Pain and Depression: A Systematic Review

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Background: Pain comorbid with depression is frequently encountered in clinical settings and often leads to significant impaired functioning. Given the complexity of comorbidities, it is important to address both pain and depressive symptoms when evaluating treatment options.

Aim: To review studies addressing pain comorbid with depression, and to report the impact of current treatments.

Method: A systematic search of the literature databases was conducted according to predefined criteria. Two authors independently conducted a focused analysis of the full-text articles and reached a consensus on 28 articles to be included in this review.

Results: Overall, studies suggested that pain and depression are highly intertwined and may co-exacerbate physical and psychological symptoms. These symptoms could lead to poor physical functional outcomes and longer duration of symptoms. An important biochemical basis for pain and depression focuses on serotonergic and norepinephrine systems, which is evident in the pain-ameliorating properties of serotonergic and norepinephrine antidepressants. Alternative pharmacotherapies such as ketamine and cannabinoids appear to be safe and effective options for improving depressive symptoms and ameliorating pain. In addition, cognitive-behavioral therapy may be a promising tool in the management of chronic pain and depression.

Conclusion: The majority of the literature indicates that patients with pain and depression experience reduced physical, mental, and social functioning as opposed to patients with only depression or only pain. In addition, ketamine, psychotropic, and cognitive-behavioral therapies present promising options for treating both pain and depression.

Keywords: cognitive-behavioral therapy, depression, ketamine, pain

INTRODUCTION

Depression is a widespread and debilitating condition, affecting 9.5% of adults in the United States[1] and over 350 million people globally.[2] If left untreated, depression can lead to suicide—the second leading cause of death among ages 15–29 in the world.[2] Similarly, pain is a prevalent condition affecting over 76.2 million people in the United States alone and 1.5 billion people worldwide.[1] The International Association for the Study of Pain defines pain as "an unpleasant subjective feeling and emotional experience associated with actual or potential tissue damage," which is an interaction of psychological, emotional, behavioral, and social factors. The same group defines chronic pain as persistent or intermittent pain for more than three months.[3] Not surprisingly, pain comorbid with major depressive disorder (MDD) is frequent and can lead to impaired functioning, lower treatment response, and limited treatment options.[4,5] The two conditions often co-occur, exacerbate one another, and may display overlapping symptoms.[6] The high variability in sensation and expression of pain observed among depressed patients may be caused by differences in physical, psychological, and emotional impairments that ultimately pose a challenge for the accurate assessment of depression for patients with comorbid pain.[7] There is evidence of synchronicity between depressive and pain symptoms; depression/anxiety and pain are positively correlated.[8] The co-occurrence of these two conditions may foreshadow common biological and, in some cases, psychological mechanisms that may lead to significant improvements in treatments and

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outcomes.[9] To date, these common mechanisms have yet to be identified, though studies have shown considerable overlap between pain and depression-induced neurobiological mechanisms. For example, injuries to sensory pathways have been shown to share the same brain regions that are involved in mood management.[10] The current review describes (1) the impact of pain and depression on functioning and (2) current treatments for treating the comorbid conditions. It is hypothesized that a common link between pain and depression may simultaneously increase susceptibility to both depression and pain. Beyond that, however, a concrete model consolidating the evaluation and treatment of both depression and pain is essential before reaching functional outcomes with patient populations.

METHODS

Search Strategy

A systematic search was conducted on PubMed, Ovid MEDLINE, and PsycINFO databases for the past 30 years (1987–2017). Each database was searched using the following keywords: pain AND depress* AND treatment. The initial search identified 706 articles. Out of these, 528 were eliminated because they were duplicates, studies in animals or children, review articles, or lacking measures. One hundred seventy-eight full-text articles were then screened using the selection criteria. Based on the consensus of two reviewers, 28 articles were selected for inclusion in this review.

Study-Selection Criteria and Methodology

Two authors reviewed the abstracts independently using the following inclusion criteria: (1) published in English or with an available published English translation; (2) published in a peer-reviewed journal; (3) original studies in human adults (no reviews; no animal studies; age $\geq$ 18 years); and any design that focused on comorbid pain and depression. The two authors independently analyzed the full-text articles and reached a consensus on the 28 studies to be included in this review. The selection process is described in Supplemental Figure 1 (available online as supplemental digital content at http://links.lww.com/HRP/A77).

