REVIEW ARTICLE

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The Interplay between Pain, Anxiety and Depression

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ABSTRACT

Pain is a subjective experience with two inseparable components: sensory and emotional. The personal property of pain experience makes it difficult to manage and treat due to the influence of genetics, age, gender, spiritual beliefs, social-economic status, and cultural factors. Similarly, medical care methods partly control pain experience and regulate pain progression. Contrary to chronic pain, which is continuous and recurrent, acute pain is primarily due to trauma, acute medical conditions, or treatment. Whatever the case, both can cause mood disorders. The interplay between mood disorders and pain upholds a progressively significant bidirectional link, as mood disorders and pain are risk factors for each other. Depression and anxiety heighten pain perception or decrease pain tolerance. Acute or chronic pain can also increase the chances of mood dysregulation. Although depression and anxiety have a close relationship with acute pain, the interplay between depression and acute pain is more comprehensively studied. Most depressed patients present pain as their sole complaint in primary care practices, which unfortunately is overlooked by physicians. Howbeit, reports on experimentally induced pain perception in depressed patients are mixed, presenting both an amplified and reduced pain threshold and tolerance. Although there are less published data about pain and anxiety, the association is regular because increased anxiety equally increases pain perception while decreasing tolerance. The aim of this review was to elucidate more on the mechanisms delineating the interconnectivity of pain and mood disorders.

Keywords: *Pain; Depression; Anxiety; Sensory; Emotional; Interplay*

INTRODUCTION

Pain is a personal experience inseparably associated with the mood of an individual, and dramatically contributes in part to why patients visit hospitals. The reason for this association is due to pain comorbidity with other affective disorders and accompaniment of conventional pharmacotherapies with side effects (Voscopoulos and Lema 2010; Bakare and Owoyele 2021; Olaseinde and Owoyele 2021). Hence, a foremost concern of humans, right from the beginning of humanity. Nevertheless, interpretation of pain varies from culture to individual, the mental state and overall feelings, and beliefs about pain (Castro et al. 2009; Oniyide and Owoyele 2018). Acute pain is short-lived, lasting from minutes to about three months. Acute pain is associated with soft-tissue injuries or temporary illnesses; thus, it characteristically wanes after the injury heals or the illness subsides (Castro et al. 2009). Worthy of note is that acute pain from an injury may advance to chronic pain if the injury does not heal correctly or if there is dyshomeostasis in the pain signalling system. Chronic pain is long-lived and can be constant or sporadic. For instance, headaches are chronic pain, especially when they do not resolve and persist over months or years, even if the pain wanes. Chronic pain is mainly related to health conditions like spine

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disorder, arthritis and fibromyalgia (Mifflin and Kerr 2014). Irrespective of pain type (acute or chronic), it has a negative effect on the quality of life of individuals as it can seriously hinder daily activities, which explicitly leads to mood disorders such as anxiety and depression (Artemiadis and Zis 2018).

Anxiety and depressive disorders are among the most reported mood disorders; they are often comorbid with each other (Michaelides and Zis 2019), and collectively they belong to the broader class of internalizing disorders. In 2017, statistics from the Substance Abuse and Mental Health Services Administration showed that about 13.3% of adolescents and 7.1% of adults worldwide had major depressive disorder (Zis et al. 2017; Kalin 2020). There is limited data for anxiety disorder; however, in 2001-2003, the prevalence of anxiety was estimated to be 19.1% in adults, and between 2001-2004 lifetime prevalence was approximately 31.9% (Kalin 2020). Women are more prone to anxiety and depressive disorder, with an estimated 2:1 ratio in women relative to men during the reproductive years (Jalnapurkar et al. 2018). Pain accounts for one of the reasons for anxiety and depressive mood disorders (Cohen and Stackman 2015). The more pain persists, the more devastating its effect on the emotional status of such individuals (Al-Sabbagh et al. 2015). It is therefore rational to believe that chronic pain conditions likely cause mood disturbances of great severity. Despite the coexistence of anxiety and depression (Gureje 2008), it is startling that the interplay between anxiety, depressive disorders, and pain has received limited research attention, with even limited focus on the mechanisms. This review focuses on delineating the interplay between anxiety and depression, and the mechanisms that connect them.

METHODS

Several databases like Google Scholar, PubMed, ScienceDirect, Scopus and BioMed Central were searched from 1995 to 2022 to review pain and its interplay with anxiety and depression. Keywords like pain (acute and chronic), anxiety, depression, interplay, association, connection, biological and psychological mechanisms, dopamine, serotonin, noradrenalin, hypothalamic-pituitary-adrenal (HPA) axis, functional magnetic resonance imaging (fMRI), amygdala, prevalence, and epidemiology were used. The objective was to address and review the current state of knowledge, issues, and concerns associated with the mechanisms of comorbidity of pain and anxiety, as well as pain and depression. Research papers used in this article are comprehensively different in their designs, methodology, aims and goal; giving a wide-ranging evaluation.

Brief Descriptions of Terms

Pain

According to the International Association for the Study of Pain (IASP), pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage (IASP 1979; Aydede 2017). Pain is the most frequent symptomatic complaint in medicine; a critical understanding of its pathophysiology and the association with other emotional disorders is vital in patient management (Raffaeli and Arnaudo 2017). In the quest to understand pain, it is worthwhile to differentiate between nociception and pain. Detection of noxious stimuli by nociceptors is nociception. Nociception precedes the transduction and transmission of sensory information from the peripheral to the central nervous system. Pain is a product of higher brain centre processing, which entails sensory and affective components concerning actual unpleasant experiences from nervous signals. Studies on pain are not just a direct result of nociception as often believed. It involves interaction with numerous inputs (attention, affective dimension, autonomic variable, immune variables and many more); and may be viewed holistically and accurately from the perspective of neuromatrix with emphasis on anxiety and depression (Raffaeli and Arnaudo 2017). Depending on the duration, pain may be acute or chronic. A brief explanation of the classes may be helpful clinically to assist in its management as a symptom and possible diagnosis of the underlying conditions.

