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Review Article

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Chronic Pain and Comorbid Depression: A Narrative Review

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ABSTRACT

This narrative review of research includes summaries of 44 papers on the comorbid conditions of chronic pain and depression that were published during the years 2022 and 2023. The publications of this period are primarily randomized controlled trials and systematic reviews/ meta-analyses of randomized controlled trials. Many of these are focused on the prevalence of chronic pain and depression which ranged from 7% to 25% in different age groups and in different countries. Many of the studies addressed the bidirectionality of chronic pain and depression and predictors including stress and inactivity. Ketamine was the most frequent intervention in this literature. And, the most frequent underlying mechanism was involvement of the amygdala. Surprisingly, very few studies focused on youth and on long-term effects of the comorbidity of chronic pain and depression. Methodological problems relate to the variability in the assessments of chronic pain and depression, the self-report measures and the cross-sectional data that are not definitive about directionality of the chronic pain and depression relationship.

This narrative review involved entering the terms chronic pain and comorbid depression and the years 2022-2023 into PubMed and PsycINFO. Although the search yielded 312 papers for the last two years, exclusion criteria, including case studies, non-English papers and study protocols, reduced the number to 44 papers. This narrative review of research includes summaries of 44 papers on the comorbid conditions of chronic pain and depression that were published during the years 2022 and 2023. The publications of this period are primarily randomized controlled trials and systematic reviews/ meta-analyses of randomized controlled trials. Many of these are focused on the prevalence of chronic pain and depression which ranged from 7% to 25% in different age groups and in different countries. Many of the studies addressed the bidirectionality of chronic pain and depression and predictors including stress and inactivity. Ketamine was the most frequent intervention in this literature. And, the most frequent underlying mechanism was involvement of the amygdala. Surprisingly, very few studies focused on youth and on long-term effects of the comorbidity of chronic pain and depression. Methodological problems relate to the varying assessment of chronic pain and depression and the self-reported, cross-sectional data. This paper is accordingly divided into sections on prevalence data, on effects of chronic pain and comorbid depression, on predictors, interventions, potential underlying mechanisms and methodological limitations.

Prevalence of Chronic Pain and Depression

The prevalence of chronic pain and comorbid depression has varied widely across different age groups and different countries (see table 1). And chronic pain has differed on severity and duration. Similarly, depression has varied in severity and duration.

Table 1. Prevalence of chronic pain and depression (and first authors).

Prevalence	First Author
25% chronic pain in adolescents, 47% of those are depressed	Soltani
23% chronic pain > 6 months in high school students	Farrani
13% comorbid pain and depression in patients >65	Pakniyat-Jahromi
61% of chronic pain individuals with depression	Yang
16% chronic pain, 33% of those are depressed in Pakistan	Amjad
21% chronic pain in U.S.	Mullins, Rikard
21% chronic pain, 58% of those are depressed in U.S.	Mullins

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40% of back pain patients in Brazil are depressed	Norris
50% of older adults with chronic pain are depressed in rural China	Bai
7-10% comorbid chronic pain and depression in worldwide sample	Chen
20-25% comorbid chronic pain and depression in global sample	Yang
16% mild pain, 35% moderate, 46% severe pain	Corriger
19% chronic depression in adolescents	Ocay

Age Differences: In a study on adolescents (N=145 at a 9-and-18-month follow-up), as many as 25% were experiencing chronic pain and as many as 47% of those with chronic pain developed a depressive disorder [1]. Calculating 47% of 25% suggests that only 12% of the entire sample was depressed.

A similar prevalence was noted in a cross-sectional study on high school students from New Zealand with 23% of the students reporting chronic pain of greater than six months duration and 3% severe pain for the same duration [2]. In this sample, females and rural adolescents were noted to have a greater prevalence. These data were not surprising given that depression is more prevalent in females and rural adolescents in the non-chronic pain population.

In contrast to the data on adolescents, in patients older than 65, the prevalence of chronic pain appears to be lower. For example, in a review of 37 studies the authors reported that the prevalence of comorbid chronic pain and depression was only 13% [3].

