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Co-Occurring Depression and Pain in Multiple Sclerosis

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Synopsis

Depression and pain are highly prevalent among individuals with multiple sclerosis, and they often co-occur. The purpose of this article is to summarize the literature and theory related to the comorbidity of pain and depression, and describe how their presence can impact individuals with MS. Additionally, the article discusses how existing treatments for pain and depression could be adapted to address shared mechanisms and overcome barriers to treatment utilization.

Keywords

Depression; pain; multiple sclerosis

Introduction

A classic element of multiple sclerosis (MS) is the presence of multiple symptoms that impact functioning. In prior reviews (1, 2), the authors have commented on the significance of individual problems, specifically pain and depression, reporting on prevalence rates and outlining recommendations for treatment of each one individually. The reality, however, is that these problems often co-occur and likely have bidirectional effects, with each amplifying the other. The purpose of this article is to summarize the theory and existing literature on the comorbidity of pain and depression, and describe how their presence impacts persons with MS. Additionally, the article discusses how existing treatments for pain and depression could be adapted to address shared mechanisms and overcome barriers to treatment utilization.

Prevalence of pain, depression, and their comorbidity

A number of prior studies have reported that pain and depression are both common in persons with MS. For example, 50% of MS clinical samples are reported to experience chronic pain at any one point in time (3). In a community sample of persons with MS and pain, 75% reported experiencing some pain and 40% reported average pain severity of 3 or greater on a 0–10 scale (4), which is understood to be pain of at least moderate intensity in

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persons with MS (5). In another community sample of persons with MS and pain, 25% described their pain as severe (6).

The 12-month prevalence of major depressive disorder in people with MS is about twice that of the general population - 15.7% versus 7.4%, respectively (7). The lifetime prevalence of depressive disorders in MS is two to three times that of the general population (2, 8). Many people with MS, as high as 50% at any one time, experience depressive symptoms that may not always reflect a clinical diagnosis of a mood disorder, but are nonetheless clinically significant (9–12).

Although many studies described the associations between pain and depressive symptoms in individuals with MS, few have reported on the prevalence of their co-occurrence (3, 6, 13, 14). A recent study using varying criteria to identify depression and pain in a community sample of persons with MS reported that pain and depression co-occurred in 6%–19% of the sample, depending on which criteria for pain and depression were used (4). Pain was experienced by 86%–100% of persons meeting depression criteria, and pain of moderate severity was experienced 67%–77% of persons meeting depression criteria. In contrast, 11%–34% of persons experiencing *any* pain met depression criteria and 15%–37% of persons experiencing pain of at least moderate severity met criteria for clinical depression. In a prior study of a community sample of persons with MS, 53% of persons with pain reported having clinically significant depressive symptomatology (6).

Amplifying effects of pain and depression on one another

Prior MS research has reported high associations between pain and depression, such that higher pain is associated with worse depressive symptomatology (3, 6, 13, 14). This suggests the possibility that the presence of one condition amplifies the presence or severity of the other. Indeed, cross-sectional studies in MS (4) and longitudinal studies in the general population (15–17) have shown that chronic pain is a risk factor for subsequent depression; similarly, depression is a risk factor for chronic pain. At the same time, a substantial percentage of individuals with MS have only pain or depression (4), suggesting that there may be both overlapping and unique aspects of the two conditions (16).

When looking at studies in this area in individuals who do not have MS, the evidence is mixed as to whether pain has a larger impact on depression than depression has on pain. For example, an earlier review of 191 studies examining the association between pain and depression in a large variety of patient and non-patient samples reported consistent support for the “consequence” hypothesis (that depression is influenced by the presence or severity of chronic pain) and inconsistent support for the “antecedent” hypothesis (that depression precedes pain) (18). A recent longitudinal study of 95 adolescents diagnosed with chronic pain or depression, reported evidence for a bi-directional association between depression and pain, although the impact of pain on depression was stronger than the impact of depression on pain (19). In contrast, a study of 500 primary care patients with chronic musculoskeletal pain demonstrated that the two had an equally adverse impact on the other (16). In their sample, change in severity of either depression or pain predicted a change in severity of the other symptom over time. Longitudinal research tracking pain and depression in people with MS would illuminate the nature and consequences of their relationships over time.

In the research literature outside of MS, researchers have suggested a number of reasons why pain and depression co-occur and why the presence of either pain or depression makes the other more likely (15, 16, 18). In terms of pathophysiology, prior reviews of depression and pain have noted that central nociceptive and affective pathways overlap (15, 18), which

supports the understanding that chronic pain is modulated centrally (20). The experience of depressive symptoms and pain also share underlying neurotransmitters, with both norepinephrine and serotonin implicated in mood disorders and in the processing of pain. Beyond pathophysiology, there are potential psychological and behavioral reasons that pain and depression may amplify one another. For example, depressive symptoms have been found to impact the evaluative and affective aspects of pain and pain-related disability (21, 22). Pain often impacts the extent to which individuals engage in physical activity, which can limit an individual's participation in activities that were previously valued or enjoyed, and thus puts the individual at risk for low mood (23). While it is highly likely that these same mechanisms play a role in individuals with MS, additional research is needed to understand the importance of these mechanisms, as well as to understand whether additional, unique factors may also be implicated in the MS population.