Acute Pain

Acute pain lasts less than three to six months, with a time-limited response due to soft tissue damage or the one that threatens to damage normal tissues, such as sprained ankle or a paper cut (Yam et al. 2018). Acute pain is sharp and more severe than the chronic type, but it is short-lived and gradually resolves as the injured tissues undergo healing (Artemiadis and Zis 2018). It is a putative belief that acute pain may transit to chronic pain; the question is, when does acute pain become chronic? The current theories opine that chronic pain arises when acute pain prolongs with an observation of long-standing alterations (biochemical and histopathological) within and outside of the central nervous system (CNS) (Voscopoulos and Lema 2010).

Chronic Pain

Chronic pain is progressive and lasts longer than six months. It continues even after the injury or the illness that caused it is resolved or healed (Liao et al. 2022). In this instance, there is pain perception within the nervous system for weeks, months, or years. As a result, this type of pain is a disease state and maladaptive. Chronic pain is associated with the nerve, back pain, arthritis, headaches, and cancer (McCracken and Eccleston 2003). Due to the long-lasting effects of chronic pain, it can result in depres-

sive/anxiety-like behaviours and fear of re-injury. The pain and mood disorders in this context result in inability to return to work or leisure activities. The development of chronic pain is biphasic: modulation or modification of nociceptive systems. The modulation indicates reversible alterations in the excitability of the primary sensory neurons and central nerve fibres, facilitated mainly by post-translational adaptation of biological transducers and ion channels through cascade activation of intracellular signalling processes (Yam et al. 2018; Ott and Nieder 2019). The modification signifies long-lasting alterations in the expression of neurotransmitters, receptors, and ion channels. It also depicts alterations in the structure, neuronal network, and survival of neurons in a manner that the cytoarchitecture adapts to changing typical stimulus-reaction features (Yam et al. 2018). Modification is more reasonably linked to the transition from acute to chronic pain (Woolf and Salter 2000).

Anxiety

The definition of anxiety covers a broad spectrum, just like depressive disorders. These include generalized anxiety disorder, panic disorder, phobia, and social anxiety disorder. For instance, anxiety, defined in the context of an anticipated negative event, is a state associated with preparation for possible upcoming adverse activities. These disorders are diagnosed when symptoms of anxiety and fear are extreme, continuing for more than six months: Thus, resulting in the dysfunction in various domains, including a performance of daily activities or other vital routines for daily living (Craske et al. 2011). Anxiety symptoms are of three responses; verbal-subjective, overt motor acts, and somato-visceral activity. Under this system and the definition of anxiety, the indicators of anxiety include worry (verbal-subjective), avoidance (overt motor act), and muscle tension (somato-visceral activity) (Lang et al. 2000). It is often contentious to distinguish between anxiety and depression as they share specific symptoms in common, while some are unique to each. The common symptoms are negative affect or general distress factor, while the manifestation of physiological hyper-arousal is specific to anxiety. The subjective anxiety manifestations are characteristically the chief marker of general pain (Kalmbach et al. 2012).

Depression

Depression is a common and severe medical condition that negatively affects the feeling, thought patterns, and actions. According to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-V), depressive disorders are categorized based on duration, timing and presumed aetiology (Del Barrio 2016). Depressive disorders, just as anxiety, have a vast spectrum ranging from dysthymia to major depressive episodes with psychotic features. Depression results in feelings of sadness and, or lack of interest in the activities once loved. It leads to emotional derangements and physical complications, and decreased ability to function optimally at work and home. Globally, depression accounts for more 'lost years' to disability than any other medical condition (Michaelides and Zis 2019). This is because many people suffer from the illness: About 350 million, according to the World Health Organization, and the fact that it persists for many years (Zis et al. 2017; Michaelides and Zis 2019). The symptoms of depression include; sad feeling or having a depressed mood, loss of interest or pleasure in activities once enjoyed, anhedonia, lack of energy or increased fatigue, poor thinking, concentrating or making decisions, death or suicidal ideation, weight gain or loss, alteration in sleep pattern, and psychomotor disturbance. Such manifestations lead to significant distress and weakening of social and occupational function (Pielech et al. 2020).

Acute pain and Anxiety

Although acute pain is an adaptive sensory experience required to avert further bodily harm, the progression of acute to chronic pain is not adaptive. It may lead to the development of stable clinical conditions (Mifflin and Kerr 2014). The link between acute pain and anxieties has a limited data (Michaelides and Zis 2019; Edge et al. 2020). However, most of the studies on acute pain and anxieties elucidate more on the psychological evidence with less information on the biological mechanisms.

Carr et al. (2005) revealed that the pre-operative levels of anxiety were high in women having major gynaecological surgery, and the patients continued to be anxious even after the operation. They also showed that four days post-operation, there were increased pain, anxiety and depression scores. This outcome might have emanated from patients' belief on pain, apprehensions surrounding its continuation post-operatively, and the probable impact on their lives thereafter (Boeke et al. 2005; Carr et al. 2005). A research was conducted on the effects of attention focus and traits anxiety on experimental acute pain tolerance. In this research, subjects having 'high' and 'low' trait anxieties were distributed into three attention-focus conditions: 'pain-focused attention, 'undirected' (no experimenter-induced attempts to influence attention focus), and distraction. It was observed that attention and anxiety are interrelated in that low-anxiety participants had high pain tolerance, and high-anxiety participants had low pain tolerance, in the undirected condition (James and Hardardottir 2002; Ross et al. 2015). The results agree with the opinion that anxiety raises alertness to possible environmental threats and might have implications for the clinical management of acute pain (James and Hardardottir 2002). This could further explain injection phobia or fear of needles (trypanophobia) and why increased pain perception is often perceived before and after injections; a pivotal reason for why

some patients' health would have to deteriorate before consulting medical caregivers (Alexander 2012).