A methodological limitation of this literature is that in several studies, the prevalence of chronic pain is given followed by the prevalence of depression for those with chronic pain, but the prevalence of comorbid chronic pain and depression then has to be calculated. In the rare study that reported comorbidity of chronic pain and depression, as many as 61% of individuals with chronic pain experienced depression and individuals with major depression were four times more likely to experience neck or low back pain [4].

Differing Prevalence by Country: The prevalence of comorbid chronic pain and depression has also varied across different countries. It has been relatively low in some countries and not in others. For example, the prevalence of chronic pain in Pakistan has been cited as 16 percent, but as many as 33% have also been depressed. That would mean that only 5% of the sample were experiencing comorbid chronic pain and depression [5].

The prevalence of chronic pain reported for the U.S. has been consistently at 21% by two different research groups. This was not surprising since both groups were analyzing the same National Health Interview Survey data [6,7]. A prevalence of 21% chronic pain was also reported in a third study. In this sample, non–Hispanic, American Indian and Native Alaskan, bisexual, and divorced/separated participants were noted to have a greater prevalence of chronic pain [7]. Of this same sample (N =244.6 million), 21% again were cited as having chronic pain with 58% of those experiencing mild depression, 22% moderate depression, and 9% severe depression [6]. The prevalence data for the non-chronic pain sample in this study was only 9% for mild depression, 2% moderate depression, and 1% severe depression. The comorbidity of chronic pain and depression in this sample was further confounded by the high prevalence of anxiety. The confounding by anxiety was not surprising given that anxiety has been reportedly comorbid with depression in as many as 33% of individuals.

In a sample of chronic back pain patients in the National Health Survey of Brazil (N=71,535), as many as 40% reported depression [8]. Individuals with physical limitations related to chronic pain had a five-fold greater prevalence of depression.

As many as 50% of older adults with chronic pain in rural China have reported being depressed (N =244) [9]. And as many as 36% reported having anxiety. These authors made a distinction between sensory pain that contributed to anxiety and affective pain that contributed to depression. Both physical and mental pain were also noted as significant predictors of both depression and anxiety. Further research is needed on the distinction between sensory and affective pain and the broader categories of physical and mental pain.

The prevalence of chronic pain in Pakistan has been reported as 16% for chronic pain and 18% for backpain [5]. Only 25% of the sample received active treatment, 67% medication and as many as 93% never visited a pain specialist. These data on the low prevalence of treatment may explain the high rate of depression at 33% and suicidality at 14% in this sample.

Widely variable ranges and problems have been reported for world samples. In one worldwide study, the prevalence of chronic pain accompanied by depression as well as anxiety and insomnia was given at 7 to 10% [10]. For chronic pain accompanied by depression for greater than three months, the global prevalence has ranged between 20 and 25% [4]. And, in a global study on different intensities of chronic pain for individuals who have experienced pain for more than 12 months, 16% reported mild pain, 35% moderate and 46% severe pain [11].

Youth with Pain and Depression

A few papers on youth with pain and depression have appeared in this literature. In a study on pain catastrophizing in youth with chronic pain (N= 197 youth who averaged 15 years of age), a multiple mediator model was explored [12]. Depression and pain intensity mediated catastrophizing and functional disability, while anxiety did not. It is not surprising that pain intensity mediated catastrophizing and functional disability, but it is not clear why depression would be a mediating factor but not anxiety. Depression and pain intensity would be an expected relationship, but catastrophizing might be more related to anxiety. These four variables could be entered into a structural equation modeling analysis to determine the variance they each explain for functional disability which would be the worst outcome in this sample.

In another study entitled "Pain and insomnia as risk factors for first lifetime onsets of anxiety, depression, and suicidality in adolescents", 25% developed chronic pain, 47% depression and

as many as 34% reported suicidality at 9 and 18-month follow-up assessments [1]. Increased pain interference and intensity, catastrophizing and insomnia severity predicted depression and chronic pain. Suicidality was predicted by pain interference and intensity reported at baseline. These data are not surprising given that high rates of suicidality (suicidal ideation) have been reported by adolescents independent of chronic pain conditions and independent of insomnia. Once again, these data are based on self-report which is not reliably free of over or under-reporting problems. Recent studies are of course more confounded by this problem given that self-report questionnaires are now invariably anonymous. Adolescents have been known to exaggerate their problems when completing self-report questionnaires that are anonymous.

