

Chapter 12

Psychological and Behavioral Therapies in Multiple Sclerosis

Peter A. Arnett, Dede Ukueberuwa, and Margaret Cadden

Abstract Depression in multiple sclerosis (MS) is very common, with a lifetime prevalence of around 50 %, which is much higher than the 8 % reported for the general population. In this chapter, we explore some of the psychological and behavioral depression treatments that have been studied in MS. Our review shows clearly that depression in MS is treatable, via both psychotherapeutic and behavioral interventions. Randomized clinical trials (RCTs) on psychotherapy have generally revealed very large effect sizes, with the one benchmarking study (one that examines treatment as it actually occurs in clinical settings) in the literature showing a still large but somewhat smaller effect size than RCTs. Exercise appears to be a promising potential treatment of depression in MS and has been shown to be correlated with lower depression. Additionally, RCTs of exercise have revealed small to moderate effect sizes on reducing depression. One problem with psychological and behavioral treatments of depression in MS is the salience of disability and travel issues that make involvement in such intensive treatment more challenging. Thus, even though treatments are often effective, patients may avoid them in favor of other interventions. Telephone-based interventions have been shown to be very effective in treating depression in MS and could represent a promising approach that circumvents such obstacles. Even though current treatments are effective, future research should explore why nearly half of patients do not respond to available treatments. A focus on the possibility that co-morbid conditions (e.g., anxiety or personality disorders) could interfere with standard depression treatments, as well as possible mediators of treatment (e.g., fatigue, disability levels, sleep disturbance), may be promising avenues for future research.

P.A. Arnett, Ph.D. (✉)

Department of Psychology, College of the Liberal Arts, Penn State University,
352 Bruce V. Moore Bldg., University Park, PA 16802-3105, USA
e-mail: paa6@psu.edu

D. Ukueberuwa, M.S. • M. Cadden, B.S.
Department of Psychology, Penn State University,
372 Moore Building, University Park, PA 16802, USA
e-mail: dedemu@gmail.com; margaret.cadden@gmail.com

Keywords Multiple sclerosis (MS) • Depression • Anxiety • Personality • Cognitive function • Mental health • Neuropsychological • Cognitive behavioral therapy (CBT) • Physical activity • Randomized clinical trials (RCTs)

Psychological and Behavioral Therapies in MS

Depression is extremely common in MS, with a lifetime prevalence rate of about 50 % [1–3], compared with only about 8 % in the general population. MS depression is treatable, but available interventions are effective in only about 50 % of patients [4–6]. Better treatments are needed for those patients who do not respond to treatment; still, treatments should be offered to all MS patients who present with clinically significant depression. In this chapter, we will first review some of the complexities in measuring depression in MS. Then we will review some of the extant psychological and behavioral therapies for depression in MS, including interventions that involve treating depression through increasing exercise.

Measuring Depression in MS

Before depression in MS can be treated, it must be accurately assessed. An important factor complicating the measurement of depression in MS is the overlap between neurovegetative symptoms of depression in MS and disease symptoms. For example, symptoms such as fatigue, sleep disturbance, and sexual dysfunction are all considered neurovegetative symptoms of depression. However, they are also prominent MS disease symptoms. When patients report such symptoms, how is it possible to determine whether they reflect depression or disease symptoms? One suggested method is through careful interviewing to try and identify the source of such symptoms. Given the time-consuming nature of such an approach, however, some investigators have suggested simply omitting neurovegetative symptoms from consideration to get an accurate measurement of depression in MS [3]. Another suggested approach is to consider neurovegetative depression symptoms as reflecting depression in MS only when they exceed what is typically reported in nondepressed MS patients [7].

At present, the most sensitive measures for screening depression in MS do not include neurovegetative symptoms and take only a few minutes to administer. The Beck Depression Inventory-Fast Screen (BDI-Fast Screen) [8] consists of only seven items and has been validated in at least two studies of MS patients [9, 10], with an optimal cutoff score (≥ 4) that mirrors what is recommended in the BDI-Fast Screen manual for medical patients more generally. The Hospital Anxiety and Depression Scale (HADS) [11] has been validated in at least one MS study, and the depression scale from this measure consists of only eight items; the optimal cutoff

score for screening depression in MS is ≥ 8 . The HADS is further appealing in that the other half of the scale measures anxiety, something that is highly co-morbid with depression in MS, and can complicate treatment if depression is identified and treatment attempted without proper identification of co-morbid anxiety.

