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CLINICAL FOCUS: NEUROLOGICAL & PSYCHIATRIC DISORDERS
REVIEW

Depression, anxiety and acute pain: links and management challenges

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ABSTRACT

Pain is a subjective experience that is influenced by genetics, gender, social, cultural and personal parameters. Opposed to chronic pain, which by definition has to last for at least 3 months, acute pain is mostly because of trauma, acute medical conditions or treatment. The link between mood disorders and acute pain has proven to be increasingly significant since the link is bi-directional, and both act as risk factors for each other. Depression and anxiety are associated with increased perception of pain severity, whereas prolonged duration of acute pain leads to increased mood dysregulation. Although both depression and anxiety have a proven association with acute pain, the link between depression and acute pain is more thoroughly studied. Pain can be the presenting or sole complaint in depressed patients who present to primary care practices and is often overlooked by clinicians. However, reports on the perception of experimentally-induced pain in depressed patients are mixed, showing both an increased and decreased pain threshold and pain tolerance across various studies. Although less data is published about anxiety and pain, the relationship is consistent across studies as increased anxiety leads to increased severity of pain perceived and decreased pain tolerance. Anxiety as well as fear, stress, and catastrophizing are also shown to be mediators in the causal pathway between pain and disability.

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Acute pain; chronic pain; anxiety; depression

1. Introduction

The experience of pain is subjective and stems from individual experiences in early life [1]. Contributing factors to the interpretation of pain include genetic predisposition, gender, and mental processes such as feelings and beliefs around pain [2,3]. Pain has a detrimental effect on patients' quality of life as it can significantly affect their activities of daily living, often leading to mood disorders such as depression and anxiety.

Depression and anxiety have a high global prevalence [4]. The link between depression and chronic pain has been well established [5]. Comorbidity of depression and pain can affect individuals of any age, but in the elderly seem to be more prevalent affecting up to 13% of the elderly population.

Although the links and the management challenges of chronic pain and mood disorders have thoroughly been studied, similar research on acute pain is limited. Since acute pain is a significant complaint in various medical settings, from primary practices to tertiary hospital departments, it's link to highly prevalent conditions such as depression and anxiety should be emphasized to clinicians. The aim of this review is to investigate the links between acute pain and its relationship with depression and anxiety.

Methods

The literature search for this narrative review was conducted in May 2019 using the Pubmed database. For the search, three Medical Subject Headings (MeSH) were used; 'acute pain', 'depression', and 'anxiety' in various combinations. Articles were limited to the human species, English language, and full text availability. The reference lists of the identified articles were scanned for further papers, which may fall within the scope of this review and were included where appropriate.

2. Definitions

Acute pain

The International Association for the Study of Pain (IASP) define pain as an unpleasant sensory and emotional experience associated with actual or potential tissue damage [1]. Acute pain does not persist for more than 3 months but is a time-limited response due to noxious stimuli which damage or threaten to damage normal tissues [6]. Acute pain can be due to traumatic injury, in the context of an underlying medical condition or secondary to treatment [6,7].

Depression

The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-V) categorizes depressive disorders according to duration, timing and presumed etiology. The spectrum of depressive disorders is very wide ranging from dysthymia to major depressive episodes with psychotic features [8]. Symptoms of depressive disorders include low mood,

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diminished interest, anhedonia, weight change, sleep disruption, psychomotor agitation, fatigue, feelings of worthlessness or guilt, poor concentration and suicidal ideation. Such symptoms cause significant distress and impairment in social and occupational functioning [8].

Anxiety

Similar to depressive disorders, the spectrum of anxiety disorders is also wide and includes generalized anxiety disorder (GAD), panic disorder, phobias, and social anxiety disorder. Such disorders are typically diagnosed when symptoms of anxiety and fear are excessive, persisting for more than 6 months, causing dysfunction in various domains including work performance or other activities of daily living [8].

