NEUROPATHIC PAIN

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NEWSLETTER of the IASP Special Interest Group on Neuropathic Pain

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Enhancing patient education and communication

In past issues of this newsletter, I have shared with the members of NeuPSIG a number of proposals that the management committee has discussed. These have included the development of a NeuPSIG speaker's bureau; methods for advancing research on the mechanisms, assessment, prevention, and treatment of neuropathic pain; and efforts to initiate a "distance-mentoring" program for investigators and clinicians around the world who are in training. An issue we have not discussed is the great importance of patient education and efforts to improve communication between patients and clinicians (and researchers). In considering what to say about this topic, and what NeuPSIG and its members could actually do about it, I could think of no better person to turn to than Penney Cowan.

Penney founded the American Chronic Pain Association (ACPA) almost 30 years ago, and has been its Executive Director ever since. After years of living with chronic pain, Penney became involved in a pain management program. She soon found others whose lives were disrupted by prolonged pain, and they began meeting to support each other. This one small group quickly multiplied, and several hundred ACPA support groups now meet across the United States, Canada, the United Kingdom, and many other countries. Unable to be personally involved with every group, Penney developed the first of ACPA's materials for people with pain seeking to improve the quality of their lives and for the professionals who help them.

The key missions of ACPA are to (1) "To facilitate peer support and education for individuals with chronic pain and their families so that these individuals may live more fully in spite of their pain," and (2) "To raise awareness among the health care community, policy makers, and the public at large about issues of living with chronic pain." I asked Penney to share with the members of NeuPSIG what she has learned over the years about the critical roles of patient education and of enhancing communication between patients and clinicians. Her eloquent comments follow.

Bob Dworkin
Chair

A picture is worth a thousand words. A large amount of time during office visits is spent asking patients how they're doing. Unfortunately, people with pain are hungry for validation of their pain and so they tend to go into great detail, hoping that their physician or healthcare provider will understand exactly how much pain they experience and will appreciate the negative impact that it has on their lives. If only we could take the pain out of our body and hold it in our hands, then validation would not be a problem. Yet, without clear understanding of not just their pain, but its effects on quality of life and functioning, it is impossible for clinicians to fully grasp the impact of pain on their patients and difficult to provide treatment.

The lines of communication between physicians and patients are a maze of detours and roadblocks that prevent clear participation from both parties. Given the limited amount of time that can be spent with patients, tools that will enhance and simplify communication to facilitate a more productive and meaningful discussion on both sides are necessary. It is important from the start, especially with neuropathic pain, to make it clear that the patient is part of the treatment team and thus shares responsibility for treatment outcomes. As with many chronic pain conditions, there may always be some level of pain, but that does not mean that the person with pain has to remain a disabled patient.

Contents:

Clearly there is room for much improvement when it comes to communication and education with patients. There are tools available through the American Chronic Pain Association at www.theacpa.org. In addition, we need to ensure that clinicians don't confuse and frustrate patients, but that they implement effective methods for educating patients, for example:

- Make sure that patients have the opportunity to ask questions before they leave the office.
- Provide paper and pens in the waiting room for patients to write their questions in advance of being seen.
- Consider using the following, available on the ACPA website, as communication tools for patients: (1) the Pain Log (www.theacpa.org/documents/8%205x11%20Pain%20Log%202-8-06.pdf); (2) the Quality of Life scale (www.theacpa.org/documents/Quality_of_Life_Scale.pdf); and (3) the Nerve Central Station, developed specifically for neuropathic pain (www.theacpa.org/nerve/hurt.asp).
- Provide easy to understand pamphlets on procedures, treatments, and health conditions to help reduce fear. We fear what we don't understand. It is imperative that written and video information is available to educate patients.
- Make it a priority to use community resources that offer support to patients. There are many disease-specific organizations focused on consumer education; find out about them and tell patients.
- Be daring and offer an evaluation form for patients to comment on their ability to communicate with you, their understanding of treatment options, and their level of fear about the future of their health.

In the end, health care is a partnership involving many people. We all need to be well informed.

Penney Cowan
Executive Director, American Chronic Pain Association

Call for Nominations – NeuPSIG Executive Committee

The current NeuPSIG management committee has proposed the following executive committee for the next 2-3 year term:

Secretary - Andrew Rice
Treasurer - Jonathan Dostrovsky
Vice chair - Maija Haanpaa
(Chair - Rolf-Detlef Treede, the current Vice chair will become chair.)

