are characterized by a typical constellation of symptoms: autonomic and inflammatory changes, motor symptoms and sensory disturbances. There is accumulating evidence that the pathophysiology may involve changes within the central nervous system. In this talk a magnetoencephalographic (MEG) study will be presented assessing possible cortical reorganization within the primary somatosensory cortex (S1) in CRPS patients. The distance between the cortical representation of the hand and the lip was markedly decreased on the affected CRPS side compared to the unaffected side. The extent of cortical reorganization was significantly correlated to the magnitude of CRPS pain and mechanical hyperalgesia. In order to investigate whether these S1 changes are reversible and how they change after treatment, we performed a follow up study and traced the somatotopy within the S1 cortex of our patients employing MEG at least one year after therapy. For the whole group, at time of second investigation the distance between cortical representations of digits one and five on the CRPS side increased to a normal size. The reduction of cortical reorganization was predicted by the reduction of pain. Finally, an fMRI study investigating motor dysfunction in CRPS will be presented. Supported by the German Research Network “Neuropathic Pain Syndromes” (German Federal Ministry of Education and Research, BMBF).

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CRPS – A DISEASE WITH LIMITED EVIDENCE-BASED THERAPIES
S.N. Raja
The Johns Hopkins University, Department of Anesthesiology and Critical Care Medicine, Baltimore, MD, USA

Complex regional pain syndrome (CRPS) is a chronic pain state that is characterized by varying combinations of a constellation of symptoms and signs: sensory, vasomotor, sudomotor/edema and motor/trophic changes. Studies in patients with CRPS have shown anatomical and functional abnormalities, e.g., changes in cutaneous innervation, alterations in sympathetic, somatosensory and somatomotor systems. How these peripheral and central changes are involved in the generation and/or maintenance of pain and hyperalgesia in CRPS is still not well understood. Not all patients with traumatic injuries to soft tissues or nerves develop CRPS. The factors that predispose a patient to CRPS are not known. Moreover, little is known of the natural course of the disease and why some patients with CRPS have a remission of the disease, while others have a progressive worsening of their symptoms with marked functional limitations.

The lack of a clear understanding of the epidemiology of CRPS, predictive factors, and the pathophysiologic mechanisms has significantly hampered the development of rational therapies for CRPS. In addition, few randomized controlled studies have examined the long-term efficacy of specific treatment strategies for CRPS. Dr. Srinivasa Raja will review the available evidence for the effectiveness of pharmacological and interventional therapies for CRPS, based on our understanding of the mechanisms of pain and hyperalgesia in CRPS. He will discuss the need for better preventive strategies since the success of available therapies have been less than promising.

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Workshop – Therapy 3: EPIDURAL STEROIDS FOR SCIATICA

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Workshop Summary: EPIDURAL STEROIDS FOR SCIATICA, AND QUALITY OF LIFE
J.C.D. Wells
Pain Relief, Pain Matters, Liverpool, UK

This workshop is dedicated to the memory of David Niv.

David was due to speak at this workshop, but his life was tragically cut short on February 6th. The neuropathic pain SIG decided to dedicate this workshop to his memory.

David was a tireless fighter for all patients with pain, whether neuropathic or otherwise. For many years he has arranged international meetings on pain and its management, and developed the concept of the “Week Against Pain” and the idea of lobbying the European Parliament in Brussels, to make them realise the burden of pain. His concept of a tagline for patients – “Don’t suffer in Silence” – was an excellent idea and a fitting epitaph to his memory. The concept should push forward the realisation that people do have a significant burden of chronic pain, they do suffer in silence and they should have their symptoms taken seriously and managed with adequate resources throughout the world.

David was also a champion of the idea of quality of life. He started introducing this concept at meetings with which he was associated or which he was organising, and this particular subject, “Epidural Steroids for Sciatica, and Quality of Life” was discussed in Prague in 2003 at the EFIC Congress.

Since that time, Stephen Butler has highlighted the potential risks of epidural steroid injections, especially if inadequate attention is paid to detail.

This workshop will look at the evidence for benefit from epidural steroids and what types of injection are carried out in which way. It will also look at potential complications. Emphasis will be placed on how to reduce complications and also to manage any that arise. After two presentations, we will invite comments and feedback from the audience; we will then look to evaluate the place of epidural steroids in today’s Pain Clinic.

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NERVE BLOCKS FOR CHRONIC PAIN – WHAT IS THE EVIDENCE?
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In the beginning, there was Bonica and Bonica said, “Thou shalt block nerves for diagnosis, prognosis and treatment in chronic pain”. This idea was the prevailing thinking in the 50’s and for many pain specialists, is the prevailing thinking today. But do we have any proof that this philosophy is founded in evidence based medicine? To date, there is very little and we have only two areas where there is some science that supports nerve blocks and invasive treatments. The first is in the use of epidural steroids for treating acute radicular pain emanating from the lumbar region of the back. Numbers needed to treat are quite high – 13 for long-term relief, 7 for short-term but we do have some reliable evidence.

The second area is in the diagnosis and treatment of facet joint involvement in neck pain of whiplash associated disorders. The Bogduk and Lord group from Australia have published an impressive collection of studies that document the accuracy of diagnostic blocks but also the lack of evidence for nerve block treatment although radiofrequency lesions are helpful.
Clearly, much more research is needed since the absence of proof is not the proof of no effect. It does not mean that Bonica’s statement was wrong.

There have been a few reviews on the subject but not recently. There is a lot of posturing by those who have a strong belief in block therapy/radiofrequency lesioning etc. which now is a very lucrative business for not only anesthetists but also radiologists, neurologists, neurosurgeons, orthopedists and rehabilitation medicine specialists who are mainly in private practice.

I will discuss this topic in more detail and try to present a balanced view of what is known.

References

Bonica JJB. The Management of Pain, Chapter 6, Lea and Febiger, 1953 (see also the third edition).


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Epidural Steroids for Back Pain and Sciatica – How Are They Done and Do They Work?

J.C.D. Wells

Pain Relief, Pain Matters, Liverpool, UK

For a treatment to be useful in chronic pain, it should reduce pain, disability and distress, or at least one of these. It must also be cost-effective and side-effects should be recognised and appreciated. Ideally, studies should show improvements in quality of life (QOL).

Sicard Cathelin (xxxx) and Burkle et al. (2002) described caudal epidurals in 1901. Intrathecal steroids were used by Boudin et al. (1955) and Lievre et al. (1957), and Robecchi used hydrocortisone via the first sacral root canal in 1952. Swerdlow and Sayle-Creer (1970) studied 325 patients with sciatica. Today millions of patients have had epidural steroid injections; however, evidence as to their efficacy is still controversial.

Variations in technique are numerous. Several approaches are used – the lumbar, caudal and cervical – and there appears to be no difference between whether the lumbar or caudal route is used for low back pain. New techniques, such as Racz catheter, transforaminal or even epiduroscopy, are now producing better researched results.

Different volumes of injectate are used for different routes and even the same route. The contents of the injectate vary, including local anaesthetic or saline mixed with steroid and other additives, including clonidine, adrenaline and ketamine. The steroid itself varies and there is no uniformly agreed dosage, nor indeed is any allowance ever made for the weight of the patient. Different types of needle are used, many Anaesthetists liking the Tuohy needle, but there being no rationale to use this for a single-shot injection. Finally, X-ray control, in my opinion mandatory, is often not used and is sometimes not reported.

Identification of level of block and correct needle placement are both notoriously unreliable, using a blind approach. Correct needle placement has been described in as few as 30% and up to 75% of patients only (Steward et al., 1987; White et al., 1980). Epidural fibrosis or adhesions (often occurring after surgery) may make spread to the affected nerve root difficult or impossible (Greenwood et al., 1952; Racz et al., 1997). Deposition of epidural steroids at the side of the pathology occurred in only 25% of patients (Fredman et al., 1999).

No wonder then that RCTs yield diverse results. Three major meta-analyses have been performed (Koes et al., 1999; Watts and Silagy, 1995; McQuay and Moore, 1998), all with disagreement on efficacy. The literature range will be discussed in this presentation, with comments on the various papers considered for the RCTs. My opinion is that the evidence suggests that epidural steroids are useful for patients with radicular pain, especially if accurately placed. There may be some motivated patients who have postural back pain with some radicular features, where they can be helpful. Consideration should be given for use in patients with cancer pain and tumour infiltration. There is no evidence to suggest that epidural steroids are effective in patients with non-nociceptive or neuropathic chronic back pain.

Here, the use of epidural steroids may be harmful – firstly in reinforcing the patient’s concept of disease causing their symptoms and secondly because of the sort of side-effects that we know can occur.

References


Steward, H. D., Quinell, R. C., & Dann, N. (1987). Epidurography in nerve injury to emphasize the multifaceted clinical phenomenon and the infrequent findings of allodynia to different stimuli. The latter is in contrast with reports from animal models of peripheral neuropathy where behavioral hypersensitivity, frequently labeled “allodynia”, is reported to be present on a group level.

Dr. Dickenson will then argue that evoked responses are most often measured in animal models yet patients mainly complain of ongoing pain. In addition, measures from animal behavior are indirect; a withdrawal response at threshold relies on sensory and motor integration. Performing neuronal recordings that also allow supra-threshold measures to be made, robust changes in both stimulus-evoked and stimulus-independent responses can be seen.

Dr. Yezierski will show that comparisons between operant and reflex-based testing paradigms have demonstrated significantly different, and in most cases opposite results. Reflex measures may therefore not appropriately reveal changes in spinal excitability that affect pain sensitivity and it appears that motor neurons and pain projection neurons can be differentially modulated. Examples will be presented comparing behavioural responses and pharmacological manipulations involving reflex and operant assessment strategies of thermal sensitivity.

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**Workshop – Assessment And Diagnosis 4: ASSESSMENT OF OUTCOMES IN NEUROPATHIC PAIN CONDITIONS AND PRE-CLINICAL MODELS. ARE WE LOOKING AT THE SAME THING?**

**Workshop Summary: RESULTS OF AN AAN/EFNS TASK FORCE ON TRIGEMINAL NEURALGIA MANAGEMENT**

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**Workshop Summary: ASSESSMENT OF OUTCOMES IN NEUROPATHIC PAIN CONDITIONS AND PRE-CLINICAL MODELS. ARE WE LOOKING AT THE SAME THING?**

P.T. Hansson

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Translational research from animals to patients is needed to provide critical insights into the mechanisms of nerve injury pain and their treatment. The main objectives of the workshop are to highlight similarities and discrepancies concerning how clinical and pre-clinical scientists approach assessment of pain in humans and animals with neuropathy.

Dr. Hansson will discuss symptoms and signs in patients with painful peripheral partial mechanical nerve injury to emphasize the multifaceted clinical phenomenology and the infrequent findings of allodynia to different stimuli. The latter is in contrast with reports from animal models of peripheral neuropathy where behavioral hypersensitivity, frequently labeled “allodynia”, is reported to be present on a group level.

In this workshop, the development and outcome of the deliberations of a task force on the management of trigeminal neuralgia is presented. The task force was set up jointly by the European Federation of Neurological Societies (EFNS) and American Academy of Neurology (AAN) and consisted of a panel of seven experienced trigeminal neuralgia (TN) experts and general neurologists with methodological expertise. The instructions to the panel were to develop scientifically sound, clinically relevant practice parameters to aid in clinical practice. The panelists carried out a systematic literature up to December 2005 (MEDLINE, EMBASE and Cochrane library) with the help of research librarians. The primary search was supplemented by secondary search using the bibliography of retrieved articles and knowledge from the expert panel. At least two members
reviewed any paper meeting inclusion criteria. An additional panel member arbitrated disagreements. All panel members contributed to the final product consisting of guidance on diagnosis and pharmacological and surgical management of classical and symptomatic TN. Draft guidelines on each section will be presented in the workshop, and they set the scene for general discussion on their clinical relevance and applicability. Prof. Cruccu will discuss diagnostics, Prof. Nurmikko will summarise pharmacological studies and Prof. Zakrzewska will elaborate on the role of surgical interventions. The report currently awaits formal approval by the two societies.

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84 AAN/EFNS GUIDELINES ON DIAGNOSIS OF TRIGEMINAL NEURALGIA
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Several issues regarding the management of trigeminal neuralgia (TN) are still unsettled. The American Academy of Neurology (AAN) and the European Federation of Neurological Societies (EFNS) launched a mixed Task Force to draw common guidelines. After a systematic review of the literature complying with AAN/EFNS rules for evidence-based documents, the Task Force came to a series of recommendations regarding diagnosis. For patients with TN without non-trigeminal neurological symptoms, routine MRI may be considered to identify symptomatic TN (Level C). Younger age of onset, involvement of the first division of the trigeminal nerve, unresponsiveness to treatment, and abnormal trigeminal evoked potentials should be disregarded as useful for disclosing symptomatic TN (Level B). Whereas the presence of trigeminal sensory deficits or bilateral involvement of the trigeminal nerves should be considered useful to distinguishing symptomatic from classical TN, the absence of these features is not indicative (Level B). Measuring trigeminal reflexes in a qualified electrophysiological laboratory should be considered useful for distinguishing symptomatic from classical TN (Level B). Although there is insufficient evidence to support or refute the usefulness of high resolution MRI to identify patients with classical TN who are more likely to respond to microvascular decompression, we still recommend to perform it (Clinical good practice point).

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85 GUIDELINES FOR SURGICAL TREATMENT FOR TRIGEMINAL NEURALGIA
J.M. Zakrzewska

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Background. Despite the vast literature on surgical management of trigeminal neuralgia most of it is of low class evidence.

Methods. Systematic review of the literature was carried out and critically appraised by a panel.

Results and conclusions. Although there is little evidence patients with refractory trigeminal neuralgia prefer a surgical option earlier rather than late.

All peripheral techniques result in pain recurrence for 50% of patients within the year. All the percutaneous procedures on the Gasserian ganglion are ablative and so result in varying degrees of sensory loss. By 5 years up to 50% of patients will have developed a recurrence. Quality of life is improved but there is little independent data on this. Mortality remains low and morbidity is mainly within the trigeminal division. The only non invasive technique is Gamma knife surgery that aims at focusing a beam of radiation at the trigeminal nerve in the posterior fossa. Results are similar to Gasserian ganglion procedures but pain relief can be delayed for a month. Sensory loss is low and there is no mortality and low morbidity. Microvascular decompression is a major neurosurgical procedure that entails access to the posterior fossa in order to decompress vessels compressing the trigeminal nerve. Mortality is in the region of 0.5% but pain relief occurs in 70% of patients at 10 years. The major long term complication is up to 10% ipsilateral hearing loss. This procedure offers the longest pain free period and highest satisfaction.

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86 AAN/EFNS GUIDELINES FOR PHARMACOTHERAPY OF TRIGEMINAL NEURALGIA
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For classic trigeminal neuralgia (CTN) multiple RCTs have been only published on carbamazepine (CBZ). Four placebo controlled trials (Class I or II) totalling 147 patients demonstrated the efficacy of CBZ to be superior to that of placebo, earning it a level A recommendation. Oxcarbazepine was as good as CBZ in controlling CTN pain in 3 RCTs involving 130 patients in total (class II, 2 meta-analyses, recommendation
level B). Single small (class II) studies suggest that baclofen, lamotrigine (as an add-on medication) and pimozide are useful in CTN (recommendation level C). Proparacaine eyedrops are not effective against CTN (single Class I study). Remarkably, there are no randomised controlled trials published on gabapentin, pregabalin, phenytoin, valproate, tizanidine or topical capsaicin in CTN. The case series regarding these agents are small and do not suggest efficacy matching that of CBZ. Long-term data are limited and only one small case series was found regarding management of an acute TN crisis using intravenous fosphenytoin. For symptomatic TN (STN) no controlled trials exist. Small open-label studies suggest some efficacy from lamotrigine, gabapentin, topiramate and misoprostol but are insufficient for recommendations. Acknowledging the paucity of RCTs, the Task Force is prepared to recommend either CBZ or oxcarbazepine as first-line treatment in CTN, and if they fail surgery as worth consideration as the next step.

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**Workshop – Basic Sciences 4: GROWTH FACTORS AND HYPERALGESIA**

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**Workshop Summary: GROWTH FACTORS AND HYPERALGESIA**

S.B. McMahon

*Wolfson CARD, King’s College, London, UK*

Over the past decade, considerable evidence has accumulated from both humans and animals that some growth factors can contribute to various pain states. The most abundant data relates to one factor, the neurotrophin nerve growth factor (NGF) which can act as a peripheral pain mediator. The best data relates to inflammatory conditions but it also appears to play an important role in some neuropathic states. NGF neutralizing molecules are effective analgesic agents in many models of persistent pain. Such molecules are now being evaluated in clinical trials. NGF regulates the expression of another growth factor, brain-derived neurotrophic factor (BDNF), in nociceptors. Another source of BDNF is spinal microglia in neuropathic conditions. There is now good evidence that BDNF is released in spinal cord in some persistent pain states and contributes to the development of pain and hyperalgesia. This workshop will review some of this literature and also present newer data on the role of other factors that may contribute to neuropathic pain.

**88**

**SYNAPTIC SECRETION AND LOCAL ACTIONS OF NEUROTROPHINS**

V. Lessmann

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In spite of the wealth of knowledge regarding their biological actions, little is known about the mechanisms involved in activity-dependent secretion of neurotrophins (BDNF, NT-3, NT-4/5 and NGF). We now addressed the signalling cascades involved in synaptic secretion of neurotrophins (NTs). GFP-tagged NTs were expressed in hippocampal neurons, and time lapse video microscopy of GFP fluorescence was employed to explore synaptic secretion of NTs in real time. Experiments were performed under conditions that allowed to identify local synaptic signaling events that contribute to NT secretion.

We show that postsynaptic NT secretion is elicited by Ca\(^{2+}\) influx, either via L-type VGCC, or via NMDA receptors. Subsequent release of Ca\(^{2+}\) from internal stores is required for the secretion process, whereas TTX sensitive Na\(^+\) channels or autocrine NT-signaling are not involved. The postsynaptic NT secretion is critically dependent on the activation of postsynaptic CaMKII and is gated by cAMP/PKA signaling. NT vesicle fusion from postsynaptic sites proceeds via a kiss and run mechanism, which accounts for the slow time course of NT secretion.

Elevation of intracellular NO inhibited NT secretion, while exogenous BDNF increased intracellular NO. These results suggest a negative feedback of BDNF on its own synaptic secretion indicating a cross talk between postsynaptic BDNF and NO signalling in synaptic plasticity.

Effects of synaptically released BDNF were investigated using whole cell patch clamp recordings in CA1 pyramidal neurons from cultured hippocampal slices, to explore the role of local BDNF secretion in synaptic plasticity.

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**THE ROLE OF BDNF IN MICROGLIA-NEURON SIGNALLING AFTER PERIPHERAL NERVE INJURY**

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Effects of synaptically released BDNF were investigated using whole cell patch clamp recordings in CA1 pyramidal neurons from cultured hippocampal slices, to explore the role of local BDNF secretion in synaptic plasticity.
Following peripheral nerve injury (PNI) in rodent models of peripheral neuropathic pain, microglia in the spinal dorsal horn mediate behaviorally-defined tactile allodynia through activation of the P2X4 purinoceptor [Tsuda et al., Nature 2003;424:778–83]. PNI has been shown to alter anion homeostasis, increasing intracellular chloride levels, in nociceptive spinal lamina I neurons [Coull et al., Nature 2003;424:938–42]. Subsequently, we discovered that this increase in chloride is due to brain-derived neurotrophic factor (BDNF), released upon P2X4 purinoceptor stimulation from spinal microglia, acting via TrkB receptors on the lamina I neurons [Coull et al., Nature 2005;438:1017–21]. We have recently investigated the intracellular mechanisms for the release of BDNF from microglia. We have found that P2X4R stimulation evokes BDNF release per se from an intracellular storage pool and, as well, causes increasing synthesis of BDNF by stimulating its transcription and translation. Thus, suppressing microglia-neuron signaling by interfering with the BDNF-TrkB pathway in neurons or with P2X4R-stimulated synthesis and release of BDNF from microglia have the potential to be the basis for new forms of therapy for chronic pain following nerve injury.

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CCL2 AS A MEDIATOR OF NEUROPATHIC PAIN STATES
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While neuro-immune interactions are increasingly recognised as important biological processes, the nature and functional significance of these interactions is poorly defined. Here we show that the chemokine CCL2 (formerly MCP-1) is produced by primary sensory neurones in neuropathic pain states, and released with activity from the central terminals of these fibres. We also show that intrathecal administration of CCL2 in normal animals leads to leads to activation of spinal microglia and induces neuropathic pain like behaviour. An essential role for spinal CCL2 is demonstrated by the significant reversal of neuropathic pain behaviour and microglial activation by a neutralising antibody to CCL2 administered intrathecally. Thus, the neuronal expression of CCL2 provides a mechanism for immune activation, that in turn regulates the sensitivity of pain signalling systems in neuropathic states.

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Workshop Summary: CHEMOTHERAPY INDUCED NEUROPATHY
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Modern chemotherapy reduce the mortality in cancer patients as well as in AIDS patients. However, accompanying side effects like chemotherapy induced painful neuropathy often limit the duration and dose regimes of these therapies. A better understanding of the underlying pathological mechanisms of pain generation is necessary to improve the quality of life of affected patients by selective analgesic therapies and to enable more effective treatment regimes of the primary disease.

The aims of this workshop are to highlight the progress of research in

1. Animal models studying chemotherapy induced painful neuropathy.
2. The molecular basis of chemotherapy induced pain mechanisms.
4. Options and aims of analgesic therapy.

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CHEMOTHERAPY INDUCED NEUROPATHY
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Chemotherapy-induced neuropathic pain is a widespread clinical problem in oncology and HIV/AIDS patients, and current treatments are only partially effective and produce side effects that are not well tolerated. At present, the doses of chemotherapy that can be tolerated by patients are limited, primarily by the development of a painful small-fiber neuropathy. Therefore, amelioration of this neuropathic pain might not only improve the quality of life of patients who receive these chemotherapeutic agents, but also increase their clinical
outcomes, by permitting the use of higher doses and longer treatment periods. Current symptom-targeted analgesic therapies can provide some relief, but also produce unacceptable side effects. The development of more effective treatments for cancer chemotherapy-induced painful peripheral neuropathy has been hampered by the lack of understanding of its underlying pathophysiological mechanisms and by unavailability of animal models in which to perform preclinical testing. Current state of cellular mechanisms contributing to chemotherapy-induced neuropathic pain will be discussed.

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Workshop – Specific Diseases 4: RECENT DEVELOPMENTS IN HERPES ZOSTER AND POSTHERPETIC NEURALGIA – MECHANISMS, PREVENTION AND TREATMENT

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Workshop Summary: RECENT DEVELOPMENTS IN HERPES ZOSTER AND POSTHERPETIC NEURALGIA: MECHANISMS, PREVENTION AND TREATMENT
M. Haanpää
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The workshop deals with postherpetic neuralgia which is, in spite of recent development in the field, a major treatment challenge in those who remain with chronic severe pain after herpes zoster.

Maija Haanpää will present a summary of the current knowledge of the pain mechanisms and the guidelines of medical treatment of acute zoster and postherpetic neuralgia. Albert van Wijck will present the possibilities of blockades in the treatment of zoster to and postherpetic neuralgia, based on the recent and ongoing studies. Michael Oxman will deal with the zoster vaccination which has shown to reduce the incidences of herpes zoster and postherpetic neuralgia and the burden of illness caused by herpes zoster, and is hence licensed for prevention of HZ and PHN for individuals 60 years of age and older in Europe and for prevention of herpes zoster in the United States.

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MECHANISM-BASED TREATMENT OF HERPES ZOSTER AND POSTHERPETIC NEURALGIA
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Herpes zoster is a prevalent and usually very painful disease caused by reactivation of the varicella zoster virus. Acute zoster pain is a combination of nociceptive and neuropathic pains due to ganglionitis, neuritis and inflammation of the skin. Antivirals, which decrease the severity and duration of acute zoster pain, are recommended to elderly patients with painful zoster, to patients with cranial zoster and to those with severe disease. In addition, effective pain relief with NSAIDs, and if needed, with opioids, is mandatory. Low-dose amitriptylin reduces the risk of postherpetic neuralgia (PHN). Gabapentinoids are recommended for the early neuropathic pain, although there are no published studies of their efficacy to prevent PHN.

After the healing of rash zoster-associated pain is neuropathic. The mechanisms are multiple, and the relative role of different pathophysiological mechanisms cannot be determined in an individual patient. Both increased activity of the peripheral nociceptors and the central mechanisms contribute. Dynamic mechanical allodynia is typical of PHN, and the spontaneous pain can have both continuous burning and episodic lancinating components. In addition, impaired sleep and depression are common.

There is strong evidence of the efficacy of tricyclic antidepressants, gabapentinoids, opioids and topical lidocaine and moderate evidence of the efficacy of tramadol, capsaicin and valproate in the treatment of PHN. Tricyclic antidepressants, gabapentinoids and topical lidocaine are recommended as the first line agents. If needed, a combination treatment with agents with different mechanisms of action can be used. The treatment aims at pain relief, improved function and better quality of life.

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ZOSTER VACCINE FOR THE PREVENTION OF POSTHERPETIC NEURALGIA
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The incidence and severity of herpes zoster (HZ) and postherpetic neuralgia (PHN) increase with age in association with a progressive decline in cell-mediated immunity (CMI) to varicella-zoster virus (VZV). The Shingles Prevention Study was designed to test the hypothesis that vaccinating older persons with a high-potency live attenuated VZV vaccine (zoster vaccine) would boost their waning CMI to VZV, and thereby protect them from HZ and PHN.

The Shingles Prevention Study was a double-blind placebo-controlled trial in which 38,546 subjects ≥60 years of age were enrolled at 22 study sites across the United States, stratified by age (60–69; ≥70 years), and
randomized to receive a single dose of investigational zoster vaccine or placebo. Subjects were actively followed for HZ with the aid of an interactive Automated Telephone Response System, and more than 95% of the enrolled subjects were successfully followed to the end of the Study. A HZ-specific assessment tool, the Zoster Brief Pain Inventory (ZBPI), was developed and validated to capture HZ pain and discomfort, including unpleasant sensations such as alldynia and pruritus not always characterized as pain by persons with HZ. Clinically significant PHN was defined as HZ-associated pain or discomfort rated as $\geq 3$ (on a 0-to-10 scale) persisting or appearing more than 90 days after HZ rash onset. ZBPI worst pain scores $<3$ are not associated with significant decrements in quality of life or ability to carry out activities of daily living, and thus were not considered to represent clinically significant PHN.

Zoster vaccine reduced the incidence of clinically significant PHN by 66.5% ($P < 0.001$), and the reduction was identical in both age strata. The zoster vaccine was well tolerated, and it neither caused nor induced HZ [Oxman MN, et al. N Engl J Med 2005;352:2271–84].

Immunological assays at baseline confirmed a progressive loss of VZV-CMI with increasing age ($P < 0.001$), and no significant age-related change in titers of antibody to VZV ($P = 0.75$). At 6 weeks after vaccination, VZV immune responses in vaccine recipients were significantly increased over baseline ($P < 0.001$) and compared to responses in placebo recipients, and significant increases were sustained at 1, 2, and 3 years. VZV-CMI responses in the vaccine group were greater in subjects 60–69 years of age than in those $\geq 70$ ($P < 0.01$). These age-related differences in VZV-CMI were paralleled by age-related differences in the incidence and severity of PHN, and in the clinical efficacy of the zoster vaccine. These results will be discussed in relation to the neuropathology and mechanisms of PHN.

References


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subgroups of patients will be discussed. Finally, Dr. Alon will consider the role of transdermal fentanyl and buprenorphine in the treatment of neuropathic pain.

Evidence for the role of these interventions together with the strengths and limitations of each treatment modality in reducing pain and increasing function will be presented. Ample opportunity will be made available for questions.

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HIGH-CONCENTRATION CAPSAICIN FOR TREATMENT OF PHN AND HIV NEUROPATHY PAIN
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High-concentration capsaicin has been studied by now in a number of studies for treatment of pain in PHN and HIV neuropathy. Early phase studies demonstrated good tolerability, in spite of the fact that concentrations used were in order of magnitude higher than currently available commercial preparations, and prolonged efficacy. These observations lead to studies which explored the dose (in the case of topical agent such as high-concentration capsaicin duration of application is proportionate to the dose) range and duration of the analgesic effect. All of the studies conducted thus far have consistently demonstrated good tolerability and prolong analgesic effect which for most patients who obtain benefit lasts up to 3 months. Because capsaicin is a pungent agent traditional placebo cannot be used so as the control low concentration capsaicin was used, and in this case it was possible to demonstrate the efficacy of high-concentration capsaicin.

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TOPICAL LIDOCAINE AND CAPSAICIN: DOES THE NEUROPATHIC PAIN NEEDS A SECOND SKIN?
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In recent years cutaneous application of lidocaine, e.g. via patches containing 5% lidocaine, has become a recommended treatment for neuropathic pain. Further, capsaicin may enjoy a renaissance according to preliminary studies of topical application in high concentration. Evidence, advantages and limitations of these topical treatment strategies are in the focus of this workshop. Further, the suggested underlying pain-relieving mechanisms will be discussed as well as the question, whether it is possible to predict the efficacy of topical agents in subgroups of patients.

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TOPICAL AND PERIPHERALLY ACTING ANALGESICS FOR NEUROPATHIC PAIN MANAGEMENT
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Topical anesthetics are being investigated as an additional option in pain management and can play an important role in the therapeutic armamentarium of the pain specialist. They may be effective in reducing pain and improving function in patients with a variety of neuropathic and non-neuropathic pain conditions. The mechanism of action of topical anesthetics is largely within the peripheral nervous system. However, recent clinical investigations suggest that the effect of topical anesthetics on peripheral processing of pain transmission may lead to the dampening of central pain mechanisms as well. Thus, indirectly, topical anesthetics may relieve the discomfort associated with central, as well as peripheral, pain states. Much of the recent clinical research on topical anesthetics has been conducted using the topical lidocaine 5% patch. Although the lidocaine patch is indicated for postherpetic neuralgia (PHN), several studies evaluated the safety and efficacy in patients with painful conditions other than PHN such as low back pain and osteoarthritis. These studies suggest that the lidocaine patch may also be effective for pain conditions not considered to be neuropathic in origin. The systemic absorption of lidocaine from the patch is minimal. The patch has demonstrated relief from pain and tactile allodynia with a minimal risk or systemic adverse effects or drug-drug interactions. Most adverse events occurred at the application sites; no
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Workshop Summary: ANXIETY, DEPRESSION AND QUALITY OF LIFE IN NEUROPATHIC PAIN
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Whilst there is an extensive body of literature addressing the influence of psychological factors in the management of chronic pain in general, there is relatively little that addresses specifically neuropathic pain. The question therefore arises whether there is a need for measures specific to neuropathic and if so what from would they take?

The aim of the workshop is to provide a review of evidence that indicates psychological factors may influence treatment options in neuropathic pain, focusing on anxiety and depression.

Further, to consider the appropriateness of psychosocial assessment tools in neuropathic pain, whether there is a need to develop neuropathic pain specific measures as opposed to generic pain measures given the unique qualities of neuropathic pain.

In addition, to consider the nature and utility of quality of life measures in neuropathic pain. Whether there is an argument for such measures to be considered as primary rather than secondary outcome measures.

Finally, pain management programmes are continuing to grow as a major source of treatment for chronic pain sufferers. Are neuropathic pain sufferers well served by such PMPs? Or there is a need to develop PMPs specifically for neuropathic pain? Several case studies will highlight patient and clinician experience of going through a pain management programme.

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THE ROLE OF PSYCHOSOCIAL FACTORS AND NEUROPATHIC PAIN
J. Haythornthwaite
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The potential impact chronic pain can have on an individual’s psychological, social and physical function and thus quality of life is well documented. Such data in the neuropathic pain literature is less well developed. Evidence from clinical and experimental studies will be reviewed in order to examine the relationship between neuropathic pain and psychological functioning. The importance of assessing psychosocial factors when determining treatment options and evaluating outcome will be addressed. Specifically, anxiety and depression have been established as risk factors for persistent pain in general, and their role in persistent neuropathic pain requires consideration. The impact of these factors on various outcomes, including pain, pain-related disability, and treatment response will be discussed.

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ASSESSMENT OF PSYCHOSOCIAL FACTORS IN NEUROPATHIC PAIN
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A large number of measures are available for the assessment of non-pain psychosocial variables in patients with neuropathic pain. This presentation will describe and critically review the validity and reliability of these measures with particular emphasis on those designed to assess anxiety, depression and/or quality of life. The utility of assessment tools in helping to determine treatment options will be considered and the extent to which generic rather than disease specific tools are useful for evaluating treatment and outcome will be discussed. The process and development of a quality of life measure for neuropathic pain will be used as a vehicle to explore the issue of patient reported outcomes and the futility of measuring pain in isolation from these contextual factors. The question of whether psychosocial variables, such as quality of life, should be considered as primary rather than secondary outcome parameters in treatment trials will be raised using evidence from published studies to support this premise.

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TREATMENT FOR NEUROPATHIC PAIN FROM A PSYCHOSOCIAL PERSPECTIVE
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The utility of non-pharmacological treatments, including pain management programmes based on cognitive behavioural principles, for specific neuropathic pain conditions will be explored and evidence for their efficacy reviewed. In particular, to consider the extent that generic pain management programmes can meet the needs of the patient with neuropathic pain. In addition, to describe and evaluate the role of the multidisciplinary team in assessing the suitability of a pain patient for either a pain management programme or spinal cord stimulation, or possibly a combination of both. Several case studies will be used to illustrate the experience of both neuropathic pain patients and clinicians on various treatment pathways.

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Workshop – Epidemiology And Health Care Systems 5: EPIDEMIOLOGY OF DIABETIC NEUROPATHY – LATIN AMERICAN EXPERIENCE

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EPIDEMIOLOGY OF DIABETIC NEUROPATHY IN MEXICO
M. Genis Rondero
AMETD, Mexico City, Mexico

Pain is a multidimensional sensory experience that is intrinsically unpleasant and associated with hurting and soreness. It may vary in intensity, quality, duration, and referral. Although it is essentially a sensation, pain has strong cognitive and emotional components; it is linked to, or described in terms of suffering. It is also associated with avoidance motor reflexes and alterations in autonomic output. All of these traits are inextricably linked to the experience of pain.

Diabetes Mellitus: In Mexico, among all Mexican states reported the prevalence of diabetes. In México is 10.8% from one hundred five million people inhabitants.

Although neuropathy has long been recognized as a complication of diabetes, the impact of this condition has not been properly adequately established. The prevalence of diabetic neuropathy is virtually unknown.

Diabetes is commonly associated with a peripheral neuropathy that often results in significant pain.

Actually in the Latin American Federation chapters of pain (FEDELAT), an investigation of prevalence of pain in Latin America is being carried out, and these conclusions will be presented on May 2007.

Our aim is to study and demonstrate that in Mexico and the rest of Latin America, the incidence, prevalence and social impact of neuropathic pain is consequence of diabetes condition.

I am certain that the results of this effort will contribute to a better understanding and treatment of pain due to diabetic neuropathy in Mexico and Latin America.

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EPIDEMIOLOGY OF PAINFUL DIABETIC NEUROPATHY IN CENTRAL AMERICA AND THE CARIBBEAN
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Diabetic neuropathy and its related pain is a world wide complication of the primary disease that affects millions of human beings around the world. It is a peripheral nerve disorder in which the symptoms may not be prominent at first but then gradually appear in the form of pain, numbness, tingling in the feet, legs or both and after time weakness in the muscles of the feet may appear. On occasions the neuropathy appears suddenly and affects specific nerves so the affected individual will develop double vision, drooping eyelids or weakness and atrophy of the thigh muscles. After years of suffering the condition, the patients may also develop problems with the digestive and sexual systems which may cause indigestion, diarrhea or constipation, dizziness, bladder infections and impotence. The loss of sensation in the feet may cause injuries in the foot to go unnoticed and so develop lesions that may later become infected ulcers.

The Latin-American Federation of IASP chapters (FEDELAT) is conducting a survey in the 20 countries of the American Continent twenty known as “Latin America” in which the epidemiology of chronic pain will be shown. The aim of our presentation is to show the incidence and prevalence of painful diabetic neuropathy in Central America and the Caribbean and let the audience known what is being done to properly diagnose and treat the condition throughout the region.

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EPIDEMIOLOGY OF DIABETES NEUROPATHY IN SOUTH AMERICA
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Diabetes is the most common cause of neuropathy in the world and of course also in Latin America.
The results of a big Latin American Pain Survey will be published soon so, we will be able to analyze the exact figures about this entity. Latin America has its own special problems in assessing, controlling and treating diabetes, more than 350 million people live in rural areas many times lacking even drinkable water. The basic medical services are also poor in health professionals, lab testing, medical and paramedical equipment and drugs for treating basic diseases such as diabetes. Nevertheless, many National Health Secretaries, WHO programs, NGO’s and other private Foundations have managed during the last 15 years to introduce programs and funds to diagnose and treat diabetes so, the numbers of diabetes neuropathy have decreased since these efforts.

The idea of treating Diabetic Peripheral Neuropathic Pain (DPNP) is now very clear in the entire region. Starts lowering glucose levels then administrate pain killers, from Aspirin to all the other NSAID’s to Controlled Release Oxicodone (available just in a few cities of some countries).

We know that almost half of all people with diabetes have some kind of neuropathy or nerve damage and this is associated with pain which can be difficult to treat, therefore we can start new assessment programs with early education, consequently a better comprehension of patient should be obtained as to what to expect when pain appears.

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Workshop – Basic Sciences 5: MOLECULAR AND SYNAPTIC MECHANISMS FOR NEUROPATHIC PAIN

108 Workshop Summary: MOLECULAR AND SYNAPTIC MECHANISMS FOR NEUROPATHIC PAIN

M. Zhuo

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Understanding molecular and cellular mechanisms of synaptic plasticity not only provides basic information for learning and memory, but also reveals potential new targets for treating disease including neuropathic pain. In this symposium, three speakers will provide their recent findings of injury-related plasticity along somatosensory pathways, from the dorsal root ganglion (DRG) cells to the anterior cingulate cortex (ACC). In the DRG level, Dr. Xu Zhang from Institute of Neuroscience in China will present the evidence for the upregulation of synaptoporin, an integral membrane component of synaptic vesicle, after nerve injury. He will also discuss the functions of other regulated vesicle-associated molecules in the modification of synaptic transmission of afferents following peripheral nerve injury. In the spinal cord dorsal horn, Professor Yoshimura from Kyushu University in Japan will discuss the functional roles of the A-beta afferents sprouting in the spinal cord dorsal horn. Using the in vivo patch-clamp recordings, he will present the data supporting that the subpopulation of A-beta afferents may carry nociceptive information at least in immature state. Finally, in the anterior region of the prefrontal cortex, Professor Zhuo from University of Toronto in Canada will report a long-lasting increase in the synaptic efficacy (or LTP) in the ACC after nerve injury. Both presynaptic enhancement of glutamate release and increased postsynaptic AMPA receptor mediated responses contribute to nerve injury-induced LTP in the ACC. Genetic studies of the use of AC1 knockout mice suggest AC1 thus may serve as a novel target for treating neuropathic pain.

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109 MOLECULAR MECHANISMS FOR MODIFICATION OF SYNAPTIC TRANSMISSION OF AFFERENTS FOLLOWING PERIPHERAL NERVE INJURY

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The peripheral nerve injury-induced modification of the molecular basis of synaptic transmission at afferent terminals would contribute to the mechanisms of neuropathic pain. Using cDNA array, we find that the expression of twelve vesicle-associated molecules is strongly changed in rat dorsal root ganglion (DRG) after peripheral nerve injury. Synaptoporin and synaptophysin are integral membrane components of synaptic vesicles. Synaptoporin is expressed in subsets of small neurons that contain either neuropeptides or isolectin B4, and is distributed in their afferent terminals in laminae I–II of the spinal cord. Synaptophysin is expressed in 57% of synaptoporin-containing small DRG neurons and in large DRG neurons. In the spinal dorsal horn, synaptophysin-immunolabeling is weak in the afferents in laminae I–II, but strong in the afferents in laminae III–IV. Peripheral nerve injury increases synaptoporin expression in small DRG neurons and synaptoporin level in their afferent terminals. Thus, synaptoporin is a major synaptic vesicle protein in nociceptive afferents in both physiological and neuropathic pain states. We will also discuss the functions of other regulated vesicle-associated molecules in the modifica-
tion of synaptic transmission of afferents following peripheral nerve injury.

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ANALOGY OF A-BETA AFFERENTS TERMINATION IN PATHOLOGICAL CONDITIONS WITH IMMATURE STATE

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Background and aims: The termination of primary afferents changes during maturation and pathological conditions, for instance, A-beta afferents terminate in lamina II (substantia gelatinosa; SG) in immature state, then retract to deeper laminae following maturation. After sciatic nerve transection or inflammation, the A-beta afferents sprout again into SG. The aims of this study are to clarify the functional role of the afferents at immature state and why the sprouting is triggered by peripheral injuries.

Methods: Patch-clamp recordings were made from SG neurons from rat in vitro and in vivo preparations.

Results: About 10% and 30% of SG neurons following the sciatic nerve transection and inflammation, respectively, received monosynaptic A-beta inputs, being analogous, at least in part with those of immature state. We, therefore, further tested whether the sprouted A-beta afferents retracted to the deeper laminae, with the behavioral changes 5 weeks after inflammation. Von Frey examination showed no difference in strength with normal; furthermore, the number of sprouted A-beta afferents significantly decreased to normal, suggesting that the reorganization of A-beta afferents is one of key factors producing pathological state. Therefore, next we tested a functional role of A-beta afferents in immature state using in vivo patch-clamp recordings. All dorsal roots, except a root that elicited only A-beta response in SG by stimulating the root were cut, then the receptive field was mechanically stimulated. Two of three neurons responded to pinch, suggesting that the subpopulation of A-beta afferents carry nociceptive information at least in immature state.

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ENHANCED PRESYNAPTIC AND POSTSYNAPTIC EXCITATORY TRANSMISSION IN THE ACC AFTER NERVE INJURY

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The anterior cingulate cortex (ACC) plays a critical role in the pain perception and emotional unpleasantness in humans and animals. We have proposed that long-term potentiation (LTP) in the ACC may serve as a neuronal basis for injury-related long-term plastic changes in the ACC. Under experimental conditions, LTP induced by different induction protocols in the ACC of brain slices seems to be mediated solely by postsynaptic mechanism. The postsynaptic enhancement of glutamate AMPA receptor-mediated excitatory responses contribute to ACC LTP, in part due to the possible trafficking of AMPA GluR1 subunit after LTP induction. However, it is unclear if postsynaptic LTP may mimic pathological pain conditions. Here we report a long-lasting increase in the synaptic efficacy (or LTP) in the ACC after nerve injury using a brain slice preparation. Both presynaptic enhancement of glutamate release as well as increased postsynaptic AMPA receptor mediated responses contribute to nerve injury-induced LTP in the ACC. This finding differs from pure postsynaptic expression of ACC LTP induced by experimental electrical stimulation. Gene deletion of AC1, a key calcium-calmodulin stimulated adenylyl cyclase, abolished or significantly reduced presynaptic and postsynaptic effects. In parallel, behavioral allodynia induced nerve injury was also reduced in AC1 gene knockout mice. Our results provide the first pathological evidence for mixed presynaptic and postsynaptic forms of LTP in neuropathic pain, and demonstrate that AC1 as a key signaling molecule for central plasticity and neuropathic allodynia. AC1 thus may serve as a novel target for treating neuropathic pain.

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Workshop – Mechanisms And Translational Research 5: THE ROLE OF ENDOGENOUS PAIN CONTROL IN NEUROPATHIC PAIN – EVIDENCE FROM RLS

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Workshop Summary: DOPAMINERGIC MECHANISMS OF PAIN CONTROL

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Although alterations in endogenous pain control systems have been implicated in neuropathic pain condi-
tions, only recently have studies turned attention to regulatory mechanisms that differ from the descending serotonergic and noradrenergic controls that arise in the brainstem. In this workshop, we will focus on dopaminergic mechanisms. Allan Basbaum will review preclinical studies of the anatomy and pharmacology of the dopaminergic contribution to pain control. Aanti Pertovaara will present functional imaging and psychophysical studies implicating an important basal ganglia dopamine contribution to the response to pain in humans. Particular attention will be paid to the importance of D2 dopamine receptors in pain modulation as revealed by PET. Finally, Karin Stiasny-Kolster will discuss Restless Legs Syndrome (RLS), which has features suggestive of a neuropathic pain condition, including profound mechanical hyperalgesia. Although the neurobiological basis of RLS has not been determined, it is significant that RLS can be ameliorated by targeting selective dopaminergic receptor systems.

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113 MODULATION OF PAIN BY THE STRIATUM, A POTENTIAL CULPRIT IN RLS
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The striatum has a role in pain regulation as indicated by the finding that painful stimulation increases neuronal activity and blood flow in the striatum. Also, electrical or chemical stimulation of the striatum attenuates pain-related responses in animals. Dopaminergic system appears to have an important role in striatal processing of pain as indicated by the following findings. Lesions of nigrostriatal neurons enhance nociception and striatal administration of dopamine D2 receptor agonists suppresses pain-related responses in experimental animals. In line with this, pain is a frequent symptom in degenerative diseases of the nigrostriatal dopaminergic system such as Parkinson’s disease, patients with Parkinson’s disease have low pain thresholds, high dopamine D2 receptor availability in the putamen is associated with low pain sensitivity in healthy subjects, and patients with some chronic pain conditions exhibit increased availability of dopamine D2 receptor in the putamen. Our recent studies in experimental animals suggest that the striatum has a bidirectional effect on neuropathic hypersensitivity via two distinct pathways descending to the spinal cord. First, hypersensitivity is reduced following activation of noradrenergic alpha-2-adrenoceptors and downstream dopamine D2 receptors in the striatum. This antihypersensitive effect descends via parallel dopaminergic and serotonergic pathways to act on spinal dopamine D2 and 5-HT1A receptors, respectively. Second, tonic activation of striatal NMDA receptors promotes hypersensitivity by suppressing spinal GABAergic inhibition. The above evidence suggests that the striatum might contribute in a complex way to symptoms in various chronic pain conditions, including RLS.

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114 NEUROPATHIC PAIN IN RESTLESS LEGS SYNDROME – A DISORDER OF PAIN CONTROL
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40 untreated patients (32 female, mean age 55 ± 13 years) with primary RLS (mean IRLS score 23 ± 6 points) for 15 years and 40 age and gender-matched control subjects (mean age 53 ± 14 years) with normal neurological examination were investigated by a standardized quantitative sensory testing (QST) protocol measuring thermal detection thresholds for perception of cold (CDT), warm (WDT) and paradoxical heat sensation (PHS); thermal pain thresholds for cold (CPT) and hot stimuli (HPT); mechanical detection thresholds for touch (MDT) and vibration (VDT); mechanical pain sensitivity including thresholds for pinprick (MPT) and blunt pressure (PPT), stimulus/response function for pinprick sensitivity (MPS) and dynamic mechanical allodynia (DMA), and pain summation to repetitive pinprick stimuli (wind-up ratio, WUR). MPT was decreased (p < 0.001) and S/R function for pinprick increased (p < 0.001) in the feet. PHS were more frequent and MDT tended to be higher in RLS patients. CDT, WDT, CPT, HPT, DMA and VDT were not significantly different indicating no A-delta-, C-fiber- and A-beta-fiber sensory deafferentation. Our results show that RLS patients exhibit a profound mechanical hyperalgesia which is a hallmark sign of neuropathic pain of the central sensitization type. The somatosensory pattern is consistent with mechanisms of central sensitization and suggests that RLS is a disorder of pain control with dysfunctional supraspinal descending control mechanisms. To test if affected family members and a subgroup of (so far) unaffected family members (presymptomatic cases) have similar pathological QST results (trait marker) we currently investigate affected and unaffected family members in RLS families.

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Workshop – Specific Diseases 5: RECENT ADVANCES IN INVESTIGATION AND MANAGEMENT OF HEADACHE AND MIGRAINE

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Workshop Summary: RECENT ADVANCES IN INVESTIGATION AND MANAGEMENT OF HEADACHE AND MIGRAINE
J.E. Charlton
Pain Management and Anesthesiology, Royal Victoria Hospital, Newcastle-On-Tyne, UK

This session will cover the assessment and diagnosis of migraine, the developing field of neuro-imaging and the hot topic of the role of calcitonin gene-related peptide in migraine. This is an enormous field and other areas can be covered by the distinguished panel in question time.

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MIGRAINE
A.J. Dowson
Kings College Hospital, London, UK

This session is designed as an update on the diagnosis and assessment of headache.

Differential diagnosis will be the first topic with reference to symptomatology including the topical central sensitization.

Diagnostic tools will be reviewed along with tools re disability and outcome assessment.

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WHAT HAVE WE LEARNED FROM NEUROIMAGING IN HEADACHE?
A. May
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Migraine is still regarded as a vascular headache despite the fact that a central nervous system cause has been suggested. Functional imaging is increasing our understanding of the pathophysiology of idiopathic headaches, focusing on identifying synaptic changes related to pain transmission.

Early studies using SPECT (single photon emission computed tomography) analysis – a semi-quantitative technique – showed no differences in blood flow between sides or in/out of an attack, in patients with migraine without aura. Positron emission tomography (PET) is the method of choice for quantitative study of metabolic and vascular changes. The question is, are there any PET changes that are specific for the pain of headache? When capsaicin is injected to induce headache in volunteers, there is activation (i.e. increase in regional cerebral blood flow (rCBF)) in the frontal cortex, both insulae, the contralateral thalamus and the cerebellum. These are all non-specific pain responses. Functional imaging is being used currently to look for any differences between migraine attacks and cluster headache attacks and the resting state. In migraine and cluster headache activations has been seen in the so-called “pain matrix”. Moreover, during the acute migraine attack, but not during the headache free interval, a highly specific activation in brainstem structures has been seen. In cluster headache a specific hypothalamic activation was demonstrated. It has been suggested that this vascular change may reflect a generator as it has not been seen in any studies of experimental headache or cluster headache or in any other models of somatic pain. Very recently MRI T1-weighted scans have been used to look for structural changes in the brains of patients with cluster headache, tension type headache and migraine. These data suggest idiopathic headaches to be a primary central nervous system disorder and demand renewed consideration of the neural influences at work in these syndromes.

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CALCITONIN GENE-RELATED PEPTIDE (CGRP) INVOLVEMENT IN MIGRAINE
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CGRP is a large signalling peptide found in unmyelinated nerve fibers predominantly around blood vessels. In the cranial circulation, most CGRP is found in terminals from the trigeminal nerve which are abundant both in dural and pial blood vessels. CGRP acts on specific receptors, the CGRP 1 or the CGRP 2 receptors located in smooth muscle. Stimulation of these receptors activates CYCLIC AMP production and causes a pronounced vasodilatation. It has been reported that CGRP may be released into the external jugular blood during a migraine attack. But more recently a larger and methodologically better study found no change in CGRP. When CGRP is infused intravenously to migraine patients in the maximal tolerated dose, it elicits a throbbing headache which in some patients fulfils the
diagnostic criteria for migraine without aura. This is solid evidence that CGRP can induce migraine in patients. The first selective CGRP receptor blocker BIBN4096BS has significant effect in the treatment of acute migraine. In conclusion, the principle of CGRP antagonism in migraine is now of proven validity, and novel drugs with this activity are awaited.

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Workshop Summary: OPIOIDS FOR CHRONIC NON-CANCER PAIN

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The history of opioid use changed dramatically from “opiophobia” to a liberal use in all situations of chronic pain. Randomised trials demonstrated efficacy of opioids in nociceptive and neuropathic pain. However, the WHO-analgesic ladder was made for cancer pain and not for all kinds of pain.

More and more studies focus on functional restoration as the main outcome criterion. At the same time, more and more papers report of opioid withdrawal as a step towards improvement. Opioids are not the remedy for all kinds of pain. A structural interdisciplinary approach is necessary to provide effective pain control and functional improvement. The workshop shall give essential hints of known evidence and clinical experience.

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OPIOIDS FOR NON-MALIGNANT PAIN – ARE OPIOIDS BETTER THAN ALTERNATIVES?

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The use of opioids in chronic non-malignant pain is profoundly messy. A simple start is to say that if somebody has severe pain which responds to opioids and for which there is no other effective remedy, then why should they not receive opioids? Two judgements are then implicit, that opioids are effective and that other remedies are not.

Opioids are often withheld to protect society or to protect the patient. The society argument is that medical availability of opioid increases street addiction. There has never been any strong evidence that medical use increases street problems, and the introduction of oral morphine in Sweden in the early 1980s was shown not to increase addiction (Agenas et al., 1982).

Withholding the opioid to protect the individual from harm might be done for physical or psychological reasons. Many notables across the centuries used opioids long term without deterioration in physical health, Florence Nightingale surviving over 40 years after first opium injection for back pain (Quinn and Prest, 1987). We know too that if the opioid sensitive pain later resolves opioids can be stopped, without patients becoming addicts. The grey areas here are the judgements about the patient’s potential for addictive behaviour and about the opioid sensitivity of the pain. We lack good tests to help with either judgement. We fear scenarios such as patients with back pain with no identifiable pathology using escalating doses of ‘minor’ and then ‘major’ opioid. This can lead to draconian guidelines and to thoughtless legislation, which restrict opioid use to the detriment of those with genuine need.

References


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CHRONIC NON-CANCER PAIN PREDOMINANTLY NEUROPATHIC AND THE LONG TERM SAFETY AND EFFICACY OF OPIOIDS

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The use of opioids for chronic non-cancer pain (CNCP) remains somewhat controversial. Despite a number of randomized controlled trials showing efficacy and safety in the short-term, issues such as tolerance, the risk of psychological dependency, quality of life and long term safety remain concerns. This study reports long-term results from a total population of 145 patients with CNCP treated with opioids. Most of the data derives from a detailed questionnaire administered to a group of 78 patients actively followed about every 3 months for a median of 8 years. Both long and short acting opioids appeared to be effective and safe in the long term.
and psychological dependency, tolerance and serious side effects were not major issues. As well, many patients reported a modest improvement in quality of life.

**Perspective.** This long-term, follow-up study of the treatment of chronic non-cancer pain treated with opioids suggests that this approach is effective and safe over many years.

**Keywords:** Chronic non-cancer pain; Neuropathic pain; Opioids; Long-term results

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**122 PRESCRIBING OPIOIDS FOR CHRONIC PAIN: A RATIONAL APPROACH**

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The role of opioids for treatment of chronic noncancer pain has been fervently debated for over 25 years. Opioids were earlier considered inappropriate for management of chronic pain due to concerns about adverse effects, tolerance, dependence and addiction. Controlled trials of opioids reporting positive outcomes in chronic pain states and case series suggesting a low incidence of addiction in patients with no history of substance abuse have led to acceptance of the use of opioids for chronic pain. However, accounts of rising rates of prescription drug abuse have appeared recently in the medical literature and the news media. In 2004, over 2.4 million people in the US aged 12 and over used prescription medications for non-medical reasons.

Pain clinicians and researchers need to work together in determining predictors of successful therapy and/or abuse with opioids and develop a rational approach to the use of these drugs in patients. Before considering an opioid trial, should the patient be assessed for predictors of opioid abuse such as a history of alcohol or substance abuse and/or drug-related convictions? Additional studies are needed to determine the propensity for treatment success for a given pain state. For postherpetic neuralgia and trauma-related pain, the literature supports at least the short-term use of opioids while in other conditions, e.g., chronic pelvic pain, evidence supporting opioid therapy is lacking. Recent studies from our laboratory investigating predictors of successful therapy with opioid in patients with postherpetic neuralgia will be presented.

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Pfizer Plenary Sponsored Symposium:
NEUROPATHIC PAIN – IS PREVENTION POSSIBLE?

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THE EVOLUTION OF CHRONIC PAIN – POTENTIAL TARGETS FOR PREVENTION
C.J. Woolf

Neural Plasticity Research Group, Department of Anesthesiology & Critical Care, Massachusetts General Hospital & Harvard Medical School, Boston, MA, USA

Pain that persists may result from several quite distinct conditions. These include the persistent activation of nociceptors mediated by the presence of an ongoing noxious stimulus (chronic nociceptive pain); persistent or relapsing inflammation producing recurrent peripheral and central sensitisation (chronic inflammatory pain), lesions to peripheral nerves triggering long-lasting changes in the nervous system (neuropathic pain), and lastly, ongoing autonomous abnormal processing of nociceptive information in the central nervous system (dysfunctional pain).

In order to successfully target the conversion of acute to chronic pain it is essential to be able to diagnose the specific condition responsible. It is also critical to understand the specific neurobiological mechanisms involved in each condition’s contribution to the initiation and maintenance of persistent pain. We need to recognise, moreover, that the mechanisms that result in the establishment of chronicity may not be the same as those that drive pain symptoms. In consequence, treatment that suppresses the sensation of pain (analgesics) may not be the most appropriate for preventing the evolution of acute to chronic pain which may require a disease-modifying approach with therapeutics that have no intrinsic analgesic activity.

While the complexity of persistent pain may seem daunting, sufficient progress is now being made in understanding the what, how and when of the syndrome, that we can begin to make rational choices for how best to prevent it.

Recommended reading


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CAN WE IDENTIFY PATIENTS WHO NEED PREVENTIVE THERAPY?
T.S. Jensen

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It is well known that only a minor proportion of patients with nerve damage (approximately 5–10%) develop neuropathic pain. As such, a general pain prevention treatment for all patients with a specific nervous system disease or lesion is not feasible. However, risk factors for the development of chronic pain have now been delineated. In post-amputation pain, severe and long-lasting pain before amputation is a risk factor. In patients with herpes zoster, severe acute pain, severe rash and old age are all risk factors for the subsequent development of neuropathic pain. A surgical procedure e.g thoracotomy may also expose a patient to a greater risk of chronic neuropathic pain. Less clear but probably also important are social, environmental and psychological factors. Expectation of pain, fear, past memories, work and levels of physical activity all influence the response to noxious stimuli and may therefore also influence the experience of pain. If the damage to the nervous system is great or confined to certain areas – and this is particularly the case for central nervous system disorders – pain may also be likely to develop. Taken together, if all these factors are combined it may be possible in the future to identify the pain-prone patient i.e. the patient who is most likely to develop neuropathic pain after a specific lesion.

Recommended reading


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PREVENTION OF CHRONIC POST-SURGICAL PAIN – CLINICAL TRIALS CONSIDERATIONS
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Development of chronic postsurgical pain has been documented in several common procedures such as groin hernia repair, mastectomy, amputation and thoracotomy. Due to the large number of procedures performed, and the current lack of sufficiently effective therapy, chronic postsurgical pain remains a major challenge for
research and improvement. The main pathogenic mechanisms include preoperative increased pain sensitivity (possibly due to genetic or psychosocial factors), intraoperative nerve damage, and acute postoperative pain.

Treatment strategies include effective – perhaps preemptive – perioperative analgesia, nerve-sparing minimally invasive surgical techniques and, potentially, preoperative identification of high-risk patients with subsequent high intensity, early and prolonged (?) acute pain treatment. However, results from analgesic trials irrespective of the technique used (systemic/ regional analgesia) have so far been rather disappointing. This is most probably due to the use of relatively insufficient and short-lasting monotherapy with limited effects on peripheral and central neuroplasticity. There is therefore a need for better-designed future clinical trials which include: (1) detailed preoperative assessment of nociceptive function (heat pain, pain genes, psychosocial factors); (2) detailed intraoperative description of the handling of nerves, and (3) detailed early and late postoperative assessment with quantitative sensory testing and magnetic resonance imaging (to determine the relative role of nerve damage vs a continued inflammatory response in the surgical field), combined with multimodal effective and prolonged (maybe 2–4 weeks) treatment in well-defined patient populations.

Recommended reading


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SCHWARZ PHARMA Sponsored Breakfast Symposium: LACOSAMIDE: A NEW ANTICONVULSANT FOR THE TREATMENT OF PAINFUL DIABETIC NEUROPATHY

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LACOSAMIDE: A NEW ANTICONVULSANT FOR THE TREATMENT OF PAINFUL DIABETIC NEUROPATHY
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The investigational anticonvulsant lacosamide selectively enhances slow inactivation of sodium channels and interacts with collapsin response mediator protein 2.

Lacosamide was potent and broadly efficacious in animal models for pain, CNS disorders and epilepsy, where it acted synergistically with other established anticonvulsants.

In preclinical studies, lacosamide showed a favourable safety profile, no evidence of teratogenicity and no indication of abuse liability or dependence.

In vitro, lacosamide is barely metabolized and binding to plasma proteins is very low (<15%). Phase I trials did not reveal appreciable drug–drug-interactions, suggesting that lacosamide has only low potential for drug–drug-interactions in clinical use.

Phase II and III clinical trials with lacosamide in painful diabetic neuropathy consistently showed clinically relevant pain reduction in short- and long-term use. Lacosamide proved to be well tolerated. Somnolence and behavioral or cognitive side effects, which are typical for anticonvulsants, were comparably low in these studies. Lacosamide acted weight neutral and did not cause edema, which is of particular interest for diabetics. The safety profile observed in a 2-year open-label trial was comparable to that found in short-term studies. Long-term analyses showed sustained patient satisfaction with lacosamide treatment and good adherence to therapy.

In conclusion, lacosamide is a potent and safe anticonvulsant which is effective in treating painful diabetic neuropathy. Its novel dual mode of action differentiates lacosamide from currently available anticonvulsants and could be the link to its favorable preclinical and clinical profile. Based on its mode of action, lacosamide might even have disease-modifying effects.

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NeurogesX Sponsored Breakfast Symposium: LOCALIZED APPROACHES TO THE MANAGEMENT OF NEUROPATHIC PAIN SYNDROMES

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LOCALIZED APPROACHES TO THE MANAGEMENT OF NEUROPATHIC PAIN SYNDROMES: PHYSIOLOGIC RATIONALE AND CLINICAL RESULTS
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Pharmacologic management of neuropathic pain is fraught with challenges. Responses to pharmacothe-
ties are variable and unpredictable, and complete relief of pain is rare. In the attempt to achieve adequate pain control, many patients are given combinations of drugs that were not designed to treat neuropathic pain, provide only temporary relief, and cause side effects and drug interactions. Most of the current treatments are poorly tolerated and associated with safety risks. These considerations particularly apply to systemic agents including orally administered tricyclic antidepressants, anticonvulsants, and opioids as well as transdermally administered systemic drugs.

Limitations of currently available therapies and advances in understanding of pain mechanisms have stimulated new interest in localized, non-systemic approaches to managing neuropathic pain. Targeted delivery of analgesics with locally applied agents confers the advantage of minimal systemic absorption so that risks of side effects and drug interactions are minimized. Recent neurobiological findings suggest that targeted delivery also facilitates drug access to key sites involved in initiating and maintaining pain. This symposium considers the physiologic rationale for localized approaches to neuropathic pain syndromes and examines clinical data on locally administered therapeutic options.

Animal models and physiologic studies in humans show that neuropathic pain is characterized by abnormal discharge of afferent pain pathways, central sensitization, and abnormal activity of efferent pain pathways. Alterations in the excitability of peripheral sensory nerves and corresponding changes in skin sensory function contribute significantly to neuropathic pain in humans. Peripheral mechanisms implicated in abnormal pain signaling include sensory afferent sensitization, altered ion channel and receptor expression, spontaneous firing of sensory afferents, altered phenotype of large nerve fibers, and nerve inflammation. Under normal conditions, innocuous tactile stimulation activates large myelinated Aβ fibers, and painful stimulation activates small unmyelinated C fibers and small myelinated Aδ fibers. Nerve injury alters these responses such that activation of Aβ fibers produces pain whereas activation of C fibers and Aδ fibers produces intensified pain. Evidence suggests that these changes in pain signaling result from changes in ion channel and receptor function at sensory nerve terminals. For example, nerve injury causes markers primarily associated with C fibers (e.g., substance P, growth factors, vanilloid receptors) to be expressed also in A fibers. Nociceptive sensory fibers contain numerous such ion channels and receptors that contribute to activation and sensitization of sensory nerves by tactile stimuli.

Several localized approaches to targeting peripheral pain mechanisms have been introduced or are in development:

- Capsaicin: Capsaicin is a transient receptor potential vanilloid 1 (TRPV1) agonist that activates vanilloid-1 ligand-gated cation channels on C fibers and some Aδ fibers to allow calcium entry into the cell. Calcium entry causes neuronal activation and release of peptides leading to transmission of pain signals to the spinal cord. With repeated application or administration of a large concentration of capsaicin, desensitization of this response occurs so that pain transmission is inhibited. Topically administered capsaicin in concentrations of 0.025% and 0.075% has been shown to provide modest relief in postherpetic neuralgia, diabetic neuropathy, and trigeminal neuralgia. At these concentrations, multiple daily applications are required, and compliance is generally poor because of the sensation of burning pain at the site of application. To avoid the discomfort of repeated capsaicin application and to increase the efficacy of capsaicin therapy, NGX-4010, a high-concentration capsaicin dermal patch containing capsaicin 8% weight to weight, is being developed for the treatment of neuropathic pain. In a program of clinical studies, a single treatment with the high-concentration NGX-4010 patch was shown to produce equal or better pain relief compared with multiple low-concentration applications. A single 60-min application provides 3 months of pain relief. In keeping with the minimal absorption of topically administered capsaicin, the tolerability and drug-interaction profiles of NGX-4010 are benign.

- Local anesthetics: Local anesthetics, particularly lidocaine, have been used in the treatment of neuropathic pain. Local anesthetics block voltage-gated sodium channels, which mediate the initiation and propagation of action potentials. The expression of specific types of sodium channels is altered in several models of nerve injury, and such alterations are thought to contribute to neuropathic pain. It is hypothesized that lidocaine blocks sodium channels on sensory afferents to decrease afferent pain transmission. Local anesthetics also appear to have anti-inflammatory effects that might contribute to relief of neuropathic pain. Lidocaine as a 5% gel or patch has been demonstrated effective in relieving pain in postherpetic neuralgia.

- Alpha adrenergic agonists: Clonidine, an α2 adrenergic agonist, binds to presynaptic receptors on noradrenergic nerve terminals to prevent release of norepinephrine. It also may have direct actions on primary sensory afferents. Intradermally administered clonidine is effective in animal models of neuropathic pain, and clonidine applied topically 4 times daily as a cream to patients with oral neuropathic pain has been demonstrated effective in a small pilot study.
Botulinum toxin: Botulinum toxin has been used for non-neuropathic pain syndromes such as migraine. Successful use of botulinum toxin for neuropathic pain has been described in several case reports. The mechanism of action of botulinum toxin in neuropathic pain has not been elucidated. It is hypothesized that botulinum toxin may prevent release of various substances that sensitize nociceptors. More systematic study is warranted to explore the potential of this approach to neuropathic pain.

Tricyclic antidepressants: Although the tricyclic antidepressants have been thought to work through a central mechanism when administered systemically for neuropathic pain, recent data show that tricyclic antidepressants can also work peripherally to produce analgesia. Some evidence suggests that antidepressant blockade of adenosine uptake might account for the topical analgesic effects of tricyclic antidepressants. In a double-blind, placebo-controlled study of topical 2% amitriptyline, 1% ketamine, or the combination, no difference between any of the active treatments and placebo were observed for pain relief. However, a 12-month, open-label study suggested some benefit. Further research is warranted.

Localized treatment targeting peripheral pain mechanisms can play an integral role in the management of neuropathic pain. Several of the localized formulations currently available or in development offer the potential for highly targeted therapy with minimal or no side effects or risk of drug interactions.

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Medtronic Plenary Sponsored Symposium: NEUROSTIMULATION THERAPY – COMPELLING NEW EVIDENCE FOR MANAGING DRUG REFRACTORY NEUROPATHIC PAIN

THE PROCESS STUDY – RCT OF NEUROSTIMULATION THERAPY VERSUS CONVENTIONAL MEDICAL MANAGEMENT IN NEUROPATHIC BACK AND LEG PAIN
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Persistent pain, disability and reduced quality of life can have a devastating effect in patients with neuropathic pain secondary to failed back surgery syndrome (FBSS). The treatment of choice in such patients is conventional medical management (CMM), which in clinical practice typically includes a spectrum of rehabilitative and drug therapies but which often results in inadequate pain relief. Spinal cord stimulation (SCS) is an effective therapy in neuropathic pain refractory to medication, but its efficacy has not been compared with CMM in a randomized controlled trial. It was hypothesized SCS plus CMM would be a more effective therapy than CMM alone in this patient population.

One hundred well-matched FBSS patients with predominant neuropathic leg pain following anatomically successful surgery for a herniated disc were randomized to receive SCS plus CMM (SCS group) or CMM alone (CMM group) for at least 6 months, with 12-months follow-up. The primary outcome was 50% or more pain relief in the legs.

Results in the intention-to-treat analysis at 6 months showed that the primary outcome was achieved by 24 SCS patients (48%), but only four CMM patients (9%) (p < 0.001). All secondary endpoints improved significantly in the SCS group compared with the CMM group (p ≤ 0.05), with greater improvements in leg and back pain relief, quality of life, functional capacity, and treatment satisfaction. At 12 months, 28 SCS patients (33%) had experienced device-related complications.

In selected patients with FBSS, SCS provided better pain relief and improved health-related quality of life and functional capacity compared with CMM alone.

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SPINAL CORD STIMULATION IN DRUG REFRACTORY NEUROPATHIC PAIN: WHERE ARE WE AND WHERE ARE WE GOING?

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Pharmacological treatment studies of peripheral neuropathic pain are abundant. Currently, the most beneficial drugs are found in the following drug classes: antidepressants, anticonvulsants and opioids. Treatment studies on central neuropathic pain are scarce.

