

Research Article

Depression Management during the Presence of Pain: An Overview

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Abstract

Background: Depression and anxiety are frequently associated with increased risk of medical problems. Severity of these problems varies from persistent pain to severe cardiovascular illness. The pathophysiology of chronic pain and depression overlap in the noradrenergic and serotonergic pathways. Antidepressants, especially dual acting which affect both pathways, are a frequent and effective choice of treatment for chronic pain. Although the co-existence of depression and pain, the treatment differs in terms of depression pain comorbidity and painful symptoms in depression. The aim of this study is to discover and integrate the data about pain.

Methods: We have searched the literature from databases with the keywords “pain”, “depression” and “painful symptoms”. The search was limited to human studies of adults published in English. Because of the large number of studies a second search was required. The extracted data that have on consensus are taken. 10 clinical trial, 3 reviews and 2 metaanalysis that all reviewers agreed have scoped.

Results: We found evidences of strong relationship between pain perception and depression.

Conclusion: The painful symptoms of depression and pain syndromes associated with depression must clearly be identified. Duloxetine has studied extensively and found to be effective in depression. Further studies with different drugs are required.

Keywords: Depression; Painful symptoms; Pain

Introduction

Pain is an unpleasant feeling often caused by noxious stimuli and represents most common reason for patients to seek for medical counsel [1]. The prevalence of chronic pain differs. In United States the prevalence of moderate to severe chronic pain in adults is 35.5 % [2] while it is 19% in Europe [3]. Depending on the definition, the worldwide prevalence is estimated to be between 11%-55% [4]. Acute pain can warn for life-threatening problems while chronic persistent pain may not. Unlike acute pain, chronic pain is associated with functional and structural changes in peripheral and central nervous system and may be a co-existing plague with different problems. Regardless from the comorbid problem, untreated or undertreated chronic pain has significant physical, psychological, social and financial consequences [5]. One of the frequent co-morbidity of chronic pain is depression. This coexistence is not astonishing according to the involvement of some common regions of brain and pathways. Some of the descending neural tracts that project to spinal cord constitute an endogenous analgesic pathway and these tracts originate from periaqueductal grey matter. Involvement of these regions in depression results with chronic pain. Three categories of chronic pain are recognized: neuropathic pain (result of a damage or dysfunction either in peripheral nerves or central nervous system), inflammatory pain and non-inflammatory non-neuropathic pain (also called functional pain). It may be difficult to identify the

painful symptoms of depression and pain syndromes associated with depression. Since the treatment approaches are different, sagacious clinical decision is important for the choice of the treatment.

The aim of this study is to review and integrate the data both about the painful symptoms of depression and pain syndromes associated with depression.

Methods

We searched the literature from several databases with the keywords “depression, pain” we obtained over 4000 clinical trial. If the keywords are “depression, painful symptoms” it is lesser but over 3000. The search was limited to human studies of adults published in English. The results of this search showed that large numbers of studies have done for the same purpose thus a second search was undertaken to identify the relationship between pain and depression. All extracted data were independently reviewed by authors and only studies that have a consensus included. For this purpose 10 clinical trial, 3 review and 2 metaanalysis were reviewed.

Results

Depression and pain

Many depression-linked physical problems (gastrointestinal like dyspepsia and loss of appetite, and fatigue, insomnia and pain) may mask emotional problems (anxiety, guilt etc.) and be refractory to

treatment. Although most interactions between depression and its physical symptoms are well known, some are still unclear. There is growing evidence that depression and depressive symptoms influence physical pathology [6].

As Bair et al. note in their review, the prevalence of pain symptoms in patients with depression range from 15% to 100% (mean 65%) [7]. The prevalence also varies according to setting: among patients in pain clinics 52%, in psychiatric clinics 38%, in orthopedic clinics 56%, in dental clinics 85%, in gynecology clinics 13%, in primary care clinics 27%. The authors also report that a major symptom of depression in primary care clinics is pain. Over 50% of these patients have somatic complaints of which at least 60% were pain related. They also found that increase of pain complaints associates with increased severity of depression. Furthermore, severity of the pain associates with poor depression outcomes. Howland et al. reported that overall pain and pain while awake predict insufficient response to antidepressants [8]. Ehnvall et al. studied 186 treatment resistant depressed patients: increase of pain during depression is associated with increased rejection sensitivity [9]. The combination of pain and depression is also associated with older age, female gender and lower education level. Rethelyi et al. found in their epidemiological survey of 12,640 Hungarian adults, among patients with pain-related disability (33%), the prevalence of depression symptoms was 30% and positively correlated with age and lower education [10]. Nicholl et al. studied the comorbidity of mood disorders and chronic pain in a British population with 149, 611 participants: multisite chronic pain was more prevalent in patients with bipolar disorder and major depressive disorder [11]

As knowledge of bio-processes influencing depression increases, the link between emotional and physical symptoms and pain may become clearer [12,13]. Hypothalamic-Pituitary-Adrenal (HPA) axis, noradrenergic and serotonergic pathways are well-established overlapping mechanisms of pain and depression [14]. Monoamines regulate both mood and pain symptoms. The ascending pathway of pain (from periphery to Central Nervous System-CNS-) modulates by excitatory glutamate and inhibitory GABA. Descending transmission (from CNS to periphery) is associated with nor adrenaline and serotonin which are the targets of dual-acting antidepressants (mirtazapine, tricyclics and Serotonin or adrenaline Reuptake Inhibitors-SNRI-).

