Health
Hunter New England
Local Health District

Reconsidering drug therapy for neuropathic pain, CRPS and fibromyalgia

Health Professional Resources
Hunter Integrated Pain Service
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Scientific evidence and clinical experience

- *Does NOT support the long term efficacy of drug therapy for neuropathic pain, Complex Regional Pain Syndrome (CRPS) or fibromyalgia.*
- *Does support drug use for 3-6 months to achieve modest pain reduction in selected cases.*
- *Does support active self-management strategies.*

Summary of evidence

1. **Neuropathic pain**: The evidence for drug therapy in neuropathic pain, CRPS and fibromyalgia is weak. Only a minority of patients respond favourably. Adverse effects are common and harm often outweighs benefit.
    a. **Trial design**: More recent higher quality trials show less benefit from drug therapy than older studies which had poorer design and greater risk of bias.
    b. **Numbers needed to treat (NNT)**: Tricyclic antidepressants, serotonin and noradrenaline reuptake inhibitors, gabapentin, pregabalin and opioids have numbers needed to treat for 50% reduction in neuropathic pain in the range of 4-10.
    c. **First line agents**: Antidepressants (tricyclics, serotonin and noradrenaline reuptake inhibitors) and anticonvulsants (pregabalin and gabapentin) can be used alone or in combination.
    d. **Second line agents:** Opioids (including tramadol and tapentadol) are second line due to tolerance, opioid induced hyperalgesia and other adverse effects. Topical 5% lignocaine patch is a second line agent for post herpetic neuralgia and other localised neuropathic pain states.
2. **CRPS**: There is insufficient data to make a recommendation about the role of drug therapy in CRPS.
3. **Fibromyalgia**: There is evidence of a modest treatment effect from duloxetine 60mg daily (NNT 8) and pregabalin 600mg daily (NNT 11) in trials of up to 12 weeks duration.
4. **Practical treatment strategy:**
    a. **Trial phase**: In clinical practice a 2 week trial is recommended before making a decision about maintenance therapy.
    b. **Maintenance phase**: A 3 month maintenance phase is typically used to facilitate active self-management strategies with a view to winding down the nervous system. After that time medication is weaned and ceased. In selected cases there may be value in longer term maintenance therapy.
    c. Standard doses should not be exceeded without discussion with an appropriate specialist.

Mechanisms contributing to pain

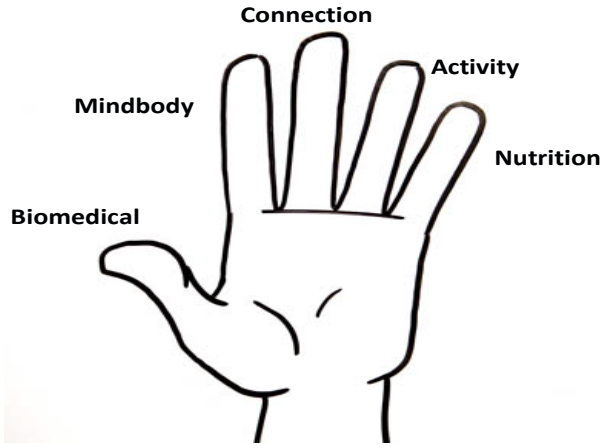
Pain is produced by the brain. There is an interpretation by the brain that the body is threatened by actual or potential tissue damage. Historically the International Association for the Study of Pain has identified two main types of pain - nociceptive and neuropathic[1]. This division is based on the structures believed to give rise to the pain. In addition, peripheral and central neuroplastic changes contribute. Psychological, social and environmental factors also play a role. The experience of pain may involve one or more of the following contributors:

1. **Nociceptive**: This term is used to describe the neural process of encoding and processing noxious (harmful or potentially harmful) mechanical, thermal, or chemical stimuli.[2]
2. **Neuropathic**: Neuropathic pain was redefined in 2008 as pain caused by a "lesion or disease" of the somatosensory system[3]. This excluded nervous system "dysfunction".
3. **Inflammation**: Inflammation is an immune response which may activate and sensitise nociceptors leading to amplification of the neural response[4].
4. **Neuroplasticity**: The nervous system is plastic; structural, chemical and physiological changes have the capacity to modulate transmission[4]. Thus nervous system sensitisation increases pain just as damping down of the system brings pain reduction. In chronic pain there is a high likelihood that plasticity in the central nervous system plays a key role.
5. **Psychological, social and environmental**: These factors are recognised as important determinants of the pain experience and can be targeted in treatment[5]. Their impact on pain is mediated via an effect on central nervous system function.

