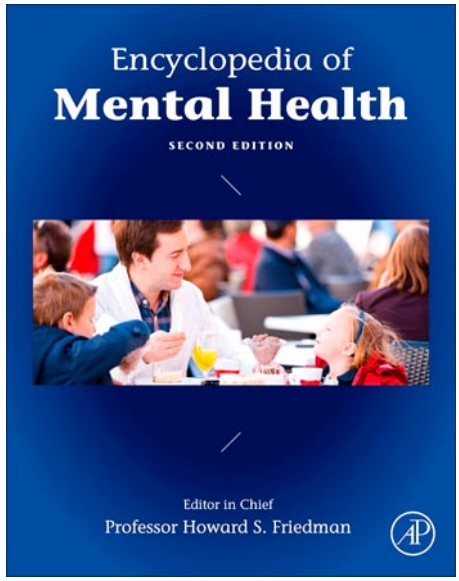

Arnett P.A., and Cadden M., Multiple Sclerosis and Other Demyelinating Disorders. In: Howard S. Friedman (Editor in Chief), Encyclopedia of Mental Health, 2nd edition, Vol 3, Waltham, MA: Academic Press, 2016, pp. 169-174.

Multiple Sclerosis and Other Demyelinating Disorders

PA Arnett and M Cadden, Penn State University, University Park, PA, USA

Glossary

Beck Depression Inventory – FastScreen (BDI – FastScreen) Brief 7-item measure of depression designed primarily for use with medical populations. It only includes mood and negative evaluative symptoms, and has been shown to be valid for detecting depression in multiple sclerosis.

Chicago Multiscale Depression Inventory (CMDI) Measure of depression consisting of three 14-item scales, with each measuring a different core domain (mood, negative evaluative, and neurovegetative) of depression. Primarily developed for use with medical populations.

Expanded Disability Status Scale (EDSS) Most commonly used measure of disability in the multiple sclerosis literature.

Hospital Anxiety and Depression Scale (HADS) A 14-item measure of depression and anxiety divided up into 7-item scales that measure depression and anxiety, respectively.

Multiple sclerosis (MS) Common demyelinating neurological disorder.

Introduction

Multiple sclerosis (MS) is the most common demyelinating disorder. Other demyelinating conditions include concentric sclerosis (also known as Balo's disease), Schilder's disease, Devic's disease, central pontine myelinolysis, and Marchiafava–Bignami disease. Acute disseminated encephalomyelitis and acute hemorrhagic leukoencephalitis are even rarer. MS is the only one of these conditions that has been adequately examined in terms of mental health issues, so the focus of this section will be on MS. Regarding mental health issues, depression has been most intensively studied in MS, but more recent work has shown that anxiety is quite common as well. There is also some evidence that personality factors may intersect with mental health issues in MS and serve as risk factors. Given these considerations, this article will focus mainly on depression in MS and will also review some important findings relating to anxiety and personality.

Depression

How Common Is Depression in Multiple Sclerosis?

Depression is very common in MS. Most research indicates that 50% of individuals with MS will experience clinically significant depression during their lifetimes, compared with approximately 8% of those in the general population (Marrie *et al.*, 2009; Sadovnick *et al.*, 1996; Jones *et al.*, 2012). Depression is more common in MS even when compared with individuals who have comparable (but nonneurological) fluctuating disease courses. For example, Holden and Isaac (2011) found that, when individuals with MS were compared with rheumatoid arthritis patients, those with MS had a 220% increased risk for clinically significant depressive symptoms. Thus, depression is very common in MS, even when compared with other chronic medical conditions.

How Is Depression in Multiple Sclerosis Treated?

Psychotherapy has been shown to be quite effective in treating depression in MS. Even when the treatment is brief or offered over the telephone, it can be very effective (Mohr *et al.*, 2000, 2005). Research has also shown that motivational interviewing that promotes increased physical activity reduces depression in MS (Bombardier *et al.*, 2013). Pharmacologic interventions in MS have also been shown to be useful in some patients, though generally not as consistently effective as psychotherapy (Ehde *et al.*, 2008; Mohr and Goodkin, 1999). With all these said, interventions for MS work in alleviating depression in only approximately half of patients, so more research is necessary to determine what may differentiate treatment responders from nonresponders. It may be that factors such as undiagnosed coexisting anxiety or personality factors complicate treatment for some individuals.