Based on available scientific data, an EFNS (European Federation of Neurological Societies) task force on neuropathic pain has recently presented guidelines for pharmacological treatment of neuropathic pain. In a separate publication, the same group also proposed a treatment algorithm for monotherapy in peripheral and central neuropathic pain; as might be expected, the algorithm was not based on an emerging hierarchy of drug effectiveness drawn from head-to-head studies (which are scarce) but on expertise and considerations regarding the balance of efficacy and adverse events.
From such treatment algorithms, extrapolations may be suggested as to when a specific condition may be regarded as refractory to monotherapy, when to initiate polypharmacy and when to consider other treatment modalities or combination therapies. For example, spinal cord stimulation (SCS) is an increasingly strong candidate for the treatment of peripheral neuropathic pain, based on an accumulation of scientific data in combination with more than 35 years of clinical use. The available evidence for the efficacy of SCS in neuropathic pain will be discussed, based on recent submitted work by a task force on neurostimulation within the EFNS. Arguments for the use of treatments such as SCS, which has proven efficacy in neuropathic pain, before the medical management of a patient will also be presented.

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CLINICAL EXPERIENCE WITH NEUROSTIMULATION THERAPY – WHICH PATIENTS WHEN?
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Neurostimulation has been shown to significantly relieve pain and improve quality of life in patients severely debilitated by chronic neuropathic pain. Yet despite its clinically proven benefits, uncertainty surrounding which patients are suitable for neurostimulation and when to refer them for treatment has led to the underprescribing of a potentially effective therapy. Instead, physicians prefer to use conventional therapies such as pharmacotherapy, even if they may not be appropriate to the individual pain experience. Clearer guidelines enabling physicians to refer more patients for neurostimulation would be beneficial.

Currently, physicians should consider neurostimulation in patients with chronic neuropathic pain who meet following criteria: the diagnosis of neuropathic pain has been confirmed; the neuropathic pain has demonstrated a chronic (longer than six months), intense and refractory character with respect to pharmacological and/or physical treatment; the patient has ‘failed’ a properly prescribed and observed pharmacological regimen; the lemniscate pathway is at least partially preserved; there is an absence of contraindications to SCS. Appropriately selected patients may expect to achieve significant benefits with neurostimulation; thus, it is worth considering earlier referral, before repeated trials of potentially inadequate treatments that may induce multiple side effects and before the problem becomes too complex and well established.

Advances in the understanding of the pathophysiology of neuropathic will help increase our ability to select patients for this modality and clarify the position of neurostimulation in the therapeutic algorithm. In the meantime, education about the potential benefits of neurostimulation is essential.

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**Grüntenthal Sponsored Symposium: VERSATIS**: A NOVEL TREATMENT APPROACH FOR POWERFUL RELIEF OF NEUROPATHIC PAIN SYMPTOMS

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CHAIRMAN'S INTRODUCTION: TOPICAL LIDOCAINE – A NOVEL STANDARD TREATMENT FOR NEUROPATHIC PAIN
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Chronic neuropathic pain is common in clinical practice, greatly impairs quality of life of patients and is a major economical health problem.

The current medical management of neuropathic pain mainly consists of systemic medications (antidepressants, anticonvulsants, tramadol and opioids). However, despite these options a considerable part of patients suffer from residual pain or side effects. This clearly indicates that currently available therapeutic approaches are still unsatisfactory and that there is a desperate need for novel therapeutic strategies.

Animal work demonstrated that nerve injury is matched by an increased expression of voltage gated sodium channels in primary afferent neurons leading to an increased electrical excitability and spontaneous activity. There is increasing evidence that also uninjured fibers running in a partially lesioned nerve may express sodium channels and thus take part in pain signaling (Wasner et al., 2005). The modern concepts of pain generation in neuropathies focus on these pathological processes of sensitization, i.e. hyperexcitability of primary afferent neurons, with the consequence of secondary central sensitization. Many patients suffer from spontaneous pain that is perceived in the affected skin and cutaneous hypersensibility, i.e. mechanical and thermal allodynia. These localized neuropathic symptoms are the subjective correlate of peripheral and central sensitization.

* Registered in UK.
Since patients with localized neuropathic symptoms likely have hyperexcitable afferents in their affected skin this patient group is ideal for the use of topical lidocaine: (a) topical lidocaine targets the sodium channels of sensitized afferents; (b) despite this effective peripheral action there is no systemic absorption of the lidocaine; (c) beside the pharmacological effect on afferent neurons lidocaine plasters have a protective component that deprives the skin from mechanical and thermal stimuli.

There is increasing evidence from randomized controlled studies in patients with neuropathic pain demonstrating efficacy of topical lidocaine plasters. Because of the topical mode of action lidocaine plasters have a favourable tolerability profile even in the long-term. Since there are no pharmacokinetic interactions an add-on therapy to systemic drugs is possible and has additional efficacy. The currently available treatment recommendations include lidocaine plasters for the treatment of focal neuropathic pain syndromes with localized symptoms as monotherapy or in combination with systemic treatments (Finnerup et al., 2005; Baron et al., 2005; Hempenstall et al., 2005).

References
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VERSATIS®*: PRACTICAL AND PHARMACODYNAMIC BENEFITS OF TOPICAL THERAPY
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Introduction: Neuropathic pain often requires multiple pharmacological agents to provide clinically meaningful pain relief. A novel treatment option has become available providing effective pain relief in the treatment of localized neuropathic pain symptoms such as burning, stabbing, shooting pains by acting on ‘activated’ sodium channels of C- and Aδ nerve fibers.

Pharmacodynamic properties: Lidocaine plasters lead after 30 min to significant reduction in pain intensity. This rapid analgesia is probably due to the specific characteristics of the plaster itself (which has a cooling effect). The analgesic effect of lidocaine becomes apparent after 4 h (significant difference in analgesia between lidocaine and placebo plasters). It can take up to 4 weeks until the maximum analgesic effect is obtained.

The penetration of lidocaine into intact skin is sufficient to produce local analgesia, but less than that necessary to produce loss of sensation and numbness.

A 12 h on/off application schedule is often maintained in order to minimize the risk of skin irritation. Clinical studies have shown that this application regimen leads to continuous analgesia, lasting for 24 h (or even longer). Local anesthetics exert a higher binding affinity to ‘activated’ sodium channels, and drug dissociation is slower. Local anesthetics display a clear frequency-dependent inhibition of conduction activity in nerve structures (phasic inhibition).

Practical benefits: Lidocaine plasters are easy to apply, can be cut and the plaster itself protects the skin from mechanical stimulation which is clinically important in patients suffering from allodynia. Long-term studies have shown that these plasters do not induce any development of tolerance.

The tolerability profile is very favourable, without systemic side effects. The most commonly reported side effects are reactions at the application site such as erythema, edema or abnormal sensation which are mild and transient. This safe side-effect profile makes the lidocaine plaster valuable in patients at risk (e.g. elderly, debilitated patients). The limited systemic absorption (≤2% of applied dose) makes this treatment particularly safe in combination with other (systemic) therapies.

Conclusion: The lidocaine plaster provides a new effective, convenient and safe treatment option in the armamentarium for localized symptoms of neuropathic pain in clinical practice.

Selected references

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TOPOICAL LIDOCAINE – EXPERIMENTAL MODELS OF NEUROPATHIC PAIN AND IMPLICATIONS FOR SYMPTOMATIC TREATMENT

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Lidocaine plasters have proven efficacy against typical neuropathic pain symptoms.

No clinical predictors of success could be defined so far for topical lidocaine (Jensen et al., 2005).

It has been generally assumed that lidocaine predominantly acts on sensitized and hyperactive cutaneous nociceptors (C-fibres).

Wasner et al demonstrated that PHN patients with intact hyperactive nociceptors did not respond to the extent expected; whereas patients with considerable small fibre nociceptor impairment responded well to topical lidocaine (Wasner et al., 2005). Since the number of patients was small further investigations are needed. It is under current research to what extent lidocaine exerts its efficacy via A-δ fibres.

The extent of effect of lidocaine on top of the cooling and protective device effect warrants further investigation.

Human experimental pain models serve as surrogate of pain and hyperalgiesia. Intra-dermal application of capsaicin is a well established model of mechanical hyperalgesia. The sunburn model is an inflammatory skin pain model of both mechanical and thermal hyperalgesia with the advantage of long lasting stable hyperalgesia (Gustorff et al., 2004; Sycha et al., 2005).

The effect of topical lidocaine was investigated using the capsaicin and sunburn model.

In a randomized double-blinded placebo-controlled cross-over-design 32 healthy volunteers were treated with lidocaine plasters or placebo. In a first study, plasters were applied 12 h before the study day, in a second study three treatment periods of 12 h each with 12 h of plaster-free intervals pre-ceded the study session. Mechanical and thermal quantitative sensory testing was performed.

After 12 h of pre-treatment the area of pin prick hyperalgesia was markedly reduced in both models with the lidocaine plaster compared to placebo (capsaicin: more than 50% reduction, sunburn: reduction of 73%).

The response to mechanical stimuli was significantly reduced for stronger stimuli in both models. Heat pain thresholds and blood flow were not changed within the sunburn after treatment with lidocaine.

These findings support the involvement of A-δ fibres within the mechanism of action.

A clear differentiation of lidocaine from placebo could be demonstrated.

Our results indicate an interesting potential of topical lidocaine within mechanism based therapy of neuropathic pain, particularly for the effective treatment of localized neuropathic pain symptoms.

References


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EFFICACY AGAINST TYPICAL SYMPTOMS OF NEUROPATHIC PAIN – CLINICAL EVIDENCE ON VERSATIS®

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Patients with neuropathic pain commonly describe their pain as burning or electric-shock like, but other symptoms are hyperalgesia, allodynia, paraesthesia and dysaesthesia. Therefore, successful treatment of neuropathic pain needs to aim for all typical symptoms.

Post-herpetic neuralgia (PHN) is commonly refractory to many treatment approaches and doses of systemic compounds are limited by side effects and the usually older age of the patients affected.

The lidocaine plaster has been evaluated in PHN in a considerable number of published double blind randomised controlled trials (RCTs).

In a four-way, single-dose crossover trial, lidocaine plaster provided significantly greater pain relief than
placebo plaster and no treatment; whereas the placebo plaster provided significantly better pain relief than no treatment, due to a device effect [Rowbotham MC, Davies PS, Verkemipinck C, Galer BS. Lidocaine patch: double-blind controlled study of a new treatment method for post-herpetic neuralgia. Pain 1996;65: 39–44].

A further RCT showed superiority of the lidocaine plaster over placebo plaster on all neuropathic pain qualities using the Neuropathic Pain Scale [Galer BS, Jensen MP, Ma T, et al. The lidocaine patch 5% effectively treats all neuropathic pain qualities: results of a randomized, double-blind, vehicle-controlled, 3-week efficacy study with use of the neuropathic pain scale. Clin J Pain 2002;18: 297–301].

Two further RCTs in PHN utilised an enriched enrolment design with time to exit due to lack of efficacy as the primary outcome [Galer BS, Rowbotham MC, Perander J, Friedman E. Topical lidocaine patch relieves postherpetic neuralgia more effectively than a vehicle topical patch: results of an enriched enrollment study. Pain 1999;80:533–8] (Gruenenthal data on file). Both trials showed significant differentiation from placebo for the lidocaine plaster. Open-label follow up of patients showed stable analgesia over 12 months without development of tolerance (Baron EFIC 2006). No serious adverse events attributable to the plaster occurred.

Furthermore, lidocaine plaster has been subject to open-label trials in diabetic neuropathy [Barbano RL, Herrmann DN, Hart-Gouleau S, et al. Effectiveness, tolerability, and impact on quality of life of the 5% lidocaine patch in diabetic polyneuropathy. Arch Neurol 2004:61:914–8]. Significant improvements in pain and quality of life without systemic adverse effects were achieved.

Combinations of the topical approach with systemic drugs have been assessed in open-label, non-randomised trials in different peripheral neuropathies (Gimbel APS 2003) [White WT, Patel N, Drass M, Nalamachu S. Lidocaine patch 5% with systemic analgesics such as gabapentin: a rational polypharmacy approach for the treatment of chronic pain. Pain Med 2003;4:321–30] resulting in significant reduction of pain and significant improvement of quality of life. Therefore, lidocaine plaster is also ideal for combination with systemic therapy, as it is devoid of systemic adverse effects or drug interactions.

These results confirm the efficacy of the lidocaine plaster against localized symptoms of neuropathic pain such as burning, stabbing and shooting pains in classical peripheral neuropathies. Lidocaine plaster could be used both as monotherapy and as adjunct to systemic therapies and has shown excellent safety in the commonly elderly patients.

Many drugs exist to treat neuropathic pain, with comparable NNTs and different levels of underlying evidence. An ideal drug would have proven efficacy in neuropathic pain, be appropriate for the expected treatment duration, would have a low side-effect profile (high number needed to harm), few interactions, can be used with problems of co-morbidities and age and would be cost-effective.

It is clear from the literature that the same drug can be effective in different conditions, and drugs with different mechanisms of action are effective in the same condition (Hansson and Dickenson, 2005). This might be a rationale for polypharmacy in neuropathic pain.

Many treatment algorithms now exist (Dworkin et al., 2003; Finnerup et al., 2005; Attal et al., 2006; Hempenstall et al., 2005); all recommend lidocaine plasters, gabapentinoids or tricyclics as first line treatments, with opioids and tramadol as first or second line, depending on the author.

Topical lidocaine has been shown to effectively reduce typical symptoms of neuropathic pain such as pain of burning, stabbing, shooting quality and allodynia. Lidocaine plasters with lack of systemic effects also have an excellent tolerability and safety profile in elderly and at-risk patients. They can, therefore, be recommended for any neuropathic pain where typical symptoms of localized neuropathic pain and/or allodynia exist, as an initial treatment.

No clear predictor of treatment success has been identified for lidocaine plasters. The plaster has been effective in alleviating different pain or symptom qualities including non-aldynic pain (Galer et al., 2002).

Lidocaine plasters, therefore, like systemic sodium channel blockers, such as carbamazepine and lamotrigine, also have a place in non-aldynic pain, alone or in combination.

Pharmacoeconomic analysis from the USA shows topical lidocaine is cost-effective in treating localized neuropathic pain because of low side-effects, short onset and greater patient acceptance (Smith and Roberts, 2007).

In this respect, widespread use in the USA might suggest both efficacy and patient satisfaction in clinical practice.

References


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Poster Presentations

Poster Session 1: Animal Models

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GABAPENTIN AND PREGABALIN SUPPRESS MECHANO-COLD ALLODYNIA IN THE SPARED NERVE INJURY (SNI) MODEL OF NEUROPATHIC PAIN
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Background and aims. Mechano-cold allodynia is a major symptom in neuropathic pain patients and the anticonvulsants gabapentin and pregabalin are frequently used for clinical treatment. Spared nerve injury (SNI) is a preclinical model of neuropathic pain where rats exhibit hypersensitivity to cold spray stimulation. Here, we evaluated the efficacy of these anticonvulsants on mechano-cold allodynia in the rat SNI model.

Methods. In male Sprague–Dawley rats, the left tibial and peroneal nerves were tightly ligated and cut distally to the ligation under isoflurane anesthesia. Following the nerve injury, mechano-cold allodynia was quantified as the time spent licking the affected hind paw in response to cold spray stimulations (ethyl chloride). Rats displaying hypersensitivity were randomly assigned to different experimental groups (n = 10–15/group) and received: vehicle, gabapentin (cumulative doses: 3 × 200 μmol/kg, 30 min interval, SC) or pregabalin (single dosing: 30, 100, 300 μmol/kg, PO).

Results. Following cumulative subcutaneous dosing of gabapentin, allodynic-like behavior was significantly reduced to 74% (240 min after dosing). Single oral dosing of pregabalin induced a dose-dependent reduction of allodynic-behavior and the maximal effect was 71% (150 min after dosing). The effect duration of both compounds were long lasting and the effect remained significant throughout the experiment (>240 min).

Conclusions. Gabapentin and pregabalin significantly reduced mechano-cold allodynia in the SNI model of neuropathic pain in rats.

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ANTINOCICEPTIVE EFFECT OF BOTULINUM TOXIN TYPE A IN EXPERIMENTAL DIABETIC NEUROPATHY
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Backgrounds and aims. Recently, we found that peripheral application of botulinum toxin type A (BTX-A) significantly reduced thermal and mechanical hypersensitivity in rats with the partial sciatic nerve transection as a classical model of surgical neuropathy. In streptozotocin-induced diabetes in rats, we investigate the possibility that BTX-A has antinociceptive effect in diabetic neuropathy.

Methods. Male Wistar rats (250–300 g) were made diabetic by a single subcutaneous (s.c.) injection of streptozotocin (80 mg/kg b.w.). Animals with a tail-vein blood-glucose concentration of above 15 mmol/l were considered diabetic. Sensitivity to mechanical stimuli was measured with the paw-pressure test. Measurements started 3 weeks following streptozotocin or saline injection. Only the animals with mechanical thresholds lower for at least for 25% compared to control group were considered neuropathic and were then subjected to peripheral (in the plantar surface of the hindpaws) BTX-A (3, 5 and 7 U/kg) or saline treatment. Mechanical sensitivity was tested on day 1, 5, 15 and 28 following BTX-A injection. Sensitivity to chemical stimuli was measured once by formalin test.

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**Results.** BTX-A 5 and 7 U/kg reduced the mechanical hypersensitivity in diabetic animals compared to the saline-treated diabetic controls (109.6 g for BTX-A vs. 86.2 g for control; \( p < 0.01 \)). The antinociceptive effect was evident on day 5 and was significant til the day 15. BTX-A also reduced the number of flinches/shakes of the formalin injected paw (324 for BTX-A vs. 478 for control; \( p < 0.001 \)).

**Conclusion.** Single peripheral BTX-A injection has a long-lasting antinociceptive effect in experimental diabetic neuropathy.

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SPINAL CORD EXCITEMENT: DESCENDING PATHWAYS THAT MODULATE DORSAL HORN EXCITABILITY IN PATHOPHYSIOLOGICAL STATES

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**Background and aims.** Developing plasticity in the RVM following peripheral nerve injury is important for the maintenance of neuropathic pain. We looked at the behavioural, electrophysiological and pharmacological consequences of ablating \( \mu \)-opioid receptor expressing (MOR) cells in the RVM (a primary source of descending facilitations) with the neurotoxin dermorphin-saporin, in rats that subsequently underwent spinal nerve ligation (SNL) surgery.

**Methods.** Anaesthetised rats received an injection of either 3 pmol dermorphin-SAP or untagged-SAP into the RVM. Two weeks later, both groups had their left L5 and L6 spinal nerves ligated. Hindpaw withdrawal responses to mechanical stimuli were thereafter assessed over a two-week period. On days 28–32 (i.e. 14+ days after ligation surgery) extracellular recordings were made from dorsal horn neurones receiving afferent input from the ipsilateral hindpaw; responses to electrical and natural stimulation of the neurone’s peripheral receptive field were characterised in anaesthetised rats, and the effects of systemic pregabalin on neuronal responses were measured and compared between the groups.

**Results.** Two days after SNL surgery, behavioural signs of hypersensitivity prevailed in the ipsilateral hindpaw in both groups. Hypersensitivity persisted throughout the 2-week postoperative period in SNL rats injected with untagged SAP, yet declined in the dermorphin-SAP population. Furthermore, in SNL SAP rats, but not dermorphin-SAP rats, pregabalin reduced neuronal responses to some peripheral stimuli.

**Conclusion.** RVM MOR cells are important for the maintenance of experimental neuropathic pain as evidenced by the attenuation of behavioural hypersensitivities in SNL dermorphin-SAP rats, and are also necessary for the inhibitory actions of pregabalin following neuropathy.

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CAPSAICIN AVOIDANCE FOLLOWING CHORDA TYMPANI TRANSECTION

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**Background and aims.** Certain chronic oral pain conditions including Burning Mouth Syndrome may be associated with damage to the gustatory system. We investigated if transection of the chorda tympani (CT) increases oral sensitivity to capsaicin as a possible model of hyperalgesia due to release of the trigeminal system from tonic gustatory inhibition.

**Methods.** Water-restricted female rats had 2-h access to 2 bottles, one containing capsaicin (0.1, 0.3, 0.5, 1 or 10 ppm) and the other water + ethanol vehicle. Each concentration was tested for 2 days with bottle positions switched daily. Two days of water-only interceded before testing the next concentration. We measured % volume of capsaicin consumed and lick counts. The concentration series was tested presurgery and at 0.5, 3, 6, 9 and 12 month postsurgery in three groups: bilateral CT transection, bilateral CT transection plus ovariecoty (CT-OVX), and sham-operated controls.

**Results.** Presurgery there was a concentration-dependent decrease in licks and volume of capsaicin consumed with a threshold between 0.1 and 0.5 ppm. The majority of drink licks occurred during the first 10 min of access. Two week postsurgery the CT-OVX group significantly (ANOVA, \( P = 0.05 \)) avoided 0.3 ppm capsaicin. At later times there were few significant between-group differences; the CT-OVX group tended to avoid capsaicin more at 6 and 9 month, whereas the CT group exhibited reduced avoidance that was significant at 6 month (ANOVA, \( P < 0.05 \)).

**Conclusions.** Overall, transection of the CT did not result in marked symptoms of chronic hyperalgesia.

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Efficacy of Tapentadol, a Novel Centrally Acting Analgesic with Dual Mode of Action, in Animal Models of Chronic Neuropathic Pain

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Background. Tapentadol [(−)-(1R,2R)-3-(3-dimethylamino-1-ethyl-2-methyl-propyl)-phenol] is a novel analgesic with a dual mode of action: µ-opioid receptor (MOR) agonism (Kᵢ = 0.1 µM for rat MOR binding), and noradrenaline (NA) reuptake inhibition (Kᵢ = 0.5 µM for rat synaptosomal NA reuptake inhibition). Due to its dual mode of action tapentadol is an interesting candidate for the treatment of neuropathic pain conditions.

Methods. The effects of tapentadol and gabapentin, the current standard in neuropathic pain treatment, were investigated in four rat models of neuropathic pain: vincristine-induced polyneuropathy (VPN), diabetic polyneuropathy (DPN), spinal nerve ligation (SNL), and chronic constriction injury (CCI).

Results. Tapentadol was much more potent than gabapentin, and resulted in numerically higher maximum effect values in each model. The ED50 values of tapentadol/gabapentin, respectively, were 5.1 mg/kg ip/372 mg/kg po (VPN), 8.9 mg/kg ip/225 mg/kg ip (DPN), 8.2 mg/kg ip/92.6 mg/kg ip (SNL), and 13.0 mg/kg ip/214 mg/kg po (CCI). The maximum effects (expressed as %MPE) of tapentadol/gabapentin, respectively, were 74%/69% (VPN), 100%/80% (DPN), 108%/91% (SNL), and 89%/65% (CCI).

The noradrenergic contribution to the analgesic efficacy was demonstrated in SNL rats, where the analgesic effect of tapentadol (10 mg/kg iv) was antagonized by the α2-adrenoceptor antagonist yohimbine (2.15 mg/kg ip) as well as by the MOR antagonist naloxone (0.3 mg/kg ip).

Daily administration of equianalgesic doses of tapentadol (6.81 mg/kg ip) and gabapentin (215 mg/kg ip) for two weeks did not reveal development of tolerance to the analgesic effect for either compound.

Conclusions. Tapentadol is a novel centrally acting analgesic with both mechanisms of action contributing to its broad efficacy profile in several animal models of neuropathic pain.

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Botulinum Neurotoxins: New Frontiers in Neuropathic Pain Therapy

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Background and aims. A number of studies have underlined a significant use of Botulinum neurotoxins (BoNTs) in the human therapy of several movement and autonomic disorders. Recently, a potential role of BoNTs as new therapeutic agent in pain relief has also been suggested. In particular, it has been demonstrated that serotype-A (BoNT/A) is able to induce analgesia in inflammatory pain conditions. The goal of the present research was to assess if BoNT/A was able to relieve also neuropathic pain symptoms.

Methods. The chronic constriction injury of sciatic nerve (CCI) was used as model of neuropathic pain in CD1 male mice. The onset of neuropathy was assessed by measuring, at different time intervals from postoperative day 3 to day 81, the sensitivity of both hindpaws to non-noxious punctuate mechanical stimuli.

Results. Peripheral administration of BoNT/A strongly reduced the mechanical allodynia associated with the neuropathy and significantly speed up the functional recovery of the injured paw. Remarkably, a single non-toxic dose of BoNT/A was sufficient to induce anti-allodynic effects, which lasted for at least three weeks. For comparison, we tested also the effect of BoNT/B, and we found that, contrary to BoNT/A, it was unable to counteract the neuropathic pain.

Conclusions. This result is particularly relevant since neuropathic pain is poorly treated by current drug therapies. This communication enlarges our knowledge on potentially new medical uses of BoNT/A in efforts to improve the health human conditions, with very important implications in the development of new pharmacotherapeutic approaches against the neuropathic pain.

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Chronic Post-Ischemia Pain: A Novel Animal Model Suggests that Ischemia–Reperfusion (I–R) Injury, No-Reflow and Chronic Tissue Ischemia Contribute to CRPS-I

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Chronic post-ischemia pain (CPIP) is an animal model of CRPS-I produced by prolonged (3 h) I–R
injury of the rodent hindpaw. Using tight fitting O-rings as ankle tourniquets, rats initially exhibit hyperemia and edema of the ischemic hindpaw for several hrs after reperfusion. Subsequently, rats and mice develop mechanical and cold allodynia for at least 4 weeks post-reperfusion. Rats also develop prolonged mechanical allodynia following I-R injury produced by clamping all blood vessels supplying the hindpaw. Light and electron microscopic analysis of the tibial nerve close to the site of the tourniquet indicates that there is no nerve injury associated with tourniquet-induced compression. These findings, as well as electrophysiological studies demonstrating that there is normal conduction velocity in the tibial nerve, suggest that CPIP rats are similar to patients with CRPS-I (i.e., no clinical signs of nerve injury). However, co-incident with mechanical allodynia, CPIP rats exhibit a no-reflow phenomena, including abnormality of capillary endothelial cells in skeletal muscle and nerve (determined by electron microscopy), and a gross reduction in blood flow to the affected hindpaw (determined by light microscopy following perfusion of India ink). Chronic tissue ischemia results in mitochondrial dysfunction in skeletal myocytes as evidenced by reduced TTC staining in hindpaw muscle. Importantly, in association with observed no-reflow in endoneurial capillaries, there is also abnormal spontaneous activity in A-beta, A-delta, and C fiber primary afferent neurons in the sural nerve. Results suggest CPIP and CRSP-I may depend on I-R injury, no-reflow and chronic tissue ischemia in muscle and nerve.

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VANILLOID RECEPTOR 1-POSITIVE NEURONS MEDIATE NEUROPATHIC PAIN
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The vanilloid receptor 1 (VR1) is expressed on the type II A-delta-fiber and C-fiber neurons, which can be selectively ablated by Resiniferatoxin (RTX), an excitotoxic agonist, when injected into dorsal root. It has been speculated that the VR1-positive neurons participate the development of neuropathic pain. However, no direct evidence has been provided so far. We present detailed data in the following studies that indicate the VR1-positive neurons mediate neuropathic pain in a rat photochemically-induced ischemic model.

The thermal hyperalgesic threshold, by hot plate, is considered as a latency value of an injured paw 30% lower than that of an uninjured paw. And the tactile allodynic threshold, by von Frey filaments, is classified as a value of a filament below 8 g which induces the paw withdrawals larger than 50% response frequency to a rat. In alldynic rats, the average threshold of 1.62 g was elevated to 5.68 g when RTX injected into L3-6 DRGs. The DRGs are labeled with VR1 and N52 antibodies that display almost all VR1 positive neurons are wiped out. In order to further investigate whether the VR1-positive neurons participate neuropathic pain development, RTX is administrated into the L3-6 DRGs prior to the nerve injury. The treatment prevents the development of tactile allodynia in 12 rats out of 14. VR1 staining reveals that the VR1 positive neurons in the DRGs are eliminated by RTX in the rats those do not develop tactile allodynia, while the VR1 positive neurons exist still in the rats those develop tactile allodynia.

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THE AUTOMATED ELECTRONIC VON FREY FILAMENTS CONSTITUTES A SUITABLE METHOD TO EVALUATE MECHANICAL ALLODYnia IN EXPERIMENTAL ANIMALS
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We performed experiments using a modification of the traditional Von Frey filaments methodology to evaluate mechanical allodynia in mice. Automated electronic (Ugo basile, Italy) apparatus, instead of manual Von Frey filaments was used. The apparatus applies a constant predetermined force until the mice withdraws the paw and automatically registers the time latency to this response. The latency to paw withdrawal response was used as the endpoint. A cutoff time of 60 s was established. The intraplantar (i.pl.) administration of 20 μl of capsaicin (0.125–2 μg) was used to sensitize the mice (female, CD1) to the mechanical stimulus. Control animals receive the same volume of solvent (1% DMSO in saline). Control animals, or non-treated animals have 60 s latency time, when a monofilament at 0.5 g force was applied. The injection of capsaicin 15 min before test produced a dose-dependent reduction of the time-latency for withdrawal response being the maximal effect those produced with 1 μg dose (6.44 ± 1.2 s latency time). The s.c. administration of the drugs clonidine (0.015–1 mg/kg), gabapentin (2–64 mg/kg) and amitryptiline (1–8 mg/kg) 30 min before capsaicin increased the latency time and produced anti-allodynic effects, being the ED50 of 0.04 ± 0.002; 3.19 ± 0.26 and 3.04 ± 0.16 mg/kg, respectively. Also exhibited antiallodinic activity the drugs tetrodotoxin (2 and 6 μg/kg), diclofenac (32 and 64 mg/kg) and...
mexiletine (16–32 mg/kg). These results suggest that this procedure is an adequate method to evaluate the antiallodynic effects of several drugs.

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SPONTANEOUS PAIN BEHAVIOUR IS RELATED TO SPONTANEOUS FIRING FREQUENCY IN UNINJURED NOCICEPTIVE C-FIBRE NEURONS AFTER SPINAL NERVE AXOTOMY
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Spontaneous pain is the primary complaint of neuropathic pain patients. It commonly occurs even without hyperalgesia (Basbaum, 2006). It remains hard to treat because its underlying mechanisms are poorly understood, possibly because most animal studies have focused on evoked pain behaviours.

We used two spinal nerve (SN) models of neuropathic pain to test the hypothesis that spontaneous activity (SA) in uninjured dorsal root ganglion (DRG) neurons causes spontaneous pain behaviour. These were axotomy of the L5 SN (SNA) and modified SNA (mSNA) that involved SNA plus loose ligation of the L4 SN with the inflammation-inducing chromic gut. Of these, only mSNA rats showed significant SFL, indicative of spontaneous pain (Koutsikou and Lawson, 2002; Djouhri et al., 2006). Intracellular recordings of evoked and spontaneously occurring action potentials in deeply anesthetised rats were made from: (a) normal L4/L5 DRG neurons in control rats, (b) axotomised L5 neurones in mSNA rats, (c) intact L4 neurons in both mSNA and SNA rats. Neurons were classified as C, Aδ, or Aβ/δ units and as non-nociceptive or nociceptive.

Seven days post-operatively, similar increases in percentages of intact nociceptive C-fibre L4 neurons with SA (from 7% to about 35%) in both SNA and mSNA rats occurred. These intact C-nociceptors showed faster spontaneous firing in mSNA (1.8 Hz) than SNA (0.02 Hz) rats, implicating intact C-neurons in SFL. Faster firing rates in intact C-nociceptive neurones, probably resulting from cumulative inflammation/degeneration fibres and chromic-gut) are required for spontaneous pain.

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MURINE MODELS OF NEUROPATHIC PAIN
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Currently available analgesics are often inefficient for the treatment of chronic pain, particularly neuropathic pain, in man. Preclinical development of prospective analgesic agents is dependent on the use of animal models of pain, however, most models utilised in investigating neuropathic pain are performed on rat. Recent years have seen an explosion of studies investigating physiological and pathophysiological function in transgenic mice, allowing correlation of alterations to genetic background, which may play a strategic role in the pathogenesis of neuropathic pain. Functional studies such as in vivo electrophysiology can prove more problematic in small rodents, thus in this study we have investigated the feasibility of transferring rat models of neuropathic pain into the mouse.

Behavioural and electrophysiological studies were undertaken in common models of neuropathic pain, including chronic constriction injury (CCI), spinal nerve ligation (Chung model), streptozocin-induced diabetic neuropathy and acute inflammation (Carra-geenan model). Results obtained were comparable to those observed in rat. The effects of gold standard analgesics were subsequently verified in these models and effects paralleled those observed in rat.

We show that mouse models of neuropathic pain, similar to those pioneered in rats, can be useful tools in the genetic, physiological and pharmacological investigation of neuropathic pain.

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OPIOIDS IN ANIMAL MODELS OF NEUROPATHIC PAIN
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Background and goal. Animal models are used to assess drug efficacy in neuropathic pain; we have analyzed the preclinical basis for the use of systemic opioids.

Methods. A PubMed systematic review of the literature. We intersect the search terms nominating different opioids (morphine, fentanyl, methadone, oxycodone, buprenorphine, codeine and tramadol) and the main experimental models of neuropathic pain (chronic constriction injury (CCI), partial ligation of sciatic (PSL), spinal nerve ligation (SNL), spared nerve injury (SNI), and streptozocin, paclitaxel, and vincristine-induced neuropathies). Sensory modalities were: mechanical allodynia (MA), cold allodynia (CA), mechanical hyperalgesia (MH) and thermal hyperalgesia (TH).

Results. See table

Conclusions. Opioids have shown different degrees of efficacy in animal models of neuropathic pain. Preclinical evidence supports the clinical use of opioids in neuropathic pains.

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CATWALK ANALYSIS AND PAIN RESEARCH: GAIT PARAMETERS AS A MEASURE OF INFLAMMATORY PAIN IN THE ACUTE BUT NOT CHRONIC PHASE

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Carrageenan-induced inflammation has been described as a model of acute inflammation through the first 24 h post injection and as a model of chronic inflammation after 1 week.

The CatWalk method is an automated quantitative gait analysis that allows the objective and rapid quantification of individual paw parameters as well as parameters related to interlimb coordination.

We evaluated the use of the CatWalk as a quantitative analysis of gait changes in both acute and chronic phases of carrageenan induced-inflammatory pain. We compare the results to the assessment of mechanical allodynia through the Von Frey test.

Von Frey results show a significant development of mechanical allodynia 4 h after the injection of carrageenan in the rat knee, and a plateau like-phase is observed up to 21 days.

CatWalk parameters related to individual paw (e.g. intensity of the paw printing) show significant changes after 24 h which last up to 48 h post injection. No difference was observed in the interlimb coordination, indicating an accurate and controlled pain induced-gait adaptation in the acute phase.

In the chronic phase (after day 7), no changes could be noted in any of the CatWalk parameters.

We conclude that the CatWalk technique is a fast, objective and reproducible test to assess the gait adaptation to acute inflammatory pain in the rat. Furthermore, the pain induced-gait adaptation after a carrageenan induced-knee inflammation is temporary. CatWalk based-gait changes can no longer be used as pain parameters in the chronic phase of this model.

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RESPONSE PROPERTIES OF NOCICEPTIVE NEURONS IN THE AMYGDALA OF THE NEUROPATHIC RAT

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The amygdala (AMY) has an important role in emotional responses to pain. It receives nociceptive inputs from the periphery and central modulatory influence from various limbic sites, including the anterior cingulate cortex (ACC). The influence of chronic neuropathy on response properties of AMY neurons and their central modulation is still only poorly known. We determined the response characteristics of AMY neurons to noxious peripheral stimulation and their central modulation by the ACC in a spared nerve injury (SNI) model of peripheral neuropathy in the rat. Moreover, in order to determine have behavioral correlates for neuronal findings, mechanically evoked spinal withdrawal responses and aversion behavior were recorded. Recordings of AMY neurons were performed in anesthetized SNI and sham-operated animals. Peripheral noxious stimuli consisted of heating and cooling, mechanical skin stimulation and colorectal distension. Furthermore, central modulation of AMY neurons was studied by injecting glutamate or an NMDA receptor antagonist into the ACC. The SNI group had a markedly reduced spinal withdrawal threshold to mechanical stimulation that was associated with a strong aversion-like response to light tactile stimulation. SNI produced changes in peripherally evoked neuronal responses that varied depending on the modality of stimulation and the recording site in the AMY. Moreover, glutamatergic modulation of AMY neurons from the ACC was changed in the SNI group. The results indicate that chronic neuropathy induces plastic changes in peripherally evoked responses and central modulation of AMY neurons. These neuronal changes are associated with behavioral changes reflecting allodynia-like spinal reflex and affective symptoms.
Results. CCI animals show a significant increase in the time of immobility: sham 146 s (132–156), CCI animals 202 s (173–225), p < 0.01; and a significant decrease in the time of climbing: sham 124 s (116–135), CCI animals 67 s (49–94), p < 0.01. No effect in the time of swimming was noted. All lesioned animals showed mechanical hypersensitivity: sham 27 g (24–30), CCI animals 11 g (8–14).

Conclusions. Mononeuropathic animals displayed depressive-like behaviour, which may be mediated by noradrenaline, since it has been well characterized that noradrenergic reuptake inhibitors decrease the time of immobility and increase the time of climbing, while the selective serotonergic reuptake inhibitors decrease the time of immobility and increase the time of swimming (Detke, Behavioural Brain Research 1996;73(1–2):43–46.). The effect of different antidepressant and analgesic drugs will be further characterized.

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EXPERIMENTAL MANIPULATIONS THAT INFLUENCE THE DEVELOPMENT OF MECHANOCOLD ALLODYNA IN THE SPARED NERVE INJURY (SNI) MODEL
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Background and aims. Mechano-cold allodynia is a major symptom of neuropathic pain in patients. In the spared nerve injury (SNI) model of neuropathic pain, we use mechano-cold allodynia as a primary end-point. The aim of this investigation was to study how development of mechano-cold allodynia was affected by different experimenters.

Methods. Following the spared nerve injury in male Sprague–Dawley rats, mechano-cold allodynia was quantified as the time spent licking the affected hind paw in response to cold spray stimulations (ethyl chloride). Groups of rats from two different suppliers (n = 20–50) were operated and tested behaviorally over several weeks by different experimenters.

Results. Not all animals developed mechano-cold allodynia, the responder rate varied from 57% to 100%. The pattern to develop a robust baseline of mechano-cold allodynia was affected by different experimenters.

Conclusions. SNI model provides long lasting stable mechano-cold allodynia between experiments. In addition, similar baseline levels of allodyina were obtained independently of the observer.

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NADPH-D AND C-FOS IMMUNOREACTIVE NEURONS IN THE RAT BRAIN STEM FOLLOWING PERIPHERAL NERVE INJURY
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Background. The common features of neuropathic pain are mechanical (tactile) allodynia, pain elicited by non-noxious mechanical stimuli and development of spontaneous pain. The specific mechanisms responsible for development of these pain states are not known. Chronic constriction injury (CCI) of the sciatic nerve as a model of neuropathic pain in rats evokes c-Fos expression and increase of nicotinamide adenine dinucleotide phosphate diaphorase (NADPH-d) at the level of spinal cord.

Aim. Here, we studied changes in c-Fos expression and NADPH-d in the brain stem areas suggested as major targets of projection neurons in superficial dorsal horn laminae, the parabrachial area and mesopontine tegmentum.

Methods. We used chronic constriction injury of the sciatic nerve of rats as a model of neuropathic pain. After two weeks of surviving spinal cords and brain stems were removed and processed for histochemical and immunohistological detection of NADPH-d and c-Fos.

Results.CCI injury caused development of tactile allodynia and spontaneous pain in rats. We did not observe any significant changes in NADPH-d staining in CCI animals when compared to controls. However, during first week following injury we found an increase in the number of c-Fos positive neurons in the parabrachial area, mainly in the pontine part where the group of c-Fos immunoreactive neurons were presented at dorsal part of lateral parabrachial nuclei.

Conclusions. This specific activation of brain stem neurons could underlie changes in the central nociceptive processing involved in altered pain states following peripheral nerve injury.

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SUCROSE LOADING DECREASES THERMAL PAIN SENSITIVITY, EVALUATED WITH TAILFLICK TEST IN DIABETIC (OLETF), BUT NOT IN NON-DIABETIC (LETO) RATS
Aim. The aim was to differentiate the effects of sucrose loading on thermal pain sensitivity in diabetic and non-diabetic rats.

Materials and methods. Five months of age male diabetic Otsuka Long-Evans Tokushima Fatty (OLETF) rats, and their age-matched non-diabetic genetic controls Long Evans Tokusima Otsuka (LETO) rats, were used. The animals were fed with standard laboratory chow and divided into the following four groups: Group O-sucrose (n = 20) – OLETF rats were loaded for 2 months with 30% sucrose in the drinking water (sucrose period). Then the rats were put again on pure tap water (washout period) until the end of the experiment. Group O-control (n = 9) – on tap water in the course of the whole experiment. Group L-sucrose (n = 16) and group L-control (n = 9) – age-matched LETO rats had the same schedule like the groups O-sucrose and O-control, respectively. Sensitivity to noxious thermal stimuli was assessed by the latency time during tail-flick test. The beam was focused on the ventral surface, 5 cm from the tip of the tail.

Results. At baseline, at the end of the sucrose period, and 2 moths later (during the washout period), respectively, the groups presented with following latencies (means ± SD): O-sucrose = 6.9 ± 1.4; 7.5 ± 0.9 and 8.4 ± 0.9 (p < 0.5 vs. baseline and vs. O-control); O-control = 7.6 ± 0.6; 7.1 ± 0.7 and 7.2 ± 1.0 (p < 0.5 vs. L-control); L-sucrose = 7.6 ± 1.0; 6.2 ± 1.0 and 5.8 ± 1.4 (p < 0.5 vs. baseline); L-control = 8.4 ± 1.4; 6.0 ± 1.4 and 6.0 ± 0.8 (p < 0.5 vs. baseline).

Conclusion. Sucrose loading decreases pain sensitivity, measured with tail-flick test in diabetic, but not in non-diabetic rats.

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amplitude of EPSPs and EPSCs. Brush or pinch stimulation was applied to the contralateral hindlimb.

Results. In normal rats, almost all SI neurons exhibited a bursting activity which had frequency of −0.9 Hz and amplitude of −90 pA. These bursts occasionally initiate a single or multispike unders the current clamp mode. In inflamed rats, the frequency was slowed and the duration of each bursting was prolonged. These burstings were completely inhibited by CNQX, indicating that the bursting activities are summation of glutamatergic inputs.

Conclusion. These findings together with our previous observations suggest that the inflammation causes the change in the synchronization of the outputs from the thalamus to SI neurons.

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157 LACOSAMIDE, AN INVESTIGATIONAL ANALGESIC, DOES NOT SHOW POTENTIAL FOR ABUSE LIABILITY OR DEPENDENCE IN PRECLINICAL TESTS
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Lacosamide is an investigational analgesic that is currently being evaluated in phase III clinical trials for painful diabetic neuropathy. It has a novel, dual mode of action: selective enhancement of sodium channel slow inactivation and modulation of CRMP-2. Since lacosamide acts in the central nervous system via a novel mechanism of action, it was assessed in a number of targeted preclinical studies in line with the EMEA “Guideline on the non-clinical investigation of the dependence potential of medicinal products”.

No binding within the therapeutic concentration range was detected in radioligand binding experiments with lacosamide and its major human metabolite for binding to 20 abuse- or dependence-related molecular targets.

When rats were trained to discriminate between lacosamide and saline in a 2-choice, lever-pressing, drug discrimination procedure, lacosamide did not evoke a robust subjective cue. Generalization testing revealed a lack of dose-related or consistent generalization to the lacosamide discriminative cue following administration of drugs with abuse potential from similar pharmacological classes (i.e. diazepam, phenobarbital, morphine and phencyclidine). Consistent with these findings lacosamide was not rewarding in a place-preference test or reinforcing in an i.v. self-administration procedure in rats.

After prolonged administration to rats and dogs, there was no tolerance to lacosamide’s pharmacological actions and abrupt cessation of treatment did not produce psychological and/or physical dependence.

Overall, the preclinical assessment predicts that lacosamide will not have any potential for abuse liability or dependence in man. This is consistent with its mode of action which has not been associated with drug abuse or dependence.

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158 COLD SENSITIVITY IS INCREASED IN SPINAL DORSAL HORN WIDE DYNAMIC RANGE (WDR) NEURONS IN SPARED NERVE INJURY (SNI) RATS
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Background and aims. In the SNI model of neuropathic pain, animals exhibit hypersensitivity to stimulation by cold spray (ethyl chloride). Here, we investigate the response properties of spinal dorsal horn WDR neurons to thermal stimuli following peripheral nerve injury in this model.

Methods. Under isoflurane anesthesia, 24 male Sprague–Dawley rats were subjected to tight ligation and transection of the left tibial and peroneal nerves. Following the nerve injury, rats developed mechano-cold hypersensitivity. Sixteen to 26 weeks later, single neuron recording was performed bilaterally on deep spinal dorsal horn WDR neurons. Sensitivity of the neurons to cold of the skin from 32 to 4 °C, and heating from 32 to 50 °C was characterized.

Results. Respectively 64 and 68 mechanosensitive WDR neurons were recorded ipsi- and contralaterally to the injury. Spontaneous activity was significantly higher on the injured side (1.44 ± 0.61 spikes/s) compared with the contralateral side (0.08 ± 0.03 spikes/s; p < 0.05, mean ± SEM). A significant increase in the number of neurons responding to skin temperatures in the range of 4–17 °C was recorded on the injured side (33/64 U) compared with the contralateral side (14/68 U; p < 0.001). In contrast, no difference between sides was observed in the sensitivity to higher temperatures, in temperature thresholds, or in the number of spikes generated by any particular stimulus.

Conclusions. Following peripheral nerve injury, cold sensitivity was increased in dorsal horn neurons and/or
peripheral afferents, which is likely to underlie, at least in part, the cold allodynic-like behavior observed in SNI rats.
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DIFFERENCES BETWEEN INFLAMMATORY RESPONSES IN DORSAL ROOT GANGLIA AND SPINAL CORD AFTER CHRONIC CONSTRUCTION OR TRANSECTION OF RAT SCIATIC NERVE
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Background. Injury to a peripheral nerve leads to activation of microglia and astrocytes in L4/5 spinal cord and influx of macrophages and lymphocytes in L4/5 dorsal root ganglia (DRGs). We have compared in rats these inflammatory responses after chronic constriction injury (CCI) with those after ligation and transection of one sciatic nerve.

Methods. Adult rats were anaesthetized with halothane (2%) or with ketamine and xylazine (60 and 10 mg/kg i.p.) for nerve lesions, and pentobarbital (100 mg/kg i.p.) prior to perfusion and immunohistochemical processing after 1 week or 10 weeks.

Results. Activating transcription factor-3 (ATF3) was expressed in 75% of sensory and 100% of motor neurones after CCI. Macrophage and glial reactions in DRGs and ventral horn were slightly greater after transection than after CCI, whereas microglial activation in the dorsal horn was greater after CCI than after transection. Rings of ED1(CD68)/OX-42(CD11b)+ macrophages beneath the glial sheath of ATF3+ medium to large diameter DRG neurones were more common after CCI. MHC II+ monocytes that lacked macrophage markers were more numerous in DRGs after transection. CD8+ T-lymphocytes aggregated more in DRGs and dorsal horn after CCI but in ventral horn after transection. Lymphocytes accumulated in the cord mainly by migration, additional T-cells being recruited only after CCI when some lacked CD8 and so were probably CD4+.

Conclusions. The data suggest that an adaptive immune response is initiated after CCI but not after axotomy and may underlie the greater inflammation in DRGs and dorsal horn and consequent pain states.
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A RAT MODEL FOR CANCER PAIN IN THE TRIGEMINAL NERVE AREA
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Background. Cancer pain is a very severe problem for patients with advanced or terminal cancer, however the neural circuit and transmitters responsible remain unknown. In addition, although various cancer pain animal models have been reported, all concentrate on the sciatic nerve areas. A cancer pain model for oral cancers has not yet been reported. Therefore, the aim of this study was to develop an animal model for cancer pain of the trigeminal nerve by inoculating Walker carcinosarcoma 256 B-cells into the right upper jaw of rats.

Methods. Thermal and mechanical sensitivities were determined by measuring withdrawal thresholds and latencies to radiant heat and the von Frey hair test, and gross behaviour was determined by measuring the grooming time.

Results. On day four, a small tumor was found on the side of inoculation which continued to grow in size thereafter. On days four and seven, the withdrawal thresholds and latencies in the right side of the face, where the cancer had developed, significantly decreased and shortened compared to the left side of the face. Ten days after inoculation however, the thresholds and latencies significantly increased. Grooming time, which may be a marker of spontaneous pain, was prolonged with each progressive day.

Conclusion. The results of this study suggest that our new facial cancer model is useful for the evaluation of cancer pain of the facial area.
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ATTENUATION OF FORMALIN-INDUCED NOCICEPTIVE BEHAVIORS FOLLOWING ORAL ADMINISTRATION OF GABAPENTIN AND PREGABALIN
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Background and aims. The anticonvulsants gabapentin and pregabalin have recently emerged as alternative
treatments of persistent neuropathic pain. In the present study we assessed the effect of these compounds in the rat formalin test.

Methods. Male Sprague–Dawley rats (n = 9/group) received by oral gavage: Vehicle, gabapentin (150, 300, 600 μmol/kg) or pregabalin (30, 100, 300 μmol/kg) 150 min prior to formalin injection. Formalin (2.0%, 100 μl, s.c.) was injected into the dorsal side of the left hind paw. The pain-behavior was analyzed by recording the time spent licking of the formalin injected paw during phase 1 (0–5 min) and phase 2 (15–35 min). Blood samples were taken after the experiments (i.e. 200 min post-drug administration) to measure plasma concentrations.

Results. We recorded a typical biphasic nociceptive behavior after formalin injection. Both compounds were inactive in phase 1 of the formalin test. Compared with vehicle, gabapentin as well as pregabalin dose-dependently and significantly reduced the formalin-induced nociception during phase 2. Both compounds induced a similar maximal pain inhibition at the higher doses tested (~67%) although pregabalin appeared to be more potent. Maximal effect of gabapentin was obtained at 600 μmol/kg and plasma exposure of 137 ± 10 μM, whereas the corresponding data for pregabalin was: 300 μmol/kg, plasma exposure of 82 ± 7 μM.

Conclusions. Gabapentin and pregabalin induced significant antinociception in phase 2 of the rat formalin test.

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INFLUENCE OF DIET ON TEMPORAL DEVELOPMENT OF TACTILE ALLODYNIA AND OPIOID HYPOSENSITIVITY FOR 22-WEEKS IN THE ZUCKER DIABETIC FATTY RAT


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Aim. To document the influence of diet composition on the incidence and temporal progression of the diabetic neuropathy parameters, tactile allodynia and opioid hyposensitivity, in the ZDF rat model of Type 2 diabetes.

Methods. Following baseline measurements of blood glucose levels (BGLs), 24 h water intake and von Frey paw withdrawal thresholds (PWTs) in ZDF rats (n = 24), rats were randomly assigned to one of four groups (n = 6 per gp) with each group administered a different diet from 7-weeks of age as follows: (i) the Purina 5008 diet, (ii) a locally-produced diet of similar composition to Purina 5008, (iii) a diabetogenic diet, and (iv) standard rat chow. The temporal development and maintenance of tactile allodynia was assessed using calibrated von Frey filaments. The anti-alldynic efficacy and potency of single bolus s.c. doses of morphine or oxycodone were assessed at 10, 20, 26 and 28 weeks of age using von Frey filaments.

Results. ZDF rats developed hyperglycaemia between 9 and 14 weeks of age. Persistently high BGLs (>20 mM) resulted in the development of tactile allodynia and opioid hyposensitivity in all ZDF rats and there was a temporal development of hyposensitivity to both morphine and oxycodone in all ZDF rats irrespective of the administered diet.

Conclusions. Sustained hyperglycaemia for a period of >16 weeks resulted in the development of tactile allodynia, the defining symptom of painful diabetic neuropathy, as well as opioid hyposensitivity in ZDF rats irrespective of the administered diet.

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TRO19622 TARGETS MITOCHONDRIA AND REVERSES PAIN IN ANIMAL MODELS OF NEUROPATHIC PAIN

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Recently, mitochondrial dysfunction leading to progressive loss of neuronal energy stores, reduced calcium buffering capacity, progressive depolarization and activation of sodium channels in nerve endings have been implicated in neuropathic pain. TRO19622 interacts with two outer mitochondrial membrane proteins, PBR and VDAC, which are part of the permeability transition pore complex. Our working hypothesis is that TRO19622 restores mitochondrial function. TRO19622 was discovered due to its neuroprotective and neuroregenerative properties for motor neurons in vitro and in vivo. Studies in models of diabetic and chemotherapy-induced neuropathy demonstrate that TRO19622 reverses nociceptive hypersensitivity in neuropathic pain models. In streptozotocin-induced diabetic rats, TRO19622 reversed thermal allodynia, mechan-
ical hyperalgesia and tactile allodynia 4 h after single oral administration. The reversal of tactile allodynia was maintained with repeated administration for 5 days. Similar reversal of tactile allodynia was seen in a model of vincristine-induced neuropathic pain. In addition, long term treatment with TRO19622 normalized motor nerve conduction in diabetic rats suggesting that this compound may improve neuropathic syndromes in addition to analgesic activity. By contrast, TRO19622 did not reverse thermal hyperalgesia in normal or neuropathic rats or pain-like behaviour in the formalin test. These data suggest that TRO19622 specifically reverses neuropathic rather than noxious or inflammatory pain. Even at very high doses TRO19622 is devoid of sedative or other adverse effects of current analgesics and therefore offers a promising new approach for treating neuropathic pain. A Phase 2 study in diabetic neuropathic pain is currently ongoing.

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164 ANXIETY-LIKE BEHAVIOUR IS OBSERVED IN TWO RAT MODELS OF MONONEUROPATHY
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Background and aims. Usually, evoked nociceptive responses are measured to determine the pain reducing potential of analgesic drugs in animal models. Behavioural aspects of ongoing pain have been neglected so far. Here we investigate whether anxiety-like behaviour is associated with neuropathic pain in rats.

Methods. Neuropathic pain was induced by chronic constriction injury (CCI) and by partial nerve ligation (PNL) in male Wistar rats (N = 15; 300 ± 40 g). In these models mechanical hypersensitivity was assessed by the electronic algometer. We determined anxiety like behaviour by elevated plus maze (EPM). Additionally, motor activity was monitored in activity boxes in darkness.

Results. CCI and PNL animals show an increased mechanical sensitivity. The paw withdrawal threshold was 26 ± 2 g in sham operated animals and decreased to 18 ± 2 g in PNL and 13 ± 1 g in CCI rats (mean ± SEM). Locomotion in the lesioned animals was not influenced. In the anxiety studies only CCI animals showed a clear behavioural effect. The amount of time in open arms is significantly reduced from 106 (47–150) s in sham animals to 37 (9–46) s in CCI rats. Entries into open arms was reduced from 7 (4–11) to 3 (1.5–4.5), respectively (median, 1,3 quartile). In the second neuropathic model (PNL) we could only observe a trend of anxiety like behaviour.

Conclusions. In the present study, we showed that animals subjected to two different models of neuropathic pain exhibit anxiety like behaviour. This was more pronounced in CCI than in PNL animals, in accordance with lower pain threshold in these rats.

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165 SPINE DEFORMATION IN RAT MODELS OF NEUROPATHIC PAIN CAN CAUSE PAIN RELATED BEHAVIOR
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The neuroma and dorsal root ganglion are key sources of the ectopic activity in rodent models of peripheral nerve injury. This ectopic activity triggers central sensitization which than induces pain related behavior. One of the still unresolved questions in neuropathic pain research is whether we can block that activity by disconnecting the source of it from the spinal cord. However, one of the obstacles in answering that question are non standardized surgery procedures used in rhizotomy and ganglionectomy. Our objective was to confirm that laminectomy performed during ganglionectomy or rhizotomy can induce lumbar column deformity. We also wanted to show that spine deformity is a potential source of pain related behavior. In order to prove our hypothesis we used control, two experimental and two corresponding sham groups. In two experimental groups, we performed L5 ganglionectomy using extensive and minimal laminectomy. After repeated behavioral testing plain X-ray in anteroposterior projection was done, while the extent of deformity was assessed by measurements of deformity angle. After the sacrifice spine was removed, cleaned to expose bone structure and photographed to validate extent of laminectomy. Lateral deformity of the spine was observed in both sham and experimental groups confirming that laminectomy can produce deformity. The extent of deformity was more pronounced in rats exposed to the extensive laminectomy. Changes in pain related behavior were observed in rats with extensive laminectomy regardless of performed ganglionectomy, confirming that surgery procedure can be the source of pain related behavior.

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PREGABALIN SUPRASPINALLY ACTIVATES THE DESCENDING NORADRENERGIC PAIN INHIBITORY SYSTEM AFTER PERIPHERAL NERVE INJURY
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Background and aims. We have previously demonstrated that gabapentin supraspinally activates the descending noradrenergic system to alleviate neuropathic pain. In this study, we investigated behaviorally and neurochemically whether pregabalin, an anticonvulsant and analgesic drug that is structurally and pharmacologically related to gabapentin, also exhibits similar analgesic effects involving the descending noradrenergic system.

Methods. A chronic pain model was prepared by partially ligating the sciatic nerve in mice. The mice received intraperitoneal (i.p.), intracerebroventricular (i.c.v.) or intrathecal (i.t.) injections of pregabalin combined with either central noradrenaline (NA) depletion by 6-hydroxydopamine or pharmacological blockade of spinal α2- adrenergceptors. Concentrations of spinal monoamines were also measured using high-performance liquid chromatography in mice after i.c.v. injection of pregabalin.

Results. Systemically administered pregabalin (10 and 30 mg/kg, i.p.) reduced mechanical and thermal hypersensitivity in mice only after peripheral nerve injury. Similar analgesic effects were obtained when pregabalin (10 and 30 μg) was injected i.c.v. or i.t. Depletion of spinal NA or blockade of spinal α2-adrenergceptors with yohimbine (1 and 3 μg, i.t.) reduced the analgesic effects of pregabalin (i.p. or i.c.v.). Moreover, i.c.v. administered pregabalin increased the spinal MHPG concentration and the MHPG/NA ratio only in neuropathic pain mice, suggesting that supraspinal pregabalin resulted in an increase in spinal NA turnover. By contrast, the concentrations of NA, serotonin, 5-hydroxyindoleacetic acid and dopamine were unchanged.

Conclusions. These results indicate that pregabalin supraspinally activates the descending noradrenergic pain inhibitory system to ameliorate neuropathic pain.

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SPINAL CORD STIMULATION IN A MOUSE CHRONIC NEUROPATHIC PAIN MODEL
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Background and aims. Development of a spinal cord stimulation (SCS) system in a mouse model of chronic neuropathic pain.

Methods. Male C57/Bl mice (n = 17) underwent a partial ligation of the sciatic nerve (t = 0). Development of mechanical hyperalgesia was tested using the withdrawal response to tactile stimuli with the von Frey test. A SCS system was implanted on day 14. On day 16, the mice were stimulated for 30 min (f = 50 Hz; pulswidth 0.2 ms and stimulation at 2/3 of motor threshold). Repeated measure analysis of variance (ANOVA) and paired Student’s t-test with Bonferroni correction were used to evaluate the development of mechanical hyperalgesia and the therapeutic effect of SCS.

Results. Fifteen out of seventeen mice developed marked mechanical hyperalgesia in the nerve lesioned paw which persisted for the duration of the study. No changes contralateral to the injury were observed. In 14 out of 15 mice a successful implantation of the electrodes followed by stimulation was achieved. Then SCS resulted in a fast and robust increase of withdrawal threshold back to pre-injury levels. After termination of the SCS the withdrawal threshold of the ipsilateral paw decreased to pre-stimulation values (60 min after cessation of SCS). No effect of SCS on the contralateral paw was noted.

Conclusion. The development of a mouse SCS system is described which is practical in use, is reproducible and shows a comparative therapeutic effect in treatment of chronic neuropathic pain as reported in rat.

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have been observed in rats as well as in humans. In addition, the immune system has been proposed to be important in the development and maintenance of neuropathic pain. Critical for immune responses are molecules encoded by genes located in the major histocompatibility complex (MHC). Accordingly, we here investigate the influence of different allelic variants of the MHC on neuropathic pain.

**Methods.** Partial peripheral nerve injury (the Seltzer model) was induced in the inbred rat strains Dark Agouti (DA), Piebald Virol Glaxo (PVG), and the MHC-congenic PVG-RT1av1, which carries the MHC locus derived from DA. Subsequently, the development of neuropathic pain-like behavior was assessed by recording of hind paw withdrawal thresholds using von Frey filaments. In a second experiment the same strains were additionally subjected to spinal cord stimulation (SCS).

**Results.** Mechanical hypersensitivity thresholds at seven and 14 days after nerve injury differed between the strains, with the PVG strain displaying a lower threshold compared with DA and PVG-RT1av1. Thus, these results suggest a genetic influence from the MHC on development and maintenance of neuropathic pain. We hypothesize that also strain-dependent differences exist in the response to SCS.

**Conclusion.** This study provides evidence of the importance of the genetic set-up for pain sensitivity and responsiveness to neurostimulation, and in particular the data presented suggests that certain variants of the MHC may act as genetic risk factors for nerve injury-induced hypersensitivity.

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**ORAL ADMINISTRATION OF STAVUDINE INDUCES MECHANICAL HYPERALGESIA AND INCREASED CINC-1 IN THE SPINAL CORD OF RATS**
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**Background and aims.** Stavudine, a nucleoside reverse transcriptase inhibitor (NRTI), which is used to treat HIV infection, can cause peripheral neuropathy, and pain, in HIV-positive patients. To determine whether changes in the spinal cord underlie the development of stavudine-induced pain in rats, we measured changes in inflammatory cytokine secretion and neuronal cell death in the spinal cord.

**Methods.** Stavudine was administered orally as a suspension in a gelatine cube to Sprague–Dawley rats once daily for six weeks at a dose of 50 mg kg⁻¹. Control rats received gelatine cubes without stavudine. The response of the rats to a noxious mechanical challenge applied to the tail was recorded weekly. In a separate group of rats, which also received 50 mg kg⁻¹ stavudine or placebo cubes daily for up to six weeks, the lumbar spinal cord was removed for cytokine analysis by ELISA and histologic examination.

**Results.** Daily stavudine administration resulted in mechanical hyperalgesia within three weeks. Cytokine-induced neutrophil chemo-attractant (CINC)-1 concentrations were significantly increased in rats that received stavudine for six weeks. Concentrations of interleukin (IL)-6 did not differ between groups. The number of spinal cord neurons and the number of TUNEL positive nuclei, indicative of apoptotic cells, did not differ between groups.

**Conclusions.** Six weeks of daily stavudine administration to rats result in an increase in CINC-1 concentration in the spinal cord, well after the three weeks during which hyperalgesia develops. Oral stavudine administration does not cause apoptosis or necrosis of spinal cord neurons in rats.

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**NOCICEPTIVE RESPONSES TO VASOACTIVE AGENTS IN AN ANIMAL MODEL OF CRPS-I**
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**Background.** Chronic post-ischemia pain (CPIP) is an animal model of CRPS-I created using an ischemia-reperfusion injury of the rat hindpaw. CPIP rats develop robust pain behaviors for at least 4 weeks post-reperfusion. Previously, we have shown CPIP rats exhibit an anti-allodynic response to sympatholytic agents suggesting that they have sympathetically-maintained pain (SMP). CPIP rats with mechanical allodynia also exhibit nociceptive behaviours following intraplantar injection of norepinephrine (NE), and enhanced vasoconstrictive responses to NE, suggesting that altered vascular reactivity contributes to pain in CPIP rats. In this study, we further characterize the response to...
NE, as well as other vasoactive agents, in CPIP rats. Intraplantar injection of NE induces nociceptive behaviors both at 2 and 7 days post-reperfusion. Intraplantar injection of another vasoconstrictor, vasopressin also induces significant nociception at 2 and 7 days post-reperfusion. Further, intraplantar injections of a non-subtype-selective nitric oxide synthase (NOS) inhibitor, L-NAME, as well as an endothelial NOS inhibitor, L-NIO, induce particularly strong nociceptive behaviors at 2 days, but less nociception at 7 days, post-reperfusion. Finally, we find that CPIP rats exhibit anti-allodynic responses to sympatholytics and other vasodilators particularly at 2 days, and less at 7 days, post-reperfusion. We conclude that vasoconstrictive hyper-responsiveness may be particularly significant for SMP in the early stages after I–R injury in CPIP rats, and possibly also early in CRPS-I patients.

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A CHRONIC COMPRESSION MODEL OF TRIGEMINAL NEURALGIA
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Trigeminal neuralgia is a chronic pain syndrome in which patients experience intense paroxysms of lancinating pain in the face along the distribution of one or more branches of the trigeminal nerve. There is overwhelming evidence that trigeminal nerve root demyelination or dysmyelination is the underlying cause of trigeminal neuralgia, usually as a result of nerve root compression. We modeled this disease in rats by stereotaxic extradural placement of a bio-inert, superabsorbent polymer immediately next to the trigeminal nerve root. We then examined consequent anatomical, electrophysiological, and behavioral changes with the purpose of determining how well this chronic compression models human trigeminal neuralgia.

Our experiments demonstrate a dysmylenation and clumping of sodium channels near the trigeminal root entry zone (see figure: Top = Normal; Bottom = Compressed; green = nodal marker; red = sodium channels). We also observed ectopic discharges and decreased sensory thresholds for trigeminal afferents, and paroxysmal (twitching) and guarding facial behaviors beginning at 3 weeks after administration of the polymer. Our model may be useful in determining the potential efficacy of treatments for trigeminal neuralgia.

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COMPARING LOCAL DELIVERY OF KETOROLAC AND PENTOXIFYLLINE IN THE CHUNG AND BENNETT RAT MODELS OF NEUROPATHIC PAIN
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Background and aims. We evaluated sustained local doses of ketorolac and pentoxifylline in the Bennett and Chung models of nerve injury.

Methods. Ketorolac and pentoxifylline were administered continuously to the perineural space via an Alzet® pump at 0.8, 4.2, and 21.0 μg/h. The effect of these compounds was measured by the following behavioral tests: thermal hyperalgesia using the Hargreaves test and mechanical allodynia using von Frey monofilaments.

Results. There was no significant difference between the test compounds and the vehicle control in the Chung model. Drug concentrations in plasma and surrounding local tissue indicated that there was effective local delivery of the drugs to the perineural space. The behavioral data from the Bennett model indicated that ketorolac or pentoxifylline significantly increased the paw withdrawal latency following a thermal stimulus when compared to vehicle control (ANOVA; p < 0.05) (Fig. 1).

Conclusions. None of the treatment groups produced significant effects on mechanical allodynia when compared to vehicle control in either model. Both drugs elicited an analgesic response in thermal hyperalgesia in the Bennett model, but failed to do so in the Chung model. This result may be due to a larger inflammatory component in the Bennett model elicited locally by the chromic gut absorbable suture relative to a pure mechanical neural injury in the Chung model.

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POSTER SESSION 1: CLINICAL – PHARMACOTHERAPY

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LOCALIZED TREATMENT WITH NGX-4010 SIGNIFICANTLY REDUCED PAIN FOR UP TO 12 WEEKS: A RANDOMIZED, DOUBLE BLIND CONTROLLED STUDY IN POSTHERPETIC NEURALGIA
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A total of 402 patients were enrolled at 52 centers in a randomized, double-blind, controlled study of NGX-4010 (trans-capsaicin, 8% w/w) patch for the treatment of postherpetic neuralgia (PHN). The treatment consisted of a single one-hour application of NGX-4010 (patch) or a low-concentration capsaicin control (trans-capsaicin, 0.04% w/w) applied to the area described as painful, following pretreatment with topical local anesthetic. Patients
recorded on a daily diary their “average pain for the past 24 h using the 11-point Numeric Pain Rating Scale (NPRS). Inclusion criteria included pain ≥6 months after lesion healing and an average baseline pain score between 3 and 9 inclusive. Patients on stable doses of oral neuropathic pain prescription medication could be eligible and represented the majority of patients included in the study. The percent change in average NPRS score from baseline as compared to weeks 2–8 and weeks 2–12 were analyzed. During weeks 2–8, the NGX-4010 group (N = 206) experienced a mean NPRS score reduction of 29.6% compared to 19.9% in the control group (N = 196; p = 0.001). During weeks 2–8, 42% of NGX-4010 subjects responded to treatment (≥30% reduction in mean NPRS scores) as compared to 32% in the control group (p = 0.034). The reduction in pain was sustained through week 12 (NGX-4010 – 31.4%, control –21.6%; p = 0.01). A single treatment with NGX-4010 results in significant pain reduction that is maintained for up to 12 weeks and; is generally well tolerated with no significant safety issues identified in patients with PHN.

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**COADMINISTRATION OF GABAPENTIN WITH LAMOTRIGINE IN NEUROPATHIC PAIN THERAPY: CAN IT IMPROVE THERAPEUTIC COMPLIANCE?**
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**Background and aims.** The use of anticonvulsants for neuropathic pain is based on common pathophysiologic changes occurring in epilepsy and neuropathic syndrome. There is not an evident correspondence between symptomatology and involved ionic channel. When used in monotherapy, anticonvulsants require high doses thus increasing adverse effects. This placebo-controlled study aims showing that the coadministration of Gabapentin with Lamotrigine (inhibition of both N-type Ca and Na channels) improves the therapeutic compliance.

