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Review Article

COMORBIDITY OF PAIN AND DEPRESSION: A REVIEW

Sukhpreet kaur*, Tanvi Dobhal, Om Prakash, SL Hari Kumar

Rayat & Bahra Institute of Pharmacy. Sahauran, kharar, Distt-Mohali (Punjab), India

ABSTRACT

Chronic pain and depression are frequently occurring co morbid disorders. Patients suffering from chronic pain are more vulnerable to depression as compare to the general population moreover depression also increases the risk of developing chronic pain. The various overlapping symptoms of pain and depression are insomnia, fatigue, psychomotor agitation/retardation, sleep disturbance etc. Inability among patients suffering from chronic pain to perform normal physical and mental activities leads to an evident symptoms of mental distress. 30-60% of the patients experiencing chronic pain suffers from depression which is linked with diminished function, insufficient response to treatment, rise in health care cost. Occurrence of both the diseases complicates the diagnosis and treatment.

Keywords: Depression, Chronic pain, insomnia

INTRODUCTION:

Chronic pain and depression are frequently occurring co morbid disorders [1]. Patients suffering from chronic pain are more vulnerable to depression as compare to the general population moreover depression also increases the risk of developing chronic pain [2,3] which affects one's physical and social well-being [4]. It is not only difficult to diagnose but is also complicated to treat comorbidity of pain and depression [5]. The various overlapping symptoms of pain and depression are insomnia, fatigue, psychomotor agitation/ retardation, sleep disturbance etc [6].

Pain is a perception that is inescapable, most permeate and one of the prevalent forms among human disorders [7]. According to International Association for the study of pain " pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage" [8]. Two main types of pain are nociceptive pain (occurs due to tissue damage) and neuropathic pain (caused by any injury to nervous system or spinal cord) [9]. Chronic pain is the pain that continues for a prolonged time than the temporal course of natural healing linked up with specific type of disorder and it is generally worsen by environmental or psychopathological stress factors [10]. It has been reported that 49 % of adults suffer from chronic pain [11] . Inability among patients suffering from chronic pain to perform normal physical and mental activities leads to evident symptoms of mental distress. 30-60% of the patients experiencing chronic pain suffers from depression which is linked with diminished function [12], insufficient response to treatment [13,14], rise in health care cost [15].

Depression is common debilitating condition affecting 121 million of people worldwide [16].

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Depression is chronic form of psychiatric disorder that occur in person s of all genders, ages and back grounds [17]moreover women are more susceptible to depression as compare to men [18]. In 1990 depression has been ranked as 4th disabling disease among human population by WHO global burden of disease study [19] and also is expected to be 2nd leading cause of disability in the world by 2020. It has been observed that symptoms of pain are common in patient suffering from depression [20]. Appetite changes, sexual dysfunction, sleep disturbance, suicidal behavior are various symptoms of depression accompanying chronic pain [21].

UNDERSTANDING PAIN AND DEPRESSION COMORBIDITY

Correlation among pain and depression is affected by number of factors for example sleep disturbance is one of the criteria to diagnose depression, pain interferes with sleep to cause sleep disturbance [22]. Depression and persistent pain appears to be strongly associated with each other and various hypotheses have been proposed to describe the nature of pain and depression comorbidity [23]. It has been reported that depression and pain are driving conditions with declining symptoms and there are biological and psychological links between pain and depression occurring during the late life [24].

1) **Psychological link:** The two psychological theories for pain and depression are self efficacy and learned helplessness [25]. Self efficacy reflects ones believe in achieving success in certain task [26]. In both chronic pain and depression occurring during late life there is decrease in self efficacy [27,28]. The decrease or absence of self efficacy is demonstrated in learned helplessness [29] which means constellation of behavioral changes exposing to stressors such as depression or chronic pain that are uncontrollable by means of behavioral responses but if the stressor is controllable that fails to occur [30].
2) **Biological similarities:** Spinothalamic tracts, multiple deep brain and cerebral areas are involved in pain processing. Also the brain area related to mood and anxiety disorder are anatomically same to the pain processing areas in brain [31,32].

Disability is a critical link between pain and depression occurring in late life which is caused by limited body activity, impaired body functioning consistent with the international classification of functioning, disability and health [33,34]. These deficits are discriminative markers of depression [35] which are commonly found in patients suffering from chronic pain.

BIOLOGY OF PAIN DEPRESSION COMORBIDITY

Some studies have shown that pain and depression are physiologically identical, considering chronic pain to be variant of depression [36,37]. Anatomically both nociceptive and affective pathways coincide. Furthermore N.E and serotonin are the two neurotransmitter most implicated in pathophysiology of mood disorder and are also involved in gate control mechanism of pain [38].