Do Certain Patient Characteristics Increase Risk for Depression in Multiple Sclerosis?

The existing research on demographic and illness characteristics in MS presents a very mixed picture. For example, some studies have shown that females are more at risk than males, with others finding no association with sex. Some research indicates that older age increases risk for depression, but other studies show no relationship with age. Regarding risk characteristics of the illness, some research shows that greater MS disability is associated with more depression, but others find no relationship (Arnett *et al.*, 2008). One possible explanation of this inconsistency could be the relationship between physical disability and depression in MS being moderated by factors such as social support and coping. In particular, patients with high levels of physical disability who have better social support and use more adaptive coping strategies may be less likely to be depressed (Arnett *et al.*, 2008). Empirical work is still necessary, however, to test such hypotheses. Patients who have had the disease for a longer

period of time often report more depression (da Silva *et al.*, 2011), but other studies show no association (Mattioli *et al.*, 2011). It may be that the continued variability reported on the relationship between demographic and illness characteristics is due, in part, to the inconsistency in the illness itself being reflected in the change in sample characteristics, scale/measure selection, as well as a failure to account for moderators or mediators.

Is Fatigue in Multiple Sclerosis Associated with Depression?

Fatigue is extremely common in MS, with many patients reporting it as their most debilitating symptom. In a seminal study, Krupp *et al.* (1988) found that almost 90% of MS patients complained of significant fatigue, with over 25% reporting fatigue as their most debilitating symptom. Research since this study has generally supported these findings. Fatigue has also been shown to affect patients' ability to continue working. Smith and Arnett (2005) found that MS patients identified fatigue as the one symptom that was most responsible for them having to cut back on their work hours. Other research has shown that fatigue is a key factor in causing patients to have to stop working entirely. Thus, there are significant real-world consequences of fatigue for MS patients.

Most recent research has shown that higher levels of fatigue are associated with depression in MS (Kale *et al.*, 2010; Koch *et al.*, 2009; Brown *et al.*, 2009; Arnett *et al.*, 2008). However, some of this association appears to be driven by the fact that fatigue is also a symptom of depression. Thus, fatigue may be associated with depression in MS because typical depression measures used for MS include fatigue items. Rabinowitz *et al.* (2011) found evidence that neurovegetative symptoms of depression (e.g., concentration problems, sexual dysfunction, etc.) in MS are more closely associated with fatigue and sleep disturbance than other depressive symptoms, indicating that there are methodological difficulties in measuring depression in MS.

How Can Depression Best Be Measured in Multiple Sclerosis?

A central problem in measuring depression in MS is that neurovegetative symptoms of depression overlap with MS disease symptoms. Common MS disease symptoms include fatigue, sleep disturbance, concentration problems, sexual dysfunction, and appetite disturbance; however, all of these symptoms are also considered neurovegetative symptoms of depression. As such, MS patients completing a questionnaire with typical depression items may have elevated scores not because they are depressed but because they simply have many disease symptoms. One of the most effective ways of circumventing this difficulty has been to give patients depression questionnaires that do not include any neurovegetative symptoms of depression. Nyenhuis *et al.* (1995) developed the Chicago Multiscale Depression Inventory (CMDI) for just this purpose. The CMDI has three 14-item scales, with each measuring a different core domain (mood, negative evaluative, and neurovegetative) of depression. They proposed that only the mood subscale be used to assess depression in MS, as it was most independent of MS disease symptoms. The use of the Beck Depression Inventory (BDI) – FastScreen (Beck *et al.*, 2000) – has also been suggested. It only includes mood and negative evaluative symptoms in a 7-item format and has been shown to be valid for detecting depression in MS (Benedict *et al.*, 2003).