The concept of mechanism based treatment

1. A mechanism based approach to the pharmacological treatment of pain has theoretical appeal but little evidence to support it.
2. Traditional wisdom supports the use of paracetamol, non steroidal anti-inflammatory drugs and opioids in nociceptive pain and antidepressants and anticonvulsants in neuropathic pain. There is moderate evidence to support this view in the acute pain setting[6]. However in chronic non-cancer pain the weight of evidence is swinging against drug therapy.
3. In neuropathic pain in particular the concept of defining specific mechanisms and hence targeting drug treatment has been enthusiastically endorsed[7]. However no progress has been made in translating this theory into practice and "empirical" trial of anti-neuropathic agents has remained the norm.
4. Painful diabetic neuropathy and post-herpetic neuralgia are the most commonly investigated subgroups in drug trials for neuropathic pain. Caution is warranted in extrapolation of results to other neuropathic pain conditions.
5. In 2008 CRPS Type 1 and fibromyalgia were excluded from the neuropathic pain category and reclassified as types of nervous system sensitisation pain related to neuroplasticity[3]. This shift in classification has not led to any advances in drug therapy.
6. Traditional self-management strategies have shown small to moderate gains in mixed chronic pain populations[8]. Cognitive behavioural and neuroscience theories are now blending. The emerging principle is that a whole person approach (Fig 1) can wind down the nervous system and reduce pain.

Figure 1. A whole person approach[5]



Diagnosis of neuropathic pain, CRPS and fibromyalgia

1. Diagnosis is based on history and examination findings and may be supported by the use of screening questionnaires (see below).
2. Clinical features suggestive of **neuropathic pain**:
    a. History of nerve injury or disease
    b. Pain within an area of sensory deficit
    c. Character: often burning, shooting, stabbing or electric shock-like
    d. Paraesthesias and dysaesthesias (unpleasant sensations)
3. Clinical features suggestive of **nervous system sensitisation**:
    a. Pain that appears disproportionate to underlying tissue damage
    b. Allodynia (pain in response to normally non-painful stimuli)
    c. Hyperalgesia (increased pain in response to normally painful stimuli)
    d. Hyperpathia (increasing pain with repeated stimulation and "after response")
    e. Spread of pain to adjacent regions
4. Diagnostic criteria for **CRPS** are shown in Table 1 below[9] :

Table 1. The Budapest clinical diagnostic criteria for CRPS

1. Continuing pain, which is disproportionate to any inciting event
2. Must report at least one symptom in three of the four following categories • *Sensory*: reports of hyperaesthesia and/or allodynia • *Vasomotor*: reports of temperature asymmetry and/or skin colour changes and/or skin colour asymmetry • *Sudomotor/oedema*: reports of oedema and/or sweating changes and/or sweating asymmetry • *Motor/trophic*: reports of decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia) and/or trophic changes (hair, nail, skin)
3. Must display at least one sign at time of evaluation in two or more of the following categories • *Sensory*: evidence of hyperalgesia (to pinprick) and/or allodynia (to light touch and/or deep somatic pressure and/or joint movement) • *Vasomotor*: evidence of temperature asymmetry and/or skin colour changes and/or asymmetry • *Sudomotor/oedema*: evidence of oedema and/or sweating changes and/or sweating asymmetry • *Motor/trophic*: evidence of decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia) and/or trophic changes (hair, nail, skin)
4. There is no other diagnosis that better explains the signs and symptoms

5. The diagnosis of **fibromyalgia** has traditionally been based on widespread pain for longer than 3 months and pain on palpation at 11 or more of 18 specified tender points[10]. More recently, a definition has been proposed based on widespread pain and symptom severity that does not rely on tender points[11].
6. Screening questionnaires include pain DETECT, Douleur Neuropathique en 4 (DN 4), Leeds Assessment of Neuropathic Symptoms and Signs (LANSS), Self reported LANSS (S-LANSS) and the Neuropathic Pain Questionnaire (NPQ). The validity of these questionnaires needs to be re-examined in the light of the current definition of neuropathic pain which has excluded nervous system dysfunction.

What is the current evidence for drug treatment of neuropathic pain?