**Methods.** Under Ethical Committee approval and after informed consent, 322 patients were enrolled during 30 months, female/male 162/160, mean age 45 ± 10, suffering from neuropathic syndrome of various eziology, clinically diagnosed and proved by Galer score (T0). Patients were blindly and randomly assigned to 2 groups: Group GP (159 patients) received Gabapentin (1200, 1800 or 2400 mg/die) + Placebo, while Group GL (163 patients) received Gabapentin (900 or 1200 mg/die) + Lamotrigine (50, 100 or 150 mg/die). Pain was evaluated by Verbal Analogical Scale (VAS) 0–10. Moreover, presence/absence of most common adverse effects was evaluated. Follow-up: 15, 30 and 60 days of therapy (T15, T30 and T60).

**Results.** The resulting VAS trend, the number of patients witch assimilated different drug doses and the percentage showing adverse effects are reported in Tables 1 and 2. Analysis has been performed by using a Z-test.

**Conclusion.** The coadministration of Gabapentin with Lamotrigine allows reducing of adverse effects and maintaining a good therapeutic compliance.

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**A COMPARISON OF TCA (AMITRIPTYLINE/NORTRIPTYLINE) AND VENLAFAXINE IN THE TREATMENT OF CHRONIC NON-CANCER PAIN**
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Introduction. TCA may cause serious adverse events and is to some patients contraindicated. Newer drugs have been developed with less serious adverse reactions. One of those is venlafaxine. It is well known that TCA can be used in the treatment of neuropathic pain. The aim of this study was to compare TCA and venlafaxine regarding pain relief and side effects in patients with mixed neuropathic/nociceptive chronic pain.

Materials and methods. The analyses were prospective and unblinded and included 50 patients from a multidisciplinary pain center. The treatment was either TCA (N = 27) or venlafaxine (N = 23). Dose was titrated to maximal effect with fewest adverse events. When the expected stable dose was reached the patients were interviewed for the results.

Results. 70% in the TCA group were satisfied with the effect and continued the treatment on a dose of 54 (10–125) mg, though only 37% reported good pain relief. The frequency for ceasing TCA was 30%. 30% in the venlafaxine group continued the treatment on a dose of 150 (37.5–300) mg, all because of satisfactory pain relief. The frequency for ceasing venlafaxine was 70%.

Conclusion. Of TCA and venlafaxine, TCA, if not contraindicated, should still be first choice for chronic complicated pain patients because of relatively better pain relief and fewer side effects, but venlafaxine is an alternative.

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176 PHARMACOLOGICAL COMPARISON OF THE COMBINED μ-OPIOID RECEPTOR AGONIST AND MONOAMINE REUPTAKE INHIBITOR NS7051 WITH TRAMADOL IN ANIMAL EXPERIMENTAL PAIN MODELS

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The atypical analgesic tramadol has a unique dual mechanism of action, displaying agonist activity at μ-opioid receptors and acting on monoamine transporters to inhibit reuptake of noradrenaline (NA) and serotonin (5-HT). Here, we compare the antinociceptive actions of the novel compound NS7051 with tramadol in rat models of experimental pain. In vitro assays showed that NS7051 had submicromolar affinity (~0.1 μM) for μ-opioid receptors. NS7051 also inhibited reuptake of 5-HT, NA and DA (IC50 = 4.2, 3.3 and 3.5 μM in cortex, hippocampus and striatum, respectively). In the hot plate test, NS7051 (1–30 mg/kg, s.c.) produced a dose-dependent naloxone-reversible increase in withdrawal latency. This NS7051-mediated analgesia was also partially reversed by the alpha2 adrenergic receptor antagonist yohimbine and the 5-HT1A receptor agonist 8-OH-DPAT implicating descending noxious inhibitory control pathways. In the formalin test, NS7051 dose-dependently attenuated flinching behaviour during the first, inter- and second phases of the test (ED50 = 2.8, 1.7 and 1.8 mg/kg). Hindpaw weight bearing deficits were completely reversed by NS7051 in the CFA model of chronic inflammatory pain. In the chronic constriction injury model of neuropathic pain mechanical allodynia and hyperalgesia were both reversed by NS7051 (ED50 = 6.7 and 4.9 mg/kg). Tramadol was also active in all pain models although at higher doses (20–160 mg/kg, s.c.). No ataxia was observed at antinociceptive doses giving a therapeutic index (ataxia/antiallodynia) of 19 for NS7051 and 3 for tramadol. NS7051 has a combined mechanism of action that is expected to contribute to its robust antinociceptive profile in rat models of acute and chronic pain.

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A MULTI-CENTER, OPEN-LABEL, FOLLOW-ON TRIAL TO ASSESS THE LONG-TERM SAFETY AND EFFICACY OF LACOSAMIDE IN SUBJECTS WITH PAINFUL DIABETIC NEUROPATHY

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Lacosamide (formerly SPM 927) is being investigated as a possible anticonvulsant with potential effect in reducing diabetic neuropathic pain. This is an open-label, follow-on trial to a previously completed double-blind trial in subjects with painful diabetic neuropathy. Subjects titrate to their optimal dose (100–600 mg/day) in weekly increments of 100 mg/day then enter a long-term maintenance period. Dose adjustments are allowed as necessary. Morning and evening pain and interference of pain with sleep and activity are assessed by daily diary entries using an 11-point Likert scale. Scores for each visit are summarized by the observed cases method. Adverse events (AEs) are recorded throughout the trial. Two hundred-fourteen (214) subjects enrolled in the trial and received lacosamide. Forty-seven percent (47%) of subjects were female, 79% of subjects were <65 and 21% were ≥65 years of age. Based on preliminary results, the maximum duration of lacosamide exposure was 518 days and the...
most commonly prescribed dose was 400 mg/day. The number of subjects on treatment for at least 6 or 12 months was 182 and 91, respectively. Marked reductions in the Likert pain score on average among the patients were observed over the whole treatment period. Eighteen (18, 8%) subjects discontinued the trial for adverse events. The most common AEs included dizziness, vertigo, headache, nasopharyngitis, fatigue, and nausea. The poster will present updated and more detailed results from an upcoming analysis.

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178 INTRAVENOUS IMMUNOGLOBULINS TREATMENT IMPROVES PAIN IN DIABETIC LUMBO-SACRAL RADICULOPLEXUS NEUROPATHY

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Background. Diabetic lumbosacral radiculoplexus neuropathy (DLRPN) is a rare painful condition that may occur in diabetic patients. At the moment there is no proven treatment for DLRPN.

Objective. To evaluate the effect of intravenous immunoglobulin (IVIg) therapy in the treatment of DLRPN.

Subjects and methods. We recruited four patients affected by type II diabetes mellitus and DLRPN. All of them complained of thoracic and abdominal pain and developed painful lower-limb proximal weakness. Clinical examination and instrumental findings were suggestive of lumbosacral plexopathy and bilateral distal neuropathy. Sural nerve biopsy showed degeneration and loss of fibers with perivascular inflammation. Treatment with gabapentin, amitriptylline, carbamazepine, clonazepam and tramadole, even at high dosages, could not alleviate truncal and lower-limb pain. All patients were treated with IVIg (0.4 g/kg/day for 5 days).

Results. After IVIg treatment all patients improved. In particular, pain was alleviated and patients could reduce the dosage of analgesic drugs. Two of the patients needed a second treatment with IVIg after a few months.

Conclusions. IVIg treatment may improve pain of patients with DLRPN. Our data could represent a starting point for a double-blind study aimed to evaluate the role of IVIg in the treatment of patients affected by DLRPN.

Reference


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179 BUPRENORPHINE PATCH IN NON-MALIGNANT LOW BACK PAIN: OUR EXPERIENCE

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Introduction. In this paper, we briefly report our ongoing study on buprenorphine TDS 35, 52.5 and 70 µg/h (B.TS) 1 patch/3 days in a cohort of patients affected by low back pain with or without radiculopathy and neuropathic pain.

Method. We evaluated effectiveness of pain relief and quality of patients sleep by means of VAS and dichotomised yes/no subjective questionnaire on changed quality of sleep.

Results. 79 patients (64% F and 36% M, age 27–86) were treated and followed for 52 days. The analgesic efficacy of B.TS was significantly high both for variables of study and on peripheral neuropathic component. Intensity of pain decreased of 59% after 9 days, of 63% after 27 days and of 70% after 52 days in patients without radiculopathy and, respectively, of 45%, 62% and 68% in patients with radiculopathy (p < 0.01 between times, NS between groups). Moreover, we observed a marked improvement of the quality of sleep, independently of the presence of radiculopathy (p < 0.01 between times, NS between groups). After 52 days only 1 patient reported him kept awake, while the sleep was restful in 23 cases. Patients with radiculopathy reported better sleep in 24 cases and sound sleep in 12 cases. Side effects were moderate and well tolerated; only 13.9% of patients suspended the treatment.

Conclusions. Since the good relation between risk and benefit, buprenorphine TDS is an useful analgesic in patients with non cancer chronic pain, with neuropathic
or nociceptive peripheral component, when the severity of pain requires use of an strong opioid.

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A DIFFERENT ANALGESIC LADDER FOR NEUROPATHIC PAIN?
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Background. The classic analgesic ladder for chronic pain was proposed by the WHO in the 1980s and was initially made up of three steps, taking the intensity of the pain as reference. It can currently be considered valid for use by many healthcare professionals, especially in chronic cancer pain. However, advances in our knowledge of the physiopathology of pain have led to the classification of two well-differentiated types of pain: nociceptive pain and neuropathic pain. Since the physiopathology and clinical characteristics of the two types of pain are completely different, they cannot be treated by the same approach.

Method. Therefore, a new and specific analgesic ladder has been proposed for neuropathic pain, taking account of its complexity, its comorbidities (sleep disorders, emotional disorders, etc.) and its highly variable response to the therapy in current use. The proposed Analgesic Ladder for Neuropathic Pain (ALNP) comprises four steps, reserving the fourth step for analgesic techniques. The first three steps give priority to the exclusive or combined use of certain antiepileptics and antidepressants, associated or not with opioids according to the intensity of the pain. Some author’s place opioids, e.g., tramadol or oxycodone, directly in the first step of Neuropathic Pain management.

Conclusion. This new analgesic approach to neuropathic pain offers greater analgesic effectiveness linked to a reduction not only in the pain but also in all of its associated comorbidities. Moreover, this new ALNP is more operative for clinicians.

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METHADONE IN MANAGEMENT OF INTRACtable NEUROPATHIC PAIN
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Background and objective. Neuropathic pain results from injury or dysfunction of nervous system. Medical treatment is the first line therapy. Methadone is a μ-opioid receptor agonist, also it acts blocking the reuptake of norepinephrine and serotonin into the dorsal horn, and it is a NMDA receptor antagonist. The objective of this study was to assess the improvement of neuropathic pain with methadone in patients of the General Hospital’s Pain Clinic in México City.

Methods. After checking medical records, we interviewed patients with neuropathic pain taking methadone. We assessed: the improvement in intensity of pain (VAS), dosing, side effects, character of pain and use of concomitant drugs.

Results. The study included 31 patients in treatment with methadone because of failing to control pain. The average age was 58 years; 58% were male and 42% were female. The diagnosis were central pain, postherpetic neuralgia and spinal cord stenosis. Most of patients reported burning pain. The patients were taking from 2.5 mg to 60 mg per day of methadone (mode 10 mg). VAS was 8.7 ± 1.2, and 4.3 ± 1.8, before and after treatment with methadone, respectively, with a decrease average of 49%. The most frequent side effects were constipation, somnolence and nausea.

Conclusion. Methadone is a useful drug in the treatment of neuropathic pain when other drugs had failed. Most patients had good tolerance and few adverse effects.

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INTRADERMAL ADMINISTRATION OF BOTULINUM TOXIN, TYPE A, IS EFFECTIVE IN TREATING NEUROPATHIC PAIN DISORDERS
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Botulinum toxin, type A (BoNTA) relieves pain associated with cervical dystonia or neuromuscular conditions. Intradermal botulinum toxin type B was shown to relieve migraines of cervical origin, suggesting an effect on afferent sensory nervous input to the spinal cord. In this study, this new administration technique was used in patients with TMJ pain, scar pain, CRPS pain, diabetic neuropathy, carpal tunnel pain and trigeminal neuralgia. No medication changes were made during the course of study, save reductions in pain medication.

Sixteen patients (9 female, 7 male, average age 50 (range 28–77) were given intradermal BoNTA by raising a skin wheal at or near the site of pain. One person received 20 U, 2 received 50 U; the rest were given 100 U intradermally. 14/16 had reduction in pain (88%). Average pain reduction, patient-rated, was 78%; average duration of 15.4 weeks (range = 8–26 weeks). Two patients had no response. In all cases patients
reported relief of muscle spasm. No side effects, other than 2 patients with flu-like symptoms, were reported.

This initial data in pain patients who had failed other attempts at treatment of their symptoms, suggests that BoNTA is effective when given intradermally. Tolerability is also excellent. It has implications for BoNTA’s effect on pain mechanisms, likely at the level of the spinal cord. BoNTA has been shown, largely in vitro or in animal models, to reduce Substance P, glutamate and CGRP. Double-blind studies are needed to replicate these initial observations in common painful disorders.

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EFFECTIVENESS OF IV THERAPY FOR PAIN IN THE CLINIC
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Aggressive pain and headache treatment belongs in the specialty headache and pain clinic, with greater cost- and time-effectiveness treating intractable headaches and migraines. Compared with the emergency room, the clinic offers a wider range of treatments and maximum success. We have used IV treatment in the clinic since 1994 and presented initial data regarding effectiveness in 1998. This study documents the degree of success of outpatient IV treatment of refractory migraines and headaches.

Total treated patients number over 1800 and 874 were treated for refractory migraines/headaches. We utilized: IV magnesium sulfate, dexamethasone, valproate sodium, lidocaine, droperidol, dihydroergotamine, pro-methazine, metoclopramide, propofol, tramadol, lev- etiracetam and ketamine, alone or in combination.

Results are measured by successful resolution of symptoms, defined by at least a 50% decrease in severity [0–10 scale] of the presenting headache/migraine, or by return to work/regular activity. 62 patients from the total pool (62/1800) [4%], and 42 from the pain treatment group (22/926) [4%] had unsuccessful treatment that required re-treatment in the clinic, hospital ED or inpatient. This represents a 96% rate of effective treatment in the clinic.

We conclude that outpatient IV therapy of refractory pain flare-ups is highly successful in the outpatient setting with very low need for re-treatment, contributing to increased productivity in the workplace, at home and in personal life. This should be a priority of pain and headache specialists and could contribute to lowered overall cost burden of pain in society.

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THE TOPICAL USE OF AMITRIPTILINE AND LIDOCAINE FOR THE TREATMENT OF CHRONIC NEUROPATHIC PAIN
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Objective. To evaluate of the analgesic effects of an open study using a topical formulation composed by amitriptiline 2%, lidocaine 7% and transdermal gel PLO, in patients with chronic neuropathic pain. In those without allergy, mentol 1% and camphore 1% were also used.

Methods. Thirty-six patients (70.3% female; mean age: 45.7 years) with chronic neuropathic pain (mean duration of pain: 34.6 months) were evaluated at a multidisciplinary pain setting. All patients were exhaustively evaluated for the origin of neuropathic pain and also other sources of pain. Complex regional pain syndrome, post herpetic neuralgia and post traumatic neuropathies were the most frequent diagnosis. VAS was used to evaluate the intensity of pain. The analgesic effect was considered as satisfactory when the improvement was above 50% and poor, when less than 50%. Personal satisfaction with the preparation was also evaluated.

Results. Previously to the use of topical analgesics, the VAS was 7.8. Immediately after the use of the medication, the pain decreased to 3.8 (p < 0.000). The results were considered as satisfactory in 64.9% of the patients. The analgesic effect lasted from 2 to 6 h (mean = 3.7 h). Few patients presented contact allergy, drowsiness or dry mouth. The mean duration of follow-up period was 13.5 months.

Conclusions. Topical application of amitriptiline and lidocaine seems to be an useful adjuvant therapy during the multidisciplinary pain program. Further studies using placebo control studies are needed.

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TRANSDERMAL BUPIVACAINE FOR NEUROPATHIC PAIN: CLINICAL DEVELOPMENT PROGRESS
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Bupivacaine transdermal therapeutic system (TTS), developed by DURECT Corporation using its
MULTICENTER, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY EVALUATING THE SAFETY AND EFFICACY OF LENALIDOMIDE IN THE TREATMENT OF CHRONIC PAINFUL RADICULOPATHY

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Background and aims. Lenalidomide, a novel immunomodulator, inhibits the secretion of several proinflammatory cytokines (TNF-α, IL-1β, and IL-6) and increases anti-inflammatory cytokines (IL-10) as well as IL-2 and IFN-γ. This study evaluated the safety and efficacy of lenalidomide in chronic painful lumbar radiculopathy where cytokines may play a pathologic role.

Methods. This double-blind study involved 181 adult subjects with chronic (>6 mos) painful (>5 out of 10 pt numerical rating scale) lumbar (sciatic) radiculopathy at 15 centers. Subjects received lenalidomide 10 mg/day or placebo orally along with their current stable analgesic regimen for 12 weeks following a one-week baseline evaluation. An open-label phase of up to 54 weeks was available to completers. Assessments covered several domains including pain, sleep, function, global impression of change and safety and included: pain intensity numerical rating scale (NRS-PI), sleep diary, short-form McGill Pain Questionnaire (SF-MPQ), Brief Pain Inventory (BPI), Profile of Mood States (POMS), Modified Oswestry Low Back Pain Disability Questionnaire and Pain Disability Index Score.

Results. The subjects were 43% male, and 84% white; an average age of 55 (±13) years, 136 out of 181 subjects completed the study. An external data monitoring committee reviewed safety and efficacy data at an interim analysis to assess risk/benefit considerations and recommended that the study be continued. Results of the double-blind phase data analysis for safety and efficacy will be presented.

Conclusions. Lenalidomide may be a promising new therapy for the symptoms of chronic painful radiculopathy.

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satisfactory result, despite the fact that vomiting became present in 2 patients (25%) and in 1 case we had to stop the medication because of edema.

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PROSPECTIVE STUDY OF THE PHARMACOLOGIC MANAGEMENT OF CHRONIC NEUROPATHIC NON-CANCER PAIN
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Aim of investigation. To evaluate the longterm effectiveness of pharmacologic management of chronic neuropathic pain (NeP).

Methods. An ongoing prospective study of 154 patients with chronic NeP non-cancer pain using a computerized database (Microsoft ACCESS) and standard outcome measures for pain (Brief Pain Inventory), level of function (Pain Disability Index), mood (Hospital Anxiety and Depression Scale), quality of life (SF-12) and overall treatment satisfaction (Global Satisfaction Scale). Patients were assessed at baseline and reviewed at 3, 6, 12, 18 and 24 months. Data analysis was carried out using SPSS with Student’s t-test for paired samples.

Results. The mean age was 49.9 ± 15.4 years with a female/male ratio of 1.5/1.0. The major pain syndromes were complex regional pain syndrome (22.1%), failed back syndrome with nerve root fibrosis (20.8%), central pain (12.3%) and peripheral nerve entrapment (9.7%) with a mean duration of 5.3 ± 6.3 years. Primary pharmacologic treatment modalities were antidepressants (40.3%), anticonvulsants (26.6%) and opioid analgesics including methadone (79.2%). Mean duration of followup was 14.3 months. There was a significant reduction in mean average pain intensity and improvement in global satisfaction at all time points relative to baseline. The number-needed-to-treat (NNT) for 30% and 50% reduction in pain intensity were 3.2 and 6.3, respectively.

Conclusions. Pharmacologic management of long-standing NeP non-cancer pain resulted in significant improvements in patients’ pain and treatment satisfaction. However, effectiveness based on real world data appears to be much less significant than efficacy determined by randomized controlled trials.

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ORAL PROLONGED RELEASE (PR) OXYCODONE/NALOXONE COMBINATION REDUCES OPIOID-INDUCED BOWEL DYSFUNCTION (OIBD) IN PATIENTS WITH SEVERE CHRONIC PAIN
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To evaluate the impact of oral PR naloxone on OIBD in patients with severe chronic pain already established on oxycodone.

In this controlled double-blind study, after a 2-week run-in period, 202 patients with chronic pain (cancer or non-cancer related) under stable oxycodone therapy (40–80 mg/day) were randomised to one of four PR naloxone groups: 10, 20, 40 mg day or placebo. After a 4-week maintenance phase, patients were followed-up for 2 weeks during which time they received oxycodone only. OIBD was evaluated from the mean of the three components – ease of defaecation, feeling of incomplete bowel evacuation and patient judgment of constipation – each assessed subjectively using a 0–100 numerical analogue scale (NAS; the greater the score, the worse the OIBD).

Bowel function improved with increasing naloxone dose. At pre-randomisation, average scores of 48.0, 52.8, 49.4 and 46.2 were observed for placebo, 10 mg, 20 mg and 40 mg naloxone groups, respectively, and at end of maintenance the equivalent scores were 45.4, 40.3, 31.3 and 26.1 (p < 0.05 for 20 mg and 40 mg naloxone vs. placebo). In a quadratic response surface model with naloxone and oxycodone dose as factors, the improvement increased with decreasing oxycodone/naloxone ratio and appeared to plateau at the 2:1 ratio, with the overall effect at 2:1 approximately 50% greater than at 4:1. No loss of analgesic efficacy with naloxone was observed (data not shown).

Addition of up to 40 mg oral naloxone significantly reduced OIBD in patients with severe chronic pain who were established on oxycodone.

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NEUROPATHIC PAIN IN ROMANIA: A PHARMA- Macoepidemiologic Approach
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Aim. Pharmacoeplidemiologic investigation regarding the frequency of associate diseases and the management of neuropathic pain.

Neuropathic pain, caused by a primary lesion or dysfunction in the nervous system, is associated with many diseases, including diabetic peripheral neuropathy, post-therapeutic neuralgia, chronic radiculopathy and cancer-related pain. Major pathophysiological mechanisms include peripheral sensitization, sympathetic activation, disinhibition, and central sensitization.

Method. This exploratory study was performed on 123 patients with neuropathic pain, with ages between 29 and 67, from a privat medical center in Romania, using a questionnaire consisting of some questions about intensity of pain, measured with the visual analogue scale (range = 0–10), associated diseases, and the treatment of neuropathic pain.

Results. Analysis and statistical processing of data shows that neuropathic pain is most frequent in male subjects (63.4%). In more than 84% of patients, the pain was reported to be intense to severe (range 6–10 to visual analogue scale). Of the patients, 48 presented with noceptive chronic radiculopathy pain, 39 with diabetic pain, 19 with neoplastic pain and 12 with post-therapeutic neuralgia. Non-opioid analgesics (acetaminophen, ketoprofen, and indometacin) were administered to all patients, antidepressants (amitriptyline) to 4% and anticonvulsants (carbamazepine) to 1% of them. Opioid analgesics (tramadol) were used only in neoplastic patients, due to legal restrictions in use in Romania until the end of 2006.

Conclusions. The study shows that neuropathic pain is often undertreated also due to economical and legal conditions in our country.

Keywords: Neuropathic; Pain; Analgesics; Opioids; Antidepressants; Anticonvulsants

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ASSOCIATION OF BUPRENORPHINE TDS AND PREGABALIN IN THE TREATMENT OF LOW BACK PAIN

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Low back pain is pain localised below the costal margin and above the inferior gluteal folds. The aim of this study was to evaluate the effectiveness of the association of the Pregabalin and Buprenorphine TDS in the long time term treatment of low back pain.

We have enrolled 22 patient affected by low back pain from $33 \pm 28$ months. During the enrolling visit we collected the VAS0. Then all patients have been treated with buprenorphine TDS (35 mg/ml) for a period of one month. At the end of this first period of observation all patients have a second visit during which another VAS1 has been collected and patients have been randomized in 2 groups. Group A has been treated with Buprenorphine TDS + Pregabalin 150 mg, while group B has been treated with Buprenorfina TDS + Placebo. Then there was a second period of observation that lasted one month. Finally there was the last visit and VAS2 has been collected.

At the end of the first month 2 patient have been excluded for little compliance. All the other VAS had a meaningful reduction (VAS0 82.75 ± 15 vs VAS138.25 ± 5 $p < 0.01$). At the end of the second month only group A presented a further reduction of the VAS (group A VAS2 10 ± 5.77 vs group B: VAS 2 32 ± 4.21 $p < 0.01$).

Buprenorphine TDS determines a notable relief from pain. More over the association of low doses of Pregabalin allows a further relief.

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EFFICACY AND TOLERABILITY OF OXICO- DONE FOR TREATING NEUROPATHIC PAIN

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Background. To evaluate the efficacy and tolerability of oxicodone on the treatment of neuropathic pain.

Materials and methods. A retrospective observational study was used to evaluate the efficacy of pain management with oxicodone for patients ($n = 60$) who undergo neuropathic pain and were treated with antiepileptic drugs. At the beginning and after two months pain was assessed on a visual analogical pain scale from 0 (no pain) to 10 (worst pain possible). Another useful information was collected: side effects, dose, epidemiological data and reasons of discontinue the treatment.

Results and discussions. The average reduction in pain from baseline (8) was 3 visual analogue scale points (5.22) at the second month of the study, with 25.4% of patients having a reduction $\geq 50\%$ pain responder. The reduction of pain score was statistically significantly ($p < 0.001$) as early at the second month. The most common side effects were constipation (31.7%), sickness (11.7%), nausea (8.3%), sleepiness (8.3%). Patients (11.7%) discontinued the treatment but we can not affirm with this study that it was due to side effects.
There is a relation between side effects and age ($p < 0.001$) and dose ($p < 0.002$).

**Conclusion(s).** Oxicodone was effective in relieving neuropathic pain combining with antiepileptic drugs.

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**HYOSCINE-N-BUTYL BROMIDE FAILED TO PREVENT TOLERANCE DEVELOPMENT TO THE ANTINOCICEPTIVE EFFECT OF PILOCARPINE**

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It was shown that parasympathomimetic drugs can increase the pain threshold, produce antiallodynic and antihyperalgesic effects in neuropathic pain. However, their peripheral side effects and tolerance development limit their systemic administration as analgesics. It was shown that combined systemic administration of some parasympathomimetic drugs with parasympatholitic drug hyoscine-n-butyl bromide (hypo) is an effective approach to provide analgesia. This study was conducted to see whether the quaternary amine parasympatholitic drug hypo has any effect on tolerance development to antinociceptive effect of tertiary amine muscarinic agonist pilocarpine in mice. In experiments both sexes of Swiss albino mice (20–33 g) were tested with tail immersion test. The animals were received; saline + saline, hypo + saline (2 mg/kg), saline + pilocarpine (4 mg/kg) and hypo + pilocarpine (2 mg/kg + 4 mg/kg) intraperitoneally three times daily for 5 days. Antinociceptive response was measured after the first drug injections at the first day and remeasured at the end of the 5 days drug treatments. According to our results, hypo did not antagonise the antinociceptive effect of pilocarpine but also could not prevent the tolerance development to this effect. It will be beneficial to find new treatments for to prevent the development of tolerance to the analgesic effects parasympathomimetics.

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**FENTANYL BUCCAL TABLET (FBT) IN THE TREATMENT OF BREAKTHROUGH PAIN IN OPIOID-TOLERANT PATIENTS WITH CHRONIC NEUROPATHIC PAIN: RANDOMIZED, PLACEBO-CONTROLLED STUDY**

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**Background.** Patients with chronic neuropathic pain controlled by around-the-clock opioids may experience exacerbations of pain (breakthrough pain; BTP). Fentanyl buccal tablet (FBT) provides rapid-onset analgesia for the management of BTP by enhancing transbuccal absorption of fentanyl. This abstract reports the first pharmacologic study of opioid-tolerant patients with chronic neuropathic pain and BTP.

**Methods.** Following dose titration, patients were randomized to 1 of 3 treatment sequences (9 BTP episodes treated with 6 FBT, 3 placebo). Patients recorded pain intensity (PI) and pain relief (PR) from 5 to 120 min post dose; PI differences (PIDs) and meaningful PR were calculated. Summed PID at 60 min (SPID60) was the primary efficacy measure. Prior BTP medication use was recorded.

**Results.** Primary pain diagnoses were diabetic peripheral neuropathy, post-therapeutic neuralgia, traumatic injury, or complex regional pain syndrome. A total of 80/102 patients treated identified an effective FBT dose (100–800 mcg); 75 were efficacy-evaluable. SPID60 was 9.6 ± 0.75 (mean ± SE) for FBT versus 5.7 ± 0.72 for placebo ($P < 0.0001$). PID and PR favored FBT at 10 min ($P < 0.05$) and each subsequent timepoint ($P < 0.01$). Meaningful PR was achieved for 69% (298/432) of BTP episodes treated with FBT versus 36% (77/213) following placebo ($P < 0.0001$). FBT-treated patients were less likely to require supplemental opioids than patients receiving placebo (RR: 0.28, 95% CI: 0.182, 0.423). AEs reported most frequently were nausea (13%; 13/102), dizziness (13%; 13/102), and somnolence (10%; 10/102). There was no reported respiratory depression.

**Conclusions.** FBT was effective and well tolerated in the treatment of BTP in opioid-tolerant patients with chronic neuropathic pain.

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**LACOSAMIDE DEMONSTRATES NO POTENTIAL FOR QTc-PROLONGATION**

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Lacosamide is an investigational drug being developed for the treatment of epilepsy and diabetic neuropathic pain. Information regarding the potential of lacosamide to prolong the QTc interval is an important aspect of its safety profile.
A thorough QTc-trial has been conducted in 247 healthy male and female subjects according to ICH E14 guideline. The electrocardiographic effects and pharmacokinetic profile after multiple oral administrations of lacosamide (400 or 800 mg/day), moxifloxacin (positive control) or placebo were determined over 6 (lacosamide, placebo), 3 (moxifloxacin) treatment days, respectively. The primary variable was the change in the QTc interval from baseline based on the individual correction method (QTcl). Electrocardiograms were obtained by a Mortara continuous recorder. The relationship between plasma concentrations of lacosamide and changes in ECG parameters were determined by linear correlation analysis.

Lacosamide demonstrated no prolongation of the QTc interval. The difference in the maximum time matched change from Baseline in QTcl between the 400 mg/day lacosamide group and placebo was −4.3 ms (−6.3 ms in the 800 mg/day lacosamide group). In both cases, the upper limit of the 90%CI was below the 10 ms non-inferiority margin (−0.5 and −2.5 for 400 mg/day and 800 mg/day groups, respectively), thereby demonstrating that there was no increase of QTcl caused by lacosamide. No correlation between the plasma concentrations of lacosamide and time-matched changes in QTcl were evident in this trial.

There was no evidence of an association between lacosamide treatment (400 mg/day or 800 mg/day) and QTc prolongation in this trial. According to ICH E14, this trial can be considered as negative QTc trial.

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LOW POTENTIAL FOR DRUG–DRUG-INTERACTION OF LACOSAMIDE
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Lacosamide is a new drug being developed for the treatment of epilepsy and neuropathic pain. Preclinical and clinical data have been established in a series of trials. Information about the pharmacokinetic drug–drug-interaction (DDI) potential of lacosamide is an important part of its safety profile.

Regarding the DDI potential the results of several preclinical studies as well as of 9 Phase 1 trials (n = 184 subjects) and a Phase 2 trial (n = 91 patients) are presented.

In vitro, lacosamide is not substantially metabolized and shows no or low potential to inhibit or to induce CYP isoforms. Since lacosamide has low binding to plasma-proteins (<15%), drug displacement interactions are unlikely.

A phase 1 trial performed in CYP2C19 extensive and poor metabolizers demonstrated the minor relevance of CYP2C19 for the clearance of lacosamide.

Further DDI trials have been performed with carbamazepine (CYP450 inducer) and valproic acid (CYP450 inhibitor) under steady-state conditions. In these trials, lacosamide had no influence on rate or extent of absorption of carbamazepine or valproic acid and vice versa. DDI trials with digoxin and metformin showed no relevant influence of these drugs on lacosamide and vice versa. Lacosamide did not modify the pharmacokinetics and pharmacodynamics of the oral contraceptive Microgynon®. Coadministration of food did not alter the absorption of lacosamide.

In epileptic patients, lacosamide showed no influence on plasma levels of common antiepileptic drugs.

No DDI have been observed in these studies. Therefore, the data suggest that lacosamide has low potential for DDI in clinical use.

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APPLICATION OF LIDOCAINE PATCHES 5%: HOW MANY PATCHES NEED TO BE APPLIED ON A DAILY BASE IN ROUTINE CLINICAL PRACTICE?
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Lidocaine patches 5% became recently available for the treatment of post-herpetic neuralgia. In addition, a growing body of evidence has become available concerning the efficacy of this topical administration of lidocaine for the treatment of other neuropathic pain syndromes and even non-neuropathic pain syndromes. Study protocols have always prescribed the daily use of 2–4 patches in order to cover the entire painful area. Daily use of such a number of patches could however have important financial implications, badly influencing patient’s compliance to this therapy.
Lidocaine patches have been used in our multidisciplinary pain center since 2002. During this period a total number of 16,403 patches was prescribed in a heterogeneous group of pain patients. Based on the hospital pharmacy prescription list we performed a retrospective analysis in order to calculate the amount of patches used on a daily base in our population. We identified 183 patients that had at least two prescriptions filled between November 2002 and December 2006, amounting to a total of 10,017 patches. Based on how many patches the patient received and the number of days between two prescriptions we obtained a median of 0.4348 patch per day (interquartile range between 0.2479 and 0.9112). This means that on average 1 entire patch is sufficient for 2.3 days of therapy. These results show that in clinical routine there is no need for daily application of one or more patches. Cutting the patch in smaller pieces significantly reduces the cost while still providing sufficient levels of analgesia.

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LASER EVOKED POTENTIALS IN CARPAL TUNNEL SYNDROME

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Background and aims. The neurophysiological aspect of the carpal tunnel syndrome (CTS) has been widely studied, in regard to motor and sensory nerve conduction of A-beta fibers. The aim of the study was to evaluate the median and ulnar a-delta fibers function at the hand level in patients with clinical symptoms of CTS, employing CO2 laser evoked potentials (LEPs) method.

Methods. Forty outpatients referring symptoms of CTS were included in the study: exclusion criteria were diabetes, renal and hepatic failure, peripheral and central nervous system diseases, psychotropic drugs intake. They were 25 females and 15 males, 23–55 aging. Twenty healthy sex matched subjects were selected as controls.

The median and ulnar nerves motor and sensory conduction were examined. The LEPs were obtained by five scalp electrodes, delivering laser stimulus at 7.5 W intensity and 25 ms duration: a 0–100 VAS scale was employed to rate the stimuli. The peri-ungueal skin of the first, second, third and fifth fingers was stimulated in random order. The latency and amplitude of N1 wave and N2–P2 complex were evaluated.

Results. Thirty seven patients exhibited unilateral and 25 patients bilateral median nerve LEPs abnormalities, consisting of N1 and N2 and P2 latency increase; in the 50% of patients, an amplitude reduction of LEPs was detectable. The LEPs showed 97% sensitivity in patients referring symptoms of CTS.

Conclusions. An early involvement of median nerve a-delta fibers may be supposed in CTS.

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PERSISTENT IDIOPATHIC FACIAL PAIN (PIFP): THE ROLE OF NEUROPHYSIOLOGICAL (NFS) EVALUATION

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Persistent idiopathic facial pain (PIFP) is considered in the chapter of facial pain (FP) and is defined by the exclusion of a demonstrable organic cause. Therefore, a complete physical and instrumental examination, in primis imaging and NFS evaluations are required.

Aim of this study was to verify the efficacy of different NFS methods in disclosing abnormalities in a group of patients with suspected PIFP, homogeneous for complaining similar symptoms in orofacial area.

We studied 15 subjects (pts) (9 female, 6 male, mean age 56 years) by: blink reflex, Masseter inhibitory reflex (MIR) evoked by electrical and laser stimulation and trigeminal laser evoked potentials (LEPs).

The pts underwent clinical examination, with drawing of the facial pain area, Quantitative sensory testing (QST) by using MEDOC TSA II and Von Frey filaments (limits method) and imaging examination (cerebral MRI, Rx and/or TC of facial bone). Only 3 pts showed NFS abnormalities: absence of LEPs (1 pt), asymmetry of electrical MIR threshold (1 pt) and MIR late silent period absence (1 pt). In 2/3 of pts the MRI was abnormal, in 1/3 pt the pain is derived from odontoiatric procedures.

In 12 pts NFS evaluation was normal.
Conclusion. The NFS evaluation disclosed a neurological involvement related to FP in a small portion of the pts; NFS data correlated with imaging results and in 2/3 patients only large-fiber assessing methods showed abnormalities. These results indicate the usefulness of performing a complete panel of NFS examinations in order to improve the diagnosis of PIFP.

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TEST/RETEST- AND INTEROBSERVER-RELIABILITY IN QUANTITATIVE SENSORY TESTING ACCORDING TO THE PROTOCOL OF THE GERMAN NETWORK ON NEUROPATHIC PAIN (DFNS)
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Introduction. Quantitative sensory testing (QST) according to the protocol of the German Network on Neuropathic Pain (DFNS) (Rolke, 2006) is a valuable instrument to assess positive and negative sensory signs and points to possible mechanisms underlying neuropathic pain. We evaluated the test–retest- and the interobserver-reliability of QST in patients with sensory disturbances of different neurologic aetiology.

Methods. Sensory profiles of twelve patients were assessed using QST according to the above protocol. It comprises 13 parameters including thermal and mechanical tests. Patients with clinical indication for QST were included consecutively. QST was performed in the clinically most affected area (test area, TA) and a control area (CA), in the morning and in the afternoon on two consecutive days by two experienced investigators (four testings per patient). Correlation analyses were assessed using Pearson’s correlation coefficient or Spearman’s rank correlation coefficient.

Results. The mean correlation coefficient over all QST- parameters was very high for both test–retest- (r = 0.84) and interobserver-reliability (r = 0.86) with only the wind-up ratio showing weaker correlation (r ~ 0.5). Correlation was significantly better in the symptomatic area compared to the control side (TA: r = 0.89 vs. CA: r = 0.81; p < 0.05). Interobserver and test–retest reliability were not different.

Conclusion. QST is a diagnostic instrument with good test–retest- and interobserver-reliability which points to a good reproducibility of QST within days and with different investigators. The higher correlation over the symptomatic test area is most likely due to systematic variance.

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Reference

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DIFFERENTIATION OF PAIN PATTERNS IN LOW BACK PAIN OF PREGNANCY WITH QUANTITATIVE SENSORY TESTING
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Background. Low back pain (LBP) of pregnancy is a common problem affecting up to 76.6% of women (To, 2003) and causes disability and cost (Mogren, 2006). Etiology is unclear and therapy is not sufficiently effective (Stuge, 2003).

Methods. 102 pregnant women (3rd trimester, aged 31.6 ± 1.0) were split into three groups based on short pain provocation tests for musculoskeletal pain (34 pain free controls, 34 provokable pain [PP], 34 non-provokable pain [NP]). Quantitative sensory testing (QST) for heat, cold (peltier thermode, TSA-II), pressure (hand-held algometer) and mechanical pain thresholds (pin-pricks) was carried out by a blinded investigator in three dermatomes (T1, forearm; T11, back and L1, pelvis).

Results. PP patients were hyperalgesic vs controls to pressure pain in the T11 (2.73/3.68 kg, p < 0.001) and L1 ventral dermatomes (2.89/3.50 kg, p = 0.033) and to heat pain in the dorsal T11 dermatome (37.66/ 40.3 °C, p = 0.005). They were hyperalgesic vs NP patients to pressure pain in the T11 dermatome (2.73/ 3.39 kg, p = 0.011). No significant difference was found between controls and NP patients in these parameters. No differences in any group was found for cold pain or mechanical pain to pin prick.

Conclusion. In a subgroup of pregnant low back pain patients, significant hyperalgesia for pressure and heat pain could be demonstrated, representing a sensitisation of nociceptors. No sensitisation is evident for mechanical or cold pain and for NP patients vs controls.

References
COMPARISON OF QUANTITATIVE SENSORY TESTING AND LASER-EVOKED BRAIN POTENTIALS IN SYRINGOMYELIA PATIENTS

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Background and aims. Thermal quantitative sensory testing (QST) and nociceptive laser-evoked brain potentials (LEPs) are both used for the assessment of lesions of thermo-nociceptive sensory pathways. A lesion of these pathways at peripheral, spinal or supraspinal level, may result in thermal sensory loss at QST and attenuation and/or retardation or even absence of LEPs. Here, we systematically compared results of LEPs and QST in syringomyelia patients. Syringomyelia represents a unique “pathological model” because the intra-spinal cavity predominantly, or even selectively, affects the spinothalamic tract.

Methods. Patients with a cervical or cervicodorsal syringomyelia, with or without neuropathic pain, were included. QST and LEPs were performed on both hands and shoulders, including at least one region of neuropathic pain in patients with pain. QST involved measurements of the detection and pain thresholds and analysis of the responses to suprathreshold thermal (heat–cold) and mechanical stimuli. In LEPs, the latency and amplitude of the N2–P2 vertex potential and the detection rate of laser stimuli were recorded.

Results. There was a robust correlation between the magnitude of sensory deficits at QST (increased warm–cold detection and heat pain thresholds) and LEP alterations (decreased N2–P2 amplitude and detection rate), both in painful and painless patients.

Conclusions. These data confirm that QST and LEPs provide reliable information regarding the functionality of thermosensory and nociceptive spinothalamic pathways. These complementary methodologies may be used in clinical settings to identify and quantify lesions of spinothalamic pathways which play a crucial role in the development of central neuropathic pain.
particularly in the early diagnosis and management of neuropathic pain.

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204 PINPRICK-EVOKED POTENTIALS (PEPS): A NOVEL TOOL TO ASSESS CENTRAL SENSITIZATION IN HUMANS

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There is no electrophysiological correlate of hyperalgesia to mechanical stimuli in the literature. Here we describe a novel technique for the recording of electroencephalographic (EEG) responses to mechanical stimulation using a flat-tip probe (diameter 0.2 mm, force 128 mN). Such stimulation activates A-delta nociceptors and is widely used to assess the presence of secondary hyperalgesia, a psychophysical correlate of central sensitisation, both in normal subjects and patients with neuropathic pain. An optical detector placed inside the stimulator enabled time-locking the EEG responses (pinprick-evoked potentials, PEPs). PEPs were recorded in 10 subjects during stimulation of the right and left hand dorsum before and after intradermal injection of capsaicin into the right hand. All subjects developed a robust secondary hyperalgesia following capsaicin injection. PEPs in response to stimulation of normal skin before capsaicin injection were characterised by large biphasic negative-positive (NP) complex, maximal at the vertex, with the N and P waves having approximate latencies of 80 ms and 200 ms, and amplitudes of 5 µV and 12 µV, respectively. Stimulation of the hyperalgesic skin resulted in a significant N amplitude increase (+63.4%, p = 0.02, one-sample t-test). In contrast, the increase of the P wave was not significant (+15.3%, p = 0.10). Between-session differences related to attention/habituation were estimated and accounted for in each subject, using the PEP results following the stimulation of the left (i.e. non injected) hand. Although, skin compliance may limit synchronicity of the somatosensory input and cause systematic underestimation of the response latency, our results suggest that PEPs are a useful neural correlate of experimentally-induced secondary mechanical hyperalgesia.

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205 NEUROPATHIC PAIN IN THE POPULATION OF OUTPATIENT ELDERLY

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Although neuropathic pain is common with the elderly, the epidemiology of neuropathic pain has not been widely studied. The population of outpatient elderly was characterized by advanced age, polymorbidity, functional disability, different stages of dementia, solitary life in their homes, and polytherapy.

The aim of the study was to show the prevalence of chronic neuropathic pain and pain characteristics in the frail aged treated in alternative care settings.

Study was designed as observational. Data was obtained by interviewing pts at their homes during the one year period (01.08.2002–31.07.2003 y).

In the sample of N = 179 (134f/45m) elderly patients (mean 78.6 ± 8.5 years old) N = 221 chronic pain syndromes were obtained. Pts had diagnoses of (ICD 10): musculoskeletal (48.8%), nervous system diseases (40.9%) and 28.1% neoplasm. According IASP classification of chronic pain, neuropathic pain was diagnosed in 29.9% (66/221) pain syndromes. Man (44.2%) suffered neuropathic pain much more than woman (25.4%), p < 0.01. Man described the pain pattern like as continuous fluctuated (59.6%) or irregularly recurring (17.3%). Pain localization was mainly in lower limbs (53%), head (16.7%) or more the three major sites (15.2%). Neuropathic pain was in 54.4% pts metabolically caused or due to trauma (10.9%), but in 25% pts of unknown etiology. Obtained diagnoses were Central Pain (43.9%), 25.8% Peripheral Neuropathy, 7.8% Headache Not Other Specified and Stump Pain (6.1%).

Conclusion. The problem of neuropathic pain in a growing population of elderly is a big and needs attention from medical professionals, as well as specialized knowledge and skills in assessing and treating elderly person.

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206 ANXIETY, DEPRESSION AND ALCOHOL ABUSE IN PATIENTS OF GENERAL PRACTITIONERS AND GP-BASED PAIN RESOURCE

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Primary health care of City of Vantaa has organized a general practitioner-based pain resource for chronic pain patients. We studied whether chronic pain patients referred to the GP-based pain consultation had different levels in symptoms of anxiety, depression or in alcohol consumption compared to ordinary GP patients or to those GP patients who were referred to psychiatric consultation. The comparison included 152 patients referred to the pain resource, 123 “ordinary” patients, and 116 patients referred to a psychiatric consultation. All patients performed self-report questionnaires: Beck’s inventory for depression (BDI) and anxiety (BAI), and World Health Organizations Audit-test for alcohol abuse. ANOVA followed by Dunn’s test was applied for statistical testing.

BDI scores were slightly higher in patients of GP-based pain resource (median = 11.5) than in “ordinary” patients (median = 6) but clearly lower than in patient who were referred to psychiatric consultation (median = 20.5). The BAI scores of patients who reached GP-based pain resource (median = 8) were similar to the scores of those who were considered “ordinary” patients (median = 7) but lower than the scores of patients who were referred to a psychiatric consultation (median = 20). No differences between the three groups appeared in Audit scores. In chronic pain patients a slight increase appeared in depressive symptoms but not in anxiety symptoms or amount of alcohol abuse in comparison with ordinary patients of GPs. The anxiety and depression symptoms of chronic pain patients were markedly lower than among the patients who were referred to psychiatrist consultation.

Reference


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HOW RESPONSE INHIBITION MODULATES NOCICEPTIVE LASER EVOKED BRAIN POTENTIALS

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Background and aims. Laser evoked brain potentials (LEPs) are increasingly used to explore the thermo-nociceptive system. Infrared CO2 lasers can produce brief and intense radiant-heat stimuli which activate selectively and synchronously the thinly myelinated Aδ- and unmyelinated C-fibers located in the superficial layers of the skin. The aim of this study was to determine how processes related to response-inhibition may affect the brain responses elicited by a nociceptive stimulus. In conventional experimental or clinical settings, recording EPs elicited by a noxious stimulus requires subjects to stand still and hold back motor responses which are urged by the salience and nociceptive nature of the evoking stimulus. Therefore, one should consider the possibility that response inhibition contributes to the recorded brain responses. To explore brain processes underlying response-inhibition, the Go/Nogo paradigm has commonly been used within other sensory modalities.
Methods. Healthy subjects performed a Go/Nogo task with a warning/imperative stimulus paradigm. Nogo-related LEPs were compared to Go-related LEPs. Two control-conditions were included: a simple reaction-time task (SRT), and a verbal stimulus-intensity rating task involving no motor preparation or execution (NM).

Results. Nogo-LEPs displayed a reduced vertex P2 and enhanced frontal P3 component. The effect sizes (Cohen’s d) on the amplitudes in the Nogo- vs Go-, SRT- and NM-conditions were respectively -1.4, -0.7 and -0.8 for P2, and 0.5, 2.0 and 1.4 for P3.

Conclusion. The observed response-inhibition effects appeared specific of the Nogo-task and unrelated to the waveforms observed in conventional LEP recordings.

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209 SENSITIVITY AND CONCURRENT VALIDITY OF THE NEUROPATHIC PAIN IMPACT ON QUALITY OF LIFE SCALE
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Background and aims. Quality of Life (QoL) measures are used to assess treatment outcomes from the patient’s perspective. Condition specific measures are advocated to counteract the reduced sensitivity of generic tools which lack disease and/or pain specificity. This paper reports on the concurrent validity and sensitivity of the Neuropathic Pain Impact on QoL (the NePIQoL). The content of the NePIQoL was derived from patient focus groups, its face and content validity have been demonstrated and its temporal stability established via a test–retest survey with correlations (Pearson’s r) between Time 1 and Time 2 subscales all above .82.

Method. The NePIQoL was administered pre and post treatment to three groups: patients undergoing surgery for trigeminal neuralgia, patients having a spinal cord stimulator fitted for chronic neuropathic pain, and patients with neuropathic pain attending a specialist outpatient centre. In addition, all completed the SF36, Hospital Anxiety and Depression Scale and the Brief Pain Inventory.

Results. Patients (N = 58) mean age 53.88 (SD 14.1) years, mean duration of pain was 10.46 (11.8) years.

Internal consistency (Cronbach’s Alpha) of NePIQoL subscales pre and post treatment ranged from .66 to .87. Correlations (Pearson’s r) between NePIQoL and the other scales demonstrated logical relationships. Significant differences were found on the HADS-A, BPI total score, SF36 social functioning and NePIQoL social activity scales with the NePIQoL demonstrating the greatest effect size and SRM.

Conclusions. These data suggest NePIQoL has the high internal consistency, temporal stability and responsiveness essential to reliable outcome assessment.

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210 MEASURING VASOMOTOR DISTURBANCES IN PATIENTS WITH A COLD INTOLERANCE AFTER NERVE INJURY
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Background and aims. Cold intolerance can be a major disabling consequence of hand injuries. Cold exposure of body parts trigger the so-called Cold Induced Vaso Dilatation (CIVD). The purpose of this study was to develop a measurement tool to analyse the CIVD response in and between the hands of healthy persons and the hands of patients with cold intolerance after nerve injury.

Methods. An aluminium plate was used through which water flows with a low temperature (5°C ± 0.5°C). The palmar side of both hands were cooled using this plate, to provoke a CIVD reaction. The CIVD reaction was recorded on the dorsal side of both hands using a thermographic camera (SC2000, Flir system).

Results. In a healthy person, in the digiti 2 of both hands, only small differences were observed in the CIVD reaction (Fig. 1A). However in a patient with a median nerve lesion, the digiti 2 in the involved extremity did not show any CIVD reaction (Fig. 1B), whereas digiti 2 in the non-injured hand showed a normal pattern in CIVD reaction.

Conclusions. We built an experimental set-up in which we can evoke and record a reproducible CIVD reaction. The preliminary results showed a diminished CIVD reaction in patients with nerve damage. This study is now carried out in larger groups.

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COGNITIVE-BEHAVIOURAL STRATEGIES DURING THE FIRST YEAR OF SPINAL CORD INJURY NEUROPATHIC PAIN

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Spinal cord injury neuropathic pain (SCI-NP) significantly affects Quality of Life (QoL) which is reflected by the use of different pain-related cognitive-behavioural strategies (Turner et al. Pain, 2002; 98(1–2): 127–134). The development of these strategies during the first 12 months of SCI has never been documented. Following approval by the Toledo Hospital Ethical Committee and patient informed consent, a total of 30 subjects with SCI-NP at 2 months were recruited. The identification of pain-related cognitive-behavioural strategies was performed using the Coping Strategies Questionnaire Revised version (CSQ-R, Riley and Robinson. Clin. J. Pain, 1997; 13(2): 156–162) and the Multidimensional Pain Inventory (MPI-SCI, Widerstrom-Noga et al. Arch. Phys. Med. Rehabil., 2006; 87(4): 516–523).

An increase in several cognitive-behavioural strategies such as coping self statements, support, life control, solicitous responses, interference, pain severity and affective distress were present during the first 12 months of SCI-NP. No significant increase in Catastrophizing was observed. At 6 months after SCI, 7-day spontaneous pain intensity correlated with pain severity and interference, while 7-day unpleasantness correlated with pain severity, coping and praying. Finally significant correlations were maintained from 2 to 6 months between pain severity and coping, support, solicitous responses and distracting responses, and between support, solicitous and distracting responses. These results have important implications for designing diagnostic protocols and assessing treatment efficacy specific for SCI-NP patients.
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MECHANISM-BASED CLASSIFICATION OF NEUROPATHIC FACIAL PAIN – USE OF CLUSTER ANALYSIS WITH QUANTITATIVE SENSORY TESTING DATA

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The differential diagnosis of idiopathic trigeminal neuralgia (ITN), trigeminal neuropathy (TNP) and idiopathic facial pain (IFP), formerly atypical facial pain, is often difficult as symptoms may overlap, especially with long standing pain. Therefore, it promises to be useful to find a new mechanism-based classification for these facial pain states (e.g. Burchiel, 2003). Forty-seven patients with ITN (26 male, mean age 59.9 years), 16 patients with TNP (2 male, mean age 57 years) and 15 patients with IFP (4 male, mean age 57.5 years) were investigated with a standardized quantitative sensory testing (QST) protocol (Rolke et al., 2006) on the affected facial sites. No patient with allodynia (pain by light stroke with brush or q-tip) was included. Six other patients (5 ITN, 1 TNP) were excluded because of extreme values in one or more of the QST variables. For comparative purposes, twenty-four healthy controls (9 male, mean age 59.3 years) were investigated with QST at all six trigeminal nerve branches in the face. QST values of patients were normalized by the values of the healthy controls. Hierarchical as well as k-means cluster analyses were performed. A two-cluster solution was the most robust description of the data where the diagnostic groups were nearly evenly distributed across the clusters. Clusters differed significantly in thermal perception and pain thresholds as well as in mechanical pain thresholds. Cluster 1 showed high perception thresholds (deafferentation?), whereas cluster 2 showed low pain thresholds (sensitization?).

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CLASSIFICATION OF LOW BACK RELATED LEG PAIN: A STUDY PROTOCOL
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This paper describes a study protocol currently in progress. The objective of this study is to explore the utility of a physical examination protocol developed to classify low back related leg pain. Low back related leg pain arising from neural structures can be classified as neuropathic pain, from musculoskeletal structures as nociceptive pain. It is proposed that neuropathic leg pain can be further divided into three subgroups according to the predominating pathomechanisms involved. The first subgroup involves denervation with axonal damage showing predominantly negative sensory symptoms and possibly motor loss, the second subgroup features central sensitization with mainly positive symptoms such as hyperalgesia and the third subgroup involves mechanosensitization of nerve tissue. Accordingly, four groups of patients with leg pain associated with structures in the lower back can be identified:

- Neuropathic denervation.
- Neuropathic central sensitization.
- Neuropathic peripheral sensitization.
- Nociceptive musculoskeletal.

An iterative process of three component validation studies will be undertaken. The studies proposed will include firstly an inter-rater reliability study and secondly an investigation of the discriminative capacity of the physical examination protocol compared with thermal and mechanical quantitative sensory testing (QST).

The third component consists of a treatment trial to investigate if a positive treatment response to neural mobilisation manual therapy techniques correlates with the diagnostic group. Main outcome measures are global perceived change, pain intensity measured on a 11 point numerical rating scale, the Roland Morris Disability score and the SF-36 score.

If valid, the classification system will facilitate diagnosis and optimal treatment.

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NEUROPATHIC COMPONENTS OF ACUTE WHIPLASH PAIN
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Background and aims. The early presence of cold and mechanical hyperalgesia, sympathetic nervous system dysfunction and moderate pain and disability are predictive of poor outcome following whiplash. As this condition is often managed in primary care it is important that these features are easily detected. The aims were: (1) determine neuropathic pain components of acute whiplash, (2) investigate the relationship of S-LANSS scores to sensory features of acute whiplash, and (3) determine relationships of S-LANSS scores and pain and disability levels.

Methods. Participants (85) with acute (<3 weeks) whiplash (WAD II) participated. The S-LANSS and NDI were completed. Measures included: cold and pressure pain thresholds at both local (cervical) and remote sites; sympathetic vasoconstrictor responses (SVR); brachial plexus provocation test (BPPT). Participants were classified into 2 groups (S-LANSS: ≥12 neuropathic; <12 non-neuropathic). Group differences were analyzed using ANOVA. Stepwise regression analyses were performed to predict S-LANSS and NDI scores with Pearson's correlation coefficient.

Results. 30% of participants demonstrated a neuropathic component (S-LANSS ≥12). This group showed higher pain and disability (NDI), cold hyperalgesia and heightened responses to the BPPT (all p < 0.015). Item 4 (pain in bursts predicted cold hyperalgesia) and items 4, 5 (burning pain) and 7 (pain with pressure) predicted NDI scores (r² = 32%, p = 0.04).

Conclusions. A predominant neuropathic pain component is prevalent in acute whiplash and is related to a more complex presentation of higher pain and disability and hypersensitivity. The S-LANSS may be a useful tool in the early assessment of whiplash, particularly in primary care practice.

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IMPACT OF SPINAL CORD INJURY PHYSICAL FACTORS ON NEUROPATHIC PAIN AND QUALITY OF LIFE DURING THE FIRST YEAR OF LESION
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An important determining role for spinal cord injury (SCI) physical factors, such as dermatomal level and completeness of central lesion, on the development of neuropathic pain (NP) has been identified (Siddall...
et al., Pain 1999; 81(1–2):187–197). Here we examine the impact of thoracic versus cervical SCI on at and below spontaneous pain, psychophysical sensory responses to tonic thermal testing and pain-related cognitive-behavioural strategies up to 12 months after SCI. Following informed consent and approval by the local ethical committee, a total of 30 patients with SCI-NP were recruited. Neurological SCI examination was performed according to the standard SCI “ASIA” scale. A 7-day spontaneous pain intensity and dermatomal analysis was recorded at 2, 3, 4, 6 and 12 months post-SCI, while the sensory response to the application of a 10–30 s thermal stimuli at 48°C at the level of the injury was assessed at 4 months. The multidimensional pain inventory -spinal cord injury version (MPI-SCI) and coping strategies questionnaire revised version (CSQ-R) were used to identify cognitive-behavioural strategies against pain.

Patients with thoracic SCI experienced a greater increase in at-level spontaneous pain and involved dermatomes and a rapid and higher pain sensibility to tonic heat stimuli. In general patients with thoracic SCI-NP perceived higher levels of Interference, Life Control, Distraction, Solicitous Responses and Support. These preliminary results suggest that specific physical factors should be taken into account in the early diagnosis and treatment of SCI-NP.

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DIFFERENTIAL CODING OF COLD ALLODYNA
A FMRI STUDY
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Background and aims. The pathophysiology of cold allodynia is unclear. Two mechanisms have been postulated: sensitization of peripheral nociceptive structures and disinhibition of central processing of C-fiber nociceptive input. Aim of this study was to explore the “peripheral sensitization” and “central disinhibition” mechanism of cold allodynia.

Methods. In eight healthy male volunteers, topical menthol (peripheral sensitization of C-fibers) or conduction block of A-fiber input (central disinhibition due to mechanical conduction block of myelinated A-fibers) was applied to evoke cold allodynia in the innervation territory of the right superficial radial nerve. fMRI was performed during menthol-induced and block-induced cold allodynia. Using a block-design, a thermode applied randomised tonic cold stimuli below/above the individual cold pain threshold. Bold signal changes were contrasted for both types of cold allodynia using SPM2.

Results. Both interventions induced stable cold allodynia (decrease of cold pain threshold of 13.4 ± 3.8 °C/10.6 ± 4.4 °C (p < 0.001)). A direct comparison of both types of cold allodynia showed stronger BOLD signal increases in left medial thalamus, anterior cingulate cortex and medial prefrontal cortex during block-induced allodynia. By contrast, menthol-induced cold allodynia activated stronger the lateral left thalamus relative to block-induced allodynia.

Conclusions. Cold allodynia is processed in different cerebral areas depending on the underlying mechanism. Peripheral sensitization favoured a preferential activation of the thermoreceptive spinothalamic pathway, whereas A-fiber block attenuated the thermoreceptive input through the lateral pathway and increased activity within the medial system. This shows that A-fiber block disinhibits activity in the ascending polymodal nociceptive channel.

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OPERCULO-INSULAR AND MID-CINGULATE GYRUS FUNCTIONAL COUPLING AFTER PAINFUL LASER STIMULATION: AN INTRA-CEREBRAL EEG COHERENCE STUDY
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The operculo-insular and cingulate cortices represent critical areas for the processing of nociceptive inputs. Numerous studies have shown that the midcingulate cortex (MCC) is activated by pain almost as consistently as the operculo-insular area. We used EEG coherence analysis to determine functional coupling between MCC and operculo-insular cortices after painful laser stimulation. Laser evoked potentials were recorded in these areas with intra-cerebral electrodes implanted in
10 epileptic patients. Spectral coherence in the δ–0 (2–7 Hz), α (8–14 Hz), β (15–33 Hz) and γ (34–45 Hz) bands was calculated for three electrode pairs: Opercular-insular (6 patients), opercular-MCC (5 patients) and insular-MCC (3 patients), and compared with the coherence levels at rest, just before the painful stimulus. The highest coherence levels were observed between the operculum and the insula for all rhythms, but almost no coherence changes appeared between these regions during pain processing relative to baseline. Decreased coherence levels following the painful stimulus were observed between both operculum/insula and the MCC in the low frequency bands (δ–0), while a coherence increase appeared in higher frequency bands (α–γ) especially between insula and MCC. Increase reached significance in the alpha band. These results indicate an enhancement of functional coupling between operculo-insular cortex and MCC after painful stimulation for relatively high frequencies, and a decrease of such coupling for lower frequencies. Enhanced coupling at selective frequency bands concomitant with decreased background coherence at other frequencies may reflect a selective ‘tuning’ between these areas during the early (<500 ms) processing of phasic thermal pain.

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EMOTIONAL MODULATION OF PAIN: IS IT THE SENSATION OR WHAT WE RECALL?
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Emotions modulate pain perception, although the mechanisms underlying this phenomenon remain unclear. In this study we show that intensity reports significantly increased when painful stimuli were concomitant to images showing human pain, while pictures with identical emotional values but without somatic content failed to modulate pain. Early somatosensory responses (<200 ms) remained unmodified by emotions. Conversely, late responses showed a significant enhancement associated with increased pain ratings, localized to the right prefrontal, right temporo-occipital junction and right temporal pole. Contrary to selective attention, which enhances pain ratings by increasing sensory gain, emotions triggered by seeing other peoples’ pain did not alter processing in SI–SII, but may have biased the transfer to, and the representation of pain in short-term memory buffers (prefrontal), as well as the affective assignment to this representation (temporal pole). Memory encoding and recall, rather than sensory processing, appear to be modulated by empathy with other’s physical suffering.

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Background and aims. Previous positron emission tomography (PET) studies have shown an activation of opioidergic neurotransmission during sustained experimental and clinical pain, including neuropathic pain. We studied whether basal \( \mu \)-opioid receptor binding potential (MOR BP) as assessed with \( [11C] \)carfentanil and PET was associated with individual pain sensitivity or pain modulation.

Methods. Twelve healthy male subjects attended a PET scan with \([11C] \)carfentanil to assess MOR BP. Psychophysical pain tests included tactile sensitivity, heat pain sensitivity, cold pain sensitivity, and pain modulation capacity by concomitant cold pain or placebo. In addition, individual catechol-O-methyltransferase (COMT) haplotypes were determined. Voxel-based analysis was applied to the PET data to correlate MOR BP with the psychophysical pain measurements and COMT haplotype.

Results. Cold pain tolerance was inversely correlated with MOR BP in the anterior cingulate cortex. Cold pain threshold did not correlate with MOR BP. Placebo-induced increase in heat pain threshold correlated directly with MOR BP in fronto-parietal cortical regions. COMT haplotype did not correlate with MOR BP.

Conclusions. Low MOR BP suggesting a high tonic level of opioidergic activity was associated with high cold pain tolerance and poor placebo response. The results of this study support the involvement of forebrain \( \mu \)-opioid receptors in pain modulation as indicated by previous studies.

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Background. The increased brain activation observed in previous neuroimaging studies of experimental hyperalgesia reflects not only the process of central sensitization, but also the increase in pain perception. This study aims to isolate brain activity specifically related to central sensitization, by matching perceived pain intensity between normal and central sensitization states.

Methods. A cohort of right handed, mixed gender healthy volunteers known to develop demonstrable hyperalgesia in response to an intra-epidermal injection of capsaicin was recruited. Punctate mechanical stimulation of varying force (64 mN, 128 mN, 256 mN and 512 mN) was applied to hyperalgesic and control areas (same site, untreated skin) in separate sessions (balanced order), and brain responses were recorded using functional magnetic resonance imaging. The visual analogue scale (VAS) was used to rate the intensity of sharp or pricking sensations.

Results. In agreement with previous studies, the comparison between activation maps following punctate stimulation of control and hyperalgesic areas with identical force, revealed significant increases in activation of the bilateral thalamus, basal ganglia, insula, secondary somatosensory cortex, pre-frontal cortices as well as the anterior cingulate cortex during hyperalgesia. However, preliminary analysis of brain activity to punctate stimulation at forces resulting in matched VAS ratings in control and hyperalgesic areas revealed additional significant activation in the brainstem.

Conclusion. To date, these results support previous findings highlighting the brainstem’s critical role in the generation and maintenance of hyperalgesia. Ongoing analyses will dissect further the neural correlates specific to the central sensitization state.
Recently, we found that serotonin 5-HT1A receptors in multiple brain areas influence cold pressor pain. Here we test the hypothesis that this serotonergic influence on pain is rather due to modulation of non-sensory factors, such as response bias, than to a specific effect on the sensory signal. Furthermore, we tested whether the influence of 5-HT1A receptors varies with the modality of cutaneous stimulation, whether 5-HT1A receptors also influence working memory for pain, and whether promoter region polymorphism of 5-HT transporter (5-HTTLPR) has a role in the study of 5-HT1A receptors. Psychophysical performance and 5-HTTLPR were assessed in healthy subjects who had participated in a positron emission tomography study using [carbonyl-11C]WAY-100635 ligand for assessment of Aδ-fiber nociceptive input to elicit reproducible event-related brain potentials (ERPs). The results indicate that the subject’s response criterion (but not discriminative capacity) for heat pain (determined by an analysis based on the signal detection theory) was associated with 5-HT1A BP particularly in the raphe and the posterior cingulum, whereas the subject’s discriminative capacity (but not criterion) for touch was associated with 5-HT1A BP in the cingulum and medial prefrontal cortex. Subjective responses in the working memory task were associated with 5-HT1A BP in the hippocampus. 5-HT1A BP varied with polymorphism of 5-HTT in the posterior cingulum. The results indicate that with respect to touch, 5-HT1A receptors predominantly influence discriminative capacity and with respect to pain, the subject’s response criterion. Moreover, 5-HT1A receptors influence performance in working memory task for pain and 5-HT1A BP varies with polymorphism of 5-HTTLPR.

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contralaterally in the cingulate gyrus, thalamus and primary sensory cortex. The average pain rating (VAS, 0–10) for CHEPS stimulation was 4/10, both inside and outside the scanner.

**Conclusions.** Combined EPs and fMRI data could thus be used to identify brain activity patterns or “signatures” indicative of pain processing in healthy subjects and chronic pain patients, particularly in neuropathic pain. As CHEPS is safe and convenient for clinical use, this technique may advance proof-of-concept clinical trials of analgesics.

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**Poster Session 1: Postherpetic Neuralgia, CRPS**

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**ACUPUNCTURE AS A ADDITIONAL THERAPY IN POSTHERPETIC NEURALGIA – PRELIMINARY STUDY**

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Post-therapeutical pain is one of the strongest neuralgia. The aim of the study was to investigate the effectiveness of acupuncture as additional treatment of neuralgia.

The criterions of including to the study were: herpes zoster infection during last three months; more than 50 years of age; no addiction to alcohol, drugs or medicaments; lack of previous treatment with Gabapentine and Tramadol; pain intensity >6 in VAS scale; agreement for participation in the study.

**Methods.** Forty patients (24 women and 16 men, 58–70 years of age), were treated in our clinic because of post-therapeutic neuralgia. All patients received standard/basic treatment: 100 mg of Tramadol twice a day and 600 mg of Gabapentine thrice a day. Twenty patients were treated only pharmalogically (Group I), while the rest (Group II) was attended with acupuncture (10 sessions, two times a week). Pain intensity was measured in VAS scale in regular one week intervals.

**Results.** Four patients (two from Group I and two from Group II) were excluded from further study because of nausea and vomiting. Rest of the patients coped well with proposed treatment and showed decrease of pain intensity similarly in both groups. Differences between studied groups were not significant.

**Discussion.** Diverse informations about effectiveness of acupuncture are found in the literature, yet results are strictly connected with diagnosis.

**Conclusion.** Our study does not show that adding acupuncture would significantly decrease pain intensity.

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**ARE THERE ANY SPECIFIC PSYCHOPATHOLOGICAL FEATURES IN PATIENTS WITH REFLEX SYMPATHETIC DYSTROPHY?**

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Patients with reflex sympathetic dystrophy (RSD) are commonly considered as presenting a specific psychical symptomatology. Are psychological features related to original personality itself? to RSD itself? to none of the two? A review of the adult and paediatric literature all over the nineties shows few evidence for such an assessment and give no conclusive attribution to psychopathological features when found in patients.

Is there any significant difference between RDS patients and other chronic painful patients?

From the study of 55 patients (psychological interview, drawings of the painful body, Rorschach), we try to answer that question:

- RSD patients show specific anxious and depressive symptoms;
- their bodily perception is characterized by a real esthetic vulnerability due so much to allodynia as to phobic, indeed persecutive features;
- on the psychological side, psychopathological features trend to severe neurotic hystero-phobic disorders.

More than the only results of that research, methodological questions are set about the literature: what is primary in psychopathological and RSD symptomatology, when are studied patients already suffering from RSD?