Additional nominations are encouraged. The management committee will be appointed by the new executive committee.

Nominations for Vice chair, Treasurer and Secretary should be proposed and seconded in written or electronic format by members of IASP and the SIG in good standing. The nomination should be accompanied by the agreement of the candidate to take part in an election and to serve if elected. Nominations should be made to the secretary, Jonathan Dostrovsky (j.dostrovsky@utoronto.ca) by **May 1, 2008.**

NeuPSIG Management Committee

The Executive Committee

Robert Dworkin (Chair, USA)
Rolf-Detlef Treede. (Vice Chair, GERMANY)
Jonathan Dostrovsky (Secretary, CANADA)
Chris Wells. (Treasurer, UK)

Committee Members

Troels Jensen, Council Liaison (Den)
Gary Strichartz (USA)
Andrew Rice (UK)
Maija Haanpaa (FINLAND)
Sara Bistre (MEXICO)
Ralf Baron (GERMANY)
Geoff Gourlay (AUSTRALIA)

Management Committee Meetings:

The management committee met on November 1 2007 at Cliff Lodge, Snowbird Mountain Conference Center, Utah, USA in conjunction with the 10th International Conference on the Mechanisms and Treatment of Neuropathic Pain. The next meeting of the committee will be on May 17 2008 in Athens, Greece, where the committee will also have a site visit in preparation for the Third International Congress on Neuropathic Pain which will be held there May 27 to 30, 2010.

The NeuPSIG management committee at Snowbird. From left to right: Treede, Gourlay, Dostrovsky, Haanpaa, Wells, Baron, Bistre, Dworkin, Rice, Strichartz.

NeuPSIG General Meeting

The triannual general meeting of the SIG will take place in Glasgow on Wednesday, August 20 at 16:30 during the World Congress on Pain. All are welcome to attend.

NeuPSIG Subcommittees Updates:

Classification and taxonomy

This committee, chaired by Rolf-Detlef Treede, is pleased to announce that the manuscript "Redefinition of neuropathic pain and a grading system for clinical use: Consensus statement on clinical and research diagnostic criteria" has now been pub-

lished in Neurology and is available for viewing on the Neurology website. 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). The next task of the committee is to obtain validation of the classification on a series of case reports and to start working on taxonomy.

Assessment

The committee, chaired by Maija Haanpaa, is finalizing a manuscript on the assessment of neuropathic pain by GPs (title 'Assessment of neuropathic pain in primary care'). The committee, in collaboration with the EFNS Neuropathic pain panel, is now working on an update of the previously published EFNS assessment guidelines and the literature search has been completed. A meeting of the committee will take place in a few months.

Treatment

The committee recently met to develop guidelines for interventional treatments for neuropathic pain, and will meet again in 2008 to develop guidelines for non-pharmacologic/non-interventional treatments for neuropathic pain, including TENS, psychological interventions, acupuncture, and physical therapy and rehabilitation.

Research

The committee, chaired by Gary Strichartz, is involved in preparing a 3-day meeting on animal and human surrogate models of neuropathic pain, and in developing an distributing a questionnaire on the efficacy of lidocaine in treating various types of neuropathic pain.

Topical Reviews

This issue of the NeuPSIG newsletter includes a review of cannabinoids for neuropathic pain. Other submissions are welcome.

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.

Topical Review

Cannabinoids for neuropathic pain? – where next?

Andrew SC Rice MB BS MD FRCA, Reader in Pain Research, Imperial College London

Introduction:

In this short review the evidence relating to the efficacy and adverse effects of cannabinoids in neuropathic pain will be discussed.

