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Chronic pain and depression. Correlation and treatment- A review of current literature

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ABSTRACT

Introduction and purpose

The comorbidity of chronic pain and depression is a prevalent medical challenge faced by both patients and healthcare providers. The purpose of this review is to examine the correlation between these conditions and to analyze current treatment methods.

State of knowledge

The relationship between chronic pain and depression is undoubtedly complex.
Over a quarter of individuals with persistent pain experience depressive symptoms, and more than half of psychiatric patients also suffer from chronic pain.

This comorbidity affects all age groups- adolescents, adults, and older adults.
Research indicates that pain involving multiple body regions is associated with a higher risk of depression.
Currently, no single treatment effectively addresses both conditions simultaneously.
The most commonly used approach involves pharmacological interventions, particularly antidepressants such as tricyclic antidepressants (TCAs) and serotonin-noradrenaline reuptake inhibitors(SNRIs). However, various non-pharmacological methods-especially when combined with medication -can also be beneficial.

Material and methods
This review was compiled through an extensive analysis of the PubMed, Cochrane, and Google Scholar databases. We primarily focused on articles published between 2020 and 2025 that included keywords such as: “depression,” “chronic pain,” “major depressive disorder,” “antidepressants,” and “nociplastic pain.”

Conclusion
The co-occurrence of chronic pain and depression is extremely common.
Antidepressants remain a standard treatment option for managing both conditions.
However, non-pharmacological methods can complement traditional approaches.
Despite the range of available treatment strategies, there is no universally effective or standardized therapy for managing depression comorbid with chronic pain.
The absence of clear protocols for managing these issues highlights the necessity for future research.

Keywords: depression; chronic pain; major depressive disorder; antidepressants; nociplastic pain

INTRODUCTION

Chronic pain

The definition of pain accepted worldwide, including by the World Health Organization, describes it as an unpleasant sensory and emotional experience associated with actual or potential tissue damage. [1] The complexity of pain is linked to an incomplete understanding of its underlying pathology and the mechanisms that produce similar symptoms. [2] Pain mechanisms can generally be categorized as neuropathic, nociceptive, or nociplastic, although many experts view pain classification as a spectrum.
Traditionally, neuropathic pain is associated with nerve injury, while nociceptive pain results from tissue damage. [3] Nociplastic pain, a more recently recognized category, is not yet fully understood. However, it appears to be primarily related to dysregulated pain modulation and impaired sensory processing. This type of pain may occur in conditions such as fibromyalgia, tension-type headaches, and chronic low back pain. Symptoms that often accompany it include fatigue, insomnia, cognitive impairment, and emotional disturbances. [4]

Chronic pain is defined as pain that persists or recurs for more than three months and may continue beyond the usual healing period. [5] It represents a significant public health issue, with some studies suggesting that up to 30% of the global population may be affected. [3] Living with chronic pain can severely reduce quality of life and hinder the performance of everyday tasks. Additionally, individuals often face a lack of understanding and support, along with negative societal perceptions that question the legitimacy of their suffering. [6]

Depression

Depression is one of the most prevalent mental health conditions globally. The number of individuals affected has increased dramatically in recent years, with some studies estimating the figure to be as high as 264 million. [7] The burden of this condition can be measured in terms of Years Lived with Disability (YLDs), and data suggest that Major Depressive Disorder (MDD) may rank second among the leading causes of YLDs worldwide. Notably, depression affects individuals across all income levels and is not confined to countries with lower economic status. [8]

In the United States, approximately 7% of the adult population may suffer from MDD. However, only about half of these individuals receive pharmacologic treatment.

MDD is defined as a mental health disorder characterized by a minimum duration of two weeks of symptoms. Common manifestations include persistent low mood, loss of interest or pleasure (anhedonia), and impaired cognitive function. [9] Additional symptoms may include fatigue, insomnia, appetite changes, and suicidal ideation or thoughts. Importantly, this condition must not be better explained by substance use or other psychiatric disorders such as schizophrenia. Furthermore, the presence of mania or hypomania excludes the diagnosis of MDD. [10]

MDD is a multifactorial and complex disorder with no single identifiable cause. Its development is influenced by the interplay between neurobiological mechanisms, psychological vulnerabilities, and environmental stressors. [11] Several hypotheses have been proposed to explain its underlying mechanisms, including receptor dysregulation, inflammatory pathways, hypothalamic-pituitary-adrenal (HPA) axis dysfunction, neuroplasticity alterations, and systemic influences. Nonetheless, the full pathophysiology of the disease remains incompletely understood. [12]