Data Extraction and Yield

Research methodology and key findings were derived from the full text and tables of the selected studies.

RESULTS

Impact on Functioning

The selected studies demonstrated lower functioning among patients with pain comorbid with depression, in comparison to those with depression or pain alone. Study findings are detailed in Table 1.

Munce and colleagues[17] found that patients with comorbid depression and pain experienced difficulties in returning to work and that the level of work-related stress was a strong predictor of depression. Similarly, Jaremka and colleagues[30] found increased loneliness to be a strong predictor for developing both pain and depression, which resulted in increased symptom-cluster levels throughout the following year. Interestingly, one study by Linder and colleagues[32] found a stronger correlation between chronic pain and sleep disturbance than between chronic pain and depression.

Relationship Between Pain and Depression

Overall, studies suggested that pain and depression were highly intertwined and may co-exacerbate physical and psychological symptoms. These symptoms could lead to poor physical functional outcomes and longer durations of symptoms. Ohayon[15] found that chronic painful physical conditions contributed to the recurrence of depressive episodes, which were characterized by longer duration, increased sadness, mood lability, and severe fatigue. Similarly, in a study of pain patients, participants with comorbid pain and depression had significantly lower mental composite scores on measures of quality of life (QOL) than those with minor or no depression.[13] This cross-sectional study utilized a health-related QOL measure, the Short Form–36, which also reported significant correlations between depressive symptoms and chronic pain. This result was supported by Geerlings and colleagues' longitudinal study,[12] which showed a correlation between pain and depression, with the correlation being more prominent in males than among females (Center for Epidemiologic Studies Depression Scale).

Several studies have investigated the effects of comorbid pain and depression on neural pathways and brain processes. Yang and colleagues[36] found depression to be an inflammatory response in the brain. This inflammation is elicited by proinflammatory cytokines, which can also trigger pain; thereby, the initiating symptoms of depression may intensify or reduce the capacity to tolerate pain. Thornton and colleagues[27] identified increased levels of stress hormones as a common physiological response to pain and depression. Mahn and colleagues[28] reasoned, however, that despite the presence of shared sensory symptomatology between pain and depression, neuropathic pain disorders and depression are different in important ways, which need to be further investigated in the future.

Treatment

Though data are scarce, the medications used for treating comorbid pain and depression vary widely. An important biochemical basis for pain and depression involves the serotoninergic and norepinephrine systems, as is evident in the analgesic effects of serotonin and norepinephrine antidepressants.[9] For example, quetiapine extended release was more effective than placebo in treating fibromyalgia pain in patients with MDD, and overall QOL also improved.[31] In a study of patients with rheumatoid arthritis, Bird and Broggini[11] found that both paroxetine and amitriptyline were effective in treating both depressive and pain symptoms. They also demonstrated, however, that paroxetine, a selective serotonin reuptake inhibitor (SSRI), was better tolerated than amitriptyline, a tricyclic

Table 1

Characteristics of Included Studies Evaluating Treatments of Comorbid Pain and Depression

