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ANTIDEPRESSANTS AS POTENTIAL ADJUVANTS IN TREATING CHRONIC PAIN AND PAIN INDUCED DEPRESSION

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ABSTRACT

Clinical studies have shown that people suffering from chronic pain are often also burdened by depression. Antidepressants are widely used to treat painful chronic rheumatic conditions but, contrary to neuropathic conditions, however, little is known about their mechanisms of action. This article reviews the available evidence on the efficacy and safety of antidepressants in major chronic pain conditions; namely, neuropathic pain, diabetic neuropathic pain, headaches, cancer pain, arthritic pain, irritable bowel syndrome (IBS) and fibromyalgia. Antidepressants exhibit a number of pharmacological actions: they block reuptake of noradrenaline and 5-hydroxytryptamine, have direct and indirect actions on opioid receptors, inhibit histamine, cholinergic, 5-hydroxytryptamine and N-methyl-D-aspartate receptors, inhibit ion channel activity, and block adenosine uptake. In summary, evidence supports the use of tricyclic antidepressants in neuropathic pain, diabetic neuropathic pain, headaches, cancer pain, arthritic pain, IBS and fibromyalgia.

KEYWORDS: **Chronic Pain, Depression, Antidepressant, Arthritic pain, Cancer pain, Neuropathic pain, Fibromyalgia, Irritable bowel syndrome.**

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INTRODUCTION

Pain is the main symptom of many inflammatory conditions, rheumatic conditions and degenerative diseases. In many cases, analgesics, non steroidal anti-inflammatory drugs (NSAIDs) or opioids control pain effectively. But, in some cases, additional treatments, such as anticonvulsants and antidepressants, are required [1-3]. The prescription of antidepressants is increasing for many conditions, including neuropathic pain, diabetic neuropathic pain, cancer pain, headache, IBS and fibromyalgia[4-5]. Although these antidepressants are used in the management of pain, their site and mechanism of action remains unclear [6] . There is a need to understand their mechanism and utility in different clinical or pathological conditions. This helps the psychiatrists and physicians to use them for treating the patients suffering from depression and painful somatic symptoms or pain associated diseases/disorders.

MECHANISM OF ACTION

Antidepressants, as a class, include diverse structures and represent several phases of development[7]. 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 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 [8]. The drugs also, to varying degrees, block a number of other receptor types involved in pain processing including a-adrenergic, H1-histaminergic and N-methylD-aspartate (NMDA) receptors. They also exhibit blocking effects on calcium and sodium channels and be a weakly stimulatory at m-opioid receptors. The best studied and most commonly used drugs are the first generation tricyclic antidepressants including amitriptyline, doxepin, clomipramine and dosulepin. These are mixed reuptake inhibitors, i.e. they have both noradrenergic and serotonergic effects [(2)].

PAIN AND DEPRESSION

Depression and chronic pain are distinct but similar disorders. But both may arise from some faulty wiring in their shared neural circuitry[9]. In both disorders, pain continues long after some initial insult has healed, disappeared or moved on, and the experience of social rejection or physical pain persists, feeds on itself and becomes chronic[10] . Although both conditions exist independently as distinct syndromes. The association between chronic pain and depression is a well-documented phenomenon[11]. In an effort to treat these patients, antidepressants have been a natural choice and their efficacy has been reasonably well established for patients[12]. Improvement of depression may be due to one or several of the following: (1) acceptance of pain, (2) mastery of the pain, (3) improved understanding of chronic pain with more realistic planning, (4) expectation of changed milieuat home resulting from family participation in the pain management program, (5) increased physical activity, (6) withdrawal from the effects of analgesics and sedatives, (7) happiness about leaving the rigor and stress of the pain center, or (8) alteration of an underlying biochemical process by some combination of the aforementioned physical and psychologic factors [13-16].

Link between pain and depression

There are two likely mechanisms that can help to explain the link between depression and pain. First, catastrophizing plays a central role in models of both pain and depression and hence might form an important link between them. Second, emotion regulation is important in both depression and pain since they both can be viewed as significant emotional stressor[17]. Pain is transmitted from peripheral sites along 2 sets of afferent nerves, i.e., the A delta and C fibers, which in turn synapse within the dorsal horn of the spinal cord. The neurotransmitters primarily involved in the descending pathways, i.e., norepinephrine (NE) and serotonin (5-HT), act synergistically in reducing the transmission of pain information from the periphery to the central nervous system (CNS)[18] . Analgesia produced by

antidepressants is thought to be mediated by enhancing the activity of NE and 5-HT present within descending pain pathways. Elevations in pro-inflammatory cytokines are routinely found in patients suffering from depression and chronic pain. TNF-α inhibits the release of norepinephrine (NE), contributing to the overall insufficiency of NE that is commonly seen in depressive illness and chronic neuropathic pain [19] .

