# NEUROPATHIC PAIN

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NEWSLETTER of the IASP Special Interest Group on Neuropathic Pain

NeuP SIG

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## How can NeuPSIG advance research on neuropathic pain?

In past issues of this newsletter, I have shared with the members of NeuPSIG a number of proposals and issues that the management committee has been discussing. One very important goal that NeuPSIG has set for itself involves advancing research on neuropathic pain. Speciýcally, our Constitution and Bylaws include the following aims and objectives that are relevant to research: (1) collaboration for basic and clinical research; (2) the study of the underlying mechanisms of neuropathic pain; and (3) the identiýcation and implementation of programs to prevent the development of neuropathic pain.

One way in which NeuPSIG has addressed these research objectives has been by sponsoring or co-sponsoring quite a few conferences in various locations around the world. It is likely that these meetings have stimulated participants to think of new research questions and methods, and that they have also provided opportunities to initiate research collaborations. This approach to advancing research is somewhat indirect, however, and the NeuPSIG management committee has been considering more direct methods for advancing "the understanding of mechanisms, assessment, prevention, and treatment of neuropathic pain" (NeuPSIG's mission).

In preliminary discussions, several possibilities have been considered. These include sponsorship for (1) pilot clinical trials involving a small number of sites that would provide a basis for designing larger international efforts that would be funded by government, private foundations, or industry; (2) meetings to advance important research areas, for example, by developing recommendations for "identifying novel treatments using animal models of neuropathic pain," "optimizing research designs for proof-of-concept studies of neuropathic pain treatments in normal volunteers and in patients;" and "identifying pain mechanisms in patients with neuropathic pain;" (3) research grants for junior investigators; and (4) research grants for highly innovative projects that are unlikely to succeed in obtaining funding from traditional sources.

This list of possible research initiatives was generated from discussions by the management committee, and we would very much like to hear your thoughts about whether these are worthwhile initiatives for NeuPSIG to undertake. Of course, these are only a few examples of how NeuPSIG could advance research on neuropathic pain, and we would also very much value your input and ideas for additional activities that should be considered by the management committee to accomplish this very important objective.

Bob Dworkin
Chair

### NeuPSIG Management committee met in Guatemala

The NeuPSIG management committee met in Guatemala City on Dec 6-7, 2006. The committee discussed future meetings including a possible meeting in Asia in 2009 in conjunction with a local regional pain meeting and also a 3rd International Congress on Neuropathic Pain in 2010. The committee talked about the impact on NeuPSIG's meetings of the recent IASP decision to hold the world congress every two years. Reports from the various NeuPSIG subcommittees were also discussed and some of the main points are summarized below. The next management committee meeting will take place in Berlin in June 2007 prior to the 2nd International Neuropathic Pain congress.

**The 2nd International Neuropathic Pain Congress will take place in Berlin June 7-10, 2007.**

The congress will take place at the InterContinental Berlin which is located in the heart of Berlin (please see conference website *http://www.kenes.com/neuropathic/* for further details).

The Main topics of the meeting are:

- Postherpetic neuralgia
- Diabetic neuropathy
- Complex regional pain syndromes
- Central pain syndromes
- Animal models in neuropathic pain
- Mechanism-based classiýcation and therapy
- Clinical assessment in neuropathic pain
- Quantitative sensory testing in neuropathic pain
- Genetics of neuropathic pain
- Design of clinical trials in neuropathic pain
- Novel molecular drug targets in neuropathic pain

Greatly reduced and subsidized registration fees will be available to trainees and a limited number of travel grants for trainees presenting posters and for physicians from developing countries will be awarded. Please note that the deadline for submission of Travel Grant application forms is Friday, April 13, 2007 (see NeuPSIG website for further details and forms)

## The U Rochester/NeuPSIG annual International Conference on the Mechanisms and Treatment of Neuropathic Pain

Last year's meeting took place in Bermuda at the beginning of November. This year's meeting will take place at **Snowbird Mountain Conference Center**, Salt Lake City, Utah, November 1 - 3, 2007. Further details and registration at: http://www.neuropathicpain.org/

## NeuPSIG Satellite meeting in London in 2008

The SIG organized satellite meeting to the 12th IASP World Congress on Pain "Recent Developments in Neuropathic Pain" has now been approved by IASP and will take place at the Royal Society of Medicine in London August 13th - 15th 2008 immediately preceding the congress. The Scientiýc Program Committee under the chair of Andrew Rice has planned an exciting meeting including plenary sessions and posters covering basic neuroscience and clinical topics. See www.kenes.com/neuropathic2008/ for list of invited speakers.

