Pharmacological management of neuropathic pain

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While pain management is best assessed and treated using a biopsychosocial model, this review focuses on recent updates in the prescription of medications for neuropathic aspects of severe pain, including opioid management.

The International Association for the Study of Pain (IASP) defines pain as “an unpleasant sensory and emotional experience associated with actual or potential tissue damage and described in terms of such damage.” Pain can be further classified as nociceptive pain or neuropathic pain (NeP). Nociceptive pain is described as “pain that arises from actual or threatened damage to non-neural tissue and is due to the activation of nociceptors”.

Examples of nociceptive pain may include: pain after surgery, inflammation, bone fractures, burns and myofascial pain.

NeP has been defined by the IASP as “pain arising as a direct consequence of a lesion or disease affecting the somatosensory system” and is thought to have an incidence of 6–8 per cent in the UK population. NeP is challenging to manage and can adversely affect patients’ physical and emotional functioning, as well as being associated with significant cost to society.

In patients presenting with pain uncontrolled with conventional analgesia, a diagnosis of NeP should be considered.

NeP can be intermittent or constant; spontaneous or provoked. Typical terms to describe NeP include stabbing, shooting, burning and electric shock. Common conditions displaying NeP include painful diabetic neuropathy (16–27 per cent), post herpetic neuralgia (8–19 per cent), trigeminal neuralgia, radicular pain, post surgical chronic pain (10–50 per cent with severe pain 2–10 per cent), neuropathic cancer pain, stroke, spinal cord injury and multiple sclerosis. A basic neurological examination may identify features associated with neuropathic pain (see Table 1) and simple tools are available to help the diagnosis, for example The Leeds Assessment of Neuropathic Symptoms and Signs (LANSS). NeP is not a discrete process but is associated with a wide range of clinical problems making classification challenging.

Management of NeP
Regardless of the cause, NeP is best assessed and managed using a biopsychosocial model. This model acknowledges that biological, psychological and social factors all play a significant role in human functioning in the context of illness.
It is thought to be related to central blockade of monoamine uptake. Pain processing is presumed to be altered by prolonging synaptic activity of these monoamines, thereby enhancing descending inhibitory action in the spinal cord, as well as effects elsewhere in the central nervous system (CNS). These drugs also block a number of other receptor subtypes involved in pain processing including alpha-1 adrenergic, H₁ histaminergic, N-methyl-D-aspartate receptors (NMDA), calcium and sodium channels, and are weakly stimulatory at mu-opioid receptors.¹³

TCAs are well absorbed from the gut and are highly protein bound. Metabolism is hepatic with large interpatient variability. Side-effects include sedation, anticholinergic effects and postural hypotension.¹⁴ These effects can be reduced by starting with low doses, at night, slow up-titration and using a secondary amine TCA (nortriptyline).¹⁵ Cardiac toxicity is a concern, therefore an electrocardiogram should precede TCA prescription if greater than 40 years of age. TCAs should be used with caution in ischaemic heart disease or ventricular conduction abnormalities.⁵

TCAs are usually prescribed as a once daily, night time dose. It is important to warn patients of the sedative side-effects. Tolerance to this should develop within 3–4 days. If daytime sedation persists, the drug should be taken earlier in the evening. TCAs should be titrated to efficacy or until side-effects hinder dose escalation.¹³

Selective serotonin noradrenaline reuptake inhibitors
Selective serotonin noradrenaline reuptake inhibitors (SSNRIs) – duloxetine and venlafaxine (unlicensed indication) – tend to be less sedative, have fewer anticholinergic effects and are less cardiotoxic in overdose in comparison with TCAs. They are however associated with gastrointestinal side-effects including nausea and constipation.¹⁴

Duloxetine has shown efficacy in painful diabetic neuropathy but has not been extensively studied in other types of NeP. Its dosing is simple with the most common side-effect being nausea. This can be avoided by commencing at the lowest dose (30mg), once daily, for one week before up-titration. Duloxetine does not cause clinically important cardiac conduction abnormalities or hypo/hypertension.⁵,¹⁶

Venlafaxine has shown efficacy in painful diabetic peripheral neuropathy and painful polyneuropathies but not in post herpetic neuralgia.⁵,¹⁵ It has been associated with cardiac conduction abnormalities and hypertension ⁵,¹⁷ and therefore care should be taken in cardiac disease. Sudden discontinuation of the drug can lead to a withdrawal state.⁵,¹⁸

Gabapentinoids
Gabapentinoids – gabapentin, pregabalin (Lyrica) – bind to the voltage gated calcium channel at the alpha₂-delta subunit in the dorsal horn of the spinal cord and inhibit neurotransmitter release. Few drug interactions are described but they produce side-effects including dose dependent dizziness and sedation. This can be reduced by starting with lower dosages and titrating cautiously. Both medications require a dose reduction in renal insufficiency which can be made in relation to creatinine clearance.⁵

