Treatment of chronic pain: antidepressant, antiepileptic and antiarrhythmic drugs

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Chronic pain is complex physiologically and there are many influences on the pain experience. The approach to treatment therefore needs to be multimodal, often with a number of different interventions, both physical and psychological, delivered in parallel. Pharmacotherapy plays an important role in the management of persisting pain and the prescription of appropriate drugs is one of the key roles of the pain physician. Standard analgesics such as non-steroidal anti-inflammatory drugs (NSAIDs) and acetaminophen alone, and in combination with minor opioids such as codeine, have often been prescribed before the patient is referred to the pain clinic. The use of strong opioids is becoming increasingly common. A number of other (‘non-analgesic’) classes of drug have important neurochemical effects on pain processing and are used frequently by pain physicians when first line therapies have failed to provide adequate pain relief. Pains associated with nervous system damage or dysfunction (neuropathic and central pain syndromes) are often refractory to conventional analgesic therapy and it is in this spectrum of disorders that non-analgesic drugs are most frequently used.

This article will describe the rationale for, and clinical use of, antidepressant, antiepileptic and antiarrhythmic drugs in the pain clinic.

Antidepressant drugs

Almost 50% of patients with pain have depression, but antidepressants are prescribed in the pain clinic for their specific analgesic (rather than mood altering) effects. The presence of a distinct effect on pain is borne out by a number of observations: (i) doses necessary to improve pain are often lower than those used to treat depression; (ii) at these doses, the onset of activity is more rapid; (iii) analgesic efficacy is usually obtained in non-depressed patients and does not correlate with improvement in mood in depressed patients; and (iv) the drugs are useful in acute and experimental pain.

The exact mechanism of the analgesic action of these drugs is as yet unknown. However, their efficacy is generally thought to be related to central blockade of central nervous system (CNS) monoamine uptake, specifically serotonin and/or norepinephrine, in addition to other neurotransmitters. They may alter nociceptive processing by prolonging synaptic activity of these monoamines, thereby enhancing descending inhibitory action in the spinal cord in addition to monoaminergic effects elsewhere in the CNS. The drugs also, to varying degrees, block a number of other receptor types involved in pain processing including α-adrenergic, H1-histaminergic and N-methyl-D-aspartate (NMDA) receptors. They may also have blocking effects on calcium and sodium channels and be weakly stimulatory at μ-opioid receptors. The best studied and most commonly used drugs are the first generation tricyclic antidepressants including amitryptiline, doxepin, clomipramine and dosulepin. These are mixed reuptake inhibitors, i.e. they have both noradrenergic and serotonergic effects.

Side-effects (which commonly limit their use) include sedation and anticholinergic effects, particularly dry mouth. Constipation and urinary retention are less common but well documented. The drugs have a number of effects on the heart including slowing of atrioventricular and intraventricular conduction. Cardiac side-effects are important as they may preclude the use of these drugs in patients with cardiac conduction disturbances or recent infarction.

It is thought by many that mixed reuptake inhibitors such as amitriptyline are more effective than selective agents, emphasising the importance of both serotonergic and noradrenergic pathways in pain perception. These medications can also relieve other common symptoms in patients with chronic pain, such as sleep disorder. It is important to note...
that, although antidepressants have been used for over thirty years to manage neuropathic pain, in the UK no antidepressant has a product licence for this indication.

Clinical use of antidepressants

Tricyclic antidepressants remain one of the first-line therapies for neuropathic pain. There are large numbers of randomized, controlled clinical trials, mostly in patients with post-herpetic neuralgia, painful diabetic neuropathy and central pain, with evidence showing the benefit of antidepressants. The number needed-to-treat (NNT) to obtain >50% pain relief is ~2.5. These clinical data endorse the importance of both serotonergic and noradrenergic activity in the analgesic effect. Comparative studies show that drugs with balanced noradrenergic and serotonergic effect are more effective, with lower NNTs than drugs with predominantly noradrenergic effects (nortriptyline, maprotiline) and selective serotonin reuptake inhibitors (SSRI). Overall, the tricyclic antidepressants are effective in relieving neuropathic pain. Of 100 patients prescribed antidepressants for neuropathic pain, 30 will obtain >50% pain relief, 30 will have minor adverse reactions and four will stop treatment because of major adverse effects.