3. Epidemiology

According to the World Health Organization (WHO) 4.4% of the world's population are affected by depression [9] Depression is more common among females (female to male ratio 3:2) [9]. It has an overall higher prevalence in older adults. Depressive disorders are the third leading cause of disability worldwide, after low back pain and headache disorders [4].

Anxiety disorders affect 3.6% of the world's population, with females also being affected more than males (female to male ratio 2:1) [9]. Prevalence for anxiety does not vary significantly between the various age groups [9].

Since pain is a subjective, vague, and multivalent experience that is influenced by cultural, social, personal and emotional phenomena, it is difficult to quantify epidemiologically. However, even with such limitations, it's been estimated that the prevalence of chronic pain is 20%, whereas 1 in 10 people are newly diagnosed with chronic pain each year [10].

Epidemiologic studies have shown that pain increases the risk for depression up to 4 times [5,11,12]. Similarly, patients suffering from a major depressive disorder are three times more likely to suffer from non-neuropathic pain and six times more likely to suffer from neuropathic pain [5,13]. Presence of pain corresponds with poorer quality of life and a less favorable outcome of depression [14–17].

4. Depression and acute pain

Barman et al. studied four different categories of acute pain: postoperative, post-labor, post-cesarean, and dental. The levels of depression were assessed during the initial period of pain, prior to medical intervention. The postoperative group perceived more pain and were more depressed compared to the other groups. This was followed by dental pain, post-cesarean and post-labor groups. In the postsurgical and the dental groups, females reported less pain than males [18]. This is based on the belief that women experience depression as a more socially acceptable reaction to pain compared to males [19,20]. Middle aged adults perceived more pain [18].

Post-partum depression and pain were investigated in more depth by Eisenach et al [21]. Women with severe acute postpartum pain had a 2.5-fold and 3.0-fold increased risk of persistent pain and postpartum depression respectively compared to those with mild postpartum pain [21]. The severity of acute pain experienced during childbirth contributed to the increased risk of persistent pain and postpartum depression, whereas mode of delivery had no influence [21].

Studies on the link between acute musculoskeletal acute pain and depression are limited. Ross et al studied depression as a mediating factor between pain and disability by analyzing acute wrist fractures [22]. Depression was evaluated within the acute phase of recovery (within 28 days) of fracture and was found to partially mediate the relationship between pain and disability [22,23].

Pain as the presenting complaint in depressed patients

It is not uncommon for depressed patients to present to primary care practices exclusively with physical symptoms [24]. A study in Norway showed that 75% of patients with a diagnosis of Major Depressive Disorder presented to the GP with their major complaints being unrelated to mood. Amongst these patients, around 50% of the presenting complaints were related to pain symptoms that included myalgia, chest pain, abdominal pain, headache, trigeminal pain and ischialgia [25].

Similarly, other studies have demonstrated that common physical symptoms that can be first manifestations in depressed patients are low back pain, neck pain, gastrointestinal pain, joint pain, muscle pain and headache [14,16,17]. More often than not, these symptoms are interpreted in the context of somatic disorder and lead to a work up of medical illness [24]. For the successful remission of depression, painful symptoms in addition to emotional and vegetative symptoms must be addressed [24].

Perception of pain in depressed patients

Conflicting data is available about the perception of experimentally induced pain in depressed patients as some studies have shown that depressed patients have a lower pain threshold [26–28], whereas others have found a higher pain threshold [15,29–33].

A case-controlled study investigating 735 depressed patients and 456 controls showed no difference in pain thresholds after adjusting for confounders but found significantly higher pain sensitivity in depressed patients [27]. Another case-controlled study by Marsala et al. measured tactile thresholds, pain thresholds and pain tolerance by experimentally inducing electrical impulses to 27 patients and 27 age matched healthy controls. Results showed no difference in tactile perception, but significantly lower pain threshold and pain tolerance in depressed patients than in controls [26]. A recent study by Nitzan et al. investigating 25 patients and 25 age and gender matched-controls, found that depressed patients had a lower thermal threshold when experimental noxious heat stimuli was applied. This was concluded to be due to a higher attention being given to initial pain stimuli. A decreasing attention with every subsequent stimulus applied causing a decreased sensitivity to pain [28].

