Adjuvant medicines for the management of neuropathic pain


Summary
The main focus of this article, part of a series on pain, is to describe the abnormal patterns that occur in persistent and neuropathic pain states. It provides an overview of the adjuvant medications available to treat this type of pain when it does not respond to conventional methods. Treatments described require the input of pain specialists; however, the purpose of this article is to encourage nurses to assess pain accurately and to identify symptoms of neuropathic pain, thereby improving patient outcomes.

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MUCH HAS BEEN WRITTEN on the subject of pain management and the use of the World Health Organization (WHO) (2010) pain ladder. However, persistent and neuropathic pain can be resistant to medical treatments and often fails to respond to conventional analgesic medications. In these cases, adjuvant medications are required and this article discusses those commonly used.

Pain pathways are complex involving multiple receptor sites and chemicals and the activation of otherwise silent nerves not associated with a normal pain response. Neuropathic pain is an abnormal pain response and is a result of damaged or atypical functioning of the central or peripheral nervous system. It is therefore important during pain assessment to establish the presence of neuropathic pain. Common signs and symptoms associated with neuropathic pain are listed in Box 1.

An adjuvant is a medicine that has different indications in other medical settings and is not usually thought of as an analgesic. These medicines can be used alone or in combination with other existing therapy regimens to optimise the management of complex pain, and may reduce the amount of opioid medication a patient requires. Common medications that are used as adjuvants include:

- Tricyclic antidepressants.
- Anticonvulsants.
- Calcitonin.
- Local anaesthetics.
- N-methyl-D-aspartate receptor antagonists.

Details of indications and doses of individual adjuvant medicines are provided in Table 1 (British National Formulary 2010).

Some of these medicines may be familiar when used in an alternative context or at different therapeutic ranges. Some are established treatments, while others are still under investigation. Not all these medications are licensed for the indication of pain, however extensive research and clinical practice has demonstrated their effectiveness.

Tricyclic antidepressants

Indications and action The clinical effectiveness of tricyclic antidepressants is well documented and this group of medicines (which includes

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amitriptyline and nortriptyline) has been used to treat neuropathic pain for more than 30 years. Tricyclic antidepressants act on descending pain pathways, blocking pain messages in the spinal cord before they are recognised as pain. Chemicals involved in these mechanisms include noradrenaline (norepinephrine) and serotonin, which modulate pain in the spinal cord (Ho et al 2008). More recently, selective serotonin-reuptake inhibitors have been investigated, for example venlafaxine. Amitriptyline remains the initial therapy for painful diabetic neuropathy and post-herpetic neuralgia because of the lack of evidence for newer therapies (Saarto and Wiffen 2007).

**Dosing and onset of action** The therapeutic range of amitriptyline is much lower than the doses traditionally used to treat depression. A gradual increase in dose to reach therapeutic effect is recommended to minimise side effects, especially in the frail and older adult populations. These medicines are taken for a longer period of time than the standard analgesics and require a slow reduction in the dose when discontinuing treatment, to minimise withdrawal symptoms.