Treating Depression in MS

Because of its high prevalence, impact on quality of life [12], effect on medication compliance [13], possible impact on cognition [3], and the fact that it is unlikely to remit without intervention [14], treatment of depression is essential in MS. What follows is a review of some of the psychological and behavioral therapies that have been employed in MS.

Psychological and Behavioral Approaches

Mohr and Goodkin [14] conducted a meta-analysis of the depression treatment literature in MS about 15 years ago and concluded that psychological and behavioral therapies were at least as effective as medication. In particular, they also found that approaches that focused on skill building (e.g., improving coping strategies, general cognitive behavioral therapy (CBT) approaches) were more effective than approaches primarily focusing on insight. Since their publication, a number of additional studies have been published supporting and refining their initial review. For example, one study showed that CBT was more effective than an approach involving supportive group therapy [5]. Further supporting the CBT approach, Mohr and colleagues found that even when cognitive behavioral therapy was administered via telephone, it was effective [15, 16]. These demonstrations were extremely important, in that they illustrated that interventions could be effective even when MS patients, because of their disability or other limitations, were unable to travel to a site where in-person therapy could occur.

Further supporting the CBT approach to treating depression in MS, Cooper and colleagues [17] found in a randomized clinical trial (RCT) that a computerized CBT approach was effective in reducing BDI-II scores in 24 MS patients. One limitation of this approach, however, was that patients displayed poor adherence to the treatment protocol. However, clearly this is a promising approach with great potential in need of further research to better understand obstacles to adherence.

Although RCTs are rigorous tests of the efficacy of treatment interventions for depression, they are limited by the fact that the approaches used within the trial and the types of patients selected for them may not be representative of what truly happens in clinical practice. Because of this, benchmarking studies that examine treatment as it actually occurs in clinical settings are conducted. With this in mind, Askey-Jones and colleagues [18] conducted what appears to be the first benchmark-

ing study on depression treatment in MS. Their study examined anxiety as well. MS patients in this study were identified for treatment if their HADS score was greater than 8, generally consistent with Honarmand and Feinstein's [11] recommendation, as noted above. In contrast to typical RCT approaches, patients were not excluded if they had co-morbid conditions, such as anxiety, if they were using medication, or if they were in the midst of an MS relapse. However, the authors did exclude those with significant cognitive problems or other severe disability that would impact their ability to attend treatment sessions. A CBT approach was used on the 29 patients enrolled in the study, and treatment was provided by MS nurse specialists. In addition to being used for participant selection, the HADS was used as the primary outcome variable. Because this study used a different outcome variable (HADS) than most published RCTs (which most often used the BDI-II), the investigators compared effect sizes between their study and the existing RCT data. The study had a 32 % dropout rate, with most non-completers reporting the primary impediment to continuing the treatment as the distance to the clinic for treatment.

Results of the study revealed significant decreases in both HADS Depression and Anxiety scale scores. The effect sizes for both were large by conventional standards (1.02 for depression and 1.18 for anxiety), though generally lower than the larger effect sizes (1.54–3.42) reported in the five RCTs to which they compared their data. The authors also highlighted their higher dropout rate compared with the computerized CBT RCT, as well as telephone-based CBT studies. Thus, although Askey-Jones et al.'s [18] study shows that depression in MS can be treated effectively in routine clinical practice, it does raise important issues involving transportation to therapy sites that may provide an impediment to treatment for some MS patients. However, because most of the non-completers in Askey-Jones et al.'s study cited travel concerns to the treatment site as their primary reason for discontinuing treatment, one possible solution to this problem might be to conduct a benchmarking study that employs telephone-based CBT.

