Health
Hunter New England
Local Health District

Reconsidering medication use for neuropathic pain

Health Professional Resources
December 2020

Hunter Integrated Pain Service Position Statement

Prescriber support
Staff at Hunter Integrated Pain Service are available to discuss medication strategy and offer support to clinicians in the Hunter New England region of NSW,

Position Summary
Medication is only modestly effective for treatment of neuropathic pain and adverse effects are common[1]. Non-pharmacological treatments, including multidisciplinary approaches, have not been tested in randomised controlled trials for neuropathic pain but are commonly used in clinical practice.

Hunter Integrated Pain Service recommends that medications can be trialled for treatment of neuropathic pain in the context of a 'whole person' multidimensional approach. If there is a positive response to the trial then a maintenance phase of 3 months can be considered with a plan to deprescribe at the end of the phase. This allows time for the person to develop active, non-pharmacological strategies. In select cases a longer maintenance phase can be considered.

Indications
In 2011 neuropathic pain was redefined by the International Association for the Study of Pain as 'pain caused by a lesion or disease of the somatosensory system' [2]. This excluded conditions caused by dysfunction in the nervous system, such as Complex Regional Pain Syndrome Type 1 and fibromyalgia (chronic widespread pain).

This position statement considers the major medications indicated for treatment of neuropathic pain. Evidence for use of tricyclic antidepressants (TCA), serotonin and noradrenaline reuptake inhibitors (SNRIs), pregabalin, gabapentin and opioids is reviewed. There is a lack of evidence supporting off-label use of these medications for pain caused by nervous system dysfunction.

Efficacy and Harms
The numbers needed to treat (for 50% pain reduction) and harm[1] are shown in Table 1. The relatively short duration of randomised controlled clinical trials, along with the modest benefits and significant risk of harms means that extrapolation to the long-term treatment of chronic pain is of questionable value.

Treatment algorithms for neuropathic pain
Treatment algorithms for medication use in neuropathic pain have been developed in recent years based on expert consensus[3].

First line: SNRIs (duloxetine and venlafaxine), TCA, gabapentin and pregabalin. These can be used alone or in combination.

Second line: Topical capsaicin and lidocaine (5% patches). Although these approaches are not clearly supported by evidence, potential benefit is recognised. Some suggest that lidocaine patches can be a first line treatment for localised neuropathic pain.

Third line: Opioids are considered third line due to problems of tolerance, opioid induced hyperalgesia and dependency/addiction. This is despite the fact that opioids are more effective than SNRI antidepressants and gabapentinoids in treating neuropathic pain over the short term.

Table 1: Efficacy (number needed to treat for 50% pain reduction - NNT) and harm (number needed to harm - NNH) [1]

Agent	NNT (95% CI)	NNH (95% CI)
Tricyclic antidepressants	3·6 (3·0 - 4·4)	13·4 (9·3 - 24·4)
SNRI antidepressants	6·4 (5·2 - 8·4)	11·8 (9·5 - 15·2)
Pregabalin	7·7 (6·5 - 9·4)	13·9 (11·6 - 17·4)
Gabapentin	6·3 (5·0 - 8·3)	25·6 (15·3 - 78·6)
Tramadol	4.7 (3.6 - 6.7)	12·6 (8·4 - 25·3)
Strong opioids	4·3 (3·4 - 5·8)	11·7 (8·4 - 19·3)

Special considerations

1. **Renal impairment**: Pregabalin and gabapentin are entirely renally eliminated with no hepatic metabolism. Hence, they can be useful in hepatic dysfunction. Dose reduction is required in renal impairment.
2. **Trigeminal neuralgia**: Carbamazepine and oxcarbazepine are the drugs of first choice[4]. The efficacy of other anticonvulsants is uncertain.

Trial and maintenance phases

1. A 2 week trial phase is recommended to test medication responsiveness. Benefit and adverse effects are evaluated and a decision made about maintenance therapy.
2. A maintenance period of 3 months is typical after which a trial of weaning and cessation is recommended. The aim is to facilitate transition to active non-pharmacological treatments.

Dose recommendations and adverse effects

1. **Antidepressants**
    a. **Tricyclics - amitriptyline and nortriptyline:**
        i. Dosage: start 10mg at night and titrate up if required to 75mg at night.
        ii. Adverse effects: common problems include drowsiness, weight gain, constipation, dry mouth, blurry vision, difficulty with urination and sexual dysfunction. Caution should be used when prescribing to the elderly and patients with cardiovascular disorders or hepatic impairment.

b. **SNRIs:**
    i. Venlafaxine: start 75mg in the morning and titrate up if required to 300mg daily.
    ii. Desvenlafaxine: start at 50 mg daily and titrate up if needed to 100mg daily.
    iii. Duloxetine: start at 30mg daily, titrate up if required to 60mg daily.
    iv. Adverse effects: common problems include nausea, dry mouth, constipation, drowsiness, dizziness, decreased appetite, sexual dysfunction and sweating. There is also the potential problem of serotonin toxicity. Doses should be reduced in renal impairment. Duloxetine is contra-indicated in hepatic impairment.

2. **Anticonvulsants**
    a. Pregabalin: in adults start at 75mg once or twice daily and titrate up if required to 150 mg bd and possibly with caution to 300mg twice daily. Reduce dose in elderly or in renal impairment e.g. starting dose of 25mg.
    b. Gabapentin: in adults start at 300mg once or twice daily and titrate up if required to 800mg three times daily. Reduce dose in elderly or in renal impairment. A 100mg capsule is available.
    c. Adverse effects: Common adverse effects of pregabalin and gabapentin include drowsiness, dizziness, fatigue, loss of coordination, blurred/double vision, tremor, dry mouth, peripheral oedema, weight gain, altered mood, included worsening depression and increased risk of suicidality. There are also risks of driving and machinery operating impairment, abuse and dependence[5].
    d. Conversion from gabapentin to pregabalin is typically achieved by discontinuation of gabapentin after an evening dose and initiation of pregabalin therapy the following morning[6, 7]. The milligram equivalent dose of pregabalin is 4 to 6 times lower than the gabapentin dose[6, 8].

3. **Topical 5% lignocaine patch:** apply to the area affected by neuropathic pain for 12 hours during the day and remove for 12 hours overnight. The maximum number of simultaneously applied patches is 3. A patch can be cut into smaller segments for localised areas of neuropathic pain. Adverse effects include skin irritation and the potential for systemic local anaesthetic toxicity.

Deprescribing recommendations

There is limited evidence regarding appropriate deprescribing regimens for antidepressants and anticonvulsants in neuropathic pain. A conservative approach involves a 20 to 30% reduction in dose every week (if the patient has been taking the adjuvant for less than 3 months) or every 2 weeks (if the patient has been taking the adjuvant for more than 3 months).

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Working Group

HIPS medical staff Drs Chris Hayes, Andrew Powell, Hema Rajappa; Ruth White (Physiotherapist); Fiona Hodson (Clinical Nurse Consultant); Kathie Nickerson, Belinda Mikaelian (Clinical Nurse Specialists). External consultant Dr Anthony Carrie (Specialist Pain Medicine Physician, Whangarei, New Zealand).

Disclosures

Fiona Hodson is Vice-President of Chronic Pain Australia. Dr Hayes is a Board member of Painaustralia and has provided pharmacotherapy advice to multiple groups including the Faculty of Pain Medicine ANZCA, Therapeutic Goods Administration, National Prescribing Service and the Agency for Clinical Innovation NSW Health. The other authors of this document declare no conflicts of interest.