An alternative approach to removing any neurovegetative depression symptom from consideration has been suggested by Strober and Arnett (2010). Their 'trunk-and-branch' model of depression in MS, rather than disregarding neurovegetative symptoms entirely, distinguishes between 'trunk' symptoms (common to the medical condition) and 'branch' symptoms (those independent of the medical condition). In their study, they compared a criterion group of likely depressed MS patients with a nondepressed MS group and a group of healthy controls on the BDI (Beck and Steer, 1987). Symptoms that were endorsed significantly more often by the MS group (depressed and nondepressed combined) compared with healthy controls were deemed 'trunk' symptoms (see **Figure 1** – used with permission). Symptoms that were endorsed significantly more often by depressed compared with nondepressed MS patients were deemed 'branch' symptoms. Additionally, some 'trunk' symptoms that were more severe in the depressed compared with nondepressed MS group were also considered core MS depression symptoms. The initial core branch symptoms combined with these more severe symptoms comprised 12 items from the original BDI (see **Figure 1**, used with permission). These investigators proposed that the 12 items could be used to provide the most complete assessment of depression that took into consideration some neurovegetative symptoms. Additional work is currently in progress to assess the validity of this scale relative to the BDI-FS and the CMDI mood subscale (Strober and Arnett, under review).

What Psychosocial and Lifestyle Factors Are Associated with Depression in Multiple Sclerosis?

There is consistent evidence that MS patients who have less social support are more likely to be depressed (Gay *et al.*, 2010; Bambara *et al.*, 2011). Stress also appears to be a risk factor for depression in MS, but patients with more positive cognitive schemas are less likely to show depression when under stress (Beeney and Arnett, 2008). Such findings suggest the possibility that helping patients develop more positive cognitive-affective schemas could provide them with a buffer against the effects of stress on mood.

Coping style appears to be very important in relation to depression in MS. Patients who use more active and problem-focused coping strategies in response to stress report less depression, whereas those who use more avoidant and emotion-focused approaches report more depression (Arnett *et al.*, 2008; Brown *et al.*, 2009). Given that coping style appears modifiable, such findings suggest that patients who use the more maladaptive avoidant and emotion-focused approaches could learn to develop more active and problem-focused strategies through treatment. Patients who engage in less physical activity are more at risk for depression, but this relationship appears to be due entirely to disability, such that