On the other hand, in smaller studies a higher pain threshold in patients with depression has been reported. Bar et al. investigated pain perception to experimentally induced stimuli across three different pain modalities (electrical, thermal and ischemic) in 30 patients with major depressive disorder and 30 age- and gender-matched controls [29]. Depressed patients showed a higher threshold for electrical and thermal pain, which is consistent with what has been reported across other case-controlled studies, which cumulatively investigated over 200 patients [15,30–33]. However, a decreased tolerance to pain because of muscle ischemia was reported in depressed patients compared to controls [29]. Similar results of decreased ischemic pain tolerance were produced in an experimental study of 11 depressed patients by Suarez-Roca et al [34]. Despite the higher pain threshold, patients with depression complain of more frequent, intense and unpleasant pain as compared to healthy controls [15,32]. This agrees with the literature which describes the 'paradox of pain' in which depressed patients have a higher threshold to experimentally induced pain but are more sensitive to endogenous pain [28]. A possible explanation for this discrepancy is that pain threshold assessed by brief stimuli are not representative of disturbances in endogenous pain inhibition [15].

This mixed data suggests the need for a more detailed assessment and standardized tool to be developed for measuring pain thresholds and tolerance across different experimentally-induced modalities.

In the clinical setting, Bistolfi et al. investigated the influence of mild depression on pain perception in 67 patients after undergoing total knew arthroplasty [35]. Patients who had subclinical depression prior to surgery reported increased pain even after 1-year post-operatively compared to patients without signs of depression pre-operatively. This emphasizes the benefit of a pre-operative psychometric assessment to identify patients that are more likely to perceive increased pain and manage them appropriately [35]. This study also highlights that depression can play a crucial role in the evolution of acute pain into chronic. Figure 1 illustrates the link between pain, depression and anxiety.

5. Anxiety and acute pain

Although less data is published about pain and anxiety, the link between the two has also been established.

Carr et al. showed that anxiety is positively correlated with pain; the higher the anxiety scores are the worst the post-operative pain is perceived. In this study it was also shown that pre-operative anxiety is predictive of post-operative anxiety, a finding that has also been established in other studies [36–38]. This relationship probably is related to the patients' expectations of pain, concerns around its continuation post-operatively, and impact on their lives thereafter [39].

Patients with lower levels of anxiety demonstrate a higher pain tolerance compared to those with higher levels of anxiety [40]. This is probably on the basis of a higher level of anxiety being associated with increased attentiveness to environmental threats and perceived pain [40]. Similarly, Kapoor et al. studied patients who presented to the Emergency Department (ED) with acute pain and showed that pain intensity was positively associated with catastrophizing and state anxiety [41]. It was suggested that the diagnostic procedures and wait times experienced during a typical ED visit contribute to patient anxiety and perception of the overall pain experience [41]. Another study by Hermesdorf et al. investigated anxiety as a predictor of pain in depressed patients. Using the pain sensitivity questionnaire score, the severity of anxiety symptoms predicted a higher pain sensitivity score in depressed patients [27].