Genetic factors also play an important role. Genome-wide association studies (GWAS) have identified 178 genetic loci associated with MDD. However, many of these findings are based on studies that used limited phenotypic criteria, raising concerns about diagnostic specificity. [13]

Recent research suggests that imbalances in gut microbiota may contribute to the development and progression of depression, representing a promising avenue for future therapeutic interventions. [14]

Depression is not only a significant mental health issue on its own, but it also contributes to the increased prevalence and worsened outcomes of several comorbid conditions, including cardiovascular diseases, diabetes, autoimmune disorders, and AIDS. [10]

STATE OF KNOWLEDGE

Correlation between chronic pain and depression

In the United States, nearly 5% of the adult population- approximately 12 million individuals- suffer from both chronic pain and depression or anxiety. Persistent psychiatric symptoms are present in approximately 24% of Americans who experience chronic pain. Conversely, around 57% of individuals with residual anxiety or depressive symptoms also report chronic pain. [15]
Focusing on older adults, the statistics are even more concerning. Nearly 13% of elderly individuals experience both major depressive disorder and persistent pain. Among this population, those diagnosed with major depression have a sixfold increased risk of developing neuropathic pain and are three times more likely to suffer from non-neuropathic pain. [16]
These challenges are not limited to older adults; they are also evident in younger populations. Among adolescents, comorbid chronic pain and depressive symptoms are associated with a significantly higher risk of suicide compared to those experiencing chronic pain alone. [17] One in eight adolescents with chronic pain is also affected by depression. Furthermore, research suggests a correlation between the number of pain sites reported and the risk of developing depressive symptoms. Experiencing pain in five or more body regions significantly increases the likelihood of depression. [18]
Pain localized to certain body regions is particularly associated with mental health conditions. For instance, headaches, gastrointestinal discomfort, and pain in the neck, shoulders, and back are frequently reported in individuals with depression. These symptoms not only coincide with depressive disorders but also tend to exacerbate them. [19]
A notable example of the comorbidity between pain and depression is painful bladder syndrome, also known as interstitial cystitis. Approximately 60% of patients with this urological condition are also diagnosed with depression. This dual burden significantly increases the risk of treatment resistance, prolongs the duration of pain, leads to more frequent hospital visits, and severely impairs quality of life. In such cases, psychiatric consultation is often warranted to evaluate the possibility of a psychosomatic origin, which may necessitate a distinct therapeutic approach and can substantially influence treatment outcomes. [20]
Animal studies further support the strong connection between depression and chronic pain. Research conducted on rodents has demonstrated a robust correlation between depressive-like behavior and three primary categories of chronic pain: neuropathic, inflammatory, and fibromyalgia-related pain. [21]

Methods of treatment

The co-occurrence of depression and chronic pain represents a significant clinical challenge. The complex interplay between these conditions is not yet fully understood and warrants further investigation. Nonetheless, a range of therapeutic strategies- both pharmacological and non-pharmacological- have been proposed and implemented to address this dual burden. [22]

Pharmacological Treatments

Antidepressants are among the most widely used medications in the treatment of chronic pain. While their exact mechanisms are still under investigation, evidence suggests that their efficacy may be related to both blocking voltage-gated sodium channels and increasing synaptic levels of serotonin and noradrenaline.
Tricyclic antidepressants (TCAs) are generally considered more effective for chronic pain management than Selective Serotonin Reuptake Inhibitors (SSRIs) or Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs). TCAs may enhance opioid receptor activity in specific brain regions and modulate sodium channels. Animal studies have shown that drugs such as clomipramine, dothiepin, amitriptyline, and sibutramine have antinociceptive properties.