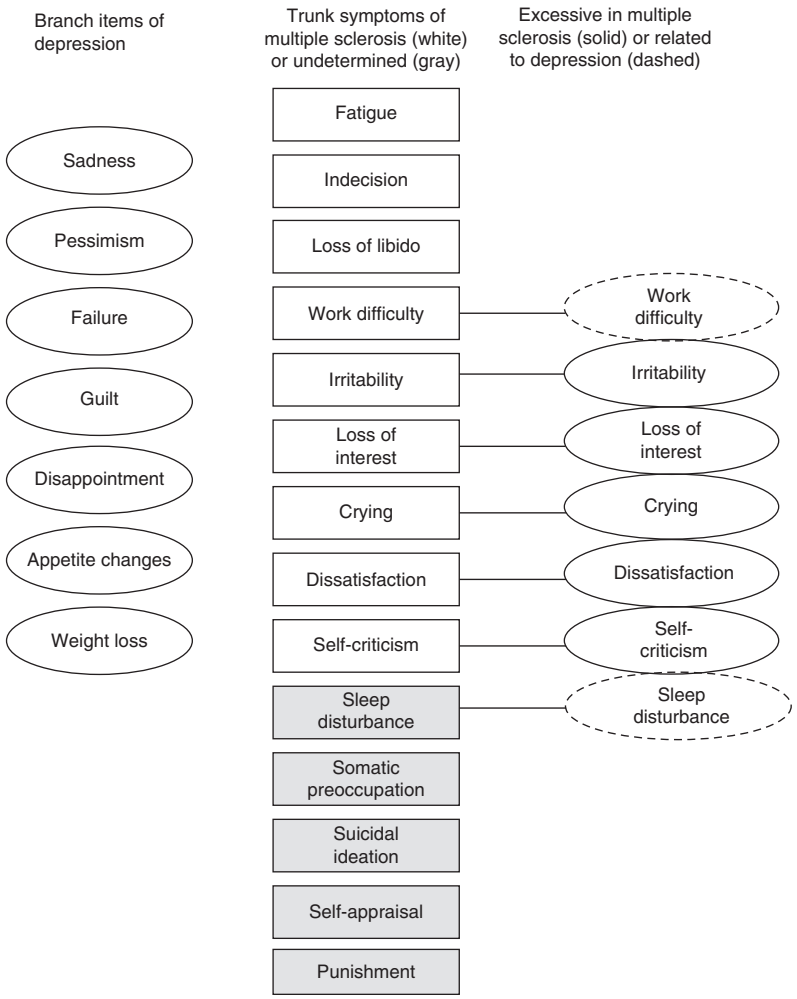

Figure 1 Modified trunk-and-branch model of depression in MS. Reproduced with permission from Strober, L.B., Arnett, P.A., 2010. Assessment of depression in multiple sclerosis: Development of a "trunk and branch" model. Clinical Neuropsychologist 24, 1146–1166.

increased disability leads to less physical activity, which in turn leads to depression (Brown *et al.*, 2009; Suh *et al.*, 2012).

Is Depression Related to Structural and Functional Brain Findings?

Not surprisingly, MS patients who have evidence of more structural brain damage report greater depression. In fact, one study found that nearly 50% of depression in MS was predicted by various measures of structural brain integrity, including lesions, brain atrophy, and the integrity of white matter tracts (Feinstein *et al.*, 2010; Bakshi *et al.*, 2000). The brain regions most often found to be compromised in MS depression are temporal and frontal areas (Arnett *et al.*, 2008; Feinstein *et al.*, 2010; Kiy *et al.*, 2011; Gold *et al.*, 2010). It is unclear, however, how such structural damage actually leads to depression in MS, that is, the mechanism by which this might occur. It may be that structural changes result in functional brain changes, which in turn predict depression in MS.

The study by Passamonti *et al.* (2009) appears to be the only published investigation that has examined functional brain activity in relation to depression in MS. They found that relapsing–remitting MS patients who reported greater depression than a control group showed decreased functional connectivity between the amygdala and the prefrontal cortex (PFC) when they performed an emotional matching task. It may be that such reduced functional connectivity reflects a disruption in an important affective processing system in the brain of MS patients early in the disease process, which might ultimately put them at risk for emotional difficulties such as depression. Clearly more research is necessary to supplement this intriguing finding. Feinstein has speculated that "a combination of inflammation, demyelination (hyperintense lesions), and atrophy within medial inferior frontal areas would disconnect neural connectivity" in frontal–subcortical circuits and lead to depression. The study by Passamonti *et al.* (2009) would seem to provide some support for decreased neural connectivity in such frontal–subcortical circuits in MS patients who report higher levels of depression than healthy controls. Still, as yet there is no published study that has empirically explored such structural/functional brain relationships in MS. It may be that disrupted connectivity between the amygdala and PFC increases proneness to depression because there is less emotional regulation from the PFC of more basic emotion

regulation systems in the brain (e.g., the amygdala). However, this is very speculative, and more research is needed to try and clarify such possible mechanisms. It should also be kept in mind that decreased connectivity between these systems may not be a cause of depression, per se, but a result of it.

Anxiety

Anxiety, although known to be highly comorbid with depression, has received less attention in MS research than depression. Most studies have employed self-report measures of anxiety symptoms, such as the Hospital Anxiety and Depression Scale (HADS), as part of a larger assessment of mental health. Typically, these studies do not focus exclusively on anxiety. However, enough literature exists from which general heuristics about anxiety and MS can be drawn.

How Common Is Anxiety in Multiple Sclerosis?

Anxiety symptoms are more common in the MS population than the general population. The prevalence of clinically elevated anxiety symptoms in an MS population varies, with an approximate range of 25–54% (Janssens *et al.*, 2003b; Feinstein *et al.*, 1999; Bianchi *et al.*, 2014). A large-scale study, with more than 4000 participants, found that 54% self-reported symptoms indicative of clinically significant anxiety (Jones *et al.*, 2012). This figure dropped to 36% in a smaller study that used structured clinical interviews for anxiety diagnoses instead of self-report (Galeazzi *et al.*, 2005). Overall anxiety is highly comorbid with MS. Whether this anxiety is due to emotions surrounding diagnosis or reactions to loss of function or is organic in etiology is less well understood. Of note, anxiety is highly comorbid with depression in other chronic medical conditions, as well as in depressed individuals more generally, with rates ranging from 58% to 79% (Newby *et al.*, 2013).