Many models have been developed that demonstrate that the fear of pain and pain anxiety have a role in the development of chronic pain and disability [42]. The fear-avoidance response pattern and fear-avoidance model are cognitive models where, in cases of acute pain, the interpretation of pain as harmful (catastrophizing) leads to subsequent fear of pain or pain-related movements. This further encourages avoidance of potential harmful movements and activities. As a consequence of physical disuse, pain disability develops in the long-term [42]. In addition to the development of disability, the avoidance-endurance model describes how patterns of dysfunctional cognitive, affective and behavioral responses to pain contribute to the development of chronic pain. Presence

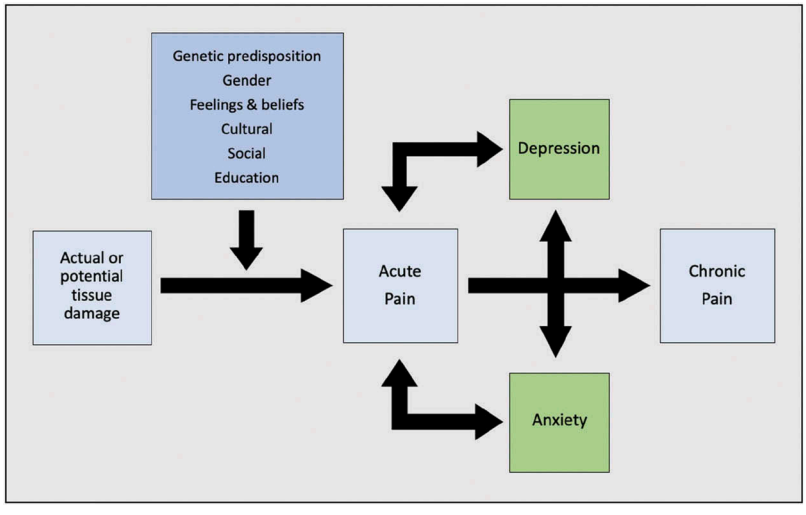

Figure 1. Links between acute pain, chronic pain, depression and anxiety.

of anxiety leads to maladaptive emotion processing, which contributes to maintenance of pain in the long-term [42].

The causal relationship between pain and disability has also been studied, with depression already being shown to mediate the relationship between the two [22]. In the same study, stress was found to be a mediator [22].

6. Biological pathways

When dealing with pain, cortical and subcortical modulatory systems are activated to prompt adaptive behaviors to stressful stimuli. Individuals with depression display heightened distress during anticipation of pain [43]. This corresponds to cognitive models that demonstrate that depressed individuals show bias toward expectations in a negative way. This anticipatory response leads to hypervigilance to impeding threats. This results in depressed patients feeling increasingly helpless which contributes to the maladaptive modulation during the experience of pain. This pathway aids in explaining the comorbidity of pain and depression when these conditions become chronic [43,44].

The coexistence of pain and depression is explained by common neurobiological pathways that involve neurotransmitters such as substance P, gamma-aminobutyric acid, glutamate, dopamine, serotonin and norepinephrine [44–49].

It is well documented that nociceptive fibers transmit painful stimuli via ascending pathways from the periphery of the body through the dorsal horn of the spinal cord to the medulla, midbrain, hypothalamus, thalamus, limbic cortical areas (anterior cingulate and insular cortex), somatosensory cortex, and posterior parietal cortex [50]. It has been suggested that the association between pain and depression is linked to a common descending pathway in the central nervous system. The mechanisms of pain modulation such as attention, expectation, distraction, and negative and positive affect are involved at the level of the descending pathway.

The periaqueductal gray (PAG) is an anatomic structure that relays signals from the limbic forebrain and midbrain to the brainstem [50]. This relay system comprises the rostral ventromedial medulla (RVM) made up of serotonergic neurons, and the dorsolateral pontine tegmentum (DLPT) made up of noradrenergic neurons [46,47]. The RVM has 2 types of cells that contribute to pain perception: 'on' cells which facilitate pain transmission, and 'off' cells which inhibit pain perception [47,50]. The bidirectional on/off system regulates the awareness of threats from both within the body and external sources by either intensifying or reducing pain impulses transmitted from the periphery [49,50].