However, due to their potential for sedative, anticholinergic, and cardiotoxic side effects, TCAs are generally not recommended for elderly patients.
Imipramine is another TCA that improves mood and reduces pain in various autoinflammatory conditions, including rheumatoid arthritis, ankylosing spondylitis, and osteoarthritis.
SSRIs are commonly used to treat depression, but their effects on chronic pain are generally less robust than TCAs or SNRIs. This may be due to their limited influence on noradrenaline levels. Nonetheless, SSRIs such as fluoxetine, paroxetine, and citalopram are frequently prescribed for conditions like headaches and migraines.
SNRIs, particularly duloxetine, have demonstrated effectiveness in managing both depressive symptoms and chronic pain. Duloxetine is FDA-approved for the treatment of osteoarthritis, diabetic neuropathy, and fibromyalgia. Although venlafaxine is not FDA-approved for pain relief, it has shown benefits in managing migraines, polyneuropathies, and atypical facial pain. [23]
A comparative study found duloxetine to be the most effective antidepressant for pain management, supported by moderate to high evidence. Milnacipran is considered the next most effective option, although the supporting evidence is weaker. Importantly, increasing the dosage of either drug does not appear to significantly enhance efficacy. [24]
In summary:

- SNRIs like duloxetine and venlafaxine are effective for neuropathic and musculoskeletal pain.
- TCAs are useful in neuropathic, cancer-related, orofacial, and fibromyalgia-related pain. [16]

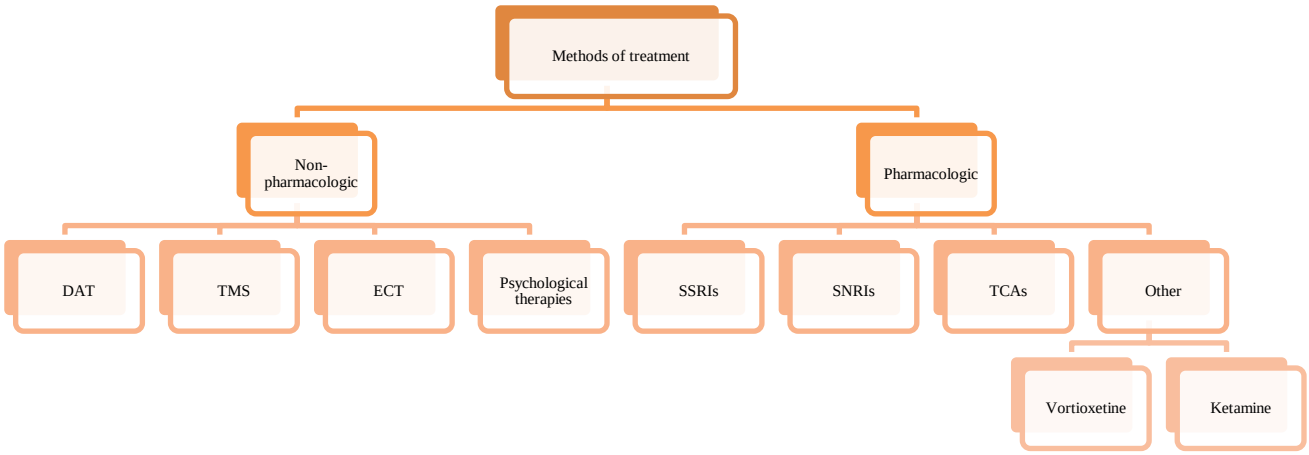
A Spanish observational study suggested that vortioxetine, a multimodal antidepressant, is effective in managing major depressive disorder with comorbid chronic pain and is generally well tolerated. Its mechanism involves modulation of multiple neurotransmitters, including inhibition of GABA release and increased release of dopamine, histamine, acetylcholine, and noradrenaline. [25]
Ketamine, an NMDA receptor antagonist long used in anesthesia, has emerged as a potential treatment for both chronic pain and depression. A single dose may provide rapid antidepressant effects, although repeated administration often yields more consistent benefits. [26] In a study comparing ketamine to electroconvulsive therapy (ECT), ECT was found to be more effective during the acute phase of depression. [27]