What Causes Anxiety in Multiple Sclerosis?

A few consistent predictors of anxiety in MS have been identified. Presence of anxiety in MS is usually associated with gender, with females being more likely than males to experience anxiety (Jones *et al.*, 2012; Korostil and Feinstein, 2007; Feinstein *et al.*, 1999). Anxiety has also been found to generally associate with certain illness-related variables such as course type, age at onset, and disability as measured by the Expanded Disability Status Scale (EDSS). Specifically, it is more common in patients with a relapsing–remitting course, younger age at onset, and less disability (EDSS < 3) (Beiske *et al.*, 2008). The disability finding is particularly illuminating, because it suggests that anxiety, unlike other symptoms of MS, does not increase linearly with overall disease burden. Other symptom-related variables found to predict anxiety in MS include high levels of pain and fatigue and a lifetime diagnosis of depression (Korostil and Feinstein, 2007). No relationship between disease-modifying medication and anxiety has been found (Janssens *et al.*, 2003b; Feinstein *et al.*, 1999; Korostil and Feinstein, 2007). Similar to depression, high levels of social stress and low levels of social support are predictive of anxiety. Additionally, high levels of alcohol abuse and suicidality are associated with anxiety in MS (Korostil and Feinstein, 2007). Personality factors are also related to higher anxiety in MS, including high neuroticism, low extraversion, low agreeableness, and low conscientiousness (Bruce and Lynch, 2011; Benedict *et al.*, 2001). Also of note, Benedict *et al.* (2001), though not examining anxiety per se, did report that MS patients had high neuroticism, low extraversion, low agreeableness, and low conscientiousness compared with healthy controls. These latter findings stress that sources external to an individual's disease burden have an effect on anxiety. These are areas where interventions to abate anxiety may be most effective.

How Does Anxiety in Multiple Sclerosis Change Over Time?

There is no consensus about the timeline surrounding anxiety in MS. Some research has found that anxiety is highest following MS diagnosis, suggesting that anxiety is best explained in MS as reactive as opposed to symptomatic (Bianchi *et al.*, 2014). However, other studies have not found any relationship between anxiety and disease duration (Beiske *et al.*, 2008; Feinstein *et al.*, 1999). Such findings suggest that anxiety, like most MS symptoms, varies across individuals and time. According to research examining newly diagnosed (two years within diagnosis or less) MS patients, 34% of the sample endorsed clinically significant symptoms of anxiety. In this sample, a significant relationship between EDSS and anxiety was also found; individuals with higher EDSS scores (more disability) endorsed more symptoms of anxiety (Janssens *et al.*, 2003a). This result contrasted with a large-scale study, which examined disease durations of all lengths, and found that those with lower EDSS scores tended to demonstrate the most anxiety (Jones *et al.*, 2012). A third study found that anxiety peaks from diagnosis to 30 days post diagnosis, but it tends to abate over time and remain stable over the next 2 years (Bianchi *et al.*, 2014). Taken together, these data imply that individuals often become anxious at time of diagnosis, with individuals with more symptoms generally experiencing more anxiety. Over the next couple of years, anxiety tends to abate in most individuals as perhaps coping mechanisms are established and the initial effect of the diagnosis fades. However, given that in most MS samples anxiety rates are above healthy population rates, it is evident that anxiety continues to ebb and flow into the individual MS patient's life and most likely varies as a function of pain, fatigue, and coping mechanisms, among other factors.

Are There Neural Correlates of Anxiety in Multiple Sclerosis?

Although studies have found brain regions that associate with depressive symptoms, no such results have been found with anxiety (Zorzon *et al.*, 2001). This finding further supports the notion that anxiety in MS is more reactive than organic in nature, or may be due to neural changes not detectable by available neuroimaging techniques. Also supporting this hypothesis is that 40% of partners of individuals with newly

diagnosed MS report clinically significant anxiety (Janssens *et al.*, 2003a). This figure is very similar to the proportion of individuals with MS who report anxiety symptoms (36%) soon after diagnosis. It is possible that approximately 35–40% of any individual learning of an MS diagnosis for themselves or a loved one experience clinically significant anxiety.