Activation of the serotonergic or noradrenergic 'off cells' in the RVM or DLTP neurons respectively, reduce the nociceptive neurons in the spinal dorsal horn [50] Under normal circumstances, this modulatory effect suppresses signals coming in from the body so that attention can be focused on significant events outside of the body. In depression, the depletion of serotonin and norepinephrine causes this system to lose its modulatory effect [45–47] Minor signals from the body are intensified, and more attention is focused on them. This explains why pain in depressed individuals is associated with heightened attention, focus, and negative affect.

The medial prefrontal insular, anterior temporal cortex, hypothalamus, and amygdala have a role in the generation of emotion. These regions send projections to brainstem structures involved in modulating pain such as PAG and RVM [50]. An increase in experimentally induced peripheral pain increases the activity of the anterior cingulate gyrus. However, studies show that this region is also activated upon expectation of painful stimuli and activated to a lesser extent during distraction from painful stimuli [50–52]. When negative anticipation is experienced, brain areas activate which cause a subject to focus on and interpret pain as more severe, whereas a distraction from pain shows a decrease in PAG activation and pain perception.

Mechanisms involving opioids have also been suggested to influence the pain-affect relationship [46]. The PAG and relay sites in the midbrain, amygdala, medulla and dorsal horn are rich in endogenous opioids such as enkephalins [35,50]. In experimental studies, peripheral pain signals are shown to be blocked when morphine is applied to these areas of the descending pathway [50] This agrees with the studies that show opiates excite off-cells and suppress on-cells which both dampen pain signals [35].

7. Management

The presence of pain has a negative effect on the recognition and management of depression [20]. A higher number of depressive symptoms and poorer outcomes (i.e. impaired activities of daily living) result when pain is increased in severity and when pain is refractory to treatment [20].

Treatment can have a bidirectional effect. Early treatment of anxiety and depression not only reduces the risk of chronic pain development, but also treating acute pain adequately reduces the risk of patients suffering from depression and anxiety.

When mood disorders and pain are comorbid, a clinician might opt to treat each separately. However, there are pharmacological and non-pharmacological approaches that can target both simultaneously.

Pharmacological approaches

Monoamine transmitters such as serotonin and norepinephrine have a role in downregulating pain perception and their depletion results in comorbid pain and anxiety or depression. Studies have shown that pain signals are blocked when giving serotonin and norepinephrine intrathecally [20]. Similarly, antidepressants that work by increasing the amount of serotonin and norepinephrine in the brain also have a role in pain modulation. Although limited data exists on the use of anti-depressants for the treatment of concomitant depression and acute pain, the most commonly used antidepressants for neuropathic pain are the selective serotonin reuptake inhibitors (SSRIs) and serotonin and norepinephrine reuptake inhibitors (SNRIs) [53]. In addition to the monoamine modulators, tricyclic antidepressant such as amitriptyline, imipramine and nortriptyline inhibit the reuptake of norepinephrine and serotonin and also enhance endogenous pain inhibition in the CNS [53]. Multiple studies have demonstrated its use in easing neuropathic pain such as postherpetic neuralgia [53].

Gabapentinoids, such as pregabalin, are agents that are used for the treatment of neuropathic pain [54] and anxiety [45]. Rickels et al. conducted a double-blinded placebo-controlled trial that showed that pregabalin was more efficacious than placebo for the management of both somatic and psychic symptoms of generalized anxiety disorder [55].

Benzodiazepines have therapeutic effects in neuropathic or inflammatory pain through their effects on the $GABA_A$ receptor [56] The $GABA_A$ receptor has different subunits that have also been found to be involved in mood regulation, demonstrating the anti-depressant potential of benzodiazepines [57].