## The 3rd International Neuropathic Pain Congress.

The NeuPSIG management committee decided to go ahead with plans for a 3rd congress which will take place in Europe in May or June, 2010.

For summary of upcoming NeuPSIG meetings see box below.

**Job Ads:** If you would like to advertise any jobs related to neuropathic pain in the NeuPSIG Newsletter and website please send details electronically to the Secretary, Jonathan Dostrovsky.

## Subcommittees updates:

### Classiýcation and taxonomy

This committee, chaired by Rolf-Detlef Treede has now completed a manuscript ñRedeýnition of neuropathic pain and a grading system for clinical use," which has recently been submitted for publication. The recommendations of this manuscript will be submitted to the IASP task force on taxonomy.

Comments and discussion regarding these recommendations will be posted on the NeuPSIG website. Please email your comments to the NeuPSIG secretary (j.dostrovsky@utoronto.ca).

### Assessment

Maija Haanpaa, the committee chair, reported that the committee met recently in Istanbul and a manuscript is almost ready for submission. The committee plans to hold an additional two day meeting within the next few months.

### Treatment

This committee which is chaired by Bob Dworkin reported that the ýrst NeupSIG sponsored guidelines have been published (Recommendations for the management of herpes zoster, Clin Infect Dis 44, supp 1, S1-S26, 2007). Plans are to have this article available on the NeuPSIG website.

The committee has also prepared a manuscript on guidelines for the pharmacologic management of neuropathic pain which has recently been submitted for publication. The committee is now working on developing guidelines for interventional treatments for neuropathic pain based on a successful workshop on this topic that was held as part of the recent University of Rochester/NeuPSIG meeting in Bermuda. The committee plans to meet in Snowbird Utah in November immediately after the next International Conference on the Mechanisms and Treatment of Neuropathic Pain. A future project of the committee is to produce guidelines for non-pharmacological and complementary therapies for the treatment of neuropathic pain (e.g., TENS, psychological treatment, acupuncture, physical therapy and rehabilitation).

### Research committee

Gary Strichartz, chair of this committee, reported on some possible activities for the committee. It was decided to look into the feasibility of holding a meeting on animal and human surrogate models of neuropathic pain. The committee was also considering developing a database on neuropathic pain treatment trials and performing a survey on the efýcacy of lidocaine in the treating various types of neuropathic pain.

## Topical Reviews

This issue of the NeuPSIG newsletter includes a review by Dr. Chris Wells on the use of opioids in the treatment of neuropathic pain, which is based on his recent lecture at the NeuPSIG Neuropathic Pain Symposium in Guatemala City. Other submissions are welcome.

**Upcoming SIG sponsored or co-sponsored meetings**:

Second International Congress on Neuropathic Pain, Intercontinental Hotel, Berlin, Germany, June 7-10, 2007. www.kenes.com/neuropathic/

10th International Conference on the Mechanisms and Treatment of Neuropathic Pain will take place at Snowbird, Utah November 2-4 2007. www.neuropathicpain.org/

Satellite meeting to the 12th IASP World Congress on Pain "Recent Developments in Neuropathic Pain" will take place in London August 13th - 15th 2008 immediately preceding the congress.

11th International Conference on the Mechanisms and Treatment of Neuropathic Pain will take place in early November 2008.

The management committee has also started initial planning for a possible meeting in Asia in 2009.

Third International Congress on Neuropathic Pain, May or June 2010, in Europe (location to be ýnalized soon).