Biochemical theory: It postulates that neurochemical imbalance or functional deficiency of various neurotransmitters like serotonin, nor-epinephrine and

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dopamine leads to pain depression comorbidity [21,39]. Serotonin is a neurotransmitter well known for its antidepressant effect. It also produces antinociceptive and prenociceptive effects which depends upon the subtype of receptor and region of central nervous system [40,41]. It has been found that patients suffering from pain and depression have low levels of serotonin [42]. Both serotonergic and noradrenergic pathways ascending into the brain mediates various emotional and physical functions [4]. Various parts of the brain like the frontal cortex, basal ganglia, and limbic areas receive the projections from serotonergic cell bodies present in raphe nucleus where they regulate mood, movement, and emotions such as anxiety [43]. The noradrenergic neurons present in the locus coeruleus also send projections to similar parts of the frontal cortex, the limbic areas, and the hypothalamus, as well as to some specific areas in the frontal cortex and hence control attention and cognition [44]. Dysfunction in these system results in evident symptoms of depression. Apart from these ascending serotonergic and noradrenergic pathways there is also a descending pathway in which they descend down the spinal cord and suppress nociceptive inputs [38,45]. The input from the intestines, skeletal muscles, and skin are inhibited by these descending pathways and their inhibitory effects are normal under normal conditions, but at the time of stress, they can completely inhibit the input from painful stimuli to survive the individual [46]. An abnormal functioning of these descending pathways can results in increased pain sensitivity and can even cause sensation of pain from non-painful stimuli.

The serotonergic and noradrenergic neuronal dysfunctioning is likely to affect both the ascending and descending pathways which may results in psychological, somatic, and physical painful symptoms [44]. In both pain and depression patients increased levels of substance P concentration in cerebro-spinal fluid have been found [47]. It is implicated in development and treatment of major depressive disorder [48]. Efferent serotonergic neurons negatively modulates the neurotransmission of substance P [49] and it has been seen that with increase in substance P levels in brain the 5-HT levels in spinal cord are also increased but the entry of substance P in spinal cord is decreased [50]. Since empirical data suggests that both substance P and biogenic amines play role in pathogenesis and treatment of pain and depression [48,51] so there is need to further investigate the role of substance P.

Nitrodative stress- induced neurogenic inflammation: Depression and chronic pain have been associated with dysfunction or deregulation of glutamate [41]. In patients with fibromyalgia an increased levels of reactive oxygen species (ROS) production have been found in mononuclear cells [52]. Thus an increased oxidative stress stimulate NF-kb production and leads to increased levels of pro-inflammatory cytokines like TNF-α, IL-6, IL-8, IL-1β [53]. In both pain and depression an increase in cytokine levels including interleukin-6, C-reactive protein, interleukin-1-beta and tumour necrosis factor alpha is often found [54,55,56]. Thus increased levels of pro-inflammatory cytokines and ROS production are responsible for the development of pain depression

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comorbidity by modulating NF-kb signaling and caspase-3 pathway [57].

Neuroendocrine abnormalities: Dysfunctioning in hypothalamic-pituitary-adrenal axis (HPA) have been found in both depression and chronic pain syndromes. Serum glucocorticoid concentration can be increased by physiological or psychological stress which can further leads to atrophic changes in hippocampal region and volume reduction which is sometimes found in patients suffering from depression disorder [58]. Also decreased serum cortisol is often seen in fibromyalgia and atypical depression disorders [59]. In depressed patients the glucoticoid receptors becomes less active and cause failure of signaling. The loss of normal diurnal cortisol pattern or HPA axis has been implicated in both pain and depression [60,61]. Autonomic nervous system (ANS) activity has been shown to be disturbed in depressive and pain syndrome, comprising of an enhanced sympathetic and decreased parasympathetic tone [41]. The HPA and ANS abnormalities for both pain and depression activate the same inflammatory pathways cause dysfunctioning of neuroimmune process [62].

Genetic factors: Various genes have been contributing to pain and depression comorbidity. The genes regulating serotonergic function such as serotonin-transporter linked promoter region (5-HTTPR) or serotonin 2A (5-HT2A) have been consistently involved in pathophysiology of depression [39,63]. Other genes regulating neurotorophic factor plays an additive role in the determination of developing pain and depression [64]. Catechol-O-methyl transferase (COMT) and monoamine oxidase (MAO) gene polymorphism alters the reaction of the HPA axis and affects the response to psychological stress [65]. 5-HTTPR, 5HT-2A, COMT polymorphism are the various genes that are also implicated in pain state [66,67]. Hence this common genetic polymorphism may corresponds to susceptible areas for both pain and depression syndrome [41].

Structural and Functional alteration: In pain and depression comorbidity some areas of the brain are found to be structurally or functionally aberrant by neuroimaging studies [58]. Studies have shown that patients suffering from depression may have diminished activity and decreased gray matter volume in Dorsolateral Prefrontal Cortex **(**DLPFC)[68] which is the area of brain that regulates influence over limbic structures and is main part of executive function network [69]. This same structural change in the DLPFC has been correlated with neurocognitive deficits in patient with fibromyalgia [70]. MRI studies have shown that for both pain and depression same CNS pathway may exist [41]. Excessive activation of amygdale and disruption/volume loss in hippocampal region are the various functional and emotional changes that are found in both depression and pain syndromes such as fibromyalgia [71,72]. Also there is disruption of functional regulation of the nucleus accumbens and the ventral tagmental area in both chronic pain and major depression [73]. These changes in the limbic system may lead to worsening of mood and pain symptoms by causing autonomic dysfunction and sympathetic response that combine with proinflammatory reactivity [74].

