Evidence-based Recommendations for the Pharmacological Management of Neuropathic Pain

Position Statement, June 2008

Australian Pain Society

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Background to this Position Statement

There are now several internationally-published evidence-based Guidelines which are worthy of recognition within the Australian context.

This Position Statement is based on the studies that have specifically addressed the management of neuropathic pain as an entity. However the Australian Pain Society recognises that any pain condition whether with or without neuropathic pain components mandates a broad approach recognizing the multidimensional physical, emotional, cognitive, social and vocational impacts of persistent pain. To this end, it is appropriate that common and easily-available non-pharmacological strategies be considered in any management plan.

However, in recognizing the overall context for assessing and treating pain, the Australian Pain Society provides this Position Statement to support and guide specific treatment, in particular pharmacologic treatment, for neuropathic pain based on best-available evidence and consensus internationally.

An important framework with a strong evidence and experiential basis for achieving the best therapeutic outcome in the management of neuropathic pain is Australia's national strategy for achieving quality use of medicines (QUM) that is found within the National Medicines policy (see Appendix for more detailed definition).

The Statement confines itself to treatment recommendations, without more broadly addressing clinical features and diagnosis of neuropathic pain for which assessment by an experienced clinician will be important.

Definition

Neuropathic pain has been defined by the International Association for the Study of Pain (IASP) as "pain initiated or caused by a primary lesion or dysfunction of the nervous system" (Merskey and Bogduk 1994). This is in contrast to the other broad type of pain, nociceptive pain, in which the pain system conveys or processes information from a pain source such as diseased tissue.

Common descriptors that may suggest the presence of neuropathic pain include sharpness, burning, ache, stabbing, spasms, and paroxysms, often in or around an area of perceived numbness, Such symptoms would occur where there is reasonable likelihood of nerve injury and is often in a scenario of inadequate response to use of opioids. Neuropathic pain can occur, however without these descriptors.

Epidemiology

Neuropathic pain is estimated to affect up to 7% of people (Gilron et al 2006, Bouhassira D et al 2007). This is approximately 15-20% of Australians who suffer from chronic pain, (17% males, to 20% females) (Blyth et al 2001). Pain (including that of neuropathic basis) is one of the commonest symptoms that people present with to their family practitioners. It is recognised that in 20 – 50% of visits to primary care practitioners, pain is part of their presenting complaint (Mantyselka et al 2001, Dobecki et al 2006). Neuropathic pain also occurs in the acute pain setting (Hayes 2001). There is evidence more than 50% of chronic pain sufferers have pain predominantly neuropathic in nature ((Kaki et al 2005)

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People with chronic pain are five times more likely to use health care services than those without chronic pain (Becker et al 1997).

Neuropathic pain can be classified as central, peripheral and mixed aetiologies. Examples of central neuropathic pain include post stroke pain, affecting up to 8% of patients post stroke, and neuropathic pain associated with multiple sclerosis, with pain reported in more than 50% (Finnerup et al 2007) and spinal cord injury 40% (Werhagen et al 2007). Peripheral neuropathic pain states include painful peripheral neuropathies, including painful diabetic neuropathy affecting approximately 25% of people with diabetes, sciatica, post-surgical and post-traumatic neuralgias. Post herpetic neuralgia is an example of a mixed neuropathic pain, with both peripheral and central mechanisms, affecting a significant proportion of patients following shingles.

Cancer-related pain very frequently has a significant neuropathic component as part of a mixed nociceptive and neuropathic pain presentation. The approach to individuals in a palliative care setting with a relatively short prognosis by its nature requires a more aggressive and intensive multimodal approach but is outside of the scope of these guidelines. There is however a significant proportion of cancer survivors with chemotherapy- and radiation-related neuropathic pain requiring ongoing management.

In the past 2 decades neuropathic pain has received increasing attention in both the clinical and research spheres. At the same time new therapies have offered promise of more effective treatment with less side-effect.

The gathering pace of such research and product development over the last two decades has resulted in the publication in recent years of several evidence-based treatment algorithms for chronic neuropathic pain.

Internationally Recognised Guidelines of Pharmacological Treatment of Neuropathic Pain.

There are several guidelines that been developed by the worlds' leading researchers in the field of neuropathic pain (Finnerup et al 2005, Attal et al 2006, Finnerup et al 2007, Dworkin et al 2007, Moulin et al 2007). Their uniform salient findings are presented in table 1 as follows:

Table 1. Evidence-based pharmacologic treatment options for neuropathic pain.

Noradrenergic antidepressants	nortriptyline, desipramine, amitriptyline, venlafaxine, duloxetine
Calcium channel alpha 2-delta ligands	gabapentin, pregabalin
Sodium channel antagonists	Topical (and intravenous) lignocaine
Opioid agonist	morphine, oxycodone, methadone
Partial opioid agonist /monaminergic	tramadol

It is acknowledged that for the specific diagnosis of trigeminal neuralgia carbamazepine is the drug of choice. However carbamazepine is of lesser effectiveness in general neuropathic pain and central pain conditions and hence does not appear in the above table.

Medications in the above table all provide a highly-effective and efficient treatment likelihood of obtaining 50% pain reduction as measured by Number Needed to Treat (NNT) of the order of 3-6.

The Canadian Pain Society went further to recommend the following order of preferences based on quality of evidence of analgesic efficacy, side-effect profiles, ease of use and cost. Moreover 'medications were considered first- or second-line if there was high-quality evidence of efficacy and if they were considered straightforward to prescribe and monitor'. Third-line may require more specialised follow-up and monitoring to assess and address issues related to opioids such as tolerance and dependency, and fourth-line medications had at least one positive RCT to support it.