Overlapping impact of pain and depression on functioning and quality of life

Depression and chronic pain have a significant negative impact on individuals living with MS (24). Major depression is associated with poorer neuropsychological functioning, lower quality of life, increased time lost from work, social disruption, and poorer health. Chronic pain in MS has been associated with poorer health-related quality of life, including greater interference with daily activities, energy/vitality, mental health, and social functioning (6, 26). Depression and pain have been linked to higher risk for unemployment (27). Both are also thought to affect fatigue negatively, another common and often disabling symptom of MS. For example, people with MS and clinically significant depressive symptoms are 6.2 times more likely to have disabling fatigue than non-depressed controls with MS (28). Studies in MS have highlighted that higher levels of depressive symptoms and pain are associated with lower quality of life independent of other confounding symptoms (29–33). Furthermore, research in other medical populations has shown that pain and depression have a reciprocal and additive adverse impact on quality of life and disability (16, 34).

Depression and pain may also impact the ability of a person with MS to self-manage their condition and its effects on daily life. Depression is believed to affect self-management through its adverse effects on energy, motivation, concentration, self-efficacy, and interpersonal interactions (35). For example, a meta-analysis found that people with depression and chronic medical illness had a 3-fold higher rate of non-adherence to self-care regimens compared to non-depressed controls (36). Consistent with these findings, depression has been associated with a decreased ability to manage MS symptoms, including adherence to disease-modifying medications (37–39). Individuals with MS and chronic pain are also more likely to be inactive (13) and to report lower self-efficacy for managing their MS, including pain (40). The extent to which comorbid pain and depression conjointly influence individuals' MS self-management is an area worthy of further exploration.

Impact on treatment utilization and effectiveness

Depression and pain likely influence healthcare utilization and treatment effectiveness. For example, in a recent study, we described how MS patients' rates of pain treatment utilization were higher among the subset of patients who were also depressed (41). Persons with comorbid pain and depression were found to have made more visits to medical providers for pain intervention, tried more pain treatments, and trended towards making more ER visits for pain intervention relative to persons with pain alone. This is consistent with research in other medical populations which has shown that pain and depression are associated with higher rates of health care utilization (e.g., (42, 43)). In other medical conditions pain and depression are also thought to reduce the effectiveness of treatments for the other condition

(see Bair et al. (15, 44) for a review of this literature). In other words, the presence of pain may interfere with depression treatment and vice versa. Such relationships have not been studied in people with MS, pain, and depression, however. Further, this prior research has suggested that the presence of pain distracts providers from detecting the presence of depression and subsequently results in the under treatment of depression in pain populations (15). Whether pain is a contributing factor to the under-identification and treatment of depression among patients with MS (11, 25) is unknown.

Interventions for comorbid pain and depression

Descriptions of pharmacologic and cognitive-behavioral interventions for depression (2) and pain (1) have been provided in prior articles. However, we are unaware of research on combined treatments for depression and pain in MS, despite their co-occurrence and presumed bidirectional impact on each other. Effective treatment of depression has been shown to have a secondary effect of improving pain in primary care patients (44). Research in other medical populations also points to the potential for successful treatment of comorbid pain and depression through antidepressant therapy, cognitive-behavioral therapy, and self-hypnosis training, although results have been far from definitive to this point (15).

Antidepressants are commonly prescribed to MS patients with neuropathic pain to address not only pain but also depression and sleep. However, little is known about the efficacy of antidepressants for treating neuropathic pain in MS (13). Tricyclic antidepressants have some evidence for their efficacy in treating chronic pain in other neuropathic pain disorders, (45) although they are typically prescribed at doses lower than those needed for depression treatment. Side effects of tricyclic antidepressants can also be a deterrent to their use for pain and depression. There is also evidence that the SNRIs Duloxetine and Venlafaxine are effective in the treatment of neuropathic pain in a range of conditions, although their efficacy in MS pain has not been studied (13). Only a few antidepressants have been evaluated for their benefits in treating depression in MS via randomized controlled trials for depression, (46, 47) and no studies were found reporting the benefits of treating depression with antidepressants on pain.

Among the available psychological treatments for depression and pain, cognitive behavioral therapy (CBT) has the most evidence supporting its efficacy in individuals with MS. In a series of randomized controlled trials, Mohr and colleagues demonstrated that CBT, delivered both in person (47) and by telephone (48, 49), is efficacious in reducing depression as well as fatigue (50), disability (51), and quality of life (52). CBT for chronic pain has been less extensively studied in MS populations, although preliminary evidence in MS (53) and a substantial body of evidence in other painful conditions (54) supports its use for chronic pain in MS. However, although CBT for depression and pain share many ingredients (such as relaxation training, cognitive restructuring, behavioral activation), treatments targeting both have not been developed or tested, to our knowledge.

One of the treatments for pain with the longest history – hypnosis – had not been tested in controlled trials until recently. However, research has established its efficacy for a number of chronic pain conditions (55, 56). Even more recently, controlled trials of hypnosis in individuals with MS and chronic pain have demonstrated its efficacy for reducing pain intensity and pain interference (57, 58). In addition, preliminary research suggests that hypnotic interventions may also be effective for reducing depressive symptoms (59–61). Although research is needed to confirm that hypnosis and hypnotic interventions are as effective in individuals with MS and depression as they are in individuals who present with pain or depression as a primary problem, there is no *a priori* reason to hypothesize the benefits would not generalize to an MS population.