Sleep problems are much more common in MS than the general population and are often co-morbid with depression and anxiety [19]. Over 50 % of MS patients complain of sleep onset problems or early morning awakening, compared with only about 10–15 % of those in the general population. With this in mind, Baron and colleagues examined data from a telephone-based CBT study to evaluate whether changes in depression and anxiety with treatment were associated with improvement in sleep difficulties. Their large group of MS participants ($n=127$) received either CBT or supportive emotion-focused therapy. About half of the patients met criteria for major depression at treatment onset, and this was reduced by almost half at the treatments' conclusion. In terms of the relationship of treatment with sleep problems, patients who continued to report insomnia posttreatment were nearly six times more likely to meet criteria for major depressive disorder and over three times more likely to have elevated anxiety scores. Thus, these investigators found that persisting depression and anxiety were highly associated with continued problems with insomnia. One caveat is that these authors found that about one-third of their sample continued to have significant problems with insomnia after treatment even when they did not meet major depressive disorder criteria or have elevated anxiety.

They reasoned that these individuals' problems with sleep may have been more related to core MS symptoms (e.g., restless legs, difficulty swallowing, upper airway weakness) than affective problems.

Behavioral Approaches Involving Physical Activity and Exercise

Exercise has emerged as an effective treatment for depression in the general population, with hundreds of published studies exploring this topic. The most recently published large-scale Cochrane review on this topic concluded that exercise has a moderate ameliorative effect on depressive symptoms at time of treatment. Albeit these gains appeared to lessen over time, they continued to exist even at treatment follow-up [20]. Although this relationship has been less explored in the MS population, the existing literature is promising. This section will review the evidence of exercise as an effective behavioral treatment for depression in MS as revealed through both cross-sectional work and randomized clinical trials. Additionally, potential mediators of this relationship will be discussed. The section will conclude with a brief discussion on the limitations of exercise as a treatment for depression specific to the MS population.

Cross-Sectional Studies

Several cross-sectional studies examining the relationship between exercise and depressive symptoms in MS exist. Although these studies differ in methods of measuring exercise and depressive symptoms, they generally all come to the conclusion that higher levels of exercise are associated with lower depressive symptoms in MS.

One of the earliest studies on this topic was conducted by Stroud and Minehan [21]. Using the International Physical Activity Questionnaire (IPAQ), the authors dichotomized MS participants in their study into exercisers and non-exercisers based on the criteria of them participating in two 30-min bouts of exercise per week. They found that regular exercisers reported having lower fatigue, lower depressive symptoms on the Beck Depression Inventory (BDI), and higher quality of life compared to non-exercisers. Ensari and colleagues [22] found that level of exercise, as measured by the Godin Leisure-Time Exercise Questionnaire (GLTEQ), was one of the several factors that contributed to depression course in MS. The authors identified two course types for depression in MS; the first course was marked by low initial levels of depression that maintained or lowered over time, and the second course was marked by high initial levels of depression that increased over time. Participating in physical activity was predictive of the first course type, or, the course type in which depressive symptoms were generally less severe. Jensen and colleagues [23] further illuminated exercise as a potential treatment for depression in MS by examining how age and level of exercise (i.e., moderate versus vigorous) moderated this relationship. Using items from the 2003 Center for Disease Control

and Prevention Behavioral Risk Factor Surveillance system (BRFSS) Survey Questionnaire, the authors measured how many minutes per week individuals in their study engaged in moderate and vigorous activity. After controlling for age and disability (EDSS), a moderate level of activity significantly predicted depressive symptoms, with higher activity indicative of fewer symptoms. The vigorous exercise findings were more complicated, with time spent in vigorous exercise being associated with fewer depressive symptoms in middle-aged individuals (45–64 years old) but not in younger or older individuals.

Thus far, the studies discussed used surveys as their measure of exercise. However, similar evidence for exercise as a treatment for depression exists when using more objective exercise measurements. Suh et al. [24] measured physical activity using accelerometers in a group of individuals early on in their MS course (5-year disease duration or less); depression was measured with the Hospital Anxiety and Depression Scale (HADS). These investigators found that higher levels of physical activity were associated with significantly lower depression levels. Path analysis revealed that this relationship could be completely explained by disability level; specifically, the analysis suggested that physical activity led to reduced disability, which in turn resulted in lower depression. Although literature exists which supports the idea that physical activity can reduce disability [25], it is also possible that individuals with low levels of disability are more likely to be physically active as well as less depressed. The results of this study are provocative, but it is important to keep in mind that this study, as well as others discussed, has a correlational design; therefore, causal relationships cannot be clearly inferred.