Opioids such as morphine have proven to be effective drugs in treating pain including pain induced by depression [53]. The three opioid receptors – μ (mu), κ (kappa), and δ (delta) – interact with endogenous opioid peptides such as β-endorphin, enkephalins, and dynorphins [53]. Recent research has also shown the opioid system is involved in the regulation of mood, so further manipulation may achieve antidepressant effects [58,59]. However, despite the fact that opioids have a proven pharmacologic effect in treating both pain and depression, studies have shown conflicting data in the clinical setting. Salas et al. and Scherrer et al. have shown that long term opioid use is associated with an increased risk of depression [60,61]. In addition, the addictive potential of opioids and benzodiazepines, makes their use controversial in patients with depression. Braden et al showed that the duration of opioid use in depressed patients was found to be three times longer compared to patients without depression [62]. These limitations demonstrate a need for further studies investigating the use of opioids in pain-induced depression.

Non-pharmacological approaches

Zanini et al. investigated the association between psychological factors and pain reduction in patients with pain who attend psychotherapy sessions. Psychotherapy in the form of cognitive behavioral therapy (CBT) and short-term integrated therapy proved to be useful in reducing symptoms of depression and anxiety which subsequently reduced pain perception [63]. In addition, other studies have shown that psychotherapy has a significant role in treating pain-induced depression [53,64,65].

In a study by Hopton et al. the management of comorbid pain and depression with acupuncture, counseling, and usual care was investigated [66]. It was shown that patients with pain and depression recover less well than patients with depression only [66]. All 3 therapies proved to be effective for both pain and depression, with acupuncture being the most effective, followed by counseling, and usual care [66]. This is supported by a recent study by Fan et al. who demonstrate that acupuncture has emerged as the most researched and efficacious non-pharmacological approach for pain management. Since acupuncture targets the endogenous opioid system, it has been proposed as an alternative to synthetic opioids which are addictive and have a proven link to increased depression [60–62]. Kaynar et al. compared the efficacy of diclofenac, acetaminophen and acupuncture for the treatment of renal colic by administering each treatment modality to a sample of 40 patients respectively. Acupuncture was associated with the most rapid pain decrease and hence it was suggested to be an effective alternative for rapid analgesia [67] Similarly, Liu et al. investigated acupuncture for alleviation of acute low back pain in 46 patients compared to 14 controls and proved to be a safe and effective method for the immediate relief of pain [68]. Tsai et al. carried out a smaller study in which auricular acupuncture for the treatment of acute pain in the Emergency Department was used in 4 patients: 3 had pain of musculoskeletal origin and 1 was appendicitis-related. The acupuncture proved to be safe, rapid and effective as an analgesic to manage acute pain [69]. Other case reports of acupuncture being used successfully for acute pain in the ED were on pain related to sickle-cell vaso-occlusive events or abdominal pain [70,71].

It must be noted that the majority of the clinical studies of the simultaneous treatment (pharmacological or non-pharmacological interventions) of mood disorders and pain are on patients with chronic pain. More clinical studies are needed in patients suffering from acute pain. Such studies should investigate the role of various approaches including pharmacological, psychological and non-conventional.

8. Conclusion

This review highlights the following key points:

(1) Data on pain threshold in depressed patients is conflicting. This discrepancy encourages standardized methods of measuring pain and is an important point of further research.
(2) Similar to chronic pain and depression, acute pain is experienced more frequently and is of increased severity in depressed patients.
(3) Patients who experience an increased severity or duration of acute pain are more likely to develop depression.
(4) An increased level of acute pain or anticipated pain predicts a higher level of anxiety.
(5) Higher anxiety levels prior to experiencing pain are predictive of a higher pain severity and lower pain tolerance.
(6) Pharmacological treatments that target both pain and depression simultaneously include SSRI's, SNRI's, tricyclic antidepressants, gabapentinoids and opioids. Opioids, however, have been associated with prolonged use in depressed patients compared to non-depressed patients, and a longer course of opioids has been associated with increased depression. Clinicians should be aware of this vicious cycle.
(7) Increasing data is being published around non-pharmacologic treatments, with emphasis on acupuncture lessening the need for opioids since both target the endogenous opioid system.
(8) Screening for anxiety and depression should be part of the holistic evaluation of a patient who presents with acute pain.

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