Utilization of and access to interventions for comorbid pain and depression

Outside of the development of treatments targeting the pain-depression comorbidity, a pressing issue is the ability of patients to access and appropriately utilize the interventions that are currently available. Specifically, prior research has shown that although effective treatments for pain and depression are available, these two conditions remain under-identified and under-treated in MS populations (6, 25, 26, 62). An estimated two-thirds of people with MS and major depression are untreated (37, 63, 64). Similarly, although psychosocial interventions specifically targeting MS and depression have been found to be effective (37), both real and perceived barriers impact follow-through with depression treatment referrals (65). The MS literature also reflects poor utilization of screening information to improve treatment referrals, even when screening is systematically implemented (11). Pain is also inadequately treated; treatments that patients identify as most helpful are not necessarily the most frequently used, and nonpharmacologic pain management strategies are used at very low rates despite their potential to reduce pain and associated suffering (66, 67). These studies highlight the need to implement and evaluate new systems of care for pain and depression to address the under-treatment of depression and pain in people with MS.

Innovative approaches to the management of comorbid depression and pain

In other medical populations where depression and/or chronic pain are common, the collaborative care model has been found to be an effective systems-based approach to managing chronic comorbid conditions. This model emphasizes implementing systemic changes complete with self-management support, clinical information systems, delivery system redesign, decision support, health care organization, and community resources (68, 69). Health professionals are not simply ‘co-located’: they use established principles of chronic care management and interdisciplinary collaborative care teams in which professionals with complementary skills work closely together to care for a population of patients with complex medical conditions. Specialist and primary medical providers actively collaborate in providing integrated care, usually assisted by a care manager who guides the patient collaboratively through various decisions about and aspects of care. The specialists, such as psychiatrists or pain specialists, supervise the care managers. The specialists are also available to consult primary medical providers on patients who are clinically challenging or who need additional specialty services, and to see patients themselves when required. Collaborative care also typically features a stepped-care approach in which interventions are titrated based on response to treatment. Collaborative care emphasizes measurement-based care, including screening and ongoing measurement and monitoring of treatment outcomes. Thus, the severity of problems such as depression and pain are repeatedly measured, and the treatment is systematically intensified or modified to ensure that the targeted improvements are achieved.

Collaborative care has repeatedly proven to be an effective model for maximizing access to, and efficacy of, medical treatment for chronic conditions. Collaborative care has improved depression outcomes and quality of care in patients with co-occurring chronic conditions such as diabetes, coronary heart disease, and osteoarthritis (62, 70–76). A meta-analysis of 37 randomized controlled trials showed that collaborative care is more effective than standard care in improving short- and long-term (up to 5 years) depression outcomes in primary care settings (70). Recent trials have successfully tested collaborative care for patients with chronic pain (with or without depression) and produced useful benefits over usual care in improving pain, depression and functional outcomes (62, 77–81).

The collaborative care approach is consistent with many of the conclusions of a 2002 MS stakeholder consensus conference on the identification and treatment of depression in MS (25). Their recommendations for improving depression care in patients with MS included standardization of depression treatment, individualized care based on patient preferences, treatment to remission, and integrated biopsychosocial treatments that include options for both pharmacological and psychosocial care (p. 332). Although they did not mention collaborative care in their published statement, their recommendations are consistent with a collaborative care model of depression care. Despite these recommendations made 10 years ago, collaborative care is not yet standard practice in MS care. In fact, we are aware of only one small, non-randomized study that used the collaborative care model to treat depression in MS (82). Results showed that at six-months post baseline, fewer (33.3%) patients who received care management met diagnostic criteria for major depression relative to historical controls who received standard care (55.2%, $p = 0.15$). Although preliminary, this study supports the need for further evaluation of a collaborative care intervention, including by tailoring the intervention to match the needs of persons with MS.

Given the tremendous barriers to receiving adequate behavioral health services (83), an additional direction for future intervention development and research is the use of technology to deliver pain and depression care. While not previously studied in persons with MS, literature from other patient populations suggests that only one-third of depressed patients receive any psychotherapy (84). Of these, 25% attend only one session, and only 50% attend 4 or more sessions (85, 86). The barriers for people with MS may be even greater, spanning across limited transportation, inability to drive, and other motivational (e.g., fatigue), cognitive, social, and financial problems that interfere with their ability to attend regularly scheduled in-person appointments. Telehealth and other forms of technology hold promise for overcoming some of these barriers to care in MS.

Evidence is building for the feasibility and efficacy of telehealth interventions in MS care. Various telehealth technologies have been used to treat MS-related fatigue (87, 88), to deliver MS self-management support (89), and to monitor MS symptoms remotely (90). It has also been used to treat depression and pain. In a series of randomized controlled trials, Mohr and colleagues (48, 49, 91) demonstrated that telephone-delivered CBT is efficacious in treating depression in MS. In our clinical trials of behavioral interventions for pain, we have found telephone-delivered CBT to also be a feasible and effective treatment for reducing chronic pain and its negative impact on functioning in people with MS (92). Neither of these lines of research specifically targeted both depression and pain, however. Telephone-based care overcomes some of the associated barriers as well as the potential stigma associated with seeking mental health care. Whether telehealth interventions will be adopted in real-world (e.g., clinic) settings remains to be seen.

Future directions for research and clinical interventions

Research on the co-occurrence of pain and depression in MS is truly in its infancy. Recent research has yielded sufficient evidence to suggest that (1) depression and pain are among the most common symptoms experienced by persons with MS, (2) greater depression severity and greater pain severity are positively associated with each other, and (3) clinical levels of depression and pain often co-occur. Little research has been conducted on the effects of the pain-depression comorbidity on quality of life, treatment utilization, and clinical outcomes.