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**ASYMMETRIC SYMPATHETIC AUTONOMIC RESPONSES TO AMBIGUOUS VISUAL STIMULATION IN COMPLEX REGIONAL PAIN SYNDROME (CRPS) TYPE 1 PATIENTS**

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Background. We have previously demonstrated that CRPS pain can be exacerbated by ambiguous visual stimuli (AVS) (Harrison et al., 2006). We investigated whether this is associated with changes in autonomic function using Laser Doppler Flowmetry.

Methods. Ten patients with upper limb CRPS type I who had previously demonstrated exacerbated pain responses to AVS had baseline autonomic responses assessed using a Valsalva manoeuvre (VM), and while viewing AVS. Mean percentage change from baseline blood flow (m%ch), and symmetry ratio (SR) between the limbs were calculated.

Results. All patients experienced acute, severe worsening of their CRPS pain within seconds of viewing AVS. Five patients demonstrated asymmetric sympathetic responses (AsyR) induced by viewing AVS and five had symmetric responses (SyR). The affected limb (AL) showed larger responses than the unaffected limb (UL) with the m%ch-AL (±standard error) = 61 (±17), and m%ch-UL = 33 (±15). The patients with SyR to AVS had similar m%ch between limbs, with m%ch-AL = 64 (±16) and m%ch-UL = 56 (±17). The asymmetric group had a high mean SR-AVS = 9.7 (±6.3), whilst the mean SR for AVS in the symmetric group and for VM in both groups approached 1 (mean SR:AVS-SyR = 1.3 (±0.2), mean SR:VM-AsyR = 1.1 (±0.1), mean SR:VM-SyR = 1.2 (±0.2)).

Conclusion. Our data indicates that AVS can induce asymmetric autonomic responses.

Reference

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230 REFLEX SYMPATHETIC DYSTROPHY1 AND FACTICIOUS DISORDERS
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What about the “blue oedema” of Charcot? A disproportionate pain after an ordinary traumatism, the difficulty to define clear physiopathological mechanisms, the lack of validated treatment lead to call for psychological factors, or at the origin, or in the maintenance of a Reflex Sympathetic Dystrophy1.

In 5 patients, (3 females, 2 males) consulting during 4 years in our Pain Clinic, despite of severe vasomotor troubles (4 patients) and serious skin disease (1 patient), morphological analysis found no problem and, after pluridisciplinary consultations, were evoked primary or secondary facticious disorders that give a pathomnemonic and perplexing symptomatology.

Because of the severity of their pain, all patients received antihyperalgesic treatments; one of them, durable locoregional nervous blocks and another one, a cordonal electric stimulation : all of them without any benefit.

Those patients raise questions we try to answer to:

– on which criteria (psychological interview, and psychopathological tests) may we valid such a diagnosis as facticious disorders? We show the results of 5 Rorschach projective tests.
– how avoid a therapeutic outbidding, as a proposal of amputation?

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231 DIFFERENTIAL EXPRESSION PATTERNS OF CYTOKINES IN CRPS I
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Background and aims. Complex regional pain syndromes (CRPS) are characterized by persistent and severe pain after trauma or surgery. Neuro-immune alterations are assumed to play a pathophysiological role. We analyzed if there is a difference between the expression of pro- and anti-inflammatory cytokines in patients suffering from CRPS I and healthy controls.

Methods. Serum cytokine mRNA and protein levels of the pro-inflammatory cytokines tumor necrosis factor-alpha (TNF), interleukin-2 (IL-2) and IL 8 and the anti-inflammatory cytokines IL-4, IL-10, and transforming growth factor-beta1 (TGFβ1) were analyzed in 42 prospectively recruited patients with CRPS I and
ST differences (Celsius) in group B were significantly lower than those in group A at T1 (0.8 ± 0.2 in group B vs. 4.5 ± 0.8 in group A, \( P < 0.05 \)), T2 (1.2 ± 0.3 in group B vs. 5.0 ± 1.4 in group A, \( P < 0.05 \)), and T3 (1.0 ± 0.2 in group B vs. 4.2 ± 0.8 in group A, \( P < 0.05 \)).

**Conclusions.** The results show that IVRB improves ST for long period in CRPS type 1 patients.

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**LONG-TERM EFFECT OF INTRAVENOUS REGIONAL BLOCK ON SKIN TEMPERATURE IN COMPLEX REGIONAL PAIN SYNDROME**

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**Background and aims.** This study was carried out to clarify whether intravenous regional block (IVRB) can improve skin temperature (ST) for long period in complex regional pain syndrome (CRPS).

**Methods.** After institutional approval and informed consent, 23 patients having low skin temperature in the limbs associated with CRPS type 1 were divided into two groups according to the treatment. Group A \( (N=12, \ 43 \pm 12 \ \text{years, mean \pm SD}) \) received medication (steroids, anti-inflammatory drugs, and anti-depressant drugs) alone. Group B \( (N=11, \ 46 \pm 18 \ \text{years}) \) received the combination of medication and IVRB. IVRB with 1% lidocaine and reserpine was repeated twice during the first 1-month. The same medication was kept for 1 year in both groups. Follow-up examination (measurement of ST in injured and non-injured limbs using thermography) was performed before treatment (T0) and 6 (T1), 12 (T2) and 24 months (T3) after the starting treatment in each group. ST differences between the limbs were obtained. Statistical significance \( (P < 0.05) \) was determined using analysis of variance and Student’s t-test.

**Results.** Period until starting treatment and ST difference at T0 were similar in both groups.
**Conclusion.** Topical application of ISDN appears to be a promising therapy for patients with cold CRPS1. Currently a double blind RCT is performed.

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**POST-HERPETIC NEURALGIA AND TRIGEMINAL NEURALGIA PAIN IMPROVED WITH INTRADERMAL BOTULINUM TOXIN-A**

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**Background.** To report on effective pain treatment using intradermal Botulinum Toxin-A (BTX-A).

**Method.** Case series

**Results.** A 63-year-old woman with chronic right-sided trigeminal neuralgia. Neurosurgical decompression 18 years ago provided 5 years relief. Subsequent treatments included injections (complicated by meningitis), phenytoin, carbamazepine. Despite gabapentin 2400 mg/day, she complained of severe burning in the cheek and “screw-like” palate pain. Cutaneous allodynia in right V2/V3 distribution. Facial EMG with blink reflexes: normal. Intradermal 1%lidocaine provided 6 h relief. Sixty units BTX-A were then injected intradermally.

**Outcome measures.** Pre-injection: Visual analogue scale pain(VAS)7/10 Neuropathy Pain scale(NPS)65/100.

Six weeks post-injection: VAS1/10 NPS16/100.

For the first time in years, she was able without pain to: brush teeth, chew food, ride in jeep (window down). After 100 U, she had temporary right facial weakness, but by 4 months, she had weaned off gabapentin with pain reduced by 85%.

Another 63-year-old female developed a left-sided painful blistering shingles rash over left V1/V2. She was treated with oral acyclovir but continued with burning, stabbing pains over the eye, temple, scalp. Treatments included morphine, demerol, amitriptyline, prednisone, carbamazepine and gabapentin 3300 mg/day (limited by fatigue). Cutaneous allodynia was found. Intradermal 0.25%marcaine provided 12–18 h of relief. Fifty units BTX-A was injected in a follow-the-pain approach.

Pre-injection: VAS10/10 NPS19/100.

Four weeks later: VAS2/10 NPS19/100.

Despite temporary left ptosis, her pain diminished by 80–90%. She discontinued opioids and decreased gabapentin by half. Two further 50-unit injections provided pain control.

**Conclusion.** BTX-A (intradermal) appears to help in alleviating neuropathic facial/head pain.

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**DIAGNOSING COMPLEX REGIONAL PAIN SYNDROME (CRPS) BY A COMPREHENSIVE ANALYSIS OF LONG-TERM SKIN TEMPERATURE CHANGES**

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**Background.** A side difference between the affected and the contralateral extremity of more than 2.2 °C is a well known criterion for diagnosing CRPS (Wasner et al., 2002). However, this criterion is still not validated.

**Methods.** Measurement of the skin temperature of the distal extremities for 6–8 h during daily activities in 29 healthy volunteers, 25 patients with CRPS and 30 patients with other painful states.

**Device.** Temperature data logger svea® TDL (Medicommerz GmbH, Kirchzarten, Germany). Calculations: mean side differences, time of a-synchronicity (Asynchr), quotient of the oscillations >1.5°C on both sides (Qoszill), regression parameters (a, r²).

**Statistics.** t-Tests, variance and discriminance analysis.

**Results.** Patients with CRPS differ significantly from healthies in nearly all parameters. However, patients with neuralgia after nerve injury or with psychosomatic diseases also demonstrated significant side differences. In patients with CRPS the temperature changed significantly more often in a direction other than contralateral (a-synchronicity) and the frequency of oscillations was significantly different on the affected side. Using a summ-score (four variables: Asynchr, Qoszill, a, r²), CRPS could be diagnosed with a specificity of 78% vs. patients with other painful diseases and 90% vs. healthies (sensitivity: 75%, respectively 91%).

**Conclusions.** The assessment of mean side differences of skin temperature is not appropriate for diagnosing CRPS in patients with limb pain. A score characterizing the dynamics of the skin temperature is a new diagnostic tool, particularly for patients with CRPS of the upper extremity.
Reference
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A CASE OF COMPLEX REGIONAL PAIN SYNDROME RESOLVED BY TEMPORARY SPINAL CORD STIMULATION

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Background. Disturbances of sensory, motor and autonomic function are the characteristics of the complex regional pain syndrome (CRPS). Conventional pain medication, physical therapy, sympathetic blocks and transcutaneous electrical nerve stimulation have been used to reduce the intensity of pain of CRPS. In some patients, spinal cord stimulation showed favorable results.

Case. We would like to report a 29-year-old patient with burning pain and allodynia in right leg. She had a recent history of repeatedly burning pain at her leg for 2 years. These symptoms were more aggravated after traffic accident 1 year ago. Burning pain and edema of right leg was resolved completely after temporary spinal cord stimulation. Now, she is free from pain for 10 months after spinal cord stimulation.

Conclusions. CRPS is resolved by temporary spinal cord stimulation.
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IMAGINED REGROWTH: NORMALISING THE MENTAL REPRESENTATION OF A CRPS ARM
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Background and aims. Body perception disturbance in CRPS is described by patients as a perceptual distortion in size, weight and shape of the affected limb. Clinically, when describing a mental image of the affected limb with their eyes closed, patients report portions of that limb are missing with telescoping of adjacent parts. These disturbances, suggestive of cortical remapping, have implications on daily functioning.

Occupational therapy (OT) aims to normalise function, furthermore, corrective cortical remapping correlates with pain reduction. A novel intervention of imagined limb ‘regrowth’ (ILR) aims to target the correction of cortical limb representation as in the following case.

Methods. A 36-year-old male with upper limb CRPS (duration 2.5 years) perceived within his baseline mental image that his right forearm was missing with telescoping of the hand to the elbow. A programme of forearm ILR involved the patient visually concentrating on successive 1 cm sections of the left unaffected forearm (topographically matching the inside border of the missing affected forearm). Then with eyes closed, transposing that image onto the right forearm mental representation. Frequent 10 min sessions were undertaken over 4 months.

Results. See Table 1.
Conclusions. Significant affected forearm ‘regrowth’ was achieved suggesting that this is an effective intervention in correcting cortical limb representation.

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CRPS AND CRPS LIKE DISORDERS INVOLVING UPPER EXTREMITY
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Background. Retrospective analysis of patients send to our department with working diagnosis of complex regional pain syndrome (CRPS).

Material and methods. Between 1996 and 2006 members of our team have seen many patients referred as chronic pain of unknown origin.

Using recently accepted research IASP criteria for diagnosis of CRPS, retrospective analysis revealed that these conditions could be divided in a few groups.

CRPS I: fulfill IASP criteria.
Borderline CRPS: they do not fulfill all criteria.
CRPS like disorders: during diagnostic evaluation well-known pathology was discovered. This group could be subsequently subdivided in:

(a) exaggerated posttraumatic reaction,
(b) immobilization or disuse syndrome,
(c) iatrogenic disorder (painful physiotherapy),
(d) painful trigger points,
(e) overlooked pathology.

Pseudo-CRPS: patients with preexisting and/or concomitant psychologic/psychiatric disorders could be subdivided as: protective guarding, pain behavior, panic reaction or SHAFT syndrome, chronic disability syndrome or simulation, malingering, etc.

Results. Eighty-six patients, 17 males and 69 females with the mean age of 55 years (range 20–84). The mean duration of symptoms before treatment was 4 months (range 1–36). The mean of follow up was 23 months (range 4–72). Forty-five patients were categorized as CRPS I, 16 as borderline group, 15 as pseudo-CRPS, the exact number of patients with CRPS like disorder was impossible to determine.

Conclusion. There are many chronic painful disorders mimicking CRPS. Without exact criteria they can be divided in proposed groups. Lack of knowledge especially in CRPS like disorders with known pathological background confirms that these patients need team evaluation and treatment.

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COMPARISON OF DEPRESSION INDEX AND QUALITY OF LIFE BETWEEN PATIENTS WITH AND WITHOUT POST-HERPETIC NEURALGIA
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Background. Chronic pain, including neuropathic pain is associated to poor quality of life and depression. The modality of pain most studied is diabetic neuropathy and its relation with depression, poor quality of life and sleep has been showed. The aim of this study is to analyze the impact of post-herpetic neuralgia in depression index and quality of life.

Method. Using de Beck depression inventory and the Short Forme-36, we compared those result between patients with post-herpetic neuralgia (Group A) and other patients without pain but similar medical conditions (age, other chronic diseases, somatometry (Group B) The results of SF-36 was compared using the χ² and Mann and Whitney test.

Results. We included 17 patients in Group A and 20 in Group B. There was no statistics differences between medical conditions but the media of BDI was 3.9 in Group A and 2.8 in Group B (p = 0.007) and there was 14 questions in SF-36 with statistics differences between these groups.

Conclusions. With these results we can conclude that post-herpetic neuralgia is a clear factor for the patient to develop depression and is necessary a psychological evaluation in every patient with post-herpetic neuralgia.

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POST-HERPETIC NEURALGIA (PHN) FOLLOWING HERPES ZOSTER (HZ): LITERATURE REVIEW OF EUROPEAN DATA
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Background. PHN is the most common and debilitating complication of herpes zoster (HZ) in Europe. HZ is caused by reactivation of varicella zoster virus which remains latent in the sensory ganglia after initial varicella infection. Declining immunity in the elderly is thought to favor symptomatic reactivation. A new vaccine, boosting specific immunity, has shown efficacy in preventing HZ and reducing the burden of PHN.

Methods. The NLM Medline database was searched for articles published between 1990 and February 2006 using terms “herpes zoster”, “shingles” and “postherpetic neuralgia”.

Results. The individual lifetime risk of developing HZ is between 23.8% and 30%, that is approximately 1 in 4 individuals, with previous varicella infection, develops HZ. After the age of 50 years, 1 out of 5 individuals may develop PHN following an episode of HZ. Pain is a major symptom, with 95.8% of patients in pain at presentation. Current management for HZ includes antiviral agents and pain control and for PHN, opiate-derived medication, antidepressants and anticonvulsants. These treatments are considered to be sub-optimal.

Conclusions. Pain is a common symptom of HZ and PHN is its major complication. Prevention of HZ and PHN is the best way forward in managing this disease. A recently licensed vaccine could make HZ and PHN prevention possible.

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DIFFERING ATTITUDES TO ANALGESIC OPTIONS IN POST-HERPETIC NEURALGIA PATIENTS: PARALLEL SURVEYS CONDUCTED IN 100 PATIENTS AND 1078 GPS IN 2006
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Post-herpetic neuralgia (PHN) is a devastating illness, with little published about the impact on lifestyle and patients’ own experience. The precise incidence of PHN in the UK is unknown, and under-treatment is associated with an incomplete understanding of the impact of the condition.

Two parallel surveys were conducted to better understand specific issues regarding PHN from the patients’ perspective, in comparison to that of prescribers.

Methods. Patients from the Barts PRG PHN Database were pre-screened and participated in a 15-min semi-structured interview in Q4 2006. (50% had pain for ≤ year; 50% considerably longer). The GPs were selected by UK regional stratification. Treatment history, pain symptoms, impact of PHN on patients’ lifestyle and emotional well-being – prior to and post-treatment, treatment satisfaction, and desirable features for future medications featured.

Results. 100/139 patients participated, with 1078 GPs in the second survey. The commonest symptom reported by patients was allodynia (70%) – 9% relieved by treatment. Amongst prescribers, allodynia featured in 50%. Medications were gabapentin, amitriptyline, pregabalin > carbamazepine. Treatment satisfaction was low in both surveys, due to AEs and inadequate efficacy, mirrored in reported inability to perform ADL, to enjoy life, poor sleep and disturbed relationships. Pharmaco-economic data and desirable features for new treatments will be presented.

Conclusion. An urgent need for improvement exists with both prescribers and patients poorly satisfied; patients responses reflected greater dissatisfaction than the clinicians’. Better symptom appreciation and improved understanding of emotional impact and psychosocial well-being are desirable.

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EPIDEMIOLOGY AND MANAGEMENT COSTS OF HERPES ZOSTER (HZ) AND POST-HERPETIC NEURALGIA (PHN) IN THE UK
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Background. Recent information on epidemiology and management of HZ and PHN, a painful complication of HZ, is scarce. With the arrival of a new HZ vaccine, it is important to document the burden of HZ and PHN in the UK.

Objectives. To estimate HZ incidence and proportion of HZ patients developing PHN (using two definitions: pain occurring or persisting at 1/3 months after HZ diagnosis or more) among individuals ≥ 50 years and to assess costs of HZ and PHN management.
Methods. Records of immunocompetent individuals diagnosed with HZ between January 2000 and March 2006 were extracted from the UK General Practice Research Database (GPRD). Total person-years for patients ≥ 50 in GPRD was used as the denominator for incidence calculations. PHN episodes were identified by disease code or specific neuropathic pain medications prescriptions. Healthcare resource use was retrieved. Costs of clinical management were assessed from the NHS perspective.

Results. 25,002 HZ patients were included (HZ incidence = 5.23/1000 patient/years (95%CI 5.17–5.29). Of those 19.5% (95%CI 19.0–20.0%) and 13.7% (95%CI 13.2–14.1%) developed PHN (1 and 3 months definition, respectively). The mean direct cost was £76.63 for HZ and £284.38 and £340.00 for PHN (1 and 3 months definition, respectively).

Conclusion. Although costs are likely to be underestimated these results suggest that HZ and PHN are frequently occurring and costly diseases in the UK. Therefore, the future implementation of a HZ vaccine is expected to have a positive effect on the clinical and economic burden of HZ and PHN.

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243 HISTAMINE-IONTOPHORESIS FOR DIFFERENTIATION OF C-FIBRE FUNCTION IN POST-HERPETIC NEURALGIAS
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Two different types of post-herpetic neuralgia (PHN) are described. (1) Irritable nociceptor type: characterized by spontaneous pain and preserved sensory function. (2) Deafferentation type: characterized by spontaneous pain with sensory deficits due to degeneration of C-fibres.

In this study 22 patients (mean: 74 ± 1 years) with PHN were examined with quantitative sensory testing (QST) and laser-Doppler imaging. Flaresize was evaluated after iontophoresis of histamine. Histamine induces an axon reflex flare. For statistical evaluation students paired t-test was used.

In 13 patients histamine flare sizes could be obtained. In 9 patients flare sizes were smaller on the affected side (p < 0.05), while flare size was unchanged or even increased in 4.

Flare size depends on the innervation density of histamine-sensitive C-fibres. Therefore diminished flare sizes should indicate C-fibre loss. Accordingly in patients with reduced flare temperature sensitivity, which is related to C-fibre function, was reduced (cold detection, warm detection, thermal sensory limen; all p < 0.05), while the functions of myelinated fibres were preserved (mechanical detection threshold, mechanical pain threshold, vibration, pressure pain; all n.s.). Mechanical allodynia occurred in five patients with deafferentation pain.

In patients with bigger flare sizes temperature sensation was not significantly impaired, while mechanical pain threshold (p = 0.06) was reduced and mechanical allodynia occurred in all of them. This indicates A-fibre sensitisation corresponding with the irritable nociceptor type.

Histamine iontophoresis seems useful for differentiation of subtypes of PHN.

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244 PRISM ADAPTATION TO OPTICAL DEVIATION ALLEVIATES COMPLEX REGIONAL PAIN SYNDROME (CRPS)
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Background. The human visual and somatosensory systems are interdependent. Using a visual subjective body-midline (vSM) judgment task, we previously confirmed that pathological pain in complex regional pain syndrome (CRPS) and deafferentation can modify visuospatial perception (NEUROLOGY07;68:152–4). Conversely, in the present study we investigated whether a change in visual experience can modify perception of pathological pain.

Methods. We used prism adaptation (PA) to modify subjects’ visual experience. Five patients with CRPS adapted to wedge prisms, producing a 20-degree visual displacement toward the unaffected-side. Further, we used several types of prisms in a longitudinal single-case study. Wearing prismatic-goggles, the subjects performed a target-pointing task once a day for 2 weeks. We evaluated pain intensity and vSM-judgment to measure the adaptive aftereffects at three time-points: before
Results. PA toward the unaffected side alleviated pathological pain and other CRPS pathological features, when measured at Post-test. None of the IA-test results showed an analgesic effect. In the longitudinal study, sham PA and 5-degree PA did not produce any effects, and PA toward the affected side actually exacerbated the subjective pain.

Conclusions. Our findings suggest that prism adaptation has a direction-specific and reproducible effect on not only pathological pain but also other CRPS pathological features. Thus, prism adaptation may be a viable cognitive treatment for CRPS (NEUROLOGY07;68:128–33).

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HIGH-DOSE KETAMINE INFUSION FOR COMPLEX REGIONAL PAIN SYNDROME
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Complex regional pain syndrome (CRPS) is characterized by pain that is out of proportion to the injury and is regional in distribution. Many treatments have been reported for CRPS. No single treatment can be considered capable of curing CRPS.

Between December 2002 and November 2006 patients suffering complex regional pain syndrome were treated for 4 days with a 10 ml/h ketamine 1% infusion increasing until 28 ml/h or adverse effects were reached; any other analgesic drug was suspended.

We treated 15 patients. Four had upper limb pain, nine had lower limb pain and two had upper plus lower limb affected. Eleven patients (73.3%) referred pain improvement, visual analogue scale (VAS) decrease range was 60–100%. Four patients (26.6%) referred no improvement. Mean age was 40, 12 years (range 18–62). Six patients referred hallucinations or vivid dreams, three of them were non responders to ketamine.

Chronic pain may lead to lowest quality of life, ketamine infusion appears to provide effective pain relief to many patients suffering complex pain regional syndrome. However, we found significant side effects, 40% of or patients experienced hallucinations or vivid dreams. Moreover, we used an inpatient basis what leads to high costs for this therapy. Recently, several groups have published studies using low-dose ketamine for the treatment of CRPS. The positive results of these studies make it possible to believe that the use of low-dose ketamine infusion might also be effective on an outpatient basis. Future studies should establish the ideal dose and duration of ketamine treatment for CRPS.

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USE OF TOPICAL CAPSAICIN IN THE TREATMENT OF COMPLEX REGIONAL PAIN SYNDROME
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Complex regional pain syndrome (CRPS) is a disease with an uncomprehended pathophysiology. Various therapeutic strategies have been proposed but their effectiveness is not well documented. One of the theories on pathophysiology describes a role for neuropeptides in CRPS. As a result of extra release of neuropeptides, topical administration of capsaicin on an involved CRPS extremity will first worsen the signs and symptoms of CRPS. However, continuing administration results in a total depletion and a ceased supply of new neuropeptides. This will result in a positive effect on the syndrome as described in some case reports about animal models and about humans with CRPS1.

In an open label study the clinical effects of topical application of capsaicin in 14 patients with CRPS1 in one extremity were measured. At the start and after 6 weeks treatment, signs and symptoms of impairment were measured and are presented as median (interquartile range). Clinically, there was a significant improvement after treatment. The VAS (0–100 mm, no pain to most pain); has decreased from 58 (43–71) to 49 (31–55), blood flow distribution as assessed by videothermography (0–1, most asymmetry to normal) from 0.69 (0.49–0.77) to 0.82 (0.60–0.92) and active range of motion (5–25, normal to most abnormal) from 16.5 (11.5–20.5) to 14.5 (11.0–17.0). Topical application of capsaicin in the treatment of CRPS1 results in a detectable clinical improvement. A randomized controlled study is necessary to confirm this observation.

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LIDOCAIN PATCH 5% REDUCE POSTSURGICAL NEUROPATHIC PAIN WITH THE CANCER PATIENTS
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Background and aims. The neuropathic pain syndromes (NPS) appear at 15–35% of cancer patients and is characterized by specific neurological disturbances. To reduce NPS oncologists usually prescribe opioids, though at neuropathic pain they are insufficiently effective and besides, they provoke some side effects.

Methods. As a therapy of the postmastectomy pain (13) and of the postthoracotomy pain (2) we have used a lidocain patch 5%. It has been applied upon the zone of allodinia during 14 days.

Results. Eight patients preferred to use the patch at night: they have reported an improvement of the quality and of the duration of the sleep. Other ones (7) have used the plaster at the day, which allowed them to enlarge their movement activity and to execute in full the complex of the rehabilitation gymnastic. To two patients, the use of the lidocain patch 5% after mastectomy has allowed obtaining the course of radiotherapy in an earlier time and in full, although before the application, because of the pain, they were unable even to raise the hand. The average daily dose of tramadol as a whole on group has decreased in 2.3 times.

Conclusions. The use of the lidocain patch 5% has never been accompanied with any side effects, including systematic lidocain effects. The use of lidocain patch 5% with the patients of peripheral neuropathic pain, induced by a tumour or by an anti-tumour therapy, is pathogenetically grounded as noninvasive and efficient.

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METHADONE IN TREATMENT OF ONCOLOGIC NEUROPATHIC PAIN
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Background and aims. The opioids are used in neuropathic pain (NP). Methadone, when blocks the NMDA receptors, offers advantages in relation of other opioids.

Methods. Inclusion approaches: age 18–70 years, histology of cancer, intensity of pain: moderate-severe, NP secondary to the cancer or its treatment. Efficacy variables (EV): intensity (I) and duration (D) of pain; treatment response (TR); Karnofsky scale (K); quality of life: dream (DR), how many times woke up in the night (WN), appetite (A), daily activity (DA) and mood (M). Variables of tolerance (VT): acception to the treatment (AT) and adverse events (AE). Methodology: Open prospective study. Evaluations: 1st (0 day), 2nd (7th day) and 3rd (28th day).

Results. We did assess 10 patients: 7 women, average: 51 years old. Duration of pain: 7.9 months. Comparison of the EV in the 1st, 2nd and 3rd valuations, respectively, were: I: 8, 4.5 and 2.8 (p < 0.001); D (frequent-constant): 77%, 33% and 25%; TR (relief of pain ≥ 50%): 0%, 44% and 75%; K: 66, 73 and 76; DR (regular-worse): 89%, 56% and 25%; WN: 3.6, 1.1 and 0.6; A (regular-worse): 78%, 44% and 38%; DA (regular-worse): 89%, 44% and 38%; AE (regular-worse): 78%, 44% and 38%. Comparisons of the VT in the 2nd and 3rd valuations were: AT (good-excellent): 67% and 100%; AE: sedation, nausea and constipation that were tolerable.

Conclusions. Methadone is effective and well tolerable in the control of NP in patients with cancer. It requires studies with a high number of patients to corroborate these results.

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IV TRAMADOL FOR TREATMENT OF REFRACTORY MIGRAINES IN THE CLINIC
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Tramadol is used orally for chronic pain in the USA, but no IV form is available. We decided to utilize an IV sterile preparation [IND applied for #73400], to treat refractory headaches, including migraines, in the clinic. Tramadol, 50 mg per ml, was given IV in the clinic to patients with intractable migraines and other headaches. Thirty-eight patients were treated with IV tramadol, after placement of an IV line and with pulse oximetry monitoring. A 50-mg test dose was given and 50–100 mg was given every 7–10 min with monitoring of headache severity by the patient on a 0–10 scale.

All patients treated had response to IV tramadol. Average dose of tramadol was 397 mg (range 250–900 mg), given over 67 min in the clinic. Average reduction in severity (0–10 scale) was 6.66/10 to 2.89/10 in severity after treatment [p < 0.001]. No side effects other than transient drowsiness or nausea were noted. Ten patients were subsequently placed on oral tramadol.
Headaches returned within 24 h in two patients not treated with oral tramadol.

IV tramadol is effective in treating intractable migraines and mixed headaches acutely in the clinic. It has virtually no toxicity IV and can be the starting point for oral treatment. Typical dosage IV compares to daily oral dosing. Tramadol IV offers a new possibility in treating intractable migraines effectively and safely in the clinic and should be studied in a double-blind manner. The mechanism(s) for its effects are discussed.

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250 PREVALENCE OF NEUROPATHIC PAIN IN CANCER PATIENTS

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Backgrounds and aims. Neuropathic pain can be seen in advanced oncological patients and it is a great challenge as it is often very difficult to treat successfully without interfering with patient’s quality of life. Our main objective is to know the prevalence of neuropathic pain among oncological patients admitted to several palliative care units in Spain over the month of November 2006.

Methods. Multicentric and retrospective study carried out in patients admitted in five palliative care units (Balaguer, Barcelona, Lleida, Madrid, Badajoz). We study age, gender, main diagnosis, incoming date, discharge date, existing neuropathic pain and treatment.

Results. Fifty-nine patients were included in the study (39 male and 20 female) with a mean age of 69 years (Male 71.1; Female 69.8). Fifteen patients were diagnosed of neuropathic pain (25.4%). Lung (n = 14) and colon (n = 8) were the most seen diagnosis.

Regarding the most used treatments in patients with neuropathic pain, dexamethasone was used in seven patients, amitriptyline in 3, NSAIDs in 5, benzodiazepines in 6, anticonvulsants in 5 and strong opioids in 14.

Discussion. According to our study, neuropathic pain can be considered highly prevalent among advanced cancer patients (25.42%) admitted in palliative care units, being lung cancer the most frequently diagnosis seen. Regarding the treatments used, gabapentine is the only anticonvulsant used. Among strong opioids, oxycodone and transdermal fentanyl are the analgesic most prescribed.

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251 SENSORY PROFILES IN PAINFUL VS. NON-PAINFUL CHEMOTHERAPY-INDUCED POLYNEUROPATHY

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Chemotherapy-induced polyneuropathy (CINP) is a common negative side effect of antineoplastic therapy. Besides sensory loss, patients often report accompanying (neuropathic) pain. Clinical symptoms and signs in patients with painful and painless CINP were assessed. Sensory dysfunction was verified using electroneurography. Sensory profiles were assessed using quantitative sensory testing (Rolke, 2006). The study aimed at pointing out differences in sensory dysfunction which might be relevant for the development of pain in only some CINP-patients.

Forty patients (mean age 56 years) with malignant solid- and non-solid tumors and clinical signs of CINP were included. Diagnostic procedure included electroneurography of the sural/peroneal nerve and QST on the right foot. QST unmasks large-/small-fiber dysfunction and detects thermal or mechanical hypo-/hyperalgesia. Sensory profiles of the painful and painless CINP-subgroup (each n = 20) were compared to a control group matched for age and gender.

Electroneurography detected sensory neuropathy in both CINP subgroups. In the QST a significant reduction thermal (cold-warm) detection (each p < 0.001) was found but perception of thermal pain was not altered. Congruently, there was a significant (p < 0.001) reduction of mechanical detection and vibration. However, mechanical pain detection was significantly reduced (p < 0.05) only in the painful CINP group.

Electroneurography and QST detected sensory dysfunction in both groups. Sensory profiles of the painful and painless CINP-subgroups were largely overlapping showing deficits in small- and large fiber-function. The detection of mechanical pain, a function of a A-Delta-fiber subgroup, was more affected in the painful CINP subgroup.
group. This could be pathophysiologically relevant for the development of pain.

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TUMOR NECROSIS FACTOR ALPHA CONTRIBUTES TO PAIN AND HYPERALGESIA IN A MOUSE CANCER/METASTASIS MODEL
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Patients with cancer in late stages and in particular with metastasis frequently experience severe pain including mechanical and heat hyperalgesia. C57BL6 mice received subcutaneous injection of carcinoma cells to the plantar and dorsal side of the hind paw. Ten days post inoculation the animals developed signs of heat hyperalgesia which were significantly reduced by systemic administration of the TNFα antagonist etanercept (EnbrelTM). We therefore used biochemical, electrophysiological and behavioural methods to elucidate a possible mechanism of TNFα affecting sensory neurons in this tumour/metastasis pain model. In vivo, TNF injections evoked heat hyperalgesia. TNFα (1 ng/ml) induced ongoing activity and a pronounced mechanical and heat sensitization of cutaneous nociceptors, in vitro. In skin preparations obtained from tumour mice, signs of nociceptor sensitization were prevented by etanercept. Dorsal root ganglion neurons responding to controlled heat stimuli with excitatory inward currents (Iheat) showed an increase of Iheat and a shift of the activation threshold to lower temperatures following conditioning stimulation with TNF. Real time RT-PCR revealed no signs of mRNA upregulation for the nociceptor specific heat sensitive ion channel TRPV1, however, Western blot analysis yielded an upregulation of TRPV1 protein, and deletion of the TRPV1 gene prevented the heat hyperalgesia, in the tumour/metastasis model. Together, our data suggest that TNFα plays a key role in cancer/metastasis pain and hyperalgesia by posttranscriptional upregulation and sensitization of TRPV1 in primary afferent nociceptors.

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EFFECTIVENESS OF IV LIDOCAINE THERAPY IN THE CLINIC FOR REFRACTORY MIGRAINES AND HEADACHES
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Lidocaine has been used to treat neuropathic pain by virtue of its ability to block sodium channels and thus block neuropathic pain signaling. And all that area migraines or other headaches may be neuropathically mediated, we tried treatment of refractory migraines with this agent in the clinic.

Twenty-two patients were treated (19 female/3 male) [average age 40.8 years] for refractory headaches in the clinic. An IV line was started with pulse oximetry monitoring. Patients had failed at home treatment for their usual migraines. The beginning severity for migraines was 7.05/10 in severity before treatment and this was reduced to 2.18/10 in severity after treatment. Seven of 22 [32%] of patients had complete abolishment of their migraines. Average time of lidocaine infusion was 135 min and average dose was 334 mg of lidocaine. This resulted in a in significant decrease in headache severity (p value of <0.001) for treatment of refractory migraines. There were four patients with transient nausea and dizziness during infusion, easily arrested by stopping or slowing the infusion rate. No other side effects were seen with treatment.

We conclude that IV lidocaine can be used in the clinic for treatment of refractory migraines and that sodium channel over activity may be playing a role in the maintenance or perpetuation of migraine headaches. Often, this allows choice of a sodium channel active agent for oral prophylaxis of migraines. The study also raises questions about mechanisms of aberrant neurotransmitter activity involving sodium channels playing a role in refractory migraine.

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GENERALIZED SOMATOSENSORY CHANGES IN PATIENTS WITH TEMPOROMANDIBULAR DISORDER
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Aim. Altered pain perception of patients with temporomandibular disorder (TMD) is often not restricted to the orofacial region. We evaluated the complete somato-
sensory profile using quantitative sensory testing (QST) to assess both myofascial pain components and possible changes in central pain processing.

Methods. We investigated 23 patients with chronic TMD. QST was performed according to the protocol of the German Research Network on Neuropathic Pain (DFNS) over face, back and hand. We determined thermal and mechanical detection and pain thresholds including cold and heat pain thresholds, mechanical detection thresholds to von Frey filaments and a tuning fork, mechanical pain thresholds to pinprick stimuli and blunt pressure using a pressure algometer. QST data were compared using 18 matched control subjects. Additionally the number of tender points was investigated.

Results. TMD patients with a high tender point count (>10) showed heat hyperalgesia (p < 0.05), and pressure hyperalgesia (p < 0.05) across all tested body areas. Cold hyperalgesia was found over face and back (p < 0.01). Pinprick hyperalgesia was detected over hand and back (p < 0.05). In TMD patients with low tender point count cold hypoesthesia was present over face (p < 0.01), tactile hypoesthesia and pinprick hyperalgesia over back (p < 0.05).

Conclusions. TMD patients with a high tender point count showed generalized sensory plus signs with an increased sensitivity to different pain stimuli. This finding is consistent with an inhibition of descending pain control mechanisms in addition to the myofascial pain component in this subgroup of TMD patients.

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QUANTITATIVE SENSORY TESTING: ASSESSMENT OF THE NEUROPATHIC COMPONENT IN CANCER PAIN
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Background. We used the QST protocol of the German Research Network on Neuropathic Pain (DFNS) to assess the prevalence of a neuropathic pain component in cancer pain.

Methods. We investigated 31 cancer pain patients (55.4 ± 11.1y, 19w, 12m). The QST protocol of the DFNS consists of seven tests measuring 13 parameters: Thermal detection and pain thresholds, mechanical detection thresholds for touch and vibration, mechanical pain sensitivity for pinprick and blunt pressure, dynamic mechanical allodynia, and pain summation to repetitive pinprick stimuli.

Results. In 25.8% of the patients all tested QST parameters were normal. Again 25.8% of the patients showed isolated sensory minus signs. Only 6.5% of the patients presented with isolated sensory plus signs, namely pinprick-hyperalgesia. A mixture of sensory plus and minus signs was found in 41.9% of the patients. Increased vibration detection threshold was the most common sensory minus sign (60%). Hyperalgesia to blunt pressure was the most common sensory plus sign (32%), followed by pinprick-hyperalgesia (17%) and dynamic mechanical allodynia (12%).

Conclusion. Using QST it was possible to detect sensory plus and minus signs in cancer pain patients. Most frequently a mixture of these signs was found or patients with an isolated sensory deficit pointing at a neuropathic pain component. Isolated sensory plus signs were rare. The finding of pinprick-hyperalgesia in the presence of dynamic mechanical allodynia is consistent with a central sensitization of nociceptive pathways in some cancer pain patients.

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Poster Session 1: Neuropathy
diabetes mellitus, because preventive interventions can be applied to decrease morbidity. Controversy exists about the use of symptom scoring in diagnosing DPN. We evaluate correlation between symptoms and nerve conduction study (NCS).

**Method.** We reviewed the medical and electrophysiological records of consecutive patients with diabetes for evaluation of DPN. We used diabetic neuropathy symptom (DNS) score and diabetic neuropathy examination (DNE) score. Patients with any other causes of sensory symptoms on the feet and with abnormal DNE score were excluded. Control data were obtained from 17 age-matched people with no sensory symptoms or signs. Routine motor and sensory NCS including medial plantar nerve (MPN) using surface electrodes were performed.

**Result.** Twenty-three diabetic patients (12 women, 11 men, 10 symptomatic, 13 asymptomatic) were enrolled. DNS score of symptomatic patients was 1 (7 patients) and 2 (3 patients). The statistically significant electrophysiological parameters between symptomatic and asymptomatic patients or control were amplitudes of sensory nerve action potential and conduction velocity of MPN and sural nerve ($p < 0.05$). But there was no significant difference between asymptomatic and control group. Abnormal rate of NCS was higher in symptomatic patients compared to asymptomatic or control group. Amplitude of sural nerve in symptomatic patients was correlated with DNS score.

**Conclusion.** DNS score is relatively simple scoring system for DPN and may reflect severity of abnormality of NCS, including MPN. This result makes easy early diagnosis of DPN.

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A PROSPECTIVE PSYCHOPHYSICAL STUDY OF OXALIPLATIN AND CISPLATIN INDUCED NEUROTOXICITY IN HUMANS

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**Background and aims.** There are no prospective data with regards to the peripheral nervous system toxicity of oxaliplatin and cisplatin in patients. The present psychophysical study aimed to characterize the effects of oxaliplatin induced toxicity, particularly with regards to its effects on cold processing by comparison with cisplatin and to detect possible early predictors of the occurrence of late chronic neuropathy.

**Methods.** Sixty-seven patients with gastrointestinal cancer treated by oxaliplatin ($n = 32$) or cisplatin ($n = 35$) were evaluated prospectively. Patients with baseline clinical symptoms or signs of peripheral neuropathy were not included. The psychophysical evaluation included measurements of thermal (heat and cold) and mechanical detection and pain thresholds and the responses to suprathreshold stimuli in the hand and foot using thermostest and von Frey filaments respectively as well as vibration thresholds using a vibrometer. Assessments were performed before the first cycle then after the fourth, seventh, tenth and twelfth cycles.

**Results.** Mean cold and warm detection, heat pain or vibration thresholds were not modified by chemotherapy during the cycles. Oxaliplatin, but not cisplatin, induced a significant increase in cold pain thresholds (i.e. cold allodynia) and of the responses to suprathreshold cold stimuli (i.e., cold hyperalgesia). The effects of oxaliplatin on cold pain were observed from the fourth cycle and were directly related to the cumulative dose received by the patients up to the twelfth cycles.

**Conclusion.** This prospective psychophysical study confirms that oxaliplatin has a high and cumulative nervous toxicity affecting preferentially cold sensory systems.

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A DOUBLE-BLIND, RANDOMIZED, PLACEBO-CONTROLLED TRIAL TO EVALUATE TIME-TO-ONSET OF CLINICALLY MEANINGFUL PAIN RELIEF IN POSTHERPETIC NEURALGIA (PHN) PATIENTS TREATED WITH PREGABALIN

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**Objective.** To evaluate time to onset of clinically meaningful pain relief in PHN patients treated with pregabalin.

**Methods.** Patients with PHN $\geq$3 months, pain VAS score $\geq$40 mm, and at least 4 daily pain score entries during the 7-day screening period (average daily score $\geq$4; 0–10 scale) were eligible. Ninety-one were randomized to flexible-dosage pregabalin (optimized for effi-
cacy/tolerability to 150, 300, or 600 mg/d, BID); 88 to 300-mg/d fixed-dosage pregabalin; 90 to placebo for 4 weeks of treatment. Primary efficacy parameter was time to onset of clinically meaningful pain relief (≥1-point improvement in daily pain score plus decrease of ≥30% in weekly pain score at endpoint), summarized with Kaplan–Meier plots and tested for treatment differences using a Cox hazards model. Secondary measures included change in mean VAS score (100-mm scale) for brush-evoked allodynia in affected areas.

Results. Patients’ mean PHN duration = 2.5 years; baseline mean pain score = 6.3–6.7. Median time to meaningful pain relief: flexible-dosage, 3.5 days (<0.0001); fixed-dosage, 1.5 days (<0.0001); among placebo patients, median time to meaningful pain relief was greater than the study observation period, with <50% achieving >30% improvement. Week 1 treatment differences from placebo in change in mean allodynia VAS score: flexible-dosage, −10.0; fixed-dosage, −7.3. Corresponding values at endpoint: −13.5, −7.2. Most common AEs: dizziness (flexible-dosage, 24%; fixed-dosage, 31%; placebo, 7%) and somnolence (11%, 19%, 2%). All-cause discontinuations: flexible-dosage, 5.5%; fixed-dosage, 20.5%; placebo, 16.7%.

Conclusions. Patients treated with 300 mg/d fixed-dosage pregabalin or flexible-dosage pregabalin had rapid onset of clinically meaningful and sustained pain relief.

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LONG-TERM RESULTS OF THE MICROSURGICAL DREZ-TOMY FOR NEUROPATHIC PAIN DUE TO BRACHIAL PLEXUS AVULSION: ANATOMICAL LEARNING AND CLINICAL DISCREPANCY
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Microsurgical DREZtomy is designed to destroy selectively afferent thermoalgic fibers, preserving the modulation deserved by recurrent branches of lemniscal tract. During such procedures, every anatomical lesions can be identified and described as well as the functional status of the different rootlets.

Among 55 patients suffering of pain secondary to brachial plexus avulsion, anatomical and functional lesions of roots and spinal cord were prospectively collected and correlated to clinical preoperative examination.

(1) If motor and sensitive clinical screening is in 70% of cases worthwhile to determine the avulsed roots, pain appears widely extended than wounded roots in 27% of cases. That observation correlates with the modality the dorsal roots penetrate the spinal cord among 3–5 myotomes.

(2) Pain appeared within a month after accident in 77% of cases, associating paroxystic and continuous components in 67% of cases.

(3) Among those patients, predominant paroxysmal pain correlated with a good relief (p < 0.05) and neuromas with a poor one (p < 0.05) (considering pain relief, drug consumption and activity retrieval).

As pain can be attended to be relieved by corrective orthopedic procedures, it remains of prior interest to promote early treatment of neuropathic pain, which would be begun within the first posttraumatic hours, whatever the orthopedic and rehabilitation procedures would be undertaken.

Anatomical observations suggest that intermediary deafferentation – as concerning both peripheral (dorsal root) and central (dorsal horn over many contiguous metameric levels) structures – may resume to intractable continuous pain over time.

260 PREVALENCE OF POLYNEUROPATHY WITH OR WITHOUT NEUROPATHIC PAIN IN TYPE 1 AND 2 DIABETIC PATIENTS
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A cross-sectional study was carried out in 40 Belgian diabetes clinics to estimate the prevalence of diabetic polyneuropathy (DPN) and of painful DPN (PDPN).

A cohort of 1194 type 1 and type 2 diabetic patients participated in this study. The diagnosis of sensory polyneuropathy was based on the Neuropen test (i.e. identification of alterations of tactile and pinprick sensivity). The DN4 questionnaire was administered to identify neuropathic characteristics in patients with DPN and pain in the lower limbs.

The overall prevalence was 43% for DPN and 14% for PDPN. The prevalence rates of both DPN (51%) and
PDPN (18%) were higher in the subgroup of patients with type 2 diabetes (n = 784), in comparison with type 1 (25% and 6%, respectively). Other diabetes complications (metabolic syndrome, micro/macroalbuminuria, retinopathy, impairment of renal function, diabetic foot complications) were significantly more frequent in patients with DPN. Neuropathic pain and DPN altered independently, but additively, the quality of life.

In conclusion, DPN and PDPN are frequent complications of diabetes which can be reliably identified with specific clinical tools.

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261 RESOLUTION OF ULCERS SECONDARY TO TREATMENT OF PAINFUL DIABETIC PERIPHERAL NEUROPATHY (DPN) WITH THE PRECISION SPINAL CORD STIMULATION (SCS) SYSTEM

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Approximately 5–10% of the diabetic population with DPN is prone to developing foot ulcers, often leading to amputation. Current management such as medication and wound care are not reliably effective. Leading to infection, ulcers can decrease mobility, activities of daily living (ADLs), and quality of life. SCS therapy is an effective treatment of DPN pain and other peripheral neuropathies. The following retrospective report describes complete healing of a diabetic foot ulcer and improved mobility following treatment of neuropathic pain with precision.

A 78-year-old male with a 30-year history of diabetes had ongoing pain from DPN and bilateral vascular insufficiency in lower extremities, but was not a candidate for peripheral revascularization or bypass surgery. A previous ulcer led to amputation of one toe. Progressive pain and discomfort from a heel ulcer over a one-year period led to difficulty in walking, and ultimately, wheelchair limited mobility. After successful trial stimulation, he received a permanent system.

Following permanent implant, patient reported complete pain relief. The day after the procedure, he was walking with the aid of a cane, and by the tenth day, he was walking without any assistance. His extremities demonstrated improved circulation, and the ulcer was 98% healed by the 10th week.

Although primary indication for SCS is pain relief, there is increasing body of evidence suggesting it may have positive effects on ADLs and quality of life. The magnitude and potential impact of these secondary benefits on public health warrants further study of SCS therapy for alternate indications.

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262 RESTLESS LEGS SYNDROME IN PAINFUL NEUROPATHY IS RELATED TO NOCICEPTIVE DEAFFERENTATION

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Restless legs syndrome (RLS) is a known manifestation of polyneuropathy, often in association with small fiber involvement, and it has been suggested that it may represent a peculiar form of neuropathic pain.

To investigate the relationship between pain and RLS, we evaluated retrospectively for the occurrence of RLS a series of 102 consecutive patients (43 men, 59 women) with polyneuropathy, and neuropathic pain or dysesthesia as main symptom, using the criteria of the International Restless Legs Syndrome Study Group.

The patients were classified on the basis of presumed pathogenic mechanisms of pain in the “hyperphenomena” subgroup (characterised by allodynia) and in the “hypophenomena” subgroup (identified on the basis of pinprick hypoalgesia).

RLS was present in 41/102 patients (40.2%), and was significantly more common in the “hypophenomena” subgroup (23/37) than in the “hyperphenomena” subgroup (9/31; p = 0.008), and in the not classifiable cases (9/34; p = 0.004).

Thus RLS is frequent in painful polyneuropathy, and it is significantly associated with nociceptive deafferentation, which may be a factor contributing to overactivity of spinal circuitry implicated in RLS.

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263 PSYCHOLOGICAL IMPACT OF NEUROPATHIC PAIN

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The psychological impact of neuropathic pain is widely studied in our Pain Clinic. It’s to be differentiated from nociceptive pain in many ways, according to its subjectivity.

From psychological interviews and drawings of the painful body, we present conclusions resulting
from the study of 527 patients suffering from neuropathic pain; post lumbar surgery (350), central pain (57), amputation (48), pain after zona (27),plexopathy (22), cancer (16), from diabetic origin (7).

These psychological distinctive features could be summarized as following:

– Consequences of the time gap between the primary pathology and the future emergence of pain, as far as 40 years.
– Never felt painful sensations lead to a new bodily experience as shown by patients’drawings.
– Frequent confusion between disability and pain.
– Lack of understanding of painful sensations leading to uneasy expression of pain, to complicated relationships with familial and medical surroundings and to increased antalgic treatments.
– Frequent self-agressivity that may go from violent scratching to self amputation.

Understanding the psychological impact of neuropathic pain is essential in undertaking any kind of treatment.

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NEUROPATHIC ITCHING SYNDROME: A PRELIMINARY STUDY
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Icht is a common manifestation in systemic disease as malignancy, haematological disorders, uraemia and allergy. Microneurography studies showed that itch is mediated by a functionally distinct subset of C-fibres and dedicated neuronal pathways.

We examined six patients (3 men and 3 woman, 55–72 years-old) complaining of itch at trunk and legs, with subacute onset, several years (1–10) before our first observation. In all itch was induced by ambient warm and was associated with a persisting burning-like heat sensation. Extensive dermatologic and allergologic investigations were unrevealing; treatment with anti-histaminergic and low-dosage oral steroids for several months did not modify the clinical picture. Physical examination was negative. Patients underwent clinical, laboratory examination, Neuropathy Pain Questionary, and nerve conduction studies (NCS). Small fibre impairment was investigated by skin biopsy at proximal thigh (Pth) and distal leg (Dl) and quantitative sensory testing (QST).

Neurological examination showed the presence of thermal hypoesthesia in 3 patients, warm hyperalgesia in 3 patients. Laboratory investigations revealed only in one pt mild eosinophilia, in 1 pt neutrophilic leukocytosis, whereas chemistry profile, serum and urine immunofixation, screening for immunologic, infectious, and neoplastic disease in all was negative. Cerebrospinal fluid examination performed in 2 patients was normal. Nerve conduction studies and needle electromyography, was normal. Intraepidermal nerve fibre (IENF/mm) density was reduced in all patients, (pth 9.46/ mm ± 4.09; dl 5.04/mm ± 2.51).

Our preliminary data show the presence in this kind of pts with distinctive feature of itch and functional and histological impairment of small fibres, of itching small fiber neuropathy.

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PERIPHERAL NERVE AXOTOMY BUT NOT TISSUE INFLAMMATION CAUSE INCREASED HCN-1 IMMUNOREACTIVITY IN RAT DRGS
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Ih (Hyperpolarization-activated current) and the associated HCN1 (hyperpolarization-activated cyclic nucleotide-modulated) channel in dorsal root ganglion (DRG) neurons have been implicated in neuropathic pain (Chaplan et al., 2003). Their reported decrease in HCN1 protein immunoreactivity in injured large DRG neurons after spinal nerve injury was inconsistent with their findings of increased Ih expression in these neurons.

We examined immunocytochemically whether HCN1 expression is altered in DRG neurons in animal models of chronic inflammatory and neuropathic pain as follows. The CFA model involved intradermal injections (100 μl) of complete Freund’s adjuvant (CFA) into the foot and knee region. The mSNA (modified spinal nerve axotomy, SNA) model involved L5 SNA plus loose ligation of L4 spinal nerve with the inflammation-inducing chromic gut. In mSNA (7 days postoperatively), CFA (4 days post-injection) and normal (untreated) rats, image analysis of HCN1 staining intensity allowed
quantitative comparison between ipsilateral and contralateral L5 DRGs within each group and between groups.

Significant increases in HCN1 immuno-intensity in cytoplasm of medium and large neurons and in rings (membrane-associated densely-staining rings) of medium-sized neurons were found in ipsilateral vs contralateral L5 DRGs after nerve injury. After inflammation the only change detected was decreased ring immuno-intensity in large neurons. The post-axotomy changes may explain Chaplan’s previous findings of axotomy-induced increased Ih expression in large DRG neurons associated with increased spontaneous firing in A-fibre neurons. Together they suggest a contribution of HCN1/Ih to neuropathic pain especially if these changes occur in nociceptors.

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SENSITIZATION OF CORNEAL COLD-SENSITIVE NERVE TERMINALS FOLLOWING SURGICAL LESION
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Alteration of membrane properties, ion channel expression and signalling molecules have been described in the soma of axotomized neurons, but it is not clear to what extent these changes occur in the nerve terminals. The cornea is densely innervated by different types of sensory receptors and provides a model for recording nerve terminal impulses (NTIs) from single endings in intact and injured tissue. We recorded activity of cold-sensitive terminals after performing a surgical injury to the guinea-pig cornea. NTIs were recorded at various time points post-surgery in the excised cornea in vitro. Corneas were pinned in a recording chamber superfused with physiological saline at 35 °C. Extracellular recordings of NTIs were made with glass electrodes and thermal stimuli were delivered using a Peltier device. Cold receptors were identified by their spontaneous activity (SA), which increases on cooling and silences on warming. Drugs were tested via application to the bathing solution. NTIs recorded in the vicinity of the lesion showed lower cooling thresholds, increased SA, and increased cold-evoked peak frequencies compared to intact corneas. Sodium channel blocking drugs attenuated SA in both intact and injured corneas but with a higher IC50 in the latter. These results indicate that injured cold-sensitive nerve endings maintain their characteristic spontaneous activity that increases with cooling, albeit at higher frequencies. This enhanced frequency may be due in part to an increased expression of sodium channels.

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THE EFFECT OF A NEW PHYSICAL THERAPY METHOD ON DIABETIC NEUROPATHIC PAIN
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Background. Diabetes mellitus is a common endocrine disease which causes several problems in different part of the body. Peripheral diabetic neuropathy is a most noticeable one, leading to bilateral pain in some diabetic patient especially in distal parts of the upper and lower limbs.

Aims. To determine the effect of a new physical therapy method in relieving the neuropathic pains in diabetic patients.

Methods. Six diabetic patients who had bilateral pain in their limbs were selected (4 men, 2 women) and received special physical therapy method for 15 days continuously as follow:

(a) Ultrasound (5 min continuous type 1 W/cm²), for forearms and hands in upper limbs and legs and feet in lower limbs.
(b) TENS (trans cutaneous electrical nerve stimulation, 20 min, Burst type), for forearms and hands in upper limbs and legs and feet in lower limbs.
(c) Neodynator (5 min LP wave, and 5 min DF wave immediately) for forearms and hands in upper limbs and legs and feet in lower limbs.

Results. Statistical analysis of the results proved the significant pain relief in diabetic patient after 15 days. (p ≤ 0.05). The cases who received the above treatment
were also followed up for a 2 month period, while in none, the pain was again observable.

Conclusion. So this study showed that above physical therapy treatment method are effective for relieving the neuropathic pains in diabetic patients.

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268 TEMPORAL SUMMATION IN CHRONIC NEUROPATHIC PAIN PATIENTS
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Background and aims. We investigated the relationship between stimulus intensity and frequency required to evoke temporal summation of pain, using a surrogate human pain model. An initial study on healthy volunteers showed a relationship between stimulus intensity and frequency required to evoke pain and excellent reproducibility of pain threshold for all frequencies, with no adverse effects. We repeated the study using patients with chronic neuropathic pain to investigate any differences compared to healthy volunteers, and to help validate the model for future analgesic studies.

Methods. Sixteen patients with chronic neuropathic pain participated in this two visit study. Electrical stimulation was delivered above the right sural nerve using adhesive electrodes. Electrical pain threshold was determined using single 1 ms square wave pulses, then Train of five 1 ms pulses were used to determine temporal summation threshold. Stimuli were delivered at different frequencies and at intensities normalized to EPT. The lowest intensity perceived as painful was described as TST. Each measurement was repeated three times and the mean value used for statistical analysis.

Results. We observed temporal summation in chronic neuropathic pain patients.

Conclusions. This study is the first to investigate temporal summation in patients with chronic neuropathic pain.

The intensity of the stimulation required to evoke temporal summation of pain decreased following an increase in the frequency of delivered stimuli.

The tolerability and reproducibility of our surrogate human pain model suggests it is suitable for use in the pharmacological characterization of analgesics.

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269 DIPYRONE-MAGNESIUM, A NEW ALTERNATIVE TO TREAT NEUROPATHIC PAIN?
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Neuropathic pain can be caused by primary lesion or dysfunction in the nervous system and is associated with abnormal sensory signs, such as allodynia and hyperalgesia. Here we studied the effect of dipyrone (DIP), a non-opioid analgesic, and magnesium (Mg2+), an NMDA receptor blocker, on the chronic constriction injury (CCI) of the sciatic nerve in male Sprague–Dawley rats (200–240 g). Guidelines of the Society for Neuroscience for the use of animals in experimentation were followed throughout. The development of hyperalgesia, allodynia and the analgesic effectiveness was monitored daily with von Frey filaments and the Hargreaves and hot plate tests. Once neuropathy was installed the animals received either 150 mg/kg of DIP, 200 mg/kg of MgCl2, or saline, (i.p.), BID, for three days and analgesia was tested 30 min later. In order to prevent the development of tolerance, another group received a combination of DIP and MgCl2 (5 min between each injection, same protocol as before). The results showed that administration of DIP or MgCl2 reversed the allodynia and hyperalgesia in neuropathic animals (p < 0.01 vs. control). However, the analgesic potency of DIP gradually decreased during the treatment (tolerance). The combined treatment of DIP and MgCl2 not only blocked the development of tolerance but also increased (p < 0.01 vs. control) the antinociceptive effect. According to these results, the combination DIP-Mg can be used: (a) As a therapeutic alternative to treat neuropathic pain, (b) to prevent tolerance to DIP when continuous administration is required, or (c) to boost up the analgesic effectiveness of the non-opioid analgesic.

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270 SELECTING AN APPROPRIATE MEDICATION FOR TREATING NEUROPATHIC PAIN IN PATIENTS WITH DIABETES: A STUDY USING THE UK AND GERMANY MEDIPLUS DATABASES
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Background and aims. Diabetic neuropathic pain (NeP), a frequent complication of diabetes, is often challenging to manage. Recently several antidepressants (e.g., paroxetine, duloxetine), anticonvulsants (e.g., pregabalin, carbamazepine), and opioids (oxycodone, hydrocodone) have been recommended/approved for treating NeP. The successful management of NeP and other diabetic comorbidities may require the use of multiple medications concurrently. Because physicians are adding to an already full palette, selecting a NeP medication that minimizes the possibility of drug-drug interactions and untoward medical consequences is imperative.

Methods. Using IMS Mediplus Databases, we evaluated the appropriateness of prescribing select NeP medications to diabetes patients based on the potential for CYP450-based interactions with medications diabetes patients were taking chronically (continuously for ≥ 3 months). A total of 40,448 (63.6 ± 16.6 years, 51% male) and 31,930 (68.9 ± 12.7 years, 46% male) patients with diabetes in UK and Germany, were identified, and patients’ medication use profiles from 4/04 to 9/05 were evaluated. The study protocol was approved by the Independent Scientific and Ethical Advisory Committee.

Results. Frequently prescribed medications included: UK (aspirin [33.7%], metformin [32.7%], simvastatin [25.5%], atorvastatin [19.4%], atenolol [18.1%]); Germany (hydrochlorothiazide [35.82%], aspirin [25.2%], metformin [21.6%], metoprolol [20.3%], simvastatin [18.3%]). Several NeP medications have potential for drug-drug interactions with medications prescribed to diabetes patients. Examples include (NeP medications vs. diabetes/comorbidities medications): duloxetine, paroxetine, and methadone (CYP2D6 inhibitors) and oxycodone, hydrocodone (CYP2D6 substrates) vs. atenolol and metoprolol (CYP2D6 substrates); and carbamazepine (CYP3A inducer) vs. simvastatin, atorvastatin (CYP3A substrates).

Conclusions. Our findings underscore the need for medical vigilance while selecting medications for treating NeP in diabetes patients.

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271 SYSTEMIC AND LOCAL LIDOCAINE SUPPRESSES ECTOPIC SPONTANEOUS ACTIVITY IN LESIONED A-AFFERENTS, BUT NOT IN C-AFFERENTS

272 SELF-ADMINISTRATION OF A CANNABINOID CB2 AGONIST IN AN ANIMAL MODEL OF NEUROPATHIC PAIN

Topical or systemic lidocaine is successfully used in treatment of neuropathic pain (Mao, Chen, Pain 2000;87:7; Meier et al., Pain 2003;106:151) and suppresses pain-like behavior in animals with an experimental nerve lesion (Jasmin et al., Pain 1998;75:367; Sinott et al., Pain 1999:80:521). It is generally believed that low concentration of a local anesthetic blocks a certain type of Na⁺ channels in lesioned primary afferents, inhibits their ectopic activity and in this way suppresses pain. However, it is still unclear which type of afferent nerve fiber is involved.

Using an in vivo electrophysiological approach, we tested whether lidocaine applied locally along the regenerating nerve (0.001, 0.01, 0.1 and 1 mg/ml) or intravenously (0.03, 0.1, 0.3, 1 and 3 mg/animal) influences ectopic spontaneous activity in regenerating afferent nerve fibers 5–11 days after sural nerve crush in Wistar rats (N = 14). Lidocaine suppressed dose-dependently spontaneous activity in most A-fibers (in 15/17 or 16/23 after systemic or local application, respectively). Most fibers tested reacted at low doses. By contrast, rate of spontaneous activity was decreased only in 4/11 C-afferents by the highest doses.

In conclusion, lidocaine given intravenously or locally suppresses ectopic ongoing activity in regenerating myelinated afferent fibers but is rather ineffective to suppress activity in regenerating unmyelinated afferent fibers. These results argue that spontaneous activity in lesioned afferent neurons with myelinated fibers may be important in central sensitization generating and maintaining in this way neuropathic pain.

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We evaluated the impact of neuropathic pain on the propensity of rats to self-administer the cannabinoid CB2 agonist AM1241. CB2 is prevalent outside the central nervous system (CNS) and is induced in the CNS by traumatic nerve injury. A unilateral spared nerve injury was performed to induce neuropathic pain. Control rats were subjected to a sham surgery and naive animals were left intact. All animals were surgically implanted with an indwelling jugular catheter to allow intravenous drug self-administration. Mechanical withdrawal thresholds were evaluated before and after surgical procedures and each self-administration session. Self-administration of AM1241, but not vehicle, increased mechanical withdrawal thresholds in neuropathic rats. Changes in mechanical withdrawal thresholds were absent following AM1241 self-administration in naive and sham-operated rats. Drug self-administration, as represented by the number of lever presses on the active but not the inactive lever, was observed in all groups receiving AM1241 on day 1. By contrast, there was no difference in the number of lever presses on the active and inactive levers in rats receiving vehicle. AM1241 self-administration was increased in neuropathic groups relative to control conditions. Pretreatment with the CB2 antagonist SR144528 blocked the AM1241-induced suppression of nerve injury-induced tactile allodynia and attenuated responding on the active but not the inactive lever. Our data demonstrate that self-administration of a CB2 agonist suppresses nerve injury-induced tactile allodynia. The contribution of central and peripheral CB2 receptors to AM1241 self-administration remains to be determined.

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ANTIEPILEPTIC DRUGS IN PAIN CAUSED BY DIABETIC NEUROPATHY

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BEHAVIOURAL RESPONSES AND PRE-EMPTIVE EFFECT OF MK-801 AND MORPHINE IN SNI MODEL IN THE ADULT RAT

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Background and aims. Neuropathic pain syndromes are changes resulted from damage to nervous system. Since, treatments of neuropathic pain are poorly understood and existing treatments are often ineffective. The purpose of this study was to investigate the behavioral responses and involvement of pre-emptive treatment of morphine and/or NMDA receptor antagonist MK-801, in Spared nerve injury (SNI) model of neuropathic pain.

Methods. Experiments were performed on six groups (n = 8) of male Sprague–Dawley rats (230–280 g). In the four groups of received drugs, two groups were injected with MK-801 (0.3 mg/kg, 20 min before, and 6 h after the operation) or morphine (8 mg/kg, 30 min prior to the operation). Another group received both drugs with the same doses and protocols. Finally, group received an equal volume of saline. The animals were tested for allodynia and hyperalgesia reactions at 0, 3, 7, 14, 21 and 28 days after SNI of the sciatic nerve. Repeated measures ANOVA was applied to the results of behavioral testing and followed by the Tukey HSD test.

Results. Our data revealed that the SNI produces mechanical and cold allodynia and a hypersensitivity to noxious stimulations. Co-injection of morphine and MK-801 markedly declined cold allodynia at the day 14 (P < 0.05) when compared with the saline group.

Conclusion. Results demonstrate that the SNI model importantly influences the behavioural responses to both the thermal and mechanical stimulations. Co-administration of both drugs seems attenuates neuropathic pain in rat.

Keywords: Pre-emptive; SNI; Amputation; Allodynia; Hyperalgesia; MK-801; Morphine

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SUBCOSTAL NERVE NEURALGIA

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The subcostal nerve is the extension of the 12th intercostal nerve. It extends from the area below the 12th rib and innervates the anterior abdominal wall, part of the back below the rib cage, the groin, and the upper leg to the trochanteric area. Nerve irritation causes pain. Faulty diagnosis is often made. Diagnosis of acute abdomen has been made. In total we have seen 6 patients who have been noted to have this neuropathic syndrome. All were treated with neuropathic analgesics with good results. Since the pain is felt over a broad area and mimics other pain processes it became important to find a unifying physical sign that allows the physician to make an accurate diagnosis. In all the patients it was found that light palpation of the 12th rib was very painful and referred pain to the areas listed above. In all cases neural blockade with local anesthetic of the 12th thoracic dorsal root ganglion provided temporary relief of the pain in all areas mentioned above. In four of the patients pulsed radiofrequency of the 12th dorsal root ganglion provided prolonged relief of the pain in the areas listed above. We feel that this syndrome is present in many patients, and physicians should be made aware of it since a combination of antineuropathic medications, neural blockade, and possibly pulsed radiofrequency can alleviate the suffering of these patients. We feel that physicians must understand the distribution of the subcostal nerve and the pain it can cause.

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SELECTIVE ACTIVATION OF CANNABINOID CB2 RECEPTORS SUPPRESSES CHEMOTHERAPEUTIC NEUROPATHY EVOKED BY PACLITAXEL AND VINCristINE ADMINISTRATION

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Activation of cannabinoid CB2 receptors suppresses neuropathic pain induced by traumatic nerve injury. The present studies were conducted to evaluate the efficacy of cannabinoid CB2 receptor activation in suppressing painful peripheral neuropathy evoked by chemotherapeutic treatment. We compared the effects of a cannabinoid CB2 agonist, (R,S)-AM1241, and its resolved enantiomers, in suppressing mechanical hyper-
sensitivity induced by treatment with two structurally distinct anti-tumor agents: the vinca alkaloid vincristine and the taxane paclitaxel. We also identified the receptor mechanism mediating AM1241-induced suppressions of paclitaxel and vincristine-evoked chemotherapeutic neuropathy. Rats received intraperitoneal injections of paclitaxel (2 mg/kg per day) on four alternate days to induce mechanical hypersensitivity. Paclitaxel preferentially induced mechanical hyperalgesia, as defined by an increase in responding to noxious levels of mechanical stimulation applied using von Frey monofilaments to the plantar hindpaw surface. Separate groups received ten once-daily intraperitoneal injections of vincristine (0.1 mg/kg per day) to induce tactile allodynia. The CB2 agonist \((R,S)-\text{AM1241}\), administered systemically, suppressed mechanical hypersensitivity evoked by treatment with paclitaxel or vincristine administration. The AM1241-induced suppression of paclitaxel-evoked mechanical hyperalgesia was completely blocked by the CB2 antagonist SR144528. Moreover, R-AM1241 was more potent than S-AM1241 in suppressing paclitaxel-evoked mechanical hyperalgesia, consistent with mediation by CB2. \((R,S)-\text{AM1241}\) partially attenuated vincristine-evoked tactile allodynia. This suppression was completely blocked by the CB2 antagonist SR144528, but not by the CB1 antagonist SR141716A.

Our data suggest that cannabinoid CB2 receptor subtypes may be important therapeutic targets for the treatment of chemotherapeutic neuropathy.

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277 REORGANIZATION OF DRG NEURONS FOLLOWING CHRONIC SCIATIC NERVE CONSTRUCTION INJURY: CORRELATION WITH TOPICAL MORPHINE AND LIDOCAINE ANALGESIA

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Chronic constriction injury (CCI) of the sciatic nerve is an animal model for neuropathic pain. In this model, the analgesic potency of systemic morphine was significantly diminished in nerve injured mice (ED50 19.4 mg/kg) compared with sham-operated mice (ED50 3.3 mg/kg) using a unilateral hot plate withdrawal test, with a similar reduction in sensitivity of intrathecal morphine. The sciatic nerve injury resulted in a reorganization of the dorsal root ganglion neurons. Immunohistochemically, the chronic constriction injury triggered a withdrawal of C-fibers from the ipsilateral dorsal horn of the spinal cord. Although A-beta terminals centrally sprouted into Lamina II of the dorsal horn of the spinal cord, the peripheral A-beta fibers in the skin retracted from the epidermis to deeper layers of the dermis. To explore the functional significance of these dermal changes, we examined topical morphine and lidocaine analgesia following chronic sciatic nerve constriction. Both morphine and lidocaine retained topical activity following chronic sciatic nerve injury, but their analgesic dose–response curves were shifted to the right when compared to sham-operated mice. Thus, the chronic nerve constriction injury model is associated with pathological changes in distribution of the central and peripheral axons of the DRG neurons that correspond to a decreased pharmacological sensitivity to topical analgesic agents.