In a study on pediatric pain, children with chronic pain were given assessments of their detection of mechanical and thermal pain thresholds, and cluster analysis was then conducted on the data [13]. Three clusters accounted for 35% of the data. Forty-six percent had high thermal and pressure pain thresholds, 19% had high level symptoms including greater sensory, affective, evaluative and temporal descriptors of pain and neuropathic pain, disability, anxiety, depression, and poor sleep. Thirty-five percent who were labeled pain–sensitive had deep tissue sensitivity and thermal hyperalgesia. These studies highlight the complexity of chronic pain and depression and its multiple comorbidities.

Effects of Chronic Pain and Depression

Surprisingly, only a few studies have reported effects of chronic pain and depression (see table 2). These have included suicidal ideation and suicidal attempts as the effects. In a study already mentioned on a sample from Pakistan who had a prevalence of 16% comorbid chronic pain and depression, 14% of those individuals were suicidal [5].

Table 2: Effects and predictors of chronic pain and depression (and first authors).

Effects	First author
14% suicidality in adults	Amjad
23% suicidality in adolescents	Wildeboer
51% suicidal ideation/attempts in older adults	Jolly
Predictors	**First author**
Chronic pain predicted depression and vice versa	Zhao, Chen
Depression predicted pain and sleep quality was a mediator	Karimi
Older age and leg symptoms predicted low back pain	Wang
Low pain inhibitory capacity and depression predicted low back pain	Lazaridou
Depressive symptoms associated with greater low back pain	Wong
Stress predicted chronic pain at four years	Lindell
Physical inactivity predicted pain	Skogberb
Extraversion predicted pain mediated by sleep problems & depression	Flowers
COVID effects on pain	Bilen, Ziadn

A higher rate (23%) has been reported for suicidality in adolescents with comorbid chronic pain and depression (N=184) [14]. In this study, based on diagnostic clinical interviews and self-report questionnaires, a regression analysis indicated that depressive symptoms and peer victimization, but not fear of pain, contributed to a significant amount of the variance in suicidality.

In a sample of patients with comorbid chronic pain and depressive disorder (N= 393,481), 13% were older adults [15]. Suicidal ideation/suicidal attempts occurred in as many as 51% of the sample with a 48% greater risk of suicidal ideation in the comorbid than the non-comorbid group. Alcohol use occurred in 17% and substance use in 8% of the participants. Women had 1.2 greater odds of having suicidal ideation than males, which was not surprising since they typically have 2.0 greater odds of being depressed.

Predictors of Chronic Pain and Depression

In most studies in this recent literature, chronic pain and depression have been considered separately (see table 2). However, some studies have reported bidirectionality, and others have reported depression as a predictor of chronic pain. Other variables that have been significant predictors include stress, inactivity and extraversion.

In a study on **bidirectionality** entitled "Disentangling the relationship between depression and chronic widespread pain", large samples were included on both depressed individuals (N= 170,756) and those with chronic pain (N=6904) [16]. In a causal analysis, a causal model showed a better fit than a non-causal model for depression leading to pain and pain leading to depression. These results suggested a bidirectional, causal relationship between chronic pain and depression.

In a paper entitled “Investigating the shared genetic architecture and causal relationships between pain and neuropsychiatric disorders”, a large sample from Europe (N=17,310) was assessed for chronic pain and depression [17]. Multi-site pain was a risk factor for depressive disorder and depression was a significant predictor of pain.

In most studies, chronic pain has been considered a predictor of depression. However, a few studies have addressed a reverse causality. In review of 49 studies (N-120,489 participants), depression was a predictor of pain and explained 13 percent of the variance [18]. Sleep quality was a significant mediator of the relationship between depression and chronic pain in this analysis. That this review was limited to studies on depression predicting pain rather than the reverse or bidirectionality reflects the bias of the research group.