In recent research on depression and pain in non-MS populations, researchers have improved our understanding of depression, pain, and their impact on quality of life by examining longitudinal outcome trajectories using newer methods of data analysis (such as

latent growth mixture modeling) to identify subsets of individuals with similar symptom trajectories (93–95). As opposed to cross-sectional analyses that identify differential outcomes at a single time point or usual longitudinal analyses that rely on comparisons of group means or change scores over time, these longitudinal analyses provide information on distinct patterns that present over time for any given variable. These methods not only identify and describe subgroups of individuals with similar trajectories over time but can also identify baseline variables that are predictive of subgroup membership. Longitudinal research with this type of analysis would greatly improve our understanding of pain, depression, their comorbidity, and their impact on quality of life.

Our recent study which found that MS patients' rates of pain treatment utilization were higher among those who were also depressed (41) suggests that the impact of comorbid pain and depression on treatment utilization is an important area for future research. Furthermore, research from other settings suggesting that depression influences pain outcomes and pain influences depression outcomes (15, 16) indicates that it would be worthwhile to explore the impact of pain and/or depression on treatment response in these conditions. Research is also needed on how comorbid pain and depression influence other important MS treatment outcomes such as adherence to disease-modifying therapies or rehabilitation interventions.

Clinically, there are many effective pharmacologic and psychological interventions for depression and pain (1, 2), but we are unaware of any research on treatment of the pain-depression comorbidity in MS. There are good reasons, however, to believe that existing treatments could be adapted to effectively treat this comorbidity. For example, Duloxetine and Venlafaxine have been shown to effectively treat depression and pain simultaneously in patients with fibromyalgia (96), another population with highly comorbid pain and depression. Similarly, cognitive-behavioral therapy is one of the most commonly-used psychological interventions for depression and for pain, with standard protocols utilizing similar components for both conditions, suggesting that it could be relatively easy to merge the two into a single, effective intervention. Finally, as noted earlier, hypnosis is effective in the treatment of pain and depression (55–61), suggesting that a protocol could be developed to have an effect on the comorbidity.

Taken together, the available research on depression and pain in MS provides the impetus for further research in this area. By better understanding the patients who present with both pain and depression, clinicians can improve their tailoring of interventions for patients (97). Consistent with the current trend in the mental health literature, transdiagnostic interventions could be effective in treating these comorbid problems that have so many shared elements (98). Research expanding our understanding of and treatments for comorbid pain and depression will ultimately reduce their morbidity and improve outcomes for individuals with MS.

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References

1. Ehde DM, Osborne TL, Jensen MP. Chronic pain in persons with multiple sclerosis. *Phys Med Rehabil Clin N Am*. 2005; 16(2):503–12. [PubMed: 15893684]

2. Ehde DM, Bombardier CH. Depression in persons with multiple sclerosis. *Phys Med Rehabil Clin N Am*. 2005; 16(2):437–48. ix. [PubMed: 15893680]
3. O'Connor AB, Schwid SR, Herrmann DN, Markman JD, Dworkin RH. Pain associated with multiple sclerosis: systematic review and proposed classification. *Pain*. 2008; 137(1):96–111. [PubMed: 17928147]
4. Alschuler KN, Ehde DM, Jensen MP. The co-occurrence of pain and depression in adults with multiple sclerosis. *Rehabilitation Psychology*. In press.
5. Alschuler KN, Jensen MP, Ehde DM. Defining mild, moderate, and severe pain in persons with multiple sclerosis. *Pain Med*. 2012; 13(10):1358–65. [PubMed: 22925457]
6. Ehde DM, Gibbons LE, Chwastiak L, Bombardier CH, Sullivan MD, Kraft GH. Chronic pain in a large community sample of persons with multiple sclerosis. *Mult Scler*. 2003; 9(6):605–11. [PubMed: 14664474]
7. Patten SB, Beck CA, Williams JV, Barbui C, Metz LM. Major depression in multiple sclerosis: a population-based perspective. *Neurology*. 2003; 61(11):1524–7. [PubMed: 14663036]
8. Patten SB, Metz LM, Reimer MA. Biopsychosocial correlates of lifetime major depression in a multiple sclerosis population. *Mult Scler*. 2000; 6(2):115–20. [PubMed: 10773857]
9. Patten SB, Metz LM. Depression in multiple sclerosis. *Psychother Psychosom*. 1997; 66(6):286–92. [PubMed: 9403917]
10. Sadovnick AD, Remick RA, Allen J, Swartz E, Yee IM, Eisen K, et al. Depression and multiple sclerosis. *Neurology*. 1996; 46(3):628–32. [PubMed: 8618657]
11. Mohr DC, Hart SL, Julian L, Tasch ES. Screening for depression among patients with multiple sclerosis: two questions may be enough. *Mult Scler*. 2007; 13(2):215–9. [PubMed: 17439887]
12. Chwastiak L, Ehde DM, Gibbons LE, Sullivan M, Bowen JD, Kraft GH. Depressive symptoms and severity of illness in multiple sclerosis: epidemiologic study of a large community sample. *Am J Psychiatry*. 2002; 159(11):1862–8. [PubMed: 12411220]
13. Ehde, DM.; Kratz, AL.; Robinson, JP.; Jensen, MP. Chronic pain. In: Finlayson, M., editor. *Multiple Sclerosis Rehabilitation: From Impairment to Participation*. London: Taylor & Francis; 2013. p. 199-226.
14. Arnett PA, Barwick FH, Beeney JE. Depression in multiple sclerosis: review and theoretical proposal. *J Int Neuropsychol Soc*. 2008; 14(5):691–724. [PubMed: 18764967]
15. Bair MJ, Robinson RL, Katon W, Kroenke K. Depression and pain comorbidity: a literature review. *Arch Intern Med*. 2003; 163(20):2433–45. [PubMed: 14609780]
16. Kroenke K, Wu J, Bair MJ, Krebs EE, Damush TM, Tu W. Reciprocal relationship between pain and depression: a 12-month longitudinal analysis in primary care. *J Pain*. 2011; 12(9):964–73. [PubMed: 21680251]
17. Husted JA, Tom BD, Farewell VT, Gladman DD. Longitudinal study of the bidirectional association between pain and depressive symptoms in patients with psoriatic arthritis. *Arthritis Care Res (Hoboken)*. 2012; 64(5):758–65. [PubMed: 22231988]
18. Fishbain DA, Cutler R, Rosomoff HL, Rosomoff RS. Chronic pain-associated depression: antecedent or consequence of chronic pain? A review. *Clin J Pain*. 1997; 13(2):116–37. [PubMed: 9186019]
19. Lewandowski Holley A, Law EF, Zhou C, Murphy L, Clarke G, Palermo TM. Reciprocal longitudinal associations between pain and depressive symptoms in adolescents. *Eur J Pain*. 2012
20. Melzack R. Pain and the neuromatrix in the brain. *J Dent Educ*. 2001; 65(12):1378–82. [PubMed: 11780656]
21. Geisser ME, Gaskin ME, Robinson ME, Greene AF. The relationship of depression and somatic focus to experimental and clinical pain in chronic pain patients. *Psychology & Health*. 1993; 8(6): 405–15.
22. Alschuler KN, Theisen-Goodvich ME, Haig AJ, Geisser ME. A comparison of the relationship between depression, perceived disability, and physical performance in persons with chronic pain. *Eur J Pain*. 2008; 12(6):757–64. [PubMed: 18160319]
23. Fordyce, WE. Behavioral methods for chronic pain and illness. St. Louis, MO: Mosby; 1976.