How Is Anxiety Treated in Multiple Sclerosis?

Regardless of the etiology of anxiety in MS, a startling consensus from research to date is that anxiety is severely undertreated. One study found that only 34% of individuals who met clinical criteria for an anxiety disorder had been given a documented diagnosis. Overall, 28% of individuals in the same sample who met criteria for an anxiety disorder had previously been given a diagnosis of an affective disorder. Finally, this same study revealed that more than half of the individuals who met criteria for an anxiety disorder were not being treated (Korostil and Feinstein, 2007). A different research group reported a similar finding; more than 30% of their sample endorsed clinically significant levels of anxiety but only approximately 10% of their sample was receiving treatment for anxiety (Beiske *et al.*, 2008). The undertreatment of anxiety in MS is problematic, especially when thought of in the context of depression in MS. Anxiety and depression have been found to be comorbid in both healthy individuals and those with MS (Jones *et al.*, 2012; Crawford *et al.*, 2001). This combination is particularly harmful, with one study finding that individuals with MS who had comorbid anxiety and depression were more likely to report ideas of self-harm than individuals with anxiety or depression alone (Feinstein *et al.*, 1999). In the general population, treatment of anxiety and depression differs when both disorders are present and often predicts worse prognosis (Ballenger, 1998). Thus, evaluation of anxiety, especially in individuals with a diagnosis of depression, is a crucial step in understanding and treating the emotional symptoms of MS.

Conclusion

As this article has shown, mental health problems are common in MS, especially depression and anxiety. Both are much more common in MS than in the general population and are often undertreated. Although there is a paucity of studies examining treatment of anxiety in MS, a range of psychopharmacologic and psychotherapy outcome studies suggest that depression is treatable in MS. Factors such as increased physical activity and use of active coping strategies in response to stress have also been shown to reduce depression in MS. With all this said, it appears that approximately 50% of MS patients who receive treatment for depression are nonresponders. It may be that those who do not respond well have undiagnosed comorbid problems (e.g., anxiety and personality disorders) that complicate treatment. Given that there are clear neuroanatomical underpinnings to depression in MS that are related to disease activity (e.g., brain atrophy, lesions, etc.), it may be that a better understanding of the mechanisms of how these organic factors relate to depression will lead to more effective depression treatment.

See also: Behavioral Medicine. Chronic Illness and Mental Health. Clinical Assessment. Cognitive-Behavioral Psychotherapy. Coping. Depression. Disability and Mental Health. Disorders of Negative Affect. Exercise, Physical Activity, and Mental Health. Major and Mild Neurocognitive Disorders. Mental Health, Medical Illness, and Treatment with a Focus on Depression and Anxiety. Midlife and Mental Health. Neuropsychological Assessment. Psychological Testing. Psychotherapy. Psychotherapy Effectiveness. Sleep Disorders. Social Support and Mental Health. Stress. Telecommunications in Mental Health Services. Telehealth, Computer-, and Internet-Based Approaches to Treating Depression and Anxiety. Unemployment and Mental Health

References

Arnett, P.A., Barwick, F.H., Beeney, J.E., 2008. Depression in multiple sclerosis: Review and theoretical proposal. Journal of the International Neuropsychological Society 14, 691–724.

Bakshi, R., Czarnecki, D., Shaikh, Z.A., *et al.*, 2000. Brain MRI lesions and atrophy are related to depression in multiple sclerosis. NeuroReport 11, 1153–1158.

Ballenger, J., 1998. Clinical guidelines for establishing remission in patients with depression and anxiety. Journal of Clinical Psychiatry 60, 29–34.

Bambara, J.K., Turner, A.P., Williams, R.M., *et al.*, 2011. Perceived social support and depression among Veterans with multiple sclerosis. Disability and Rehabilitation 33, 1–8.

Beck, A.T., Steer, R.A., 1987. BDI: Beck Depression Inventory Manual. New York, NY: Psychological Corporation.

Beck, A.T., Steer, R.A., Brown, G.K., 2000. BDI-FastScreen for Medical Patients Manual. San Antonio, TX: The Psychological Corporation.