ANTIDEPRESSANTS AND PAIN

Despite the close association between chronic pain and depression, the pain-relieving effect of antidepressants is independent of their mood-elevating properties[20] . Among depressed pain patients, antidepressants can produce analgesia faster and at doses far lower than those required for antidepressant effects[21]. Hence, direct pain-mitigating effects arise from something other than the antidepressant effects of these medications[22] . Pain is transmitted from peripheral sites along 2 sets of afferent nerves, i.e., the A delta and C fibers, which in turn synapse within the dorsal horn of the spinal cord.The neurotransmitters primarily involved in the descending pathways, i.e., norepinephrine (NE) and serotonin (5-HT), act synergistically in reducing the transmission of pain information from the periphery to the central nervous system (CNS)[23-26] . Antidepressants have been postulated to modulate pain through the central and peripheral nervous system. The mechanisms involve noradrenaline and serotonin (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 [27] . The approved indications for the various antidepressants are given in table 1.

Table 1
Approved indications for various Antidepressants

Class of ADs	Neuropathic	Fibromyalgia	Nociceptive
MAOI(Monoamine-oxidase inhibitor)	negative	negative	negative
TCAs(Tricyclic-Antidepressants)	negative	negative	negative
SSRIs(Selective serotonin reuptake inhibitors)	negative	negative	negative
Atypical Antidepressants	negative	negative	negative
SNRIs (Serotonin-norepinephrine reuptake inhibitior)	negative	negative	negative
Venlafaxine	negative	negative	negative
Desvenlafaxine	negative	negative	negative
Duloxetine	positive	positive	positive
Milnacipran	negative	positive	negative

ROLE OF ANTI-DEPRESSANTS IN DIFFERENT PAINFUL CONDITIONS

Neuropathic pain

Antidepressants are generally used to treat all forms of neuropathic pain. Clinical experience suggest that antidepressants are often very helpful, especially in the cases of peripheral neuropathic pain. The effective dose is disputed for amitriptyline, but mainly 75 mg at night is sufficient. The mean numbers needed to treat to obtain a beneficial outcome, set at 50% reduction of pain, calculated in the early studies of amitriptyline were impressive[28]. The antinociceptive effects of controlled release desipramine, amitriptyline and placebo pellets were studied for three weeks using the hot plate method in rats. The animals treated with desipramine at total doses of 50 mg (8 mg/kg/day) and 100 mg (16 mg/kg/day) displayed analgesia for up to 48 h compared with the matching placebo groups. Amitriptyline did not produce significant analgesia at the same doses[29]. By 72 h until the final evaluation period at 21 days, the antinociceptive action of desipramine was no longer evident. These results suggest that relatively small continuously released doses of desipramine produce analgesia within 24 h in this animal model, but an apparent analgesic tolerance develops within three days. Reports suggest that medications such as TCAs like

desipramine, amitriptyline and nortriptyline help decrease pain along with sleep and mood[30-32]. TCAs are multipurpose analgesics and may be considered for a trial in any type of persistent pain [33,34] . The analgesic effect of TCAs is separate from their antidepressant effects. The dosage should depend on the degree of pain relief balanced against the emergence of adverse effects[35] .

Diabetic Neuropathy

A focus on the treatment of diabetic neuropathy with antidepressants was selected because of the recent approval by the United States Food and Drug Administration (FDA) of duloxetine for this specific disease state. Although numerous studies have been published with TCAs in various pain syndromes including diabetic neuropathy[36] , only a relatively small number of studies that have compared TCAs with SSRIs have explored the requirement of a noradrenergic effect in an agent for analgesia to occur in patients with diabetic neuropathy. Studies with SNRIs in this population of patients have also been conducted. In addition, combination therapy for diabetic neuropathy (e.g., pregabalin) can be prescribed where different pharmacologic approaches are used to maximize therapeutic efficacy in reducing these painful symptoms.