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278 INTRAEPIDERMAL NERVE FIBER DENSITY IN PATIENTS WITH CHEMOTHERAPY-INDUCED NEUROPATHY: A PROSPECTIVE STUDY


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Background and aims. Neuropathy is a main problem of chemotherapy. To describe the appearance of small fibre neuropathy, we set up a prospective study on skin biopsies in newly diagnosed cancer patients without other known cause for neuropathy.

Methods. Punch skin biopsy was obtained standardized from the distal leg using routine techniques. Specimens were routinely fixed in formalin. Using light microscopy, protein gene product 9.5 immunopositive nerves were counted morphometrically per epidermal
Results. So far we have obtained 31 biopsies from 17 patients (13M, 4F; aged 28–67 years): 3 biopsies from 4 patients, 2 biopsies from 6 patients and 1 biopsy from 7 patients. Four patients had colorectal or prostate cancer, 2 patients had lung or ventricle cancer, and 5 patients had other primary cancer. Platina derivatives were used in 7, taxanes in 6, vinca alkaloids in 2 and combination treatment in 2 cases. In the first sample, the fibre density was pathologically reduced in 12 and within normal limits in 4 patients. In patients with initially reduced fibre density and subsequent samples obtained (7 cases), improvement of the fibre density was observed in 6 cases. The updated data will be shown in the final poster.

Conclusions. The neuropathy seen in the majority of our patients receiving chemotherapy was actually present already before the treatment. We suggest advanced age and subclinical paraneoplastic neuropathy as explanations for our findings.

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LEUKOCYTE-DERIVED OPIOIDS PRODUCE PERIPHERAL ANTINOCICEPTION IN NEUROPATHIC PAIN

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Background and aims. Immune cell-derived opioid peptides can decrease inflammatory pain in response to injection of corticotropin-releasing factor (CRF). Neuropathic pain results from nerve injury that can lead to inflammation. Here we examine the contribution of leukocyte-derived opioids and peripheral opioid receptors to CRF antinociception in the chronic constriction injury (CCI) neuropathic pain model.

Methods. At 2 and 14 days after CCI, we examined the expression of CRF- and mu-opioid receptors by immunohistochemistry, the quantity of opioid-containing leukocytes by flow cytometry, and nociceptive thresholds in hind paws by the von Frey test before and after CRF injected at the CCI site alone or together with antibodies neutralizing opioid peptides, antagonists at CRF- and opioid-receptors, or after intraperitoneally injected antibody blocking intercellular adhesion molecule-1 (ICAM-1) in wild type and beta-endorphin knockout mice.

Results. At the injury site we found accumulation of mu-opioid receptors and opioid-containing leukocytes expressing CRF receptors. In wild type mice, but not in beta-endorphin knockout mice, CRF injected at the CCI site produced local antinociception that was reversed by antibodies against beta-endorphin, met-enkephalin and dynorphin, by selective mu-, delta- and kappa-antagonists, by a peripheral opioid receptor antagonist, by a CRF receptor antagonist, and by anti-ICAM-1 antibody.

Conclusions. CRF antinociception apparently results from activation of peripheral opioid receptors by opioids derived from leukocytes which use ICAM-1 to accumulate at the injured nerve. Thus, challenging the notion on predominate detrimental effects of neuroimmune interactions, our studies suggest that neuropathic pain can be diminished when leukocyte-derived opioids come into play.

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280 DRUG SELECTION ALGORITHM FOR LONG TERM INTRATHECAL THERAPY IN THE MANAGEMENT OF NEUROPATHIC PAIN


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Introduction. Neuropathic pain is usually refractory to a conventional therapy so we can look for alternatives like intrathecal therapy. There are many different drugs we can administer but the use of most of them alone or in combination is under discussion. Which one, when, what doses and how long to use are the keys to a good clinical practice.

It needs an evidence based medicine criteria to establish safety and efficacy in clinical practice.

Method. Based on clinical experience and up to date published data we consider five lines of treatment. We establish as well a step by step strategy to manage different drugs considering synergistic and or additive association to reduce the secondary effects and potentiate the analgesic ones.

Results. We have design a consensus document under the format of algorithm with two main goals: to help in the decision making process to health care providers and
to offer a therapeutic alternative with high efficacy and safety profile.

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CHARACTERISTIC SENSORY PROFILE IN FABRY PATIENTS
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Background. Anderson–Fabry disease is an X-linked recessive lysosomal storage disorder resulting from deficient alpha-galactosidase and causes neuropathic pain, progressive renal impairment, cardiomyopathy, and cerebrovascular disease. Even though an effective treatment with recombinant human alpha-galactosidase is available since 2001, the current problem is often the delayed or missed diagnosis. Neuropathic pain is mostly the first symptom, has the highest prevalence and gives the opportunity to detect Fabry patients earlier.

Methods. Between November, 2005, and July, 2006, 12 male Fabry patients aged 33–57 years were examined at the back of the hands and feet with the standardized quantitative sensory testing (QST) protocol of the german research network on neuropathic pain (DFNS), which characterizes the somatosensory phenotype of patients with neuropathic pain.

Results. Ten of 12 male Fabry patients had an isolated and uniform small fiber loss with an extraordinary increase of cold detection threshold and pathological raised warm detection threshold and thermal sensory limen. The remaining 2 patients had large fiber participation due to long lasting renal failure.

Conclusions. We have shown a characteristic sensory profile in heterozygous Fabry patients which differs significantly from the sensory profile of painful sensory neuropathies and of painful small-fiber neuropathies of other origin. As a result of these findings, it is possible to establish a simplified neurological testing procedure to detect Fabry disease in an early stage of the disease.

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THE CANNABINOID AGONIST WIN 55,212-2 BOTH REVERTS AND PREVENTS SIGNS OF PERIPHERAL NEUROPATHY INDUCED BY CHRONIC CISPLATIN IN THE RAT
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Backgrounds and aims. Cannabinoids exerted antinociception in a model of neuropathic pain induced by chronic administration of the antitumoral drug paclitaxel (Pascual et al., 2005). Our aim was to investigate whether cannabinoids could revert and/or prevent signs of neuropathic pain (mechanical allodynia) induced by
chronic administration of other antitumoral drug, cisplatin.

Methods. Overall health of male Wistar rats was checked 5 days a week for 6 consecutive weeks (W0–W5). Drugs were administered on Monday (except for W0) and the threshold for mechanical allodynia (using von Frey filaments) was tested on Friday each week. Each rat received an injection of saline or cisplatin (1 mg/kg/week, i.p.). The non-selective cannabinoid agonist WIN 55,212-2 (WIN, 1 mg/kg, i.p.) was administered either: (1) at the end of the chronic treatment with cisplatin (on Friday, W5, the threshold for mechanical allodynia was tested twice, before and 30’ after administration of WIN); (2) during the chronic treatment with cisplatin (the rats received WIN before each cisplatin administration and the thresholds were evaluated as described).

Results. The cannabinoid was able to both revert (a) and prevent the allodynic effect of chronic cisplatin (b).

Conclusions. These results confirm the antinociceptive properties of cannabinoids in another model of peripheral neuropathy. More interestingly, cannabinoids could be useful to prevent this adverse effect of chemotherapy.

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283 NEUROPATHIC PAIN IS ATTENUATED BY A VIRAL VECTOR TARGETING NORADRENERGIC INPUT TO THE DORSAL RETICULAR NUCLEUS

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Neuropathic pain represents a therapeutic challenge as it is often refractory to conventional therapies. As an alternative approach, virus-mediated gene transfer to the peripheral nervous system has proven efficient. We sought to attenuate the behavioural manifestations of neuropathic pain in the spared nerve injury (SNI) model by targeting a supraspinal pro-nociceptive nucleus, the dorsal reticular nucleus (DRt), using a herpes simplex virus type 1 (HSV-1) vector containing the tyrosine hydroxylase (TH) promoter, thus restricting activity to catecholaminergic neurons. This viral construction was elected because we showed previously that injection of HSV-1 into the DRt leads to transduction of its noradrenergic brain afferents and that DRt administration of α1 and α2 adrenoreceptor agonists affects behavioural nociceptive responses in the SNI model. Fourteen days after SNI induction, male Wistar rats were stereotaxically injected in the DRt with an HSV-1 vector containing the TH promoter driving transcription of the TH cDNA in antisense orientation or driving lacZ in the virus control. Mechanical hyperalgesia and cold allodynia, evaluated by the pinprick and acetone tests, respectively, were significantly attenuated 4 days after injection of therapeutic virus, but not the control. Attenuation of mechanical hyperalgesia and cold allodynia, by the therapeutic virus, persisted for 22 and 60 days, respectively, and was reversed by DRt injection of the α1 adrenoreceptor agonist phenylephrine. The results demonstrate that the selective manipulation of the supraspinal noradrenergic pain modulation system by gene therapy is a useful strategy for a sustained reversal of neuropathic pain.

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284 TREATMENT OF PAIN SECONDARY TO DIABETIC PERIPHERAL NEUROPATHY (DPN) WITH THE PRECISION SPINAL CORD STIMULATION (SCS) SYSTEM: A CASE SERIES

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The most common complication of both types I and II diabetes mellitus present among more than 50% of diabetic individuals is DPN, characterized by superficial burning, numbness, skin hypersensitivity, and pain affecting the feet and lower extremities. Although pain management via oral medications and topical creams comprises the most common treatment approach, lack of efficacy renders neuropathic pain a physically and emotionally debilitating burden. While limited, some data suggest that SCS may have utility as a treatment modality for neuropathic pain associated with DPN. The following five case descriptions based on retrospective chart review support these earlier literature reports.
All patients complained of burning, throbbing pain, “pins and needles”, and numbness in their lower extremities, characteristic of DPN. Previous treatments which had provided various levels of temporary relief included nerve blocks, sympathectomy, TENS unit, and opioid therapy. All patients reported immediate and significant pain relief during the trial stimulation as well as maintained pain relief after implantation of the permanent system. In addition to improved sensation and decreased numbness, the feet were described as warmer, reflecting improved circulation. Other positive treatment outcomes included decreased use of opioids and increased comfort during sleep.

SCS treatment was successful in providing continuous pain relief in five patients who had failed other therapies. Secondary to pain relief, patients experienced improved peripheral sensation and circulation, decreased opioid use, and improved sleep. We conclude that SCS therapy should be considered in treating neuropathic pain associated with diabetes, suggesting that the benefits may extend beyond pain relief.

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ABNORMALITIES IN SMALL FIBRE STRUCTURE AND FUNCTION IN FEMALE FABRY PATIENTS
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Background. Fabry’s disease is a rare X-linked lysosomal storage disease caused by dysfunction of the enzyme α-galactosidase with subsequent accumulation of glycosphingolipids in multiple organs.

Neurological manifestations are evident from youth in male patients and include small-fibre neuropathy and early strokes. Females with X-linked diseases usually show no or only minor symptoms, but in female Fabry patients severe neuropathic symptoms may occur. So far, there has been no systematic study of peripheral nerve function or structure in female Fabry patients.

Aim. The aim was to study peripheral nerve structure and function with emphasis on small fibres and whether the phenotypic heterogeneity is due to skewed X-chromosome inactivation.

Methods. In 19 females patients and in a sex- and age-matched control group (N = 19) extensive examinations were performed. These included history, neurological examination, quantitative sensory testing (QST), capsaicin challenge followed by Laser Doppler flow, sudomotor testing (QSART), immunohistochemical examination of skin biopsies and X-chromosome inactivation measurement in blood and fibroblast.

Results and discussion. For the first time, we have shown that females carrying the Fabry mutation have a reduced number of C fibres (p < 0.05). Small-fibre function is impaired evidenced by a reduced capsaicin flux and hyperalgesia response (p < 0.05), as well as a reduced total sweat response to QSART (p = 0.04). No correlation of X-chromosome inactivation and the degree of C-fibre loss was detected. This disputes skewed X-chromosome inactivation as the current speculation of phenotypic heterogeneity.

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DIFFERENCE BETWEEN HEAT PAIN AND WARM PERCEPTION THRESHOLDS IN PATIENTS WITH POLYNEUROPATHY AND HEALTHY INDIVIDUALS
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Background and aims. Elderly individuals and patients with polyneuropathy often perceive heat pain instead of or almost at the same time as warm perception when quantitative sensory testing (QST) is performed. We therefore compared the difference between heat pain and warm perception thresholds (DiffHP-WT) in order to explore whether this parameter is more strongly expressed in patients with peripheral neuropathy than in age and gender matched healthy individuals.

Methods. Thirty six patients (23 women, 13 men, 52.8 ± 12.2, range 33–75 years) with symptoms and signs of peripheral polyneuropathy matched according the age and gender with 36 healthy persons (53.0 ± 12.3, range 34–74 years) were included. QST (using method of limits) was performed with SENSELab-THERMOTEST (Somedic, Sweden) recording warm, cold and heat pain perception thresholds on the distal calf and on the dorsal foot. DiffHP-WT in these locations was then calculated.

Results. DiffHP-WT in the lower calf of the patients was 3.4 ± 3.5 and 5.9 ± 3.6 °C in the controls (p = 0.007), while on the foot it was 3.6 ± 2.9 versus 5.3 ± 3.8 centigrades (p = 0.03). Only DiffHP-WT in the foot was significantly associated with age in patients (r = 0.63, p = 0.0001) as well as in controls (r = 0.45, p = 0.006). There were no differences between patients with and without neuropathic pain.
Conclusions. QST with recording of temperature and pain perception thresholds is a useful and sensitive method in evaluation of patients with small fiber polyneuropathy. We propose difference between heat pain and warm perception thresholds (DiffHP-WT) as an additional parameter reflecting the functional condition of unmyelinated C-fibres.

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VASCULAR AND NEUROPROTECTIVE EFFECT OF COMP-ANGIOPOIETIN-1 IN DB/DB MICE DIABETIC NEUROPATHY MODEL
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Background. Vascular and neuropathic processes have been recently seen as underlying the pathogenesis of diabetic neuropathy. Angiopoietin-1 (Ang1) plays essential roles in regulating vascular growth, development, maturation, permeability, and inflammation. We used a soluble, stable, and potent Ang1 variant, cartilage oligomeric matrix protein (COMP)-Ang1.

Methods. db/db mice were treated with recombinant adenovirus expressing either COMP-Ang1 or LacZ. Epidermal nerve and dermal vascular changes of foot skin were evaluated and measured current perception threshold of the epidermal nerve fiber function.

Results. COMP-Ang1 significantly decreased fasting blood glucose level, epididymal fat weight to body weight ratio, and epididymal adipocyte size in diabetic db/db mice. After intraperitoneal glucose challenge, COMP-Ang1 significantly lowered plasma glucose levels and increased current perception threshold in epidermal nerve C-fiber. COMP-Ang1 significantly preserves the epidermal nerve fiber density and skin capillary number.

Conclusion. We conclude that COMP-Ang1 preserve epidermal skin nerve and capillary vessels in the foot dorsum of diabetic db/db mice through its vascular and metabolic effects and preserve epidermal C-fiber function.

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THE EFFECT OF ACUPRESSURE ON PHANTOM PAIN IN CLIENT WITH EXTREMITIES AMPUTATION
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Background. This is clinical trial, single blind study that has been conducted in order to determine the effect of acupressure on Phantom pain in client with Extremities amputation.

Material and methods. Forty-one patients were selected according to special characteristics was interviewed some demographic data such as; gender, age, marital status, number of family, data of amputation, reason and area of amputation, intensity and appeased factors of phantom pain and severity of pain was determined and controlled with MC GILL visual Analogue scale before and after acupressure findings were statistically by using SPSS software.

Results. Analyzing statistical tests, indicates that acupressure treatment can decrease intensity of phantom pain (p < 0.0001) and decrease amount of medications (p < 0.005) and both of hypothesis were accepted.

Keywords: Phantom pain; Acupressure; Amputation

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CANNABINOIDs SUPPRESS CHEMOTHERAPY-EVOKED PAINFUL PERIPHERAL NEUROPATHY THROUGH SPINAL SITES OF ACTION
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Chemotherapeutic treatment can induce several severe side-effects including neuropathic pain. The present studies were conducted to evaluate the sites of action of cannabinoids in suppressing mechanical hypersensitivity (tactile alldynia) induced by treatment with the anti-tumor agent vincristine in rats. Tactile alldynia developed over the course of ten once-daily injections of the vincristine relative to groups receiving saline at the same times. Systemic administration of the cannabinoid agonist WIN55,212-2 suppressed painful peripheral neuropathy evoked by vincristine administration in rats. This suppression was mediated by both CB1 and
CB2 receptors. Intrathecal administration of WIN55,212-2 (10 and 30 µg i.t.) induced a dose-dependent suppression of vincristine-evoked tactile allodynia. By contrast, WIN55,212-3, the receptor-inactive enantiomer of WIN55,212-2, failed to alter vincristine-evoked tactile allodynia. Intrathecal co-administration of both the CB1 antagonist SR141716 (30 µg i.t.) and the CB2 antagonist SR144528 (30 µg i.t.) blocked the cannabinoid-induced suppression of vincristine-evoked tactile allodynia. These data suggest that the anti-allodynic effects of WIN55,212-2 were mediated by both CB1 and CB2 receptors. WIN55,212-2 suppressed vincristine-evoked tactile allodynia following intrathecal administration at doses that did not alter mechanical withdrawal thresholds following local administration into the hindpaw. Our results demonstrate that cannabinoids suppress the maintenance of vincristine-induced tactile allodynia through actions mediated, at least in part, at the level of the spinal cord. Our data further suggest that cannabinoid CB1 and CB2 receptor subtypes may be important therapeutic targets for the treatment of chemotherapeutic neuropathy.

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EFFICACY AND SAFETY OF PREGABALIN AS TREATMENT OF PAINFUL DIABETIC PERIPHERAL NEUROPATHY (DPN): A 13-WEEK RANDOMIZED CONTROLLED TRIAL AND 6-MONTH SAFETY EXTENSION

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Objective. To evaluate the efficacy and safety of pregabalin 600 mg/d (BID) as treatment of painful DPN.

Methods. Eighty-two patients were randomized to pregabalin, 85 to placebo. After 1-week dosage escalation, pregabalin patients received 600 mg/d for 12 weeks. Primary efficacy measure was endpoint mean pain score (MPS) on a 0–10 scale from patients’ daily diaries. Secondary efficacy measures included weekly MPS and endpoint and weekly sleep-interference scores (0–10 scale). Safety endpoints were amplitude and conduction velocity for median-motor, median-sensory, ulnar-sensory, and peroneal-motor nerves assessed at baseline, endpoint, and 2-week follow-up.

Results. Endpoint MPS was significantly lower in pregabalin versus placebo patients (mean difference, −1.28; P = 0.0003), and improvement with pregabalin was statistically significant at every weekly timepoint. Pregabalin was significantly superior for reducing pain-related sleep-interference score at every weekly timepoint (except Weeks 9, 10) and at endpoint (mean difference, −1.08; P = 0.0019). No statistically significant difference in amplitude or velocity was observed for the four nerves tested. In this trial’s open-label extension, patients received 150–600 mg/d pregabalin (BID), adjusted to optimize efficacy/tolerability, for up to 6 months. Patients (97%) received ≥ 300 mg/d. Pregabalin was generally well tolerated: 70/104 patients completed 24 weeks of open-label treatment, while 15/104 withdrew because of AEs. Peripheral edema, dizziness, and somnolence were the most common AEs associated with treatment.

Conclusions. During 13-week double-blind treatment, pregabalin 600 mg/d showed robust efficacy for improving pain and sleep with no meaningful effect on nerve conduction. Pregabalin was generally well tolerated during 13-week double-blind and 6-month open-label treatment.

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EXPRESSION OF PERIPHERAL OPIOID RECEPTORS AND PEPTIDES IN A NEUROPATHIC PAIN MODEL

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Background and aims. Inflammatory pain can be effectively controlled by exogenously applied and immune cell-derived opioids (released from leukocytes by corticotropin-releasing factor [CRF]), acting at peripheral opioid receptors. Neuropathic pain due to traumatic nerve injury (e.g. compression, limb amputation) can involve inflammation. Our aim was to investigate the expression of peripheral opioid receptors, opioid peptides and CRF receptors in the chronic constriction injury (CCI) model of neuropathic pain in mice.
Methods. We assessed nociceptive thresholds in the hind paws with the von Frey test before and up to 21 days after CCI of the sciatic nerve. At 2 and 14 days after CCI we investigated the expression and quantified opioid receptor-positive cells in the lumbar (L4-5) dorsal root ganglia (DRG) with immunohistochemistry. In the sciatic nerve we analyzed the co-expression of opioid receptors with calcitonin gene-related peptide (CGRP), and of opioid peptides with CRF receptors using double immunofluorescence.

Results. All mice developed mechanical allodynia. Mu- and kappa-opioid receptors were expressed in the DRG cells, and their numbers did not significantly change within the course of CCI neither in the ipsilateral nor in the contralateral DRG, as compared with sham-operated animals. In the ligated nerve mu-, kappa- and delta-receptors were co-expressed with CGRP, a marker of sensory nerve fibers. Furthermore, beta-endorphin, met-enkephalin and dynorphin as well as CRF receptors were expressed in immune cells accumulating at the ligated nerve.

Conclusions. Our results demonstrate a cellular basis for the peripheral antinociception mediated by exogenous and immune cell-derived opioids in neuropathic pain.

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T LYMPHOCYTES CONTRIBUTE TO OPIOID PAIN CONTROL IN NEURITIS
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Background and aims. Inflammatory pain can be attenuated by leukocyte-derived opioid peptides (e.g. beta-endorphin) in response to injection of corticotropin-releasing factor (CRF). Neuropathic pain resulting from the nerve injury can involve inflammation. Our goal was to investigate the impact of T lymphocyte deficiency on opioid-mediated pain control in neuropathy.

Methods. Experiments were performed at early (2–3 days) and late (14–15 days) stages after chronic constriction injury (CCI) of the sciatic nerve in wild-type and mice with severe combined immunodeficiency (SCID). Nociceptive thresholds were measured with the von Frey test before and after CRF injected alone or together with beta-endorphin antibody or opioid receptor antagonist at the CCI site. Leukocyte subpopulations were analyzed with flow cytometry.

Results. Wild-type and SCID mice developed allodynia in CCI paws. In wild-type mice about 35% of leukocytes accumulating at the ligated nerve contained opioid peptides at both stages after CCI. Granulocytes and macrophages dominated at early stage while later also T cells were present in wild-type mice. Injection of CRF at the ligation site produced a similar-degree antinociception at both stages that was blocked by beta-endorphin antibody and by peripheral opioid receptor antagonist. In SCID mice, leukocyte subpopulations and CRF antinociception were not different from wild-type mice at early CCI stage. However, at late stage T cells were absent and CRF antinociception was significantly decreased in SCID mice.

Conclusions. Our data suggest that T lymphocytes contribute to the endogenous opioid-mediated antinociception in painful inflammatory neuropathy.

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dependent profiles during a pause (0 Hz, open bar), baseline stimulation (0.25 Hz) and tetanus (2 Hz, filled bar) characteristic of C-nociceptors, showing abnormal bursts of spontaneous impulses (arrows). DNA profiling is underway, but no definitive answer is available yet.

Conclusions. We have identified ectopic impulse generation from diseased C-nociceptors in these two patients with familial erythromelalgia. This finding probably explains the experience of spontaneous burning pain in this condition.

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women in the reference group. After 1 written reminder 225 (85.2%) of the breast cancer patients and 575 (74.2%) of the reference subjects had returned the questionnaire.

We found that the prevalence of PMPS was 31.8%. In the reference group 10.8% of the women reported pain that fulfilled the criteria of the PMPS. The odds ratio for developing PMPS was 2.95 (95% confidence interval 1.89–4.62). The possible risk factors for developing PMPS, determined by odds ratios, were having undergone breast surgery at an earlier stage, location of the tumour, mastectomy (vs. lumpectomy) and postoperative chemotherapy.

Conclusion. This study shows that, although recent advances in the diagnostic and surgical procedures have reduced the frequency of the more invasive surgical procedures, there is still a considerable risk of developing PMPS after treatment of breast cancer.

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**Poster Presentation 2: Central Pain**

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**TOPOGRAPHIC DISTRIBUTION AND POSTSYNAPTIC RESPONSES OF NOCICEPTIVE NEURONS OF THE SOMATOSENSORY CORTEX DURING PAINFUL STIMULATION**

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Studies were made on the topographic and layered distribution of nociceptive and convergent neurons of somatosensory cortex and neurophysiological characteristic of its synaptic reaction.

Activity of cortical neurons were registered intracellularly with the use of standard methodical receptions.

Convergent neurons with wide receptive fields are seen on the superficial neurons of I and II layers of somatosensory cortex. Nociceptive neurons are registered mostly in II, IV and seldom in V layers. Single sub-threshold stimulation of the tooth pulp elicited EPSP only of the low amplitude, while increasing of the nociceptive stimulation, along with increased amplitude of EPSP, induced hyperpolarization of the membrane potential and during the supra-threshold stimulation the response consisted of EPSP-peak-IPSP. An intracellular reaction of cortical convergent neuron as a response on the nociceptive and non-nociceptive afferent pathways consists of a complex response: EPSP with spikes, followed by the membrane potential hyperpolarization of significant amplitude and length.

Nociceptive and non-nociceptive afferent projections overlap in the somatosensory cortex and the characteristics of postsynaptic reactions, evoked as a result of painful stimulation is similar to postsynaptic reactions of other sensory modalities.

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**INVOLVEMENT OF G-PROTEIN COUPLED SIGNALING IN THE MODULATION OF GLIAL PROINFLAMMATORY CYTOKINE EXPRESSION**


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In terms of pain hypersensitivity, glia cells are known to modulate the neuronal activity and neurotransmission. Although it is generally accepted that neurotransmitters from neurons modulate glial function by way of the activation of receptors in glia, the related mechanism is still unclear. We studied the effect of G-protein coupled signalings on the cytokine expression in human astroglialia CRT-MG cells. Carbachol, an agonist for muscarinic receptors, increased the cytosolic Ca2+ in a concentration-dependent manner. Pirenzepine (an antagonist of M1 muscarinic receptor), also inhibit the carbachol-induced intracellular Ca2+ increase. We found that histamine also increase the intracellular Ca2+ in CRT-MG cells. Chlorpheniramine and astemizole, which are H1 receptor antagonists, inhibited the histamine-evoked intracellular Ca2+ increase in concentration dependent manners. Interestingly, the pretreated histamine decreased the following carbachol-induced response. Considering this heterologous desensitization manner, the results suggest that possibly histamine and muscarinic receptors share the same signal pathway. Carbachol decreased poly(I:C)-induced TNF-alpha expression whereas histamine did not. The expression level of IL-8 was enhanced by histamine whereas carbachol showed no effect. The results suggest that muscarinic and histamine receptor share the same signal pathway (such as phospholipase C activation and increase in cytosolic Ca2+), their modulations of cytokine expression can be different in human astroglioma CRT-MG cells.

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A BILATERAL LESION OF THE INSULAR CORTEX DIMINISHES NEUROPATHIC AND INFLAMMATORY NOCICEPTION

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Recent evidence has shown the affective and cognitive role of the insular cortex in the modulation of chronic pain. The injury in this structure provokes a disconnection of sensory input to the limbic system which, subsequently, produces a lack of response to painful stimulation. Our group has tested the role of the insular cortex regarding neuropathic nociception in relation to dopaminergic transmission. With this framework, we decided to test the effect of a bilateral lesion of the insular cortex regarding nociceptive modulation using neuropathic pain and secondary inflammatory hyperalgesia (SIH) models in the rat.

A bilateral radiofrequency lesion was performed to all experimental groups. A sham was used as a control.

Neuropathic nociception

Forty-eight hours after the lesions, under general anaesthesia, a thermonociceptive stimulus was applied, 30 min later a sciatic denervation was performed. Chronic nociception was measured by autotomy score, onset and incidence.

The results show a decreased autotomy score when compared to sham, with a significance between days 20 and 25.

Inflammatory nociception

Acute nociception (plantar test) and SIH (plantar test 30 min and 24 h after a single injection of intraplantar carrageenan) were tested.

The SIH showed an increased withdrawal latency in both 30 min and 24 h after the carrageenan injection. The acute nociception experiment showed no differences.

The bilateral lesion of the insular cortex produces a significant decrease in nociceptive parameters. This is evidence that the insular cortex plays an important role in the modulation of both chronic and inflammatory nociception, but not acute nociception.

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ELECTROPHYSIOLOGICAL AND ANATOMICAL EVIDENCE OF AN OXYTOCINERGIC PAIN CONTROL SYSTEM

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Recent evidence suggests that oxytocin (OT), secreted by descending fibers of the paraventricular hypothalamic nucleus (PVN), produces antinociception and analgesia. Here, we show that a local increase in OT produced by electrical stimulation of the PV or local application produced the specific reduction of the incoming Ad and C primary afferent at the spinal cord Lamina II neurons. This result indicates a supraspinal descending control of pain processing. Moreover, the PVN is a primary source of OT in the central nervous system and direct PVN projection to the spinal cord has been demonstrated by retrograde and anterograde tracers. This OT descending projection is proposed to be an endogenous system that controls the nociceptive information arriving at the spinal cord. However, we have no information about the specific organization of the OT descending innervations to the different spinal cord segments. With this purpose in mind we combined OT-immunohistochemistry technique with retrograde neuronal tracers in the spinal cord. We applied Diamidino Yellow for the superficial layers I and II dorsal horn cervical segments and True Blue for the lumbar segments. The majority of the stained PVN cells presented double labeling, and some were single labeled. Combining the retrograde tracer techniques and the OT immunohistochemical detection procedure, we observed triple-labeled neurons.

Our results demonstrate by electrophysiological methods that the PVN plays an important role in the somatosensory system, and they support anatomic evidence of an endogenous mechanism involved in analgesia.

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INCREASED ZIF268 RESPONSE TO EVOKED ABOVE-LEVEL NEUROPATHIC PAIN FOLLOWING SPINAL COMPRESSION INJURY IN RATS

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Spinal cord injury commonly causes debilitating chronic neuropathic pain in human patients that is not relieved by available treatments. The underlying mechanisms likely reflect central sensitization to innocuous and nociceptive stimuli, thus the aim of this study was to investigate if changes in neuronal inducible transcription factors in rat spinal cord correlated with sustained allodynia above the level of spinal cord injury. Adult male Sprague–Dawley rats were anesthetized and either subjected to spinal cord compression (50 g calibrated clip at T11) or laminectomy only. No effect on forepaw withdrawal threshold was detected with an automated Von Frey test 3 weeks after surgery, but mechanical thresholds were reduced in injured but not sham groups after 5 weeks (34 ± 12%) and further at 7 weeks (56 ± 9%, n = 5). After 9 weeks post-surgery, the left forepaw was subjected to Von Frey stimulation at withdrawal threshold every 2 min for 60 min, and immunohistochemistry for the inducible transcription factor zif268 was performed on spinal cord. Unilateral forepaw stimulation of compressed spinal cord animals increased the numbers of zif268 neurons in both ipsilateral and contralateral superficial dorsal horn, specifically in the cervical six spinal segment that receives forepaw afferent sensory input. Zif268 neurons did not increase following compression injury without forepaw stimulation. The increased expression of the activity-dependent transcription factor zif268 is evidence that a delayed and persistent change in neural plasticity develops after a compression injury to the spinal cord, occurring in parallel with a behavioral correlate of above-level neuropathic pain.

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DOES PAIN MEASUREMENT DISTINGUISH PATIENTS WITH CPSP FROM PATIENTS WITH TYPICAL CLINICAL FEATURES BUT NO PAIN?
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Patients with stroke who develop pain are most likely to have a lesion affecting the nociceptive conducting pathways which project through the spinothalamic tract (STT). This study was designed to compare two groups of patients; those with pain after stroke, and those with comparable clinical and imaging findings but without pain. We aimed to delineate whether sensory assessment could identify the pain patients. Ten patients with pain and seven without pain, but with clinical deficits typical of those who develop pain, were recruited into the study. Validated psychometric and semiquantitative psychophysical methods were used.

Using the Gracely Scales a significant group interaction effect was found whereby pain intensity was higher in the pain group as expected, but the two groups had comparable unpleasantness ratings. The LANSS scores between the two groups were significantly different, with a higher mean score in the pain group compared to the control group. There were no group differences in the number of words chosen on the MPQ. Tactile and vibratory acuity was uniformly expressed across all patients, and thermal discrimination was affected regardless of the manifestation of CPSP. However, it was found that heat and cold pain thresholds were more severely affected in the pain group as was the mean side-to-side differences of tactile sensibility. Further correlations indicated that hyperpathia generally coexisted with allodynia and was exclusive to the pain group.

These results provide a baseline for the exploration of new methods to predict, assess and treat central neuropathic pain from stroke.

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STRUCTURAL REMODELLING OF DIFFERENT CLASSES OF PRIMARY AFFERENTS AND DESCENDING PROJECTIONS IN THE DORSAL HORN FOLLOWING SPINAL CORD INJURY
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Remodelling in the dorsal horn is a proposed mechanism of spinal cord injury (SCI)-induced neuropathic pain, which is often untreatable. A detailed examination of structural changes of different classes of predominantly small fibre, nociceptive afferents and descending projections after SCI is lacking. Using specific markers of different classes of afferents and descending projections, fibre density in the dorsal horn and marker expression in the dorsal root ganglia (DRG) was analysed after complete transection at spinal level T13 in rats. A transient reduction in the density of CGRP-positive afferents in the dorsal horn at 2 weeks was reversed by 12 weeks, except in the segment closest to injury. Unaltered CGRP expression in the DRG indicated that the changes in fibre density represent degeneration of fibres, followed by regeneration. In contrast, GFRαx1-positive afferents were unaf-
fected by transection and many GFRα2-positive afferents were permanently lost from the outer laminae of spinal segments close to the injury. Following SCI there was also a transient up-regulation of GFRα2 expression in deeper laminae of the dorsal horn. The density of descending catecholamine fibres was increased at 2 weeks in the superficial laminae only, and was sustained in the segment closest to injury at 12 weeks. In contrast, descending serotonergic fibres were not altered by transection. These results reveal structural remodelling leading to an altered balance of afferent inputs and descending modulation that may contribute to neuropathic pain following SCI.

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PAIN AND PAIN_THRESHOLDS IN PARKINSON’S DISEASE
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Background. Pain is the important part of Parkinson’s diseases (PD) clinical presentation. Pain is estimated to occur in approximately 50% of patients. However, the mechanisms underlying such painful symptoms, structure of pain syndrome and treatment approaches are poorly investigated.

Patients and methods. A total of 68 subjects with PD participated in this study (mean age 58.5 ± 7.3 years, mean duration of disease 4.3 ± 2.6 years, stage of disease according Hoehn–Yahr 2 and 3). To estimate painful sensation we used visual analogue scale. Pain thresholds were estimated by compressing air in cuff with acicular inner surface which consist of several rows of needles (I.A Maseikin, 2005). Comprehensive neurological testing was using for assessment of cognitive and affective impairment.

Results. Forty-two patients (61%) had pain. Patients with pain had lower pain thresholds, more severe motor deficit, motor fluctuation, depression and cognitive impairment (especially disexecutive type) compare to patients without pain (p < 0.05). Pain thresholds on more affected side was lower than on less affected side (p < 0.05). There was also negative correlation between pain thresholds, motor deficit and depression.

Conclusion. Pain in PD is associated with reduction of pain thresholds. Pain is frequently observed in patients with higher progression tempo of PD and frequently accompanied with affective and cognitive impairment.

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EFFICACY, BY BASELINE SEVERITY OF ANXIETY SYMPTOMS, OF PREGABALIN FOR TREATING CENTRAL NEUROPATHIC PAIN IN PATIENTS WITH SPINAL CORD INJURY (SCI)
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Objective. Pregabalin demonstrated robust, rapid-onset efficacy as treatment of central neuropathic pain associated with SCI in a recently reported randomized clinical trial. This post hoc analysis examined whether the presence of clinically meaningful anxiety symptoms at baseline-identified using the Hospital Anxiety and Depression Scale-Anxiety sub-scale score (HADS-A)-influenced pregabalin’s efficacy for treating central neuropathic pain.

Methods. One hundred and thirty seven patients were randomized to flexibly dosed pregabalin (150-600 mg/d) or placebo for 12 weeks. Efficacy was measured by mean change from baseline to endpoint in pain score (based on an 11-point NRS from patients’ daily pain diaries). The HADS was administered at baseline and endpoint. Patients were stratified by baseline HADS-A score to those with HADS-A ≤ 10 (no-or-mild anxiety symptoms) and those with HADS-A > 10 (moderate-to-severe anxiety symptoms).

Results. Fifty-eight pregabalin and 47 placebo patients had baseline HADS-A ≤ 10, while 11 pregabalin and 20 placebo patients had baseline HADS-A > 10. Pregabalin-treated patients had significantly greater pain-score reduction from baseline to endpoint than did patients receiving placebo: HADS-A ≤ 10, −1.69 vs −0.58, P = .001; HADS-A > 10, −4.12 vs 0.41, P < .001. Similarly, a significantly greater proportion of pregabalin patients in each stratum were responders (≥30% reduction from baseline to endpoint in mean pain score) than were placebo patients. Pregabalin was also associated with significant reduction in HADS-A score relative to placebo (−1.72 vs −0.66, P < .05).

Conclusions. Pregabalin efficaciously treated pain in patients with and without prominent comorbid anxiety symptoms. Treatment with pregabalin was associated with a statistically significant decrease in HADS-A score from baseline to endpoint, suggesting improvement in comorbid anxiety.

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THE REHABILITATION PROGRAM FOR THE COMPLEX REGIONAL PAIN SYNDROME TYPE I TO THE HAEMIPLEGIC PATIENT
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Background and aims. Half of the patients admitted in the Univeristy Rehabilitation Clinique (Medical Complex Filantropia) in Bucharest are diagnosed with haemiplegia of various etiologies. This study intends to analyze the clinical-functional dynamic of different groups of patients with haemiplegia and CRPS type I following a complex rehabilitation program.

Methods. Evaluation scales used to examine from clinical and functional point of view our patients were the Barthel Index and Modified Rankin Scale. We followed a group of 327 patients selected from the patients admitted in our clinique between January 2005 and October 2006. Selecting criteria: we included in our study the patients with status poststroke and peripheral overreacting neurovegetative response affecting both upper and lower limb. Patients evaluation: patients have been evaluated when they have been admitted and discharged and periodically for check-up scheduled at 3 and 6 months.

Results. Obtained data were statistically analysed considering age and sex distribution, haemiplegia etiology, CRPS type I localisation, risk factors of stroke. We present results from initial and second clinical evaluation,and check-up at 3 and 6 months.

Conclusions. (1) Patients with haemiplegia and CRPS type I secondary to poststroke status were numerous and raised problems of diagnose and treatment. (2) CRPS type I secondary to poststroke status is a complication and impose an early diagnose for a promptly start of the treatment. (3) CRPS type I complicates the evolution of the haemiplegic patient; the rehabilitation team has to conceive a different complex rehabilitation program for each patient.

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LONG-TERM USE OF SATIVEX IN MULTIPLE SCLEROSIS CENTRAL PAIN; DOSING AND CHANGES IN CONCOMITANT ANALGESIA
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Background. Poor is known on chronic pain in PD. Patients, assess co-morbidities (i.e depression) and to measure quality of life.

Methods. DOPAMIP study is a cross-sectional survey conducted in 450 non-demented PD patients randomly selected by neurologists and 98 control outpatients visiting general practitioners for any disorder other than PD. Data were collected using (1) a self-administered patient questionnaire [anxiety and depression (HADS scale), sleep disorders (Pittsburg scale), quality of life (PDQ 39)] and (2) a standardized clinical examination [assessing PD and chronic pain (VAS, MacGill short form), clinical presentation, treatment, aetiology and relationship with PD]. Relationship between chronic pain and PD was based on clinical assessment (chronological or topographical link, impact of antiparkinsonian medication, ON-OFF fluctuations) and patient opinion.

Results. Sixty-five percent of our 450 PD outpatients (mean age = 70 ± 8 years, mean disease duration = 6 ± 4 years) suffered from any type of chronic pain. In 39% patients, PD was considered to cause directly or to contribute indirectly to chronic pain (PD Chronic Pain Group). In 26% patients, pain was considered to be unrelated to PD (Non-PD Chronic Pain Group).

Different types of chronic pain related to PD were observed (i.e. peripheral mechanisms = 45%). CPPD patients had more severe PD, more severe anxiety and depression score. Fifty percent of patients were receiving an analgesic.

Conclusions. One-third of outpatients with moderately advanced PD reported chronic pain, probably related to various peripheral and central mechanisms.

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modulator, was investigated in a randomised-controlled trial of 66 MS patients with CP. Sixty-three patients (95.5%) entered a long-term, open-label extension study. Each Sativex oromucosal spray, delivered 2.7 mg THC and 2.5 mg CBD. Patients self-titrated their dosage within pre-determined guidelines.

**Results.** In the randomised trial, Sativex achieved significant improvements in pain (NRS-11, \( p = 0.005 \) and Neuropathic Pain Scale \( p = 0.044 \)) and sleep disturbance (NRS-11, \( p = 0.003 \)) compared to placebo. The mean duration of open-label treatment was 463 days (range 3–917, SD 378). Twenty-eight patients (44%) completed the study and took a mean of 6.5 sprays per day (range 0.5–24.8, SD 5.8). Twenty-six subjects took less than 11 sprays per day. Most Sativex was taken after 4 pm. At least one dose was taken by at least one patient in each of the 24 h.

Thirty-one concomitant analgesics and 32 medications which could have affected neuropathic pain (e.g. anti-spasmodics) were taken by patients completing the open-label study. The doses of 32 of these medications remained unchanged, 3 were reduced, 17 stopped and 11 increased. Twenty such medications that were commenced during the trial were continued at its end.

**Conclusion.** In long-term use Sativex showed maintenance of analgesic effect without associated increases in dose and use of concomitant analgesia remained relatively stable.

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**PAIN SEVERITY, MANAGEMENT AND PATIENT FUNCTIONING IN CENTRAL NEUROPATHIC PAIN: RESULTS FROM A CROSS-SECTIONAL SURVEY IN SIX EUROPEAN COUNTRIES**

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**Background and aims.** To describe the burden of central neuropathic pain (CNeP) on patient-reported functioning and health resource utilization (HRU).

**Methods.** We surveyed 70 patients with CNeP resulting from stroke (\( n = 38 \)) or spinal cord injury (\( n = 32 \)) recruited from general practitioners in six European countries as part of an overall study of NeP (\( N = 602 \)). Physicians recorded demographic and treatment information. Patients completed the short-form Brief Pain Inventory (BPI), the EuroQol (EQ-5D), productivity and HRU questions. Impact of pain severity on functioning and HRU was also evaluated.

**Results.** Mean (s.d.) patient age was 65.5 (13.0) years, 54% were male. Pain duration was \( \geq 1 \) year in 76% of patients; \( \geq 3 \) years in 55% of patients. Most patients (90%) were prescribed pain medications including analgesics, anti-depressants, sedative/hypnotics, and anti-epileptics. Despite high adherence (91%), 63% still reported moderate pain and 22% severe pain. Patients received prescriptions for comorbid anxiety (29%), depression (30%), and sleep disturbance (34%). Greater pain severity was significantly \( (P < 0.0001) \) associated with poorer EQ-5D scores (mild = 0.6, moderate = 0.4, severe = −0.1). CNeP affected employment status in 58% of patients. During the past month, 80% made \( \geq 1 \) visits to their physician for their pain, 46% had \( \geq 1 \) telephone consults, and 60% saw a pain specialist.

**Conclusions.** CNeP patients reported substantial pain interfering with daily functioning and resulting in frequent HRU. The degree of interference was proportional to CNeP severity. Pain severity was greater than the aggregate NeP population, and telephone consults, specialist visits, and disruption in employment status were also higher than in the overall NeP population.

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**PAIN DETECTION THRESHOLD IS DECREASED IN THE MIGRAINE PRE-ATTACK STATE: EVIDENCE FOR SLIGHT GENERALIZED HYPERALGESIA?**

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**Background and aims.** Migraine patients may have cutaneous allodynia during attacks. Prodromal symptoms are common in migraine. In order to investigate if pain physiology also changes before the next attack we estimated heat pain and cold pain detection thresholds (HPT and CPT) on three different days in 41 migraine patients and 28 controls. A headache diary allowed us to define a subgroup of 15 migraine patients who had been tested within 24 h before their next attack and in another interictal non-headache state.

**Methods.** A thermode was applied at four sites on both sides: head (frontal region), face (maxilla), neck (below processus mastoideus) and hand (thenar). Baseline temperature was 32 °C. The temperature range was 5–50 °C. The rate of change was 1 °C/s. Investigators were blinded to clinical information. Right and left
side was averaged. Student’s t-test (two-group and paired) was applied.

Results. Mean frontal HPT was 15.3 °C in controls and 13.8 °C in migraine (p < 0.02; day 1, 2, 3 – average). In the hand, mean HPT was 15.2 °C in controls and 14.2 °C in migraine (p < 0.05).

In the pre-attack state mean HPT was lower than at the (paired) interictal recording for the hand (13.4 °C versus 14.3 °C, p = 0.007) and the neck (14.7 versus 16.3 °C, p = 0.003). Neck mean CPT was lower before attack than interictally (21.1 °C versus 23.7 °C, p = 0.02).

Conclusion. Thermal pain thresholds in migraine patients were lowered by approximately 1 °C in the pre-attack state. Extratrigeminal involvement suggest generalized pain dysfunction in migraine, possibly a slight central sensitization to pain.

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310 THE DEJERINE ROUSSEY SYNDROME: THE DISCLOSURES OF ROUSSEY

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The description of the thalamic syndrome by Dejerine and Roussy in 1906 was the outcome of the Dejerine concept on the “sensorial relay” of the postero lateral thalamus. In his thesis (1907), Roussy detailed the clinical cases and noted that one patient (“Hud”) did not present pain whereas pain was a main component of the clinical picture of the syndrome.

We studied the original material of the “Hud” case and compared with the “Jos” case who presented pain.

Material. We found many sections concerning the patients at the Fondation Dejerine localized in “Musée Dupuytren” in Paris. Annotated outlines were also available as the original anatomic works of Dejerine.

Results. The thalamic lesions were very similar in the two cases above the CA-CP line. On the other hand, the “Jos” lesion extended more medially at the CA-CP level, including the posterior median complex while it is not the case of the “Hud” lesion which, interestingly, extended in the subthalamic region.

Discussion. The accurate anatomic descriptions of the thalamic lesions correlated with the clinical status are interesting in the study on the central pain syndrome, even though the pain mechanisms cannot be reduced to the anatomic lesion. The part of the median complex and the VPL is debated, especially according to their cortical connections.

Conclusion. The revisiting of the historical Dejerine Roussy works gives the opportunity to present new insights on their studies and to remind their misunderstood analysis.

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311 MOTOR CORTEX STIMULATION FOR THE TREATMENT OF DIFFERENT NEUROPATHIC PAIN SYNDROMES

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Background and aims. Motor cortex stimulation is an invasive treatment option for different chronic neuropathic pain syndromes if pharmacological or conservative treatment options fail. The current theory for the mode of action favours the orthodrome activation of subcortical areas like thalamus, brainstem, cingulate gyrus and insular region. The authors want to present their experience and results with this method over the last 12 years.

Methods. Twenty-five patients with neuropathic pain of different origin were treated. Trigeminal neuropathic pain (TNP) was present in 14 patients, post-stroke pain (PSP) in 7 patients and posttraumatic plexus avulsion (PPA) in 4 patients. Using neuronavigation and intraoperative neurophysiology a quadripolar or octapolar lead was placed over the hand and face area. During a test-phase with subthreshold stimulation various lead combinations and also double-blind stimulation was performed.

Results. Pain reduction was achieved in 9/14 (64%) patients with TNP, 3/7 (43%) patients with PSP and 4/4 (100%) patients with PPA. This effect was not observed during the blinded testing phase. In these cases no side effects were evaluated and the stimulation device was internalized. Five false positive responders (20%) could be identified during the double-blind stimulation phase.

Conclusion. Motor cortex stimulation is a safe and effective treatment option for a selected group of patients with well-located regional neuropathic pain syndromes like trigeminal neuropathic pain or neuropathic pain after plexus lesion. The operative procedure
is technically complex and should be performed only in centres with outstanding experience for neurosurgical pain management.

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312 MORPHINE-INDUCED MYOCLONUS IN MULTIPLE SCLEROSIS PATIENT (CASE REPORT)
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Introduction. Myoclonus is one of the adverse events of opioid therapy. It is defined as brief, shock-like jerks, lasting typically 25–200 ms. Myoclonic cramps do not depend on the way of application but more frequently appear during spinal or intravenous application and are dose-related.

Pain occurs in 50–60% of multiple sclerosis patients as a paroxysmal dysesthetic pain or painful tonic spasm of legs and low back pain.

Case report. Female (49 years old) had 6 years sclerotic multiplex, dysesthetic and painful form. Stable dose (320 mg) of morphine orally and 20 mg intrathecally had to be increased because of pain worsening. Intrathecal analgesia was effective for 7 weeks until next progression.

Myoclonus appeared after 25 mg of intrathecal morphine. It disappeared after intravenous application of benzodiazepin.

Discussion. Local causes of myoclonus, affected spinothalamic tract, ectopic excitation, and other aspects of the demyelinising disorder of central nervous system will be discussed.

Conclusion. Pain occurs in 50–60% of multiple sclerosis patients. For therapy-refractory cases, intrathecal analgesia can be considered. Morphine with local anaesthetics is frequently used. The diagnosis and the resolution of adverse events is essential part of pain therapy.

References

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313 DISCOMPLETE LESIONS OF THE SPINOTHALAMIC TRACT PREDICT THE PRESENCE OF NEUROPATHIC PAIN FOLLOWING SPINAL CORD INJURY
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Chronic neuropathic pain below the level of injury occurs in ~35% of people following spinal cord injury (SCI). The underlying mechanism is unknown, but it is hypothesized that the pain originates at the level of the spinal injury. Previous studies suggested that a spinothalamic tract lesion is necessary, but not sufficient for the development of SCI pain, since deficits of spinothalamic function were equally severe in SCI patients with and without pain. Here, we present data suggesting that a “discomplete” lesion of the spinothalamic tract predicts the development of neuropathic pain. In 13 SCI people with pain below the level of injury and 9 matched SCI people without pain, spinothalamic tract function was tested by measurement of thermal thresholds (cold, warm, cold and heat pain) before and after application of capsaicin and menthol. All patients were “sensory complete” (no sensation to touch and pinprick). However, 8/13 pain patients responded to one of the thermal stimuli after pretreatment with either drug, reporting a sensation of the same quality as one of their major pain sensations. No sensation was induced in any of the people without pain. Therefore, residual spinothalamic tract function distinguished people with central pain from those without. The ability to mimic chronic pain sensations by activation of thermosensory neurons implies a crucial role of residual spinothalamic afferents in the underlying pain mechanism in a sub-group of patients.

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CASE SERIES OF MULTIPLE SCLEROSIS PATIENTS WITH NEUROPATHIC PAIN IMPROVED WITH THE ORAL CANNABINOID NABILONE

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Background. To present a case series of nine multiple sclerosis (MS) patients with neuropathic pain improved with the oral cannabinoid, Nabilone.

Methods. MS patients with neuropathic pain referred from family physicians and neurologists were pre-screened with the DN4 questionnaire for neuropathic pain and the EDSS. Exclusion criteria included severe psychiatric disease and addiction risk. Patients were assessed with the Numerical rating scale for pain, Short-form McGill Pain Questionnaire, Pain Disability Index, Neuropathic Pain Scale, Pain Diagram. Physical examination also included jamar grip dynamometry and neurological assessment.

Interventions. Patients were initiated with low dose Nabilone (0.5 mg) at night. Some patients were titrated up to higher doses. Two patients were highly medication sensitive and responded better to a sublingual aqueous mixture of Nabilone (0.2 mg/ml). Concomitant medications and therapies were monitored. Duration of treatment varied from one to 18 months.

Results. Neuropathy Pain scale on average improved from 51.5/100 down to 35/100. Improvements were noted in the sleep, mood, quality of life. There was evidence of opioid sparing/reduction. No major adverse reaction, habituation or tolerance developed. No changes were noted in grip strength and there was no deterioration in neurological status (1 was primary progressive, 2 secondary progressive, 2 relapsing remitting).

Conclusion. This study suggests that Nabilone appears helpful in MS patients with neuropathic pain. A recent RCT (J. Wissel, J Neurol 2006) also supports this. Findings of need for very low dose immunomodulation titrations are suggestive of the endocannabinoid hypothesis of the aetiology of MS.

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MOVEMENT IMAGERY EVOKES PAIN IN SPINAL CORD INJURED PATIENTS

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Background and aims. Over the past decade, there has been growing interest in the role of the motor system in pain processing. The aim of this investigation was to determine the effects of movement imagery on the level of on-going pain in spinal cord injury (SCI) patients with neuropathic pain.

Methods. We compared the effects of imagined right ankle plantarflexion and dorsiflexion on perceived pain intensity in SCI subjects with clinically complete (ASIA A) thoracic injuries (T2–T10), with (n = 7) and without (n = 7) neuropathic pain below the level of their injury. A recorded engine sound was used to assist in the timing of movements. Imagined movements were rehearsed for one week prior to assessment.

Results. In every SCI subject with neuropathic pain, ankle movement imagery resulted in a significant increase in pain intensity. In no SCI subject did either attention directed towards the right ankle or movement imagery involving the right wrist evoke any change in pain or non-painful intensity or distribution. In each SCI subject without neuropathic pain, but with phantom sensations, ankle movement imagery did not evoke pain, but instead evoked a significant increase in the intensity of perceived phantom sensation. One patient reported new unpleasant phantom sensation during imagery.

Conclusions. In contrast to studies employing motor cortex stimulation which typically reduces pain, movement imagery significantly increases neuropathic pain and phantom sensations in patients with SCI. Furthermore, movement imagery can evoke unpleasant phantom sensations in SCI patients without on-going phantom sensation and/or pain.

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INFLUENCE OF AGE ON CENTRAL POST-STROKE PAIN

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Introduction. Central post-stroke pain (CPSP) is a 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 CSPS is not clear.

Methods. We randomly investigated 297 patients (mean age 72 ± 5.4 years) with first-time stroke over a 1-year period. Patients were evaluated 6 months and 12 months following stroke onset. Pain was assessed using a visual analogue scale ranging from zero mm (no pain) to 100 mm. Using the scale, zero was defined as no pain, 10–30 as mild pain, and 40–100 as moderate to severe pain. Depression was evaluated on a depression scale. Logistic regression was used to analyse the associations.

Results. Twenty-seven (9.2%) patients developed CPSP. Factors significantly associated with an increased likelihood of having moderate to severe pain included younger age and higher scores on a depression scale (p < 0.01). Pain was reported as constantly present in 37% patients, and it disturbed sleep in 67% patients.

Conclusions. We concluded that CPSP was associated with younger age stroke patients. Depression is an important factor in CPSP.

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facial pain. Neurological examination remained normal. Enhancement of medical treatment remained partially successful. Cerebral imaging revealed a developmental venous anomaly draining the homolateral ponto-cerebello-mesencephalic structures, running along the trigeminal tract. Partial rhizotomy was performed. Patient remained free of pain and resumed all his professional activities with a five years follow-up.

The second case concerns a 19 years-old woman presenting with a two-years lasting supra-orbitary neuralgia associated to a chronic otitis. Neurological examination remained normal. CT-scan revealed a huge enlargement of the ovale foramen; MRI, a trigeminal neuroma extending from the gasserian ganglia to the inferior dental canal. Surgery permitted a quite complete removal assuming pain relief, audition improvement without any complications at three years.

These two cases illustrate the importance of clinical screening when an "essential" neuralgia is diagnosed, especially by a young patient, of imaging investigations and of neurosurgical etiology-oriented procedures for pain relief.

This is a report of two patients suffering from brachial plexus avulsion (BPA) of traumatic origin successfully treated with Spinal cord stimulation (SCS).

After a traumatic brachial plexus lesion about 80% of the patients develop pain in the deafferentated arm. This pain is considered very resistant to many forms of therapy.

In the early 1970s, SCS was introduced in the treatment of BPA pain, with disappointing results. There are only about 20 cases of BPA pain treated with SCS. Many avulsion injuries are due to motorcycle vehicle accidents so that patients are often young and require long-term pain relief.

We are presenting the effectiveness of spinal cord stimulation (SCS) in two patients suffering pain from brachial plexus avulsion (BPA).

During the SCS trial the pain relief was more than 50% with an absolute improve in the quality of life and significant drug reduction. The results of the SCS were excellent in these two patients, defined as more than 50% pain relief at 6 and 18 months.

Some patients with extensive root avulsions still felt stimulation in the area of the pain. This emphasizes that a trial of SCS should be offered to any patient, even when the findings on suggest a severe BPA.

SCS is expected to be effective in patients with partial root avulsion or intact roots, nevertheless the success rate is unpredictable. Therefore, SCS should be an early choice of treatment for BPA.

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Case report: Efficacy of Ziconotide in mixed neuropathic and nociceptive pain
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Background. Ziconotide is an intrathecaally administered, non-opioid analgesic used to treat severe, chronic pain.

Case report. Mr E has been diagnosed with neuropathic pain related to failed back surgery syndrome
and nociceptive pain related to cervical and lumbar spondylosis. Amitriptyline, nortriptyline, venlafaxine, gabapentin, pregabalin and opioids (MST continuous, oxycodone and fentanyl patches) have either been badly tolerated or failed to provide significant relief; maximum pain rating of 9/10 on the visual analogue scale of pain intensity (VASPI). In 2004, intrathecal analgesia was recommended and ziconotide was judged preferable over opioids. Ziconotide was administered via an external catheter and delivery pump system at a starting dose of $2.4$ & micro;g/day and titrated to $6.0$ & micro;g/day over 3 weeks. Good pain relief (VASPI 3-4 out of 10) was achieved and opioid use was decreased. Adverse events, which were not severe, included dizziness, tiredness, poor concentration and headaches. Due to the positive response an intrathecal infusion device was implanted and ziconotide was titrated from $2.4$ & micro;g/day to $7.2$ & micro;g/day, which was maintained over 5 months. Complaints about lack of concentration prompted opioid discontinuation. This was achieved with specialist help in managing withdrawal symptoms. During opioid withdrawal, ziconotide dosage was temporarily reduced to $4.0$ & micro;g/day when paranoid thought content was expressed along with fever and tachycardia. Mr. E has been on a stable ziconotide dose of $6.9$ & micro;g/day for the past year with an average VASPI score of 5.5/10.

Conclusion. In this patient, a stable dose of ziconotide provides pain relief without additional systemic analgesia.

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RAPID TITRATION OF ZICONOTIDE FOR THE TREATMENT OF SEVERE INTRACTABLE BACK PAIN FROM METASTATIC SPINAL ANAPLASTIC EPENDYMOMA

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Background. Ziconotide (Prialt) is an N-type calcium channel antagonist used as an intrathecally delivered analgesic for the treatment of malignant and non-malignant pain. Initial trials indicate that slow titration of Ziconotide decrease the incidence of neurotoxic side effects. This report describes the successful treatment of an acute pain crisis in a patient with chronic intractable malignant pain using rapid titration of Ziconotide.

Case report. A 36 year-old male with a history of anaplastic ependymoma and chronic back and bilateral lower extremity neuropathic pain was admitted for resection of an S1 nerve root metastasis. He was previously maintained on intrathecal infusions of morphine, bupivacaïne and clonidine, which suboptimally controlled his pain. Post-operatively, the patient experienced an acute pain crisis refractory to escalation of intrathecal and intravenous opiate medications. A midazolam intravenous infusion was subsequently started for pain control. While in the ICU setting, intrathecal medications were replaced with Ziconotide at an $8$ mcg/day infusion, which resulted in moderate pain relief within hours of initiation. Within 72 h the infusion was rapidly titrated to $25$ mcg/day. With each adjustment, significant incremental pain relief was achieved allowing for the discontinuation of the midazolam infusion and intravenous opiates. Intrathecal monotherapy with Ziconotide continued during the entire hospital admission without evidence of neurotoxicity.

Conclusions. Rapid titration of Ziconotide was beneficial for the treatment of intractable acute pain in a patient with preexisting chronic neuropathic malignant pain. This case demonstrates safe rapid titration of Ziconotide to control acute pain when standard post-operative pain treatments failed.

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NEUROPATHIC CHRONIC PAIN FOLLOWING TRAUMATIC BRACHIAL PLEXUS TOTAL SECTION MANAGED BY TRANSDERMAL BUPRENORPHINE PATCH (TDS): ORIGINAL CASE REPORT

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Male, 24 years old, total section of the brachial plexus, Tinel/B. Horner signs: +. Suture of the accessory on suprascapular nerve, front and rear, and a wrapping of four 8 cm junctions, between C6 and the branches of the SPT, has been acted. Burning, continuous pain, VAS8, and clusters of intermittent shocks, VAS9, begun after surgery. Pain was, initially, treated with: carbamazepin 200 mg. SR/bid, amitriptilin 25 mg, tramadol 100 mg SRbid increasing of 100 mg, every two days, up to 400 mg/die; RD: tramadol drops 50 mg. Two weeks after, because of pain relief absence, tramadol was replaced by TDS37. 5 mcg/h with titration scheme: 1/4 for 7, 1/2 for 21, 1 for 28 days; RD: buprenorphin s.l. 0.2mg. Weekly, for a period of 8 weeks, have been checked: Vas, side effects (number of episodes) and number of RD.

Results: see enclosed figure.
Conclusions: a difficult case of neuropathic chronic pain, refractory to the therapy, has founded significative improvement by TDS that, joint with anticonvulsant and triciclic antidepressant drugs, has allowed significative basal pain control and reduction of the number of the breakthrough pain episodes.

For further informations, in our department, before 2006 S.C. Stimulators were applied to patients with arteriopathy at lower grade than 4 according to FONTAINE.

Therefore, the absence of collateral effects and the clinical improvements bring to the conclusion that the application is advisable even in the other pathologies mentioned above.

APPLICATION OF SPINAL CHORD STIMULATOR IN DIFFERENT CASES OF CHRONICAL PAIN

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In 2006, at the department of Pain Medicine of regional hospital, Ancona (Italy) six, Spinal Cord Stimulators were enforced to the following cases:

Group 1: one case of FAILED BACKSURGERY SYNDROM (male, 80 years old).

Group 2: three cases of STENOSIS OF VERTEBRAL CHANNEL (males, 70–72–74 years old).

Group 3: two cases of OBSTRUCTIVE ARTERIO-ATHY of inferior limbs at grade 4 according to FONTAINE.

No collateral effects were noticed in any case.

Particular improvements were noticed in arteriopathy cases (group 3) with restoration of walking and pain disappearance.

In conclusion it can be said that the use of Spinal Cord Stimulator is fit for these pathologies.

RECHARGEABLE SCS SYSTEMS WITH INDEPENDENT CURRENT CONTROL BENEFIT PATIENTS AND THE HEALTH CARE SYSTEM: CASE REPORTS

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Background. Due to anatomical and technical issues it is more difficult to achieve paresthesia coverage and pain relief with SCS in axial back pain (Oakley, 2006). It is of clinical significance to capture the lower back because pain relief via SCS is dependent upon the best possible pain-paresthesia overlap (Holsheimer, 1997).

Methods. Two patients (male (64), female (60)) with chronic back pain following back surgery were each implanted with a SCS system (PrecisionTM Advanced Bionics Corporation, Valencia, CA). Two 8-contact percutaneous leads were positioned close to the midline at T7/T8 and T8/T9, respectively. The stimulator was pro-
grammed using an automated, patient-controlled system through which current at each electrode was fractionalized. An economic model was developed to compare the total cost with Precision™ to non-rechargeable devices.

Results. Good pain/paresthesia overlap was attained in both patients by using complex programme configurations and high pulse widths (690 μs and 360 μs). Pain reduction varied between 50% and 80% 2 weeks post implantation. Both patients reported positive impact on quality of life. Battery devices were recharged every 5–14 days.

The economic analysis showed that rechargeable devices avoid costly replacements and are cost saving already after 3 years.

Conclusions. Although past reports have demonstrated difficulty in relieving axial back pain, the new independent current controlled rechargeable SCS system overcame some of the technical issues and provided good pain relief by delivering high stimulation parameters not available with previous technology. Rechargeable devices may also benefit the health care system by reducing long term follow-up costs.

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OPTIMAL PARESTHESIA COVERAGE WITH OFFSET DUAL PARALLEL LEADS IN SPINAL CORD STIMULATION FOR CHRONIC PAIN
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Spinal cord stimulation for chronic pain often uses dual parallel leads to superimpose electric fields. Independently, controlled current on adjacent contacts allows precise shaping of the electric field between leads. However, percutaneous leads may migrate longitudinally, so that stimulation programs lose efficacy. Paresthesia coverage may be regained by harnessing the offset between leads. Two patients were implanted with rechargeable spinal cord stimulators (Precision™, Boston Scientific) and two 8-contact percutaneous leads (Linear™) to treat: (#1) piriformis syndrome with left leg pain; and (#2) sciatic neuropathy with right leg and foot pain and midline back pain. Patient 1 lost adequate paresthesia coverage, and fluoroscopy confirmed that the leads remained parallel, but offset longitudinally. Patient 2 was implanted with leads offset. Optimal paresthesia coverage required simultaneous stimulation through adjacent contacts on opposite leads (Figure). For Patient #2, cathodal current was adjusted to Left – 29% of total current and Right – 71% to improve paresthesia coverage. Knowledge of lead offset guides appropriate reprogramming to recover optimal paresthesia, reducing lead revision surgeries. Lead offset is determined radiographically, but a new technique electrically generates a scan of lead offset with no X-ray exposure (Kosek, P. et al., 2006. Electronically Generated Lead (EGL) Scan: Report of First Clinical Use. NANS, Las Vegas, NV.).

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INTRAVENOUS ADMINISTRATION OF ADENOSINE (ADENOCOR®) IN THE TREATMENT OF SEVERE, THERAPY-RESISTANT, CENTRAL NEUROPATHIC PAIN
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Adenosine is a neuromodulator with complex effects on nociceptive pathways. It has been shown that in humans, intravenous (i.v.) infusions of adenosine can reduce inflammatory and postoperative pain. We present the case of a patient suffering from a severe central neuropathic pain syndrome who showed significant analgesia to adenosine.

A 42 yr old female developed a central nervous system (CNS) demyelinating syndrome. Neuroimaging revealed demyelination foci in the cervical and tho-
racic spinal cord. Clinically, she developed muscular weakness and hypotonia on the left side of her body. In addition, she reported dysesthesias as well as pronounced mechanical and thermal allodynia below the level of the spinal cord lesions. Treatment with gabapentine (900 mg) resulted in some pain reduction, but increasing the daily dose led to intolerable side effects. Additional (poly)pharmacological treatments were tried, but all in vain. It was decided to perform an i.v. infusion of lidocaine (4 mg/kg) but lidocaine infusion had to be stopped due to development of bronchospasm. Finally, it was decided to administer an i.v. infusion of adenosine (Adenocor®). A first administration of 3 mg was well tolerated and caused a significant reduction of both spontaneous and evoked neuropathic pain. Considering this positive result, repeated administrations with increasing doses were performed (up to 5 mg, continuous infusion during 90 min). Despite its short half-life, infusion of adenosine causes a prolonged reduction of neuropathic pain symptoms (for up to 6 weeks). Patient has been treated with i.v. adenosine for 14 months now, without any signs of development of tolerance to the analgesic effects.

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CASE SERIES OF FIBROMYALGIA (FMS) PATIENTS WITH NEUROPATHIC PAIN IMPROVED WITH THE SUBLINGUAL CANNABINOID SATIVEX
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Background. We present the first ever case series of Fibromyalgia (FMS) patients with neuropathic pain improved with the sublingual cannabinoid Sativex.

Method. Setting: University Teaching hospital outpatient clinics.

Subjects. Forty-one FMS patients with neuropathic pain referred from family physicians and rheumatologists. Patients were pre-screened with the DN4 questionnaire for neuropathic pain and algometry tender point measurements (American College of Rheumatology criteria). They were excluded if there was significant addiction risk or psychiatric comorbidity.


Interventions. Twenty-three patients initiated on Nabilone did well with titrated higher doses. Four did not tolerate Nabilone but responded to low dose Sativex (one spray in the evening and another before sleep; then titrated up to 4–6 sprays/day). Fourteen patients already on night-time Nabilone but too sedated to tolerate daytime use, responded well to the shorter-acting Sativex for daytime break-through pain. Concomitant medications and therapies were monitored. Treatment varied from 1 to 12 months.

Results. These patients improved significantly in most outcome measures. In several cases, the use of opioids and psychotropic medications were reduced or eliminated. No major adverse reaction, habituation or addictive behaviour developed. Quality of life, mood, functional capacity and sleep were also improved subjectively in patient diaries.

Conclusion. This ongoing study suggests that cannabinoids appear helpful in FMS patients with neuropathic pain. Further randomized controlled trials would be needed to validate this preliminary finding.