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**Table 1. Features associated with NeP**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Description</th>
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<tbody>
<tr>
<td>Allodynia</td>
<td>Pain produced by a stimulus that is non-painful</td>
</tr>
<tr>
<td>Hyperalgesia</td>
<td>Increased response to a painful stimulus</td>
</tr>
<tr>
<td>Dyssyndrome</td>
<td>Unpleasant abnormal sensations. Not necessarily painful</td>
</tr>
<tr>
<td>Paraesthesia</td>
<td>An abnormal sensation. Not painful or unpleasant</td>
</tr>
<tr>
<td>Hyperaesthesia</td>
<td>Increased sensitivity to stimulation</td>
</tr>
<tr>
<td>Hyperpathia</td>
<td>Abnormal pain response to stimuli applied to an area of decreased sensitivity</td>
</tr>
<tr>
<td>Hypoaesthesia</td>
<td>Decreased sensitivity to stimulation</td>
</tr>
<tr>
<td>Hypoalgesia</td>
<td>Decreased sensitivity to painful stimuli</td>
</tr>
</tbody>
</table>

**Table 2. Factors to be explored at consultation⁶**

- Severity of pain
- Impact on daily living and sleep
- Risks and benefits of pharmacological treatments
- Individualised information regarding drug titration
- Coping strategies for pain
- Non-pharmacological treatments (physical and psychological therapies and surgery)
- Need for referral to specialised pain service
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### Gabapentin Pharmacokinetics
Gabapentin pharmacokinetics are non-linear and dosing requires careful titration. It is not protein bound and has a terminal half-life of 5–7 hours. It is excreted unchanged in the urine and does not affect hepatic enzyme systems. Dosing is three times daily and should be initiated at low doses and increased until pain relief or dose limiting adverse effects are encountered.

Pregabalin kinetics are predictable and its oral bioavailability is greater than 90 per cent. It readily crosses the blood brain barrier and has a terminal elimination half-life of six hours. It is not metabolised and is excreted unchanged in the urine.

Dosing is more straightforward than gabapentin involving a twice daily regime and may afford a timelier onset of analgesia.

Dosing regimens for first-line medications in NeP are suggested in Table 3. Patients who may benefit from further increases in these medications, or show no response to treatment should be referred to a specialist pain centre/pain clinic for ongoing management.

Topical lidocaine (5 per cent) patch/gel is also considered a first-line medication. It should be considered in post herpetic neuralgia with allodynia or localised allodynia due to other subtypes of NeP. It is an attractive option, especially in the elderly, due to its minimal systemic absorption and therefore favourable side-effect profile. The most common adverse effects are mild local reactions.

**Prescribing advice for first-line medications**
If appropriate, a TCA should be prescribed as the first treatment for NeP. In the case of painful diabetic neuropathy, this should be substituted for duloxetine. These drugs should be titrated to effect as suggested in Table 3. If substantial pain relief with tolerable side-effects is achieved, the treatment should be continued. If the initial first-line treatment is not effective/tolerated, a gabapentinoid should be offered. This may be in addition to the first treatment if partial pain relief and tolerable side-effects were described by the patient. There may be a small difference in the side-effect profile of the gabapentinoids, therefore if one is not tolerated it may be appropriate to trial the other.

Lidocaine patches or gel can be used in conjunction with any of the above if appropriate. For those patients who cannot receive or tolerate first-line agents, have pain that is difficult to manage, or may benefit from an interventional technique, early referral to a specialist pain clinic is advised.

### Second-line medications
If first-line NeP medications are only partially effective, ineffective or not tolerated, second-line medications may be considered. These patients may also benefit from assessment at a specialist pain clinic. This would include rationalisation of their pharmacotherapy, consideration of interventional techniques if appropriate and/or assessment for self management via the Pain Management Programme.

**Tramadol and opioid analgesics**
These have proven useful in NeP in multiple randomised controlled trials; however, concern regarding their long-term safety has rendered them second-line treatment for those who cannot tolerate first-line medications. There are a number of exceptions to this including patients presenting with acute neuropathic pain, neuropathic pain secondary to cancer and episodic exacerbations of severe neuropathic pain. In these instances it may be appropriate to consider opiates as a first-line treatment.

Oral administration of these drugs allow for easy dose titration. Lipid soluble opioids (pethidine, fentanyl) and short-acting preparations of morphine and oxycodone have greater misuse potential and should be avoided if possible. The transdermal route is another means of administering opioids, providing a constant rate of delivery without a rapid plasma rise. Injectable opioids should not be used for the management of persistent pain.