A Connection between acute pain and negative affect like anxiety has been demonstrated in the younger population, though reports vary (Gilam et al. 2020). Moreover, there have been minimal reports on the connection between acute pain and anxiety in older adults (Feeney 2004; Gilam et al. 2020). An investigation conducted on relative contributions of state and trait anxieties, depression, and state and trait anger to acute pain in an aged, post-surgical population showed that the only prognosticator of pain in this population was anxiety, and this variable alone resulted in 27 % alteration in pain (Feeney 2004). In the same vein, reports on patients who presented at the Emergency Department (ED) with a history of acute pain, revealed a positive connection between pain catastrophizing and state anxiety. Queue times and the diagnostic procedures experienced during a typical ED visit might have influenced patients' anxiety and pain tolerance of the overall pain experience (Kapoor et al. 2016). Another study which focused on the predictive effect of anxiety on pain catastrophizing in anxious patients using the pain sensitivity questionnaire score concluded that the severity of anxiety symptoms predicted a low pain threshold score in depressed patients (Hermesdorf et al. 2016).

Ploghaus et al. (2001) used event-related functional magnetic resonance imaging (fMRI) to focus on how anxiety can exacerbate pain sensation, and compared activation responses to noxious thermal stimulation; while by alterations in either physical intensity or induced anxiety manipulated professed pain intensity. A single visual signal consistently predicted moderate intensity of noxious stimulation, and suggested decreased anxiety about the impending pain. Additional visual signals sporadically followed the same moderate intensity of noxious stimulation in most of the trials but distinguishable in stronger noxious stimuli. This result suggested an increased level of anxiety. Moreover, entorhinal cortex of the hippocampal formation reacted differently to the same noxious stimuli, subject to enhancement of the professed pain intensity by pain-relevant anxiety. During emotional pain modulation, entorhinal reaction predicted activity is closely associated with affective (perigenual cingulate), and intensity coding (mid-insula) areas. This finding suggested that adequate preparatory information during medical procedures lessens pain perception by disengaging the hippocampus. Hence, the finding from the research supports the theory that during anxiety, the hippocampus amplifies aversive situations to prime behavioural reactions that are adaptive to the worst possible outcome.

In 2005, a study examining the combined effects of state, and trait anxieties on pain threshold and subjective pain intensity revealed that higher state anxiety led to heightened pain intensity for all participants. Again, individuals with high trait-anxiety had considerably increased levels of anxiety and pain intensity than low trait-anxiety individuals across all pain and anxiety conditions (Tang and Gibson 2005).

A study in 2008 also investigated the effects of preferred music listening on anxiety and pain perception in patients undergoing haemodialysis. The study used a two-group experimental design. Sixty patients diagnosed with end-stage renal failure undergoing haemodialysis treatment took part in this study with the application of preferred music listening intervention. Pre- and post-test anxiety and pain levels evaluated revealed that the control group had considerably higher state anxiety than the experimental group and experienced significantly increased pain sensitivity in the post-test phase (Pothoulaki et al. 2008).

The body of knowledge is limited about the connection between anxiety and pain in animals. To evaluate whether trait anxiety modulates nociception in animals, Roeska and his colleagues measured hypersensitivity after chronic constriction injury in rats specifically bred for high (HAB) or low (LAB) anxiety-like behaviours. They observed that HAB and LAB rats displayed similar levels of mechanical hypersensitivity seven days post-injury. However, on days fourteen and twenty-one post-surgery, mechanical pain stimulation thresholds were significantly low in HAB rats relative to LAB rats. Findings further indicated that trait anxiety increases mechanical hypersensitivity in chronic constriction injury though at the chronic phase of pain, thereby opinionating that emotional processes influence even simple pain-related behaviour (Roeska et al. 2009). Other studies have also reported the influence of anxiety on pain perception in animals (Rivat et al. 2010; Bakare and Owoyele 2021).

Advanced models show that algophobia and pain-related anxiety play a significant role in developing chronic pain and disability. The fear-avoidance reaction pattern and simulation are cognitive activities to profess acute pain as harmful (catastrophizing) with a consequent phobia for pain or pain-associated movements. This further stimulates avoidance of possible harmful movement, environment, and activities. Because of physical disuse, pain disability emanates in the long term. Apart from the disability development, the avoidance-endurance models explain how patterns of dysfunctional cognitive, affective, and behavioural reactions to pain contribute to the development of chronic pain. The existence of anxiety leads to maladaptive affective processing, which in turn positively affects the maintenance of pain in the long term (Hasenbring et al. 2014). Stress is an influencer and causative link between pain and disability in mood disorders (Ross et al. 2015).

Anxiety and Chronic Pain

Chronic pain and anxiety disorders are prevalent in the general population, and epidemiological reports suggest a bidirectional association exists between

these two. Functional imaging observations showed that this bidirectional association was due partly to common neural mechanisms (Hooten 2016). There are shreds of evidence to propose the connection of anxiety to the progression of pain experience, most especially in men relative to women. Elklit and Jones (2006) found anxiety to be positively associated with the level of general disability in men than women. One thousand seven hundred and nine people with whiplash (1,349 women, 360 men); completed a battery of questionnaires evaluating demographic, psychologic, and pain-related parameters (including frequency of painful episodes, level of pain interference, number of anatomic regions involved in pain perception, and the level of general disability). A trend variance in correlation scale existed between men and women when comparing anxiety with pain frequency and the scale of correlation was higher in men.