Study	Measures	Demographics	Number of subjects	Study setting	Main outcomes
Bird & Broggini (2000)[11]		Depressed patients with rheumatoid arthritis	191	Longitudinal	Paroxetine and amitriptyline were equally effective in treating depression and pain Paroxetine was better tolerated by patients, with adverse experiences of 56.4% in the paroxetine group versus 67.7% in the amitriptyline group
Geerlings et al. (2002)[12]	CES-D	Random community in Netherlands: 325 nondepressed persons 327 depressed persons	652	Longitudinal	Using generalized estimating equations as part of longitudinal analyses, pain and depression are significantly associated; this relationship is more prominent in males than in females Age did not have an effect on pain-depression relationship Unpredictably, disability also did not have an effect on the pain-depression relationship
Elliott et al. (2003)[13]	Patients reported health-related quality of life (SF-36), pain, pain type and diagnoses, mental health diagnoses, and patient demographics	Chronic non-cancer pain patients: 160 women 82 men Age 19–83 years	242	Cross-sectional	SF-36 health survey showed a high correlation between depression type and chronic pain The type of depression was also highly correlated with SF-36 mental composite score: chronic pain patients with MDD had significantly lower mental composite t-score when compared to those with minor or no depression (34.1 and 47.6, respectively [$p < .001$])
Goldstein et al. (2004)[14]	Visual analogue scales Somatic Symptom Inventory HAM-D	Adults 18 years and older diagnosed with MDD	Study 1: 353 Study 2: 245 Study 3: 267	Longitudinal	Significant reductions in painful physical and emotional symptoms of depression in the duloxetine group compared to placebo conditions Effects were maintained at follow-up
Ohayon (2004)[15]	Sleep-EVAL expert system Interview on sociodemographic info, sleep/wake schedule, sleeping habits, psychiatric symptoms, medical treatment, and physical illnesses DSM-4	Between 15–100 years of age who were representative of the general population of 5 European countries: UK (n = 4972) Germany (n = 4115) Italy (n = 3970) Portugal (n = 1858) Spain (n = 4065)	18,980	Cross-sectional	Chronic painful physical conditions increased the severity of physical symptoms of depression such as fatigue, insomnia, psychomotor retardation, and weight gain. Chronic painful physical conditions also increased the duration and recurrence of depressive episodes and should be considered in the expression and progression of MDD

Table 1

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Study	Measures	Demographics	Number of subjects	Study setting	Main outcomes
Brannan et al. (2005)[16]	HAM-D CGI-S BPI Patient Global Impression of Improvement Symptom Questionnaire: Somatic Subscale	Adult outpatients 18 years and over with MDD	282	Longitudinal	Duloxetine (60 mg once daily) was effective in treating painful physical symptoms compared to placebos Improvements in pain symptom severity were independent of changes in depressive symptom severity
Munce et al. (2006)[17]	Canadian Community Health Survey Cycle	Working individuals with chronic pain	78,593	Cross-sectional	7.6% qualified for MDD, but that percentage increased to 12% in those also reporting chronic pain Comorbid pain and depression was more common in women than men Chronic pain conditions on top of work stress is a strong predictor of depression
Siedliecki et al. (2006)[18]	McGill Pain Questionnaire CES-D Pain Disability Index Power as Knowing Participation in Change Tool (Version II)	Age 21–65 years African American and Caucasian people were selected	60	Cross-sectional	Listening to self-selected music for 1 hour over 7 days increased sentiment of power, decreased pain, depression, and disability for African American and Caucasian men and women with chronic back, neck, or joint pain Music intervention increased feeling of power but had no effect on pain or disability scores
Jensen et al. (2006)[19]	11-point numerical rating scale for pain Chronic Pain Coping Inventory Coping Strategies Questionnaire BPI CES-D	Adults with cerebral palsy–related chronic pain: 92% Caucasian 6% Native American 2% African American 65% of study participants needed wheelchair or other motility aids	48	Longitudinal	Changes in pain-coping strategies over time can bring about higher functional outcomes in persons with cerebral palsy and chronic pain Some of the strategies (catastrophizing, rest, task persistence) are more closely linked to depression and pain interference than others
Angst et al. (2008)[20]	SF-36 Hospital Anxiety and Depression Scale Multidimensional Pain Inventory	Chronic pain patients with three subtypes of patients: (1) "interpersonally distressed group" (characterized by relatively low-support, high-punishing, low-solicitous, and low-distracting responses) (2) "dysfunctional" (3) "adaptive copers/minimizers"	273	Cross-sectional	Multidimensional Pain Inventory pain severity scale and Hospital Anxiety and Depression Scale showed maximum correlations at .27 and .29 Between the three types of patients, the correlation was moderate in patients characterized by low-support and high-punishing responses The correlation was also weak in "dysfunctional" populations and absent in "adaptive" populations