Randomized Clinical Trials

Findings such as those reviewed above that show greater levels of physical activity are associated with fewer depression symptoms have resulted in efforts to research exercise as a treatment for depression. The goal of a randomized controlled trial (RCT), in which participants are randomly assigned to a treatment or control group, is an examination of an intervention for which causal inferences about outcomes can more clearly be made. Thus far, intervention studies of the therapeutic benefits of exercise for depression show mixed results [26]. In general they indicate a small positive effect of exercise interventions in reducing depression symptoms in MS [22].

Different types of exercise programs have been examined in RCTs. Exercise may consist of strength and resistance training, such as repetitive training of the arms and legs with elastic resistance bands. Aerobic exercise may include walking, running, biking, swimming, or even climbing indoors or outdoors. Practices such as yoga and tai chi, which are thought to improve muscle relaxation, posture, and balance, have also been studied for potential therapeutic effects on mood in MS [27]. In a typical research design, assessments of patients' physical and emotional functioning are collected at baseline before administration of the intervention. At the end of the exercise intervention period, typically 8–12 weeks, outcome measures are then

administered to patients to assess for changes in depression symptoms. One RCT evaluated an exercise training program as a treatment for depression symptoms in addition to physical and cognitive functioning and fatigue in patients with progressive MS [28]. The study involved 8–10 weeks of arm strengthening, rowing, or cycling, with 2–3 sessions per week, and the specific training program was tailored to the fitness level of each participant at baseline. Nearly half of participants had moderate to severe clinical depression scores at baseline, and symptoms decreased significantly in the groups with arm or bicycle training compared to a waitlist control group.

Exercise programs can be set up remotely by telephone or through a website, sometimes known as *telerehabilitation*. Patients may then engage in the activities at home or with a local physical therapist, thus expanding the reach of the trial and reducing barriers to accessibility of the program due to other responsibilities or limitations of transportation that people with MS may experience [29]. Telephone-based counseling may consist of motivational interviewing, an evidence-based technique for counseling patients to change behaviors such as engaging in an exercise program [30]. Web-based programs use a website to describe exercise activities through video or text and to offer advice to patients [31]. While a physical therapist may offer additional in-person guidance for carrying out exercises, a home-based intervention program may aid in long-term adherence [32]. In one RCT, patients in a home-based exercise program engaged in aerobic endurance training and were also provided with elastic bands for resistance training [33].

In a meta-analysis that included all of the 13 randomized controlled trials of exercise as a treatment for depression in MS, Ensari and colleagues [22] found an overall reduction in depression symptoms as a result of an exercise routine. This reduction was seen across studies, regardless of the specific method of exercise that was prescribed or the demographic or clinical characteristics of the MS samples. However, the effect of the treatment was small – these studies indicate that the treatment would have a 59 % chance of successfully reducing depression symptoms. These studies also typically used patients on a waitlist as a control group, and thus we are not able to make direct comparisons between exercise and other types of interventions for depression. Overall, the results are promising but indicate that we need more information to conclude that exercise is a consistently effective treatment for depression in MS, and additional trials of the therapeutic benefits of exercise in MS should include depression as a measure of outcome.

Mediators and Confounds

While the primary goal of these research studies reviewed in this section has been to examine the relationship between exercise and depression, changes in depression symptoms could be an indirect outcome of other effects of exercise. We are beginning to understand some factors that influence how exercise interventions could lead to changes in depression. Among adults with major depressive disorder, greater frequency and longer duration of physical activity led to increased positive affect

[34, 35]. Kratz, Ehde, and Bombardier [36] examined affective components of depression in people with MS within a randomized controlled trial and found that increases in positive affect and not decreases in negative affect mediated the effects of a physical activity intervention on reduced symptoms of depression. In this study, one-third of patients showed at least 50 % reduction in symptoms. Statistical mediation models indicated that increased physical activity leads to increased positive affect, but physical activity was not significantly related to changes in negative affect. Assignment to an intervention group – telephone-based motivational interviewing versus a waitlist control – had a direct effect on changes in both positive and negative affects, regardless of changes in physical activity. These results indicate that a counseling intervention had a general benefit for patients' affect and that physical activity could specifically improve depression symptoms in patients with MS by increasing positive affect. The authors reasoned that physical activity becomes a rewarding behavior and is associated with increased positive affect. Additional research suggests that changes in physical disability and perceived stress levels during an exercise intervention could be mediators of changes in depression symptoms [37].