Other studies on the positive connection between anxiety and pain are revealed in some other disease conditions (Ploghaus et al. 2001; Van Middendorp et al. 2010; Yoshino et al. 2010). For instance, among female patients having fibromyalgia, anger and sadness increased their pain experience (Van Middendorp et al. 2010). In irritable bowel syndrome (IBS) patients, IBS-related-anxiety/fear appreciably increased pain perception (Wiech et al. 2008; Wiech and Tracey 2009). In post-traumatic stress disorder patients, a chronic and devastating anxiety disorder significantly increased the progression of chronic pain and pain perception (Smith et al. 2002; Geuze et al. 2007). In agreement with these findings, procedures or manipulations that decrease anxiety and anxiolytic drugs have been observed to play critical roles in reducing pain experienced in chronic pain patients (Wiech and Tracey 2009). In addition, pre-operational anxiety level can foretell the intensity of pain distress in patients having post-surgery pain (Kain et al. 2000; Kain et al. 2006). Increased pre-operative anxiety levels leads to more painful postoperative recovery, insomnia, and other problems among people who have chronic pain (Kain et al. 2000). An anxiety-pain association also exists in the animal model of visceral pain. Robbins et al. (2007) reported that chronic psychological stress increased nociceptive responses

Table 1: Studies showing the Coexistence of Anxiety and Chronic Pain

S/N	Author	Study Objectives	Major Results
1	Lerman et al. (2015)	Investigation of the longitudinal association between pain, pain-related disability, and symptoms of depression and anxiety. Four hundred and twenty-eight patients with chronic pain (mean age 54.84 years, mean pain duration 85.21 months) completed questionnaires regarding pain.	More than half of the sample on all waves significantly reported depression and anxiety symptoms. High levels of depression and anxiety increased their pain sensitivity and pain-related disability.
2.	Benore et al. (2015)	The authors examined the association between anxiety reduction and functional outcomes in 119 children and adolescents receiving intensive interdisciplinary rehabilitation services for chronic pain between 2007 and 2012. The specific evaluation was on whether: (1) anxiety changes throughout the treatment; (2) anxiety co-varies with functional outcomes to rehabilitation; and (3) change in anxiety predicts change in functional outcomes from rehabilitation for chronic pain	Measures of anxiety-related constructs considerably correlated with measures of impairment and functioning, both at admission and at 1-month post-discharge.
3.	Koga et al. (2015)	Examination of the synaptic mechanisms role in reenforcing interaction between anxiety and chronic pain. Characterization of presynaptic (pre-long term potentiation that requires kainate receptors) and a postsynaptic (pre-long term potentiation that requires N-methyl-D-aspartate receptors.	Chronic pain and anxiety resulted in selective occlusion of pre-long term potentiation. Microinjection of hyperpolarization-activated cyclic nucleotide-gated (HCN) channel blocker, ZD7288, into the anterior cingulate cortex *in vivo* produced both anxiolytic and analgesic effects. These results indicated that long-lasting anxiety induced by chronic pain depends on presynaptic plasticity.

4.	Kawai et al. (2017)	The authors examined the adverse impacts of chronic pain on physical and psychological health and work productivity. Chronic pain groups were abdominal, back, joint, multisite, and neuropathic in 591 patients, or no chronic pain in 150 participants.	One third of patients with multisite pain (33%) and neuropathic pain (32%) reported mild/major depressive symptoms.
5.	Zale et al. (2019)	The authors conducted cross-sectional relationships between pain-related anxiety, gender, and alcohol use. Adults with chronic pain (N = 234; M_{age} = 29.54, 67% Female) self-reported pain-related anxiety, gender, and alcohol use	Pain-related anxiety positively related to alcohol-associated consequences and alcohol dependence symptoms. The result indicated that pain-related anxiety might be an essential factor to consider in the context of alcohol research and treatment among drinkers.
6.	Rogers et al. (2019)	Authors investigated if anxiety sensitivity may be one factor associated with the relationship between pain intensity and opioid misuse among opioid-using adults with chronic pain.	Results showed that anxiety sensitivity total score considerably related to pain intensity and opioid misuse, as well as pain aggravation and severity of opioid dependence. The results proposed that anxiety sensitivity may be a vital factor to note in pain assessment and intervention targets to ultimately reduce the rates of opioid misuse among individuals with chronic pain
7	Grunberg et al. (2021)	The authors investigated explanatory mechanisms of alteration in emotional distress following a mind-body and activity intervention among 82 participants (21 – 79 years old, 65.85% female, 80.48% White) with depression and anxiety as outcomes. They hypothesized that potential mediators would include pain catastrophizing, mindfulness, and pain tolerance.	Improvements in depression from baseline to post-treatment mostly explained by pain catastrophizing, followed by mindfulness and pain tolerance. Improvements in anxiety from baseline to post-treatment mostly explained by pain catastrophizing and mindfulness but not by pain tolerance. These results indicated that pain catastrophizing and mindfulness appear to be vital intervention targets to improve emotional functioning for chronic pain patients.

in the urinary bladder in rats with high levels of anxiety. Table 1 shows more studies.

Depression and Acute Pain

Epidemiological studies on the comorbidity of pain and depression in primary care and population samples revealed that: (1) pain is significantly connected with anxiety and depression; (2) features that foretell depression are diffuseness of pain and the degree to which pain affects daily routines; (3) manifestation of some psychological parameters (decreased energy level, sleep disturbance, and apprehension) are prominent among patients that experience painful conditions, while others (guilt and loneliness) are not; (4) pain and depression dysfunction are presented in the early history of pain; and (5) amidst primarily dysfunctional pain patients whose disturbance is mainly chronic, depression levels do not resolve nor increase over time with the chronicity alone. These results agree with the mechanisms of comorbidity of pain and depression: (1) an attribute of predisposition to both dysphoric physical signs (including pain), and a state of somatosensosry intensification in which psychological distress increases dysphoric physical sensation (including pain); (2) psychological illness and behavioural disturbance being associated attributes of a maladaptive reaction to pain evident in the usual history of the condition, and often resolving during an early recovery phase; and (3) pain involving significant psychological and physical stressors that may stimulate or increase the psychological stressors. Thus, pain and physiological disorders have both physiological and affective properties involving both processing of illness expression and adaptation, as well as pain with detailed effects on emotional state and behavioural function (Von Korff and Simon 1996).

Different classes of acute pain: postoperative, post-labour, post-caesarean, and dental have been extensively studied (Barman et al. 2015; Michaelides and Zis 2019). Barman et al. (2015), examined depression levels during pain onset and before medical intervention. According to them, the postoperative patients professed increased pain perception and were more depressed relative to the dental pain, post-caesarian, and post- labour groups. Post-surgical and dental groups had more females who reported less pain than their male counterparts. The result is in accordance with the belief that women experience depression as a norm and a more socially acceptable reaction to pain relative to males (Geerlings et al. 2002; Arnow et al. 2006). Barman et al. (2015) reported that middle-aged male adults have higher pain perception than their female counterpart. Furthermore, women having severe postpartum pain have a 2.5-fold and 3.0-fold heightened risk of persistent pain and postpartum depression, respectively, relative to women with mild postpartum pain. The intensity of acute pain encountered during parturition contributed to the vulnerability of developing persistent pain and postpartum depression, whereas the delivery method had no effect (Voscopoulos and Lema 2010).