Management of pain in depression

Antidepressants: The hypothesized mechanism of antidepressants in the treatment of pain depends on common neurotransmitters involved in depression, especially serotonin and noradrenaline. The use of antidepressants dates back to the 1960s, since when they have been used for neuropathic pain, chronic back pain and fibromyalgia.

Mirtazapine is a well-known antidepressant agent with a combined receptor affinity that acts with 5-HT_{1A} agonism and 5-HT₂ and 5-HT₃ antagonism. Freynhagen et al. used mirtazapine in an observational study of 594 patients with chronic pain and comorbid depression: mirtazapine significantly reduced the symptoms [15]. However due to the common adverse effect of antidepressants acting through the 5-HT₁ receptor (mirtazapine, mianserin, nefazodone etc.) mirtazapine may cause arthralgia [16]. Yeephu et al. compared

15 mg/day and 30 mg/day doses with placebo in 40 patients with fibromyalgia and found no difference between groups [17].

Dual-acting antidepressants (venlafaxine, duloxetine, milnacipran) modulate selective reuptake of serotonin and noradrenaline and are known to be SNRIs. The analgesic effect of SNRI seems to be due to the shared neurotransmitter pathways of pain with depression. Moreover, relief of pain with the administration of venlafaxine and mirtazapine may be partly due to their affinity to opioid receptors [18].

SNRIs are extensively studied in chronic pain without depression, especially in fibromyalgia, but isolated studies in depression with pain are limited. Huang et al. studied 102 depressed patients with painful physical symptoms treated with 75-225 mg/day venlafaxine for 8 weeks and found that venlafaxine is effective and safe to treat depression plus painful physical symptoms [19]. Berge et al. studied 0-450 mg/day venlafaxine in Swiss patients and found it beneficial [20]. Reports about milnacipran is limited regarding chronic pain without depression. A broadly studied SNRI in depression with pain is duloxetine. Li et al. evaluated duloxetine for depression and anxiety in 55 patients with ankylosing spondylitis and reported significant improvement both in spinal pain, BASDAI scores and depressive symptoms [21]. In two 8-week trials with a total of 641 patients Ruskin et al. and [22] and Brecht et al. [23] concluded that duloxetine is superior to placebo.

Despite these few studies of antidepressants, debates continue on the roots of pain in depression and which cases can be accepted as in remission. Some authors suggest that appropriate control of pain in patients with depression may lead to remission in depressive symptoms. For this point of view only duloxetine has been reported. Further studies are required with other treatments. Robinson et al. studied 523 patients with major depression plus pain and remission in depression symptoms was due to the direct effect of treatment, 41% due to pain reduction, and 43% due to functional improvement. Path analysis also indicated 51% of improvement in functioning was due to pain improvement and 43% to mood improvement [24]. Fava et al. [25], Arnold et al. [26] and Beesdo et al. [27] had similar findings.

Other medications: Many clinical trials offered different options from simple analgesics to anticonvulsants and opioids for chronic pain. However, studies of chronic pain and depression are of limited value. Further studies in this population need more analysis of interactions between antidepressants, anticonvulsants and opioid analgesics and addiction. Some studies point to cover prescription of analgesics and frequent administration of opioids [28] and opioid addiction [29] in depressive patients.

Opioids like tramadol have antidepressant as well as analgesic effects. Reeves [30] and Nyhuis [31] et al. revealed that opiates can be used for treatment-resistant depression.

Data about the analgesic effectiveness of anticonvulsants except for gabapentin and pregabalin vary. Pregabalin and duloxetine are approved by the FDA for fibromyalgia. The efficacy and safety of these drugs are well established [32]. Regardless of the evidence, other anticonvulsants, especially gabapentin and carbamazepine are still prescribed both for fibromyalgia and for pain in depressive patients [33,34].

Non-drug treatments of pain in depression: Psychotherapy alone or together with medication has improved physical symptoms and pain in depression. The psychotherapy techniques vary [35,36]. The most frequently-used techniques are cognitive-behavior therapy, operant behavior therapy and psycho dynamically oriented psychotherapy.

Supportive and adjunctive therapies include hypnosis, biofeedback, acupuncture and relaxation trainings.

Conclusion

Major depression increases the risk of several medical problems and there is a link between painful symptoms, anxiety and depression [37]. Probably the most frequent comorbidity is pain and depression. Clinically, severe pain at onset of symptoms predicts poor response to the depression treatment. Alterations of serotonergic and noradrenergic pathways in the central nervous system are the common pathological roots of depression and chronic pain. Severe pain at onset of the symptoms predicts poor response to the depression treatment. Serotonin has a unique role in pain pathways. It plays an algogenic role in peripheral tissues although it acts as an endogenous analgesic role in central nervous system. Unfortunately, this paradigm supports the use of antidepressants which inhibit monoamine and serotonin reuptake for the treatment of painful physical symptoms in depression and anxiety. Dual-acting antidepressants (venlafaxine, duloxetine, milnacipran) have more specific actions on the overlapping pathology of depression and pain. They interact with serotonergic and noradrenergic receptors with different affinity. Moreover, the subtypes of the receptors they interfere may differ leading various analgesic effects. Although some authors do not confirm the difference of their analgesic effects [38], review of the literature suggests that the efficacy of antidepressants (especially SNRIs) may differ and their action may be disease specific. These drugs, especially duloxetine, are broadly studied in the literature. Large clinical trials are about the chronic pain syndromes without depression and the lack of data about the treatment of pain in depression and anxiety continues. Further studies are required concerning the treatment of isolated chronic pain symptoms in depressed patients.

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