1. A 2007 Cochrane review[12] found that tricyclic antidepressants have an NNT of 3.6 (95% CI 3 to 4.5) and venlafaxine 3.1 (2.2 to 5.1). This means that for every 3 or 4 patients with neuropathic pain treated with these drugs, one will get at least 50% short term pain relief. There was limited evidence that other antidepressants may be effective but the data was insufficient to calculate NNTs. Approximately 20% of study participants withdrew because of intolerable side effects.
2. A further Cochrane review was undertaken in 2012[13] to include new trials using amitriptyline and also to incorporate improved methods of analysis. No high quality studies were found. A second tier of lower quality studies with significant risk of bias were analysed. Amitriptyline showed no benefit in cancer-related or HIV-related neuropathic pain. In a group combining painful diabetic neuropathy, postherpetic neuralgia, post-stroke pain and fibromyalgia the NNT was 4.6 (3.6 to 6.6).
3. A 2009 Cochrane review[14] of duloxetine (60 mg daily for 12 weeks) for painful diabetic neuropathy showed an NNT of 6 (5 to 10). 16% of participants withdrew due to adverse effects.
4. A 2013 Cochrane review[15] analysed anticonvulsant use in neuropathic pain. No high quality studies were found and a second tier of lower quality studies was analysed. There were reasonable quality second tier studies of gabapentin and pregabalin in painful diabetic neuropathy and postherpetic neuralgia and of pregabalin in central neuropathic pain. NNTs were in the range of 4 to 10. There were no trials of clonazepam or phenytoin of reasonable quality. There was inadequate evidence on which to judge the efficacy of valproic acid. The evidence in regard to carbamazepine was of low quality with a high likelihood of bias. There was reasonable quality evidence showing little or no benefit from lamotrigine, oxcarbazepine and topiramate.
5. A 2013 Cochrane review[16] analysed opioid use in neuropathic pain. There were no high quality studies. Lower quality studies with duration up to 12 weeks were analysed. These showed an NNT for 50% pain relief of 5.9 (3 to 50). There was no improvement in emotional or physical functioning. More participants withdrew from the opioid group due to adverse effects (13%) than from placebo (4%).
6. A 2007 Cochrane review[17] analysed the use of topical 5% lignocaine in post herpetic neuralgia. Although a benefit of lignocaine over placebo was reported there was insufficient evidence to recommend it as a first-line treatment.

What is the current evidence for drug treatment of CRPS?

1. There is no high quality evidence to inform drug treatment of CRPS.
2. There is a suggestion that Vitamin C supplementation may prevent development of CRPS after wrist fractures[18] and limb surgery or trauma[19].
3. There is insufficient data to comment on antidepressants/anticonvulsants[9], ketamine[20] or bisphosphonates[21].

What is the current evidence for drug treatment of fibromyalgia?

1. A 2012 Cochrane review[13] referenced above addressed amitriptyline use in fibromyalgia. No high quality studies were available. 36% of participants treated with amitriptyline reported benefit compared to 12% with placebo. NNT was not calculated.
2. A 2013 Cochrane review[15] analysed the role of anticonvulsants in fibromyalgia. There were no high quality studies. For pregabalin the NNTs for 50% pain reduction were 14 (9 to 33) for 300mg daily and 11 (7.1 to 21) for 600mg daily. In a small low quality study of gabapentin up to 2400mg daily the NNT for 30% pain reduction was 5.4 (2.9 to 31).
3. A 2014 Cochrane review[22] analysed duloxetine 60 mg daily for up to12 weeks in fibromyalgia. The NNT for 50% pain reduction was 8 (4 to 21).

Choice of Agent

1. First line agents for neuropathic pain are antidepressants (tricyclics or serotonin and noradrenaline reuptake inhibitors) and anticonvulsants (pregabalin or gabapentin). These can be used alone or in combination.
2. Second line therapies to be considered for time limited use are opioids (including tramadol and tapentadol) and 5% lignocaine patches (for post herpetic neuralgia or localised neuropathic pain states).
3. Pregabalin and gabapentin are renally eliminated with no hepatic metabolism. Hence they can be useful in hepatic dysfunction. Dose reduction is required in renal impairment. Pregabalin was PBS listed for neuropathic pain in Australia in 2012.

Trial and maintenance phases

1. A 2 week trial phase is recommended. Benefit and adverse effects are then considered and a decision made about maintenance therapy.
2. A maintenance period of 3 months is typical after which the drug is weaned and ceased. The aim is to facilitate development of active self-management strategies.
3. In selected cases a longer period of maintenance therapy may be considered.

Dose recommendations and adverse effects

1. **Antidepressants**
    a. **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.
    b. **Venlafaxine XR:**
        i. Dosage: start 75mg in the morning and titrate up if required to 300mg daily.

ii. Adverse effects: common problems include nausea, dizziness, drowsiness, insomnia, dry mouth, sexual dysfunction and sweating.

c. **Duloxetine**:
   i. Dosage: start 30mg daily and titrate up if required to 60mg daily.
   ii. Adverse effects: common problems include nausea, dry mouth, constipation, drowsiness, dizziness, decreased appetite, sexual dysfunction and sweating.

2. **Anticonvulsants**
   a. **Pregabalin**: in adults start at 75mg twice daily and titrate up if required to 300mg twice daily. Reduce dose in elderly or in renal impairment. A 25mg capsule is available.
   b. **Gabapentin**: in adults start at 300mg 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. Common adverse effects of pregabalin and gabapentin include drowsiness, dizziness, loss of coordination, blurred/double vision and tremor.
   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[23, 24].
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 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.

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Hunter Integrated Pain Service (HIPS)

HIPS medical staff are available to discuss medication strategy and offer support to prescribing doctors in the Hunter New England region of NSW, Australia.

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Working Group

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Conflict of interest

Dr Hayes has undertaken sponsored consultancy and educational work with Pfizer, Janssen and Mundipharma.