Depression and Chronic Pain

The relationship between depression and chronic pain is a complex one. Both depression and chronic pain may develop independently or secondary to each other, or both may co-occur (Fig. 1). Diagnosis of the coexistence of the two conditions can be challenging (Surah et al. 2014). The occurrence of chronic pain is a risk factor for the development of depression. Also, physical sickness can manifest symptoms of depression (Williams et al. 2006; Surah et al. 2014). A typical puzzle encountered while delineating the relationship between chronic pain and depression is whether depression precedes or follows chronic pain. Some theories, however have been put forward (Blackburn-Munro 2004): (1) Antecedent hypothesis opines that depression precedes the development of chronic pain. A Large number of depressed patients experience pain, which can be excruciating. Depression can heighten pain perception and lower pain threshold (Michaelides and Zis 2019); (2) consequence hypothesis opines that depression occurs due to chronic pain. The progression of chronic pain can worsen depression (Blackburn-Munro 2004). Essentially, chronic pain leads to devastating physical conditions with decreased physical and social functions, which ultimately results in self-isolation, loss of self-worth, and other psychological attributes of depression (Von Korff and Simon 1996).

Investigating pain as a physical symptom or occurrence in depression is progressively becoming a research interest. Worthy of note that pain is not in the Diagnostic and Statistical Manual of Mental Disorders-Fourth Edition (DSM-IV-TR) criteria; nevertheless, it is a commonly reported symptom (Zis et al. 2017; Michaelides and Zis 2019). A review probing the epidemiology coexistence of pain and depression emphasized the significance of including pain as a sign or part of the diagnostic criteria for depression (Peres et al. 2017).

Mechanism of the Association between Pain and Anxiety

In contrast to animal models with limitations, reports from human imaging have provided better support for clinical observations of the association between pain and anxiety (Ploghaus et al. 2001; Wiech and Tracey 2009). For instance, patients with anxiety about pain have increased pain perception, and the anterior cingulate cortex (ACC) is the critical area of the brain for such action. Most importantly, brain imaging studies have shown that ACC is activated when there is anticipation of pain (Clark et al. 2008). ACC function relates to emotional valence. Looking at sad facial expression heightens pain-rating in healthy individuals, and is accompanied by increased stimulation of ACC and the amygdala (Yoshino et al. 2010). Although other brain areas have been implicated in a possible anxiety-pain relationship, the role of ACC is well spelt, and plays a key component in the neuronal pathway involved in enhanced pain perception (Wiech and Tracey 2009). The amygdala, being the seat of affective responses, has been thoroughly investigated for its crucial role in emotional anxiety and fear. There were anxiety/fear responses when the amygdala was electrically stimulated in humans and animals, whereas the lesion of the amygdala inhibited the expression of these emotional conditions. Painful stimuli reach the amygdala through afferent projections from the thalamus. The sensory information flows from the lateral to the basolateral amygdala, and then it finally reaches the central amygdala. From here, efferent nerve fibres reach the periaqueductal gray matter, brainstem, and the hypothalamus (van Rooij et al. 2021).

Mechanism of the Association between Pain and Depression

Pain and psychiatric illness have some psychological and behavioural factors in common (Von Korff and Simon 1996; Barman et al. 2015). The fundamental mechanism of the reciprocal association between pain and depression is still elusive; nevertheless, biological and brain imaging studies have assisted in underscoring this relationship.

Biological Relationship

Two major neurotransmitters are strongly implicated in the link between pain and depression, serotonin (5-HT) and noradrenaline (NA) (Elklit and Jones 2006; Williams et al. 2006). Concerning depression, an appreciable body of knowledge supports the opinion that 5-HT and NA play a crucial role in controlling many physiological and pathophysiology aspects of the body systems (Williams et al. 2006; Ghoneim and O'hara 2016). Perturbations in these chemical transmitters affect the general well-being and motivation, and primarily responsible for some of the common symptoms of depression. Serotonin also has a significant role on the processing of pain and on pain perception in the peripheral nervous system. Remarkably, the effect of serotonin on nociception can be biphasic: either a pro-nociceptive or an anti-nociceptive, depending on the subtype of the serotonin receptor activated, and the region of the CNS where binding takes place. For instance, the pro-nociceptive function of serotonin in the periphery is through activation of the 5-HT3. In contrast, the primary anti-nociceptive actions of serotonin are elicited through 5-HT1A and 5-HT2 receptors, most especially the ones located centrally in the descending anti-nociceptive pathways. The anti-nociceptive action of NA is through α-2 adrenoreceptors in descending anti-nociceptive axis. NA decreases the sensitivity of dorsal horn neurons to nociception. Serotonergic (Fig. 2) and noradrenergic (Fig. 3) axes from the brainstem ascend into the forebrain and mediate affective and physical functions. Asides, they descend the spinal cord for down-regulation of nociceptive signals (Delgado 2004; Stahl and Briley 2004). Dyshomeostasis of 5-HT and NA within the CNS (Fig. 3 and 4) may contribute partly to the mediation of increased pain perception among depressive disorder patients through modulation of the ascending pain sensation from the spinal cord.

Hypothalamic-pituitary-axis (HPA) also plays a vital role in the aetiology of both chronic pain and depression. Major depression also arises from dyshomeostasis of the HPA axis through up-regulation of adrenocorticotropic hormone and plasma cortisol (Blackburn-Munro 2004). Stress reaction is under the control of the neuroendocrine HPA axis. Activation of neuroendocrine HPA axis is in response to a physical or emotional stressor and aids adaptation. Pain may be associated to alterations of the central regulation of the HPA axis. Negative feedback mechanisms regulate homeostasis. However, ongoing and prolonged tension, and stress-related pain alter this reaction, which in turn down-regulate 5-HT levels and causes dyshomeostasis of other biological transducers (Fig. 5) implicated in depression.

