Review Article

Use of Antidepressants in the Treatment of Chronic Pain

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Abstract

There is a high prevalence of chronic pain disorders in the population and the individual and societal costs are large. Antidepressants have been used in the treatment of chronic pain and the pain-relieving effects are independent of the mood-elevating properties. We reviewed randomised-controlled trials, systematic reviews and meta-analyses of antidepressants in the treatment of chronic pain disorders which were identified through searches of MEDLINE and EMBASE. Antidepressants have proved to be effective in the treatment of fibromyalgia, chronic low back pain, diabetic neuropathy, postherpetic neuralgia and chronic headache, in particular tricyclic antidepressants (TCAs). There is emerging evidence that newer dual-action antidepressants are equally efficacious. Antidepressants provide a viable option in the management of chronic pain disorders. Further research into novel antidepressants will aid the pain clinician in optimising treatment for patients.

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Introduction

Pain, as defined by the International Association for the Study of Pain, is "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage".[1] Chronic pain is widely defined as pain that lasts longer than 3 months.[2]

Chronic pain affects almost 20% of the adult population in the United Kingdom,[3] while up to 66.4% of adults in the United States suffer from it.[4] In Singapore, the prevalence of chronic pain in the population had been estimated to be 9%.[5] The prevalence of chronic pain varies greatly in different studies due to inconsistencies and differences in definitions of chronic pain.[6]

Chronic pain impacts greatly on the individual and society at large. It reportedly costs society $43 billion per year in terms of lost productivity, substance abuse and/or suicide.[7] There is also a high correlation with depression, perhaps more so than with other chronic illnesses.

The treatment modalities for chronic pain are varied and include both non-invasive and invasive interventions. Non-invasive interventions include drug treatments using analgesics, anticonvulsants and antidepressants. Invasive interventions involve facet joint injections and various nerve blocks.[8]

Methodology

In our review, English-language articles of randomised-controlled trials, systematic reviews and meta-analyses of antidepressants in the treatment of chronic pain disorders were identified through searches of MEDLINE and EMBASE, from 1966 to March 2009. The search terms included "serotonin selective reuptake inhibitors", "tricyclic antidepressants", "monoamine oxidase inhibitors", "venlafaxine", "duloxetine", "trazodone", "nefazadone", "mirtazapine", "bupropion", "reboxetine", "moclobemide", "chronic pain", "fibromyalgia", "back pain", "neuropathy", "neuralgia", "headache", and "migraine".

Antidepressants and Pain

Despite the close association between chronic pain and depression, we now know that the pain-relieving effect of antidepressants is independent of their mood-elevating properties.[9,10] In a meta-analysis of 39 placebo-controlled studies, antidepressants were shown to effectively reduce chronic pain.[11] Antidepressants thus provide clinicians an effective option in the treatment of chronic pain conditions.

Antidepressants have been postulated to modulate pain through the central and peripheral nervous system. The mechanisms involve noradrenaline and serotonin

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(5-HT) neurotransmission, actions on opioid, adrenergic, 5-HT, GABA and N-methyl-D-aspartate receptors, ion channel activations, and possible effects on inflammatory cytokines.[12] Effects on peripheral nociceptors, descending inhibitory pain pathways, central sensitization and brain areas involved in pain and emotional processing have been described.[13]

Types of Antidepressants (Table 1)

Tricyclic Antidepressants (TCAs)

TCAs are widely used in the treatment of pain disorders. Their therapeutic effects are attributed to inhibition of norepinephrine and serotonin reuptake at synapses. However, their use can be limited by intolerable side effects. Anticholinergic side effects such as blurring of vision in glaucoma patients, urinary retention, constipation and dry mouth are common. Anti-histaminergic side effects such as oversedation and weight gain can preclude its use. TCAs can also prolong QT intervals and induce orthostatic hypotension and should be used with caution in patients with underlying cardiac diseases. They are lethal if accidentally or intentionally overdosed.