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Study	Measures	Demographics	Number of subjects	Study setting	Main outcomes
Ullrich et al. (2009)[21]	SF-36 Beck Depression Inventory	Adult burn survivors aged between 18–60 years after discharge from burn care at 1- and 2-year follow-ups	64	Cross-sectional	Co-occurrence of pain and depression provides greater risks for reduced physical functioning over time for burn survivors The assessment and treatment for both these conditions are adversely affected by their co-occurrence, at least in patients with burn injury
Sherbourne et al. (2009)[22]	BPI Patient Health Questionnaire–2 item GAD-2	Male veterans	528	Cross-sectional	Results show the necessity for targeted depression and anxiety screening for patients with moderate to severe pain Patients with depression are more likely to report physical symptoms
Wohlreich et al. (2009)[23]	HAM-D CGI-S Geriatric Depression Scale Visual analogue scales	Patients 65 years and older with recurrent MDD	172	Longitudinal	Patients with or without arthritis on duloxetine therapy experienced significant reductions in MDD symptom severity Pain reduction in patients with arthritis and MDD
Kroenke et al. (2009)[24]	Hopkins Symptom Checklist–20 item BPI Global Rating of Change GAD-7	Patients with comorbid musculoskeletal pain and depression	250	Longitudinal	Antidepressant therapy (venlafaxine, an SNRI) in conjunction with a pain self-management program led to reductions in depression and pain severity
Marta et al. (2010)[25]	Visual Analogue Scale for Pain Beck Depression Inventory Pittsburg Sleep Quality Index	Elders with chronic non-oncologic pain	30	Cross-sectional	8 sessions of therapeutic touch therapy were effective in decreasing pain intensity and depressive symptoms (self-score)
Wong et al. (2010)[26]	Chronic Pain Grade Questionnaire Numerical Rating Scales Chronic Pain Grade Questionanaire disability score Hospital Anxiety and Depression Scale–7-item depression subscale SF12-MCS SF12-PCS	Chinese professional teachers	385	Cross-sectional	Pain and depression differentially affected the physical versus mental aspects of QOL The effect of both pain and depression on QOL accentuated the negative effects of depression on mental functioning The relationship among pain, depression, and QOL should be assessed tentatively until more investigations are done

Table 1

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Study	Measures	Demographics	Number of subjects	Study setting	Main outcomes
Thornton et al. (2010)[27]	Brief Pain Inventory Fatigue Severity Index Center for Epidemiological Studies Depression Scales	Advanced cancer patients	104	Cross-sectional	Cortisol and epinephrine showed moderate correlation with pain, depression, and fatigue; this correlation provides evidence that stress hormones might share a co-occurrence with pain and depression Elevated sympathetic nervous system and HPA-axis hormones, in terms of a system of neuroendocrine-immunologic alterations, could be concurrent with alterations in neurotransmitter metabolism, which are responsible for psychological/behavioral responses (pain, depression)
Mahn et al. (2011)[28]	Medical Outcomes Study Sleep Scale Patient Health Questionnaire–9 item painDETECT Questionnaire	Patients with neuropathic pain Over 18 years of age	2094	Cross-sectional	There are differences between painful radiculopathy and neuropathic disorders (depression), despite sharing many similarities in sensory symptoms
Nicholas et al. (2012)[29]	Roland and Morris Disability Questionnaire Multidimensional Pain Inventory Depression Anxiety Stress Scale Pain Self-Efficacy Questionnaire Pain Response Self-Statements Scale Tampa Scale for Kinesiophobia	52% women 48% men 88.4% were taking one or more types of medication for their pain at admission	567	Cross-sectional	Worse outcomes with less consistent practice of pain self-management strategies in terms of pain, disability, and depression at post-treatment This result could mean that the strategies affect more than the cognitive process variables alone and that, like the long-standing cognitive-behavioral formulations of treatment, they change the way patients think, and so feel
Jaremka et al. (2014)[30]	New York University Loneliness Scale RAND-36 Multidimensional Fatigue Symptom Inventory–Short Form CES-D Charlson Index Pittsburgh Sleep Quality Index	Study 1: Cancer survivors and benign control Study 2: Elder caregivers for spouses with dementia	Study 1: 115 Study 2: 229	Longitudinal	Patients with loneliness experienced more comorbid pain and depression as well as an increase in symptom-cluster levels in the next year compared to less lonely patients