Practical issues in prescribing

The drugs are usually prescribed as a once daily, night-time dose. It is important to warn patients of the sedative effects of these drugs (which may often be an advantage in those whose sleep is disturbed because of pain). Most patients will still feel somewhat sedated in the morning for the first few days of therapy but will often become tolerant of this effect within 3–4 days. If daytime somnolence persists, the drug should be taken earlier in the evening. Beneficial effects on sleep usually come on within a few days whereas the improvement in pain will take a week or longer. There is considerable inter-individual variation in pharmacokinetics so dose requirements vary widely. Typical doses are shown in Table 1. The drugs should be titrated to efficacy or until side-effects preclude dose escalation.

Antiepileptic drugs

Antiepileptic drugs are widely used in pain clinics to treat neuropathic pain. They have a long track record in this regard, phenytoin having first been used in the early 1940s for the treatment of trigeminal neuralgia. Subsequently, carbamazepine was studied and found to be successful in this alleviating this condition. There is good support in the literature for use of antiepileptic drugs in the treatment of post-herpetic neuralgia, trigeminal neuralgia and painful diabetic neuropathy. This has led to their use in other neuropathic pain conditions such as post-stroke pain, phantom limb pain and pain following spinal injury although the published evidence for their use in these conditions is less robust.

Mechanism of action

Antiepileptic drugs work in a number of different ways, all of which have relevance to their effect on pain. Some drugs have more than one mechanism of action. Several pathophysiological mechanisms are responsible for neuropathic pain and we now know that there may be mechanistic commonality in different diagnostic groups and that patients who have similar diagnosis may have different mechanisms responsible for their pain. Poly-pharmacy using different antiepileptic drugs or antiepileptic drugs in conjunction with other classes of medication, particularly antidepressants represents a rational approach. Typical doses are described in Table 2.

Older antiepileptic drugs such as phenytoin and carbamazepine reduce neuronal excitability by means of frequency-dependent blockade of sodium channels. Phenytoin is now used infrequently although given i.v. may have some utility in the management of acute flare-ups of neuropathic pain. Carbamazepine remains the treatment of choice in trigeminal neuralgia. About 70% of patients get significant pain relief. It causes both a reduction in pain intensity, pain paroxysms and triggering stimuli. Oxcarbazepine is a newer chemically related drug with a more favourable side-effect profile.

Lamotrigine also has action at sodium channels and probably by this mechanism suppresses the neuronal release of glutamate, an excitatory amino acid involved in central neuronal hyperexcitability and persisting pain. The drug has been shown to be of benefit in patients with central pain, and as an add-on treatment in trigeminal neuralgia. It has been used in other types of neuropathic pain. Sodium valproate probably elevates levels of the inhibitory amino acid GABA in the central nervous system and by potentiation of GABAergic functions, particularly in the brain, inhibits pain.

Gabapentin is an antiepileptic drug that, despite its name, has no interaction with GABA receptors or GABA metabolism.

Table 1 Commonly used doses of antidepressants for chronic pain

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose range</th>
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<tbody>
<tr>
<td>Amitriptyline</td>
<td>Initially 10–25 mg, increasing to 75 mg nocte</td>
</tr>
<tr>
<td>Dosespin</td>
<td>25–75 mg nocte</td>
</tr>
<tr>
<td>Nortriptyline</td>
<td>Initially 10–25 mg, increasing to 75 mg nocte</td>
</tr>
<tr>
<td>Venlafaxine</td>
<td>37.5–75 mg nocte</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>20 mg nocte</td>
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</tbody>
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Table 2 Commonly used doses of antiepileptic and antiarrhythmic drugs for neuropathic pain