Beeney, J.E., Arnett, P.A., 2008. Stress and memory bias interact to predict depression in multiple sclerosis. Neuropsychology 22, 118–126.

Beiske, A., Svensson, E., Sandanger, I., *et al.*, 2008. Depression and anxiety amongst multiple sclerosis patients. European Journal of Neurology 15, 239–245.

Benedict, R.H.B., Fishman, I., McClellan, M.M., *et al.*, 2003. Validity of the Beck Depression Inventory – Fast Screen in multiple sclerosis. Multiple Sclerosis 9, 393–396.

Benedict, R.H.B., Priore, R.L., Miller, C., *et al.*, 2001. Personality disorder in multiple sclerosis correlates with cognitive impairment. Journal of Neuropsychiatry and Clinical Neurosciences 13, 70–76.

Bianchi, V., De Giglio, L., Prosperini, L., *et al.*, 2014. Mood and coping in clinically isolated syndrome and multiple sclerosis. Acta Neurologica Scandinavica 129, 374–381.

Bombardier, C.H., Ehde, D.M., Gibbons, L.E., *et al.*, 2013. Telephone-based physical activity counseling for major depression in people with multiple sclerosis. Journal of Consulting and Clinical Psychology 81, 89–99.

Brown, R.F., Valpiani, E.M., Tennant, C.C., *et al.*, 2009. Longitudinal assessment of anxiety, depression, and fatigue in people with multiple sclerosis. Psychology and Psychotherapy 82, 41–56.

Bruce, J.M., Lynch, S.G., 2011. Personality traits in multiple sclerosis: Association with mood and anxiety disorders. Journal of Psychosomatic Research 70, 479–485.

Crawford, J., Henry, J., Crombie, C., *et al.*, 2001. Normative data for the HADS from a large non-clinical sample. British Journal of Clinical Psychology 40, 429–434.

Ehde, D.M., Kraft, G.H., Chwastiak, L., *et al.*, 2008. Efficacy of paroxetine in treating major depressive disorder in persons with multiple sclerosis. General Hospital Psychiatry 30, 40–48.

Feinstein, A., O'Connor, P., Akbar, N., *et al.*, 2010. Diffusion tensor imaging abnormalities in depressed multiple sclerosis patients. Multiple Sclerosis 16, 189–196.

Feinstein, A., O'connor, P., Gray, T., *et al.*, 1999. The effects of anxiety on psychiatric morbidity in patients with multiple sclerosis. Multiple sclerosis 5, 323–326.

Galeazzi, G., Ferrari, S., Giaroli, G., *et al*., 2005. Psychiatric disorders and depression in multiple sclerosis outpatients: Impact of disability and interferon beta therapy. Neurological Sciences 26, 255–262.

Gay, M.C., Vrignaud, P., Garitte, C., *et al*., 2010. Predictors of depression in multiple sclerosis patients. Acta Neurologica Scandinavica 121, 161–170.

Gold, S.M., Kern, K.C., O'Connor, M.F., 2010. Smaller cornu ammonis 2-3/dentate gyrus volumes and elevated cortisol in multiple sclerosis patients with depressive symptoms. Biological Psychiatry 68, 553–559.

Holden, K., Isaac, C.L., 2011. Depression in multiple sclerosis: Reactive or endogenous? Clinical Neuropsycholog 25, 624–639.

Janssens, A., Doorn, P., Boer, J., *et al*., 2003a. Impact of recently diagnosed multiple sclerosis on quality of life, anxiety, depression and distress of patients and partners. Acta Neurologica Scandinavica 108, 389–395.

Janssens, A.C., Van Doorn, P., De Boer, J., *et al*., 2003b. Anxiety and depression influence the relation between disability status and quality of life in multiple sclerosis. Multiple sclerosis 9, 397–403.

Jones, K.H., Ford, D.V., Jones, P.A., *et al*., 2012. A large-scale study of anxiety and depression in people with multiple sclerosis: A survey via the web portal of the UK MS Register. PLoS One 7, e41910.

Kale, N., Agaoglu, J., Tanik, O., 2010. Neuropsychiatric manifestations in multiple sclerosis: Correlation of fatigue and depression with disease progression. Neurology Research 32, 221–223.