**TABLE 1**

<table>
<thead>
<tr>
<th>Adjuvant medication</th>
<th>Type of adjuvant</th>
<th>Indications</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amitriptyline</td>
<td>Tricyclic antidepressant</td>
<td>Painful diabetic neuropathy, Post-herpetic neuralgia</td>
<td>10-75mg orally administered at night</td>
</tr>
<tr>
<td>Nortriptyline</td>
<td>Tricyclic antidepressant</td>
<td>Painful diabetic neuropathy, Post-herpetic neuralgia</td>
<td>10-75mg orally administered at night</td>
</tr>
<tr>
<td>Venlafaxine</td>
<td>Selective serotonin-reuptake inhibitor</td>
<td>Painful diabetic neuropathy</td>
<td>75-375mg orally divided into two daily doses</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>Anticonvulsant</td>
<td>Painful diabetic neuropathy, Post-herpetic neuralgia</td>
<td>300-3600mg orally divided into three daily doses</td>
</tr>
<tr>
<td>Pregabalin</td>
<td>Anticonvulsant</td>
<td>Painful diabetic neuropathy</td>
<td>25-600mg orally divided into two daily doses</td>
</tr>
<tr>
<td>Carbamazapine</td>
<td>Anticonvulsant</td>
<td>Trigeminal neuralgia</td>
<td>100-1600mg orally divided into two daily doses</td>
</tr>
<tr>
<td>Ketamine intravenous loading dose*</td>
<td>N-methyl-D-aspartate receptor antagonist</td>
<td>Opioid-resistant pain, Allodynia</td>
<td>2.5mg every 5 minutes up to a maximum of 10mg</td>
</tr>
<tr>
<td>Ketamine oral suspension†</td>
<td>N-methyl-D-aspartate receptor antagonist</td>
<td>Opioid-resistant pain, Allodynia</td>
<td>25-400mg orally divided into four daily doses</td>
</tr>
<tr>
<td>Lidocaine</td>
<td>Topical local anaesthetic</td>
<td>Painful diabetic neuropathy, Allodynia, Post-herpetic neuralgia</td>
<td>Once every 24 hours with the transdermal plaster in situ for 12 hours only</td>
</tr>
<tr>
<td>Calcitonin*</td>
<td>Amino peptide hormone</td>
<td>Phantom limb pain, Vertebral fractures</td>
<td>One injection of 100 units daily for three days</td>
</tr>
</tbody>
</table>

*Guidelines used in the author’s trust.
†Guidelines for ketamine trial in the author’s organisation suggest up to 75mg four times daily dosing for maintenance once a response has been noted following an intravenous trial of 2.5mg at five-minute intervals up to a maximum of 10mg.
(Adapted from the British National Formulary 2010)

**BOX 1**

**Signs and symptoms of neuropathic pain**
- Allodynia — a painful response to a usually non-painful touch stimulus.
- Hyperalgesia — an increased painful response to a usually painful stimulus.
- Dysesthesia — an unpleasant sensation, not always painful.
- Parasthesia (pins and needles).
- Burning, piercing pain.
- Electric shock sensation.
- Crawling sensation.
- Stabbing.
- Shooting.
- Tingling.

(Baron and Tille 2008)
Contraindications and adverse effects  This group of medicines is contraindicated in patients with cardiac disease, particularly those with arrhythmias, heart block and recent myocardial infarction, and also in patients with epilepsy (BNF 2010). Common side effects include drowsiness (however, improved sleep is often a bonus to the person in pain), dry mouth and constipation. Approximately one in 30 patients stop taking these medications because of intolerable side effects (Saarto and Wiffen 2007). Patients should be encouraged to persevere with treatment as some tolerance to these side effects can develop.

Anticonvulsants  

Indications and action  Anticonvulsant medicines are an established method of managing neuropathic pain by stabilising nerve membranes (sodium and calcium channels), preventing them from carrying pain messages. Recent evidence suggests they may act as N-methyl-D-aspartate receptor antagonists. Gajraj (2007) advocated the use of anticonvulsants to treat pain arising from painful diabetic neuropathy and post-herpetic neuralgia.

Dosing and onset of action  The therapeutic range is close to that of anticonvulsant dosing range. As with the tricyclic antidepressants group, slow dose increases are advised to minimise side effects. Pregabalin may be a useful alternative to gabapentin because of its side-effect profile, and doses may be increased more rapidly to achieve therapeutic levels.

Contraindications and adverse effects  Common side effects of anticonvulsants include nausea and vomiting, diarrhoea, dry mouth, dizziness, drowsiness, peripheral oedema and weight gain. Patients are encouraged to persevere with taking these medications as some side effects will cease over time. Patients with renal or hepatic impairment may require dose reduction.