In several studies, depression has exacerbated a chronic pain condition. For example, in a five- year follow-up study of patients with low back pain (N= 225), scores on the Hospital Anxiety and Depression Scale at baseline as well as older age and leg symptoms contributed to disability at their five-year follow up (N = 111) [19]. In another study on patients with chronic low back pain (N= equals 107), **lower pain inhibitory capacity** was associated with elevated self - reported pain intensity in adults with chronic lower back pain, particularly among those with more depressive symptoms [20].

In a meta-analysis on 62 studies (N=63,326) on outcomes for low back pain, acute low back pain and depressive symptoms were associated with disability and worse recovery [21]. For chronic low back pain, depressive symptoms were associated with greater pain intensity as well as disability and worse recovery.

Other predictor variables for pain and depression include stress, physical inactivity, and even extraversion. In a paper entitled "Stress, non-restorative sleep and physical activity as risk factors for chronic pain in young adults", a longitudinal study on 19-to-24-year-old participants was reviewed [22]. **Stress, low restorative sleep and inactivity** were predictors of chronic pain at one year, but stress was the only significant predictor of chronic pain at four years.

In a similar study entitled "Pain tolerance in chronic pain patients seems to be more associated with physical activity than with depression and anxiety", adults with different pain conditions were included (N =78) [23]. A **lower pain tolerance threshold** was noted in patients with pain conditions versus controls. Greater pressure pain tolerance was associated with male gender, with less pain intensity, fewer painful regions, greater self-efficacy, and greater physical activity.

In a paper entitled "Introversion, **extraversion** and worsening of chronic pain impact during social isolation", adults with chronic pain were seen 4 to 8 weeks after the social distancing mandates of COVID-19 (N=150) [24]. Those who were extraverted had greater pain interference which was mediated by greater sleep disturbance and depression.

In a study entitled "Pain intensity, depression, and anxiety levels among patients with chronic pain during COVID-19", significant pandemic-related increases were noted on several problems [25]. These included increased depression (75%), anxiety (66%), analgesic need (60%), and limited access to analgesic drugs (40%).

In a paper entitled "A longitudinal investigation of the impact of **COVID-19** on patients with chronic pain", treatment for chronic pain was notably effective in a large sample (N=1270) [26]. Those who had treatment had less pain intensity, catastrophizing, anger, anxiety, and sleep problems over the two-year longitudinal period.

Interventions for Chronic Pain and Depression

A variety of interventions have been offered for chronic pain and depression (see table 3). These have included support, Internet, cognitive behavior therapy, transcranial magnetic stimulation, ketamine, other antidepressants, opioid and non-steroidal anti-inflammatory drugs (NSAIDs), nerve blocks, acupuncture, physio and psychotherapy [4].

Table 3. Interventions for chronic pain and depression (and first authors).

Intervention	First author
Facebook peer support versus professional group support	Pester
Internet intervention	Bisby
Cognitive behavior therapy	Ploutarchou
Tai chi in class and at home practice	Alende
Dog-assisted, marijuana, transcranial, CBT, anti-depressants	Pakniyat-Jahromi
Transcranial magnetic stimulation	Corlier, Zhu
Ketamine	Voute, Corriger, Subramanian
Tricyclic antidepressants	Bonilla-Jaime, Yang
Exercise and pharmacotherapy	Cheng

In a study that compared **Facebook peer support** with professional group support (N=30 each), the two types of interventions were equally effective [27]. Pain decreased as did depression after four weeks of the intervention. In a paper entitled "Can Internet–delivered pain management programs decrease psychological distress in chronic pain?" (N= 1333), greater pain intensity was associated with increased odds of elevated anxiety or depression symptoms at baseline [28]. **Internet intervention** led to greater reductions in anxiety and depression, and a 30% decrease in pain intensity led to a 30% improvement in psychological symptoms.

A meta-analysis was conducted on 14 studies that used **cognitive behavior therapy** for chronic neck pain [29]. Collectively, the studies showed a decrease in kinesiophobia (an excessive, irrational and debilitating fear of physical activity), depression, and anxiety.