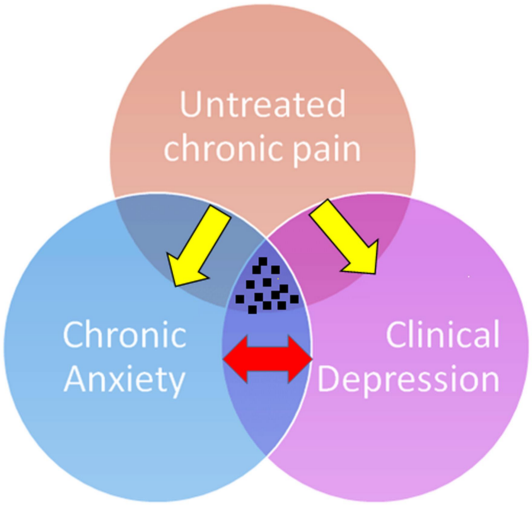

Fig. 1: A simplified model depicting possible association among untreated pain, clinical depression, and chronic anxiety. Areas of connection between the two conditions show comorbidity. In the condition of concurrent pain and depression, the evidence in the literature proposes one-way causality (yellow arrow), e.g. undertreated or untreated pain may result in depression, unlike vice versa. A similar association exists between pain and anxiety. Nevertheless, the association between anxiety and depression has a two-way causality (red arrow), e.g. chronic anxiety may result in depression, as well as depressive episodes may lead to manifestations of anxiety. The area within the triangle between pain, anxiety, and depression represents the contemporary manifestation of the three conditions, and a 'gray' section represents many unanswered questions. Adapted from Yin et al. (2015)

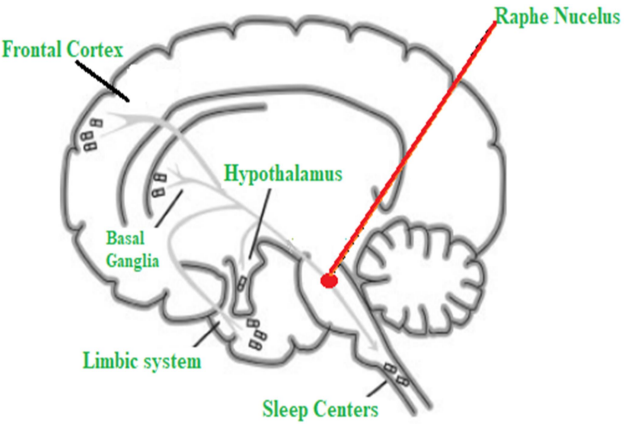

Fig. 2: Serotonergic axis in the brain. Projections of serotogenic neurons to: 1. Frontal cortex for mood regulation; 2. Basal ganglia for movement regulation; 3. Limbic areas for modulation of emotions, particularly anxiety and depression; Hypothalamus for eating, appetite, weight and sex regulation; 5. Sleep centres for sleep-wake cycle regulation. Adapted from Stahl and Briley (2004)

The mesolimbic system, a circuitry majorly concerned with the supply of dopamine from the ventral tegmental area to some critical neural structures such as nucleus accumbens, prefrontal cortex, ACC, and amygdala (Fig. 6) is involved in pain and affective disorders. The mesolimbic system partly controls the executive, affective, and motivational functions. Chronic pain patients suffer from decreased levels of dopamine production and low supply in this system. The volume of structures that make the mesolimbic system is known to decrease in such patients. Administration of dopaminergic medications to control chronic pain and increase dopamine levels in the mesolimbic system was effective in patients with Parkinson's disease, restless leg syndrome, fibromyalgia, dry mouth syndrome, lumbar radicular pain, and chronic back pain. Even though, few researchers confirmed these results, dopaminergic medications are less used to treat the various diseases causing chronic pain (Yang et al. 2020).

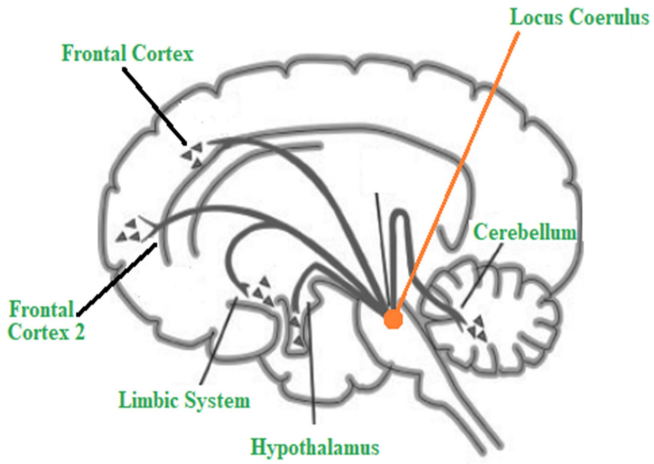

Fig. 3: Noradrenergic network in the brain. Projections of noradrenergic neurons to: 1. Frontal cortex for mood regulation, cognition and attention; 2. Basal ganglia for movement regulation; 3. Limbic areas for modulation of emotions, particularly anxiety; Hypothalamus for eating, appetite, weight and sex regulation; 5. Sleep centres for sleep-wake cycle regulation; 6. Cerebellum for regulation of movement. Adapted from Stahl and Briley (2004)