**Current SIG information**

As of March 3, 2007, the NeuP SIG has 820 members in 58 countries representing 36 specialties.

# TOPICAL REVIEW

## Opioids for Neuropathic Pain

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As neuropathic pain became recognised as an entity, several authorities suggested that opioids were not useful for its management (Bowsher, Arner). One of the reasons for this was its unsuitability for some acute, intermittent, episodic pains such as trigeminal neuralgia, and it was also felt that burning pain was better treated with drugs such as Amitriptyline than with opioids. Arner's paper was often quoted as showing that neuropathic pain was not treatable with opioids, but this looked at just 12 patients with neuropathic pain who had not responded to any treatment, and 4 were actually still on opioids when they entered the trial. Intravenous opioids were used, but mainly Buprenorphine, with negative beneýt. Arner himself never meant this to be a reason not to consider investigating the use of all opioids for different types of neuropathic pain.

However, Max in 1988 and then authors such as Kalso, Rowbotham and Jadad over the next 5 years showed that opioids could and did work for neuropathic pain. In the last 5 years, there have been 100 papers or more regarding efýcacy of opioids for neuropathic pain, most of which were more-or-less positive with a few dissenting voices (Raja, Rowbotham, Watson, Gimbel, Morley, Boreau and Gilron). And yet, Eisenberg in the Journal of the American Medical Association, and later, in a Cochrane review, argues that the use of opioids is controversial and describes mixed results in short-term usage, whilst accepting intermediate studies demonstrating signiýcant efýcacy of opioids over placebo, which is likely to be clinically important. He does, however, insist that further randomized controlled trials (RCTs) are needed to establish their long-term efýcacy, safety and effects on quality of life.

***LESSONS FROM RECENT PAPERS***

Raja (2002) looked at 76 patients with post-herpetic neuralgia in a RCT crossover trial. There were 3 groups—opioids versus tricyclics versus placebo—with titration to relief or unacceptable side-effects. Average dosaging at titration was 91 mg of morphine per day, 15 mg of Methadone per day, 89 mg of Nortriptyline per day and 63 mg of Desipramine per day. All reduced pain, with no appreciable effect on cognitive function, and the reduction was said to be 20 to 30 per cent. Fifty four per cent preferred the opioid, with 30 per cent preferring the tricyclics. Adverse events occurred in both groups, with constipation, nausea and drowsiness greater in the opioid group than in the other groups.

Rowbotham (2003) reported on 2 doses of Levorphanol in central and peripheral neuropathic pain. The low dose showed a 21 per cent reduction in pain, the high dose a 36 per cent reduction. There was some improvement in function and sleep, not reaching statistical signiýcance. Better results were obtained in peripheral than in central neuropathy.

Watson (2003) looked at 36 patients with diabetic neuropathy in a RCT. An active placebo of Benztropine was used, versus up to 80 mg of Oxycontin. This produced a 50 per cent better reduction of pain than the placebo and disability was lessened in the active group. There was also beneýt in the SF36 and in sleep, and adverse events were similar. However, 7 withdrew in the Oxycontin group and only one in the placebo group. Main side-effects were nausea, constipation and sweating, with both groups reporting sleepiness in 50 per cent of patients.

Gimbel (2003) also reported on diabetic neuropathy, from a RCT of 59 patients. Titration took place up to 120 mg of controlled-release Oxycodone, with an average of 37 mg. Pain reduction was 40 per cent, which was statistically superior to a placebo response of 20 per cent. There was an improvement in sleep, but minimal effect on disability. Ninety six per cent of the Oxycodone group reported adverse events, versus 68 per cent of the placebo group. Main adverse events were 42 per cent with constipation, 40 per cent with somnolence, 36 per cent with nausea, 32 per cent with drowsiness and 24 per cent with pruritis.

Gilron (2003) looked at 154 patients with diabetic neuropathy, 41 per cent opioid-naive. Ten per cent received opioids by the clock, but 25 per cent received opioids prn. He reported that barriers included both physicians, patient fear of addiction, adverse events and administrative.