Calcitonin  

Indications and action  Calcitonin is a 32 amino acid peptide hormone. The form of calcitonin used in the clinical setting is a derivative of salmon and is 40 times more potent than mammalian forms. Although calcitonin (salmon) (salcatonin, synthetic or recombinant salmon calcitonin) is commonly used to treat acute pain following vertebral fractures, it can also be used in the treatment of phantom limb pain (Visser 2005). Jaeger and Maier (1992) showed that at one-week post treatment with salmon calcitonin, phantom limb pain decreased significantly and 76% of patients were pain free. The mechanism of action is not understood fully, and research is limited within the management of phantom limb pain; however, it may play a role as a neurotransmitter in the central nervous system and also on the regulation of calcium.

Dosing and onset of action  Doses of 50-100 units are usually administered subcutaneously once a day for three days, however it can be delivered via intranasal, rectal or transdermal routes. Despite its short half-life, the analgesic effects are noticed rapidly after this brief dosing period, although optimal dose, duration and route of administration for analgesia have yet to be clarified (Visser 2005).

Contraindications and adverse effects  Common side effects include flushing, nausea and vomiting (BNF 2010). Therefore the administration of an anti-emetic one hour before administration of calcitonin may be useful.

Topical local anaesthetics  

Indications and action  de Leon-Casasola (2007) demonstrated the growing body of evidence on the efficacy and safety of topical analgesics. When a painful stimulus is evoked, sodium channels in the nerve membrane become active, delivering pain messages to the brain. When a 5% lidocaine plaster is applied to painful skin the lidocaine binds to the sodium channels, ‘blocking’ the pain message route.

Lidocaine plasters have also been shown to reduce allodynia – a painful response to a usually non-painful touch stimulus (Meier et al 2003). The plaster can provide a physical barrier to the painful area. Some patients with allodynia are not even able to tolerate bedclothes against their skin. This medicine provides useful pain relief and a physical barrier, without the problems of medication interactions, dose increases or systemic side effects discussed earlier.

Dosing and onset of action  The plaster is applied once every 24 hours by the patient or healthcare professional for 12 hours at a time without disrupting the analgesic effect. Up to three patches can be applied at once, allowing large areas of painful skin to be treated.

Contraindications and adverse effects  The lidocaine plaster should not be applied to broken skin. Adverse effects are few, but can include mild skin irritation, warming and itching at the plaster site.

N-methyl-D-aspartate receptor antagonists  

Indications and action  Ketamine is an anaesthetic agent that is being used in subanaesthetic doses to provide analgesia. In normal pain transmission, the N-methyl-D-aspartate receptor is inactive. In chronic and severe acute pain states, the N-methyl-D-aspartate receptor can become active. This receptor is thought to be responsible for
central sensitisation, also known as ‘wind-up’ phenomena associated with persistent or neuropathic pain. Ketamine produces analgesia by blocking the N-methyl-D-aspartate receptor. This can provide relief for neuropathic pain states and reduce the opioid requirements for some patients.

Dosing and onset of action An intravenous test dose is recommended to determine if the N-methyl-D-aspartate receptor is active. When small doses (up to 10mg) are given intravenously, rapid-onset analgesia is achieved without major adverse effects (Chumbley 2010). Oral ketamine has also been shown to provide good pain relief and this may be useful for people with chronic pain (Eichenberger et al 2008). The development of N-methyl-D-aspartate antagonists with a more favourable balance between analgesia and adverse effects is warranted.

Contraindications and adverse effects
Disassociation and unpleasant dreams are the most common reasons for patients to stop taking ketamine. This medication should not be administered to patients in whom an elevation in blood pressure would cause a serious hazard, for example those with head injury or severe coronary or myocardial disease (Chumbley 2010).

Conclusion
There are many alternative medications that can be used for the effective treatment of complex pain when traditional approaches such as opioid analgesics are inadequate. Adjuvant analgesics are often medications with indications for treating other medical conditions and are sometimes used at different dosing ranges than their original licence. Close patient monitoring is essential to minimise side effects and adverse reactions, and use of these medicines should be overseen by a pain specialist NS

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References