**Tramadol**
This is a cyclohexanol derivative with agonist properties at all opioid receptors (mu-receptor predominance). It also inhibits the reuptake of noradrenaline and serotonin and stimulates presynaptic serotonin release providing analgesia via descending inhibitory pathways. It is available in enteral form in a variety of strengths, with immediate or modified release, and in parenteral preparation. Its analgesic potency is one-fifth to one-tenth that of morphine.

It is well absorbed with 70 per cent oral bioavailability, increasing to greater than 90 per cent with repeated doses. It provides relatively rapid pain relief. It is metabolised by the liver with an elimination half-life of 5–6 hours. Tramadol has the potential to interact with drugs including TCAs, SSRIs and SSNRI s, which can result in serotonin syndrome and seizures. It should therefore be avoided in patients with epilepsy.

A suggested initial dosing regimen for tramadol is displayed in Table 4.

**Tapentadol**
(Palexia) is a mu-opioid receptor agonist and a noradrenaline reuptake inhibitor with favourable pharmacokinetics and less gastrointestinal side-effects compared to pure opioids and tramadol. Tapentadol has been studied for use in nociceptive pain but recently, the Food and Drug Administration approved it for use in nociceptive pain.
Neuropathic pain remains a challenge to manage despite much research. It can adversely affect patients’ physical and emotional functioning, impacting on their quality of life, and is associated with substantial costs to society.\textsuperscript{3,4,5}

Treatment of NeP requires a biopsychosocial approach which is beyond the scope of this article, where the focus is on pharmacological management alone. NICE guidelines have suggested a number of safe and cost-effective pharmacological treatments used to manage NeP outside of specialist pain management services\textsuperscript{6} which may help to reduce reliance on long term opioids. If this is not achievable or further advice is required, referral to a specialist pain centre is encouraged. Referral is also advised for those patients requiring to be assessed for escalation to second- and third-line medications, interventional techniques, and self-management programmes.

References

Conclusion
NeP remains a challenge to manage despite much research. It can adversely affect patients’ physical and emotional functioning, impacting on their quality of life, and is associated with substantial costs to society.\textsuperscript{3,4,5}

Third-line medications
These should be reserved for patients who cannot tolerate, or who do not respond adequately to, first or second-line treatments and should not be prescribed for neuropathic pain without input from specialist pain service\textsuperscript{6} (the exception being carbamazepine which is considered first-line treatment for trigeminal neuralgia\textsuperscript{6}). There is substantially less evidence for the efficacy of these medications in NeP. Table 5 displays examples of third-line medications.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Trail duration</th>
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<tbody>
<tr>
<td>Tramadol</td>
<td>50mg twice daily – up to 400mg/day Caution in elderly, hepatic and renal dysfunction</td>
<td>4 weeks</td>
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Table 4. Dosing regimen for second-line NeP medications\textsuperscript{5}

Administration (FDA) have widened its indications to include NeP associated with diabetic peripheral neuropathy.\textsuperscript{21} NICE have not included tapentadol in their recent guidelines and further studies are required to consolidate its role in NeP.

Other opioids
A number of randomised control trials have shown that opioids provide greater pain relief than placebo in a variety of NeP subtypes\textsuperscript{5,22} and were comparable with gabapentinoid and tricyclic antidepressant as analgesics.\textsuperscript{23} However, due to concerns with long term safety (adverse effects on endocrine and immunological systems and opioid induced hyperalgesia), prescription should be undertaken with care and follow the British Pain Society guidelines for opioid prescribing.\textsuperscript{19}

Good opioid prescribing should include:\textsuperscript{19}
- Physical and psychological assessment
- Risk assessment for opioids misuse
- Appropriate route of administration
- Establish therapeutic expectations
- Establish terms and long term goals of opioids therapy
- Discuss side-effects (long and short term) and fitness to drive
- Repeat assessment and monitoring.

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- Antidepressants: citalopram, paroxetine, bupropion
- Antiepileptics: lamotrigine, levetiracetam, carbamazepine (other than for trigeminal neuralgia), oxcarbazepine, topiramate, valproic acid, lacosamide
- Methadone
- Dextromethorphan
- Memantadine
- Cannabinoids (multiple sclerosis only)
- Ketamine
- Capsaicin patch (8%)

Table 5. Third line medications for NeP\textsuperscript{5,6}

Declaration of Interests
None to declare.

Dr Lindsay is a specialist trainee in anaesthesia and Fellow in Pain Management, Northern Ireland and Dr Conor Farrell is consultant in anaesthesia and pain management, Ulster Hospital Dundonald, Northern Ireland