24. Zwibel HL, Smrtka J. Improving quality of life in multiple sclerosis: an unmet need. *Am J Manag Care*. 2011; 17(Suppl 5):S139–45. Improving. [PubMed: 21761952]
25. Group GC. The Goldman Consensus statement on depression in multiple sclerosis. *Mult Scler*. 2005; 11(3):328–37. [PubMed: 15957516]
26. O'Connor AB, Schwid SR, Herrmann DN, Markman JD, Dworkin RH. Pain associated with multiple sclerosis: systematic review and proposed classification. *Pain*. 2008; 137(1):96–111. [PubMed: 17928147]
27. Honarmand K, Akbar N, Kou N, Feinstein A. Predicting employment status in multiple sclerosis patients: the utility of the MS functional composite. *J Neurol*. 2011; 258(2):244–9. [PubMed: 20835872]
28. Chwastiak LA, Gibbons LE, Ehde DM, Sullivan M, Bowen JD, Bombardier CH, et al. Fatigue and psychiatric illness in a large community sample of persons with multiple sclerosis 3981482. 2005; 59(5):291–8.
29. Göksel Karatepe A, Kaya T, Günaydn R, Demirhan A, Ce P, Gedizlio lu M. Quality of life in patients with multiple sclerosis: the impact of depression, fatigue, and disability. *Int J Rehabil Res*. 2011; 34(4):290–8. [PubMed: 21946317]
30. Kargarfard M, Eetemadifar M, Mehrabi M, Maghzi AH, Hayatbakhsh MR. Fatigue, depression, and health-related quality of life in patients with multiple sclerosis in Isfahan, Iran. *Eur J Neurol*. 2012; 19(3):431–7. [PubMed: 21967324]
31. Solaro C, Uccelli MM. Management of pain in multiple sclerosis: a pharmacological approach. *Nat Rev Neurol*. 2011; 7(9):519–27. [PubMed: 21844896]
32. Brochet B, Deloire MS, Ouallet JC, Salort E, Bonnet M, Jové J, et al. Pain and quality of life in the early stages after multiple sclerosis diagnosis: a 2-year longitudinal study. *Clin J Pain*. 2009; 25(3):211–7. [PubMed: 19333171]
33. Newland PK, Naismith RT, Ullione M. The impact of pain and other symptoms on quality of life in women with relapsing-remitting multiple sclerosis. *J Neurosci Nurs*. 2009; 41(6):322–8. [PubMed: 19998683]
34. Arnow BA, Blasey CM, Lee J, Fireman B, Hunkeler EM, Dea R, et al. Relationships among depression, chronic pain, chronic disabling pain, and medical costs. *Psychiatr Serv*. 2009; 60(3):344–50. [PubMed: 19252047]
35. Katon WJ. Clinical and health services relationships between major depression, depressive symptoms, and general medical illness. *Biol Psychiatry*. 2003; 54(3):216–26. [PubMed: 12893098]
36. DiMatteo MR, Lepper HS, Croghan TW. Depression is a risk factor for noncompliance with medical treatment: meta-analysis of the effects of anxiety and depression on patient adherence. *Arch Intern Med*. 2000; 160(14):2101–7. [PubMed: 10904452]
37. Mohr DC, Likosky W, Bertagnolli A, Goodkin DE, Van Der Wende J, Dwyer P, et al. Telephone-administered cognitive-behavioral therapy for the treatment of depressive symptoms in multiple sclerosis. *J Consult Clin Psychol*. 2000; 68(2):356–61. [PubMed: 10780138]
38. Mohr DC, Goodkin DE, Likosky W, Gatto N, Baumann KA, Rudick RA. Treatment of depression improves adherence to interferon beta-1b therapy for multiple sclerosis. *Arch Neurol*. 1997; 54(5):531–3. [PubMed: 9152109]
39. Tarrants M, Oleen-Burkey M, Castelli-Haley J, Lage MJ. The impact of comorbid depression on adherence to therapy for multiple sclerosis. *Mult Scler Int*. 2011; 2011:271321. [PubMed: 22096632]
40. Osborne TL, Jensen MP, Ehde DM, Hanley MA, Kraft G. Psychosocial factors associated with pain intensity, pain-related interference, and psychological functioning in persons with multiple sclerosis and pain. *Pain*. 2007; 127(1–2):52–62. [PubMed: 16950570]
41. Alschuler KN, Jensen MP, Ehde DM. The association of depression with pain-related treatment utilization in patients with multiple sclerosis. *Pain Med*. 2012; 13(12):1648–57. [PubMed: 23137071]
42. Katon W, Berg AO, Robins AJ, Risse S. Depression--medical utilization and somatization. *West J Med*. 1986; 144(5):564–8. [PubMed: 3716416]