The recent basic science advances in cannabinoid pharmacology have been reviewed in detail elsewhere[1;2] and will only be briefly summarised as an introduction to the clinical focus of this article. The late 1980s and early 1990s saw a series of major advances in our understanding of cannabinoid pharmacology, which have justified the consequent substantial research activity in this area that is still ongoing: The most important of these advances were the characterisation of two G protein coupled cannabinoid receptors (CB1 & CB2) and the discovery of endogenous ligands at these receptors (endocannabinoids). CB1 receptors are expressed, in general, by neurones of the central and peripheral nervous systems and one of their major functions is to negatively modulate neurotransmitter release at a variety of synapses, by means of a form of retrograde signalling. CB1 receptors are strategically located for analgesia at several points along the sensory axis: in brain[3], spinal cord[4] and primary sensory neuones[4;5]. CB2 receptors are most often expressed by immune cells, both outside and within the central nervous system, and very broadly speaking the effects of agonists at CB2 receptors is towards suppressing immune responses. Thus, both CB1 and CB2 could potentially have analgesic functions. There are multiple reports of cannabinoid analgesia in a range of animal models of pain. Of relevance to neuropathic pain, is the observation that the hypersensitivity of limb withdrawal that is seen in models of traumatic neuropathy is reversed by cannabinoids (see[1;2]). Furthermore, similar effects of cannabinoids have been observed in models of diabetic neuropathy[6], HIV and antiretroviral-induced neuropathy[7;8], cancer chemotherapy-induced neuropathy[9] and varicella zoster associated pain[10]. One factor to consider when comparing the results from trials of cannabinoids in rodent models of neuropathic pain to those from clinical trials in patients is the type of cannabinoid examined: In general, most animal studies employ highly potent synthetic cannabinoid agonists which are either active at both CB1 and CB2 (e.g. Win55,212-2) or which are relatively selective at CB1 (e.g. HU210) or CB2 (e.g. AM1241). This contrasts with the human studies which have in general used either plant extracts (cannabis medical extract – CME) or synthetic analogues of the major psychoactive ingredient of cannabis Sativa - Δ9tetrahydrocannabinol (THC).

Clinical trials for efficacy in neuropathic pain:

The new knowledge about cannabinoid pharmacology emanating from basic science, particularly with regards to analgesia, has naturally prompted a number of clinical trials. Some of these trials have been in the field of neuropathic pain and these have recently been subjected to systematic review[11]: Seven trials (nine reports) of neuropathic pain conditions were included in this review; five of these examined patients with multiple sclerosis, a data set comprising 617 patient episodes for pain, including one particularly large study which followed patients for up to 12 months (pain data on 356 patients to 12 months)[12;13]. All of these reports either compared various CMEs or Δ-9THC to placebo and the majority of studies demonstrated efficacy for pain relief. Two studies reported responder rates for 50% pain relief and similar "numbers need to treat" (NNT) of 3.5 (95% confidence interval 1.9–24.8)[14] and 3.7 (2.2–13.0)[15] were calculated. These NNTs compare favourably to the small number of other therapies which have been evaluated for central pain[16]. Conversely, efficacy was not demonstrated in two trials which examined cannabinoid efficacy in peripheral neuropathic pain (181 patient episodes). One trial which compared two CMEs to placebo in patients with pain associated with brachial plexus avulsion reported an NNT of 46 (15.7- ∞) for one CME and there where no responders for the other preperation[17]. The other trial examined a variety of neuropathic pain conditions and compared CT-3 (ajulemic acid, a synthetic derivative preparation of a THC metabolite) to placebo. The NNT for CT3 was 9.5 (4.11–30.56) for pain with no efficacy demonstrated against the measures of mechanical hypersensitivity which were tested[18;19].

Since this systematic review was conducted further clinical trials of cannabinoids in peripheral neuropathic pain have been reported: One trial randomised 125 patients with allodynia-associated neuropathic pain of peripheral origin to treatment with a CME or placebo in a self-titrated regimen[20]. Like many of the other reported trials of cannabinoids this was an "add on" design with, for example, 63-74% patients continuing to take opioids. The CME tested was more efficacious than placebo for pain relief, but the NNT was 8.5 which does not compare favourably with other efficacious therapies for peripheral neuropathic pan[16;21]. The NNT for 50% reduction of allodynia was 7.5 for dynamic mechanical allodynia and 13.4 for punctate mechanical allodynia. A 52 week open label extension study suggested that this efficacy was maintained over this period.

Another study randomised 55 patients with HIV-associated peripheral neuropathy smoked cannabis or smoked placebo[22]. There was a greater reduction in pain intensity scores in the cannabis group compared to the placebo group. For responder rates the NNT for 50% pain relief were not given and could not be calculated from the published data, but for 30% pain reduction was 3.6, which compares favourably with the limited dataset for other therapies tested for HIV-associated peripheral neuropathy[16]. Nevertheless, the health risks of smoking must be considered when evaluating smoked cannabis as a therapeutic.