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose range</th>
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<tbody>
<tr>
<td>Gabapentin</td>
<td>Day 1, 300 mg od; day 2, 300 mg bd; day 3, 300 mg tds, increasing up to 800 mg tds if ineffective</td>
</tr>
<tr>
<td>Pregabalin</td>
<td>75 mg bd, increasing to 150 mg bd then 300 mg bd</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>100–400 mg bd</td>
</tr>
<tr>
<td>Sodium valproate</td>
<td>200 mg bd, increasing to 1 g bd</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>150 mg, increasing to 500 mg od</td>
</tr>
<tr>
<td>Mexiletine</td>
<td>400–1200 mg daily in divided doses</td>
</tr>
</tbody>
</table>
It appears to have an inhibitory action at voltage-gated calcium channels where it blocks the \(\alpha_{2,3}\) subunit, which is upregulated in experimental pain models. Although it is not known what function, if any, gabapentin plays in modulating calcium channel flow, effects on intracellular calcium influx would disrupt an entire series of NMDA-activated events involved in central sensitisation. Efficacy is comparable with older agents but it is remarkable for its favourable side-effect profile, lack of interactions and straightforward pharmacokinetics.

Pregabalin is a more recently developed drug that (like gabapentin) is licensed for the treatment of peripheral neuropathic pain. It too acts on the \(\alpha_{2,3}\) subunit of voltage-gated calcium channels although its pharmacokinetic properties are not identical to those of gabapentin. The drug has been well studied in the treatment of painful diabetic neuropathy and post-herpetic pain. It too acts on the same \(\alpha_{2,3}\) subunit, which is upregulated in experimental pain models. Although it is not known what function, if any, gabapentin plays in modulating calcium channel flow, effects on intracellular calcium influx would disrupt an entire series of NMDA-activated events involved in central sensitisation. Efficacy is comparable with older agents but it is remarkable for its favourable side-effect profile, lack of interactions and straightforward pharmacokinetics.

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### Side-effects of antiepileptic drugs

Side-effects of antiepileptic drugs reported in clinical trials usually relate to acute toxicity. Careful dose titration may minimize the likelihood of adverse events. Information regarding longer-term adverse events can be derived in part from the use of these drugs for the treatment of epilepsy. Side-effects of the antiepileptic drugs are usually those affecting the CNS, gastrointestinal and haematological systems. Minor adverse events associated with antiepileptic drug use are common but do not always lead to discontinuation of therapy. There are insufficient data to make robust comparisons between drugs regarding very rare adverse events. The practical prescription of these drugs is also influenced by a number of important pharmacokinetic issues including variable oral absorption, induction of hepatic enzymes and extensive protein binding. Clinicians must be aware of the many interactions that these drugs have with other medications. Important side-effects of antiepileptic drugs are summarized in Table 3.

### Local anaesthetics and antiarrhythmics

After nerve injury, regenerating axonal sprouts may form neuro-mata, which, in common with dorsal root ganglia, demonstrate spontaneous electrical activity. This results, at least in part, from alteration in the quantity and disposition of ion channel protein. Such discharges can provide sustained afferent input to the spinal cord from the damaged nerve and may be self-sustaining or persist long after a triggering stimulus has subsided. In addition to antiepileptic drug drugs (described above) local anaesthetic drugs and antiarrhythmics are observed to suppress such hyperexcitability by means of non-specific sodium channel blockade. Additionally, low-dose lidocaine may block glutamate-evoked activity in the dorsal horn of the spinal cord.

Lidocaine given systemically was initially reported to be effective for postoperative pain relief and more recently for the reduction of deafferentation pain, central pain and diabetic neuropathy. The results of randomized controlled trials of i.v. lidocaine assess acute changes in pain levels and, whilst interesting and informative, are not helpful in the management of chronic neuropathic pain. The drug is not suitable for long-term use as it cannot be given orally but continues to be used i.v. to predict possible utility of other membrane stabilizing drugs, although such practice is not supported by the literature. Lidocaine 5% is available as a 10 × 14 cm patch with a polyethylene backing and has been shown to have efficacy and tolerability in the management of postherpetic neuralgia.

There are open-label data suggesting that it may also be useful in other neuropathic pain syndromes such as post-thoracotomy pain and complex regional pain syndrome (CRPS).

Mexiletine is the oral analogue of lidocaine and has been studied in a number of chronic (neuropathic and central) pain models with conflicting and overall disappointing results. Gastrointestinal side-effects of mexiletine are very common and frequently limit treatment; other problems include worsening of existing arrhythmias and neurological symptoms (particularly tremor). The use of other antiarrhythmic agents is now precluded because of the incidence of severe adverse events.

### References


See multiple choice questions 10–13.