Use of antidepressants in chronic pain

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Many antidepressants have analgesic effects independent of their antidepressant effects and can be effective analgesics even in patients without concurrent depression. They should be prescribed in a systematic manner and with care to avoid drug interactions.

Key points

- **Antidepressant medications have an important role in the treatment of chronic pain.**
- **The analgesic effects of antidepressant medications are independent of their antidepressant effect; they can therefore be prescribed for chronic pain syndromes even in the absence of comorbid depression.**
- **Tricyclic antidepressants and serotonin and noradrenaline reuptake inhibitors are generally the antidepressants of choice when treating patients with chronic pain.**
- **It is important that both prescribers and patients are clear about the indication for prescribing and the symptoms being targeted.**

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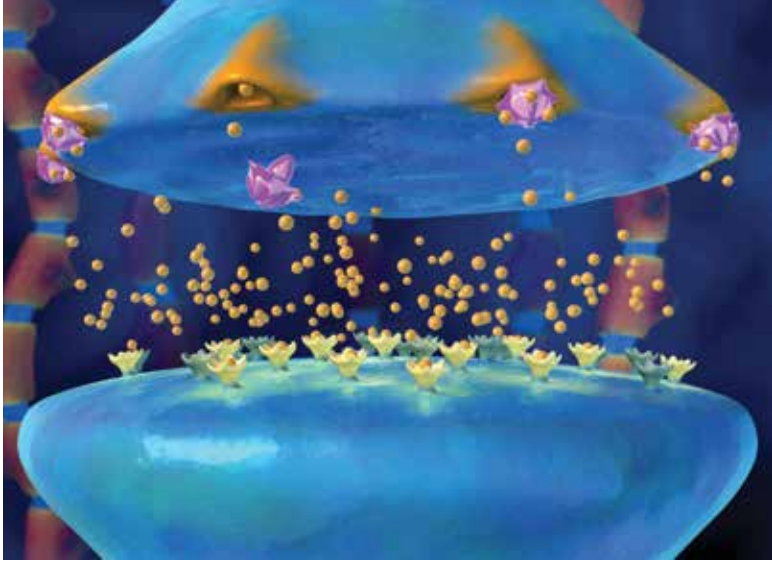

Antidepressants can be used in patients with chronic pain to treat comorbid depression or to specifically treat pain symptoms by utilising their analgesic properties. They may be initiated for both of these indications simultaneously.

When prescribing antidepressants for patients with chronic pain, it is important that prescribers are clear about what symptoms are being targeted. This will help ensure that an appropriate antidepressant is selected and that the response to treatment is accurately monitored. It is not unusual for pain specialists to assess patients with chronic pain who have been prescribed two or more antidepressants concurrently at doses that are either too high or too low. In these cases polypharmacy at nonstandard doses has prevailed over the sequential and systematically evaluated use of single antidepressant medications at standard recommended dosages.

There are over 20 antidepressants available in Australia (see the Box). Although the range of antidepressants may seem overwhelming, the application of the basic principles outlined in this article should make the task of prescribing antidepressant medications for patients with chronic pain states easier and hopefully improve patient outcomes.

Antidepressant medication will generally be just one part of a comprehensive pain management plan that should include appropriate nonpharmacological strategies.

Treatment of comorbid depression

All the major classes of antidepressants are generally equally efficacious in the treatment of major depression.[1] An exception is the antidepressant reboxetine. A more complete analysis of studies of reboxetine concluded that it is ineffective in major depression and showed no superiority over placebo when all studies – published and unpublished – were considered.[2]

Notwithstanding such controversies, if the aim of treatment is solely to alleviate symptoms of comorbid depression, then the prescriber can select an antidepressant in the usual manner. The prescriber does, however, need to be particularly diligent in considering the risk of any potential drug interactions.

In my experience a significant number of patients with chronic pain have difficulty tolerating antidepressant medications. Thus it is important to consider the tolerability of the selected antidepressant and to commence treatment at a low dose and slowly titrate upwards, according to response and tolerability. Antidepressants should be prescribed within the standard recommended dose range for that particular agent.

It is not unusual for patients with chronic pain to be prescribed a combination of antidepressant, anticonvulsant and opioid medications in an endeavour to optimise analgesic efficacy. The prescriber should be mindful of the potential for additive central nervous system depressive effects such as sedation and cognitive dysfunction.