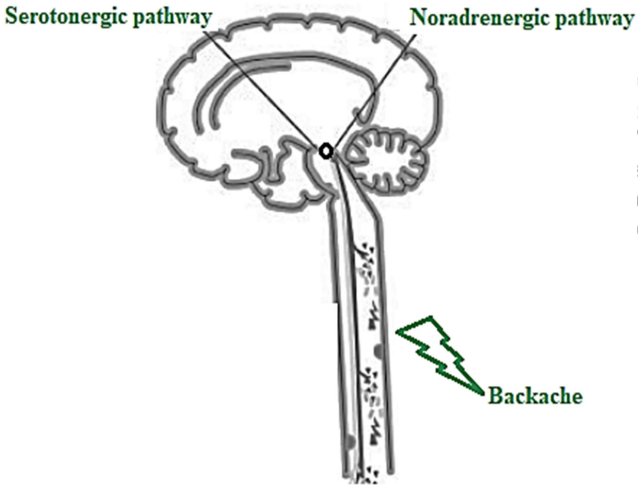

Fig. 4: Symptoms associated with dysfunction of descending serotonergic and noradrenergic pathways. Descending serotonergic and noreadrenergic pathways arise from raphe nucleus and the locus ceruleus. They are involved in suppression of sensations associated with pain and feedback from the musculoskeletal system throughout the body. Adapted from Stahl and Briley (2004)

Furthermore, the amygdala plays a fundamental role in the reciprocal association between pain and negative emotional states (Veinante et al. 2013). The amygdala is a known control centre in the brain and controls emotional behaviour and memorial processing (Yang et al. 2020). Amygdala alters the functions of the endocrine and the autonomic nervous system. Dyshomeostasis in the function of the amygdala results in negative affective states. The amygdala is typically involved in the inhibition and enhancement of pain, with heightened activation and negative effect that is associated with stimulating the pain excitatory axis. Nonetheless, there are various reports regarding the level of activity of the amygdala in reaction to the pain, with different reports showing increased activation (Mcewen and Gianaros 2010), while some reveal a decrease (Becerra et al. 2001), and others suggest its reliance on the context of pain. This report shows that the amygdala is instrumental in the association between pain and depression.

Brain Imaging (fMRI) Studies

Functional magnetic resonance imaging (fMRI) also depicts the relationship between depression and chronic pain. fMRI shows the connection of pain with the amygdala and the ACC. The ACC is the part of the brain identified with significant involvement in mood disorders and its regulations (Mechawar and Savitz 2016). There are significant alterations in the amygdala of patients with emotional disorders (Yang et al. 2020). Activation of large groups of neurons in the ACC was associated with painful stimuli. For instance, application of pressure pain on the index fingers of eight healthy subjects activated unconnected central clusters in the ACC (Williams et al. 2006; Michaelides and Zis 2019). Moreover, electrolytic lesion of the ACC differentially regulates mechanical hypersensitivity and escape/avoidance behaviour (LaGraize et al. 2004). *Ab initio*, investigations on the cerebral representations of pain with the aid of functional imaging failed to adequately explain the emotional components of pain (Jensen et al. 2016). To further explain the affective component of pain, Feng et al. (2020) used resting-state (rs-) fMRI to measure pain-associated alterations in the brain of patients with osteonecrosis of the femoral head (ONFH). In their experiment, they examined spatial patterns of spontaneous brain actions by

measuring the amplitude of low-frequency fluctuation of oxygen level-dependent signals. They reported that ONFH patients showed altered brain activities in the sensorimotor network, pain-associated network, and emotion and cognition network.

Ploghaus and his colleagues applied painful hot and non-painful warm stimuli to twelve healthy individuals. They established that pain stimulated the mid-insula, caudal ACC and anterior cerebellum. In contrast, expectation of pain stimulated a more anterior region, the anterior medial frontal cortex, anterior insula and posterior cerebellum (Ploghaus et al. 2001). Furthermore, when the cold pressor pain was administered to the twelve healthy individuals, the ACC, alongside the superior frontal gyrus and right cuneus, were activated (Fulbright et al. 2001).

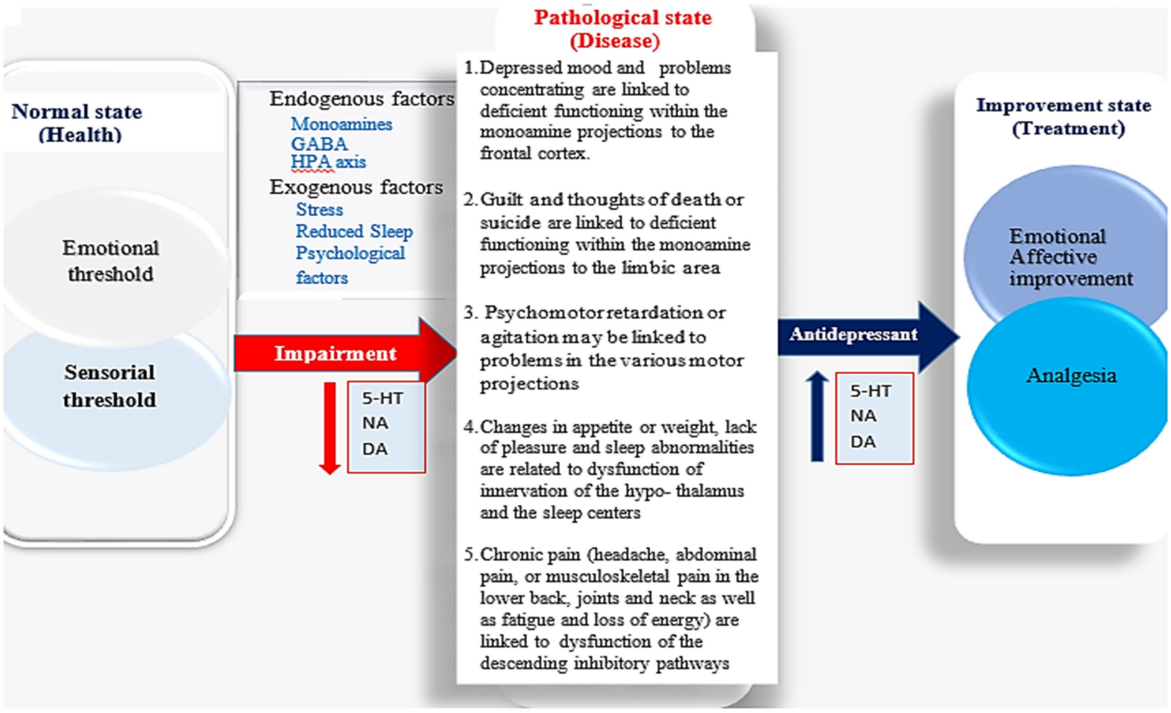

Fig. 5: Pain and depression. Pathological conditions of chronic pain and depression are associated with a decrease in the levels of both noradrenaline and serotonin. Treatment with some antidepressant drugs can improve both conditions. Adapted from Micó et al. (2006)