In a randomized controlled trial (N=38) entitled "Investigating inter-and intra–individual differences in **Tai Chi** practice time, pain, and mood among participants with chronic nonspecific neck pain", those participants with high anxiety practiced more when pain intensity was greater [30]. A combination of class time plus home practice had the greatest effect on the reduction of pain.

In a review of 37 articles on older adults (greater than 65 years old) with chronic pain and depression, several different therapies were reported [3]. These included **dog-assisted therapy, medical marijuana, transcutaneous magnetic stimulation, cognitive behavior therapy, anti-depressants and daloxetine.**

In a paper entitled "Repetitive transcranial magnetic stimulation treatment of major depressive disorder plus comorbid chronic pain"(N= 162 major depressive disorder participants and 65% with chronic pain), **transcranial magnetic stimulation** was applied to the left dorsolateral prefrontal cortex for 30 sessions [31]. Following this treatment protocol, both depression and pain decreased. Participants with severe pain (27%) were less likely to respond to the treatment protocol. A systematic review and meta-analysis of high frequency transcranial magnetic stimulation over the dorsolateral prefrontal cortex yielded similar results [32]. The results suggested the relief of pain as well as an alleviation of depression symptoms. The focus on the prefrontal cortex is not surprising given that abnormal changes in fMRI signals have been noted in the prefrontal cortex of those with chronic pain, but changes have also been noted for the anterior cingulate cortex [4].

Ketamine has been a frequently studied intervention for chronic pain and depression. In research that involved patients reporting every month by telephone (N = 329), the Hospital Depression and Anxiety Scale was given, as well as the Numerical Pain Rating Scale [33]. Ketamine was noted to reduce pain via decreased depression, which was called a mediator. In another study, ketamine was used for refractory pain involving mild neuropathic to severe fibromyalgia pain [11]. Ketamine reduced the pain associated with depression. In a paper entitled "Ketamine as a therapeutic agent for depression and pain", ketamine via intravenous administration was, not surprisingly, more bioavailable than it was via intranasal administration [34].

The hypothalamic pituitary adrenal axis has been involved in stress activated- pain pathways that lead to chronic hyperalgesia [4]. In at least one paper entitled "Depression and pain: use of antidepressants", **tricyclic antidepressants** are reported as being more effective in reducing pain than SSRI's and serotonin -noradrenaline reuptake inhibitors (SNRI's) [35]. This likely derives from the relationship between the serotonergic and norepinephrine systems. As these authors have suggested, hyperactivity of the hypothalamic pituitary adrenal axis decreases brain derived neurotrophic factor "implicating neurotrophins as needing antidepressants". Antidepressants and cognitive behavior therapy have been effective in alleviating both pain and depression [4]. Brain derived neurotrophic factor is essential for the growth of neurons that can regulate pain.

In at least one paper, the authors have specified different pain conditions that can benefit from different interventions. For example, in a meta-analysis on 182 studies, exercise was the most effective intervention for arthritis and **pharmacotherapy** for neuropathic pain [36]. Exercise has been effective for many conditions involving pain and depression [37]. An increase in serotonin (an anti-pain and anti-depression neurotransmitter) typically follows exercise.

Potential Underlying Mechanisms for Comorbid Chronic Pain and Depression

Several potential underlying mechanisms have been explored for comorbid chronic pain and depression (see table 4). These include inflammatory cytokines, oxidative stress, astrocytes, a reduction in gray matter, and dysfunction of the amygdala and locus coeruleus. Pain and depression have been regulated by **immune-inflammatory mechanisms** like cytokines including TNF-alpha, IL-1 and IL-6 [4]. In a study entitled "Oxidative stress is associated with characteristic features of the dysfunctional chronic pain phenotype", oxidative stress was assessed in patients with osteoarthritis (N= 84) [38]. In this research, oxidative stress was associated with greater pain intensity, catastrophizing and pain interference.

Table 4: Potential underlying mechanisms for chronic pain and depression (and first authors)

Mechanism	First author
Inflammatory cytokines (TNF-alpha, IL-1, IL-6)	Yang
Oxidative stress	Bruehl
Astrocytes	Chen
Less gray matter volume	Liu
Amygdala	Chen
Locus coeruleus	Suarez-Pereira

Another potential underlying mechanism is the involvement of **astrocytes** [10]. According to this theory, astrocytes which are the most abundant cell type in the central nervous system, are highly involved in regulating pain signaling under health and disease. Targeting detrimental astrocyte subtypes and activity is reputedly a promising pain management strategy.