Monoamine Oxidase Inhibitors (MAOIs)

Classical MAOIs inhibit monoamine oxidases type A and B irreversibly, with antidepressant effects attributed to MAO-A inhibition of the breakdown of serotonin, epinephrine, and norepinephrine. However, MAOIs are infrequently used due to their extensive adverse effects, need for dietary restrictions and varied drug interactions, as a result of their mechanism of action. Adverse effects range from headaches, dizziness and blurred vision to weight gain, weakness and sexual dysfunction. Patients on MAOIs need to avoid food with tyramine, common in cheese and wine, to prevent hypertensive crises. TCAs and serotonin selective reuptake inhibitors (SSRIs) should be used cautiously in combination with MAOIs due to the risk of precipitating serotonin syndrome. Over-the-counter medications containing sympathomimetics, such as cold and weight loss products, can potentially interact with MAOIs to cause adverse reactions. Moclobemide is a reversible inhibitor of monoamine oxidase (RIMA) and is a safer alternative but its use in treating chronic pain remains limited.

Serotonin Selective Reuptake Inhibitors

SSRIs exert their therapeutic effects by selectively inhibiting the reuptake of serotonin. They have a milder side effect profile and are safer in overdoses, compared with TCAs and MAOIs. Gastrointestinal side effects like nausea, vomiting, diarrhoea are common but transient. Sexual dysfunctions have been reported but are reversible.

Table 1. Types of Antidepressants[14]

1. Tricyclic and tetracyclic antidepressants:
   Imipramine. amitriptyline, clomipramine, desipramine, nortriptyline, amoxapine, doxepin, protriptyline, trimipramine, maprotiline
2. Enzyme inhibition
   a) Irreversible and nonselective classical MAO inhibitor
   Isocarboxazid, phenelzine, tranylcypromine
   b) Reversible inhibitor of MAO-A (RIMA)
   Moclobemide
3. Serotonin selective reuptake inhibitors (SSRIs)
   Citalopram, escitalopram, fluvoxamine, fluoxetine, paroxetine, sertraline
4. Dual serotonin and norepinephrine reuptake inhibitors (SNRIs)
   Duloxetine, venlafaxine
5. Serotonin-2 antagonist and reuptake inhibitors (SARIs)
   Nefazodone, trazodone
6. Noradrenergic and specific serotonergic antidepressant (NaSSA)
   Mirtazapine
7. Norepinephrine and dopamine reuptake inhibitor (NDRI)
   Bupropion
8. Noradrenaline reuptake inhibitors
   Reboxetine

SSRIs inhibit cytochrome P450 isoenzymes leading to drug interactions. SSRIs can potentially elevate TCAs, which are widely used in chronic pain disorders, to toxic levels in serum by inhibiting their metabolism. The use of MAOIs and SSRIs in combination should be avoided due to the risk of serotonin syndrome.

Serotonin and Norepinephrine Reuptake Inhibitors (SNRIs)

SNRIs inhibit the reuptake of both serotonin and norepinephrine at synapses. Venlafaxine blocks the reuptake of serotonin at lower doses; at higher doses it predominantly blocks the reuptake of norepinephrine. There is some concern of increased blood pressure when higher doses of venlafaxine are used. Duloxetine does not have these effects. Both drugs have similar side effect profiles of dry mouth, dizziness, headaches and sexual dysfunction. Drug interactions are reportedly minimal but they should not be used in combination with MAOIs due to the risk of serotonin syndrome.

Serotonin-2 Antagonist and Reuptake Inhibitors (SARIs)

SARIs antagonise the post-synaptic 5-HT2 receptors and inhibit the reuptake of serotonin, leading to a net increase in serotonin neurotransmission. It is widely used in the US and the UK as a hypnotic agent. Common side effects of trazodone include nausea, headache, dry mouth and orthostasis. It should be prescribed with caution in patients with underlying cardiac disease due to the risk of cardiac rhythm abnormalities and hypotension. Rare cases of priapism have been reported. Nefazadone is similar to

trazodone but was suspected to be associated with 56 cases of liver failure worldwide since its introduction in 1994. The drug has been voluntarily withdrawn from sale in Singapore since 2004 due to low usage here. In the US, the FDA has added a Black Box Warning since 2002.