Headache

Antidepressants are included in evidence-based guidelines for the prophylactic therapy of migraine. Although, depending on the neurochemical activity they can cause several side effects and are to be used with caution in older patients, some of them have a well-documented efficacy. The US Headache Consortium classified as a group 1 drug the Tricyclic Antidepressants (TCA) Amitryptyline, as a Group 2 drug the SSRI drug Fluoxetine and as Group 3 drugs the TCAs Nortriptyline, Doxepine and Imipramine, the SSRIs Fluvoxamine, Paroxetin and Sertraline and other antidepressants such as Trazodone and Serotonin Norepinephrine Reuptake Inhibitors (SNRI) Venlafaxine and Mirtapine[37] .

Cancer pain

Pain of cancer is very frequent, mainly in advanced stages, where patient experience moderate to severe pain[38]. Many different causes including bone metastases, visceral tumour infiltration and chemotherapy induced neuropathy may lead to cancer pain[39] . Along with anti-epileptics and corticosteroids, antidepressants are considered as adjuvant analgesic, in evidence based guidelines, and are proposed in patients how have unsatisfactory responses to minor or major analgesics[40,41] . Among tricyclic antidepressants, imipramine and amitriptyline are widely prescribed. Nortriptyline does not have a sedative effect; desipramine is relatively nonsedative and has minimal anticholinergic effect. A dose as low as 10 mg nortriptyline may be appropriate for some patients, but most can take 25-50 mg. The dose in terms of sedation should be increased to 30-50 mg as rapidly as can be tolerated, postural hypotension and dry mouth. After that, increments should be made on a weekly basis until the pain is relieved or adverse effects preclude further escalation. The total daily dose should be given at bed time except with nortriptyline, because most of the tricyclic antidepressants have sedative effect. An analgesic effect is seen in many patients after a few days on doses of 50-100 mg nortriptyline [42] .

Arthritic Pain

Tricyclic antidepressants are used extensively for chronic pain in man without an adequate explanation for their activity. Some studies tested the effect of TCAs in a chronic animal pain model: the arthritic rat [43] . Sprague-Dawley rats with adjuvant-induced arthritis were injected daily for four weeks with imipramine or amitriptyline (10 mg/kg) or saline, beginning twenty one days after the induction of arthritis. Baseline evaluation were made prior to the injection series and at four weeks, 24 h after the last injection. TCAs significantly reduced ‘scratching’ and increased ‘exploring’ behavior, without changing the response to graded foot pressure. This study showed that imipramine and amitriptyline both decrease the arthritis and pain behaviour in this chronic pain model. For rheumatoid arthritis patients Dothiepin 150 mg daily is an effective analgesic. It also has a beneficial efficacy on disability and duration of early morning stiffness. They suggest that this

effect is likely to be principally mediated by direct analgesic mechanism and partly by an antidepressant action [44] .

Irritable Bowel Syndrome

Most studies has benefits not necessarily shared across the antidepressant class. Daily dosages of TCAs that are below the psychiatric range for antidepressant effect typically are effective in IBS, producing at least a moderate response in more than 85% of patients in open label use. Onset of action is rapid with the TCAs, effects appear sustained without tachyphylaxis, and the benefits are unrelated to changes in measures of anxiety or depression—findings supporting a mechanism of action that is distinct from recognised psychiatric effects of the medications[45,46]. Reported experience with contemporary antidepressants, including the selective serotonin reuptake inhibitors, is much less robust [47] . These medications typically are used in full psychiatric dosages, onset of effect on IBS symptoms is not rapid, and the benefits may be related more to a reduction in associated anxiety or depressive symptoms and an indirect effect on IBS symptom reporting. The mechanistic difference between contemporary antidepressants and TCAs in IBS symptom management has not been completely determined, but clinical experience favours important distinctions between antidepressant types [48] .

Fibromyalgia

Antidepressants are now the most widely studied and, for certain, the most successful therapy of fibromyalgia[49]. There is no evidence that monoamine oxidase inhibitors (MAOI) are effective in the treatment of FMS. The only study to investigate the activity of irreversible MAO Is in FMS found them to offer no benefit with the possible exception of combination of 5-HTP and MAOI [50] . The stress- and/or diet-related adverse events seen in this study indicate that these drugs are not suitable for FMS patients. A study comparing the reversible MAOI, moclobemide, and the tricyclic antidepressant (TCA), amitriptyline, and placebo in the treatment of FMS in women without psychiatric disorder, concluded that moclobemide was not helpful[51] . TCAs include the drugs desipramine, or Norpramin, imipramine, or Tofranil, cyclobenzaprine, or Flexeril, and amitriptyline, or Elavil. The TCAs Elavil and Flexeril have been shown in numerous studies to be effective at treating fibromyalgia. Tricyclic antidepressants work by inhibiting reuptake of the neurotransmitters serotonin and norepinephrine back into the brain cells. This prolongs the time the neurotransmitters are signaling. Side effects of TCAs include reduced ability to tear, rashes, dry mouth, constipation, jaundice, sexual dysfunction, daytime sleepiness and infrequent urination.