Finally, a recently published crossover study compared the efficacy of daily escalated dosing of dihydrocodeine (maximum of 240 mg) to nabilone (2mg), over a 6 week treatment period23. Nabilone is a synthetic cannabinoid structurally closely related to Δ9THC. Ninety-six patients, who suffered from a variety of neuropathic pain conditions characterised by allodynia and sympathetic dysfunction, were randomised. Neither treatment was associated with dramatic evidence of efficacy, the mean change from baseline on a 100 mm pain intensity scale was 9.67mm for nabilone and 11.02mm for dihydrocodeine (i.e. both treatments were associated with a ~10% improvement in baseline pain intensity). In terms of responder rate (defined as a >10mm change on a 100 mm pain intensity scale), only 3 of the 64 patients in the per protocol dataset achieved this response in the nabilone arm compared with 12 patients in the dihydrocodeine arm. Forty-nine patients had no significant analgesic response to either therapy.

Adverse effects in neuropathic pain:

In the above systematic review, we were also able to extract limited evidence relating to adverse effects, which were reported as "number needed to harm" (NNH)[11]. The responder definition of NNHminor was any patient reporting any adverse effect, irrespective of the number of adverse events reported. Where these data could be extracted NNHminor was in a similar range to that for other neuropathic pain therapies[16;21]. Data for NNHmajor (withdrawal from study) were more difficult to interpret and we probably need more data before making statements on this aspect. Dizziness, drowsiness/light-headedness, dry mouth, and gastrointestinal symptoms were the most frequently reported treatment-associated adverse effects. However, there is something of a confound in interpreting the adverse events data in most of these studies since the dosing regimens often permitted self-titration against effects/adverse effects.

Regarding the reports which have appeared since the systematic review: In a trial of CME in peripheral neuropathic pain 91% of patients in the CME group reported at least one adverse effect during the course of the study compared with a, perhaps surprisingly, high figure of 77% patients in the placebo group NNHminor [7.66 (3.89 - 266.22)][20]. Furthermore, 18% of CME treated patients compared to 3% of those treated with placebo withdrew during the study [7.03 NNHmajor (4.07 - 25.74)]. In the smoked cannabis trial in HIV neuropathy, anxiety, sedation, disorientation, confusion and dizziness were more severe in the cannabis group compared to placebo, although no patients withdrew from the study due to adverse effects[22]. Finally, in the nabilone study both dihydrocodeine and nabilone were associated with similar adverse events profiles[23]: 4 patients withdrew from the study due to adverse effects from nabilone compared with 8 from dihydrocodeine. Overall, 334 adverse effects were reported on the nabilone arm and 305 on the dihydrocodeine arm.

Implications of the risk of mental illness with cannabis abuse:

In any discussion of the evidence for clinical effectiveness of cannabinoids in neuropathic pain the issue of the potential long-term risks of therapeutic cannabinoid administration requires serious consideration. One major consideration arises from the cannabis abuse literature and relates to the long term risk of precipitating mental illness, particularly psychosis and schizophrenia. No episodes of acute psychosis were reported in the systematic review of neuropathic pain trials[11], but in a subsequent study[20] one major psychiatric adverse event was recorded in both control (confusion) and CME (emotional stress associated with paranoid thinking) groups. However, the therapeutic trials of cannabinoids for neuropathic pain reported to date are insufficiently large to detect infrequent, but significant, adverse events. Furthermore, although some therapeutic trials have followed patients for up to one year, this may be an insufficient period to detect the long term adverse effects of cannabinoids which have emerged from the epidemiological literature examining psychiatric illness and cannabis abuse: There is a now consistent epidemiological literature supporting a dose-related association between cannabis abuse and a subsequent long-term risk of developing psychotic illness or schizophrenia, which we have discussed in more detail elsewhere[11]. A systematic review encompassing 9 studies identified consistent findings between studies of different methodologies in different settings[24]: Cannabis users are two to three times more likely to subsequently develop serious psychotic illness, including schizophrenia than non-cannabis users. Similar findings were reported in a subsequent systematic review[25]. This observation is strengthened by a dose-response relationship between cannabis use and schizophrenia or the development of psychotic symptoms[26;27]. Populations at enhanced risk can also be identified, for instance there is an 18.2% higher risk of cannabis-associated psychotic symptoms in persons who possess baseline risk factors for the development of psychosis[27]. There is also a genetic element to such risk, individuals who carry a functional polymorphism in the gene encoding the enzyme catechol-O-methyltransferase are more likely to exhibit psychotic symptoms and to develop schizophrenia if they use cannabis[28]. Polymorphisms in this same enzyme are associated with variations in pain sensitivity and of the risk of developing chronic pain conditions such temporomandibular joint dysfunction[29]. It should be noted that these data have emerged largely from studies in adolescents, so the extent to which they can be generalised to the wider population are unknown. Finally, a frequent criticism of such epidemiological studies is the "self-medication" hypothesis, whereby individuals with early pre-clinical psychosis could self-medicate with cannabis – but this hypothesis has recently been refuted[27].