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Table 1

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Study	Measures	Demographics	Number of subjects	Study setting	Main outcomes
	Godin Leisure-Time Exercise Questionnaire Beck Depression Inventory Older Americans Resources and Services Generalized Estimating Equations				
McIntyre et al. (2014)[31]	HAM-D	Nonpsychotic MDD-diagnosed outpatients aged 18–65 years	72	Longitudinal	Significant improvements in depression scores from baseline to week 8 in the quetiapine XR group compared to placebo group Also observed improvements in secondary outcomes, such as quality of life
Linder et al. (2014)[32]	Comprehensive Psychopathological Rating Scale for Self Administration Montgomery-Åsberg Depression Rating Scale Depression Rating Self-Report Questionnaire	Patients who experienced difficulty returning to work 62.8% women Median age 39.2–52.5 years 53% were unemployed	1206	Cross-sectional	In patients with long-term illness who experienced difficulties in returning to work, depression occurred in 64% of the patients with no/mild pain and in 75% of the patients with moderate/severe pain.
Lopez et al. (2014)[33]	Moderation and moderated mediation analyses approach	Elder patients with osteoarthritis: 102 in nursing homes 106 in community	208	Cross-sectional	Confounding results of interaction effect between pain intensity and activity restriction on depression; an alternative way to treat pain would be to mediate how pain alters patient's lives, on top of treatment
Tarakci et al. (2015)[34]	Geriatric Depression Scale Visual analogue scales Nottingham Extended Activities of Daily Living scale	Age 65–90 years First subgroup with no chronic pain: 40 men 64 women Second subgroup with chronic pain: 58 men 24 women	186	Cross-sectional	More than 50% of the geriatric population in nursing homes reported chronic pain Moderate to severe pain was associated with more depressive symptoms Depression is a crucial condition to consider when treating geriatric population with chronic pain There was no correlation between pain and age

Table 1

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Study	Measures	Demographics	Number of subjects	Study setting	Main outcomes
Stein et al. (2015)[35]	CESD Patient Health Questionnaire–2 item ANOVA Pearson's x^2 test of independence Holm's step-down method Multinomial logit models	Opioid-dependent buprenorphine patients	328	Cross-sectional	Opioid-dependent patients who used over-the-counter or prescribed buprenorphine, as well as other antidepressants, continued to have pain and depressive symptoms Confounded by high percentage of cohort self-medicating with nonprescribed psychoactive drugs (e.g., cocaine, alcohol)
Yang et al. (2016)[36]	Korea National Health and Nutrition Examination Survey	19 years and older	4866	Cross-sectional	Participants with depression had a higher prevalence of dental pain compared to those without depression Depression has the potential to intensify pain and reduce the capacity to tolerate pain Prevalence of depression in chronic pain patients was estimated to be 30%–54% It was suggested that depression might be a form of inflammatory disorder, which is mediated by pro-inflammatory cytokines and ultimately triggers the sensation of pain
Sekine et al. (2016)[37]	HAM-D	Japanese outpatients with melancholic MDD	100	Longitudinal	Responsiveness to SNRIs (most received duloxetine, some milnacipran) was higher in groups with painful physical symptoms than those without
Smith et al. (2016)[38]	British Pain Society Pain Rating Scale Patient Health Questionnaire–9 item	65 years or older	285	Cross-sectional	In a sample of low-income, community-dwelling elders, linear regression data indicated that depression fully mediated the relationship between pain levels and functional limitations

ANOVA, analysis of variance; BPI, Brief Pain Inventory–Pain Interference Scale; CES-D/CESD, Center for Epidemiologic Studies Depression Scale; CGI-S, Clinical Global Impression Scale–Severity of Illness; DSM-4, *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition; GAD-2, Generalized Anxiety Disorder–2 item; GAD-7, Generalized Anxiety Disorder–7 item; HAM-D, Hamilton Depression Symptom Severity Scale; HPA axis, hypothalamic-pituitary-adrenal axis; MDD, major depressive disorder; QOL, quality of life; RAND-36, 36-item measure of health-related quality of life; SF-36, Medical Outcomes Study 36-item short-form health survey; SF12-MCS, Medical Outcomes Study 12-item Short-Form Health Survey–Mental Component; SF12-PCS, Medical Outcomes Study 12-item Short-Form Health Survey–Physical Component; SNRI, serotonin and norepinephrine reuptake inhibitor.

antidepressant.[11] Goldstein and colleagues[14] found significant reductions in pain, as well as the physical and emotional symptoms of depression, when administering duloxetine (a serotonin-norepinephrine reuptake inhibitor [SNRI]) to participants versus placebo controls. By contrast, Stein and colleagues[35] found buprenorphine, a long-acting partial opioid agonist, to be ineffective in treating opioid-dependent patients with comorbid pain and depression.