DISCUSSION

The association between chronic pain and depression is a well-documented phenomenon[11] .In an effort to treat these patients, antidepressants have been a natural choice and their efficacy has been reasonably well established for certain group of patients [12] .Among depressed pain patients, antidepressants can produce analgesia faster and at doses far lower than those required for antidepressant effects[11]. Certain antidepressants may augment opiate effects within the CNS. For example, morphine analgesia is potentiated by amitriptyline, imipramine, clomipramine, fluoxetine, sertraline, and nefazodone[52-54] . Some antidepressants, e.g., tricyclic antidepressants (TCAs), also possess a sodium-channel blockade function, which can mitigate activity of pain-relaying neurons from the CNS, e.g., in sympathetically mediated and neuropathic pain [55]. The efficacy of TCAs appears to be related to the reuptake inhibition of NE and 5-HT. Those TCAs with a broad spectrum of activity may have greater efficacy in pain reduction than those with neurotransmitter-specific effects[56]. Thus, amitriptyline and imipramine, both of which exert prominent NE and 5-HT influences, appear to be more effective than desipramine, which has a prominent NE effect, or clomipramine, which has a prominent 5-HT effect. The adverse effects of the TCAs, e.g., dry mouth, constipation, tachycardia, orthostasis, blurred vision, can limit their utility. The tertiary amine TCAs, e.g., amitriptyline and imipramine, have more troublesome side

effects than the secondary amines, e.g., nortriptyline and desipramine. TCAs would be contraindicated in patients with several conditions, e.g., those with closed-angle glaucoma, recent myocardial infarction, or cardiac arrhythmias, among others. The SSRIs offers the advantages of greater tolerability of side effects and relative safety in overdose as compared with TCAs[57] . The Serotonin-norepinephrine reuptake inhibitor (SNRI) drugs have broad spectrum of activity like Venlafaxine has a broad spectrum of activity including NE and 5-HT and displays some promise with respect to efficacy in certain pain disorders[53]. Venlafaxine has fewer risks of drug interactions as compared with other agents, e.g., fluoxetine and paroxetine. If TCAs are intolerable, venlafaxine may prove to be a viable alternative for the patient with chronic pain. Compared with other antidepressants with analgesic effects, duloxetine an Serotonin-norephinephrine reuptake inhibitor likewise simultaneously and directly affects noradrenergic and serotonergic neurotransmission. Such neurotransmitter influences would be expected to confer upon duloxetine a co-analgesic effect as well as its antidepressant effect. Initial animal studies have been employed to assess its pain-mitigating effects [54] . The tricyclic antidepressants such as amitriptyline, nortriptyline, amoxapine, desipramine, and imipramine show antinoceptive activity in patients with or without depression disorder. These drugs including the antidepressants from selective serotonin reuptake inhibitor and selective norepinephrine reuptake inhibitor classes act by the blockade of reuptake of norepinephrine and serotonin. The tricyclic antidepressants can show benefit in different painful conditions such as neuropathic pain, arthritic pain, cancer pain, diabetic neuropathic pain, central post-stroke pain and irritable bowel syndrome.

CONCLUDING REMARKS AND FUTURE PERSPECTIVES

Chronic pain is an intrapersonal experience not a specific diagnosis. Patients with chronic pain should receive treatment for underlying medical conditions, and should be evaluated for anxiety and distress. Major depression is a common psychiatric comorbidity of chronic pain, is associated with severe consequences, and is very responsive to treatment. In addition to being a primary treatment for depression, antidepressants are effective in the treatment of many chronic pain syndromes such as neuropathic disorders. The complexity of chronic pain requires an extensive knowledge of the potential actions of many pharmacological agents[52] . Antidepressants have become, common drugs for the treatment of chronic, mainly neuropathic, pain, even though their efficacy is limited. Research in the field of antidepressants has evolved substantially in recent years but there are still many issues to be elucidated in both preclinical and clinical research.

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