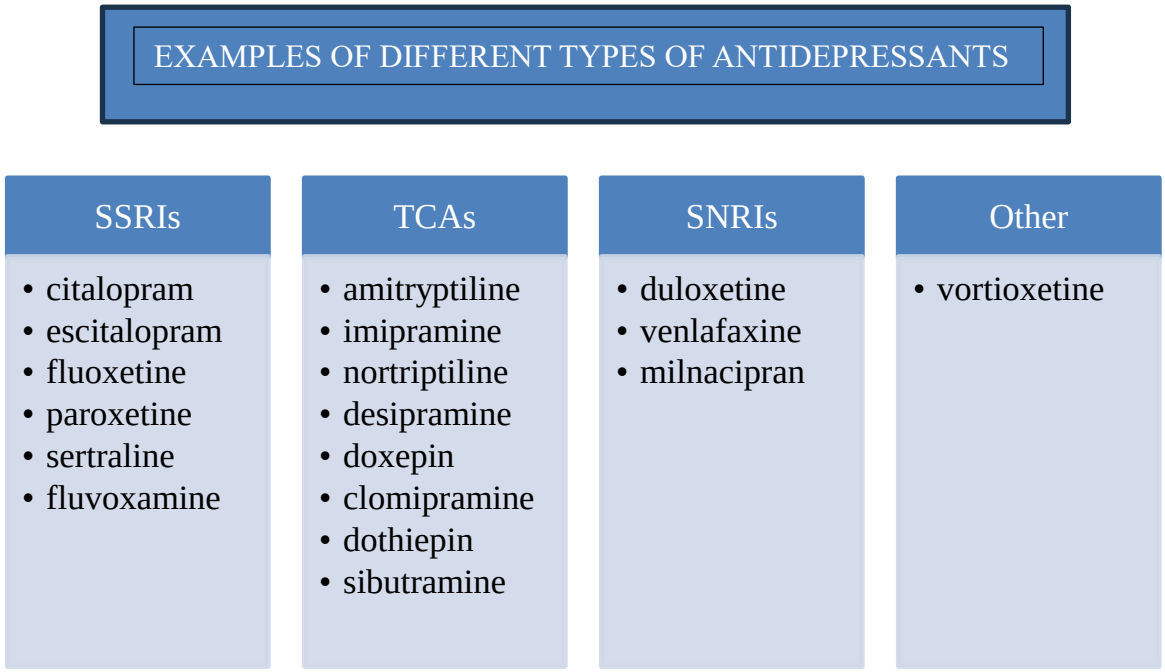
Non-Pharmacological Treatments
Several non-pharmacologic therapies can complement or even enhance the effects of medication:

- Dog-assisted therapy (DAT) has shown promise in reducing both pain and depressive symptoms in elderly patients.
- Transcranial Magnetic Stimulation (TMS) is typically used for treatment-resistant depression and obsessive-compulsive disorder (OCD) but has shown potential benefits for unipolar depression and chronic pain.
- Mindfulness-Based Cognitive Therapy (MBCT) can provide similar effects to TMS. [16]

Psychological interventions such as Cognitive Behavioral Therapy (CBT), Behavioral Therapy (BT), and Acceptance and Commitment Therapy (ACT) have been studied for chronic pain. However, findings suggest that no single psychological therapy is sufficient as a stand-alone treatment. [28]
The most effective approach involves an interdisciplinary strategy, combining pharmacologic and non-pharmacologic interventions. [16] This is especially true for pediatric patients, for whom multidisciplinary treatment- including medication and psychological support like CBT or ACT- is essential. [29]

Future Directions
Emerging research highlights epigenetic mechanisms as potential targets for new therapies. For example, DNA methyltransferases (DNMTs)—particularly DNMT1—are implicated in the comorbidity of depression and chronic pain. One hypothesized mechanism involves epigenetic downregulation of GAD67, leading to reduced GABAergic activity. DNMT1 may therefore represent a promising focus for future therapeutic strategies. [30]





CONCLUSION:

Depression and chronic pain are deeply interconnected conditions, with each capable of influencing and exacerbating the other. Chronic pain can contribute to the onset of depression, while depressive symptoms can heighten the perception and intensity of pain. A range of therapeutic options exists for managing these co-occurring disorders, including both pharmacological and non-pharmacological approaches.

Antidepressants remain a cornerstone of treatment. However, there is no clear consensus on the most effective pharmacological agent. While some studies suggest that tricyclic antidepressants (TCAs) offer superior pain relief, others highlight the effectiveness of serotonin-norepinephrine reuptake inhibitors (SNRIs). In addition, psychotherapy, pet therapy, and transcranial magnetic stimulation (TMS) show promise as adjunctive treatments.

A multidisciplinary approach, involving collaboration among healthcare providers across different specialties, is widely regarded as the most effective strategy for managing patients with comorbid chronic pain and depression.

These two conditions are not only highly prevalent but also pose a significant burden on patients and healthcare systems alike. The lack of standardized treatment protocols and limited availability of consistently effective interventions represent ongoing challenges for clinicians and patients. Therefore, there is an urgent need to expand research efforts aimed at identifying more targeted, efficient, and accessible treatment options.

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Disclosures

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