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SUCCESSFUL TREATMENT OF LEG AND LOWER BACK PAIN USING A SINGLE PROGRAM WITH A NEXT GENERATION SCS DEVICE: CASE REPORT
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Introduction. Spinal cord stimulation (SCS) is minimally invasive and effective for chronic intractable neuropathic pain when other surgical and non-surgical options have been exhausted. Localized spinal stimulation provides precise overlapping of paresthesia to painful areas, yielding optimal outcomes. Reported here is the first implant in Germany of an SCS system with 16 current-controlled independent channels, a rechargeable battery, and novel real-time patient fitting system (Precision™ SCS System, Boston Scientific) for treatment of leg and lower back pain.

Methods. A 56-year old male with severe pain of unknown etiology in both feet, rating 9–10 on a Visual Analog Scale (VAS), presented with allodynia and strong “jerks” radiating upward from the feet to the legs while standing or walking, for greater than 2 years duration. He also reported lower back pain as a secondary
complaint. An SCS system was implanted using a single lead at T12, and programmed at pulse widths (pw) between 760 and 850 µs.

Results. Optimal pain coverage was achieved with a pw of 760 µs. Stimulation reduced the patient reported VAS to 5–6 with complete relief of allodynia and jerking in the legs. Furthermore, the same programming reduced pain in his lower back.

Conclusions. The new SCS technology allows successful treatment of very complex cases with multiple pain distributions. Relief of pain in both feet and lower back has been achieved by the use of a single lead with independent contact control and a single program utilizing pulse width of 760 µs.

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THE SYNDROME OF INTRACTABLE PAIN OF UPPER LIMB OF A YOUNG GIRL
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Aim of the study. Our study presents the case of a girl born in 1990, suffering from serious impairment of her sight by perinatal retinopathy. In April 2005, she had a hyperpyrethic condition of unclear ethiology, followed by pains in palms and forearms. In mid-July, diffusive feelings of pain and alodynia of the left hand and forearms were also accompanied by growing oedema, a defect in the mobility of palms and insomnia. Check-ups brought an apparent finding – the defect of osseous density (the Sudeck type) and the diagnosis of CRPS.

Methods and results. A continual axillary catheter was inserted with intermittent application of bupivacain (0.25%), with a dramatic reduction of the pain, while the swelling of the palms receded. It was removed on November 21, 2005. On December, the patient hit by chance the back of her palm, causing a serious pain. The condition was assessed as Clenched Fist Syndrome.

Conclusions. Certain warning factors of the occurrence of CRPS were underestimated in the case of this young handicapped girl in the “risky” adolescent age which must be also taken into consideration in this type of illness. Invasive methods had a dramatically positive effect on her cure, but it must be borne in mind that a right psychological approach is indispensable in the treatment of such psychologically and socially affected girl.

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DIAGNOSIS AND TREATMENT OF VAGAL NEURALGIA IN A PATIENT WITH LARYNGOPHARYNGEAL REFLUX: A CASE REPORT
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We describe a case of a patient suffering from laryngopharyngeal reflux (LPR) in whom vagal neuralgia was diagnosed and successfully treated by the use of Pregabalin. The patient presented to the pain clinic with a right-sided sore throat of a year’s duration.

Our patient’s clinical symptoms were characteristic for the diagnosis of LPR, which was successfully treated before his presentation at the pain clinic. His pain, however, remained. This was the first time that pain of neuropathic origin was suspected due to the severe nature of the throat pain, along with its localization to the right side and its failure to resolve with treatment with H2 blockers and proton pump inhibitors. Findings of bowing of the right vocal cord and decreased abduction on laryngoscopy confirmed our diagnosis of nerve involvement (vagal neuralgia).

While Pregabalin, an anti-seizure medication, has been FDA approved for treatment of diabetic neuropathy and post-herpetic neuralgia, it has not previously been reported to be effective for vagal neuralgia. In this case, the patient’s previously severe pain was reduced to a tolerable level after only a month of therapy with Pregabalin 250 mg PO, with no noticeable side effects.

Interestingly, in tandem with its analgesic properties, Pregabalin has been shown to contain antidepressive and anxiolytic properties which are important in the treatment of patients with chronic pain. We believe that Pregabalin is an effective treatment for both the somatic and psychic symptoms caused by vagal neuralgia and should be of interest to the pain management physician.

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MADAME OUI-NON: DIAGNOSTIC DYSPRAXIA AND CENTRAL PAIN
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We are presenting an original case associating diagnostic dyspraxia and central pain in the context of a callosal dysconnection syndrome associated with a left anterior cingulum lesion. The discussion concerns the cortical pain mechanisms.

Case report. After the rupture of a pericallosal artery aneurysm, a 55 years old patient presented a callosal dysconnection syndrome with an original diagnostic dyspraxia. Abnormal behaviors involved the left hand in bimanual tasks but also whole body and thoughts in more complex actions resulting in decision-making troubles. The patient answered simple questions by “oui-non”.

Moreover, an intensive burning pain appeared quickly afterwards, first axially, then lateralized with predominance over the left foot and hand. The clinical examination showed a sensitive extinction of every quality on the left side compared to the right.

Explorations. Imagery showed lesions of the corpus callosum (CC) and the anterior left cingulum without visible lesions of the somato-sensory pathways. Neuropsychological explorations confirmed the split-brain syndrome and the behavioral disorders.

Discussion. The lesions may result in diagnostic dyspraxia. The respective part of the CC and the cingulum lesions are discussed. It is hypothesized that the same lesions also result in central pain even an invisible somato-sensory lesion cannot be excluded. The lateralization of the medial cortical pain projections and the connections between the lateral and the medial pain systems could be involved.

Conclusion. This particular case allows to discuss the still mysterious mechanisms of pain at the cortical level.

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LAMOTRIGINE IN INTRACTABLE TRIGEMINAL NEURALGIA ASSOCIATED WITH MULTIPLE SCLEROSIS: A CASE REPORT
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Trigeminal neuralgia (TN) is a well-defined pain condition. Chronic inflammatory disorders in the CNS could cause “secondary TN”. The incidence of TN in patients with multiple sclerosis (MS) is higher than in the general population. Although the principles of pharmacotherapy are the same in patients with idiopathic and secondary TN, invasive procedures are rarely performed in patients with TN and MS due to inconsistent results.

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Thirty-two-year old men (181 cm, 57 kg) presented with progressively worse TN in left V3. He had secondary-progressive MS for 5 years (mild predominantly right-sided spastic tetraparesis, ataxia), TN for 4 years. Touching the V3 area on the left side, opening the mouth or attempt to chew produced a 40 s of repetitive sharp, stabbing and drilling excruciating pain attacks without irradiation outside V3. He was prescribed carbamazepine (600 mg/d), gabapentine (1800 mg/d) and baclofen (75 mg/d). Attempts to raise the doses resulted in intolerable side effects. He complained of sleep disturbance, fear of eating and suicide ideation.

On examination hypalgesia in left V3 was found. MRI demonstrated a demyelinisation plaque in brainstem. AEPs demonstrated absence of left N2, N3 and N4, with barely detectable N5 of much prolonged latency.

Slow titration of lamotrigine to 500 mg/d produced marked sustained relief of pain for 3 years, increase of weight to normal and no side effects. The rest of the drugs were slowly tapered off.

We conclude that high doses of lamotrigine can safely produce significant pain relief in patients with MS and TN.

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NICOTINE AND NEUROPATHIC PAIN IN SPINAL CORD INJURY
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Background and aims. We discovered two individuals with chronic spinal cord injury, one with at level neuropathic pain, and one with below level neuropathic pain. They had had this pain for many years. When they stopped smoking prior to skin flap surgery, they both noted that their pain was substantially reduced. They resumed smoking after surgery and pain intensity returned to baseline. We conducted a pilot study to explore the possible relationship between nicotine and neuropathic pain more rigorously.

Methods. Nicotine and placebo gum with three individuals with chronic spinal cord injury and neuropathic pain in a double-blind, cross over trial; trials were one week apart.

Results. The Figure illustrates the significant increase in pain on nicotine compared to placebo.

Conclusions. There has been nothing published in the SCI literature about a relationship between nicotine and neuropathic pain. Anecdotally, this is reported with nicotine patches and chewing tobacco also. We have begun a larger trial investigating this phenomenon.

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CASE REPORT: POSITIVE CLINICAL EXPERIENCE OF TREATING CHRONIC NON-CANCER PAIN WITH ZICONOTIDE
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Background. Ziconotide was licensed for the treatment of severe, chronic pain in the European Union in February 2005. Ziconotide must be administered intrathecally (IT); it blocks N-type voltage-sensitive calcium channels to prevent pre-synaptic release of glutamate.

Case report. JN was diagnosed with cervical spondylisis in 1969. By 1991 he had low back pain, increased neck pain and bilateral occipital neuralgia. A variety of therapies including cervical discectomy, lumbar root decompression, neurectomy, transcutaneous electrical nerve stimulation and strong opioids, were unsuccessful. In 2002, aged 59 years, he was referred to the Leeds Pain Service. Initial treatment with celecoxib, amitriptyline and gabapentin reduced pain on the visual analogue scale (VAS) from 10/10 to 2/10 in 2 months. Pain then increased and adverse drug events (AEs) of weight gain and sedation occurred. In 2004, JN received ziconotide titrated from 0.48 to 0.54 µg/day over 9 days, in increments of up to 0.02 µg/day via an external IT catheter.
Pain scores were reduced by 40%; apart from headache there were no AEs. A Medtronic IT drug delivery system was implanted and ziconotide was titrated in increments of up to 0.2 µg/day from 0.25 to 2.4 µg/day over 11 days. Other than headache and postoperative wound pain, no AEs occurred. Ziconotide was increased to the present dose of 8 µg/day with good pain relief with no AEs; fentanyl, morphine and gabapentin were titrated down and stopped.

Conclusion. Ziconotide provided effective analgesia with few AEs in a patient with difficult non-cancer pain, using slow dose titration.

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336 TREATMENT OPTIONS IN PATIENTS AFFECTED BY PERSISTENT VEGETATIVE
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Background and aims. The use of Lioresal (Baclofen) in implantable pumps, for its continuous release in the subarachnoid lumbar space, is an innovative method to reduce doses and potential secondary effects for treatment of spasticity in patients affected by persistent vegetative status.

Methods. All patients were tested before the operation. Test procedure regarded the response to the intrathecal baclofen injected in bolus for three consecutive days at increasing doses. Patients who presented a good response were submitted to the definitive implant.

From March 2000 to May 2005 30 patients affected by a persistent vegetative status, all males with age ranging from 15 to 40 (mean 29), secundary to head trauma (60%), spinal cord traumatisms (35%), hemorrhagic events (15%) were treated with the positioning of an implantable pump of baclofen in the subarachnoid lumbar space.

Each patient was exhamined for its personal grade of spasticity. The Ashworth scale varied from 3 to 5 (mean 4.6), spasm index varied from 1 to 3 (mean 2.2).

Results. All patients treated with the intrathecal baclofen have had an initial amelioration in the spasms beneath the persistence of the hypertonic status. In the long time follow up (mean 12 months) the hypertonic status improved following the initial good response in the spasms. The drop of the Ashworth scale was from 4.6 to 3.5 and, the spasm index, from 2.2 to 1.5.

Conclusions. Our experience declare that intrathecal baclofen is an useful tool for the treatment of spasticity in the persistent vegetative status.

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337 THE UTILITY OF PREGABALIN IN NEUROPATHIC PAIN PATIENTS – DEGREE OF BENEFIT IN RESPONDERS AND NON-RESPONDERS TO GABAPENTIN
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Background. The new gabapentinoid, pregabalin (PGB), is effective in therapy of neuropathic pain (NeP) in patients with diabetic peripheral neuropathy (DPN), and possibly in patients with other forms of peripheral neuropathy (PN). It is uncertain as to whether PGB is more effective and better tolerated than gabapentin (GBP) in this patient population.

Methods. Patients with NeP due to PN diagnosed at a tertiary care neuromuscular clinic were initially treated with GBP, with a minimum dose of 1200 mg daily. Both responders [defined as >30% decrease in visual analog score (VAS) of pain], and non-responders had therapy exchanged for PGB, which was commenced immediately with discontinuation of GBP, no washout period, and no overlap of therapy.

Results. A total of 23 responders and 10 non-responders to GBP were switched to PGB. Approximately 40% of patients had a diagnosis of DPN, with other various forms of neuropathy identified. The duration of PGB therapy averaged 6 months. The average dose of 2000 mg of GBP was replaced by an average dose of 375 mg of PGB, with a further 25% improvement in VAS in responders, and 21% in non-responders over GBP. Sixty percent of GBP non-responders were deemed a successful responder to PGB. Side effects due to either GBP or PGB were more common in non-responders to GBP, and discontinuations were only identified in GBP non-responders.

Conclusion. PGB may improve NeP relief in both responders and non-responders to GBP. Future studies are needed which include quality of life assessments and head-to-head comparisons.

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338 OXYCODONE IN NEUROPATHIC PAIN: A CLINICAL EXPERIENCE
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Background and aims. The aim of this study is to prove the need of opioids, oxycodone in this case, as a coadjuvant treatment in neuropathic pain.
Methods. Fifty patients with neuropathic pain between 50 and 60 years old were selected, all of them with an unremarkable clinical history except a bilateral radiculopathy in both legs secondary to a lumbar disc hernia at L3–L4 level. These patients were treated with Oxycodone, Pregabalin, Duloxetine. A VAS assessment and a Lattinen test were performed at the beginning of the study and after 2 months of treatment.

Results. A mean decrease in VAS of 3 points ± SD was obtained in 80% of cases and of 5 points ± SD in Lattinen. A 15% of cases presented adverse reactions. A 5% of cases did not experience any improvement.

Conclusion. Oxycodone is an acceptable option in association with Pregabalin and Duloxetine in neuropathic pain due to lumbar discopathy.

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CASE REPORT: ZICONOTIDE TREATMENT FOR A NEUROPATHIC AND A DEGENERATIVE PAIN PROBLEM

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Background. Ziconotide, an intrathecal non-opioid analgesic, was approved in the European Union in 2005 for severe, chronic pain.

Case report. Following three unsuccessful operations for herniated discs, RS was diagnosed in 2001 with bilateral neuralgia in the T5–T8 region. In 2002, thoracic pain was compounded with low back and leg pain due to L5–S1 disc degeneration. Spinal cord stimulation was not effective, obesity was a contraindication for morphine and surgery was not advised. The multidisciplinary team recommended enrollment into a randomised controlled trial with ziconotide. At study start (January 2005), RS was receiving tramadol, gabapentin, chlorothiazide, morphine immediate release, paracetamol/codeine, indomethacin and sertraline. Ziconotide was titrated over 25 days via an IT catheter, placed at the T9–T10 level, and external pump from a starting dose of 2.4 µg/day to 3.12 µg/day. RS responded favourably, with Visual Analogue Scale of Pain Intensity (VASPI) being reduced from 84 mm to 45 mm. A SynchroMed® infusion system was implanted and RS was enrolled in a follow-up study, during which ziconotide was titrated from 2.4 µg/day to 6.0 µg/day. VASPI varied between 65 mm and 46 mm. RS is currently on ziconotide 8.4 µg/day. Gabapentin, morphine and paracetamol/codeine have been withdrawn. Side effects, e.g. dizziness and blurred vision, have been successfully managed by dose reduction.

Conclusion. A stable dose of ziconotide has provided an acceptable level of pain reduction in a dual problem: neuropathic pain on a thoracic level and degenerative low back and leg pain.

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Poster Session 2: Molecular/Cellular studies I & II

340 NUMBERS, DENSITIES AND CO-LOCALIZATION OF AMPA AND NMDA RECEPTORS AT INDIVIDUAL SYNAPTIC CONTACT AREAS IN THE SUPERFICIAL SPINAL DORSAL HORN

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The well established role of AMPA- and NMDA-type ionotropic glutamate receptor mechanisms in the induction of spinal LTP and consecutive pain makes these receptors exceptionally important in spinal processing of nociceptive sensory signals. Here we applied the SDS-FRL method to laminae I–II of the spinal dorsal horn of rats and investigated the numbers, densities and co-localization of AMPA and NMDA receptors at individual postsynaptic active zones with a high molecular resolution. We demonstrated that the average surface area of glutamatergic postsynaptic active zones in laminae I–II was 0.0546 µm². We also showed that all glutamatergic postsynaptic membranes in laminae I–II expressed AMPA receptors, and most of them (96.2%) were immunostained also for the NR1 subunit of NMDA receptors. The numbers of gold particles labeling AMPA- and NMDA-type glutamate receptor ion channels at individual postsynaptic membranes varied in the range of 8–214 and 5–232 with mean values of 50.98 and 41.6, whereas their densities varied in the range of 325–3365 µm²/C0 and 84–2263 µm²/C0 with a mean of 1136.2 µm²/C0 and 786.8 µm²/C0, respectively. Concerning the subunits of AMPA receptors, it was revealed that virtually all (98.8%) investigated postsynaptic membranes expressed GluR2 subunits, and most of them (90.4%) were also immunoreactivity for GluR1. The size of postsynaptic surface areas showed a more or less linear correlation with the numbers of AMPA and NMDA receptors.
receptors. However, GluR1 expression was exceptionally low in postsynaptic active zones larger than 0.1 µm².

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NEUROPATHIC PAIN AND SPINAL GLIA: CHARACTERIZATION OF C-JUN N-TERMINAL KINASE (JNK) ACTIVATION IN ASTROCYTE CULTURES
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Pain hypersensitivity and central changes following peripheral nerve injury are not only mediated by neurons. Recent evidence has demonstrated the activation of glia plays an important role in the generation/maintenance of neuropathic pain. For instance, spinal nerve ligation induces activation of JNK in spinal astrocytes and intrathecal administration of JNK inhibitors can alleviate neuropathic pain. In order to define how JNK is activated in spinal astrocytes, we set up an in vitro assay to study JNK activation. Primary cultures of astrocytes from neonatal mice were stimulated with proinflammatory cytokines and trophic factors (TNFalpha, IL-1beta, BDNF, FGF and IL-6). The astrocyte cultures were harvested at different times after stimulation. The activation of JNK pathway was assessed by Western blot using antibodies against the phosphorylated forms of JNK (pJNK) and c-jun (p-c-jun). Data obtained from triplicate wells showed that among these agents, TNFalpha induced a substantial and reproducible increase of both p-JNK and p-c-jun levels at 15 min and 30 min. These data have demonstrated that in cultured astrocytes JNK pathway is readily activated by physiologically-relevant mediators. This in vitro model of JNK activation is valuable to determine downstream mechanisms of JNK activation. We are currently assessing JNK-mediated transcriptional regulation of targeted genes with quantitative RT-PCR after blocking the JNK pathway with the peptide inhibitor D-JNKI-1. The identification of downstream elements of JNK pathway in astrocytes will provide new insights for the understanding of glial regulation of neuropathic pain and may lead to development of new approach for pain treatment.

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MAPPING THE SIGNALLING PATHWAY OF THE CANNABINOID SYSTEM IN THE HUMAN BRAIN
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The endocannabinoid system is centrally involved in pain modulation. The endocannabinoid anandamide is produced ‘on demand’ by a phospholipase D selective for N-acyl-phosphatidylethanolamine (NAPE-PLD) and targets the cannabinoid receptor type 1 (CB1). CB1 stimulation is terminated by reuptake of anandamide or inactivation through hydrolysis. Fatty acid amide hydrolase (FAAH) is the pivotal enzyme for the hydrolytical degradation of the endocannabinoids anandamide and 2-arachidonoyl-glycerol.

We characterized the mRNA- and protein expression patterns of NAPE-PLD, CB1 and FAAH in human post-mortem brain tissue. NAPE-PLD mRNA was expressed in moderate amounts in cingulate cortex, thalamic nuclei and PAG, whereas the amygdala was nearly devoid of this transcript. CB1 mRNA was highly expressed in distinct populations of interneurons in the regions investigated. Albeit at a lower level, several primary neurons in cortex, amygdala, hippocampal formation, basal ganglia, thalamus and cerebellum expressed CB1 mRNA. This finding was confirmed by immunohistochemistry. FAAH mRNA was enriched in regions which express considerable amounts of CB1 mRNA like the cingulate cortex and amygdala, or contain high densities of CB1-immunoreactive fibers like the thalamic nuclei.

Our results confirm that the expression of the CB1 system is widespread in the human brain. With the exception of the amygdala, the tight regional coexpression of the CB1 receptor and the enzymes synthesizing and metabolizing anandamide indicates that endocannabinoid signalling is organized to serve mainly local circuitry.

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THE CONTRIBUTION OF TRPA1 AND TRPM8 TO COLD ALLODYNIA AND NEUROPATHIC PAIN
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Cold allodynia is a common symptom of neuropathic pain. However, the underlying mechanisms of this enhanced sensitivity to cold are not known. TRPM8 and TRPA1 are non-selective cation channels expressed by sensory neurons that have been proposed as candidates for cold transducers. We have investigated the role of these ion channels in cold allodynia by examining their expression and function following nerve injury.

We used a chronic constriction injury of the sciatic nerve to model neuropathic pain in mice. We dissected lumbar dorsal root ganglia (DRG) at 7 and 14 days post-surgery and used real-time RT-PCR, in situ hybridization, immunohistochemistry and calcium microfluorimetry to examine the expression and function of TRPM8 and TRPA1 after nerve injury.

We found no gross change in the expression level or profile of TRPM8. However the number of cells expressing TRPA1 was reduced and shifted towards peptidergic nociceptors following injury. We also examined functional properties of cold transduction using calcium imaging. Our experiments revealed a down-regulation of TRPA1 in the DRG after nerve injury, although no change in the number of cold responsive neurons.

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RALFINAMIDE ACTS THROUGH NMDA RECEPTOR COMPLEX: A CENTRAL ROLE FOR CHRONIC PAIN TREATMENT
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Ralfinamide is an alfa-aminoamide derivative with ion channel blocking properties and antinociceptive activity in animal models of pain.

Ralfinamide inhibits Na+ currents in a voltage and use-dependent manner in rat DRGs. It blocks high voltage-activated Ca2+ currents in DRG neurons, and modulates the substance P release in spinal cord synaptosomes. Blockade of Na+ and Ca2+ channels has been confirmed with human hortologue recombinant channels, in particular subtypes Nav1.3, Nav1.8 and Cav2.2, that play an important role in pain conditions.

To further investigate a possible central mechanism of action, ralfinamide effects on ligand-gated NMDA receptors were explored. In patch-clamp experiments, ralfinamide inhibits NMDA-induced currents in primary rat cortical neurons with an IC50 of 7.3 µM. Comparison with NMDAr reference modulators suggests that ralfinamide is not an open channel blocker, and its blockade is not mediated by the glycine or the NMDA binding sites. Data suggest that ralfinamide acts as an antagonist at the polyamine binding site with a mechanism different from ifenprodil (allosteric antagonist on the polyamine binding site) but similar to arcaine (namely a competitive antagonist at the polyamine binding site).

In parallel pulse-chase experiments, pre-incubation with ralfinamide reduces the NMDA-induced neuronal cell death (EC50 = 42 µM) suggesting neuroprotective effects by functionally blocking the consequences of NMDA current activation.

All these findings indicate that ralfinamide acts both peripherally and centrally through different targets important in pain control. This multiple mechanism of action of ralfinamide might explain its strong analgesic effect in animal models and supports therapeutic potential for pain treatment.

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PERIPHERAL EFFECT OF CANNABINOIDS: WIN 55,212-2 INHIBITS AXONAL ACTIVITY IN THE RAT SKIN-NERVE IN VITRO PREPARATION
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Background. Formalin induces a biphasic response when administered into the hind paw of the rat. The late phase of the nociceptive response has been attributed to an inflammatory reaction in the peripheral tissue that leads to the hyperexcitability of the second-order neurons. This phase may be maintained by peripheral input from A afferent fibres.

Cannabinoid agonists are able to attenuate nociception in some in vivo models.

Aim. To test, avoiding central components, if cannabinoid system could be involved in the peripheral control of the nociception.

Methods. The rat skin-nerve in vitro preparation (Neurosci. Lett. 66 (1986) 141–146) was used to evaluate the effect of a cannabinoid agonist (WIN 55,212-2) in rats that where injected with formalin and in control rats.
Results. The mechanical stimulation of skin receptive fields of sensorial A-fibres induces the discharge of action potentials; this response was similar in control animals and after the formalin intraplantar injection.

Administration of three separated concentrations of WIN (10^-6, 5 x 10^-6 and 10^-5 M) induced dose and time dependent significant inhibition of the frequency of discharge in 62% of the fibres in formalin treated rats (mean ± S.E.M. of inhibition: 10^-6 M: 44.7 ± 10.2; 5 x 10^-6 M: 63.7 ± 6.8; 10^-5 M: 80.7 ± 6.9) but it did not modify the response to mechanical stimulation in control skin-nerve preparations obtained from control rats. Effect of WIN was significantly reversed by the CB1 antagonist SR141716A.

Conclusions. Present results suggest that the antinociceptive effect of cannabinoids could include peripheral mechanisms which involve A-fibres and CB1 cannabinoid receptors.

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EXPRESSION OF IL-15 IN THE SPINAL CORD AFTER CHRONIC CONSTRICTION INJURY
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Chronic pain mechanisms that lead to abnormal sensitivity are frequently associated with inflammation after spinal cord injury (SCI). Inflammatory mediators released from immune cells contribute to persistent pain and probably have a crucial role in neuropathic pain generation. Neural tissue infiltration by macrophages and T-cells, that are activated and proliferate, is the hallmark of neuropathic pain. Astrocytes and microglia are concomitantly activated and produce further proinflammatory cytokines that maintain inflammation. Reactive astrocytes and microglia are the local source of inflammatory agents, including TNF-α, IL-1β, and nitric oxide. Both cell types are antigen presenting cells (APC) in the CNS and are the main regulators of both innate and adaptive CNS immune responses.

We described recently the expression in the CNS of interleukin-15 (IL-15). Here we show that IL-15 seems essential in the early inflammatory events that develop in the spinal cord following a peripheral lesion that generate neuropathic pain. It appears to have a major role regulating the physiology of central neurons and astrocytes. The expression of IL-15 in the dorsal horn starts very early after the peripheral lesion and the time-course of its proliferative and chemotactic properties relates to the infiltration and activation of the peripheral immune cells.

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INDUCTION OF FILOPODIAL STRUCTURES BY OVER-EXPRESSION OF TRPV1
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Background and aims. TRPV-family members of non-selective cation channels are expressed in a variety of neuronal and non-neuronal cells and are involved in the detection of varying physical and chemical stimuli. While channel properties of TRPV proteins have been
characterized intensively, their role for the cellular morphology is not explored.

Methods/Results. We demonstrate that the over-expression of TRPV1 strongly induces the formation of filopodia-like membrane protrusions in dorsal root ganglia neuron-derived F11 cells as well as in non-neuronal cells. As a result of this motile structure formation, the TRPV1 over-expressing cells often become highly elongated and reveal in addition 10-fold increase in neurite-like extensions. We demonstrate that some of the TRPV1 positive small protrusions contain microtubules and microtubule associated components. These structures localize to cell-to-cell connections. Using live cell microscopy we observe them to retract after exposure to TRPV1-specific ligands. However, both initiation of protrusion formation and cell-to-cell connection formation is independent of the TRPV1 channel activity. Instead, expression of an N-terminal fragment of TRPV1 is sufficient. Finally we demonstrate that over-expression of TRPV1 induces higher expression and altered cellular distribution of non-conventional myosin motors, which might underlie the protrusion formation.

Conclusions. Our results shade lights on novel inherent properties of the TRPV1 ion channel, which potentially contribute to the regulation of neuronal morphology and migration.

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348 EXCITABILITY AFTER THE ACTION POTENTIAL INDICATES CHANGES IN MEMBRANE POTENTIAL OF ISOLATED NOCICEPTIVE C-FIBERS
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The method of microneurography enables the recording of action potentials from single unmyelinated nerve fibers in peripheral human nerve and may help to improve the understanding of nociceptive C-fiber function in neuropathic pain. However, the interpretation of such data can be difficult because axonal membrane potential is not revealed in conventional microneurography recordings. An electrophysiological parameter with a good correlation to the axonal membrane potential seems to be the recovery cycle of excitability which follows a single action potential. In the present study, a threshold tracking technique similar to microneurography has been applied to isolated rat and human nerve preparations to follow the post-spike excitability of thin axons to various stimuli with known effects on membrane potential. We found that (1) some depolarising inflammatory mediators (e.g. ATP or serotonin) produce a reduction or loss of post-spike superexcitability; (2) membrane hyperpolarisation due to blockade of axonal Ih currents produces an enhancement of superexcitability; (3) an elevation of extracellular calcium concentration produces an increase in membrane threshold without a shift in membrane potential and/or an alteration in post-spike superexcitability. In addition, we demonstrate that membrane depolarisation and hyperpolarisation induce opposite post-spike latency shifts (changes in supernormality) in isolated C-fiber segments. Thus, recording of post-spike excitability and/or shifts in latency are sensitive techniques for the detection of various types of neuromodulation in correlation with changes in membrane potential of unmyelinated peripheral axons, and may help to understand observations obtained by microneurography in painful human neuropathies.

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349 NOVEL DUAL MECHANISM OF ACTION OF THE ANTIEPILEPTIC LACOSAMIDE
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Lacosamide is an investigational drug which shows potent analgesic and anticonvulsant effects in various animal models and is currently being evaluated in phase III clinical trials. The aim of the present experiments was to identify lacosamide’s mechanisms of action.

Fishhook experiments with affinity ligands in rat brain homogenates and radioligand binding to recombinant proteins were performed to identify binding partners for lacosamide. Since CRMP-2 is involved in neuronal differentiation and axonal outgrowth, the effects of lacosamide on neurotrophin-
induced axonal outgrowth were examined. Lacosamide specifically reduced axon outgrowth induced by neurotrophic factors without effects on basal outgrowth further supporting an interaction of lacosamide with CRMP-2. Detailed electrophysiological studies revealed that lacosamide shifted the voltage-dependence of slow inactivation of VGSCs to more negative potentials thereby regulating the long-term availability of sodium channels. Unlike other analgesics and anticonvulsants targeting the sodium channel (e.g. lidocaine) lacosamide did not influence fast inactivation of VGSCs.

These findings suggest that lacosamide has a novel, dual mode of action. Since slow inactivation of Na-channels is an endogenous mechanism by which neurons reduce stimulated or ectopic hyperactivity, this represents one important molecular mechanism for lacosamide. Given the important role of neurotrophic factors in the pathophysiology of chronic pain, the interaction of lacosamide with CRMP-2 might potentially have disease modifying effects. This, however, remains to be further investigated.

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CHARACTERIZATION OF ENDOGENOUS PKC- EPSILON IN F11 CELL, A MODEL SYSTEM FOR STUDYING PAIN SIGNALLING
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Background and aims. Involvement of PKCe in the development of hyperalgesia is well established. Detailed knowledge of signalling-components involved remains patchy partially due the inaccessibility of primary DRG neurons for biochemical analysis and the lack of an surrogate model system.

Methods/Results. We demonstrate that F11 cells, a DRG neuron-derived cell line, express different PKC isotypes, including a, b, g, e, i and l. In contrast to other PKC isoforms, we find the majority of PKCe to be present in a Triton X100 insoluble complex. Activation of PKCe by exogenous stimuli can be observed by its translocation to the plasma membrane as well as by the partial release from the insoluble complex. The localization of PKCe to the complex is resistant against different detergents as well as the cytoskeleton drugs nocodazole, cytochalasin B, cytochalasin D and acrylamide, disruptors of the microtubule, actin and neurofilament cytoskeleton, respectively. We further show that the PKCe present in this insoluble fraction is partially resistant to the proteases Factor Xa and trypsin treatment.

Conclusion. Our results suggest F11 cells to be a suitable model system to study pain-signalling pathways in vivo as well as in vitro. Further analysis of the components of the insoluble complex might reveal new components central to PKCe-signalling in pain.

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AN INCREASED AMOUNT OF ED-1+ CELL PROFILES IN DRG FOLLOWING SCIATIC NERVE LIGATION AND VENTRAL ROOT TRANSECTION
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Macrophages increase in number in DRG following nerve injury, and their activities are referred to induce neuropathic pain.

Macrophages exhibiting ED-1+ immunostaining were examined quantitatively in L4-L5 DRG from both ipsi- and contralateral side of naive rats and those following unilateral sciatic nerve ligation (SNL) or ventral root transection (VRT) under aseptic condition.

An amount of ED-1+ macrophages were found in naive DRG (nDRG) without intimate location to the neuronal bodies. In comparison to nDRG, area of ED-1+ was significantly enlarged in ipsilateral DRG (iDRG) 2 and 4 weeks from SNL. The ED-1+ macrophages and their processes were frequently located close to neuronal bodies to become their satellite cells. Contralateral DRG (cDRG) also displayed an increased amount of ED-1+ macrophages, but significant enlargement was found only following 4 weeks when compared with nDRG or cDRG after 2 weeks. In all cases, cDRG contained significantly lower amount of ED-1+ cells than iDRG.

VRT for 2 and 4 weeks resulted in an increased amount of ED1+ cells in both i- and cDRG in comparison to naive ones. However, the enlargement was similar on both sides after 2 weeks, but greater elevation was observed only in iDRG 4 weeks from VRT.

The results indicate that SNL and VRT stimulated invasion of ED1+ macrophages predominantly into iDRG, and later to contralateral ones. Our results suggested that Wallerian degeneration produces signals for invasion of macrophages to contralateral DRG.
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DIFFERENTIAL CHANGES IN TRPV1 EXPRESSION IN TRIGEMINAL GANGLION NEURONS FOLLOWING TRIGEMINAL SENSORY NERVE INJURY
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We have recently demonstrated that activation of glia and microglial p38 MAPK activation in medullary dorsal horn contributes to pain hypersensitivity following inferior alveolar nerve and mental nerve injury (Piao et al., 2006). It was also found that neuronal loss of trigeminal ganglion (TG) was not correlated with glial activation and pain hypersensitivity in our model. In this study, we have examined changes of TRPV1 expression in the injured and uninjured TG neurons using immunohistochemical analysis 3 days after surgery, the time point where we observed significant pain hypersensitivity. Injured neurons were identified by positive immunoreactivity for activating transcription factor 3 (ATF3). ATF3 immunoreactivity was exclusively observed in the nuclei of subpopulation of ipsilateral mandibular TG region, whereas there was no change in the expression of ATF3 in the naïve and the contralateral TG neurons. TRPV1 immunoreactivity was increased in ipsilateral TG neurons, compared to that of the naïve and the contralateral TG neurons. Interestingly, the expression of TRPV1 was mainly increased in the uninjured neurons rather than the injured neurons. Our results demonstrate that trigeminal sensory nerve injury induces differential change in TRPV1 expression in the injured and uninjured TG neurons. The upregulation of TRPV1 in uninjured TG neurons may play an important role in pain hypersensitivity after trigeminal nerve injury.

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INHIBITION OF COX-2 EXPRESSION IN RAT SPINAL DORSAL HORN BY ELECTROACUPUNCTURE IN NEUROPATHIC PAIN

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COX-2 may play a role in the neuropathic pain as it has been reported to increase in the spinal dorsal horn following a L5 spinal nerve ligation (SNL). Though electroacupuncture (EA) has long been used to treat pain including neuropathic pain, its effect on COX-2 expression has not yet been investigated. Using the SNL rat model, we have investigated the effect of EA on neuropathic pain in the current study. Immunocytochemical staining demonstrated that low frequency (2 Hz) EA can significantly reduce COX-2 expression in the spinal L4–L6 dorsal horn. The present results suggest that EA may reduce neuropathic allodynia at least partially by inhibiting COX-2 expression in the spinal cord.

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THE EXPRESSION OF CA-CHANNEL ALPHA2DELTA SUBUNIT AND TRPM8 IN DORSAL ROOT GANGLION OF TWO NEUROPATHIC PAIN RAT MODELS
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Background and aims. Peripheral nerve injury induces up-regulation of Ca-channel alpha2delta subunit and TRPM8 in dorsal root ganglion (DRG) which might contribute to allodynia development. We investigated the expression of alpha2delta subunit and TRPM8 regulation in DRG of damaged primary afferents after nerve injury in two rat models of neuropathic pain.

Methods. For sympathetically maintained pain (SMP) model, the L5 and L6 spinal nerves were ligated tightly distal to the dorsal root ganglion. For sympathetic independent pain (SIP) model, the tibial and sural nerves were ligated and transected, while the common peroneal nerve was spared. After a 7-day postoperative period, tactile and cold allodynia was assessed using von Frey filaments and acetone drops, respectively. Then the expression of alpha2delta subunit and TRPM8 in L5 and L6 DRG were examined by Western blot.

Results. There were no significant differences between the two rat models in the thresholds for tactile and cold allodynia. Western blot resulted that alpha2delta subunit in ipsilateral DRG to the injury was increased compared with that of contralateral or sham-operated DRG in SMP model, but no differences in SIP model. And there were no differences on the expression of TRPM8 between ipsilateral

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CAPSAICIN INDUCED CELL DEATH IN PRIMARY CULTURED NEURONS
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Purpose. To determine the effect of capsaicin to central nervous system, we prepared morphologic changes and biochemical assay were investigated in mouse primary cultured CNS neuron.

Methods. The susceptibility of capsaicin differs for different brain area. Cerebral cortex and hippocampus were more sensitive, and striatum, thalamus and midbrain area were less sensitive to capsaicin susceptibility. After capsaicin treatment, cortical and hippocampal neurons were died in dose- and time-dependent manner. By observation of nuclear fragmentation of capsaicin treated neuron, it is thought that the type of cell death is apoptosis rather than necrosis. The capsaicin receptor immunoreactive cells were observed in the cortex and hippocampus. It is consistent with area of damaged neuron. In case of capsaicin treated neurons, NOS activity stain was positive , the product of nitrite and anti-nitrotyrosine immunoreactivity were increased, and agmatine, which is a competitive nitric oxide synthases (NOSs) inhibitor significantly protect cortical and hippocampal neurons from capsaicin-induced apoptosis.

Results. These results indicated that capsaicin induced influx of cation ions. These results showed that capsaicin induced influx of Ca^{2+}, followed by neuronal NOS is activated by Ca^{2+} and induced cell death. Also, the activity of caspase 3 was increased after capsaicin treatment in the cortical and hippocampal neurons.

Conclusions. These results demonstrate that capsaicin induced the apoptosis through acting with capsaicin receptors. Calcium influx due to capsaicin receptor activation may induce apoptosis, which is triggered the formation of peroxynitrite by activating NOS activity or is mediated by activating caspase 3 pathway.

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EUGENOL INHIBITS VOLTAGE-GATED POTASSIUM CURRENTS IN TRIGEMINAL GANGLION NEURONS
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Eugenol, a natural capsaicin congener, is widely used in dentistry. Eugenol inhibits voltage activated sodium and calcium channels in a transient receptor potential vanilloid 1 (TRPV1)-independent manner. We hypothesized that eugenol also inhibits voltage-gated potassium channel (VGPC) currents and investigated this in rat trigeminal ganglion (TG) neurons and in a heterologous system using whole-cell patch clamping. Eugenol inhibited VGPC currents and the inhibitory effects of eugenol were observed in both capsaicin-sensitive and capsaicin-insensitive TG neurons. Pretreatment with capsazepine (CZP), a well-known antagonist of TRPV1, failed to block the inhibitory effects of eugenol on VGPC currents, suggesting no involvement of TRPV1. Eugenol inhibited human Kv1.5 channel currents stably expressed in Ltk – cells, where TRPV1 is not endogenously expressed. We conclude that eugenol inhibits VGPC currents in a TRPV1-independent manner. The inhibition of VGPC currents is likely to be a molecular mechanism underlying the irritable action of eugenol.

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A COMPARATIVE GENE EXPRESSION STUDY IN METABOLIC AND TRAUMATIC MODELS OF PAINFUL PERIPHERAL NEUROPATHY
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Comparative gene expression studies in different animal models of persistent pain are needed for a better understanding of the molecular mechanisms underlying different pain states.

We used real time quantitative PCR in order to accurately detect changes in expression through a comprehensive set of tissues from three rat pain models: chronic constriction injury of the sciatic nerve (CCI); sciatic nerve axotomy and streptozotocin induced diabetes (STZ). Here we report results on expression modula-
tion for known pain key players, namely: galanin type 1 receptor (GALR1), substance P (TAC1), bradykinin receptor 1 (BDKRB1), protein kinase C epsilon (PKCepsilon) and transient receptor potential vanilloid (TRPV1) channel.

Results. A significant up-regulation of GALR1 and BDKRB1 mRNA and down-regulation of substance P mRNA and TRPV1 are detected in all the studied models. More interestingly PKCepsilon mRNA is significantly up-regulated in traumatic pain models and not in the metabolic one (STZ). Moreover GALR1, substance P, TRPV1, and PKCepsilon change in gene expression was detected both at DRG and DH levels, while for the BDKRB1 mRNA, modulation was found only at the DRG level. Finally, the substance P, TRPV1 mRNA was modulated in the brainstem neuronal tissue sample.

Conclusions. This approach allows consistent study of distinct differences in expression changes that occur in the spinal cord and primary afferent neurons during traumatic and dysmetabolic conditions resulting in nociception. With the presented set of data we give a simultaneous and comparative overview of gene expression for key players in different animal models.

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UP-REGULATION OF MICRORNA-16 IN THE DORSAL ROOT GANGLION AND SPINAL CORD DORSAL HORN FOLLOWING PERIPHERAL NERVE INJURY
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Background and aims. MicroRNAs (miRNA) are short non-coding RNAs that inhibit translation of target genes by binding to their mRNAs. The expression of numerous brain-specific miRNAs with a high degree of temporal and spatial specificity suggests that miRNAs play an important role in gene regulation in health and disease. Here we investigate the expression profile of miRNA-16 in the dorsal root ganglion and in the spinal cord dorsal horn under physiological condition as well as in animals with neuropathic pain.

Methods. Male BALB/c mice weighting 20–25 g were used. Neuropathic pain was induced by partial sciatic nerve ligation (Seltzer model) whereas naïve mice were used as control. The development of tactile hypersensitivity following nerve injury was monitored by von Frey filaments. The expression of miRNA-16 was investigated in the dorsal root ganglion and in the spinal cord dorsal horn by RT-PCR in naïve mice and 1, 3, and 7 days post-nerve injury. β-Actin gene was used as a loading control.

Results. Under physiological conditions, miRNA-16 is robustly expressed both in the dorsal root ganglion and in the spinal cord dorsal horn. However, its expression is significantly up-regulated after peripheral nerve injury. Although no change occurred at day 1 post-injury, a 2- to 3-fold increase was observed at days 3 and 7 after nerve lesion (p < 0.05 one-way ANOVA).

Conclusions. Our results indicate that miRNA-16 expression is affected by peripheral nerve injury and may participate in the regulatory mechanisms of genes associated with the pathophysiology of neuropathic pain.

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ESTROGEN REDUCES THE HEAT-ACTIVATED VANILLOID RECEPTOR (TRPV1) CURRENT IN ADULT FEMALE RAT NOCICEPTIVE NEURONS
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Aim. The capsaicin receptor TRPV1, expressed by primary sensory neurons, functions in thermal nociception and inflammatory hyperalgesia. As therapies that reduce TRPV1 function are effective in treating interstitial cystitis most commonly experienced by females, we determined if estrogen had effects on TRPV1 in cultured DRG neurons from adult female rats.

Methods. After anesthesia and decapitation, DRG's (L1-2, L6, S1) were removed from rats, enzymatically dissociated, and neuronal cultures maintained in Neurobasal A. On day 2, drugs were added to cultures overnight prior to whole-cell patch clamp recording. Drugs were applied during recordings by local perfusion with a fast-switch system. TRPV1 activation was also measured by treating neurons with capsaicin in an extracellular cobalt solution, and measuring precipitated cobalt in fixed cells with densitometry.
**Results.** Maximal capsaicin currents were significantly reduced when neurons were cultured overnight in 17β-estradiol (10–100 nM), but not 17α-estradiol, which is inactive against estrogen receptors (ERs). Capsaicin currents were also inhibited by the ER-β selective agonist diarylpropionitril but not the ER-α agonist propylpyrazole trio. Tamoxifen (1 μM) prevented estrogen from inhibiting capsaicin currents. ATP-induced currents, which were recorded in most capsaicin-sensitive neurons, were not affected by estrogen treatment. Inhibition of neuronal TRPV1 activation by estrogens was also identified by the cobalt precipitation method.

**Conclusion.** These data suggest TRPV1 function in adult female DRG sensory neurons is inhibited by estrogen activation of ER-β. This mechanism could be important in regulating the development and maintenance of somatic and visceral neuropathic pain involving TRPV1-expressing sensory neurons in human females (NIH ROI DK069351-02).

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**EXPRESSION OF OPIOID GENES IN NEUROPATHIC AND INFLAMMATORY PAIN**

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**Background and aims.** A role of endogenous opioids in chronic pain is still poorly understood. While opioids efficiently alleviate even severe chronic inflammatory pain, neuropathic pain appears to be resistant to their actions.

**Methods.** In order to establish how the endogenous opioid system contributes to the differences between those types of pain, we have compared the expression (by using qPCR) of prodynorphin, proenkephalin and proopiomelanocortin as well as m-, d- and k-opioid receptors in the spinal cord and dorsal root ganglia (DRG) in rat models of neuropathic and inflammatory pain.

**Results.** We found that the expression of all three types of opioid receptors in the DRG was 2- to 3-fold lower in neuropathic pain than inflammatory pain. mRNA corresponding to opioid receptors in the spinal cord showed no change in chronic pain. On the other hand, we found low but robust expression of prodynorphin in the DRG, which increased up to 15 times in neuropathic pain as compared to inflammatory pain model. At the same time, expression of proenkephalin in the DRG was decreased up to 3-fold in neuropathic vs inflammatory pain.

**Conclusions.** The changes in expression of opioid peptides in the DRG clearly differentiate those types of pain, and provide a plausible explanation for the different symptoms associated with neuropathic and inflammatory pain, as well as clues towards the etiology of neuropathic pain.

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**SHORT-TERM EXPOSURE TO HYPOXIC/HYPERGLYCEMIC CONDITIONS IS ASSOCIATED WITH FUNCTIONAL CHANGES OF TRPV1 CURRENTS**

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**Background and aims.** Cultured rat dorsal root ganglia (DRG) neurons have been tested for the effects of hypoxic/hyperglycemic exposure on the vanilloid receptor (TRPV1) currents, to see whether in vitro exposure to these “diabetic” conditions alters the cell excitability as in streptozotocin-induced diabetic rats.

**Methods.** Male adult rats were killed by CO2 inhalation and decapitation, and DRG neurons were dissociated and kept in culture for 24 h at 37 °C in normoxic/normoglycemic (7% and 7.4 mM glucose) and hypoxic/hyperglycemic (4% and 25 mM glucose) conditions. Whole-cell patch and intracellular Ca2+ recordings using 2 μM Calcium Green-1 AM were made from small and medium DRG neurons (Cm < 45 pF) at 25 °C under 1 μM capsaicin application.

**Results.** The results indicate an increase in “diabetic” conditions of the mean peak current density (132.6 ± 22.19 pA/pF, n = 17) compared to normal conditions (65.40 ± 14.03 pA/pF, n = 11), P < 0.005. The ratio of the 2nd/1st application although 12.6% higher in “diabetic” conditions, was not significantly different from the normal (P > 0.005) while 1 μM PMA (phorbol myristate acetate) application did not significantly reduced the capsaicin-induced desensitisation. Under the same conditions, three populations of “diabetic” neurons classified according to their amplitude and
kinetics of activation, responded at capsaicin with a fluorescence signal ($\Delta F/F_0$) significantly higher ($P < 0.005$) than in similar normal neurons.

**Conclusions.** The short-term exposure of cultured rat primary sensory neurons to hypoxic/hyperglycemic conditions seem to alter the activity of TRPV1 currents which are directly involved in the excitability of the cells.

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**STATE-DEPENDENT INHIBITORS OF THE NAV1.3 SODIUM CHANNEL FOR TREATING NEUROPATHIC PAIN**

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Neuropathic pain and ectopic firing can be blocked by low concentrations of TTX without disrupting action potential signaling, implicating TTX-sensitive (TTX-S) sodium channels in this disease process. Expression of the TTX-S Nav1.3 channel is upregulated throughout the pain signaling pathway of neuropathic animals, and underlies the increased firing in axotomised DRG neurons. Antisense knockdown of Nav1.3 abrogates hyperexcitability and pain-related behaviours in rat models of neuropathic pain. We therefore used the human Nav1.3 channel as the primary target for our neuropathic pain drug discovery program.

Many of the drugs showing greatest oral efficacy in treating neuropathic pain, such as anticonvulsants and tricyclic antidepressants, target the inactivated state of the Nav1.3 channel. Use- and frequency-dependent inhibition of sodium channels is also seen with some of these off-label compounds, as well as with several preclinical candidates. Accordingly, we used voltage clamp protocols that reveal such state-dependent mechanisms of drug block to categorise hits previously identified in a primary screening campaign. Several lead series were developed further, with SAR guided by manual and automated patch clamp electrophysiological assays. Exemplar compounds from three lead series exhibited in vivo activity in the rat formalin assay, reducing late phase neuropathic pain behaviour by 25–57% ($p < 0.05$) at 5 mg/kg.

High affinity, state-dependent Nav antagonists promise more effective relief of neuropathic pain with fewer side-effects compared to existing treatments.

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**INSULIN AND INSULIN-LIKE GROWTH FACTOR-I MODULATE THE ACTIVITY OF CAPSAICIN-SENSITIVE CULTURED DORSAL ROOT GANGLION NEURONS**

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Noicceptive primary sensory neurons (PSNs) express thermo-sensitive transient receptor potential (TRP) channels, including the capsaicin-sensitive vaniloid-type 1 (TRPV1) receptor. Neurotrophins, acting on tyrosine kinase receptors, are key regulators of TRP activity. Here we studied whether stimulation of the tyrosine kinase insulin receptor (IR), which is co-expressed with the TRPV1 channel in a sub-population of PSNs, might also modulate the activity of TRPV1.

Neuronal cultures were prepared from dorsal root ganglia of rats and wild type or TRPV1−/− mice. Capsaicin-, insulin ($10^{-3}$ M to $10^{-7}$ M)-, insulin-like growth factor I (IGF-I; $10^{-7}$ M to $10^{-9}$ M)-, menthol- or heat-induced whole cell currents were recorded.

In rat, insulin evoked inward currents (EC$_{50}$ = $8 \times 10^{-7}$ M) in 30.9% of capsaicin-sensitive, but none in capsaicin-insensitive PSNs. IGF-I also induced inward currents in insulin- and capsaicin-sensitive neurons. In the TRPV1+/+ mice, insulin evoked responses in 9.3% of neurons (all capsaicin-sensitive); however in TRPV1−/− only 5% of the cells were activated. While in TRPV1−/− mice none of the cells were sensitive to capsaicin, three insulin-responsive neurons we tested exhibited heat-evoked currents. In rat PSNs both moderate cooling ($\geq 18$ °C), and warming ($\leq 41$ °C) influenced the insulin-induced current; while warming mainly enhanced it, in menthol-sensitive neurons cooling also produced potentiation. Retrograde labelling studies with the fluorescent dye diaminidino-yellow suggested that far larger proportion of visceral (bladder) afferents express IR than muscle or cutaneous afferents.

These findings indicate that insulin and IGF-I acutely influence the function of a subpopulation of capsaicin-sensitive PSNs possibly by modulating the thermo-sensitive TRP channels, including TRPV1.

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T-TYPE CALCIUM CURRENT IS A MOLECULAR DETERMINANT OF EXCITATORY EFFECTS OF GABA IN ADULT SENSORY NEURONS
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GABA, a major inhibitory neurotransmitter, is deeply involved in the control of somato-sensory sensations including pain under physiological and pathological conditions. In addition to its inhibitory action, reports have shown that, in adult sensory neurons, GABA can be responsible for excitatory effects leading to painful behavior. The cellular mechanisms for these excitatory effects remain largely unknown. Intracellular chloride concentration measurements of adult mice sensory neurons in primary cultures demonstrate a high concentration, allowing GABA receptor activation to depolarize all adult sensory neurons. However, we show that GABA, acting through GABA receptors, can generate, in vitro, action potential and intracellular Ca2+ increase only in a subset of neurons expressing a prominent T-type Ca2+ current. Moreover we demonstrate that T-current is responsible for GABA-induced cell excitability and intracellular Ca2+ increase. Together our results demonstrate, for the first time, a positive cross-talk between T-channel and GABA receptor in adult sensory neurons and indicate that T-type Ca2+ channel may be the molecular determinant for excitatory effects of GABA in peripheral somato-sensory system.

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NEUROPATHIC PAIN LEVELS FOLLOWING SURGICAL NERVE INJURY ARE CONTROLLED BY GENOTYPES AND HAPLOTYPES OF COMT – THE GENE ENCODING CATECHOLAMINE-O-METHYLTRANSFERASE
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Background. Catecholamine-O-methyltransferase (COMT) catabolizes dopamine, epinephrine, and norepinephrine, neurotransmitters having a role in peripheral and central neuropathic pain mechanisms. However, recent reports were inconsistent about the role that variations in the COMT gene have in explaining the inter-individual variability in neuropathic pain levels.

Aim and methods. We genotyped several single nucleotide polymorphisms (SNPs) in COMT in 315 Jewish women with breast cancer >1 year following mastectomy, axillary lymph node dissection and radio-, chemo- and hormonotherapy. Genotyped SNPs included rs2097903 and rs6269 (located in promoters of the splice variants MB-COMT and S-COMT), rs4633, rs4818, and rs4680 (val158met). Their genotypes and haplotypes were examined for association with having PMPS, a syndrome of neuropathic pain postmastectomy.

Results. Using multiple logistic regression, adjusting for covariates (age, ethnicity and surgical details), and correcting P-values with the False Discovery Rate method, genotypes of rs6269, rs4818 and rs4680 were significantly associated with PMPS at \( P = 0.0084 - 0.024 \) and OR = 2.7–2.4, respectively. LD analysis identified two haploblocks, one containing the three significant SNPs. Two reconstructed haplotypes (ACC, GCGG) accounted for >90% of COMT haplotypes and their diplotypes significantly associated with PMPS at \( P = 0.0086, \text{OR} = 2.9 \).

Conclusions. Polymorphisms in rs6269, the S-COMT promoter, may affect pain chronicity by controlling the levels of the soluble form of COMT. Alternatively, carrying rs4680met/met, that compared to rs4680val/val encodes the catabolically-weaker form of COMT, may cause less PMPS by increasing the level of catecholamines in the brain. Finally, certain COMT haplotypes may affect pain levels via mRNA 3D folding, altering its stability and translation into the enzyme.

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HTS ASSAY CONFIGURATION FOR CGMP-DEPENDENT PROTEIN KINASE I-ALPHA, A POSSIBLE DRUG TARGET IN PAIN THERAPY
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Several lines of evidence have shown that cGMP-dependent Protein Kinase I-alpha (PRKG1) plays a primary role in pain perception, acting as a downstream mediator of nitric oxide signaling. Hence, specific PRKG1 inhibitors are considered potential novel drugs for pain treatment.

To promote the access of PRKG1 into the drug discovery process, we have developed a functional assay for PRKG1 compatible with the requirements of the high-throughput screening (HTS).

Human PRKG1 was cloned and recombinantly expressed in insect cells. The expression was optimized to identify the conditions supporting high yield of protein production. A two-step purification strategy based on affinity and ion-exchange chromatography achieved near-to-homogeneity pure enzyme preparations. The PRKG1 catalytic activity was optimized on a matrix of 250 conditions and adapted to a 384 well/plate homogeneous format. In the final configuration, the PRKG1 reaction was detected with both a fluorescence-based and a luminescence-based readout under physiological ATP concentration (1 mM). To profile the substrate specificity of PRKG1, a kinase focused-library of 1040 peptides was screened and the positive surrogate substrates were ranked according to their catalytic efficiency. PRKG1 activity underwent a complete kinetic characterization, displaying a marked cGMP-dependent activity and a dose-dependent inhibition upon incubation with reference pharmacological inhibitors. Lastly, the protein production was upscaled to provide a purified PRKG1 batch supporting a screening campaign of over 1,000,000 compounds.

The configuration of an HTS assay for recombinant PRKG1 may represent a key contribution for the identification of specific inhibitors with a potential for therapeutic intervention in pain treatment.

THIAMINE INHIBITS HYPEREXCITABILITY AND MODULATES SODIUM CURRENTS OF NOCICEPITIVE NEURONS IN RATS WITH GANGLION COMPRESSION

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Neuropathic pain is severe and often intractable and continues to pose major clinical challenge. Our recent studies show that B vitamins thiamine, pyridoxine and cyanocobalamin and their combinations may relieve pain and hyperalgesia in rats with sciatic nerve injury or dorsal root ganglion (DRG) compression, suggesting the possible clinical utility of B vitamins in treatment of neuropathic painful conditions following injury, inflammation, degeneration or other disorders of the nervous systems in patients. Neural mechanisms underlying such analgesia remain unknown. Injury or inflammation affecting the axons or somata of sensory neurons having their somata in DRG often causes hyperexcitability that may lead to spontaneous firing and neuropathic pain. We further investigated possible roles of the B vitamins in hyperexcitability of the sensory neurons in rats with DRG compression. Intracellular and whole cell patch-clamp recordings were made in vitro from intact and/or dissociated DRG neurons. Administration of thiamine in vitro (1–10 mM, DRG perfusion) or in vivo (i.p., 33–100 mg/kg day$^{-1}$, 7–10 days until the day of electrophysiological recording) significantly reversed the decreased threshold current and increased discharge rate of action potential of the DRG somata. DRG compression-induced reduction of slow sodium currents in the nociceptive neurons was significantly reversed by thiamine treatment in vivo or in vitro. These results suggest that thiamine may reduce pain and hyperalgesia by depressing the neural hyperexcitability via modulating the abnormal expressed sodium currents. This study was supported by PCCBRF-VB002.

DOES THE C-FOS ACTIVATION MEDIATE THE EXPANSION OF CORTICAL SOMATOSENSORY FIELDS IN PHANTOM PAIN?

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Introduction. Phantom pain is a devastating chronic pain condition that complicates limb amputation surgery. Delineation of molecular signaling mechanisms underlying this process is essential to understand the basis of how the brain constructs and updates body image in response to changes of sensory inputs.

Methods. Sprague-Dawley rats were used in the experiments. Denervation of the left upper limb was
produced by brachial plexus axotomy. Two weeks later
the somatosensory receptive fields were stimulated by
vibration of ipsilateral whiskers for 30 s. One hour after
the whisker stimulation, the brain was harvested for
immunohistochemical analysis. The c-Fos was immuno-
stained as described previously (Radulovic et al., 1998).

Results. See Fig. 1.

Conclusions. This study shows that molecular signal-
ing processes which lead to c-Fos activation may be
involved in the expansion of areas of somatosensory
cortical representation of a denervated limb in response
to non-painful stimuli applied to adjacent cortical areas.
We postulate that the observed enhancement of c-Fos
activation in the denervated areas of the somatosensory
cortex is responsible for generation of phantom sensa-
tions and phantom pain.

Reference

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Two-photon excitation (2-PE) laser scanning micros-
copy is a relatively new technique for imaging living cells
(Denk et al., 1994). It was developed for resolving the
problems arising in the traditional technique for live cell
imaging, confocal laser scanning microscopy. These
problems, phototoxicity and low image contrast, are
due to a high amount of scattering of both excitation
and emission photons (Piston, 2005). 2-PE microscopy
reduces the impact of both problems. Excitation photons
have to arrive at the same point simultaneously for fluo-
rescence to be evoked, and for scattering excitation pho-
tons the chance that this happens is negligible. Thus, if
there is no absorption, there is no background fluores-
cence. Since there is no pinhole in a 2-PE microscope, a
much larger fraction of the emitted photons is detected
than in a confocal microscope (Svoboda and Yasuda,
2006).

In the present study, the effects of neuropathic pain
inducing agents on live axonal transport of mitochon-

Fig. 1. C-fos expression in rat somatosensory cortex following ipsilateral whisker stimulation. (A) and (B) cortex in sham operated rat. (C) and
(D) cortex in left brachial plexus axotomy rat. Barrel cortex (1), Upper limb cortex (2).

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TWO-PHOTON EXCITATION MICROSCOPY AS
A RESEARCH TOOL IN THE ANALYSIS OF
AXONAL TRANSPORT IN A MODEL OF NEU-
ROPATHIC PAIN

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dria in both SH-SY5Y cells and cultured dorsal root ganglia were investigated via 2-PE microscopy. It proves that this technique is suitable for imaging live cells, since it enables high-contrast time-series of moving mitochondria within an axon. However, practical challenges in using this technique remain. As with confocal imaging, photobleaching remains a problem for acquiring useful images. For example, scanning for 10 min at a 3.5 s time interval can result in the inability to discern fluorescent mitochondria from the background. In the present study decreasing laser power and exposure time proved to be the solution for bleaching.

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**Poster Session 2: Animal studies – Systems**

**370 RECEPTIVE PROPERTIES OF LAMINA I SPINO-PARABRACHIAL NEURONS FOLLOWING A CHRONIC CONSTRICTION INJURY**

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Recent in vitro studies (Ikeda et al. Science 2003;299:1237; Science 2006;312:1659) have postulated an important role in hyperalgesia for spinal lamina I neurons with axons that project to the midbrain. In the current experiments I have begun to investigate whether this hypothesis could provide a mechanistic explanation for the behavioural signs of neuropathic pain that are observed in vivo, following a chronic constriction injury (CCI) the rat sciatic nerve.

Experiments were performed on two groups of male Sprague-Dawley rats. One group were unoperated controls and the other had behavioural signs of peripheral neuropathy. We assessed whether striatal dopamine D2 receptors contribute to pain regulation also in neuropathic conditions. The spared nerve injury model of neuropathy was induced by unilateral ligation of the tibial and common peroneal nerves in the rat. In awake nerve-injured animals, pain-related withdrawal responses to calibrated monofilaments or noxious heat stimulation were attenuated following striatal administration of a dopamine D2 receptor agonist quinpirole. Pain-related responses were attenuated only in the nerve-injured limb ipsilateral to the injection and in the midline (tail). In unoperated controls, striatal administration of quinpirole did not influence withdrawal responses to mechanical stimulation. Attenuation of pain-related responses induced by striatal administration of quinpirole was reversed by intrathecal administration of a dopamine D2 receptor antagonist (eticlopride) or a non-selective 5-HT receptor antagonist (methysergide), but not by an α2-adrenoceptor antagonist (atipamezole). In the rostroventromedial medulla of lightly anesthetized neuropathic animals, striatal administration of quinpirole significantly decreased the activity of presumably pronociceptive cells that are activated by noxious stimulation. The innocuous H-reflex in lightly anesthetized control animals was not suppressed by striatal administration of quinpirole at an antihypersensitive dose. The results indicate that striatal dopamine D2 receptors attenuate neuropathic hypersensitivity. The antihyperalgesic effect induced by striatal dopamine D2 receptors in peripheral neuropathy involves suppression of impulse discharge of presumably pronociceptive neurons in the rostroventromedial medulla, and a descend-
ing influence acting on spinal 5-HT and dopamine D2 receptors.

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372 CORRELATION BETWEEN PAIN-RELATED BEHAVIOUR AND SPINAL MICROGLIOSIS IN DISTINCT MODELS OF TRAUMATIC, HIV AND VARICELLA ZOSTER INDUCED NEUROPATHY

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The role of spinal glia in the development of persistent pain states is becoming increasingly recognised. Peripheral nerve injury is associated with a rapid glial response within the spinal cord which has been correlated with the development of reflex hypersensitivity. This study investigated the correlation between behavioural measures of neuropathic hypersensitivity and spinal microgliosis in three distinct rat models of neuropathy; a model of traumatic neuropathy (L5 spinal nerve transection (SNT)), a model of HIV related neuropathy (combination of perineural HIV-gp120 and antiretroviral (ddC) treatment) and a model of varicella zoster virus (VZV)-associated neuropathy.

In all models, changes in hind limb withdrawal threshold in response to punctate mechanical, thermal and cold stimuli were measured. As a novel, integrated behavioural measure of pain-related anxiety, spontaneous exploratory behaviour was assessed in an “open field” arena. Peripheral neuropathy associated spinal microgliosis was quantified ex vivo by immunohistochemical image analysis and flow cytometry in which microglia were identified by OX-42 expression.

A persistent mechanical hypersensitivity as well as thigmotaxis (anxiety-like behaviour) developed in all neuropathic rats. However, only L5 SNT rats developed persistent thermal and cold hypersensitivity. Spinal microgliosis was evident in the SNT and HIV models but not the VZV model suggesting that microglial activation does not directly correlate with behavioural indices of neuropathic pain.

These results suggest that behavioural hypersensitivity and thigmotaxis are not necessarily linked to microglial activation and highlights the diversity of mechanisms underlying neuropathic pain of distinct origins.

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373 NEUROPATHIC PAIN IS DECREASED IN A2A ADENOSINE RECEPTOR KNOCKOUT MICE

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Background and aims. We have evaluated the possible involvement of A2A adenosine receptor in the development and expression of neuropathic pain. Methods For this purpose, partial ligation of the sciatic nerve was performed in A2A knockout mice and wild-type littermates. The development of mechanical and thermal allodynia, as well as thermal hyperalgesia was evaluated by using the von Frey filament model, the cold-plate test and the plantar test, respectively.

Results. In wild-type mice, sciatic nerve injury led to a neuropathic pain syndrome revealed in these nociceptive behavioural models. A significant decrease of the mechanical allodynia and a suppression of both thermal hyperalgesia and allodynia were observed in A2A receptor deficient mice.

Conclusions. These results reveal the involvement of A2A in the control of neuropathic pain and suggest a new potential therapeutic use of A2A antagonists.

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374 SPINAL CORD CHANGES IN RATS AFTER IMMOBILISATION

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Aim of investigation. Abnormal central sensory processing is considered a part of CRPS. Central changes have been shown in animals and man after immobilisation and may be linked to CRPS. This study looked at c-fos, c-jun induction and microglial activation in rats after immobilisation.

Methods. Sprague-Dawley rats, 200–250 g were used. Five + five control rats were followed. Ten + ten rats had fibreglass casts immobilising the left upper limb for 2 weeks. Following cast removal, study and control rats were perfused with formalin, the cervical spinal cords removed and stored in sucrose at −70 °C. Immunostaining for c-fos, c-jun and microglial activity were done on serial slices from the cervical enlargement.
Slides were reviewed by a blinded reviewer for fos induction and microglial activation.

Results. Unilateral increases in c-fos, less with c-jun and microglial activation were seen in the immobilised rats only. Cell death in the ventral horn was also noted in the immobilised rats.

Conclusions. Immobilisation alone produces spinal cord changes in rats that indicate changes in central processing. This may explain some of the signs and symptoms of patients with CRPS.

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VINCRISTINE-INDUCED NEUROPATHIC PAIN IN RATS: SPINAL CHANGES OF 5HT2A RECEPTOR AND FOS EXPRESSION, AND MICROARRAY ANALYSIS

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Vincristine, a chemotherapeutic drug used to treat a wide variety of cancers has neurotoxic effects on peripheral sensory neurons, leading to severe neuropathic pain. Vincristine-induced neuropathic pain is characterized in humans by painful burning paresthesias, and dysesthesia in limb extremities, and hypersensitivity to noxious and non-noxious stimuli. In this study, we used an animal model of this neuropathic pain disorder in the rat and studied the changes in 5-HT2A receptors and Fos expression in the spinal cord and DRGs in these animals at day 15 post-injection. We observed an increase in the number of Fos positive neurons in superficial (I–II), deep laminae (V–VI) and in lamina III. 5-HT2AR immunostaining increased in the whole lumbar dorsal horn, and in particular in layer II. In addition, the number of nociceptive DRG cells expressing the 5-HT2AR was also increased in Vincristine-treated animals compared with controls. These results suggest that 5-HT, via the 5-HT2AR, could be involved (1) in the peripheral sensitization of nociceptors, (2) in a wide central sensitization affecting the majority of neurons in the whole lumbar dorsal horn.

In a second part of this study, we analyzed changes in gene expression in the spinal cord of Vincristine-treated animals (compared with controls) using microarray analysis of genes potentially involved in the development and/or maintenance of chronic neuropathic pain. We established a list of 39 interesting genes. Twenty-two of which were up-regulated and 17 down-regulated. These targeted genes merged into five protein classes involved in different cellular mechanisms: receptors, kinases, transcription factors.

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OLIGONUCLEOTIDE IMT504 REDUCES NEUROPATHIC PAIN AFTER PERIPHERAL NERVE INJURY


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IMT504, the prototype of the PyNTTTTG class of immunostimulatory oligonucleotides, is a potent stimulatory signal for Mesenchymal Stem Cell (MSC) expansion both in vitro and in vivo. We have previously found that exogenous bone marrow-derived MSCs preferentially migrate to the tissues affected by a peripheral nerve injury and attenuate neuropathic pain. In this study, we have evaluated the effect of IMT504 administration on the development of mechanical and thermal allodynia induced by a sciatic nerve crush. Rats were treated either with IMT504, MSCs or saline and evaluated using the von Frey and Choi tests at different times after injury. Animals receiving either IMT504 or MSC treatment did not develop mechanical allodynia and presented a significantly lower number of nociceptive responses to cold stimulation when compared to controls. Control animals developed mechanical allodynia three, 7 and 10 days post-injury, and presented the major number of nociceptive responses to cold stimuli 3 days after the lesion. Preliminary data show that MSCs attenuate the changes in neuropeptide expression induced by the nerve lesion in primary afferent neurons, thus modifying pain neurotransmission. MSCs have been proposed as a possible therapeutic strategy for tissue repair therapies. The alleviation of pain induced by IMT504 was similar to that achieved after the administration of MSCs. However, systemic treatment with IMT504 has the advantage of avoiding ex vivo cell manipulation. Our results indicate the feasibility of using IMT504 as a therapeutic approach for the treatment of neuropathic pain.