Role of IDO: Indoleamine2,3-dioxygenase (IDO) is an enzyme

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encoded by gene IDO1 in human beings and is predominately expressed in various tissues like brain, lungs , heart, kidney and intestine [75]. IDO is involved in tryptophan metabolism as it catalyses the reaction of tryptophan to l-Kyneurine. Tryptophan (an essential amino acid) is a precursor of serotonin. It has been found that increased levels of pro-inflammatory cytokines results in increased activity of IDO [76,77]. IFN-α causes induction of IDO indirectly by leading to an increased production of IFN- [78]. Over activity of IDO results in lowering of plasma concentration of tryptophan ultimately leading to decrease in serotonin concentration in the brain [79] hence leads to depression. Also IDO causes the central degradation of 5-HT hence lowers the serotonin concentration in brain [80]. Upregulation of IDO also results in increased Kyneurine concentration hence activate glutamate receptors [79]. Glutamate is the primary excitatory neurotransmitter for linking limbic and cortical areas as well as facilitating or inhibiting pain transmission in CNS [41]. IFN-α therapy in patients with hepatitis C causes decrease in TRP (4-6 months after starting therapy) and an increase in Kyneurine plasma levels seen at two weeks after starting therapy, with Kyneurine plasma levels remaining the same at 2 weeks when measured at weeks 4, 16 and 24 indicating higher IDO activity [81].

TREATMENT OPTIONS

Most of the depressive patients presenting to their physician often show the physical rather than emotional symptoms [82]. Occurrence of obscure or excessive physical and painful symptoms complicates the diagnosis of pain and depression comorbidity [83,84].

Pharmacological treatment:

Antidepressants: According to several randomized clinical trials majority of antidepressant acting on serotonin and noradrenalin neurotransmitters have been used not only to treat psychological symptoms of depression but also the physical symptoms such as pain [4]. Tricyclic antidepressants acts by inhibiting serotonin and nor epinephrine reuptake at synapse. Secondary amines like desipramine, nortriptyline etc. acts by inhibiting nor-epinephrine while tertiary amines like imiperamine, amitriptyline etc. inhibits serotonin to higher extent. Besides the antidepressant effect tricyclic antidepressants also provide the analgesic effect [85] which is due to increasing descending spinal serotonergic and noradrenergic inhibitory neurons [86].

Serotonin-Nor epinephrine reuptake inhibitors have been introduced to treat depression and its physical symptoms like pain [87] by specifically inhibiting both serotonin and nor epinephrine reuptake, the two neurotransmitter found in pathophysiology of comorbid pain and depression. Research studies have shown that SNRIs treat the occurrence of pain in depression more effectively as compare to the single action agents (serotonin reuptake inhibitors or nor epinephrine reuptake inhibitors) [38,45,88]**.** Duloxetine and Venlafaxine have been evaluated in treatment of associated pain and depression [89,90]. Venlafaxine may also produce analgesia through opoid mediated antinociceptive effect produced due to its affinity towards opiate receptors [91]. SNRIs are less anti cholinergic, anti histaminic and adrenergic and are likely to be less lethal in overdose as compared to TCAs which is one of the notable advantages over TCAs [22].

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Mood stabilizer/Anticonvulsant:
Anticonvulsant drugs' acting by decreasing neuronal excitation also provides the analgesic effect and have been approved for treating bipolar disorder by acting as mood stabilizer [22]. Carbamezipine is the choice of drug for neuralgia [92] and is also successful in treating chronic pain condition associated with depression [93]. Recently it has been demonstrated that Pregabalin can be useful in treating chronic pain and depression comorbidity [94].

Non pharmacological techniques:
Various psychological therapeutic techniques have been used [95,96] either in combination with antidepressant or alone and are effective in treating depression and its physical symptoms. The most frequently psychological techniques used to treat pain depression comorbidity includes cognitive behavioral therapy, inter-personal therapy, operant behavioral, psycho dynamically oriented psychotherapy and supportive therapy [87].

CONCLUSION:

Chronic pain and depression are strongly associated with each other. There is evidence that patients suffering from chronic pain are at higher risk of developing depressed and also 30-60% of patients with depression suffers from pain syndrome. Hence it can be concluded that pain leads to depression and depression also increases the risk of developing chronic pain causing decrease in quality of life, increased disability and deleterious social implications. Moreover co-occurrence of both chronic pain and depression complicates the diagnosis and treatment of disease. There is bidirectional relationship between pain and depression.

Tricyclic antidepressants have been standard treatment of chronic pain for many years. They may act on various pharmacological pathways which are common to both pain and depression. Though various studies have been done on pain and depression comorbidity but further research is necessary to understand the biological underrippening of this shared comorbidity so as to get better treatment for the same.

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