In addition to these possible therapeutic mechanisms, other factors may be further examined as potential confounds in understanding the relationship between exercise interventions and changes in depression. The symptoms of fatigue and depression overlap, and fatigue is a common problem for people with MS [38]. One study, which was not an RCT, found that change in fatigue was a mediator between exercise training and change in depressive symptoms [39]. Specifically, exercise resulted in reduced fatigue, which in turn predicted lower depression. Future trials should include measures of fatigue and examine pathways leading from physical activity to depression. An additional confounding factor in these studies could be the benefits of social interaction between researchers or physical therapists and patients in the treatment group. In the cross-sectional assessment by Suh et al. [37], physical activity and social support each had independent relationships to depression. This suggests that patients in the treatment group are likely to experience a reduction of depression compared to a waitlist control group, regardless of the specific features of the treatment, such as an exercise program. These results also suggest that increasing social support could be an additional target of future depression treatment studies in people with MS, in addition to separately examining the benefits of engaging in exercise.

Limitations

Although exercise has been found to be an effective treatment for depression in the general population, it is important to consider the limitations that having MS may pose to successfully exercising. First and foremost, individuals with MS may face barriers to exercising such as physical impairments that limit their ability to participate in certain activities (such as walking if ambulation is poor). Additionally, individuals with MS may face physical barriers such as a lack of transportation to

appropriate exercise facilities or a lack of accessibility to these facilities (i.e., not available in their area or not handicap accessible). According to one recent study, individuals with MS reported fatigue, impairment, and a lack of time as the three biggest barriers to exercising [40]. This same study found that the more perceived barriers to exercise individuals reported, the higher their self-reported depressive symptoms and the lower their self-reported perceived health. Therefore, special attention should be given when designing exercise regimens for individuals with MS that account for their disability, as well as physical and emotional barriers they may face. Asano et al. [40] suggested creating exercise regimens that are short in duration in order to address perceived barriers such as fatigue and lack of time. Morrison and Stuifbergen [41] found results which indicated that increasing physical and social expectations of exercise outcomes may increase the likelihood of exercise engagement in MS as well.

Summary and Conclusions

Depression is very common in MS, with lifetime prevalence rates around 50 % compared with 8 % in the general population. Because of these high prevalence rates, there has been an intense focus on identifying effective treatments for depression in MS. The results of this review show that depression in MS is treatable, via both psychotherapeutic and behavioral interventions. The effect sizes for most psychotherapy RCTs are very large; the one benchmarking study in the literature also reported large effect sizes, albeit somewhat smaller than the RCTs. Studies involving exercise show that exercise is a promising potential treatment of depression in MS. Exercise has been shown to be correlated with lower depression in MS; furthermore, RCTs involving exercise have revealed small to moderate effects of exercise on depression, with at least one study showing that the effect may be through increasing positive affect rather than reducing negative affect per se.

One problem with treating depression in MS is that patients have far more impediments to treatment, especially surrounding getting to treatment sites, than typical non-MS individuals seeking treatment. Thus, although existing psychological and behavioral treatments are often effective, patients may not seek out treatment because they are unable to get to treatment. One way of circumventing this that has been explored in the literature is by using treatment delivery systems that occur via telephone or through web-based strategies. Telephone-based CBT appears to be very effective in treating depression in MS, so it could be a viable way of providing patients with treatment when travel/disability issues are paramount.

A concern raised by psychological and behavioral treatment studies conducted thus far is that, although effect sizes on reducing depression are often large, around half of patients treated do not respond to treatment. Given the costs of depression to the well-being of patients and their families, more research is necessary that attempts to understand why some patients do not respond to treatment. It may be that comorbid conditions (e.g., anxiety or personality disorders), when not accurately

identified and then treated, interfere with standard depression treatments. It may also be that more attention needs to be paid to possible mediators of treatment (e.g., fatigue, disability levels, sleep disturbance) so that they can be addressed, as well as more direct depression symptoms.

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