43. Rowan PJ, Davidson K, Campbell JA, Dobrez DG, MacLean DR. Depressive symptoms predict medical care utilization in a population-based sample. *Psychol Med.* 2002; 32(5):903–8. [PubMed: 12171384]
44. Bair MJ, Robinson RL, Eckert GJ, Stang PE, Croghan TW, Kroenke K. Impact of pain on depression treatment response in primary care. *Psychosom Med.* 2004; 66(1):17–22. [PubMed: 14747633]
45. Saarto T, Wiffen PJ. Antidepressants for neuropathic pain: a Cochrane review. *J Neurol Neurosurg Psychiatry.* 2010; 81(12):1372–3. [PubMed: 20543189]
46. Ehde DM, Kraft GH, Chwastiak L, Sullivan MD, Gibbons LE, Bombardier CH, et al. Efficacy of paroxetine in treating major depressive disorder in persons with multiple sclerosis. *Gen Hosp Psychiatry.* 2008; 30(1):40–8. [PubMed: 18164939]
47. Mohr DC, Boudewyn AC, Goodkin DE, Bostrom A, Epstein L. Comparative outcomes for individual cognitive-behavior therapy, supportive-expressive group psychotherapy, and sertraline for the treatment of depression in multiple sclerosis. *J Consult Clin Psychol.* 2001; 69(6):942–9. [PubMed: 11777121]
48. Mohr DC, Likosky W, Bertagnolli A, Goodkin DE, Van Der Wende J, Dwyer P, et al. Telephone-administered cognitive-behavioral therapy for the treatment of depressive symptoms in multiple sclerosis. *J Consult Clin Psychol.* 2000; 68(2):356–61. [PubMed: 10780138]
49. Mohr DC, Hart SL, Julian L, Catledge C, Honos-Webb L, Vella L, et al. Telephone-administered psychotherapy for depression. *Arch Gen Psychiatry.* 2005; 62(9):1007–14. [PubMed: 16143732]
50. Mohr DC, Hart SL, Goldberg A. Effects of treatment for depression on fatigue in multiple sclerosis. *Psychosom Med.* 2003; 65(4):542–7. [PubMed: 12883103]
51. Mohr DC, Hart S, Vella L. Reduction in disability in a randomized controlled trial of telephone-administered cognitive-behavioral therapy. *Health Psychol.* 2007; 26(5):554–63. [PubMed: 17845107]
52. Cosio D, Jin L, Siddique J, Mohr DC. The effect of telephone-administered cognitive-behavioral therapy on quality of life among patients with multiple sclerosis. *Ann Behav Med.* 2011; 41(2): 227–34. [PubMed: 21069585]
53. Ehde DM, Jensen MP. Feasibility of a cognitive restructuring intervention for treatment of chronic pain in persons with disabilities. *Rehabilitation Psychology.* 2004; 49(3):254–8.
54. Eccleston C, Williams AC, Morley S. Psychological therapies for the management of chronic pain (excluding headache) in adults. *Cochrane Database Syst Rev.* 2009; (2):CD007407. [PubMed: 19370688]
55. Patterson DR, Jensen M. Hypnosis and clinical pain. *Psychol Bull.* 2003; 29:495–521. [PubMed: 12848218]
56. Jensen MP. Hypnosis for chronic pain management: a new hope. *Pain.* 2009; 146(3):235–7. [PubMed: 19596518]
57. Jensen MP, Ehde DM, Gertz KJ, Stoelb BL, Dillworth TM, Hirsh AT, et al. Effects of self-hypnosis training and cognitive restructuring on daily pain intensity and catastrophizing in individuals with multiple sclerosis and chronic pain. *Int J Clin Exp Hypn.* 2011; 59(1):45–63. [PubMed: 21104484]
58. Jensen MP, Barber J, Romano JM, Molton IR, Raichle KA, Osborne TL, et al. A comparison of self-hypnosis versus progressive muscle relaxation in patients with multiple sclerosis and chronic pain. *Int J Clin Exp Hypn.* 2009; 57(2):198–221. [PubMed: 19234967]
59. Alladin A. Cognitive hypnotherapy for major depressive disorder. *Am J Clin Hypn.* 2012; 54(4): 275–93. [PubMed: 22655331]
60. Alladin A. Evidence-based hypnotherapy for depression. *Int J Clin Exp Hypn.* 2010; 58(2):165–85. [PubMed: 20390689]
61. Alladin A, Alibhai A. Cognitive hypnotherapy for depression: an empirical investigation. *Int J Clin Exp Hypn.* 2007; 55(2):147–66. [PubMed: 17365072]
62. Lin EH, Katon W, Von Korff M, Tang L, Williams JW Jr, Kroenke K, et al. Effect of improving depression care on pain and functional outcomes among older adults with arthritis: a randomized controlled trial. *JAMA.* 2003; 290(18):2428–9. [PubMed: 14612479]