Noradrenergic and Specific Serotonergic Antidepressant (NaSSA)

Mirtazapine blocks presynaptic alpha-2 adrenergic receptors, leading to higher levels of norepinephrine and serotonin in synapses. Its blockade of 5HT2 receptor reduces anxiety and enhances sleep while 5HT3 receptor antagonism reduces incidence of nausea. Common side effects are oversedation and increased appetite with weight gain, a result of its anti-histaminergic effect. It is generally safe in overdose and has minimal drug interaction.

Norepinephrine and Dopamine Reuptake Inhibitor (NDRI)

Bupropion predominantly blocks the reuptake of dopamine and is a weak norepinephrine and serotonin reuptake inhibitor. Due to its minimal effects on the serotonin system, it does not cause sexual side effects common to other antidepressants, in particular SSRIs. Cardiac and anticholinergic effects are absent. There is a risk of seizures with high doses, which should not exceed 450 mg per day. Bupropion is also used in smoking cessation therapy.

Noradrenaline Reuptake Inhibitors

Reboxetine selectively inhibits the reuptake of noradrenaline with little effect on other neurotransmitters. Common side effects include dry mouth, constipation, headache, drowsiness, dizziness and excessive sweating but it is generally well tolerated. It is not available in Singapore.

Chronic Pain Conditions

Fibromyalgia

Fibromyalgia presents with a variety of signs and symptoms which includes fatigue and sleep disturbance and is defined as a syndrome of chronic widespread pain and tenderness at a minimum of 11 to 18 defined tender points by the American College of Rheumatology (ACR).[15]

There have been reviews on the use of antidepressants in the treatment of fibromyalgia. In the latest meta-analysis,[16] which included 18 randomised controlled trials involving 1427 patients, antidepressants improved pain, depression, sleep disturbances and health-related quality of life. The effect size was the largest for TCAs, in particular amitriptyline, with smaller effect sizes for SSRIs (fluoxetine), SNRIs (duloxetine) and MAOIs (moclobemide). The findings are consistent with previously reported meta-analyses.[17,18]

It was shown that the effective doses for pain relief by TCAs were between 12.5 and 50 mg per day, less than that required for antidepressant action. It was also demonstrated that duloxetine exhibited efficacy regardless of whether patients were depressed or not. This further strengthens the observation that antidepressants are analgesics independent of their mood-elevating effects.

Duloxetine has emerged in recent years as a credible alternative to TCAs from the results of well designed, randomised controlled trials.[19-21] TCAs are now recommended[22] and duloxetine has been approved by the US FDA for the treatment of fibromyalgia. There is a lack of placebo-controlled studies investigating the use of venlafaxine in fibromyalgia.

Chronic Low Back Pain

Low back pain is often a benign and self-limiting condition but up to 45% of patients experience persistent symptoms.[23] Low back pain is defined as chronic in nature when it lasts for more than 3 months.[24] Pain intensity in low back pain predicts disability.[25] Because of the debilitating nature of the persistent symptoms, it is a major reason for medical consultations and leads to reduced productivity, work absence and early retirement, contributing to large economic losses.

In a recent review,[26] 10 trials involving patients with chronic low back pain were included for analysis. The antidepressants investigated included TCAs and SSRIs. The authors concluded that there was no clear evidence that antidepressants reduce pain, depression or functional status in patients with chronic low back pain. This is in contrast to previous findings.

In 1 meta-analysis[27] and 2 systematic reviews[28,29] reported earlier, antidepressants were found to be effective, with the analgesic effect mainly provided for by TCAs and independent of a patient's depression status. SSRIs unfortunately do not seem to alleviate chronic back pain. The 3 reviews cautioned that the analgesic effect of antidepressants must be weighed against their adverse effects, which affected up to 14% of patients and was more common with TCAs than SSRIs.

The American College of Physicians and the American Pain Society[30] had jointly issued a guideline which recommended the use of TCAs, but not SSRIs, as an option for pain relief in chronic back pain. Clinicians were reminded to assess and treat depression, which is a common comorbid condition.