Table 2. Canadian Pain Society pharmacologic treatment priorities for neuropathic pain.

First-line treatments	Tricyclic anti-depressants (eg amitriptyline) , gabapentin, pregabalin
Second-line treatments	Serotonin noradrenergic reuptake inhibitors (venlafaxine), topical lignocaine
Third-line treatments	tramadol, controlled-release opioids
Fourth-line treatments	cannabinoids, methadone, anticonvulsants with lesser efficacy (lamotrigine, topiramate, valproic acid)

It is recognised that cannabinoids are not readily available for prescription, but this does not preclude its addition to this list as there is a substantial research base that supports some efficacy in some varieties of neuropathic pain such as multiple sclerosis.

There are many other medications in common use for historical, cost and perceived benefit reasons, but have either been shown not to, or for some have not yet been shown (due to a lack of studies) to have the same order of effectiveness as those indicated in the above table. These include:

Antiepileptic medications: carbamazepine (except for trigeminal neuralgia), valproic acid, lamotrigine, topiramate, oxcarbazepine, clonazepam;

Antidepressant medications : citalopram, paroxetine, bupropion;

Others: mexiletine, NMDA receptor antagonists (including ketamine), topical capsaicin, cannabinoids.

The APS recognizes that the existing pharmacological treatments as exemplified in the above table used for neuropathic pain provide a limited albeit proven benefit However successful treatment obtaining approximately 50% relief of pain or greater occurs in no more than 40-60% of such patients with mono-therapy. It is therefore likely that a multiple drug regime may increase the successful outcome rate, the drugs may require rotation, and the continued effectiveness and side-effects for the patient under consideration must be continually monitored (Dworkin et al 2007).

For clinically relevant and practical guidelines in the Australian context, the Western Australian Therapeutic Advisory Group (WATAG, 2007) has formulated a condition-specific hierarchy of medications for a range of Neuropathic conditions, generally utilizing the established evidence as described in the above tables and including dosage regimens.

It is also recognized that among the many non-pharmacological treatment strategies, there is evidence which supports good outcomes for chronic pain in general being cognitive-behaviourally based Pain Management Programs (Norrbrink et al 2006). For chronic neuropathic pain where all other pain management strategies have failed to sufficiently alleviate the pain intensity neuromodulation by spinal (Sundaraj SR et al 2005) and peripheral stimulation (Mobbs et al 2007) has established itself as an effective and efficient contributor to the management of neuropathic pain in selected candidates.

AUSTRALIAN PAIN SOCIETY POSITION STATEMENT ON

PHARMACOLOGIC MANAGEMENT OF NEUROPATHIC PAIN.

It is thus incumbent upon the Australian Pain Society to acknowledge the growing recognition of the benefits, and limitations, of the current range of pharmacological treatments for chronic neuropathic pain by developing and promulgating its own treatment recommendations.

To this end the Australian Pain Society recognises that the following medications as listed in Table 3 are preferred treatments available within Australia in a range of neuropathic pain conditions. These are presented by non-prioritised classes, within each of which there are options that can be considered.

Table 3. Australian Pain Society evidence-based recommendations for the pharmacologic management of neuropathic pain.

Noradrenergic antidepressants	nortriptyline, amitriptyline, venlafaxine, duloxetine
Calcium channel alpha 2-delta ligands	gabapentin, pregabalin
Sodium-channel blockers	topical lignocaine
Opioid agonist	morphine, oxycodone, methadone
Partial Opioid-agonist/monaminergic	tramadol

Conversely it is recognized that other medications of probable overall lesser effectiveness may warrant consideration particularly in the scenario where first–line medications have proven to be insufficiently effective, poorly tolerated, or are contraindicated. It is recognised that carbemazepine is a first-line treatment for trigeminal neuralgia, one particular form of neuropathic pain, but it has not shown effectiveness for the wider range of neuropathic pain conditions.

It is recognised that there is a paucity of studies comparing medications within and across these classes.

Neuropathic pain related to cancer and its sequelae presents its own urgency and priorities whereby it is acknowledged that the above Guidelines may assist in pharmacological management but that many other options may be required to assist in pain control. The guidelines are not designed to be prescriptive or restrictive.

The Australian Pain Society commends these guidelines as one more step along the way of assisting the people of Australia and their treating clinicians obtain efficacious pain control as efficiently and effectively as possible.

As a final comment, it is difficult to surpass the concluding comments in ‘An Evidence-based Algorithm for the Treatment of Neuropathic Pain’ (Finnerup et al 2007):

“Clearly, improvements can be made to this treatment algorithm, and as more evidence is generated from high-quality, randomized, controlled, head-to-head comparative clinical trials, **this treatment algorithm can be refined to ultimately benefit the patient with neuropathic pain**”. (APS emphasis).

APPENDIX

Definition of Quality Use of Medicines, within the National Medicines Policy, Commonwealth Department of Health.

Quality use of medicine means:

- Selecting management options wisely by:
  - Considering the place of medicines in treating illness and maintaining health, and
  - Recognizing that there may be better ways than medicine to manage many disorders

- Choosing suitable medicines if a medicine is considered necessary so that the best available option is selected taking into account:
  - The individual
  - The clinical condition
  - Risks and benefits
  - Dosage and length of treatment
  - Any co-existing conditions
  - Other therapies
  - Monitoring considerations
  - Costs for the individual, the community, and the health system as a whole,

- Using medicines safely and effectively to get the best possible results by:
  - Monitoring outcomes
  - Minimizing misuse, over-use, and under –use; and
  - Improving people's ability to solve problems related to medication, such as negative effects or managing multiple medications.

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