Antidepressants as analgesics

General principles

Although all antidepressants are generally equally efficacious in the treatment of depression, not all antidepressants are equally efficacious in the treatment of pain. Dual-acting antidepressant agents – tricyclic antidepressants (TCAs) and serotonin and noradrenaline reuptake inhibitors (SNRIs) – are generally superior to selective serotonin reuptake inhibitors (SSRIs) in the treatment of chronic pain.

Numerous studies support the observation that the analgesic effect of antidepressants is independent of their antidepressant effect, and as such antidepressants can be effective analgesics even in patients without concurrent depression.[3] The use of antidepressants to treat chronic pain is off-label in Australia, with certain exceptions (see the Box).

Neurobiology of analgesic action of antidepressants

Antidepressants suppress pain by diverse mechanisms and have both central and peripheral actions. The main mechanism through which analgesia may be achieved appears to be via the reinforcement of descending inhibitory pathways by increasing levels of the neurotransmitters noradrenaline and 5-hydroxytryptamine (5-HT) in the synaptic cleft at both supraspinal and spinal levels. Analgesic action appears to be strongest in antidepressants with mixed-receptor or predominantly noradrenergic activity, although there are exceptions to this rule.

TCAs have particularly diverse mechanisms by which they may potentially effect analgesia. Peripheral actions of TCAs that may modulate persistent pain signalling include reduced production of inflammatory mediators, blockade of voltage-gated sodium channels and blockade of peripheral noradrenergic receptors and a multiplicity of other actions. These peripheral mechanisms of action can be exploited in limited situations through the use of topically applied TCAs. This approach, however, is not commonly used in clinical practice, and I do not recommend its use outside specialised pain clinics.

Tricyclic antidepressants

TCAs function well as analgesics independent of their antidepressant effects and may improve pain symptoms at lower therapeutic doses than those used for treating depression. In the neuropathic pain conditions of diabetic neuropathy and postherpetic neuralgia, TCAs have a number needed to treat (NNT) of approximately three.[4] However not all types of neuropathic pain respond to TCAs. Patients with phantom limb pain, pain associated with HIV neuropathy and chemotherapy-induced peripheral neuropathy generally do not respond to TCAs.

Antidepressants available in Australia

First-generation (classic) antidepressants
- Tricyclic antidepressants
- Irreversible monoamine oxidase inhibitors (MAOIs)

Second-generation (newer) antidepressants
- Selective serotonin reuptake inhibitors (SSRIs): fluoxetine, fluvoxamine, paroxetine, sertraline, citalopram, escitalopram
- Serotonin and noradrenaline reuptake inhibitors (SNRIs): venlafaxine, desvenlafaxine, duloxetine,* milnacipran†
- Noradrenaline reuptake inhibitors (NRIs): reboxetine
- Noradrenergic and specific serotonergic antidepressants (NASSAs): mirtazapine
- Melatonergic agonist antidepressants: agomelatine
- Reversible inhibitor of monoamine oxidase (RIMA): moclobemide

* Approved by the TGA for the treatment of diabetic peripheral neuropathic pain.
† Approved by the TGA for the treatment of fibromyalgia but not yet available in Australia.

Serotonin and noradrenaline reuptake inhibitors

Evidence supports the use of duloxetine in patients with diabetic peripheral neuropathic pain and fibromyalgia. In addition, recent evidence appears to support the use of duloxetine for patients with chronic low back pain and pain associated with osteoarthritis. Its current clinical use, however, remains largely for neuropathic rather than nociceptive pain states.

Venlafaxine is also generally efficacious in the treatment of neuropathic pain with a reported NNT similar to that of TCAs.[4] It should be noted that at low doses venlafaxine inhibits almost exclusively the reuptake of 5-HT, thus essentially acting as an SSRI. As the dose is increased the reuptake of noradrenaline is progressively inhibited. It is generally accepted that clinically meaningful noradrenaline reuptake inhibition is achieved only at doses of venlafaxine over 150 mg daily.

The SNRI antidepressant desvenlafaxine may be an exception to the rule that SNRIs are effective in the treatment of chronic pain. This is curious given that desvenlafaxine is the major active metabolite of venlafaxine. A recently published study of desvenlafaxine treatment in patients with diabetic peripheral neuropathy did demonstrate analgesic efficacy at higher doses; however, the efficacy benefit of the higher dose was mitigated by a clear increase in adverse events.[5] Apart from this single study, there are no published data or evidence to support the use of desvenlafaxine in any pain syndrome.

Selective serotonin reuptake inhibitors

SSRIs may be effective in a range of chronic pain states, but there are fewer data to support their use. The evidence for efficacy of SSRIs in the treatment of neuropathic pain is limited and moderate at best, and the results for SSRIs in fibromyalgia are limited and inconsistent.[6] Furthermore, the risk of pharmacodynamic and pharmacokinetic drug interactions makes the use of SSRIs in patients with chronic pain potentially problematic (discussed below).