Duloxetine has been a frequently utilized medication for managing both pain and depression. Wohlreich and colleagues[23] found duloxetine to yield a significant reduction in MDD symptoms among elderly patients with and without comorbid arthritis, as well as pain reductions in patients with comorbid arthritis. In a study of the effect of painful physical symptoms in outpatients with melancholic MDD, Sekine and colleagues[37] showed that patients with such symtpoms were significantly more responsive to duloxetine than those without such symptoms. Similarly, Brannan and colleagues[16] observed that duloxetine (60 mg daily) effectively treated painful physical symptoms in patients with MDD. However, improvements in pain severity occurred independently of improvements in depressive symptoms severity. A clinical study compared the efficacy of doxazosin (alpha blocker), sertraline (SSRI), and duloxetine (SNRI) for treating pain disorders in chronic prostatitis/chronic pelvic pain syndrome. The effective rates in the doxazosin group were 4.88%, 19.51%, and 56.10% after 1, 3, and 6 months, respectively; the effective rates in the sertraline group were 9.76%, 36.59%, and 63.41% after 1, 3, and 6 months, respectively; and the effective rates in the duloxetine group were 36.36%, 88.64% and 88.64% after 1, 3 and 6 months, respectively.[39]

In a randomized, controlled trial by Kroenke and colleagues,[24] 250 depressed patients with lower back musculoskeletal pain and moderate depression were randomized to usual care (n = 123) or intervention (n = 127). Those randomized to the intervention received 12 weeks of antidepressant therapy, followed by six sessions (12 weeks) of a pain self-management program and then by a continuation phase of six months.[24,40] The results of the study indicated that optimized antidepressant therapy, coupled with a pain self-management program, produced substantial reductions in depression severity and that it enhanced response and remission rates.[24,40] The intervention also resulted in moderate reductions in both pain severity and pain-related disability, with sustained effects over the 12 months of the trial, including the 6-month continuation phase. The trial used an antidepressant algorithm rather than a single antidepressant, and more than half of the patients discontinued or switched from their initial antidepressant by 12 months.[24]

Furthermore, cognitive-behavioral therapy (CBT) may be a promising tool in managing chronic pain. Although CBT has shown weak effects in improving pain when compared to traditional treatments, it is effective in improving mood outcomes.[41] A recent study demonstrated that intensive short-term dynamic psychotherapy and CBT reduced pain symptoms.[42] The two treatments also reduced psychological distress, depression, and catastrophic thinking.[19,42]

Other studies have outlined therapeutic approaches, but with inconsistent success. Siedliecki and Good[18] found music to be effective in treating depression alone. Marta and colleagues[25] found therapeutic sessions to be effective in decreasing pain and depression scores in elders. In addition, Jensen and colleagues[19] found coping strategies to be effective in treating pain alone. According to Nicholas and colleagues,[29] consistent self-management of pain, anxiety, and mood causes changes in cognitive patterns and subjective feelings, leading to reduced depression and pain.

DISCUSSION

Comorbid depression and pain have significant detrimental effects in several areas of patient functioning, including but not limited to social and occupational impairments. Thus, the painful physical symptoms commonly experienced in depressed patients suggest that both pain and depression should be addressed concurrently. Although duloxetine was the most commonly used therapeutic, the present review did not identify an optimal treatment that efficiently treated comorbid pain and depression. In order to establish non-opioid effective treatments, further research on medical and therapeutic approaches is necessary. Although the contributory effect of chronic opioid use in depression is beyond the scope of this review, the relationship between chronic opioid use and depression appears to be bidirectional. For example, opioid use can enhance apathy, lethargy, and other vegetative symptoms observed in depression. Likewise, a depression diagnosis is a risk factor for opioid misuse, as misuse is correlated with severity of depressive symptoms.[43] The relationship between pain and depression suggests a bidirectional relationship that is manifested in the exacerbation of its counterpart.[44] Furthermore, the two conditions detrimentally affect each other in terms of recovery time and symptom duration,[21] suggesting a synchronicity in symptom severity.[38] This connection is supported by several mechanistic pathways underlying comorbid pain and depression, such as stress hormones, cytokines, and other neuropathic pathways.[36]