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Neuropathic pain results from injury or malfunction in the peripheral or central nervous system. Injury to the nervous system is usually also associated with functional motor deficits. A relief from neuropathic pain and a recovery of impaired body functions may be achieved via appropriate regeneration of the injured tissue. The injured central nervous system regenerates rather difficult, thereby contrasting the regenerative nature of the injured peripheral nervous system. However, once the lesion gaps within the peripheral nervous system become too wide (more than a few millimeters), regeneration is strongly impaired. Hence, the last decade has seen many attempts to therapeutically bridge such large peripheral lesion gaps with (autologous) biological and synthetic materials. In order to test the efficacy of these materials in peripheral nerve repair, animal models are needed, which show both the presence of neuropathic pain and functional impairments. In addition, appropriate functional tests are required, which are essential in the correct assessment of pain-related behavior and impairments in body functions. Here, we completely resected the adult rat sciatic nerve. Neuropathic pain was assessed with von Frey filaments (mechanical allodynia) and CatWalk gait analysis (pain-induced gait adaptations), whereas motor impairments were assessed with the BBB locomotor rating scale and CatWalk gait analysis. The functional outcome associated with this peripheral nerve injury model will be discussed together with its suitability for testing therapies to relieve pain and induced functional recovery.

**Results.** Exposure to ultrasonic (versus sham) stress resulted in 3-fold elevation in plasma corticosterone levels and significantly prolonged PWL in WT mice. In alpha2A KO mice the corticosterone elevation was blunted and PWL significantly shortened following ultrasonic stress. Alpha2A KO mice subjected to adrenalectomy still exhibited stress-induced thermal hyperalgesia. Guanethidine sympathectomy or prazosin did not affect baseline thermal sensitivity, but blocked stress-induced thermal hyperalgesia in alpha2A KO mice. WT mice and rats pretreated with rauwolscine and idazoxan also exhibited stress-induced hyperalgesia.

**Conclusions.** Alpha2A KO mice, and WT mice and rats pretreated with alpha2 antagonists, exhibited stress-induced hyperalgesia, rather than stress-induced analgesia. This finding reflects a balance in the effects of stress on pain, probably via spinal inhibitory pathways and sympathetic nerves, that is shifted towards analgesia by alpha2A receptors.

**Background and aims.** Modulation of pain signaling at many levels in the nervous system involves adrenergic pathways. Despite the signaling role of alpha2 receptors in these pathways, alpha2 KO mice have normal baseline sensitivity to thermal stimuli. We hypothesized that a pain phenotype would become apparent in the presence of stress and that alpha2A KO mice would be useful for investigating the effect of stress on pain sensation.

**Methods.** Wild-type (WT) and alpha2A KO mice were exposed to 10 min ultrasonic sound stress (24–75 kHz, 100 dB) and tested for paw withdrawal latency (PWL) on a 50 °C hotplate. The effects of adrenalectomy, guanethidine sympathectomy and pretreatment with the alpha1 antagonist prazosin or the alpha2 antagonists rauwolscine and idazoxan were assessed.

**Results.** Exposure to ultrasonic (versus sham) stress resulted in 3-fold elevation in plasma corticosterone levels and significantly prolonged PWL in WT mice. In alpha2A KO mice the corticosterone elevation was blunted and PWL significantly shortened following ultrasonic stress. Alpha2A KO mice subjected to adrenalectomy still exhibited stress-induced thermal hyperalgesia. Guanethidine sympathectomy or prazosin did not affect baseline thermal sensitivity, but blocked stress-induced thermal hyperalgesia in alpha2A KO mice. WT mice and rats pretreated with rauwolscine and idazoxan also exhibited stress-induced hyperalgesia.

**Conclusions.** Alpha2A KO mice, and WT mice and rats pretreated with alpha2 antagonists, exhibited stress-induced hyperalgesia, rather than stress-induced analgesia. This finding reflects a balance in the effects of stress on pain, probably via spinal inhibitory pathways and sympathetic nerves, that is shifted towards analgesia by alpha2A receptors.
measurement of peptide levels, respectively. Diabetes was induced with streptozotocin in adult male Wistar rats. In a cranial window preparation, epidural application of capsaicin (10⁻⁷ to 10⁻⁶ M) produced distinct vasodilatory responses in control animals. In diabetic rats, capsaicin-induced vasodilatation was significantly reduced or even abolished 6 but not 2 or 4 weeks after the induction of diabetes. However, vasoconstriction, a non-neurogenic response to capsaicin at higher concentrations (10⁻⁵ M) was not altered in diabetic rats. The vasodilatory effects of histamine (10⁻⁵ M), acetylcholine (10⁻⁴ M) and CGRP (10⁻³ M) were similar in control and diabetic animals. In diabetic rats, in vitro experiments revealed a significant decrease in capsaicin-induced release of CGRP. In conclusion, the present study revealed a marked reduction in sensory neurogenic vasodilatation in streptozotocin-treated rats indicating an impairment of meningeal nociceptor function. The findings suggest that diabetes-induced alterations in neurogenic inflammatory reactions resulting in a limited removal of inflammatory mediators and/or tissue metabolites from meningeal tissue may contribute to the enhanced incidence of headaches in diabetics.


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380 LACOSAMIDE: OVERVIEW OF THE ANALGESIC EFFICACY IN ANIMAL MODELS OF PAIN
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Lacosamide is a novel investigational analgesic which is currently being evaluated in phase III clinical trials in patients suffering from painful diabetic neuropathy. It has a novel dual mode of action: it enhances the slow inactivation of voltage-gated sodium channels and modulates collapsin response mediator protein 2. The aim of the current experiments was to profile lacosamide in various animal models for chronic pain.

Lacosamide in the dose range 3–30 mg/kg given i.p. was evaluated in the streptozotocin (STZ) model for diabetic neuropathic pain, the vincristine model for chemotherapy-induced neuropathic pain, a bone cancer model, the monosodium iodo acetate (MIA) model for osteoarthritic pain and the tumour necrosis factor alpha (TNFa) model for chronic muscle pain. In each model various endpoints were assessed including thermal and tactile allodynia and thermal and tactile hyperalgesia.

In the STZ model lacosamide was active on all pain parameters. Moreover, when compared to clinically used analgesics such as amitryptiline, pregabalin, gabapentin, levetiracetam, lamotrigine or venlafaxine lacosamide was the compound with the broadest efficacy. Lacosamide was also active in models for cancer pain, as evidenced by potent effects against vincristine-induced hyperalgesia and bone cancer pain. Furthermore, muscle hyperalgesia induced by TNFa was more potently reduced by lacosamide as compared to pregabalin. Finally, lacosamide attenuated arthritic pain induced by MIA in rats.

These results suggest that lacosamide may specifically have antihyperalgesic activity under conditions of chronic neuropathic, cancer, inflammatory and musculoskeletal pain.

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381 DIFFERENTIAL PHARMACOLOGY OF TRPV1 ANTAGONISTS DETERMINES THE MAGNITUDE OF BODY TEMPERATURE CHANGES IN RATS
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The vanilloid receptor TRPV1 is a cation channel that serves as a polymodal detector of pain-producing stimuli such as capsaicin, protons and heat. TRPV1 antagonists that block capsaicin, proton and heat activation act as anti-hyperalgesics in animal models of pain, suggesting their utility as analgesics. Recently, we showed that TRPV1 antagonists representing various chemotypes cause an increase in body temperature (hyperthermia) in multiple species suggesting that TRPV1 is tonically activated in vivo and regulates body temperature.

In an effort to eliminate hyperthermia associated with TRPV1 antagonism, we have characterized several molecules exhibiting differential pharmacology in vitro using agonist-induced 45Ca²⁺ uptake assays and in vivo by radiotelemetry.

Some TRPV1 antagonists blocked capsaicin but modulated proton and heat activation differentially. For example, some capsaicin antagonists blocked heat activation but potentiated proton activation, whereas others
potentiated both proton and heat activation. Radiotelemetry experiments showed that antagonists of capsaicin that potentiate both proton and heat activation cause a marked drop in body temperature (hypothermia). However, compounds like JYL1421, which block capsaicin and potentiate pH 5 activation, did not cause significant changes in body temperature. A variety of other combinations of antagonism or potentiation of these different modes of TRPV1 activation resulted in mild to marked hyperthermia or hypothermia in rats.

Results of these studies indicate that body temperature regulation are a predominant function of TRPV1. Interestingly, it appears that the ability of capsaicin antagonists to potentiate proton activation results in lack effects on body temperature.

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ASSESSMENT OF NEUROPATHIC PAIN AND LOCOMOTOR DEFICITS USING THE CATWALK GAIT ANALYSIS
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A large number of neurological disorders, including spinal cord injury, are associated with neuropathic pain and deficits in a wide range of locomotor functions. Although there is a range of test specifically designed to assess neuropathic pain or locomotion, a test which can measure both phenomena is lacking. Obviously, neuropathic pain and locomotor deficits may both affect the gait of the animal. Therefore, the recently developed CatWalk gait analysis could be a test that appreciates both pain behavior and locomotor deficits. In the present study, we tested whether a range of gait parameters, which can be linked with pain behavior, are also altered after spinal cord injury in the adult rat. The pain-related gait parameters were selected from an additional study using animals with inflammatory pain and no injury. Many pain-related gait parameters were related to the size of the paw prints, including print area, max area, box width and box length, but also the swing speed of the paw. We show that spinal cord injury of the adult rat resulted in impaired pain-related parameters in addition to many locomotor deficits, including interlimb coordination, a parameter which is unaltered after inflammatory pain. Our data, therefore, suggest that the CatWalk gait analysis can be used to detect both neuropathic pain and locomotor deficits after spinal cord injury in the adult rat.

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PERINEURAL CAPSAICIN AND RESINIFERATOXIN INDUCE SELECTIVE REGIONAL ANALGESIA AND PHENOTYPIC SWITCH OF PRIMARY SENSORY NEURONS EXPRESSING TRPV1
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Perineural treatment with the potent transient receptor potential vanilloid type 1 receptor (TRPV1) agonists, capsaicin and resiniferoxin (vanilloids) produce long-lasting selective regional analgesia in the rat. Capsaicin treatment has also been suggested to induce central sprouting of large myelinated spinal primary afferents labelled with the B subunit of cholera toxin (CTB), which specifically binds to GM1 ganglioside. The present study was initiated to clarify the role of capsaicin-sensitive C-fibre afferents in these phenomena. In control rats, injection of CTB-horseradish peroxidase (HRP) conjugate into the sciatic nerve resulted in an intense labelling of the spinal dorsal horn except laminae I–II. Vanilloid treatment of the sciatic nerve 2 weeks prior to the injection of CTB-HRP resulted in an intense labelling also of these superficial laminae and a significant increase in the proportion of labelled small neurons and unmyelinated axons in relating spinal ganglia and dorsal roots. In addition, selective elimination of capsaicin-sensitive sciatic afferents prevented CTB-HRP-labelling of small ganglion cells and of laminae I-II of the spinal dorsal horn. These findings indicate that vanilloid-induced transg anglionic labelling of spinal laminae I–II cannot be attributed to a sprouting response of myelinated primary afferents but rather to an increased uptake and transport of CTB-HRP by capsaicin-sensitive primary afferents, i.e. a phenotypic switch linked to an increase in neuronal GM1 ganglioside content. The findings suggest an important role of GM1 ganglioside metabolism in the regulation of nociceptor function and may provide a novel approach to interfere with pain mechanisms.


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NERVE INJURY TRIGGERS GLIAL ADAPTATION IN THE PERIAQUEDUCTAL GRAY (PAG) OF RATS WITH DISABILITY AND PAIN, BUT NOT PAIN ALONE
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Following constriction injury of the sciatic nerve (CCI) rats develop allodynia and hyperalgesia. We have shown that approximately 30% of CCI rats develop also complex behavioural disabilities identical to those shown by patients in chronic pain clinics. These disabilities include altered: (i) social behaviour; (ii) sleep-wake cycles; (iii) responses to stress, (iv) activity of HPA and HPG axes; and (v) thyroid function. The PAG has been shown to mediate changes in each of these functions. It has also been a focus of our experiments to define CCI-evoked adaptations in supraspinal regions likely to underlie the disabilities characterising the chronic pain state. Rats received a CCI and were tested each day for allodynia/hyperalgesia and ‘disability’. There were no differences in the magnitudes of allodynia/hyperalgesia between rats with ‘disability’ and those without. GeneChip and RT-PCR techniques applied to isolated PAGs identified significant up-regulation of the mRNAs coding GFAP and vimentin in ‘disability’ but not in ‘non-disability’ rats. Increased translation of GFAP and vimentin was confirmed by Western Blotting and the anatomical location of these changes was determined using immunohistochemistry. Compared to CCI rats with pain alone (which did not differ from un-injured control rats), rats with CCI-evoked ‘disability’ and pain showed increased numbers of GFAP and vimentin immunoreactive cells in the rostro-lateral and caudo-ventrolateral PAG columns, these cells were significantly larger and occupied a significantly greater medio-lateral extent of each PAG column. Glial adaptation in the PAG may underlie the disabilities seen in nerve-injury triggered chronic pain states.

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Results. Different CWSS regimes (0.5–3 min) induced time-dependent analgesia. Nerve ligation did not alter the CWSS induced analgesia. Caerulein (0.025, 0.05 and 0.1 mg/kg) induced analgesia in both nerve ligated and intact animals. Different doses of proglumide (20, 40 and 60 mg/kg) alone produced analgesic effect. The response of caerulein was not inhibited by proglumide. In the stressed mice, both drugs and the combination of them showed analgesia but they appeared no potentiation in CWSS-induced analgesia.

Conclusions. Our results indicate no significant relationship between CCK receptors and the CWSS-induced analgesia. Nevertheless, the CWSS, as an alternative to drug treatment in neuropathic pain, remains to be more studied.

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MINOCYCLINE AND PENTOXIFYLLINE ATTENUATE ALLODYNIA AND HYPERALGESIA AND POTENTIATE THE EFFECTS OF MORPHINE IN ANIMAL MODELS OF NEUROPATHIC PAIN
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Background and aims. Recent research has shown that microglial cells which are strongly activated in neuropathy can influence development of pain. Therefore, we investigated how glial inhibitors influence neuropathic pain symptoms and effectiveness of morphine.

Methods. Using von Frey and cold plate tests we examined antinociceptive effects of intraperitoneal administration of minocycline and pentoxifylline and their influence on morphine analgesia after chronic constriction injury (CCI). The experiments were carried out according to IASP rules (Zimmermann, 1983).

Results. Here we demonstrated that preemptive and repeated i.p., administration (16 h and 1 h before injury and then after nerve ligation twice daily for 7 days) of minocycline (15; 30; 50 mg/kg), a potent inhibitor of microglial activation, significantly attenuated the allostodynia and hyperalgesia measured on day 3, 5, 7 after CCI in rats. In mice, i.p., administration of minocycline (30 mg/kg) or pentoxifylline (20 mg/kg) according to the same schedule also significantly decreased allodynia and hyperalgesia on day 7 after CCI. Antiallodynic and antihyperalgesic effect of morphine (30 µg; i.t.) given by lumbar puncture in mice was also significantly potentiated in minocycline-treated group.

Conclusions. These findings indicate that preemptive and repeated administration of glial inhibitors suppresses development of allodynia and hyperalgesia and potentiates effects of morphine in models of neuropathic pain.

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DIABETIC NEUROPATHY IS ASSOCIATED TO INCREASED NEURONAL ACTIVITY AT THE SPINAL DORSAL HORN: A TIME-COURSE STUDY OF C-FOS EXPRESSION
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Animals with painful diabetic neuropathy exhibit mechanical allodynia and spontaneous pain, which appears to be associated with hyperexcitability of spinal nociceptive neurons. In the present study, we performed a time-course evaluation of c-fos expression to study neuronal activation at the spinal dorsal horn of streptozotocin (STZ) diabetic rats. Male Wistar rats were i.p. injected with STZ (60 mg/kg) and sacrificed, under chloral hydrate anaesthesia, at 1, 2, 4 and 6 weeks post-injection (n = 5 rats per time-point). Age-matched, non-injected, animals were used as control (time-point 0). Upon vascular perfusion, sections from segments T13-L5 were immunoreacted against Fos protein (Ab5; Oncogene), using the ABC method. The numbers of Fos-immunoreactive (Fos-IR) neurons in the superficial (laminae I–II) or deep (laminae III–V) dorsal horn were counted and compared by ANOVA, followed by the Tukey post-hoc test. During all the time of analysis, STZ-injected animals developed hyperglycaemia (>270 mg/dl) and behavioural signs of diabetic neuropathy. In segments T13-L5, the numbers of Fos-IR neurons were moderately increased 1 and 2 weeks after STZ injection. At 4 weeks a large increase in Fos expression was detected in the superficial (laminae I–II) or deep (laminae III–V) dorsal horn and compared by ANOVA, followed by the Tukey post-hoc test. During all the time of analysis, STZ-injected animals developed hyperglycaemia (>270 mg/dl) and behavioural signs of diabetic neuropathy. In segments T13-L5, the numbers of Fos-IR neurons were moderately increased 1 and 2 weeks after STZ injection. At 4 weeks a large increase in Fos expression was detected in the superficial dorsal horn of all segments analysed, while in the deep dorsal horn this increase was only observed in T13-L3 segments. At 6 weeks, Fos levels returned to values obtained at the initial time-points. The present data indicate that during diabetic neuropathy spinal neurons present functional changes,

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which may be related to the described sensory abnormalities.

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INTRAPERITUNEAL ADMINISTRATION OF ASCORBIC ACID ATTENUATE HYPERALGESIA IN A RAT MODEL OF NEUROPATHIC PAIN

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Neuropathic pain is a chronic pain condition which is resistant to therapy with traditional analgesics. Reactive oxygen species are critically involved in chronic pain conditions. Vitamin C is a well known antioxidant but its antinociceptive effect on chronic pain is not known.

To investigate the efficacy of vitamin C in neuropathic pain condition, 32 male rats were allocated to four groups. Pain induced by chronic constriction injury of sciatic nerve. Thermal and mechanical nociceptive thresholds were assessed respectively with paw withdrawal latency to radiant heat and paw withdrawal threshold in response to linearly increasing pressure.

Chronic intraperituneal injection of 3 mg/kg vitamin C for three weeks increase pain threshold from the second week after CCI. Acute administration of 1 mg/kg vitamin C on second week after CCI did not produce any changes in pain threshold of neuropathic rats but acute injection of 5 and 10 mg/kg of vitamin C significantly alleviate pain 15 and 30 min after injection in the second week following CCI, which is the maximum pain period in CCI model.

These data suggest that vitamin C produces analgesia in neuropathic rats and treatment that increase ascorbate concentration may be beneficial for patients with chronic pain conditions.

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A DOPAMINE D2 PARTIAL AGONIST, ARIPIPRAZOLE, DIMinishES NOCICEPTION IN A NEUROPATHIC PAIN MODEL IN THE RAT

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Aripiprazole has been used as a novel antipsychotic drug that has shown good results in improving positive and negative symptoms. It has shown to be a partial dopamine D2 receptor agonist and to increase dopamine release in the prefrontal cortex as well as other cerebral nuclei. In this context, our group has documented that dopamine D2 agonists microinjected into the anterior cingulate cortex has proven effective in reducing chronic nociception. With this framework, we decided to test if oral aripiprazole has an antinociceptive role in a neuropathic pain model.

In all groups a single dose of aripiprazole (0.1, 1, 10 and 40 mg/kg; n = 10 each) or distilled water (control, n = 14) was orally administered. Next, under general anaesthesia (halothane), a thermonociceptive stimulus was applied (hind paw immersion in water at 55 °C) and 30 min later a sciatic denervation was performed. Chronic nociception was measured by the autotomy score, onset and incidence.

The results show a decreased autotomy score in all groups when compared to control, with a significant difference between aripiprazole 10 and 40 mg/kg as compared to control. The onset also showed a delay in all aripiprazole groups when compared to control with significance in group 40 mg/kg.

This study is the first evidence that the oral administration of aripiprazole can diminish chronic nociception measured as autotomy behaviour in the rat with a dose dependent tendency. The results open a new alternative in the management of neuropathic pain.

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EFFECTS OF THE MGLUR5 ANTAGONIST MPEP AND THE MGLUR7 AGONIST AMN082 ON ALLODYNIA, HYPERSENSITIVITY AND MORPHINE ANALGESIA IN NEUROPATHIC PAIN

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Background and aims. Metabotropic glutamate receptors mGluR5 and mGluR7 are present in spinal cord
regions important for nociceptive transmission, but their involvement in neuropathy has not yet been defined. We studied the effects of MPEP and AMN082 on development of neuropathic pain states and morphine effectiveness.

Methods. Applying the von Frey and cold plate tests we examined the influences of i.p. administration of MPEP and AMN082 on development of allodynia and hyperalgesia and on morphine analgesia in mice after sciatic nerve ligation (SNL). The experiments were carried out according to IASP rules (Zimmermann, 1983).

Results. In mice administration of MPEP and AMN082 showed dose-dependent attenuation of allodynia and hyperalgesia at day 7 after SNL. Moreover, chronic injections of lower than single doses of MPEP and AMN082 attenuated the development of allodynia and hyperalgesia. The effect of morphine (20 mg/kg; i.p.) administered 30 min after single dose of MPEP (30 mg/kg; i.p.) was significantly potentiated in von Frey and cold plate tests. However, the effect the same dose of morphine administered 30 min after AMN082 (3 mg/kg; i.p.) was significantly potentiated in von Frey test but not in cold plate test.

Conclusions. These results demonstrate that both mGluR5 and mGluR7 receptors play a role in nociceptive transmission during neuropathic pain. The data also indicate that mGluR5 antagonists and mGluR7 agonists potentiate the effects of morphine in mice model of neuropathic pain.

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A SELECTIVE ESTROGEN RECEPTOR BETA AGONIST MODULATES NEUROPATHIC AND INFLAMMATORY PAIN STATES
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Background and aims. The effects of estrogens on pain perception remain quite controversial. Depending on the animal models, both beneficial and detrimental effects of non-selective estrogens have been reported in the literature. Further, the results of multiple human clinical trials examining the potential beneficial effects of estrogens in breast, bone, pelvic pain have been inconclusive as well. While the underlying mechanisms for these discrepancies are not understood, we believe they are likely to arise from the lack of selectivity of estrogens for their two cognate receptors, the nuclear hormone receptors ER alpha and ER beta.

Results and conclusions. Using a proprietary functional cell-based platform technology (R-SAT®: Receptor Selection and Amplification Technology), non steroidal ER beta pharmacophores were identified. They define two classes of small molecule agonists, with low nanomolar affinity for ER beta and a high degree of selectivity (>100–1000-fold) versus ER alpha and other nuclear receptors. A prototype lead molecule, ERb-131, was evaluated in several pain animal models involving nerve injury or sensitization. ERb-131 reversed tactile allodynia caused by spinal nerve ligation (Chung model) and chemical insults. ERb-131 also alleviated tactile or thermal hyperalgesia in both acute and chronic inflammation models (capsaicin, CFA, formalin). Finally, ERb-131 did not influence the pain threshold of normal healthy animals. Thus, ER beta agonism is a critical effector in the mediation of broad anti-nociceptive states.

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SYNERGISTIC EFFECTS BETWEEN THE INVESTIGATIONAL ANALGESIC LACOSAMIDE AND OTHER ANALGESIC DRUGS IN THE RAT FORMALIN TEST
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Lacosamide is an investigational analgesic with a novel dual mode of action: enhancement of slow inactivation of voltage-gated sodium channels and modulation of collapsin response mediator protein 2. It is currently being evaluated in phase III clinical trials for painful diabetic neuropathy. Since polytherapy is common in clinical practice the aim of the current
The experiment was to investigate, in an animal model, potential pharmacodynamic interactions between lacosamide and other clinically used analgesics with different modes of action.

In the first experiments, minimally effective doses of lacosamide, the anticonvulsant gabapentin, the opioid morphine, the antidepressant duloxetine, and the glutamate NMDA antagonist memantine were determined in the formalin test. Rats were pre-treated with either vehicle or several doses of one of the test drugs, followed 10 min later by intraplantar injection of formalin. The number of formalin-induced flinchings and the time of formalin-induced licking served as experimental parameters.

In the second phase, combinations of minimally effective doses of lacosamide with that of one other drug were tested and compared to the effects of either drug alone. The results suggest pure additive effects between lacosamide and gabapentin. Weak synergistic interactions (i.e. stronger analgesic effect of the combination than the sum of the effects of each substance alone) were found between lacosamide and memantine. Combinations of lacosamide with either duloxetine or morphine resulted in synergistic effects.

These results suggest potentially beneficial pharmacodynamic interactions between lacosamide and clinically used analgesics.

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EFFECTS OF BBB EFFLUX ACTIVATION ON CNS ACTIONS OF PHENOBARBITAL IN SWISS WEBSTER MICE

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Background. LNS5661 is an experimental BBB efflux activator. Phenobarbital is a transporter ligand.

Methods. Mice (250 g) received (IP) LNS5661 (0/50/100 mg/kg) 10 min prior to 50 mg/kg (SQ) phenobarbital. Sedation was monitored.

Results. LNS5661 (100 mg/kg) significantly attenuated sedation.

Conclusions. BBB efflux activation may favorably alter ligand bioavailability.

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LOCAL PERIPHERAL ANTINOCICEPTIVE EFFECT OF VENLAFAXINE ON RAT FORMALIN TEST

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Tricyclic antidepressants, given systemically, have been widely used for the treatment of various chronic
and neuropathic pain conditions in humans for 40 years. Venlafaxine is a novel antidepressant drug that is chemically unrelated to tricyclic or other available antidepressants. Clinical trials indicate that venlafaxine is effective in chronic pain patients, some of whom are insensitive to other analgesics.

Antidepressants induced analgesia was attributed to central actions within spinal cord and at supraspinal sites. However, recently the local peripheral administration of some antidepressants was demonstrated to produce analgesia in the formalin and neuropathic pain models. In the present study, we determined whether venlafaxine could produce peripheral antinociceptive actions in formalin test, a model for acute and tonic pain. For this purpose we treated different groups of male Sprague Dawley rats with venlafaxine locally and systemically. For checking the effect is local or not, we obtained blood at different times after both the local and systemic application to determine the levels of venlafaxine. Venlafaxine induced antinociception at 100, 200 and 400 μg/paw concentrations with local peripheral and at 20 and 40 mg/kg doses with the systemic application.

Our results showed that venlafaxine has antinociceptive effect when applied locally to the periphery. By the local application it may be possible to reach high levels at application site and also to get rid of some systemic side effects. Such an activity may led to trials for to use this drug as a gel and cream formulation for analgesia in clinics in the future.

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DOWNREGULATION OF M4 BUT NOT M2 MUSCARINIC RECEPTORS IN DORSAL HORN AFTER PERIPHERAL NERVE INJURY RELATES TO RESPONSIVENESS TO SCS
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Background. Spinal cord stimulation (SCS) is an effective tool in alleviating neuropathic pain. Previously, we have demonstrated that SCS produces an increased release of acetylcholine in the dorsal horn in SCS responding rats, and that the SCS effect involves activation of M4 and M2 muscarinic receptors. The aim of the present study was to examine whether the expression of these receptors relates to the presence of tactile hypersensitivity ("allodynia") after partial sciatic nerve injury and to the SCS responsiveness.

Methods. Tactile allodynia was assessed with von Frey filaments. A miniature electrode for SCS was implanted in the lower thoracic spinal canal. After having assessed withdrawal thresholds and the allodynia suppression effect of SCS, the lumbar spinal cord was removed and immunostained for M4 and M2 muscarinic receptors as well as for NeuN.

Results. M2 receptors in the dorsal horn were unaffected by the sciatic nerve injury. In contrast, the expression of M4 receptors was significantly reduced as compared to normal rats and this effect was more prominent in allodynic than in non-allodynic rats. Further, among the allodynic rats the decreased expression was more marked in the SCS non-responding than in SCS responding ones. The reduced M4 receptor expression was not associated with a loss of neurons.

Conclusions. The results indicate that M4 receptors are downregulated in spinal dorsal horn neurons following peripheral nerve injury and suggest that this effect relates to SCS responsiveness. Conversely, M2 receptors do not seem to be directly linked to the variable likelihood to respond to SCS.

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EFFECTS OF TRAUMATIC AND SELECTIVE CHEMICAL LESIONS OF PERIPHERAL NERVES ON TRPV1 RECEPTOR EXPRESSION: IMPLICATIONS FOR VANILLOID-INDUCED ANALGESIA

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Changes in the expression of the capsaicin receptor TRPV1 expressed in nociceptive sensory ganglion cells were studied after epineural application of vanilloids and sciatic nerve section using immunohistochemistry and color in situ hybridization. In control rats, analyses of TRPV1 receptor mRNA expression in L4-5 dorsal root ganglion cells revealed distinct populations of large TRPV1-negative (type A), and small (type C) and small to medium (type B) TRPV1-positive neurons with very high and moderate optical density of the hybridization signal, respectively. Immunohistochemistry revealed populations of large TRPV1-negative and small and small to medium TRPV1-positive neurons with strong and moderate fluorescence intensity, respectively. The number of TRPV1-immunopositive neurons was mark-
edly decreased after all treatments. In situ hybridization revealed dramatic decreases (up to 85%) of type C neurons 3, 14 and 30 days after sciatic nerve transection. In contrast, perineural treatment with capsaicin or resiniferatoxin resulted in a similar substantial decrease in the proportion of type C neurons only at 3 days, while after 14 and 30 days the reduction in the number of these neurons was less profound and amounted 60% and 40%, respectively.

These observations suggest the involvement of distinct cellular mechanisms in the regulation of TRPV1 mRNA expression triggered specifically by the particular event which affect the integrity of the sensory neuron. It is concluded that the anti-nociceptive and anti-inflammatory effects of perineural capsaicin/resiniferatoxin treatment involve distinct changes in neuronal TRPV1 mRNA expression and long-lasting alterations in the regulation of translation.

Acknowledgements


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IS UP-REGULATION OF NEUROSTEROID SYNTHESIS IMPORTANT FOR THE MAINTENANCE OF NEUROPATHIC PAIN?

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Injury to peripheral nerve induces neuropathic pain-like responses in rodents. To search for molecules involved in neuropathic pain, we investigated the genes that are differentially expressed in the spinal cord by nerve injury using microarray techniques. Peripheral benzodiazepine receptor (PBR) mRNA was found to be up-regulated in the spinal cord of mice with spinal nerve injury as compared with sham operated mice. Up-regulation of PBR mRNA by peripheral nerve injury has also been reported in dorsal root ganglion neurons (Xiao et al., 2002; Karchewski et al., 2004) and implicated its role in sensory axon regeneration (Mills et al., 2005). PBR has been named to distinguish it from the central benzodiazepine receptor, which is the component of the GABAA receptor. PBR functions as a cholesterol transporter which delivers cholesterol to CYP11A1 in the inner mitochondrial membrane. This is the initial step of neurosteroid synthesis. Interestingly, neurosteroid synthesized then facilitates the activation (at a lower concentration) and directly activates (at a higher concentration) GABAA receptor. It has been shown recently that the increase in intracellular chloride concentration in spinal neurons caused by the reduction of potassium-chloride co-transporter KCC2 expression in the neuropathic pain state has converted the inhibitory outcome of GABAA receptor activation to the excitatory one (Coull et al., 2003, 2005). In the present study, we have tested whether enhanced neurosteroid synthesis is responsible for the activation of GABAA receptor leading to neuropathic pain in nerve injured mice and found it is the case.

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EARLY CYTOKINE EXPRESSION IN MOUSE SCIATIC NERVE AFTER CHRONIC CONSTRICITION NERVE INJURY DEPENDS ON CALPAIN

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Background and aims. Peripheral nerve injury leads to Wallerian degeneration with subsequent alterations in cytokine expression that may contribute to the development of neuropathic pain. Here we set out to characterize the very early temporal pattern of cytokine regulation after chronic constriction nerve injury (CCI) in mice.

Animals and methods. One hundred and forty mice of C57Bl/6J background were investigated after CCI of the right sciatic nerve. The relative mRNA expression of the pro-inflammatory cytokines tumor necrosis factor-alpha (TNF) and interleukin-1beta (IL-1β) and of the anti-inflammatory cytokines IL-4 and IL-10 were measured with quantitative real-time PCR (qRT-PCR). 1, 3, 6, 9, 12, 24 h, and 3 and 7 days after CCI the cytokine expression was investigated in ipsi- and contralateral sciatic nerves and dorsal root ganglia (DRG). Possible upstream regulatory mechanisms were studied with inhibitors to the N-methyl-d-aspartate (NMDA) receptor ((+)-MK-801) and to calpain (MDL-28170).

Results. TNF, IL-1β and IL-10 mRNA levels increased as early as 1 h after CCI ipsilaterally in the sciatic nerve. MDL-28170, but not (+)-MK-801 inhibited TNF and IL-1β upregulation 1 h after CCI.

Conclusion. Calpain may be one of the earliest mediators of cytokine upregulation after peripheral nerve
injury. The calpain system might be a promising target for neuro- and algo-protective agents.

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DIRECT INHIBITORY EFFECTS OF GABAPENTIN ON SPINAL MECHANOSENSORY NEURONS FOLLOWING PERIPHERAL NEUROPATHY IN THE RAT
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In the present study, we examined the effects of spinal administration of gabapentin on rat dorsal horn neuron activity following spinal nerve ligation (SNL) at various time points post-operation (PO). Wide-dynamic-range (WDR) neurons, but not the high-threshold (HT) neurons, showed a significant increase in spontaneous activity following SNL compared to sham controls at PO day 7–14, but not PO day >21. The proportion of neurons responding to noxious mechanical stimulation of the hind paw significantly increased at PO day >21, but stimulus-response functions to graded mechanical stimulation remained unchanged. Spinal administration of gabapentin dose-dependently inhibited WDR neuron responses to mechanical stimulation at PO day >21 (IC50 = 30.94 mM), but had no effect on sham controls (100 mM). The inhibitory effect of gabapentin (100 mM) on spinal neuron responses was correlated with time PO, such that at PO day >21 gabapentin produced maximum efficacy by inhibiting responses to 35.11 ± 8% of control. These results demonstrate that gabapentin directly inhibits spinal mechanosensory neuron activity following peripheral neuropathy through a spinal mechanism of action. The inhibitory action of gabapentin on spinal mechanosensory neurons is consistent with its antinociceptive effects in preclinical behavioral models of neuropathic pain.

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PERINEURAL HIV-1 GP120 IS ASSOCIATED WITH REDUCED INTRAEPIDERMAL NERVE FIBRE DENSITY AND ALTERED SENSORY NEURONE PHENOTYPE
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The HIV coat protein, gp120, is thought to play a key role in the pathophysiology of neurological disorders associated with HIV, including painful peripheral neuropathy. We have characterised a rodent model of gp120-induced neuropathic pain in which gp120 is applied to the rat sciatic nerve. Animals develop a persistent hypersensitivity to punctate mechanical stimuli as well as anxiety-like behaviour in the open field paradigm.

Using immunohistochemical techniques at times of peak behavioural sensitivity (day 14), we have assessed (a) DRG expression of the nerve injury marker ATF3 and apoptosis markers caspase-3 and c-Jun, and (b) the intraepidermal nerve fibre density (IENFD) of the glabrous skin of the hind paw via immunostaining for PGP9.5.

DRG neurones (26.9%) were immunopositive for ATF3 and 29.6% for caspase-3 as opposed to >5% in sham or contralateral DRG. In contrast, there was no significant up regulation of c-Jun. In line with clinical data in which patients present with a small fibre “die back” neuropathy, we found there to be a significant reduction in the IENFD ipsilateral to gp120 (22.5 ± 0.5/mm) as compared to sham (32.1 ± 0.8/mm) or contralateral (29.7 ± 1.6/mm) controls.

These data suggest that perineural gp120 leads to neuropathic changes in the DRG and the induction of specific apoptotic pathways, paralleled by a degeneration of C-fibre peripheral axon terminals. The similarity with the clinical scenario suggests that this model merits further investigation for the elucidation of mechanisms underlying HIV neuropathy.

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DYNAMIC RESPONSES OF DEEP SPINAL DORSAL HORN NOCICEPTIVE-SPECIFIC NEURONS TO PERSISTENT NOCICEPTION
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Background and aims. The aim of the current study was to investigate the roles of deep spinal dorsal horn (DH) wide-dynamic range (WDR) and noci-
ceptive-specific (NS) neurons exposed to subcutaneous bee venom (BV) induced inflammation and central sensitization under intact and spinalized conditions.

Methods. Male Wistar rats weighing 260–320 g were used. We extracellularly recorded 107 single deep spinal DH WDR and NS neurons. The BV (0.2 mg/50 μl) was injected subcutaneously into the cutaneous receptive field of the recorded neurons. Intrathecal injection of L-703,606 (NK-1 receptor antagonist; 20–80 nmol/50 μl) was applied for the exploration of substance P-related central mechanisms.

Results
(1) In contrast to the monophasic long-lasting (34–81 min) WDR neuron responses in both intact and spinal conditions, BV in NS neurons elicited short-term (<10 min) firing in intact, and long-term (>1 h) biphasic firing in spinalized rats.
(2) L-703,606 dose-dependently inhibited the mechanically-evoked WDR and NS neurons responses in intact condition. In contrast, L-703,606 only depressed the nociceptive responses of WDR, but not NS, neurons after the spinalization.
(3) Early (15 min), but not late (30/60 min), treatment with L-703,606 after the BV injection inhibited the facilitated mechanically-evoked NS neurons responses.

Conclusions
(1) A transitory (about 5–13 min) spinal segmental inhibitory control and a long-lasting descending inhibitory control govern deep spinal NS, but not WDR, neurons activity.
(2) While the descending inhibitory control either is absent or decays, deep spinal NS neurons play a crucial role in the development of central sensitisation in pathological nociception.

Acknowledgement
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EFFECTS OF A NOVEL P2X3/P2X2/3 ANTAGONIST RO-4 ON COLD AND MECHANICAL ALLODYnia IN TWO RAT NEUROPATHIC PAIN MODELS
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Peripheral and spinal P2X3 and P2X2/3 channels may play a role in neuropathic pain. We investigated the effects of a novel P2X3/P2X2/3 antagonist RO-4 on cold allodynia in the chronic constriction injury model (CCI) and mechanical allodynia in the spared nerve injury model (SNI). For cold allodynia, rats were placed on a metal plate in cold water (2–3 °C). Lifts of the injured paw within 1 min were recorded. For mechanical allodynia, each paw was stimulated 10 times with a 10 g von Frey filament and % response was recorded. In the CCI model, a single dose of RO-4 (30 or 60 mg/kg, sc) and gabapentin (100 mg/kg, sc) significantly inhibited cold allodynia (p < 0.05, n = 15–24). When dosed repeatedly (po BID for 7 days), RO-4 (6, 20 and 60 mg/kg) dose-dependently decreased cold allodynia with inhibition rates of 10.8 ± 10.3%, 32.1 ± 9.6% and 37.2 ± 10.3%, respectively (p < 0.05, n = 10). Repeat administration of gabapentin (60 mg/kg) produced a 47.4 ± 6.4% inhibition in CCI (p < 0.01, n = 10). In the SNI model, RO-4 (10, 30 and 90 mg/kg, sc) dose-dependently inhibited mechanical allodynia with 23.5 ± 13.2%, 52.5 ± 10% and 56.1 ± 8.5% inhibition, respectively, compared to vehicle (0 ± 13.6%, p < 0.05, n = 10–16). Morphine (1 mg/kg, sc) and gabapentin (100 mg/kg, sc) also produced significant inhibition in SNI (84.4 ± 4.7% and 72 ± 9.9%, respectively, p < 0.01 n = 9–10). In conclusion, the P2X3/P2X2/3 antagonist RO-4 significantly inhibited cold and mechanical allodynia in the CCI and SNI models, supporting a contribution of P2X3 and P2X2/3 receptors in modulation of neuronal sensitization. Antagonism of these receptors may have potential for ameliorating neuropathic pain.

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Poster Session 2: Clinical – Other Treatments

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NEUROLITIC EPIDURAL BLOCK WITH 5% PHERNOl IN CANCER PATIENTS
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Aims. After incurability, cancer patients have ranked pain as the most fearful aspect of their illness. Particularly in advanced stage, pain control with ordinary drugs have not successful results. In this paper, we evaluated the efficacy of repeated epidural injection of 5% phenol in cancer patients.

Methods. Advance cancer patients that did not respond to WHO’s analgesic ladder approach and had NPS (numerical pain scale) of five or more were
included as candidates. Epidural catheter was inserted at the level of the middle dermatome of pain region. Bupivacaine 0.5% (5 ml) was injected with incremental dose every 12 h until the pain was relieved. After that we started injection of 5% phenol in water with the estimated volium and repeated it every 12 h until pain relief was achieved or motor disturbance occurred.

**Results.** This technique was used for six patients with advanced cancer (breast cancer two cases, colon cancer three cases, ovarian cancer one cases). The frequency of phenol injections for each patient was about three times. Injections of phenol reduced pain in all patients (NPS of 2–3). One patient with breast cancer returned again because of abdominal and cervical pain secondary to invasion of tumor. Five patients were free from pain three months after injection of phenol.

**Conclusions.** Phenol injection through epidural catheter is a safe and effective method for cancer pain control and it is free of neuromotor disfunction.

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### 405

**LONG-TERM RESULTS OF THE MICROSURGICAL DREZ-TOMY FOR NEUROPATHIC PAIN DUE TO BRACHIAL PLEXUS AVULSION: CLINICAL LEARNING ABOUT PAIN MECHANISM**

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Brachial plexus avulsion is produced by any stretching forces exerted on nerves and roots of the brachial plexus; lesions may appear from the spinal cord down to the limb's extremity. Bikers, alpinists, parachutists and, overall, young people are particularly exposed to such lesions. In 50–90% of cases, evolution is marked by intractable chronic pain distributed among those concerned dermatomes.

Such chronic pain is classically described as a continuous burning background associated to electric-shocks like pain crises, these two components being usually poor relieved by antalgic, antiepileptic or antidepressant drugs. Such severe persistent pain is usually accompanied by psychological diseases. In 1972, Sindou described the dorsal root entry zone, that particular anatomical structure regrouping ending of the thermoalgic fibers, recurrent branches from the lemniscal tract and superficial layers of the dorsal horn and characterized by its specific fibers organization. Drez-tomy was described in the aim to interrupt selectively the thermoalgic afferent fibers, preserving at the same time the sensitive modulation exerted by the lemniscal tract.

Among 55 patients followed up for 6 years, 75% presented a good pain relief (> 50%). Drez-tomy appears to be more effective on paroxysms than on pain background.

Clinical results may also suggest that ectopic pain generators might appear above the spinal cord or the avulsion’s level as it was first described by Dreval. Actually, the more recent functional imaging studies tend to reveal such ectopic pain generators as suspected regarding the thalamic hypermetabolism corrected by neuro-stimulation techniques.

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### 406

**PRECISION RECHARGEABLE SPINAL CORD STIMULATION (SCS) SYSTEM: PROGRAMMING PARAMETERS AND BATTERY LONGEVITY**

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New SCS technology may benefit more patients because of increased ability to individualize therapy for neuropathic pain without compromising battery life. Although all implantable SCS devices share common features, specifics of technology and individual system components exhibit variable manufacturer-specific capabilities. The rechargeable Precision™ SCS system has an expanded range of stimulation parameters that allows rates up to 1200 Hz and pulse widths (PW) up to 1000 μs.

As previously reported, analysis of user profiles for 467 patients revealed that majority of patients (53%) implanted with Precision utilized a maximum PW > 500 μs, which exceeds values traditionally available for SCS therapy. To address potential device lifetime concerns, we have investigated the expected battery longevity of this patient population. Using a mathematical model based upon known characteristics of the Precision hardware and typical stimulation impedances, we estimated the useful life of rechargeable Li-ion cell in the Precision IPG.

Using a single channel stimulation program containing the maximum PW from each patient, we found that 98% of IPGs would have an expected battery life of >10 years, and 89% would have >25 years. We also investigated whether use of higher PWs would affect rechargeable battery longevity. Of the 248 programs with a PW > 500 μs, 96% had an estimated expected battery life of >10 years and 81% had >25 years. Hence, we conclude that choice of SCS system should be made based on patient requirements for optimal therapy and the impact
on quality of life and health care utilization, including battery replacement, rather than initial device cost.

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SYMPATHETIC BLOCK TREATMENT FOR RSD IN CHILDREN
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We have, in our unit, a particular interest in sympathetic block for RSD in children, and receive referrals from throughout the UK. The blocks are performed as part of a pain management program including physiotherapy, which is essential for a successful outcome. Forty-six children were treated with lumbar sympathetic block using bupivacaine. The children required an average of 2.15 blocks each for permanent relief. Each successive block resulted in increased time of pain relief. There were five failures who experienced little or no improvement. Two of these children developed spinal headache, the possible mechanism for this is puncture of a dural cuff around the sympathetic nerves. RSD in the upper limb is much rarer in children. Six children had a stellate ganglion block with bupivacaine. Only one needed a second block and all had permanent pain relief. All blocks were performed using bi-planar screening in the cardiology laboratory under general anaesthesia.

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NERVE BLOCKS CAN INTERRUPT AXONAL REFLEX AND AVOID PERSISTENT PAIN TO TRANSLATE INTO CHRONIC AND NEUROPATHIC PAIN
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Chronic painful shoulder is often multifactorial and patients are typically treated with antinflammatories. In shoulder and its surrounding tendons pain is often felt anterolaterally, at insertion of deltoid and rotator cuff muscle; usually patients develop hyperalgia and allodinia radiating down the triceps and forearm muscles, resulting in a diagnostic challenge. Nerve blocks could inhibit wind up phenomena and noteworthy phenomenon named “progressive tactile hypersensitivity”. We postulate that blocks can prevent chronic pain from traducing into hypersensitivity and neuropathic pain throw the inhibition of the “axonal reflex”.

Method. Bynow we evaluated 49 patients receiving Suprascapularis nerve blocks. Our protocol foresee weekly blocks andrehabilitation.

Results. All patients reported prompt reduction of the pain (effectiveness pain >75%) but above disappearance of radiated neuropathic-like pain. Compared to patient refusing SSNB, they achieved significantly higher effectiveness on pain relief.

Conclusions. SSNB can selectively disrupt sensory pathways providing temporary pain control. Integrated in a well-planned rehabilitation program SSNB can stop signals carried by peripheral C-fibers from shoulder per-

Fig. 1. Axonal relex leading to “wind-up”. On the left tissutal lesion causing primary hyoeralgia, rubor, dolor and calor. On the right side, the healthy tissue around the lesion is secondary involved and develop seconday hyperalgia.
ceived as pain and prevent CSP from traducing into hypersensitivity and neuropathic pain.

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MINIMALLY INVASIVE EPIDURAL STIMULATION UNDER LOCAL ANAESTHESIA IN THE TREATMENT OF NEUROPATHIC PAIN
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Background and aims. Optimize the placement of epidural surgical electrodes using a minimally invasive approach, in the treatment of refractory neuropathic pain.

Methods: The place of spinal epidural stimulation in the treatment of refractory peripheral neuropathic pain is nowadays well recognized. Two techniques are used: percutaneous technique under local anaesthesia, which permits optimal positioning of a small electrode; and surgical open laminectomy under general anaesthesia which permits positioning of a more stable surgical electrode, without the possibility of per-operative testing.

Minimally invasive approach has the advantage of implanting a large surgical epidural electrode under local anaesthesia and light sedation, allowing the realisation of intra-operative testing.

This minimally invasive technique leads to less muscular dissection and trauma, thus to less pain and to a rapid recovery, using a tubular retractor system (Metr’x, Medtronic). Access to epidural space is achieved after excision of ligamentum flavum and laminotomy. Surgical electrode (Resume, Medtronic) is then placed under fluoroscopy. Stopping sedation allows realisation of stimulation tests, leading to optimal positioning of the electrode.

Results. Five female patients underwent epidural electrode placement using minimally invasive technique ( pudendal neuralgia: two patients; neuropathic post-operative radiculopathy: three patients). Intra-operative stimulation was realised, while mobilizing the electrode untill obtaining complete covering of the painful region. No complaint of intra- or post-operative discomfort was noted, and all patients were mobilized on day 0.

Conclusion. This new technique, which allows intra-operative stimulation, is very promising for the treatment of peripheral neuropathic pain, by allowing optimal placement of large stable surgical electrodes.

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SPINAL FLEXOMETER: MEASUREMENTS THAT POTENTIALLY REFLECT CHANGES IN PAIN

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One manifestation of pain in spinal stenosis is extension and patients attempt to achieve relief through flexion. Surgeons are queried by instrumentation candidates about pain and mobility. Surgeons can acquire results of function with a novel device, the Spinal Flexometer, which involves patient interaction.

This instrument was developed to provide a reproducible measurement device useful in clinical settings. The instrument is comprised of a standing platform approximately 12 in. x 12 in. A pair of handles is attached to a measuring tape on the platform. When the patient was in position they were asked to flex as much as possible. If full flexion was not possible, the handles were placed in their hands by the medical examiner. This lengthened the measuring tape which then showed the distance from the patient’s hands to the floor. Then, the patient was asked to pull the handles to hip level which was the zero point from which point their range of extension was measured. The patient’s knees were held in extension. Measurements were taken pre- and post-operatively to monitor change.

Thirteen patients were measured. In extension post-operatively, patients experienced an average of 1.6 in. increase. In flexion, there was no change on average. Pain analog scales revealed >50% did not experience a decrease in pain post-operatively than pre-operatively.

The novel Spinal Flexometer easily and reproducibly determined limitations of spine motion. Subjective patient pain analog scales should be followed for several months to determine the correlation between the Spinal Flexometer results and pain.

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HEALTH-RELATED QUALITY OF LIFE IN CHRONIC NEUROPATHIC PAIN PATIENTS: RESULTS OF THE PROCESS STUDY
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Background and aims. This randomised controlled trial compared the clinical effectiveness of spinal cord stimulation (SCS) with conventional medical management (CMM) to CMM alone in chronic medically refractory neuropathic pain patients, using standardized pain and health related quality of life (HRQoL) measures.

Methods. One hundred well-matched patients with predominant leg pain following anatomically successful surgery for a herniated disc, were randomised to SCS (Synergy, Medtronic Inc.) with CMM or CMM alone. Patients received appropriate medical therapies and were followed for 24-months. Patients could request crossover after 6 months. The primary outcome of leg pain relief (at least 50% change on VAS) and secondary endpoints of HRQoL (SF-36, EQ-5D), and adverse effects were assessed at each study visit.

Results. At baseline, patients were severely debilitated with average leg pain VAS scores of 75/100. HRQoL values ranged from 4 to 55 on the eight domains measured on SF-36, and averaged 0.2 on EQ-5D; scores comparable to terminal cancer or severe heart failure patients. At 6 months (intention-to-treat analysis), SF-36 and EQ-5D scores did not change significantly in the CMM group. In the SCS group SF-36 measures (except role emotional) improved significantly \((P < 0.006)\) as did EQ-5D score \((0.1–0.5, P < 0.0001)\). Twenty-four SCS patients (48%) and four CMM patients (9%) achieved greater than 50% leg pain relief \((P = 0.0001)\). Fourteen (29%) of the 48 SCS patients experienced complications requiring corrective intervention.

Conclusions. Adjuvant SCS significantly improves pain relief and HRQoL, in pharmacologically refractory chronic neuropathic pain patients at 6 months over CMM alone.

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DYSAESTHESIC PAIN AND BURNING SKIN SENSATIONS AS ADVERSE EFFECTS TO SPINAL CORD STIMULATOR IMPLANTATION FOR TREATMENT OF ANGINA PECTORIS
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Background and aims. Spinal cord stimulation (SCS) has become an established pain treatment for patients with angina pectoris or neuropathic pain. However, several reports indicate that the implantation of SCS devices itself may cause chronic pain conditions. Five male patients with known refractory angina pectoris developed painful dysaesthesia or burning skin sensations after implantation or reimplantation of SCS devices. The pain symptoms were constant and not related to the electrical stimulation. Two patients had painful dysaesthesia and burning skin sensations located to their faces, arms and genitals. Two patients reported pain located to the extension leads. One patient slowly developed painful dysaesthesia in both hands and feet. Four of the patients had their SCS devices removed. Further examinations showed negative patch tests to all product ingredient samples and no signs of infection.

Methods. Interviews with all five patients were made.

Results. Two patients reported that after the spinal cord stimulator was removed, their symptoms slowly decreased in intensity and disappeared. Two patients had still pain and burning skin sensations three years after the SCS devices had been removed. In one case, the symptoms were concluded to be due to diabetic neuropathy and not SCS. The patient that refused to have his spinal cord stimulator removed has still painful dysaesthesia more than three years after the implantation of the SCS devices.

Conclusion. It seems likely that in four of the five case reports, the pain and burning skin sensations reported by the patients were due to implantation of SCS devices.

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MOTOR CORTEX STIMULATION FOR COMPLEX REGIONAL PAIN SYNDROME (CRPS TYPE I) RESULTS IN PAIN RELIEF AND FUNCTIONAL RECOVERY
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b Institute of Psychiatry, São Paulo, Brazil

Background and aims. Besides intractable pain, CRPS originates trophic modifications in the affected limb and in severe cases functional loss may occur. In this report the authors describe the case of two patients severely affected by chronic pain, progressive limb paralysis
and complete sensitive deficit treated by motor cortex stimulation (MCS).

Methods. Both patients have developed CRPS with treatment-resistant pain and severe motor and sensitive loss in upper limb, after a minor trauma in distal phalanges. Various oral medication, epidural opioid analgesia and spinal cord stimulation were applied with partial responses. Before addressing to MCS, both patients were studied by electromyography, brain MRI, TMS cortical mapping and PET scan. Results were computed by visual analog scale (VAS) and also motor and sensitive analysis.

Results. Preoperative TMS mapping revealed enlarged motor responsive area in contralateral cortex in both patients. They had important improvement in pain, from VAS of 9 and 10 to 2 and 0 after 18 and 6 months follow-up, respectively. The first patient also had clear sensitive and motor improvement in the affected limb, including the hand and fingers. The second patient had sensitive recovery on the forearm, starting 20 days after the implant, improving progressively during the follow-up.

Conclusion. This initial experience suggests that MCS may benefit CRPS type I patients with significant relief of pain and also promote functional improvement.

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THE UTILITY OF ZERO-VOLT BATTERY TECHNOLOGY WHEN BATTERY CHARGE IS DEPLETED
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c Riverside Spine and Pain Physicians, Jacksonville, FL, USA

Rechargeable batteries for spinal cord stimulation (SCS) systems have improved cost effectiveness and introduced a new level of flexible programming without regard for power consumption. Although rechargeable, most SCS batteries are damaged by extensive or repeated discharge, and require surgical replacement. A ‘zero-volt’ battery has been developed that can undergo successive recharge cycles following extensive discharge to near zero volts, without damage or loss of capability. Here, we present case reports in which usage patterns of SCS systems demanded the application of zero-volt technology.

Patients were two women implanted with two 8-electrode percutaneous epidural leads and a 16-channel, current-controlled pulse generator (Advanced Bionics, Valencia, CA) for chronic back and leg pain. After implantation, each pulse generator migrated too deep to allow effective recharging. Low battery charge caused each device to inactivate and cease recording information; thus, the true extent of battery depletion cannot be accurately ascertained. After surgical revision of the implant, each device was recharged without incident using a longer charging cycle. Neither patient has since reported any charging problems.

There are many events that can occur during the life of a permanently implanted device that can necessitate the discontinuation of SCS charging for an extended period of time. Batteries may deplete during this time, risking damage and possible surgical replacement unless zero-volt technology is used. The use of zero-volt technology allows for greater flexibility in the management of coincident medical events and in accommodating individual patient requirements without risking permanent battery damage.

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NEUROPATHIC PAIN IN DENTISTRY: THREE CASE REPORTS
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Although persistent neuropathic pains in dentistry are well described in the literature, little is known about these disorders by practicing physicians as well as dentists. It is also often not clear whose competency the treatment of neuropathic orofacial pain is. Causes can be trauma, metabolic disorders, inflammation or infections but also idiopathic conditions and iatrogenic injuries. Direct injuries to the inferior alveolar nerve and the lingual nerve resulting in chronic posttraumatic neuropathic pain can occur after wisdom tooth extraction, incorrect implant placement, and by needle injuries during dental anesthesia. Multiple surgical procedures in the jaw area can often be seen in the history of idiopathic persistent neuropathic orofacial pain. Furthermore, it has recently been suggested that primary burning mouth disorder may be a neuropathic pain disorder as well, since neurosensory and gustatory anomalies have been found. It is important to pronounce that neuropathic pain conditions are a clinical and economical problem in dentistry as well, because
patients usually see a multitude of dentists and physicians and have had excessive and mostly ineffective surgical procedures, including multiple tooth extractions, done before they get adequate help. It is also important to emphasize that these conditions are also within the diagnostic and therapeutic scope of dentists specializing in orofacial pain. To illustrate this, three typical neuropathic pain cases in dentistry, chronic posttraumatic neuropathic pain idiopathic persistent neuropathic pain and burning mouth disorder are presented with their history, symptoms and the therapeutic approach that has been tried.

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PAIN SYNDROME TREATMENT IN VERTEBROGEN RADICULOPATHY WITH VERY HIGH FREQUENCY MILLIMETRIC WAVES
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Aim. Treatment efficiency appreciation with very high frequency millimetric waves, in the vertebrogen radiculopathy pain syndrome.

Methods. The study included 65 patients (38 men and 27 women) with vertebrogen radiculopathy diagnosis. The pain syndrome was confirmed by patient’s evince, anamnesis, clinical examination, simple radiography, CT mielography, MRJ. Patient’s average age was 34.6 and disease average length – 2 months. Base group (45 patients) were treated with specific drugs – anti-inflammatory nonsteroids, associated with millimetric waves applying. Were stimulated acupuncture points, selected according with traditional Chinese medicine, for 20 min, by applying 5.6 mm wave length, with devices “Iavi-1” and “KVC-MTA”. The treatment cure was 10 procedures. The Control group (20 patients) have received only drug treatment, same as the base group. Treatment efficiency appreciation was made using the analogical visual pain scale it 1st, 5th and 10th day of treatment.

Results. Positive treatment effect was obtained in both cases. In the base group, compared to the control group, the recovery was faster and more evidenced at all evaluation steps.

Conclusion. Very high frequency millimetric waves treatment method proved to be efficient and can be included in the vertebrogen radiculopathy pain syndrome complex treatment.

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PAIN MANAGEMENT OF LOW BACK PAIN IN A DISTRICT HOSPITAL
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b 2nd Orthopaedic Department, University of Athens, Konstadopouleio General Hospital of Nea Ionia, Athens, Greece

Background and goal of the study. The objective of this study was to document the therapeutic options in a district hospital for patients with radicular leg symptoms or neuropathic low back pain (LBP).

Materials and methods. We pooled data from 71 patients who visited the pain department. We noted the number of visits needed for a patient to have a pain reduction greater than 50% and the type of treatment which was performed.

Results. We observed a reduction of 17% in the number of patients who required more than three visits for adequate pain relief to the pain department during 2006. The available methods included oral medication with non steroid anti-inflammatory drugs plus pregabalin when indicated, combination of drugs with epidural steroids and acupuncture.

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<td></td>
<td>24 patients</td>
<td>57 patients</td>
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<tr>
<td>1st visit</td>
<td>6 25%</td>
<td>22 38.7%</td>
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<td>2nd visit</td>
<td>6 25%</td>
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<td>3rd visit</td>
<td>5 20.8%</td>
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<tr>
<td>4th visit</td>
<td>4 16.7%</td>
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<td>5th visit</td>
<td>3 12.5%</td>
<td>3 5.3%</td>
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<tr>
<td>Total number of visits</td>
<td>64 visits</td>
<td>121 visits</td>
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<tr>
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<th>Year 2005</th>
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<tr>
<td></td>
<td>24 patients</td>
<td>57 patients</td>
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<tr>
<td>(1) Oral medication</td>
<td>13 54.17%</td>
<td>25 43.85%</td>
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<tr>
<td>(2) Oral medication plus epidural steroids</td>
<td>9 37.5%</td>
<td>28 49.13%</td>
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<tr>
<td>(3) Acupuncture</td>
<td>2 8.33%</td>
<td>4 7.02%</td>
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Conclusions. The systematic and more frequent use of pregabalin or the increase of the number of epidurals performed during 2006 compared to 2005 could have contributed in the reduction of patients who paid a forth or a fifth visit to the pain management specialist.

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SUCCESSFUL CONTROL OF BACK AND LEG PAIN WITH A NEXT GENERATION SPINAL CORD STIMULATION (SCS) DEVICE FOLLOWING INITIAL TREATMENT FAILURE

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SCS is an effective treatment for chronic intractable back and leg pain. SCS systems produced by different manufacturers vary in their technical capabilities. These differences, which include current vs. voltage control and independent contact control vs. splitting pulses between contacts, may determine the ability of a given system to address particular pain patterns. Hence, device selection is key in achieving satisfactory outcomes.

Outcomes, based on cases in medical practice, were reported after replacement of each patient’s original constant voltage (Cases 1 and 2) or constant current (Case 3) SCS system with another, having 16 independently current-controlled contacts.

Case 1: Two SCS systems were trialed sequentially in the operating room. With the first system, coverage of painful areas could not be achieved. The second system achieved complete coverage in 20 s.

Case 2: The patient classified paresthesia with the replacement system as a “massage”, with broader and more complete coverage of painful areas. Moreover, he described reduced use of medications, and “100%” improvement in quality of life.

Case 3: Three months after SCS system replacement, the patient reported complete discontinuation of pain medications, a dramatic increase in quality of life, and stimulation perceived as “smoother and softer”.

SCS technologies of different manufacturers may produce differences in pain coverage and sensations of paresthesia in the same patients. Selecting the ‘best’ system for each individual can have implications for quality of life and concomitant health care utilization, such as medication use. We suggest judicious consideration of technical capabilities when selecting an SCS system.

EFFECT OF MONOCHROMATIC NEAR INFRARED ENERGY ON NEUROPATHY, PLANTAR PRESSURE DISTRIBUTION AND BALANCE IN PATIENTS WITH DIABETIC NEUROPATHY

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Background and aims. This study investigates whether treatment with monochromatic near infrared energy (MIRE, Anodyne Therapy LLC) for six weeks is associated with an improvement of peripheral neuropathy, plantar pressure distribution and balance indices in patients with diabetic polyneuropathy.

Methods. Fifteen consecutive subjects with diabetic peripheral neuropathy were recruited from Diabetic Clinic and treated with MIRE at the frequency of three sessions per week. Assessment at baseline and six weeks included: United Kingdom screening score, Michigan neuropathy screening index (MNSI), Michigan diabetic neuropathy score (DNS), Tinetti balance score, visual analog scale (VAS), Semmes–Weinstein monofilament examination by 10-g monofilament in five standard points of each foot, vibration perception with 128 Hz tuning fork, electrodagnostic study, biodex balance study and pedography. All collected data were statistically analyzed by SPSS 10 software.

Results. There was a statistically significant improvement in UK score (P = 0.016), MNSI (P = 0.007), DNS (P = 0.001), and VAS (P = 0.024) and monofilament perception (P = 0.02). Neuropathy score with electrodagnostic criteria was significantly improved (P = 0.003). Balance improvement by Tinetti score was significant (P = 0.04). There was an apparent, but not statistically significant (P = 0.07) improvement in dynamic balance parameters evaluated by biodex system (Model-945320). Static footplantar pressure distribution also improved (P = 0.02), but there was no significant change in other aspects of plantar pressure distribution.

We conclude that the use of MIRE is associated with significant improvement in diabetic neuropathy and this is apparent and significant within six weeks of treatment. This can be expected to reduce complications from diabetic neuropathy including foot ulceration and amputation.

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420 DEVELOPMENT AND IMPLEMENTATION OF AN INTERDISCIPLINARY PAIN COURSE
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Background. Research has shown that pain is not adequately addressed in health care education, including medicine, pharmacy, and nursing, occupational therapy and physical therapy. Pain education is only minimally addressed in these programs, particularly at the undergraduate level. Given this lack of education, concerns are reasonable, regarding levels of preparedness for working with this challenging population.

Methods. This course was designed as a one semester program (36 class hours), based on the International Association for the Study of Pain guidelines for pain education, offered as an elective at the Medical University of South Carolina. This program was designed to facilitate: (1) basic pain education, (2) pain assessment techniques, (3) interdisciplinary pain education (guest speakers) and (4) implementation of multidisciplinary case studies/practicals to assist students in learning to work collaboratively. The pilot course employed 10 students, five medical students, three nursing students, and two physician assistants. The second implementation involved 45 students, including 12 physical and occupational therapy students, eight medical students, 13 nursing students, 10 physician assistant students and two pharmacy students.

Results. Pre-course assessment demonstrated that in each of the programs, with the exception of pharmacy, pain education received little attention, including less than 2 h within medical education. Post-course assessment indicated satisfaction with the course, as well as the aims of an interdisciplinary approach to pain education.

Conclusion. Goals of this project include the compilation of a curriculum, including teaching materials, powerpoints, and other tools to assist in the implementation of similar programs at other institutions.

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421 EFFECTS OF SLOW REPETITIVE TRANSCRANIAL MAGNETIC STIMULATION (TMS) ON COMPLEX REGIONAL PAIN SYNDROME (CRPS)
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Background. The key symptom of CRPS is continuous, intense pain out of proportion to the injury. Red skin, increased temperature, sweating and swelling are common. These symptoms suggest an inflammatory process. One theory is that an auto-immune process triggers the immune response. A single 20-min session of prefrontal repetitive TMS can alleviate pain, as shown by a 40% reduction in total morphine use after gastric bypass surgery. A similar single session applied to the motor cortex can decrease the pain of CRPS, as reported by seven of 10 patients.

Aims. The aims of this study are to: (1) replicate the finding that one session of TMS provides temporary relief from CRPS pain; (2) determine if 10 sessions provide more lasting relief and (3) determine if molecular markers support the theory that CRPS is an inflammatory process.

Methods. Ten participants will receive 10 real and 10 sham TMS treatments; five will start with real, and five with sham. Patients will rate the intensity of pain on a visual analogue scale. C-reactive protein and lipoprotein-associated phosholipase A2 (known molecular inflammatory markers) will be measured at baseline, after sham TMS and after real TMS.

Results and conclusions. This study is not yet complete; results and conclusions will be added to the abstract by March 31, 2007.

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422 PULSED RADIOFREQUENCY TREATMENT (PRF) WITH PASHA CATH IN NEUROPATHIC PAIN
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Introduction. The Pasha Cath is a multifunctional catheter used for diagnostic and therapeutic aims. The catheter is placed exactly on the wished nervous root, using the fluoroscopic images, the impedance values and sensory stimulation a 50 Hz current. This current evokes paraesthesias on the metameric area related.

At this point it can proceed to the selective infusion of drugs and/or PRF.

Objective. To evaluate the analgesic effectiveness of PRF treatment in periferal neuropathic pain.

Design. Prospective, open-label, nonrandomized trial.

Setting. Department of Pain Medicine, Private Hospital, Italy.

Inclusion criteria. All patients affected by lumbar radiculopathy for more than six months, with pathogenetic diagnosis of periferal neuropathic pain.
Interventions. In all patients it has been used a PRF treatment for 240 s using Pasha Cath, on the target root, through sensory neurostimulation.

Effectiveness assessments. NRS at rest and incident, Oswestry test, QUID test (Italian Pain Questionary) at baseline, first and third month.

Results. Follow-up in progress.

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MULTICENTRIC TRIAL FOR THE ASSESSMENT OF ANALGESIC EFFECTIVENESS OF PULSED RADIOFREQUENCY TREATMENT (PRF) WITH PASHA CATH IN LUMBOSACRAL MONORADICULOPATHY
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Introduction. The Pasha Cath is a multifunctional catheter used for diagnostic and therapeutic aims. The catheter is placed exactly on the wished nervous root, using the fluoroscopic images, the impedance values and a sensory stimulation of a 50 Hz current. This current evokes paraesthesias on the metameric area related. At this point we can proceed to the selective infusion of drugs and/or PRF.

Objective. To evaluate the analgesic effectiveness of PRF treatment in lumbosacral monoradiculopathy (L4-L5-S1).

Design. Multicentric, prospective, open-label, non-randomized trial.

Setting. Multicenter (public and private hospitals, Italy).

Inclusion criteria. All patients affected by lumbar monoradiculopathy for more than four months, nonsurgically treated.

Interventions. In all patients it has been used a PFR treatment for 240 s using Pasha Cath, on the target root, through sensory neurostimulation (<0.3 V).

Effectiveness assessments. NRS, Oswestry Disability Questionnaire and analgesic therapy at baseline and third month.

Results. Follow-up in progress.

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REPETITIVE TRANSCRANIAL MAGNETIC STIMULATION OVER THE MOTOR CORTEX CAN CHANGE THE PAIN PERCEPTION IN PATIENTS WITH COMPLEX REGIONAL PAIN SYNDROME
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Background and aims. There are evidences that rTMS of the motor cortex is effective to treat chronic pains. The aim of this study was the evaluation of the analgesic effects of the rTMS in patients with refractory pain due to CRPS.

Methods. Twenty-three CRPS patients in one upper limb were randomly selected and treated with conventional treatment plus ten daily sessions of placebo-TMS or rTMS over the motor cortex (M1). The Visual Analogical Scale of Pain (VAS), the McGill Questionnaire, the Pain Impact Questionnaire, the Disabilities of the Arm, Shoulder and Hand Questionnaire (DASH), the Hamilton Depression and Anxiety Rating Scales were used for the evaluation. The evaluations were performed before, during and up to three months after the end of the treatment.

Results. During the treatment, in both groups there was a significant reduction in the VAS scores; mean reduction in placebo patients was 2.18 and in the rTMS group 4.65 (p < 0.001). The reduction was higher in the rTMS patients (p < 0.05). The significant reduction in the VAS scores continued up to the seventh day after the end of the treatment, but no difference occurred between the groups (p = 0.5561). The reduction was not related to the increase in other variables, except for the emotional aspects in the SF-36 Questionnaire in both groups.