Individual differences in **gray matter volume** are reputed to accompany pain catastrophizing [39]. In a study on Chinese community dwellers who experienced pain more than three months (N=160), MRI scans and pain catastrophizing scores suggested that those with pain catastrophizing had lower regional gray matter volume levels in the inferior temporal area in the right fusiform gyrus (a region implicated in emotional regulation).

The **amygdala** has also been implicated as an underlying mechanism for chronic pain and depression by a few research groups. In a review paper entitled "Size reduction of the right amygdala in chronic pain patients with emotional stress", 13 studies (N=738 chronic pain patients with emotional stress and 813 controls), the right amygdala was reputedly reduced [40].

The **locus coeruleus** has also been implicated in pain and associated stress-related disorders [41]. Acute pain is noted to trigger a robust locus coeruleus response, producing spinal cord mediated endogenous analgesia. However, the protective biological system fails in chronic pain and locus coeruleus activity produces pain facilitated anxiety, aversive memory and despair, acting at the prefrontal cortex and amygdala levels.

Methodological Limitations of the Recent Literature

Several methodological limitations can be noted for this literature. They include differences in definitions of chronic pain and depression including types of chronic pain as well as variable thresholds for pain, severity and duration of the conditions. The chronic pain conditions are also differentially affected by confounding psychological variables that are often comorbid with depression including stress, anxiety and insomnia.

The research groups may be biased in their selection of the direction of effects, with some electing to explore the effects of chronic pain on depression and others selecting the opposite direction of depression predicting chronic pain. A group of individuals with comorbid chronic pain and depression is rarely compared to chronic pain or depression alone.

The definitions of chronic pain vary by severity and duration including various intensity levels. Chronicity or the duration of pain has varied from greater than 3 months to greater than 6 or 12 months. Pain intensity and thresholds are not always assessed including mechanical and thermal thresholds. And pain catastrophizing and kinesiophobia have been known to affect the pain tolerance levels. But they are not always assessed for their confounding effects.

The type of pain condition is highly variable. Although arthritis is one of the most common forms of chronic pain, low back pain and neck pain are more frequently targeted problems in this literature, likely because they are more often samples of convenience for their seeking medication and other treatments.

Other psychological variables that are often comorbid with depression confound the assessment of depression as an outcome or a predictor variable. Sometimes they are assessed as mediator variables. These include anxiety, stress and insomnia. Other predictor variables like physical inactivity, alcohol and substance abuse are frequently not measured.

Potential underlying mechanisms are often interrelated such as inflammatory cytokines and oxidative stress, although different mechanisms are rarely compared. fMRI studies are focused on gray matter volume in single areas, for example the prefrontal cortex, amygdala and the locus coeruleus rather than considering the interrelatedness of function in multiple areas of the brain. Multiple interventions are also related and often combined and not compared, for example, medications and physical therapy. Ketamine has been used both as an antidepressant and anti-pain medication but the differential effects of ketamine on depression and pain have not been reported. Clinical samples are compared rather than individuals being randomly assigned to different interventions. Surprisingly, exercise only appeared in one meta-analysis as being effective for arthritis despite its known effectiveness for boosting serotonin levels and decreasing both pain and depression.

And the models that are used for recruiting and following individuals with chronic pain are not robust. Cross-sectional rather than longitudinal research is the typical model. The measures are frequently self-report. And, although mediation analysis has been used in some studies, regression analysis has rarely been used to determine the relative amount of variance explained by the predictor variables. The large number of variables often lend themselves to more complex models like structural equation modeling.

Despite these methodological limitations and confounding variables, the current literature has highlighted the effects of chronic pain on depression and the opposite direction predictive validity of depression for chronic pain. Future research that corrects for these limitations will likely suggest multivariate interventions that can reduce both chronic pain and depression effects independent of their relative contribution to functional disability.

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