Pain and depression may co-occur because they are affected by the same modulatory neural system.[45,46] Functional imaging studies have shown a bidirectional relationship between pain and depression in which depression is a risk factor for pain, and pain is a risk factor for depression. Chronic conditions such as fibromyalgia, abdominal pain, and lower back pain have been associated with alterations in brain regions responsible for the processing of emotional stimuli, including the anterior cingulate cortex and prefrontal cortex.[47] Goesling and colleagues[44] highlighted the brain regions and neurotransmitters that underlie the neuropathic pathways in processing both physical and psychological pain. Physical pain appears different from psychological pain (sadness and grief) because the latter does not involve a noxious bodily stimulus. Both types of pain signal threat, however, and consequently

activate neural mechanisms to assess and deal with the threat. In addition, pain processing and mood are both controlled by common neurotransmitters such as serotonin, norepinephrine, and glutamate. If pain and depression are in response to overlapping neurotransmitter systems, it follows that these symptoms would respond to similar pharmacological treatments. In particular, inhibition of the descending pain pathway of the central nervous system is influenced by serotonin and norepinephrine neurotransmitters.[44] For example, pain can be inhibited by antidepressants via the descending pathways in the midbrain and the brain stem—specifically, the periaqueductal gray matter, nucleus raphe magnus, and locus coeruleus. Via endogenous opioids, serotonin, or norepinephrine as inhibitory mediators, these descending fibers block pain by preventing the afferent sensory neurons from sending pain signals to the somatosensory cortex.[48] Thus, the utilization of medications that target serotonin or norepinephrine show potential for treating comorbid pain and depression.[44]

Appraisal of the literature showed a scarcity of studies looking at antidepressants for comorbid pain and depression, though several studies looked at pain symptoms in depressed patients. Overall, the range of medications used to treat depression and associated pain is widely variable. Some of the antidepressants commonly used are SNRIs (e.g., venlafaxine, duloxetine, milnacipran), SSRIs (e.g., paroxetine, sertraline), opioid partial agonist-antagonists (e.g., buprenorphine), antipsychotics (e.g., quetiapine XR), and tricyclic antidepressants (e.g., amitriptyline). With the exception of buprenorphine, all above medications appear to be effective by partially reducing symptoms of depression and pain. The type of pain may also be considered when assessing the outcome of antidepressant therapy. It has been suggested that the analgesic effect of antidepressants is effective in treating neuropathic pain, headache, and fibromyalgia, whereas they are not always effective in musculoskeletal pain, such as nonspecific lower back pain. Nevertheless, when antidepressants were optimized for 12 weeks and combined with a pain self-management program, significant improvement in both depression and pain were observed in patients with lower back, knee, and hip pain.[24] Future research should seek to compare the efficacy of SNRI drugs.

Behavioral therapies such as intensive short-term dynamic psychotherapy and CBT have proven to reduce depression and pain symptoms.[42] Despite the lack of guidelines in treating depressive patients with pain, the management of MDD in patients with physical pain should be part of a unified effort of pain management, with particular attention to the patient's mental health and social conditions. This concern is especially relevant in relation to the medically ill; since their pain is seen as primarily attributable to the illness, their depression may be overlooked and untreated. Patients who were comorbid with pain and depression, but whose depression was untreated, received more medications and less psychosocial treatment, resulting in worse outcomes.[47] Since pain and depression often co-occur, exacerbate one another, and may display overlapping symptoms, early identification and treatment are critical. Fortunately, detection is becoming more common, with outpatient settings routinely using the Patient Health Questionnaire, a self-report questionnaire that screens for depression by assessing the frequency of certain depressive symptoms.[49] Due to the small number of medical trials that have addressed depression and pain, further investigations are necessary in order to understand the distinct relationship between the two conditions. While more research is needed to accurately assess psychotherapeutic treatment outcomes, the existing results are promising and have implications in clinical practice.