Morley et al (2003) described the treatment of 18 patients with neuropathic pain with Methadone versus placebo, and found that 20 mg of Methadone daily gave a signiýcant reduction of pain, however, with adverse events including nausea, vomiting, dizziness and headache. Seven of the patients withdrew because of adverse events.

Boreau (2003) reported on 127 patients with post-herpetic neuralgia. Tramadol was given, up to 400 mg per day, with a signiýcant reduction of pain versus placebo, but only a 9 per cent reduction on average. Adverse events were infrequent but included nausea and constipation.

### *REVIEWS*

Several papers over the last 6 years have reviewed the results of treatment of neuropathic pain, and produced league tables of useful drugs (eg, Argoff 2004).

Sindrup and Jensen (2000) reported NNTs for tricyclics of 2.6, Carbamazepine of 2.5, Gabapentin of 4.1, Tramadol of 3.4 and SSRIs of 6.7. Capsaicin came in at 5.9 and Mexiletine is 38! At that time, opioids were not mentioned.

Hemptonstall et al (2004) reported the following NNTs for post-herpetic neuralgia: tricyclics 2.64, opioids 2.67, Pregabalin 3.42, Gabapentin 4.39, Tramadol 4.76 and Capsaicin 3.26; Lidoderm patch 2.0. They recommended tricyclics and anticonvulsants as ýrst line treatments, with opioids as second line.

Dworkin et al (2003) stated that there was good evidence for opioid efýcacy, and recommended Oxycodone, up to 120 mg per day, morphine up to 240 mg per day, with 300 mg in phantom pain. They reported that there was a decrease in disability and improvement in sleep. Adverse events included constipation, sedation and nausea, with cognitive impairment and decreased mobility reported in the elderly. They felt that tolerance might occur, but dependence was probably low.

Dworkin, however, reported that "we hold diverse opinions regarding the algorithm for administering opioids". Nevertheless, in general, the authors recommended short-acting morphine in a dose of 5 to 15 mg, given 4-hourly or equivalent, to titrate the required dosage, once steady state had been reached conversion could be made to long-acting opioids such as controlled-release morphine or Oxycontin, transdermal Fentanyl, Levorphanol or Methadone Hydrochloride.

Finnerup et al in Pain 2005 recommended Lidoderm patches for allodynia, with Gabapentin and tricyclics for this and other pain as ýrst line drugs, with opioids and Tramadol only used after these had been tried, either singly or in combination.

Breivik in 2005 pointed out that there were no long-term double-blind RCTs, whilst accepting that these might be difýcult. He commented on the Denmark experience, where there has been liberal use of opioids for more than 15 years. Erikkson in 2003, in Pain in Europe, described Pain Clinics seeing patients with opioid abuse problems and stated that three-quarters of patients referred to Pain Clinics were already on an opioid from their family practitioner, with an average dose of 70 mg of morphine per day. Erikkson estimated that 40 per cent of these were problem users and that up to 19 per cent of chronic pain patients were suffering from an addictive disorder.

Watson, in 2004, described long-term experience of 102 patients with chronic, non-cancer pain, having been on medication for more than a year with a median of 8 years. Forty four per cent were satisýed with pain relief, despite side-effects, and 54 per cent were less disabled. Thirty four per cent had intolerable side-effects, and overall the reduction in pain was modest. He did report using opioids in a few patients with dependency, with successful results due to very careful management.

### *COMBINATIONS OF OPIOIDS AND ANTI-CONVULSANTS*

Gilron's trial in 2005 was a RCT on 57 patients with post-herpetic neuralgia or diabetic neuropathy. There were 4 groups, one placebo group, one on Gabapentin, one on morphine and one on a combination of morphine and Gabapentin. There was a titration to tolerance, with a maximum dose of 120 mg of morphine and 3200 mg of Gabapentin. Mean dosages of the morphine group were 45 mg, the Gabapentin group 2207 mg and in the combined group 34 mg morphine and 1705 mg of Gabapentin.

The best results were obtained in the combined group, with 45 per cent, compared with 35 per cent relief in the morphine group and 30 per cent from the Gabapentin group. Pain relief, mood, sleep and activity were all assessed, and results were better than with placebo.