Diabetic Neuropathy

Painful diabetic neuropathy affects up to 3.6 million people in the US, representing up to 21% of patients with type 2

diabetes mellitus of more than 10 years duration.[31]Like most chronic pain conditions, it is closely associated with depression, disruptions in activities of daily living and lowered quality of life.[32]

TCAs (amitriptyline, clomipramine, imipramine) and SSRIs (fluoxetine, citalopram, paroxetine) were shown to be effective analgesic agents in a recent systematic review,[33] with an overall effectiveness of 1.3 in terms of NNT.

The results of some studies have suggested that TCAs are more effective than SSRIs. In a randomised, double-blind, cross-over trial,[34] paroxetine was found to be less effective than imipramine. In another study,[35] patients in both desipramine and amitriptyline groups improved significantly but not in the fluoxetine group.

SNRIs are increasingly being considered as alternatives to TCAs and SSRIs. Three large double-blind, placebo controlled trials[36-38] investigated the efficacy of duloxetine in reducing diabetic neuropathy pain and found that duloxetine at 60mg/day was the best effective dose. Duloxetine has been approved by the FDA for the treatment of diabetic neuropathic pain. Venlafaxine in the extended release form and at doses of 150 to 225 mg/day was found to be effective in reducing pain in one randomised, double-blind, placebo-controlled study.[39] A more recent study of similar design also reported similar findings.[40]

Postherpetic Neuralgia

Postherpetic neuralgia results from herpes zoster infection and often manifests itself years after the initial infection. It is common in the elderly population and causes persistent and distressing pain that defies easy treatment.[41]

Antidepressants were able to provide pain relief in postherpetic neuralgia as reported in a systematic review.[33] The antidepressants that were effective included TCAs (amitriptyline, desipramine and nortriptyline) and SSRI (fluoxetine).

Other Neuropathic Pain Conditions

Central neuropathic pain occurs due to lesions in the central nervous system, leading to spinal cord injury pain or brain-related central pain. The former commonly occur secondary to traumatic spinal cord injury while the latter, cerebral vascular accidents.[42]

Antidepressants have shown mixed results. A small study[43] reported that amitriptyline was superior to placebo in relieving post-stroke pain but in another study of 84 spinal cord injury patients,[44] it was of no effect. Clomipramine and nortriptyline was found to be superior to placebo in providing pain relief to a group of 39 patients with central pain of various causes.[45] Two studies investigating amtriptyline in the treatment of HIV-related neuropathy did not show that it was effective.[46,47]

Chronic Headache

Chronic headache is common and includes migraine and chronic tension type headache. Chronic tension type headache occurs for at least 15 days per month and lasts for at least six months.[48] In Singapore, migraines affect up to 9.3% of the population, while 2.4% suffer from chronic tension type headache.[49]

A meta-analysis[50] reported that antidepressants were effective, with the evidence for amitriptyline the strongest on subgroup analysis. The authors of a systematic review[51] concluded that SSRIs are not better than placebos in patients with migraine. In patients with chronic tension type headaches, SSRIs are less efficacious than tricyclic antidepressants.

Newer dual action antidepressants have been investigated. Venlafaxine is effective in treating migraines and tension-type headaches.[52-54] In a trial involving patients who suffered from treatment resistant chronic tension-type headache, mirtazapine was found to be effective and comparable to that of amitriptyline.[55]

The Singapore Ministry of Health clinical practice guidelines[56] recommend amitriptyline, clomipramine, maprotiline and mirtazapine to treat chronic tension-type headaches. For the treatment of migraines, the antidepressants recommended include amitriptyline, fluoxetine and venlafaxine.

Treatment Considerations in the Use of Antidepressants

Drug Tolerability

The use of TCAs is often limited by their intolerable side effects, which are dose-dependent. Anti-cholinergic side effects are often most uncomfortable. Orthostatic hypotension, oversedation and cognitive impairment are not well tolerated by elderly patients. SSRIs are generally better tolerated compared to TCAs but gastrointestinal and sexual side effects are common.