Interestingly, a novel and promising approach in treating comorbid pain and depression is ketamine—a common dissociative anesthetic that has been used as an analgesic for decades.[50] Ketamine shows promise in treating chronic pain in controlled dosages. If pain and depression are linked, it is plausible to assume the possibility of neurophysiological overlaps and consequently the existence of common activating factors that play a role in the central nervous system.[36] If ketamine does indeed target the shared areas of pain and depression, it might serve as a new frontier in treating patients expressing comorbidity in depression and pain. The effects and duration of ketamine varies largely by delivery and dosage. For patients with depression, ketamine provides an ultra-rapid onset of therapeutic action (5–40 minutes), with intranasal administration delivering nearly immediate relief.[51] For longer-lasting effects, administration of multiple intravenous infusions has produced improvements in treatment-resistant unipolar and bipolar depression.[52] Ketamine shows favorable results in treating depression, albeit in sample sizes that frequently lack a formal regime of delivery, monitoring, and data collection.[53]

Ketamine can cause psychedelic effects at lower than anesthetic doses.[54] Ketamine is also effective for pain management, especially in patients with respiratory depression and other neuropathic junctions, as seen in a few small, nonrandomized trials. Though not without adverse effects, ketamine is a promising candidate in facilitating opioid and benzodiazepine withdrawals, and may have utility as an opioid substitute for treating chronic pain.[54] A larger and proper examination of ketamine in pain management is needed to determine its feasibility, as randomized, clinical trials with regulated protocols are lacking. It should be noted that although ketamine is effective in treating pain and depressive symptoms, no trials have measured both conditions together. One case series reported the improvement of depressive symptoms from severe/suicidal to mild and from severe pain to tolerable pain in a patient with advanced Parkinson's disease. The changes were qualitatively reported, however, with no standardized measures used determine the improvement.[55]

Similar to ketamine, cannabinoids are also a potential treatment for comorbid pain and depression. Four studies examined effects on mood and QOL in patients receiving cannabinoids for analgesic purposes.[23,56–58] For example, Fitzgibbon and colleagues[56] suggested that pain and depression may arise due to dysregulation of the endocannabinoid system. In another

study, Woolridge and colleagues[59] showed that cannabis intake improved not only muscle and nerve pain but also depression and anxiety symptomatology in a group of HIV patients. In a randomized, clinical trial, a 1:1 combination of delta-9-tetrahydrocannibinol and cannabidiol (marketed under the trade name Sativex) significantly improved total pain scores. Interestingly, pain scores improved to a greater extent in depressed (versus non-depressed) patients with chronic diabetic neuropathy.[57] Weber[58] showed that patients with chronic central neuropathic pain or fibromyalgia who were prescribed oral delta-9-tetrahydrocannibinol (dronabinol) supplemental to existing medication reported improved symptoms of both anxiety and depression after seven months of treatment as assessed by the Hospital Anxiety and Depression Scale. These beneficial effects should be tempered, however, by the fact that nearly 25% of patients withdrew due to intolerable side effects from dronabinol.

More extensive research of the relationship between pain and depression will likely provide a solid foundation of diagnosis, treatment, and treatment efficacy.

CONCLUSION

The majority of the literature indicates that patients with depression and pain experience reduced physical, mental, and social functioning compared to patients with only depression or only pain. While the precise biological mechanisms between pain and depression are still being investigated, there are indicative trends and symptomatic relationships. Since pain induces physical and psychological distress, the causative-relationship hypothesis between depression and pain is supported. There might be an underlying neurobiological relationship between pain and depression. It is worth noting, however, that physical pain alone may not be the only causitive factor and that psychological "pain" could also further exacerbate the conditions of a patient with depression and, in turn, cause physical pain. Given the paucity of studies on using cannabinoids and ketamine to treat co-occurring pain and depression, practical recommendations for practitioners are not yet possible for these pharmacological alternatives. Although the comparative superiority of specific SNRIs is unknown, a practical recommendation for current practitioners may be to prescribe an SNRI for treating pain and depressive symptoms. Finally, psychotropic and behavioral therapies that are usually aimed at treating depression may become promising options in alleviating both pain and depression.

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