63. Feinstein A. An examination of suicidal intent in patients with multiple sclerosis. *Neurology*. 2002; 59(5):674–8. [PubMed: 12221156]
64. Mohr DC, Hart SL, Fonareva I, Tasch ES. Treatment of depression for patients with multiple sclerosis in neurology clinics. *Mult Scler*. 2006; 12(2):204–8. [PubMed: 16629424]
65. Mohr DC, Hart SL, Howard I, Julian L, Vella L, Catledge C, et al. Barriers to psychotherapy among depressed and nondepressed primary care patients. *Ann Behav Med*. 2006; 32(3):254–8. [PubMed: 17107299]
66. Jensen MP, Ehde DM, Gertz KJ, Stoelb BL, Dillworth TM, Hirsh AT, et al. Effects of self-hypnosis training and cognitive restructuring on daily pain intensity and catastrophizing in individuals with multiple sclerosis and chronic pain. *Int J Clin Exp Hypn*. 2011; 59(1):45–63. [PubMed: 21104484]
67. Ehde, DM.; Osborne, TL.; Hanley, MA.; Jensen, MP.; Alschuler, KN.; Kraft, GH. Use and perceived effectiveness of treatments for pain associated with multiple sclerosis. Under review
68. Bodenheimer T, Wagner EH, Grumbach K. Improving primary care for patients with chronic illness: the chronic care model, Part 2. *JAMA*. 2002; 288(15):1909–14. [PubMed: 12377092]
69. Bodenheimer T, Wagner EH, Grumbach K. Improving primary care for patients with chronic illness. *JAMA*. 2002; 288(14):1775–9. [PubMed: 12365965]
70. Gilbody S, Bower P, Fletcher J, Richards D, Sutton AJ. Collaborative care for depression: a cumulative meta-analysis and review of longer-term outcomes. *Arch Intern Med*. 2006; 166(21):2314–21. [PubMed: 17130383]
71. Katon WJ, Von Korff M, Lin EH, Simon G, Ludman E, Russo J, et al. The Pathways Study: a randomized trial of collaborative care in patients with diabetes and depression. *Arch Gen Psychiatry*. 2004; 61(10):1042–9. [PubMed: 15466678]
72. Katon WJ, Lin EH, Von Korff M, Ciechanowski P, Ludman EJ, Young B, et al. Collaborative care for patients with depression and chronic illnesses. *N Engl J Med*. 2011; 363(27):2611–20. [PubMed: 21190455]
73. Rollman BL, Belnap BH, LeMenager MS, Mazumdar S, Houck PR, Counihan PJ, et al. Telephone-delivered collaborative care for treating post-CABG depression: a randomized controlled trial. *JAMA*. 2009; 302(19):2095–103. [PubMed: 19918088]
74. Roy-Byrne P, Craske MG, Sullivan G, Rose RD, Edlund MJ, Lang AJ, et al. Delivery of evidence-based treatment for multiple anxiety disorders in primary care: a randomized controlled trial. *JAMA*. 2010; 303(19):1921–8. [PubMed: 20483968]
75. Roy-Byrne PP, Craske MG, Stein MB, Sullivan G, Bystritsky A, Katon W, et al. A randomized effectiveness trial of cognitive-behavioral therapy and medication for primary care panic disorder. *Arch Gen Psychiatry*. 2005; 62(3):290–8. [PubMed: 15753242]
76. Zatzick D, Roy-Byrne P, Russo J, Rivara F, Driesch R, Wagner A, et al. A randomized effectiveness trial of stepped collaborative care for acutely injured trauma survivors. *Arch Gen Psychiatry*. 2004; 61(5):498–506. [PubMed: 15123495]
77. Kroenke K, Bair MJ, Damush TM, Wu J, Hoke S, Sutherland J, et al. Optimized antidepressant therapy and pain self-management in primary care patients with depression and musculoskeletal pain: a randomized controlled trial. *JAMA*. 2009; 301(20):2099–110. [PubMed: 19470987]
78. Dobscha SK, Corson K, Perrin NA, Hanson GC, Leibowitz RQ, Doak MN, et al. Collaborative care for chronic pain in primary care: a cluster randomized trial. *JAMA*. 2009; 301(12):1242–52. [PubMed: 19318652]
79. Kroenke K, Theobald D, Wu J, Norton K, Morrison G, Carpenter J, et al. Effect of telecare management on pain and depression in patients with cancer: a randomized trial. *JAMA*. 2010; 304(2):163–71. [PubMed: 20628129]
80. Ahles TA, Wasson JH, Seville JL, Johnson DJ, Cole BF, Hanscom B, et al. A controlled trial of methods for managing pain in primary care patients with or without co-occurring psychosocial problems. *Ann Fam Med*. 2006; 4(4):341–50. [PubMed: 16868238]
81. Chelminski PR, Ives TJ, Felix KM, Prakken SD, Miller TM, Perhac JS, et al. A primary care, multi-disciplinary disease management program for opioid-treated patients with chronic non-cancer pain and a high burden of psychiatric comorbidity. *BMC Health Serv Res*. 2005; 5(1):3. [PubMed: 15649331]