To minimise the occurrence of adverse effects, it is advisable to start at low dosages and titrate over time. Patients should be informed of the potential side effects, which are frequently transient, so that they are not alarmed by them. The pain-relieving effects of antidepressants generally appear from 1 to 3 weeks after initiation of treatment and this should be conveyed to patients to help them better manage expectations. The newer antidepressants are well-tolerated and are appropriate options should patients not tolerate TCAs and SSRIs, or fail to experience improvement with them.

Drug Interactions

Most antidepressants are metabolised in the liver via isoenzyme CYP2D6 in the cytochrome P450 system. Many of them also inhibit this isoenzyme. The use of

SSRIs (except escitalopram/citalopram), in combination with TCAs, is cautioned due to the inhibitory effect of SSRIs on the metabolism of TCAs by CYP2D6. This can lead to dangerously elevated levels of TCAs, which can be life-threatening.

Drug interactions can result between antidepressants and analgesic agents. The analgesic property of tramadol and codeine is reduced by medications inhibiting CYP2D6, including antidepressants like fluoxetine.[57,58] It has also been reported that more patients request for peptic ulcer drugs when taking a combination of SSRI and NSAID than those taking TCA with NSAID.[59] The use of tramadol in combination with bupropion could potentially induce seizures in vulnerable patients.[60]

Serotonin Syndrome

It is a rare condition associated with high levels of circulating serotonin and can be fatal. It is characterised by psychiatric, neuromuscular and autonomic features. These include confusion, agitation, tremors, myoclonus, rigidity, hyperreflexia, ataxia, hyperthermia, tachycardia, diarrhoea, hyper/hypotension.[61] It usually occurs in the context of initiation or dose increase of serotonergic agents – the maxim of "start low and go slow" would be most appropriate here. In addition the combination of MAOIs with SSRIs, and to a lesser extent MAOIs with TCAs and SSRIs with TCAs, is avoided to prevent rapid escalation of serotonin levels which may lead to serotonin syndrome

Presence of Depression

Psychiatric comorbidities are common in patients suffering from chronic pain, especially depression. Up to 85% of such patients suffer from depression but unfortunately, the presence of pain often obscures its diagnosis and treatment. Chronic pain patients with depression report greater severity of pain symptoms, experience more functional impairments and had greater likelihood for non-recovery.[62]

There is a close biological link between depression and pain. Serotonin and norepinephrine descending pathways in the spinal cord from the brain stem suppresses pain.[63] In depression, there is dysfunction in the serotonin and norepinephrine neurotransmitter systems, which could account for the greater intensity of pain experienced. Recent evidence of a central hyperexcitability state with changes in pain thresholds among depressed patients further reinforces the close relationship between pain and depression.[64]

Optimisation of depression treatment would seem to improve pain symptoms. TCAs, duloxetine and venlafaxine have shown efficacy in relieving pain and improving mood when prescribed to chronic pain patients with comorbid depression.[65] SSRIs are not able to sustain the analgesic effect but their mood elevating properties prove to be longer lasting. In addition to pharmacological treatment, social interventions and established psychotherapeutic treatments like cognitive behavioural therapy should be utilised to address the psychosocial factors in the depressed patient experiencing pain.

Conclusion

Antidepressants are effective in the treatment of chronic pain disorders. The safe use of antidepressants requires the clinician to consider drug tolerability and interactions and to counsel patients appropriately. Psychiatric comorbidities, if present, need to be treated to provide patients with the best chance of recovery.

There are established recommendations and guidelines for the use of antidepressants in the treatment of fibromyalgia, chronic low back pain, chronic headache and diabetic neuropathy. Good scientific evidence supports treating postherpetic neuralgia with antidepressants.

TCAs remain the most-studied and consistently provide better analgesia than SSRIs in a broad range of pain conditions. SNRIs have emerged as viable alternatives, especially with their better safety and side effect profiles and reduced risk of drug interactions. In addition, TCAs and SNRIs are able to treat comorbid depression and pain with good results. Further research into the use of other novel antidepressants will increase the therapeutic options available to the pain clinician.

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