Other antidepressants of interest

There is insufficient evidence to recommend the routine use of either mirtazapine or reboxetine for analgesia in patients with chronic pain.

Agomelatine is the most recently available antidepressant in Australia and is a synthetic analogue of melatonin, which acts as a melatonin MT_1 and MT_2 receptor agonist and a 5-HT_{2C} receptor antagonist. It is a novel 'first in class' antidepressant indicated for the treatment of major depression. There is no published literature on its use in chronic pain. It is contraindicated in patients with hepatic impairment, and monitoring of liver function is required. It is not yet available through the PBS.

Milnacipran is an SNRI antidepressant that blocks noradrenaline and 5-HT reuptake with equal affinity and is the most balanced of the SNRIs. Milnacipran was approved by the TGA in November 2011 for the management of fibromyalgia but is not yet available in Australia.

The use of irreversible monoamine oxidase inhibitors (MAOIs) for the treatment of depression has declined over the past decades because of the availability of a wide range of alternatives and concerns about food and drug interactions and side effects. The use of irreversible MAOIs should be avoided in the chronic pain setting and indeed in any setting other than under specialised psychiatric supervision. There is no evidence to support the use of the reversible MAOI moclobemide to treat chronic pain states.

Antipsychotics

There is a growing literature on the use of second-generation antipsychotics in the treatment of major depression so it is appropriate to consider whether they might have a potential role in the treatment of chronic pain. In contrast to antidepressant medications, there is no clear theoretical basis for the use of antipsychotic medications in chronic pain. The results of studies on their use in the treatment of a range of painful conditions are mixed, and further and better studies are required.[7]

If the aim of treatment is to alleviate specific comorbid symptoms for which an antipsychotic medication would normally be indicated, such as schizophrenia or bipolar disorder, then the prescriber can select and commence antipsychotic medication in the usual manner. There would generally be no particular expectation of analgesic efficacy.

Adverse effects: drug interactions

Pharmacokinetic interactions

It is important for prescribers to be aware of potential pharmacokinetic drug interactions when prescribing antidepressants for patients with chronic pain. A clinically important example is concurrent use of antidepressants with the analgesics codeine or tramadol. The clinical effects of these analgesics rely on the formation of their more potent metabolites by a metabolic pathway mediated by the enzyme cytochrome P450 2D6. However, 10% of patients of European ancestry are cytochrome P450 2D6 poor metabolisers and are unlikely to gain full benefit from these analgesics. This potential reduction in analgesic efficacy can also occur when a patient is administered a cytochrome P450 2D6 inhibitor, including certain antidepressants, in particular fluoxetine and paroxetine. Inhibition of cytochrome P450 2D6 by fluoxetine and paroxetine may also increase the risk of dose-dependent tramadol-induced seizures by increasing tramadol levels, as well as increasing the risk of serotonin toxicity (discussed below).

Pharmacogenomic testing for cytochrome P450 2D6 genetic polymorphisms to identify individual patient metaboliser status is available in Australia, but does not attract a Medicare rebate.

Pharmacodynamic drug interactions – serotonin toxicity

A common dilemma that confronts clinicians is how to treat depression when the patient is taking tramadol. The major concern is that the concomitant use of an antidepressant medication and tramadol could lead to serotonin toxicity as well as increase the risk of seizures. Although serotonin toxicity may develop during tramadol monotherapy – more so at higher doses of tramadol – it is more likely to emerge with the co-administration of other drugs, particularly serotonergic antidepressants.

MAOI antidepressants are strictly contraindicated in patients taking tramadol. The combination of either SNRI or SSRI antidepressants with tramadol risks a potential drug interaction of major severity. The TCAs clomipramine and imipramine should also be avoided in patients taking tramadol because of their serotonergic potency. However, low doses of other TCAs are occasionally prescribed together with low-dose tramadol (less than 200 mg daily) in our pain clinic, albeit with caution and with appropriate explanation to patients about potential serotonergic toxicity.

The centrally acting analgesic tapentadol has recently been approved for PBS listing and may avoid some of the liabilities of tramadol. However, clinical experience with prescribing tapentadol is limited to date.

Conclusion

Antidepressant medications play a pivotal role in the management of chronic pain. They should be prescribed in an informed and methodical manner to optimise outcomes and to minimise the risk of complications. **PMT**

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COMPETING INTERESTS: None.