82. Patten SB, Newman S, Becker M, Riddell C, Metz L. Disease management for depression in an MS clinic. *Int J Psychiatry Med.* 2007; 37(4):459–73. [PubMed: 18441632]
83. Simon GE, Von Korff M, Rutter CM, Peterson DA. Treatment process and outcomes for managed care patients receiving new antidepressant prescriptions from psychiatrists and primary care physicians. *Arch Gen Psychiatry.* 2001; 58(4):395–401. [PubMed: 11296101]
84. Katon W, von Korff M, Lin E, Bush T, Ormel J. Adequacy and duration of antidepressant treatment in primary care. *Med Care.* 1992; 30(1):67–76. [PubMed: 1729588]
85. Young AS, Klap R, Sherbourne CD, Wells KB. The quality of care for depressive and anxiety disorders in the United States. *Arch Gen Psychiatry.* 2001; 58(1):55–61. [PubMed: 11146758]
86. Horvitz-Lennon M, Normand SL, Frank RG, Goldman HH. “Usual care” for major depression in the 1990s: characteristics and expert-estimated outcomes. *Am J Psychiatry.* 2003; 160(4):720–6. [PubMed: 12668361]
87. Moss-Morris R, McCrone P, Yardley L, van Kessel K, Wills G, Dennison L. A pilot randomised controlled trial of an Internet-based cognitive behavioural therapy self-management programme (MS Invigor8) for multiple sclerosis fatigue. *Behav Res Ther.* 2012; 50(6):415–21. [PubMed: 22516321]
88. Finlayson M, Preissner K, Cho C, Plow M. Randomized trial of a teleconference-delivered fatigue management program for people with multiple sclerosis. *Mult Scler.* 2011; 17(9):1130–40. [PubMed: 21561960]
89. Miller DM, Moore SM, Fox RJ, Atreja A, Fu AZ, Lee JC, et al. Web-based self-management for patients with multiple sclerosis: a practical, randomized trial. *Telemed J E Health.* 2011; 17(1):5–13. [PubMed: 21214498]
90. Zissman K, Lejbkowitz I, Miller A. Telemedicine for multiple sclerosis patients: assessment using Health Value Compass. *Mult Scler.* 2012; 18(4):472–80. [PubMed: 21965420]
91. Mohr DC, Vella L, Hart S, Heckman T, Simon G. The Effect of Telephone-Administered Psychotherapy on Symptoms of Depression and Attrition: A Meta-Analysis. *Clin Psychol (New York).* 2008; 15(3):243–53. [PubMed: 21369344]
92. Ehde, DM. Efficacy of telephone-delivered cognitive behavioral therapy for chronic pain. National Institutes of Health, National Institute of Child Health and Human Development, National Center for Medical Rehabilitation Research Grant; 2008–2013.
93. Dunn LB, Cooper BA, Neuhaus J, West C, Paul S, Aouizerat B, et al. Identification of distinct depressive symptom trajectories in women following surgery for breast cancer. *Health Psychol.* 2011; 30(6):683–92. [PubMed: 21728421]
94. Miaskowski C, Cooper B, Paul SM, West C, Langford D, Levine JD, et al. Identification of patient subgroups and risk factors for persistent breast pain following breast cancer surgery. *J Pain.* 2012; 13(12):1172–87. [PubMed: 23182226]
95. Bonanno GA, Kennedy P, Galatzer-Levy IR, Lude P, Elfstrom ML. Trajectories of resilience, depression, and anxiety following spinal cord injury. *Rehabil Psychol.* 2012; 57(3):236–47. [PubMed: 22946611]
96. Bellato E, Marini E, Castoldi F, Barbasetti N, Mattei L, Bonasia DE, et al. Fibromyalgia syndrome: etiology, pathogenesis, diagnosis, and treatment. *Pain Res Treat.* 2012; 2012:426130. [PubMed: 23213512]
97. Thieme K, Turk DC, Flor H. Responder criteria for operant and cognitive-behavioral treatment of fibromyalgia syndrome. *Arthritis Rheum.* 2007; 57(5):830–6. [PubMed: 17530683]
98. Craske MG. Transdiagnostic treatment for anxiety and depression. *Depress Anxiety.* 2012; 29(9): 749–53. [PubMed: 22949272]

Key points

1. Depression and pain are highly prevalent among persons with MS, often co-occur, and likely make each other worse
2. Both depression and pain impact quality of life, medical utilization, and the effectiveness of interventions
3. Although there are effective interventions for depression and pain, no interventions have yet been developed that target comorbid pain and depression in individuals with MS