A trial by Peramo (2003), an open trial on 60 patients with neuropathic pain, showed a better result in a Gabapentin and Fentanyl group over 72 hours than Gabapentin alone. There was similar nausea and vomiting, and constipation, in both groups, but a greater problem with pruritis in the Fentanyl group.

### *SIDE-EFFECTS*

Whilst opioids have good efýcacy, there is no doubt that signiýcant side-effects occur. The most common are constipation, nausea, drowsiness, dizziness, pruritis, with some patients reporting vomiting, headache, dry mouth and sweating. Respiratory depression, always cited as a potential risk, has never really been noted in clinical practice in patients who have pain, with the use of sensible dosaging.

Physical addiction is physiological and manageable. Psychological dependence, a behavioural pattern of drug abuse where medication is taken for psychic and mental effects, is always a fear. However, it is clear that most patients exposed to opioids do not become drug abusers.

McQuay wrote (BMJ 2001) that "opioids are our most powerful analgesics, but politics, prejudice and our continuing ignorance still impede optimum prescribing. What happens when opioids are given to someone in pain is different to what happens when they are given to someone not in pain. The medical use of opioids does not create drug addicts, and restrictions on its use hurts patients".

***COST***

Different opioids cost different amounts in different countries. Methadone is usually inexpensive, whilst slow-release Oxycontin and Fentanyl can be four times the price and therapeutic dosages can mean a cost of $3,000 to $4,000 a year per patient.

Tramadol. This drug, with a complex action including opioid receptor afýnity, is also a potent inhibitor of serotonin re-uptake and blocks noradrenaline uptake. There is signiýcant trial evidence for its usage in neuropathic pain and the generic formulation is inexpensive. Comparison should take place with pure opioids to assess its place.

***WHAT CONDITIONS MIGHT RESPOND TO OPIOIDS?***

In intermittent shooting pain, such as trigeminal neuralgia, there is no evidence of them being useful. In brachial avulsion injuries, only a paper on Tramadol by Waikukul has shown beneýt. In central pain syndromes, such as central post-stroke pain and even phantom limb pain, trials are limited with small numbers of patients, and generally a small response. However, post-herpetic neuralgia and diabetic neuropathy, as well as polyneuropathy, have been studied in ever-increasing numbers with good beneýt.

Results in patients with allodynia in experimental trials show mixed results, but intravenous titrations have been useful and there are certainly sub-groups with allodynia who do respond. Lidoderm patches are clearly the ýrst line treatment in allodynia.

***SUMMARY***

Opioids work, especially in post-herpetic neuralgia and diabetic neuropathy. Expect a 30 per cent reduction in pain only, less with Tramadol. Signiýcant adverse events can be a major problem and often lead to patients discontinuing medication in spite of pain relief. Most trial work is short-term or intermediate-term, and it is clear that the majority of patients withdraw from opioid treatment after a year or so, although some have been shown to be on this long-term with beneýt.

There are possibly signiýcant differences between the various drugs, which have slightly different properties. There are also barriers of various types, including physician, patient and administrative. There are potential beneýts and drawbacks to its use in the elderly (Ahmad 2002). There is no evidence that increasing the dose above 200 mg of morphine, or equivalent, per day produces beneýt, and average doses in trials are around 100 mg of morphine daily or its equivalent. If the dose needs to be increased above 200 mg this may well lead to problems.

In the future, we need to examine the reason why some patients do become addicted, which may well be because they did not have true neuropathic (or nociceptive) pain in the ýrst place. We need to consider potential rotation of opioids if tolerance occurs. Side-effects need to be managed aggressively and it appears to be clear that the combination of opioids with anticonvulsants is beneýcial.

We may be able to reduce the total dose of opioid given by the use of Devazepide. Cholecystokynin has been found to affect neuropathic pain and reduce opioid efýcacy. This drug is a cholecystokynin antagonist, and both pre-clinical and pilot studies have suggested an enhancement of opioid beneýt with consequent reduced doses and less toxicity.

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