Conclusions. There was an important placebo effect in the treatment of CRPS patients. rTMS influenced pain perception, but the effect was not prolonged and did not reflect the changes in other variables.

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CLINICAL EXPERIENCE WITH A NEW RECHARGEABLE STIMULATION DEVICE FOR SPINAL CORD STIMULATION – A TWO YEARS FOLLOW-UP
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Background and aims. In patients with regional and well located chronic neuropathic pain, spinal cord stimulation (SCS) is an effective treatment option if conservative or pharmacological therapy fails. Because of
power consumption an exchange of the implanted neurostimulator was necessary if battery capacity was exhausted. The authors want to present two years of clinical experience with a newly developed rechargeable stimulation device called Restore®.

Methods. Twenty patients with chronic neuropathic pain of the upper (1) or lower (19) extremities were screened for SCS. The majority of patients (15) suffered from chronic radicular pain after one or multiple operations of the lumbar spine. Three patients suffered from ischemic pain due to peripheral atherosclerotic disease and two patients after traumatic peripheral nerve lesion. The octapolar lead was inserted and a testing phase after optimal lead positioning was conducted.

Results. In all patients a sufficient coverage of the pain area with evoked paraesthesias was achieved. In 19/20 patients the test trial was positive and pain reduction of >50% was documented. In these 19 cases the Restore® was implanted. All patients were able to successfully recharge the neurostimulator percutaneously every 3–8 weeks, depending on the stimulation parameters.

Conclusions. The new stimulation device Restore® offers a safe and effective opportunity to adapt stimulation parameters individually. The hard- and soft-ware is easily to understand for physicians and patients. The estimated prolongation of the battery capacity up to 9 years is cost saving, especially in patients with high power consumption.

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USE OF METHADONE FOR PAIN TREATMENT AND PROLONGED SEDATION IN CRITICALLY ILL PATIENTS
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Critically ill patients are often in need of prolonged opioid therapy on the intensive care unit. Methadone is an attractive choice for opioid analgesia due to its long half-life and its low cost. We present the case of two adult patients suffering from severe pain due to critical illness neuropathies.

Both patients suffered from septic syndromes due to necrotizing soft tissue infection. This led to multiple cutaneous abscesses requiring surgical therapy. Operative treatment employed wide incision, routine subfascial examination and aggressive debridement. Both patients developed painful polyneuropathies due to the combination of sepsis, large skin erosions and surgical impairment of cutaneous nerve endings. Clinically this became relevant through the presence of generalised mechanical allodynia, with manipulation leading to tachycardia and facial expressions of severe discomfort. Both patients were initially sedated with intravenous sufentanil. Dose increases of sufentanil not only led to clinical signs of even more pronounced mechanical allodynia and non-evoked pain. As patients remained uncomfortable, it was then decided to perform an opioid rotation to intravenous methadone. A continuous infusion of methadone was instituted at a rate of 20 mg/24 h. Over the next days the dose of methadone was increased until no further hemodynamic nor behavioural signs of pain were observed. Although both patients remained on methadone treatment for several weeks, they never again displayed any signs of spontaneous or evoked neuropathic pain symptoms.

These case reports show that intravenous methadone is an attractive option for use in critically ill patients, requiring long-term administration of opioids and suffering from painful neuropathies.

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ONE OF THE CAUSES OF BUTTOCK AND NUMBNESS OF LOWER EXTRIMITIES
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Background and aims. There was the waist pain of lower extremities that could not be improved only by the sympathetic nerve block. As one of the causes, it is suggested that the inflammation of the pseudarthrosis which was produced between the transverse processus of the fifth lumbar vertebral and the lateral part of vertebral sacrum might be the cause of low back pain. As the sympathetic nerve branch approaches anatomically around iliosacral joints with involved this pseudarthrosis, we may make a mistake in judgment whether this reffured pain from buttock to lower extremities or lumbar radiculoneuropathic pain. The aim of this study is to clarify the cause.

Methods. The study was performed in 100 patients with suspected neuropathic low back pain. We con-
firmed the kissing on X-rays and the improved pain by local anesthesia to trigger points. After stimulating at the kissing site that lower limbs did not move, we rizotomied to the kissing site during 90 or 180 s at about 90° Centigrade under X-rays, by using specific needle that the tip turns on electricity.

Results. Pain relief was observed like following 0–25%, 26–50%, 51–75%, and 76–100% in the patients of 0.7%, 18.1%, 30.6%, and 50.6%, respectively. Moreover, numbness relief was observed 76% of patients, respectively.

Conclusions. The pain relief was obtained more than 80% of the patients.

These results suggest that the pain was released in the patients cause by neuropathic inflammation network on this site of buttock and numbness of lower extremities but only transiently in another patients causing included others factor (ex.LCS, LDH).

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DOES TENS HAVE AN EFFECT ON NEUROPATHIC PAIN? A PILOT STUDY IN MS
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Aim. To establish whether conventional TENS produces an effect on neuropathic pain in MS. That is, to compare the hypolagesic effects of conventional TENS with a placebo (sham TENS) and to examine whether different frequencies (40 and 110 Hz) affect TENS efficacy.

Background. MS, one of the most common neurological diseases, is a variable and complex condition, with chronic pain being a significant symptom. TENS is a non-pharmacological technique that has proved effective to control pain in various conditions. However, its efficacy for MS is not established because of the paucity of supporting research.

Method. Design: a randomised double-blind placebo controlled pilot study, with 15 MS patients randomly allocated to three groups (n = 5): group 1 (40 Hz–100 µ), group 2 (110 Hz–100 µ), group 3 (placebo).

Intervention. Home treatment, 4 h/day, during 14 consecutive days.

Outcome measures. Brief Pain Inventory (BPI), Neuropathic Pain Scale Inventory (NPSI) and unpleasantness of pain (NRS) applied before and after the treatment.

Results. Analysis revealed no statistically significant effects. Nevertheless, both active groups demonstrated a trend for improvement on most of the outcome measures.

Conclusion. Conventional TENS was possibly more effective than placebo TENS in reducing neuropathic MS-related pain, although results were not statistically significant. Moreover, the selected frequencies appeared to affect neuropathic pain symptoms differently. Thus, this study suggests that TENS might have clinical relevance as a method to relieve MS-related neuropathic pain. Further research using RCT with larger number of participants should be conducted.

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DREZ OPERATION IN BRACHIAL Plexus PAIN: LONG TERM RESULTS
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We report the study of long-term follow-up of 137 patients with brachial plexus avulsion pain who underwent DREZ lesioning to evaluate the incidence of surgical technique and predictive factors on the results.

Material. Patients (224) were operated between 1980 and 2006. A questionnaire was mailed by an independent expert to 158 patients with more than 5 years follow-up and returned by 137 patients. The cause of the lesion is a motocycle crash in the majority.

Results

– Pain relief, noted by 119 patients (87%), was total: 36 patients (26%), good: 65 (47%), fair: 18 (13%), poor: 18 (13%).
– Recurrence of pain occured in the first post operative year.
– Fair and poor results decreased in more recent cases.
– Pain recurrence factors concerning the lesions were incomplete surgical lesioning “end zone pain”, preserved injured roots.
– Ongoing pain and dysesthesia, painful fantom and allodynia were less relieved pain.
– Comorbidities like serious psychological and family problems led to worse results.

Discussion. A complete destruction of the deafferented dorsal horns is mandatory and requires long experience and right technique. The results were improved by modifications of the original Nashold’s procedure.

DREZ lesioning suppresses the dorsal horn pain generator (paroxysmal pain) but is ineffective on
higher pain generators (continuous and painfull fantom).

Conclusion. DREZ procedure long term results are very satisfying. Predominant ongoing pain and painfull fantom are not good indications. Comorbidities must be considered as in other chronic pain.

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EPIDURAL ADHESIOLYSIS AND PULSED RADIOFREQUENCY TREATMENT (PRF) WITH PASHA CATH VS ADHESIOLYSIS WITH RACZ CATHETER
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Introduction. Percutaneous epidural adhesiolysis and PRF are interventional pain management techniques that play an active role in managing chronic intractable lower extremities pain.

The Pasha Cath is a multifunctional catheter used for neuroselective (with sensory and motor stimulation) infusion of drugs and pulsed radiofrequency treatment in radicular pain.

Objective. to compare the effectiveness of epidural adhesiolysis and PRF with Pasha Cath versus adhesiolysis with Racz catheter.

Design. Prospective open-label randomized trial

Setting. Department of Pain Medicine, Private Hospital, Forli, Italy.

Inclusion criteria. All patients affected by sensitive lumbar monolateral mono or bi-radiculopathy for more than 6 months, with pathogenetic diagnosis of periferic neuropathic pain.

Interventions. All patients were randomized to undergo epidural adhesiolysis and PRF with Pasha Cath and adhesiolysis with Racz catheter.

Effectiveness assessments. NRS (resting/incident) Oswestry Disability Questionnaire, QUID test (Italian Pain Questionary) at baseline, first and third month.

Results. Follow-up in progress.

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SPINAL CORD STIMULATION IN ALLODYNIC SPINAL CORD INJURY (SCI) PAIN
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Below level pain in SCI are challenging as there are few treatments shown to be effective. Particularly the results of spinal cord stimulation are generally considered to be very disappointing. We looked if we could define a subgroup of patients who may benefit from this treatment.

Study. This prospective study included patients with alldyinic unilateral below level pain. Clinical examination showed a lesion of the spino-thalamic pathway. The lemniscal pathways are relatively preserved, proved by somato-sensory evoked potentials.

If the pain evaluation requirements were satisfied, patients were included and a percutaneous spinal cord stimulation test was performed.

Results. We included six patients between 2001 and 2006. Four patients improved more than 60% and the system was definitively implanted. The long term results (1–6 years) are presented. Good results (more than 50% relief) remained.

Discussion. The crucial point is the selection of patients.

We discuss:

– the pain assessment
– the type of the lesion: the preservation of the lemniscal pathway seems to be deciding;
– the percutaneous test for its prognostic interest and as an element of care;
– the technical aspects as the level of stimulation and the choice of parameters.

Conclusion. This short series and the limited long term results do not allow to draw definite conclusions. Nevertheless, even a treatment considered as disappointing like spinal cord stimulation in SCI can be of benefit to a subgroup of patients when the indications are specified accurately.

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CHRONIC MANAGEMENT OF TOTAL IMPLANTABLE PUMPS FOR PAIN TREATMENT: REVIEW OF PERSONAL EXPERIENCE AND OBSERVATIONS
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Background and aims. Neurosurgical treatment of intractable pain syndromes comprise the possibility to implant pump delivering pharmacological systems. We report our experience in the long term follow up and gen-
eral management of total implantable pumps for the drug delivering in the subarachnoid or epidural space.

**Methods.** A total number of 64 patients were treated from January 2000 to December 2005. Mean age was of 56 years old, female were predominant (68%). Patients were affected by pain syndromes regarding intractable deafferentation pain (myelopathies), failed back surgery syndrome, intractable low back pain and oncological pain.

Drugs commonly utilized were morphine, buprenorphine and tramadol.

**Results.** Patients affected from chronic benign pain (56 cases) were treated with tramadolo or low doses of morphine or buprenorphine. These patients reached a good response in a percentage variable from 60% to 85% of cases and needed frequent dosage variation.

Patients suffering from cancer pain (8 cases) were almost considered as good responders, they were treated with morphine in all cases.

Patients initially treated with tramadol sumministered in the epidural space have had no response for pain control beneath their initial good response to it. All these patients were then treated with buprenorphine with a good and long standing effect on pain relief.

Infusion of intrathecal drugs have had a high percentage (40%) of secondary effects if compared to the epidural sumministration (12%).

**Conclusions.** The usefulness of the total implantable pumps for chronic pharmacological sumministration is an almost standardized technique with low surgical risks.

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**COST EFFECTIVENESS OF SPINAL CORD STIMULATION FOR NEUROPATHIC PAIN: A EUROPEAN SURVEY ON QUALITY OF LIFE AND HEALTHCARE RESOURCE UTILISATION**

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**Background and aims.** Faced with rising healthcare costs, payers increasingly require evidence on costs and cost effectiveness of healthcare technologies. To date, information on the cost effectiveness of spinal cord stimulation (SCS) for neuropathic pain due to failed back surgery syndrome (FBSS) has been limited. A recent decision analytic model analysis showed that the addition of SCS to usual care is potentially cost effective. However, the report authors highlight the need for more definitive data, i.e. health-related quality of life, health-care resources and costs. European survey on utilities and resource utilisation in failed back surgery syndrome (SURF) was set up with the aim of collecting such data.

**Methods.** Between January 2005 and September 2006 data was collected in FBSS patients who had had been implanted with SCS or were receiving conventional medical management (CMM) across nine centres in France, Spain, Germany and UK. Generic health-related quality of life data was collected using the EQ-5D. Health care resources were assessed retrospectively and costed at 2005-6 prices. Cost effectiveness is reported as the incremental cost per quality adjusted life year (QALY).

**Results.** Data has been collected on a total of 169 neuropathic patients with FBSS. This data will be used to populate the previously published economic model with the purpose of reassessing the cost-effectiveness of SCS.

**Conclusions.** This presentation presents costs and quality of life data collected in the SURF project and updates the cost effectiveness of SCS vs. CMM in patients with neuropathic pain due to FBSS.

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**PREDICTION OF RESULTS OF MOTOR CORTEX STIMULATION IN TREATMENT OF BRACHIAL PLEXUS AVULSION PAIN BY TRANSCRANIAL MAGNETIC STIMULATION**

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**Background and aims.** Brachial plexus avulsion (BPA) often originates intractable pain. Motor cortex stimulation (MCS) has been employed as a treatment option for various neuropathic pain conditions with encouraging results. However, not all patients respond equally to this technique. In this study the authors aimed to test transcranial magnetic stimulation (TMS) as a prediction tool for results of MCS in treatment of pain related to BPA.

**Methods.** Thirty-five patients with BPA underwent TMS cortical mapping. Eight of them were addressed to MCS electrode implantation. Changes in visual analog scale within one year follow-up were computed and compared to preoperative TMS responses.

**Results.** Fourteen (40%) of the patients (age 18–79 years, average = 37.2 ± 11.7) showed evoked paresthesias on the contralateral upper limb when the central region
was magnetic stimulated. This area on the surface of scalp varied from 2.1 to 42.8 cm² (average = 10.6 ± 11.11 cm², median = 6.1 cm²). The pain scores in (VAS) were 8 or higher (average 9.5 ± 21). The results were considered good and excellent in five patients, fair in one and the other two had bad or no response after one year follow-up. The best responses were achieved in patients who demonstrated enlarged areas responsive to TMS mapping, while the bad responders to MCS had small or no cortical response to TMS. However this association was not statistically significant.

**Conclusion.** MCS may be a good treatment option for pain related to BPA, especially when associated to TMS as a predictive tool.

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**TOPICAL ESSENTIAL OILS FOR FIBROMYALGIA NEUROPATHIC PAIN: A RANDOMIZED CONTROLLED TRIAL**

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**Background**

**Objective.** To test that topical O24 essential oils are superior to placebo in fibromyalgia (FMS) patients

**Design.** Double-blind, randomized placebo-controlled study (RCT).

**Participants.** A total of 153 subjects with American College of Rheumatology criteria for FMS.

**Method**

**Intervention.** Treatment period of one month with topical O24 or placebo (peppermint oil identical in smell and consistency). Oils applied into tender areas 4x/day. Topical O24 consists of a proprietary blend of seven essential oils (aloevera, camphor, eucalyptus, lemon, orange, peppermint, rosemary).

**Main outcome measures.** Primary end points: pain visual analogue scale (VAS) ratings and diary, fibromyalgia impact questionnaire (FIQ), Jamar grip strength, pressure algometry of tender point (TP) pain threshold and number of TPs. Secondary end points: seven-point Lanier rating (from 1 markedly worse to 7 markedly better) of treatment and tolerability of the oils.

**Results.** In the 133 participants (65 active, 68 placebo) with complete data, the active (over placebo) demonstrated improvements in the VAS night pain ($p = .018$), Jamar grip strength ($p < .001$), number of TPs ($p < .001$) and average TP pain threshold ($p < .001$), and the Lanier scale ($p = .001$) rated 5.6 as mildly to moderately effective. No significant differences were noted with the FIQ or VAS activity pain scores. Forty-three participants (19 placebo and 24 active) complained of smell sensitivity. Only 1 active and 1 placebo participant complained of skin irritation.

**Conclusion.** This pilot RCT suggest that FMS patients may be effectively and safely managed for pain with topical O24. This would need to be confirmed with larger and longer randomized controlled trials.

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**APPLICATION OF STELLATE GANGLION BLOCK FOR THE TREATMENT OF NEUROPATHIC HEAD, NECK, ARM AND CHEST PAIN**

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**Background and aims.** To summarize the experience of application of stellate ganglion blocks for the treatment of neuropathic head, neck, arm and chest pain during 2004–2006.

**Methods.** The retrospective analysis of all stellate ganglion blocks performed by the author during 2004–2006.

**Results.** During 2004–2006 period 96 stellate ganglion blocks were performed. This procedure was used for the treatment of following pain syndromes: postoperative pain in the region of incision or due to nerve lesion, complex regional pain syndrome, postherpetic neuralgia, traumatic nerve injury, phantom pain, pain due to degenerative shoulder joint diseases, pain due to malignant diseases, cranial nerves neuralgias, atypical facial pain, cervical radiculopathy, syringomyelia and pain of undetermined origin. Pain duration at the time of procedure ranged from 10 days to 30 years. Sympathetic hyperactivity was observed in 24% of patients. In 85% of cases procedure was performed accurately (estimated as positive Horner’s syndrome after procedure). In 72% of patients pain decreased or disappeared after procedure. The effect duration ranged from several hours till disappearance of pain without returns. In 4% of cases procedure was not tolerated and in 3% of cases the puncture was bloody.

**Conclusions.** Stellate ganglion block may be an effective means for the treatment of neuropathic head, neck, arm and chest pain of different origins. The method used is safe and reliable enough. This experience show sympathetic hyperactivity to be involved
in a very wide range of pain syndromes, much more often than is seen clinically.

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PROSPECTIVE OUTCOMES STUDY ON THE RESTORE® RECHARGEABLE NEUROSTIMULATION SYSTEM FOR NEUROPATHIC PAIN: A MULTI-CENTER STUDY

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Background and aims. Spinal cord stimulation (SCS) is a treatment option for patients with chronic neuropathic pain. Patients enrolled in the study and implanted with the Restore rechargeable neurostimulation system were followed to characterize pain outcomes over 12 months.

Methods. This prospective open-label study was conducted in 12 European centers. Patients’ ability to recharge was assessed one month post-implant. Outcome measurements including pain VAS, pain relief, Oswestry Disability Index and EQ-5D were collected 3, 6, and 12 months (12 months) post-implant. Overall satisfaction with SCS was collected at 12 months.

Results. Of 45 patients enrolled, 42 were implanted. Of these, 41 met prospective analysis criteria for the primary objective assessing ability to recharge. All 41 successfully recharged independently. The majority of the patients (79%) rated recharging easy or somewhat easy. Comparing baseline to 12 months, the mean VAS score for the primary pain area was reduced from 7.2 ± 1.5 to 4.4 ± 2.8 (p < 0.001). Patients (80%) reported more than 50% pain relief at 12 months. EQ-5D health status improved from 0.21 ± 0.32 to 0.46 ± 0.36 (p < 0.001). Oswestry scores improved from 52 ± 12, categorized as severe disability, to 38 ± 19 (p < 0.001), categorized as moderate disability. Physicians rated the system favorably for most patients (95%). Patients (93%) would elect SCS again for the same result, and 98% would recommend SCS to a friend with similar pain.

Conclusions. All patients independently recharged the neurostimulator battery. Significant improvements in pain reduction, quality of life, and functional status were observed throughout 12 months post-implant, with a high rate of patient satisfaction with the therapy.

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PULSED RADIOFREQUENCY (PRF) FOR THE TREATMENT OF OCCIPITAL NEURALGIA: A CLINICAL AUDIT

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Introduction. Occipital neuralgia is a non-throbbing neck pain spreading ipsilaterally to the occipito-temporo-frontal area and is relieved by injection of local anaesthetics at the greater and or lesser occipital nerve. There is no gold standard for treatment.

Methods and materials. Patients fulfilling the International Headache Society criteria for occipital neuralgia underwent PRF after a positive diagnostic block of the occipital nerves (>50% reduction on VAS). Target nerves were identified with the external landmarks described by Vital and needle position was controlled with electrical stimulation at 50 Hz (threshold <0.5 V) PRF was performed during 4 min.

Results. Tabel 1.

<table>
<thead>
<tr>
<th></th>
<th>Pre PRF</th>
<th>1 Month (n = 6)</th>
<th>2 Months (n = 4)</th>
<th>6 Months (n = 2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>VAS (SD)</td>
<td>7.3(±1.6)</td>
<td>3.3(±3.6)</td>
<td>1.5(±1.7)</td>
<td>1(±1.4)</td>
</tr>
<tr>
<td>GPE &gt; 50%</td>
<td>n = 4</td>
<td>n = 3</td>
<td>n = 2</td>
<td></td>
</tr>
</tbody>
</table>
Conclusions. These preliminary data suggest PRF is a promising treatment for occipital neuralgia and justifies further controlled trials. The vital surface landmarks are reliable for the greater and lesser occipital nerve localisation.

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439 TENS IN NEUROPATHIC AND NOCICEPTIVE PAIN
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This study aims to compare the pain relief provided by TENS in patients with neuropathic and nociceptive pain, and to find simple criteria predicting pain relief.

Methods. Retrospective study of chronic pain outpatients seen from 2000 to 2006. Only patients who received TENS as single treatment at their clinic visit were included. Patients completed the brief pain inventory at each visit. Pain relief was measured on a numerical rating scale (0–100%). R (Development Core Team, 2006) was used for statistical calculations. For predictive models regression trees were grown for neuropathic and nociceptive pain (function “rpart”). Trees were pruned to three levels.

Results. 478 Patients had predominantly neuropathic, 501 nociceptive pain. The pain relief was similar in both groups ($X^2 = 0.9354; p = 0.3335; ns)$:

<table>
<thead>
<tr>
<th>Pain type</th>
<th>Mean ± SD</th>
<th>Median</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neuropathic</td>
<td>31.1 ± 26.79</td>
<td>30</td>
<td>0–100</td>
</tr>
<tr>
<td>Nociceptive</td>
<td>28.6 ± 26.06</td>
<td>20</td>
<td>0–100</td>
</tr>
</tbody>
</table>

Recursive partitioning found the predictors impairment of activity (>5/10), lack of impairment of work (0/10), and maximal pain in the last week of >7/10 in neuropathic pain, while in nociceptive pain average pain over the last week (>6/10), impairment of work (>6/10), and moderate impairment of mood (<5/10) were more important.

Conclusion. TENS is moderately successful in both neuropathic and nociceptive pain. Items of the brief pain inventory predict treatment outcome.

Reference
R Development Core Team. R Installation and Administration, version 2.3.1, 06/01/2006.

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440 OPIOIDS AND THEIRS POSITION IN THE TREATMENT FAILED BACK SURGERY SYNDROME
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Background and aims. Failed back surgery syndrome (FBSS) is very common and very complicated mixed pain condition. We have used the multidisciplinary approach, including opioids, for the treatment of FBSS. We have used opioids in various drug forms. When FBBS is not manageable with standard approaches we have used intrathecal drug delivery devices.

Methods. We have treated more than 300 patients with FBSS in our two pain centers for last 5 years since we introduced drug delivery systems in our practice. Since 2001 we have implanted 28 port systems and 13 pump systems (Synchromed) for delivery morphine in very carefully selected patients with severe FBSS.

Results. Every approach has its own advantages and disadvantages. We describe our experience-results, achievements and complications with use of our approaches of opioids in the treatment of FBSS. Our results are good, but not satisfactorily good. It seems that implantable delivery devices allow more comfortable and more effective long-term morphine administration.

Conclusions. It is hard to strictly decide whe and/or what approach of opioids is the best for using in each patient with FBSS. When the patients with FBSS cannot be controlled by less invasive opioid management than long-term delivery morphine systems, mainly pump systems, seem an appropriate analgetic method for strictly selected patients with severe FBBS.

Acknowledgement
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441 COMPARING THE EFFICACY OF THORACIC TRANSFORAMINAL INJECTION OF MAGNESIUM VERSUS INTERCOSTAL NERVE BLOCK WITH METHYLREDNISOLONE FOR CHRONIC POST THORACOTOMY PAIN SYNDROME
M. Yosry
Pain therapy and quality of life (QOL) are very important in patients with post thoracotomy syndrome. I evaluated the pain relieving efficacy, and effects on QOL of thoracic transforaminal (i.e. nerve root approach) injection of magnesium diluted with lidocaine versus intercostal nerve block with methylprednisolone and lidocaine in management of chronic post thoracotomy pain syndrome.

The study protocol was approved by the local ethics committee. Patients were randomly divided into two groups. Magnesium group; GM, N = 20 were treated with magnesium (transforaminal approach), whereas the patients in steroid group; GS, N = 20 were treated with methylprednisolone (intercostal nerve block). The VAS values, codeine consumption, and quality of life (QOL) (assessed by patient satisfaction scale, PSS; and performance status, PS) were evaluated prior to the procedure and at 2 weeks intervals after the procedure for 14 weeks.

The demographic data were found to be similar. The comparisons of difference of VAS values were found to be significantly lower in GM than GS in every control till the 12th week. GM patients were found to decrease the codeine consumption significantly more than GS till the 14th week. GM patients had significant improvement in QOL values especially after 4 weeks (assessed by Patient satisfaction scale, PSS; and performance status, PS).

Comparing the pain relieving efficacy, QOL – effects of the methods, thoracic transforaminal (i.e. nerve root approach) injection of magnesium may be an alternative to traditional intercostal nerve block with steroids in adult patients with post thoracotomy syndrome.

Keywords: Chronic pain; Post thoracotomy syndrome; Quality of life; Transforaminal injection; Magnesium; Intercostal nerve block; Steroid

doi:10.1016/j.ejpain.2007.03.456

INVOLVEMENT OF SPINAL ASTROCYTES AND GLUTAMATE TRANSPORT GLT-1 IN PROCESSING TETANICALLY SCIATIC STIMULATION-INDUCED MECHANICAL ALLODYNIA IN RAT
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Tetanically electrical stimulation of the sciatic nerve produces both long-term potentiation of C-fiber-evoked field potentials in the spinal cord and long-lasting mechanical alldynia. This work investigated the mechanism underlying these processes. (1) The immunocytochemical study showed degeneration in sciatic myelinated fibers, especially in large fibers, on 4 days after tetanically sciatic stimulation. On day 35, degeneration was observed in both myelinated and unmyelinated fibers. Myelinated fibers displayed structural changes of...
the myelin with dark axonoplasm and unmyelinated fibers exhibited a looser alignment with a larger compartment between bundles. Tetanically sciatic stimulation is capable of induce nerve injury evoking neuropathic pain. (2) Tetanically sciatic stimulation up-regulated expression of glial fibrillary acidic protein in astrocytes and produced mechanical allodynia, which were blocked by glia inhibitor fluorocitrate (FC, 1 nmol/1 µl, i.t.). Following astrocyte-derived D-serine, an endogenous ligand for the glycine site of NMDA receptor, was degraded by D-serine D-amino acid oxygenase (50 µg/ml i.t.), mechanical allodynia was reduced, suggesting involvement of astrocytes in neuropathic pain. (3) Tetanically sciatic stimulation induced an upregulation of expression of glutamate transporter-1 (GLT-1) by astrocytes and mechanical allodynia. GLT-1 specific inhibitor dihydrokainate (3.0 mM, 10 µl i.t.) abolished tetanically sciatic stimulation-induced mechanical allodynia and spinal LTP. Conclusion: spinal astrocytes and GLT-1 play an important role in tetanically sciatic stimulation-induced neuropathic pain.

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Poster Session 2: Human studies

NEUROPHYSIOLOGICAL CHARACTERIZATION OF POSTHERNIORRHAPHY PAIN

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Background. Chronic pain affecting everyday activities are reported in ~10% of patients following inguinal herniorrhaphy. However, the neurophysiological changes and underlying pathophysiological mechanisms are not known in detail.

Methods. The primary endpoint was to identify sensory disturbances specific for chronic postherniorrhaphy pain patients. Thirty-five patients reporting chronic post-herniorrhaphy pain were compared with a control group of 10 patients without postoperative pain. Sensory tests were carried bilaterally and included detection and pain thresholds to thermal and mechanical stimuli and response to repetitive pinprick stimulation. Side to side and inter-group differences were compared.

Results. Sensory disturbances on the operated side were found in patients and controls.

Thermal and tactile detection thresholds were significantly increased in the pain group compared to controls. Direct pressure pain detection threshold was significantly lower in pain-patients compared with controls. Evoked/increased pain to repetitive punctuate stimulation was found only in the pain-patient group and only on the operated side. After sensations to repetitive pinprick stimulation were reported by 11/35 (28%) pain patients and not by the controls.

Conclusion. Similar to other types of chronic postoperative pain syndromes (i.e. mastectomy) we found that sensory disturbances are present including sensitization indicating that this is a neuropathic pain state. The finding that pressure pain detection was significantly decreased only in the pain group suggests that the origin of pain is from deeper structures rather than the skin. However, whether the underlying pathophysiological mechanisms are related to an intraoperative nerve injury or inflammation of nervous tissue remains to be explored.

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TEMPORAL SUMMATION OF PAIN – REPRODUCIBILITY IN NORMAL VOLUNTEERS

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Background and aims. The phenomenon of Temporal Summation refers to an increase in the experienced intensity of pain as a consequence of repeated stimulation.

The aim of our study was to investigate the relationship between stimulus intensity and the stimulus frequency required to evoke pain as well as the reproducibility of repetitive stimulation for evaluation of pain.

Methods. Two groups of 12 healthy male volunteers participated in a two-visit study. A constant current electrical stimulator (Digitimer) was used to produce 1 ms square wave pulses that were applied to the area above the right sural nerve. Detection threshold (DT), pain threshold (PT) and pain tolerance threshold (PTT) were established in the beginning of each session. Temporal summation of pain was induced by repeated electrical stimuli and temporal summation threshold (TST) determined for different stimulus frequency and intensity. Pain was assessed by NRS and VAS.
Results. In all subjects, but one, TST was obtainable and reproducible. We also observed that it is dependent on the intensity and the frequency of stimuli. DT showed the greatest intrasubject variability. PT and PTT showed a low intrasubject variability. Intrasubject variability for PT, PTT and TST indicated that the sample size required to detect a 25% difference is approximately 7, 3 and 14 subjects, respectively.

Conclusions. Using single 1 ms electrical pulses we were able to demonstrate good intrasubject correlation for PT, PTT and TST. The present study supports the use of this model for evaluation of TS in healthy individuals and pharmacological characterization.

Acknowledgement
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A PROSPECTIVE STUDY OF PAIN AFTER HYS-TERECTOMY IN WOMEN WITH BENIGN UTERINE DISORDERS
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d Section of Surgical Pathophysiology, Rigshospitalet, Copenhagen, Denmark

Background. Pain is a frequent symptom before hysterectomy on benign indication, and it is reported by up to 85% of women. At long term follow-up, 5–31% report pain, but it is unknown whether the postoperative pain is identical to the preoperative pain. Chronic postsurgical pain without obvious pathology is recognized after other surgical procedures, as for example amputation and inguinal herniorrhaphy. The underlying mechanisms of chronic postsurgical pain are incompletely understood, but sensitization of the central nervous system after surgical trauma is of major importance. Yet, psychosocial factors may also play a role, and the causes of chronic pain in post-hysterectomy patients are unknown.

The primary aim is to study whether preoperative factors can predict the presence of pain in the acute postoperative period and at 4 months follow-up. Secondly we aim to describe pain characteristics.

Methods. One hundred women with uterine fibromata and bleeding disorders scheduled for hysterectomy will be included. Quantitative sensory testing is performed preoperatively, the first day, 3-weeks and 4 months postoperatively, together with questionnaires about pain, gynecological symptoms and coping strategies. Possible predictive factors are: previous surgery, preoperative pain, type of hysterectomy, anesthesia, pain pressure thresholds, 24 h analgesics consumption and pain coping strategies.

Results. The study is ongoing, and 66 women are enrolled at January 15, 2007. End of enrolment is expected at April 1, 2007. Preliminary results up to 3-weeks postoperatively will be presented.

Acknowledgement
The study is supported by a grant from the Lundbeck Foundation.

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HYPERALGESIC AND ALLODYNIC EFFECTS OF NOCEBO SUGGESTIONS
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Background and aims. One of the main features of neuropathic pain is that an innocuous stimulus can be turned into a painful sensation, a phenomenon which is known as allodynia. By extending previous findings, here we show that nocebo suggestions, in which expectation of pain increase is induced, are capable of producing both hyperalgesia and allodynia. We also investigate the role of learning in the nocebo effect via classical conditioning.

Methods. To do this, verbal suggestions of pain increase were given to healthy volunteers before administration of either tactile or low-intensity painful electrical stimuli. In learning experiments, the nocebo procedure was carried out after a pre-conditioning session in which two different conditioned stimuli were associated to either pain or no-pain. Pain perception was assessed by means of a numerical rating scale (NRS), ranging from 0 = no-pain to 10 = unbearable pain.

Results. We found that verbal suggestions turned both tactile stimuli into pain and low-intensity pain into high-intensity pain. Similarly, conditioned stimuli that were associated to pain were capable, when presented alone, of turning both tactile stimuli into pain and low-intensity pain into high-intensity pain. Therefore, in contrast to the learning effects in placebo analgesia of previous studies, here we did not find significant differences between conditioned and no-conditioned responses.
**Conclusions.** These data indicate that: (1) nocebos can produce both hyperalgesia and allodynia and (2) the mechanisms of the nocebo effect do not necessarily involve learning phenomena, which suggests that the nocebo effect is not the mirror counterpart of the placebo effect.

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**EFFECT OF TRAMADOL ON LASER EVOKED POTENTIALS IN HUMANS: PRELIMINARY RESULTS**

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**Aim.** Laser evoked potentials (LEPs) consist of a lateralized component (N1) generated by the opercular regions, and a vertex potential (N2–P2) generated by the anterior cingulated cortex (ACC).

There are sparse reports that opiates attenuate LEP components in humans. Our aim was to assess the effect of tramadol on LEPs. We recorded LEPs after hand stimulation in nine healthy volunteers. All subjects underwent two separate experiments, one with tramadol and the other with placebo. Each experiment consisted of four recording sessions: pre-drug, 30- and 65 min post-drug (tramadol 100 mg im or placebo), and post-antagonist (naloxone 0.4 mg i.v. or saline).

We found that tramadol caused a reduction of N2–P2-LEP amplitude of 35% at 30 min and 45% at 65 min after tramadol administration (P < 0.05); conversely N1-LEP amplitude did not change significantly (P > 0.05). The effect of tramadol was not completely reverted by naloxone; however the N2–P2 amplitude difference between the pre-drug and the post-naloxone session failed to reach the statistical significance (P = 0.055). LEP latency did not change after drugs administration (P > 0.2). Placebo did not affect LEP data (P > 0.2).

Our data indicate that tramadol influences LEPs; the incomplete recovery induced by naloxone suggests that the influence is mediated by both the opioid and the adrenergic effect. The lack of modulation on N1-LEP may be related to a specific effect of tramadol on ACC. This study could be useful to better understand the role of ACC in pain processing.

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**MICROVASCULAR DECOMPRESSION (MVD) IN TRIGEMINAL NEURALGIA (TN) TREATMENT**

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**Aim.** Optimization of treatment for patients with TN.

**Methods.** Hundred forty-five patients TN underwent MVD from 1997 till 2006. Hundred eighteen patients had classic TN signs and 27 patients had atypical TN signs.

High-resolution MRI in 3D SPRG GAD regimen is used for trigeminal nerve and adjacent vessels imaging.

**Results.** Ninety-five percent of “classic” TN subgroup had complete pain relief in a year after surgery, 3% had incomplete (over 70%) pain relief, 2% had no relief; 3 years after surgery: 82%, 11% and 7% correspondingly.

Seventy-six percent of “atypical” TN subgroup had complete pain relief in a year after surgery, 18% had incomplete pain relief, 6% had no relief; 3 years after surgery: 64%, 24% and 14% correspondingly.

Paroxysmal pain component regressed at all the patients but constant (burning) pain component often remained, which prevented patients from evaluating the treatment results as “excellent”. Anamnesis analysis showed that all the “atypical” TN patients had gone destructive procedures more than once, which led to posttraumatic trigeminal nerve neuropathy. Thus, “atypical” trigeminal neuralgia can be regarded as a combination of “classic” trigeminal neuralgia (which patients had initially) and posttraumatic neuropathy. After MVD neuralgia regressed but neuropathic manifestations often remained, which left incomplete patient satisfaction with treatment results.

**Conclusion.** Treatment results analysis in different TN patients subgroups let us recommend the early use of MVD as a primary surgical technique before any destructive procedure.

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**PAIN, ANXIETY AND DEPRESSION IN NEUROPATHIC AND NON-NEUROPATHIC PAIN PATIENTS COMPARED WITH HEALTHY CONTROLS. A QUANTITATIVE STUDY**

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**Aim.** Pain, anxiety and depression in neuro-pathic and non-neuropathic pain patients compared with healthy controls.

**Methods.** Hundred forty-five patients TN underwent MVD from 1997 till 2006. Hundred eighteen patients had classic TN signs and 27 patients had atypical TN signs.

High-resolution MRI in 3D SPRG GAD regimen is used for trigeminal nerve and adjacent vessels imaging.

**Results.** Ninety-five percent of “classic” TN subgroup had complete pain relief in a year after surgery, 3% had incomplete (over 70%) pain relief, 2% had no relief; 3 years after surgery: 82%, 11% and 7% correspondingly.

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Paroxysmal pain component regressed at all the patients but constant (burning) pain component often remained, which prevented patients from evaluating the treatment results as “excellent”. Anamnesis analysis showed that all the “atypical” TN patients had gone destructive procedures more than once, which led to posttraumatic trigeminal nerve neuropathy. Thus, “atypical” trigeminal neuralgia can be regarded as a combination of “classic” trigeminal neuralgia (which patients had initially) and posttraumatic neuropathy. After MVD neuralgia regressed but neuropathic manifestations often remained, which left incomplete patient satisfaction with treatment results.

**Conclusion.** Treatment results analysis in different TN patients subgroups let us recommend the early use of MVD as a primary surgical technique before any destructive procedure.

doi:10.1016/j.ejpain.2007.03.464
Background. Pain is often associated with anxiety and depression, which could be the result of disturbances in common neurotransmitter systems, e.g. the monoamines in the brain and spinal cord.

Aim of the study. To determine the association between pain, anxiety and depression parameters.

Hypothesis. Patients with non-neuropathic pain have a generalized hypersensitivity to all types of stimuli, which makes them sensitive to stimulation both in the painful and non-painful areas of the body. They also have high scores on psychopathological parameters (including depression and anxiety) as opposed to patients with neuropathic pain, who are only hypersensitive to stimuli in the painful area and score lower on psychopathological parameters. Healthy controls have the lowest scores on all parameters compared to the two patient groups.

Materials and methods. Twenty-five patients with neuropathic and 25 with non-neuropathic pain (fibromyalgia) will be examined using quantitative sensory testing as well as qualitative measures. Test procedures include determination of pain perception thresholds and pain tolerance thresholds to heat, cold and pressure. Pain rating scales include Pain Catastrophizing Scale, Coping Strategies Questionnaire and McGill Pain Questionnaire. Anxiety and depression are measured with Symptom Checklist-92, Hamilton Depression and Anxiety Rating Scales, Major Depression Inventory, Anxiety Inventory GAD-10 and SF-36 Health Survey. The patients are compared to 25 age- and gender-matched healthy controls.

Results. Data collection is ongoing. Preliminary results will be ready for presentation at the conference.

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451 SPATIAL AND TEMPORAL STIMULUS PARAMETERS OF CONDITIONING STIMULATION AFFECT THE MAGNITUDE AND DIRECTION OF HUMAN PAIN PLASTICITY

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Memory-like long-term potentiation (LTP) and depression (LTD) rule nociceptive plasticity. In a recently established model of LTP- and LTD-like bidirectional plasticity of human pain perception [Klein et al., J Neurosci 2004; 24: 964–71.] we investigated the impact of variations in spatial and temporal stimulus parameters on the magnitude and direction of plasticity.

The skin of the thigh was stimulated through a multipolar electrode array (? 30 mm area, 48 pin electrodes) with 500 or 1000 conditioning electrical pulses at 1, 10 and 100 Hz in 12 healthy human volunteers (intensity: 10x detection threshold). LTP magnitude grew linearly with the frequency of conditioning stimulation (significantly different between frequencies, at least $p < 0.05$). Longer pulse trains (1000 pulses) tended to give stronger LTP ($p = 0.07$). Unexpectedly, LTD-like responses at low frequency (1 Hz) were never seen.

Testing at the conditioned and an adjacent (unconditioned) test site revealed highly correlated responses of similar magnitude ($r = 0.91$) suggesting that heterosynaptic facilitation was the dominant underlying process at both test sites. The direction and magnitude of the response depended significantly on the number of electrodes and on the size of the stimulated skin area. Namely, stimulation through a small 10 pin electrode resulted in significant LTD, while stimulation through the large 48 pin electrode resulted in significant LTP.

We conclude that spatial and temporal stimulus parameters affect the magnitude and direction of pain plasticity. Heterosynaptic facilitation leading to frequency-dependent LTP plays a substantial role in nociceptive plasticity, and easily overrides competing homosynaptic LTD. (Supported by DFG-Tr236/16-2 & BMBF-01EM0506).

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452 INHIBITION OF CORTICAL LASER EVOKED POTENTIALS BY TRANSCUTANEOUS ELECTRICAL NERVE STIMULATION

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Introduction. Laser evoked potentials (LEPs), consisting of a N2 and P2 component are seen in the EEG 175–500 ms after laser stimulation of the skin. The amplitude of LEP relates to subjective pain rating. With transcutaneous electrical nerve stimulation (TENS) tactile afferent input is thought to inhibit nociceptive processing. Are LEP characteristics a means to evaluate the effects of TENS?

Methods. With a 980 nm diode laser, 10 stimuli (0.25–0.6 W; 50 ms) were delivered to the blackened dorsum of the hand of 13 volunteers and averaged offline. Area
under the curve (AUC175 – 500 ms) and total amplitude of N2 and P2 (N2–P2) were calculated. TENS (110 Hz) was applied to the dorsolateral forearm. LEPs were recorded following 1 and 10 min of TENS and 10 min after stopping TENS. For each stimulus, the intensity of pain was recorded on a numeric rating scale (NRS: 0–10; 0: no pain, 10: worst imaginable pain).

Results. A significant reduction in the AUC175 – 500 ms was found after 10 min of TENS (mean reduction 26%; 95% CI: 1.2–50.4), but not after 1 min of TENS. The AUC reduction remained significant 10 min after stopping TENS (mean decrease 28%, 95% CI:3.0–52.9). There was no reduction in N2P2 during or after TENS. The mean NRS decreased by 1 point (range –2.5 to 3) during TENS. Ten min after stopping TENS, the mean NRS increased by 1 point (range 0–2).

Conclusions. TENS is accompanied by a significant reduction in AUC of LEP.

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HIV-POSITIVE OUTPATIENTS ON ANTIRETROVIRAL THERAPY HAVE THE SAME PAIN INTENSITY BUT GREATER RISK OF NEUROPATHIC PAIN THAN TREATMENT NAÏVE PATIENTS
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Background and aims. Infection with HIV, and its treatment with nucleoside reverse transcriptase inhibitors (NRTIs), is associated with the development of pain, including neuropathic pain. We investigated whether the incidence of neuropathic pain differs between HIV-positive patients on antiretroviral drug (ARV) therapy and treatment naïve patients.

Methods. We administered translated versions of the Brief Pain Questionnaire and the Neuropathic Pain Symptom Inventory to 108 HIV-positive outpatients attending a Johannesburg state hospital.

Results. Twenty-eight patients were on the ARV regimen of efavirenz and two NTRIs, stavudine and lamivudine [8 male, 20 female; age (mean ± SD) 38 ± 7 years; CD4 count (median, range) 148, 13 to 494 cells mm⁻³], and 80 HIV-positive patients were treatment naïve [15 male, 64 female; age 36 ± 8 years; CD4 count 238: 2–712 cells mm⁻³]. Patients on ARV therapy had been on therapy for between 1 and 21 months (median: 5 months). In the previous 24 h, all patients had experienced mild to severe pain, which they ascribed to their illness. There were no differences in pain intensity, nor the number of pain sites per person (~3 per person), between the two groups. However, 57% of patients on ARV therapy had symptoms of neuropathic pain (typically in the feet), compared with 44% of treatment naïve patients (odds ratio: 6.1). We found no association between the presence of neuropathic pain symptoms and the length of time on ARV therapy.

Conclusion. ARV therapy increases the risk of developing neuropathic pain, but does not alter the self-reported pain intensity experienced by patients.

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SOMATOSENSORY PERCEPTION THRESHOLD ALTERATIONS DO NOT PREDICT THE PRESENCE OF PAIN IN PERIPHERAL NERVE INJURY. PRELIMINARY RESULTS
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Background and aim. Why seemingly identical types of peripheral nerve injuries cause pain in a fraction of inflicted patients is still unknown. With regard to somatosensory aberrations the literature provides only limited information about similarities and discrepancies in patients with or without pain after a traumatic peripheral nerve injury (Jääskeläinen et al., 2005). No common sensory denominator was found. The aim was to study if somatosensory dysfunction profiles in patients with peripheral nerve injury predict the presence of neuropathic pain.

Methods. Thirty-four patients with partial peripheral traumatic nerve injury were studied. Eighteen patients presented with neuropathic pain and 16 patients without pain. The nerve injury had been surgically sutured in all patients in the non-painful group and in none of the patients in the pain group. In the area of nerve injury and in the corresponding contralateral area perception thresholds to warmth, cold, light touch, pressure pain, cold and heat pain were assessed as were pain intensities at suprathreshold heat pain stimulation. The mean difference between the affected and the unaffected side was calculated in each group for each parameter and was then compared on a group level.

Results. No significant difference in any single parameter was found comparing the painful and the non-painful group. Further analysis of patterns of sensory dysfunction and stimulus response functions for suprathreshold heat pain will be completed.
Conclusion. Sensory dysfunction in single modalities at perception threshold level did not define painful compared to non-painful neuropathy after peripheral nerve injury.

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REPRODUCIBILITY OF PAIN DESENSITIZATION PRODUCED BY CONTINUOUS 2HZ ELECTRIC STIMULATION

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Background. Noxious 2 Hz electrical stimulation fails to produce constant ongoing pain. A combination of facilitatory and inhibitory activation systems during stimulation initially leads to sensitization (Temporal Summation) followed by desensitization (“fade, habituation, long term depression”). These processes modulate pain perception.

The aim of this study was to characterize the reproducibility of the pain-time trend in response to continuous noxious 2 Hz electric stimulation with constant intensity.

Material and methods. Our study, which was approved by the Institutional Ethics Committee, tested 12 healthy volunteers. Electrical stimulation at 2 Hz was applied to both forearms. The intensity of stimulation was initially titrated, targeting a pain intensity of NRS = 5, and then kept constant for 10 min. Throughout the stimulation ongoing pain was measured every 30 s. Two identical experiments, at least one week apart, were conducted to assess reproducibility and tolerability.

Results. There was high variability in the pain-time trend in response to continuous noxious electric stimulation with constant intensity between volunteers. During 10 min of stimulation the decrease in pain was in the range of 20–100%. However, this response is highly reproducible within the same volunteer and could be used to characterize individual pain response.

Conclusion. A new experimental approach to characterize the human dynamical response to noxious stimuli has been proposed. The method is non-invasive and takes only 10 min. The tolerability and reproducibility profile supports the use of this new pain model for investigating pain mechanisms and the development of new pharmacological therapies.

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SOMATICSENSORY PROCESSING IN PINK1 (PARK6) AND PARKIN MUTATION CARRIERS: ITS POTENTIAL ROLE IN PARKINSON’S DISEASE

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Background. Sensory symptoms are not uncommon in Parkinson’s disease (PD). It is unclear whether these symptoms are primary or secondary. Mutations in the PINK1 and PARKIN gene have been identified as one cause of recessively inherited PD. Asymptomatic mutation carriers represent individuals at risk who may develop PD later in life and therefore serve as a model to detect sensory abnormalities before subjects show pronounced clinical signs of PD. This might shed light on the pathomechanisms related to sensory abnormalities in patients with the more frequent idiopathic PD.

Methods. Fourteen family members with PINK1 mutation as well as 9 family members with PARKIN mutation and their healthy controls were examined clinically, with nerve conduction studies and quantitative sensory testing (QST).

Results. Nine PINK1 and three PARKIN mutation carriers showed signs of PD (affected) whereas five PINK1 and six PARKIN mutation carriers did not (unaffected). Thresholds for mechanical detection, mechanical pain and pain pressure were higher not only in affected homozygous but also in heterozygous PINK1 mutation carriers compared to controls, but they did not differ from controls in unaffected PINK1 and PARKIN mutation carriers.

Conclusion. These data suggest that: (1) PINK1-associated PD is linked with primary somatosensory changes, not only in homozygous, but even heterozygous PINK1 mutation carriers and (2) different aetiologies of PD might lead to different somatosensory abnormalities.

As nerve conduction studies did not reveal differences between PINK1 mutation carriers and controls, we propose that the somatosensory impairment of PINK1
mutation carriers is related to abnormal central somatosensory processing.

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SYSTEMATIC REVIEW OF THE PREVALENCE OF NEUROPATHIC PAIN
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Aim. To identify the prevalence of different types of neuropathic pain (NeP) in general and for specific disorders according to world regions, settings and populations.

Methods. We searched MEDLINE and EMBASE from 1990 onwards for epidemiological studies reporting on prevalence data published in English. Methodological quality was assessed for risk of biases. The influence of potential effect modifiers will be assessed using meta-regression.

Results. The searches yielded 3790 titles/abstracts; 79 studies met inclusion criteria. Forty-one studies were conducted in Europe, 20 in North America, 10 in Asia, 6 in Australia, 1 in Africa and 1 in South America (including altogether 182, 395 subjects). Sample sizes varied from 22 to 121, 523 individuals. Three studies were conducted in the general population: one in the USA (reporting prevalence of CRPS I 0.021% and CRPS II 0.009%), one in the UK (detecting probable NeP in 8.2% of the general population) and one in India (looking at prevalence of peripheral neuropathies). Six studies were conducted in primary care settings and 43 in specialized or rehabilitation clinics, in patients with spinal cord injury, multiple sclerosis, herpes zoster, diabetes, AIDS, stroke, low-back pain and chronic pain. Prevalence estimates ranged from 0 to 96% for individual conditions.

Conclusions. (a) Prevalence rates for specific disorders vary widely due to differences in populations and settings and (b) The prevalence of NeP in the general population seems to be much higher than previously thought. This needs to be confirmed by high quality epidemiological studies in general populations of countries other than the UK.

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RESULTS FROM TRPM8 AND TRPA1 ACTIVATION THROUGH MENTHOL AND CINNAMALDEHYDE IN PATIENTS WITH COLD ALLODYnia FOLLOWING COLD INJURY
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Aims. We evaluated the psychophysical and axon-reflex-flare effects of TRPM8 and TRPA1 activation in patients with cold allodynia in comparison to healthy subjects.

Methods. The patients had no signs of neuropathy except cold allodynia, which resulted from severe cold injury. We applied 20% cinnamaldehyde and 40% menthol solutions in the cold-allodynic area of the patients and in a comparable area in healthy subjects and obtained sensory ratings during application. Thermo-testing and laser-doppler-imaging was performed before and after exposure to the compounds.

Results. After menthol application the cold pain threshold was increased in healthy subjects resulting in cold allodynia. In patients there was no significant increase in cold pain threshold. In some patients even a decrease in cold pain threshold was observed. Menthol application caused not more pain sensation in patients than in healthy subjects. Menthol produced neither in subjects nor in patients an axon-reflex-flare in contrast to cinnamaldehyde, which produced in 9 of 10 patients an axon-reflex-flare. There was no difference in the ratings or changes in temperature thresholds after/during cinnamaldehyde application between subjects and patients.

Conclusions. In our special patient group:

- Pathological expression of TRPM8 on silent C nociceptors is unlikely.
- TRPM8 activation through Menthol or coldness evokes different effects (cold allodynia versus similar pain ratings to Menthol), so that it is unlikely that the cold allodynia is purely transmitted through TRPM8 abnormality.
- TRPA1 activation through Cinnamaldehyde has similar effects compared to healthy subjects, so that TRPA1 pathology is unlikely to be the predominant cause for the cold allodynia.

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LOW BACK PAIN AND NEUROPATHIC PAIN IN IRANIAN NURSES
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Over 80% of adults experience low back pain some times their life; low back pain is leading cause of neuropathic pain and disability among health worker, particularly nurses.

This study was planned to evaluate the risk factors of low back pain in nurses.

A descriptive–analytic study was carried out including 42 nurses (21, case and 21, control) who worked on orthopedic wards of general hospitals at Tehran.

Data were collected by a questionnaire.

The results showed that correlation exists among low back pain and neuropathic pain and age, obesity, bad posture and no exercise.

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460 COMPARISON OF EVOLED POTENTIALS IN RESPONSE TO PAINFUL STIMULATIONS DELIVERED BY YAP OR CO2 LASER

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We compared the morphology, latency, amplitude, scalp topography and intracranial generators of laser evoked potentials (LEPs) obtained in response to a CO2 (wavelength 10.6 μm) and a Nd:YAP (wavelength 1.34 μm) laser stimulators. 32-channel LEPs and reaction times were recorded in 11 healthy subjects (6 males and 5 females, mean age 39 ± 10 years). Laser stimuli were delivered on the dorsum of the right and left hands (intensity slightly above pain threshold, matched for each individual). For both the CO2 and YAP lasers stimulations we obtained classical N1/P1, N2 and P2 LEP components with similar topographic distribution. As compared with the responses obtained by the CO2, responses evoked by the Nd:YAP had significantly earlier latencies (30 ms) and were more synchronised, yielding higher N2 amplitudes that those obtained with a CO2 laser (−14 μV vs. −6 μV). For both YAP and CO2 lasers, source localization analyses showed a similar distribution of intracranial generators. The early N1/P1 component was dominated by an insular activity more pronounced for the YAP laser. The late N2–P2 component was dominated by a singular activity. In conclusion, both CO2 and YAP lasers stimulations induced similar and very reproducible LEPs, obeying to the same generators. However, the fact that YAP responses are quicker and its N2 larger in amplitude suggests a more efficient recruitment of nociceptive fibers by this type of laser beam. This study permitted to collect normative data of LEPs obtained by both CO2 and YAP lasers, which should be useful in clinical and/or experimental research.

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461 HOMOTOPIC STIMULATION CAN REDUCE THE AREA OF ALLODYNIA IN PATIENTS WITH NEUROPATHIC PAIN

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Allodynia is a common, troublesome feature of neuropathic pain. The region of allodynia is often stable over time and its area has been used as a measure of sensitisation. In our previous study of postherpetic neuralgia we observed reduced areas of allodynia in some patients after tactile stimulation. After obtaining hospital ethical approval we have further characterised this phenomenon in patients with mixed neuropathic pains and allodynia (n = 17). We assessed the area using punctate and dynamic touch stimuli, and thermal quantitative sensory testing (Medoc TSA-II). On separate occasions, repeated (10 cycles over 1 min) noxious heat (first session) or cotton bud strokes (second session) were applied bilaterally.

Tactile stimulation of the affected area caused pain and a reduction in the area of allodynia (>30%) in 8/15 patients (−48 ± 9% maximum). This effect persisted for >1 h and was present the following day in all patients tested (n = 5). No patient showed an increase in area following allodynic stimulation. Two of these subjects also showed reduced areas after contra-lateral (non-painful) tactile stimulation. There was no change in heat pain threshold at a distant site, suggesting DNIC was not activated. Repeated thermal noxious stimulation (either ipsi- or contra-lateral) also elicited changes (>30%) in the area of allodynia in some patients (reductions in 7/17 and increases in 3/17).

We have identified a homotopic (possibly segmental) mechanism which acts to diminish allodynia in patients...
with neuropathic pains. This has implications for the conduct and interpretation of future studies, and for understanding mechanisms of endogenous pain modulation.

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TOPICAL MENTHOL: STABILITY OF A SENSORY PROFILE IN A HUMAN SURROGATE MODEL

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Background and aims. Human experimental pain models play an important role to study mechanisms of pain and efficacy of analgesic compounds. Prerequisite therefore is the stability of human surrogate models. Thus, aim of this study was to explore stability of the menthol surrogate model.

Methods. In 12 male healthy right-handed volunteers 13 QST parameters according to the DFNS-(GNNP)-protocol were assessed at the dorsum of the right-hand: mechanical-detection-, (MDT), vibration-detection-, cold-detection-, cold-pain-, (CPT), warm-detection-, heat-pain- (HPT), thermal-sensory-limen, paradoxical-heat-sensations, mechanical-pain-, (MPT), pressure-pain-threshold and wind-up (all within the application-area), mechanical-pain-sensitivity (MPS) for pin-prick stimuli and dynamic-mechanical-allodynia (both 1 cm apart application-area). After topical menthol application (400 mg/20 min) QST parameters were assessed immediately and every 45 min thereafter up to 225 min. Differences of Z-score-transformed data were analysed using Wilcoxon-test (p < 0.05: significant).

Results. The application of menthol induced a highly significant decrease of the CPT (mean 6.93 ± 6.5 °C/20.23 ± 6.8 °C) and HPT (mean 45.5 ± 2.1 °C/44.1 ± 1.5 °C) compared to baseline up to 180 min (all time points p < 0.01) displaying cold- and heat-hyperalgesia. At 225 min CPT fell off statistical significance (9.5 °C ± 7.9 C, p < 0.07) whereas HPT remained to be significantly decreased (p = 0.002). The MPT was reduced significantly (p < 0.001) whereas the MPS increased significantly (p < 0.001), both indicating pin-prick-hyperalgesia. All other parameters were not altered significantly.

Conclusions The menthol surrogate model induces long-lasting pin-prick-, and cold- hyperalgesia. CPT increased (i.e. reversal of cold-hyperalgesia) on average by 1.5 °C within 45 min whereas HPT and MPT/MPS remained stable. Thus, if studying cold allodynia in the menthol surrogate model, time-dependent changes in the CPT should be taken into account.

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S100 BETA IN PAIN


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The S100 beta, expressed by astrocytes and swann cells, plays a trophic role to neurites and it is a marker of cranial injury. It shows a raising of its serum levels (normal range 0.02–0.15 mcg/l) in patients (pt) with paraesthetic notalgia, sciatic neuritis by herniated disk, and in rats after sciatic nerve ligation. The aim of this study is to evaluate serum levels of S100 beta in neuropathic pain (NP) and acute pain (AP) models.

We recruited:

Fifteen patients with peripheral NP (9 diabetic neuropathy, 2 GuillainBarre`, 4 vasculitic neuropathy, 29–56-years-old [yr], 9M and 6F) (GrNPp);

Nine patients with central NP (post-herpetic neuropathy lasted >3 yr, 57–72 yr, 2M and 7F) (GrNPc);

Thirteen patients with postoperative AP (36–67 yr, 6M and 7F) (GrAP);

Fifteen healthy volunteers (27–54 yr, 8M and 7F) as controls (GrC).


The statistical comparison among the considered Gr values (average ± SD) was made using Student’s T distribution (p < 0.01);

GrNPp: mean value (MV) mcg/l 1.285 ± 0.628 (r: 0.413–2.01)*;

GrNPc: MV 0.064 ± 0.035(r: 0.02–0.09);

GrAP: MV 3.944 ± 2.297(r: 1.43–6.9)*;

GrC: MV 0.135 ± 0.03(r: 0.02–0.14);

*p < 0.01.

The S100 beta seems to be correlated with a peripheral nervous lesion and its raising could be used to confirm the presence of this injury even in peripheral NP, whereas the absence of significance in central NP makes less understandable its role in pain disorders.
References


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NEUROPATHIC PAIN IS COMMON, DISABLING, AND GREATLY IMPAIRS QUALITY OF LIFE AND EARNING POTENTIAL IN CANADIANS: A POPULATION-BASED SURVEY
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Background. Previous attempts to quantify neuropathic pain (NeP) have not been population based. A greater understanding of the extent of the NeP population and its needs is necessary to determine health care allocations.

Methods. A population study telephone survey laboratory at the University of Alberta contacted 1207 subjects aged 18 years and over. Relevant epidemiological data were acquired along with determination of the presence of pain and its duration in each subject. In subjects with pain, the history portion of the DN4 questionnaire was administered to derive an estimate of the prevalence of features of NeP and non-NeP, and quality of life (QoL) (EQ-5D) measurements were also acquired.

Results. Chronic pain of ≥6 months duration was present in 390 subjects (32%). A score of ≥3 on the history portion of the DN4 questionnaire, suggesting features of NeP, was recorded in 208 (53%) subjects. Subjects with features of NeP (sNeP) were more likely to be female (62%), under 60 years of age (77%) and were more likely to be unemployed. Despite similar education levels, sNeP had lower incomes, as well as lower QoL, particularly in the realms of mobility, pain/discomfort, and anxiety/depression. Younger subjects with NeP had the greatest decline in QoL scores.

Conclusion. It is possible that NeP is considerably more prevalent in the general population than previously estimated. NeP is most common amongst subjects in their income earning years and lowers QoL. Clearly, new strategies are required for the management of the large population of sNeP.

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PATHOPHYSIOLOGY OF NEUROPATHIC PAIN IN CARPAL TUNNEL SYNDROME: A CLINICAL AND NEUROPHYSIOLOGICAL STUDY – PRELIMINARY RESULTS
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Neuropathic pain is a frequent symptom of carpal tunnel syndrome (CTS). We aimed at seeking information on the pathophysiology of neuropathic pain in CTS.

We enrolled 19 patients with a clinical diagnosis of CTS (34 hands, 15 patients had bilateral CTS). The DN4 questionnaire for neuropathic pain was administered to all patients, for each hand separately. When the DN4 score was >4, the neuropathic pain scale inventory (NPSI) was administrated. All patients underwent the recording of standard nerve conduction study (NCS), cutaneous silent period (CSP) after stimulation of the II and V digit, and laser evoked potentials (LEPs) after stimulation of the median nerve territory.

Seventeen CTS hands had neuropathic pain (DN4 score >4). II digit-CSP was shorter and LEP amplitude smaller in CTS hands with neuropathic pain than in CTS hands without neuropathic pain. (

P = 0.03), NCS data did not differ between these two groups (P > 0.2). Up to now correlations between NPSI score and neurophysiological data failed to reach statistical significance (P > 0.05).

Our data suggest that neuropathic pain in CTS may be related to a selective damage of the small myelinated afferents. A larger sample of patients is needed to achieve further information on the correlations between NPSI score and neurophysiological data.

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A RANDOMIZED SHAM-CONTROLLED TRIAL OF MIRROR THERAPY FOR LOWER LIMB PHANTOM PAIN DEMONSTRATES EFFICACY OF MIRROR THERAPY
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Background/aims. Mirror therapy reduces phantom limb pain (PLP) in upper limb amputees, but has not been examined in lower limb amputees. Since the critical ingredient of mirror therapy might be the induction of limb imagery, we conducted a sham-controlled trial of mirror versus imagery therapy for lower limb amputees with PLP.

Methods. Fourteen (14) subjects with a unilateral lower limb amputation and daily PLP were randomly assigned to three treatment groups: mirror (M), n = 6; covered mirror (CM), n = 4; mental visualization (MV), n = 4. Subjects in the M and CM groups were asked to move their intact foot while simultaneously imagining moving their amputated foot for 15 min daily for 1 month. Subjects in the MV group were asked to imagine moving their amputated foot only. Each day, all subjects reported their PLP level using a 10 cm visual analogue scale (VAS) as well as the number of and duration of episodes.

Results. Baseline median VAS pain scores were similar in all groups: M, 3.1 cm (range: 1.5–9.3); CM, 3.8 cm (1.8–7.0); MV, 2.7 cm (2.2–6.3) (p = 0.63). After 1 month of therapy the M group had a median VAS pain score of 0.5 cm (0–3.9), while CM was 3.5 cm (1.9–6.9), and MV was 5.8 cm (5.0–6.0) (p = 0.006). The number and duration of PLP episodes decreased in 100% of M-treated subjects and 50% of MV-treated subjects. Of the CM-treated subjects, 25% had reduced pain while 75% had increased pain.

Conclusions. Mirror therapy, compared to covered mirror or mental visualization therapies, is highly effective for treating lower limb PLP.

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467 PERSISTENT PAIN AFTER CARDIAC SURGERY: A NEUROPATHIC PROBLEM?
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Aim. In previous work, the majority of coronary artery bypass graft (CABG) patients reported considerable pain at hospital discharge. Therefore, this study examined pain, related interference, and analgesic use of patients at home in the first 3 weeks following CABG surgery.

Method. As part of a larger RCT (N = 406), 312 patients (42 women) were followed at home after discharge. Patients received 3 weekly telephone calls to determine pain (MPQ-SF), related interference (BPI-I), and analgesic intake.

Results. For the 69% of patients with moderate to severe pain intensity at discharge (≥4/10), 48% reported ≥4 pain at week 1, 35% week 2, and 20% week 3. The consistent worst pain site was the sternotomy/chest site (65%, 52%, and 43%). Pain descriptors (MPQ-SF) rated as moderate-severe for over 10% of patients included shooting, stabbing, hot/burning and tender. Pain-related interference was particularly problematic in all 3 weeks for 20–25% and analgesics were used minimally. Using repeated measures for the total group, no differences were found in any outcome measure by intervention group, sex, or age. However, women discharged home with moderate-severe pain had significantly more pain-related interference in activities than did men [F = 5.47 (2, 113), p > 0.01].

Conclusions. About 20% of CABG patients continued to report moderate-severe pain at 3 weeks after discharge using neuropathic pain descriptors. Whether this persistent pain post-sternotomy is neuropathic needs further examination. Our current research aims to determine the risk factors in the transition from acute to a persistent pain after cardiac surgery over a 2-year period.

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468 CORRELATIONS BETWEEN CLINICAL NEUROPATHIC PAIN RESPONSES AND EXPERIMENTAL PAIN MEASURES IN POSTAMPUTATION PAIN
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Background/aims. There is wide interindividual variability in analgesic responses. Improved predictability of clinical pain responses would increase the efficacy and tolerability of analgesic treatment. This study investigated the usefulness of experimental pain measures in predicting clinical neuropathic pain responses.

Methods. Fifty-two post-traumatic, analgesic-naïve amputees with phantom limb pain (PLP) received oral placebo or combined tramadol 37.5 mg/paracetamol 325 mg thrice daily in double-blind, randomised fashion for 4 weeks. PLP intensity was recorded twice daily
(VAS 0-100). Electrical sensory testing (pain threshold and suprathreshold stimulation: 2× pain threshold for 10 s) was performed on the stump and contralaterally before and after treatment. Experimental and clinical pain data were correlated in all patients.

Results. Overall mean (95% CI) pre- and post-treatment PLP intensity was 53 (48–57) and 4 (1–7) (p < 0.000001). Respective suprathreshold stimulation pain ratings on the stump were 49 (44–55) and 21 (17–25) (p < 0.000001). Correlations on stump: Suprathreshold stimulation pain pre-treatment: vs. PLP pre-treatment: \(R = 0.51, p = 0.01\); vs. PLP post-treatment: \(R = 0.60, p = 0.005\); vs. change in PLP pre–post-treatment: \(R = 0.39, p = 0.007\). Suprathreshold stimulation pain post-treatment: vs. PLP post-treatment: \(R = 0.82, p = 0.000008\). Change in suprathreshold stimulation pain pre–post-treatment: vs. change in PLP pre–post-treatment: \(R = 0.48, p = 0.03\). Similar correlations existed on the contralateral limb.

Conclusion. Suprathreshold electrical stimulation correlated significantly with clinical pain and analgesic responses irrespective of treatment in patients with post-amputation pain. The clinical usefulness of the experimental pain measures in the prediction of chronic pain and of analgesic responses needs to be validated in larger patient cohorts.

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CONTACT HEAT EVOKED POTENTIALS AND SPINOthalamic TRACT CONDUCTION VELOCITY DETERMINATION

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Peripheral application of short contact heat stimuli at sufficiently high temperatures to the skin activates Aδ-fibres within the spinothalamic tract (STT) and elicits a painful pinprick-like (PP) sensation. The temporal arrival of this nociceptive signal can be measured in terms of scalp evoked potentials, thereby enabling the calculation of the STT conduction velocity. This is clinically relevant as damage to the STT, resulting in reduced conduction velocity, is crucially involved in the development of neuropathic pain after spinal cord injury.

In order to obtain normative values healthy subjects were stimulated at three levels at the back, and at the ankle. The nominal stimulation temperature was set 3 °C higher than the previously obtained PP threshold. Pain-evoked potentials were recorded using a 32 channel EEG system. The P2 vertex positivity was used for calculations of latencies (corrected for different PP thresholds) and conduction velocity.

P2 latencies after ankle stimulation correlated significantly with the height of the subjects. The individual conduction velocity of the fibres mediating P2 was calculated using the three latencies obtained from back stimulation and the respective distances to the brain; it equalled 15 m/s, well in the range of Aδ-fibre velocity commonly published in the literature.

The study shows that contact heat evoked potentials are suitable to estimate conduction velocities of the STT in healthy volunteers. This is a precondition for future clinical applications that aim at assessing the damage to the STT after a spinal cord injury.

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