Another evidence-base to be borne in mind in any discussion of the psychiatric side-effects of therapeutic interventions

which perturb the endocannabinoid system is the experience with the CB1 receptor antagonist rimonabant, which recently received regulatory approval in Europe for appetite suppression in obesity therapy. This drug increases the risk of depression, anxiety and suicide[30].

Conclusions:

There is good evidence of efficacy for some CMEs and Δ-9THC for multiple sclerosis related pain, which compares favourably to the small dataset of other agents evaluated for central pain. These data led the NeupSIG Sub-committee on Treatment to recommended cannabinoids as second line therapy for multiple sclerosis associated pain, with a proviso that caution is required, particularly with regards to long term safety[31]. The evidence for efficacy of cannabinoids in other neuropathic pain conditions is, to date, inconsistent and more data is probably needed before recommendations about efficacy across a range of neuropathic pain conditions can be confidently made. Clinical effectiveness comparisons with the increasing range of evidence-based therapies for peripheral neuropathic pain will need to be made[16;21]. The short term adverse effect profiles of cannabinoids evaluated in neuropathic pain trials to date is, in very general terms, comparable for that of other systemically administered therapies which have efficacy in neuropathic pain.

However, the implications of the strong and consistent epidemiological data associating cannabis abuse with a dose-dependant long term risk of mental illness cannot be isolated from any discussion of the therapeutic use of potent cannabinoids. This is particularly germane to chronic conditions such as neuropathic pain, when long term therapy may be required. The precise magnitude, relevance and implications of this risk for therapeutic use of cannabinoids are currently unknown. Certainly, patients both in trials and the therapeutic setting must be educated about this potential risk as part of the informed consent process. Therefore, until we have such data it would seem prudent to exclude, both from clinical therapy and trials, any patients with risk factors, including genetic, for psychosis or schizophrenia. However, it is salutary to note that exclusion patients with risk factors did not prevent the increased risk of mental disorders associated with rimonabant treatment[30]. Furthermore, it might also be prudent to, given the long term nature of such risk, to execute long term follow up of patients treated with cannabinoids, in both contexts of clinical practice and trials, to examine whether such adverse events are revealed years after therapy. A centralised database would be an efficient way of delivering this.

What might the future hold for the development of clinically effective cannabinoids for use in neuropathic pain? Clinical effectiveness is a combination of efficacy and therapeutic index and there is much interest in drug development strategies which have the potential of developing clinically effective cannabinoids with analgesic efficacy, but which also possess an improved adverse effects profile. Intuitively, brain CB1 receptors would appear the most likely mechanism of many of the reported acute adverse effects, and perhaps of long term risk of mental illness, and therefore is probably a target to avoid. Current drug developments strategies include CB2 agonists[32]; inhibitors of enzymes which degrade endocannabinoids (fatty acid amide hydrolase (FAAH) and monoacylglycerol lipase)[33;34], palmitoylethanolamide and analogues[35-37] and targeting CB1 expressed by primary sensory neurones, for peripheral neuropathic pain[38].

Conflicts of interest- The author has advised several pharmaceutical companies engaged in the development of cannabinoids and other agents for use in neuropathic pain. He is named as inventor on a palmitoylethanolamide related patent (WO 2005/079771).

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MARK YOUR CALENDARS!

NeuPSIG Satellite Meeting to the 12th World Congress on Pain

August 13 – 15, 2008, London, UK

Current SIG information

As of February 20, 2008, the NeuPSIG has 978 members in 68 countries representing 44 specialties.

Please submit your contributions, ideas and comments for the NeuP SIG newsletter to the SIG Secretary/ Newsletter Editor:

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