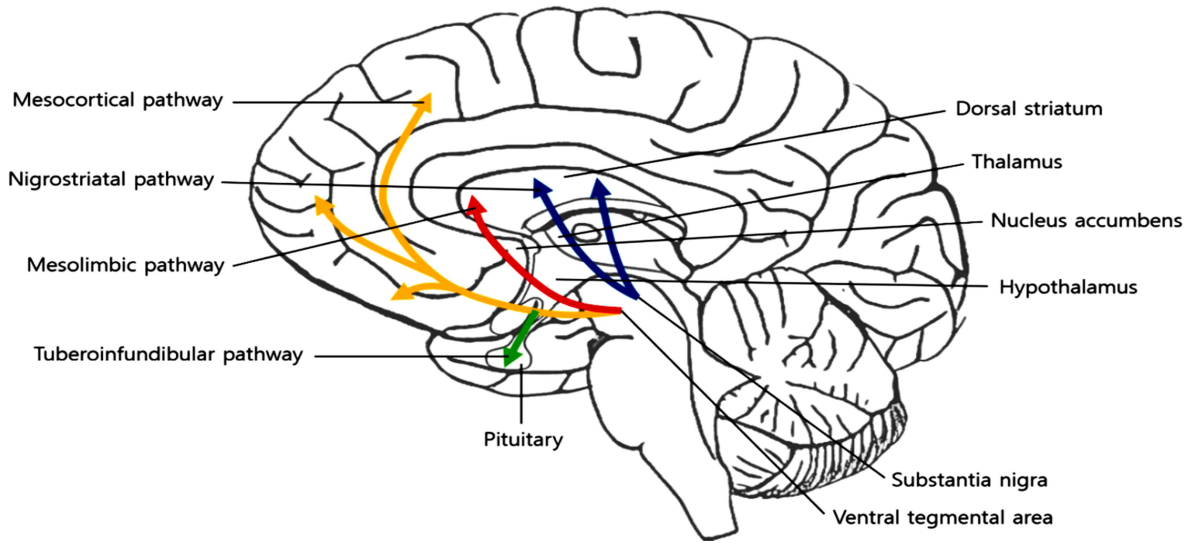

Fig. 6: Four main dopaminergic axis in the brain: the nigrostriatal, mesolimbic, mesocortical, and tuberoinfundibular pathways (Yang et al. 2020).

Management of Pain, Depression and Anxiety

Managing patients with comorbid chronic pain and affective disorders, especially depression, can be challenging. Patients can receive treatment for each condition independently based on relevant guidelines. However, there are some pharmacological approaches worth mentioning. Studies have shown that pharmacotherapy's attention to depression and chronic pain in the aged population may produce more outstanding results than focusing on only one condition (Williams et al. 2006).

Duloxetine is a known 5-HT and NA reuptake inhibitor. It is highly effective in the treatment of depression and chronic pain in the aged population (Bidari et al. 2019). The analgesic effect involves its action on neuropathic pain, such as diabetic neuropathy (Hossain et al. 2016), and in the management of chronic musculoskeletal pain.

Amitriptyline, clomipramine, and nortriptyline are widely used tricyclic antidepressants (Elklit and Jones 2006; Williams et al. 2006; Rico-Villademoros et al. 2015). Tricyclic antidepressants have been shown to decrease pain perception (Janakiraman et al. 2016). They are used in managing various forms of pain including, fibromyalgia (Rico-Villademoros et al. 2015), central neuropathic pain (Mendlik and Uritsky 2015), peripheral neuropathic and orofacial pains (Finnerup et al. 2015). In the treatment of peripheral neuropathic pain, amitriptyline and nortriptyline are considered equally as monotherapy or as part of combination therapy present with equivalent levels of adverse effects and discontinue rates, whereas clomipramine is significantly effective in the treatment of central pain compared to nortriptyline (Williams et al. 2006).

Pregabalin is a new generation of gabapentinoid that functions similarly as gabapentin (Murnion 2018). Both are known for their first line of treatment for neuropathic pain (Hagen et al. 2015; Davari et al. 2020) and generalized anxiety disorder. The two drugs are effective in the treating neuropathic pain secondary to post-herpetic neuralgia (Davari et al. 2020) and diabetic peripheral neuropathy (Zhang et al. 2022). There are reports about the safety and efficacy of pregabalin and gabapentin in the management of neuropathic pain associated with spinal cord injury. Many researchers compared pregabalin or gabapentin to placebos (Hagen et al. 2015; Davari et al. 2020). Nonetheless, lack of evidence for a direct comparison between the two drugs makes it difficult to select the most effective for treating neuropathic pain.

The use of drugs primarily meant for treating depression and anxiety disorders in the treatment of chronic pain further emphasizes the relationship between pain, depression, and anxiety disorders. This is partly dependent on the mechanisms of action of the anti-anxiety and anti-depressants. Worthy of note is that this is peculiar to the treatment of many types of neuropathic pain.

Conclusion

The significance of ameliorating pain experienced in anxious and depressed patients cannot be overestimated. Restoration of energy, zeal, or motivation is possible only after reduction in pain perception.

Decreased levels of 5-HT, NA, and dopamine, alongside dyshomeostasis in the HPA-axis are so far the most well recognized connecting factors between pain, anxiety, and depression, and these conditions are likely to occur simultaneously. Looking at existing literature, we conclude that full understanding of monoaminergic and serotoninergic systems would offer an effective treatment for several types of acute and chronic pains.

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Conflict of Interest

None declared.

Authors Contribution

Conception: BVO; Writing of manuscript: BVO and POA; Literature search and data collection: BVO and POA

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