Kiy, G., Lehmann, P., Hahn, H.K., *et al*., 2011. Decreased hippocampal volume, indirectly measured, is associated with depressive symptoms and consolidation deficits in multiple sclerosis. Multiple Sclerosis 17, 1088–1097.

Koch, M., Mostert, J., Heerings, M., *et al*., 2009. Fatigue, depression and disability accumulation in multiple sclerosis: A cross-sectional study. European Journal of Neurology 16, 348–352.

Korostil, M., Feinstein, A., 2007. Anxiety disorders and their clinical correlates in multiple sclerosis patients. Multiple Sclerosis 13, 67–72.

Krupp, L., Alvarez, L., LaRocca, N.G., Scheinberg, L.C., 1988. Fatigue in multiple sclerosis. Archives of Neurology 45, 435–437.

Marrie, R.A., Horwitz, R., Cutter, G., *et al*., 2009. The burden of mental comorbidity in multiple sclerosis: Frequent, underdiagnosed, and undertreated. Multiple Sclerosis 15, 385–392.

Mattioli, F., Bellomi, F., Stampatori, C., *et al*., 2011. Depression, disability and cognitive impairment in multiple sclerosis: A cross sectional Italian study. Neurological Sciences 32, 825–832.

Mohr, D.C., Goodkin, D.E., 1999. Treatment of depression in multiple sclerosis: Review and meta-analysis. Clinical Psychology: Science and Practice 6, 1–9.

Mohr, D.C., Hart, S.L., Julian, L., *et al*., 2005. Telephone-administered psychotherapy for depression. Archives of General Psychiatry 62, 1007–1014.

Mohr, D.C., Likosky, W., Bertagnolli, A., *et al*., 2000. Telephone-administered cognitive-behavioral therapy for the treatment of depressive symptoms in multiple sclerosis. Journal of Consulting and Clinical Psychology 68, 356–361.

Newby, J.M., Mackenzie, A., Williams, A.D., *et al*., 2013. Internet cognitive behavioural therapy for mixed anxiety and depression: A randomized controlled trial and evidence of effectiveness in primary care. Psychological Medicine 43, 2635–2648.

Nyenhuis, D.L., Rao, S.M., Zajecka, J., *et al*., 1995. Mood disturbance versus other symptoms of depression in multiple sclerosis. Journal of the International Neuropsychological Society 1, 291–296.

Passamonti, L., Cerasa, A., Liguori, M., *et al*., 2009. Neurobiological mechanisms underlying emotional processing in relapsing-remitting multiple sclerosis. Brain 132, 3380–3391.

Rabinowitz, A.R., Fisher, A.J., Arnett, P.A., 2011. Neurovegetative symptoms in patients with multiple sclerosis: Fatigue, not depression. Journal of the International Neuropsychological Society 17, 46–55.

Sadovnick, A.D., Remick, R.A., Allen, J., *et al*., 1996. Depression and multiple sclerosis. Neurology 46, 628–632.

da Silva, A.M., Vilhena, E., Lopes, A., *et al*., 2011. Depression and anxiety in a Portuguese MS population: Associations with physical disability and severity of disease. Journal of the Neurological Sciences 306, 66–70.

Smith, M.M., Arnett, P.A., 2005. Factors related to employment status changes in individuals with multiple sclerosis. Multiple Sclerosis 11, 602–609.

Strober, L.B., Arnett, P.A., 2010. Assessment of depression in multiple sclerosis: Development of a "trunk and branch" model. Clinical Neuropsychologist 24, 1146–1166.

Strober, L.B., Arnett, P.A., under review. Depression in multiple sclerosis: The utility of common self-report instruments and development of a disease-specific measure. Clinical Neuropsychologist.

Suh, Y., Weikert, M., Dlugonski, D., *et al*., 2012. Physical activity, social support, and depression: Possible independent and indirect associations in persons with multiple sclerosis. Psychology, Health & Medicine 17, 196–206.

Zorzon, M., de Masi, R., Nasuelli, D., *et al*., 2001. Depression and anxiety in multiple sclerosis. A clinical and MRI study in 95 subjects. Journal of Neurology 248, 416–421.