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Telephone-Based Physical Activity Counseling for Major Depression in People With Multiple Sclerosis

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Objective: Physical activity represents a promising treatment for major depressive disorder (MDD) in people with multiple sclerosis (MS). We conducted a single-blind, two-arm randomized controlled trial comparing a 12-week physical activity counseling intervention delivered primarily by telephone ($n = 44$) to a wait-list control group ($N = 48$). ***Method:*** Ninety-two adults with MS and MDD or dysthymia ($M_{age} = 48$ years; 86% female, 92% White) completed an in-person baseline assessment and were randomized to wait-list control or an intervention involving motivational-interviewing-based promotion of physical activity. The treatment group received an initial in-person session; 7 telephone counseling sessions (Weeks 1, 2, 3, 4, 6, 8, and 10), and an in-person session at Week 12. The primary outcome, treatment response, was defined as those with 50% or greater reduction in the Hamilton Depression Rating Scale (HAM–D) score. ***Results:*** Our primary hypothesis, that the proportion of responders in the treatment group would be significantly greater than in the control group, was not confirmed. However, compared with the control group, those in the treatment group evidenced significantly lower depression severity on the HAM–D, on self-reported depression, and on a measure of potential side effects and at 12 weeks were less likely to meet the criteria for MDD as set forth in the *Diagnostic and Statistical Manual of Mental Disorders* (4th ed.). Physical activity increased significantly more in the treatment condition, though it did not mediate improvement in depression severity. ***Conclusions:*** Telephone-based physical activity promotion represents a promising approach to treating MDD in MS. Further research is warranted on ways to bolster the impact of the intervention and on mediators of the treatment effect.

Keywords: multiple sclerosis, depression, physical activity, motivational interviewing, telephone counseling

Multiple sclerosis (MS) is a demyelinating disease of the central nervous system affecting an estimated 400,000 persons in the United States; it is more common in women (Hirtz et al., 2007). The disease causes demyelination and axonal loss in an unpredictable pattern and may result in a relapsing or progressive clinical course (Trapp et al., 1998). MS causes a wide variety of symptoms including fatigue, weakness, sensory impairments, cognitive impairment, and depression (Kraft, 1999).

Major depression is both prevalent and disabling in people with MS. 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 (Patten, Beck, Williams, Barbui,

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& Metz, 2003). In people with MS, major depression is associated with poorer neuropsychological functioning, lower quality of life, increased time lost from work, social disruption, poorer health, and possibly greater disease progression (Goldman Consensus Group, 2005). People with clinically significant depressive symptoms are 6.2 times more likely to have disabling fatigue than nondepressed controls (Chwastiak et al., 2005).

Unfortunately, treatment of major depression in people with MS is not yet optimal. An estimated two thirds of people with MS and major depression are untreated (Feinstein, 2002; Mohr, Hart, Fonareva, & Tasch, 2006). Standard treatments such as antidepressant medications may be less effective in the context of MS than in people without neurological conditions (Ehde et al., 2008; Mohr, Boudewyn, Goodkin, Bostrom, & Epstein, 2001). Cognitive–behavioral therapy is an effective treatment for depression in this population, but about 50% do not respond to treatment (Mohr et al., 2001; Mohr, Hart, & Julian, 2005). Factors that may contribute to low treatment rates include poor tolerance of medication side effects (Mohr et al., 2001); not wanting to take additional medications; and the time requirements, cost, and potential stigma associated with psychotherapy (Collins, Westra, Dozois, & Burns, 2004). Consequently, there is a need for research on alternative or adjunctive treatments for major depression in this population.

Exercise is a promising treatment for major depression in the context of MS for several reasons. People with MS are plagued by fatigue, deconditioning, and inactivity (Coyle, Santiago, Shank, Ma, & Boyd, 2000; White & Dressendorfer, 2004). Inactivity is associated with higher rates of depression in able-bodied persons (Brosse, Sheets, Lett, & Blumenthal, 2002) as well as people with MS (Sutherland & Andersen, 2001). Exercise is an effective form of treatment for depression among healthy human subjects, psychiatric patients, and the elderly (Brosse et al., 2002). Exercise may be as effective as antidepressants in older adults (Blumenthal et al., 1999). Both aerobic and nonaerobic exercise has antidepressant effects (Brosse et al., 2002). Exercise has widespread health benefits in people with MS, including improved physical and psychosocial functioning (Petajan et al., 1996), less disability, (Snook & Motl, 2008), improved quality of life (Motl, McAuley, Snook, & Gliottoni, 2009), less fatigue (Patti et al., 2002, 2003), and less functional decline over a 5-year period (Stuifbergen, Blozis, Harrison, & Becker, 2006). Exercise is popular among people with MS. In clinic and community samples, 77%–86% of people with MS were interested in obtaining help to exercise (Blake, Bombardier, Cunniffe, Dollar, & Kraft, 2002). Finally, a physical activity intervention is appealing because it (a) is low cost in terms of health care utilization, (b) is universally available (if successful, the paradigm could be easily adopted in many settings), (c) is a nonstigmatizing form of mental health treatment, and (d) places the power to improve emotional functioning within the control of the person with MS. In addition, physical activity is related to better health with regard to cardiovascular disease, Type 2 diabetes mellitus, obesity, osteoporosis and some forms of cancer (Haskell et al., 2007).

Therefore, we designed a study to determine whether an intervention to increase physical activity might be an effective treatment for major depression in people with MS. We chose to study moderate intensity home-based physical activity promotion because long-term adherence is likely to be better for home-based than clinic-based exercise interventions (Ashworth, Chad, Harrison, Reeder, & Marshall, 2005). Telephone counseling was selected as the intervention delivery mode because it is an effective behavior change approach that overcomes barriers to participation such as distance, accessibility, and limited transportation (Castro & King, 2002; Castro, King, & Brassington, 2001), barriers that may be even more prominent among people with MS. We used motivational interviewing (MI) as the counseling style because it is a highly regarded, teachable, evidence-based behavior change approach supported by over 70 randomized controlled trials with moderate to large effect sizes in the area of health or exercise promotion (Burke, Arkowitz, & Menchola, 2003).

Our primary hypothesis was that the group randomized to physical activity counseling would demonstrate a significantly greater response rate—that is, at least a 50% reduction in depression severity on the Hamilton Depression Rating Scale (HAM–D; Hamilton, 1960)—compared with a wait-list control group. Secondary hypotheses were that the treatment group would demonstrate a significantly greater decrease on measures of depression severity and be less likely to meet criteria for MDD at follow-up than the control group. As a manipulation check, we also compared changes in self-reported physical activity between groups and hypothesized that increased physical activity would mediate decreases in depression severity. As a check on potential negative side-effects of increased physical activity, we compared the two groups on magnitude of common MS-related symptoms before and after the trial.

Method

Design

This was a two-group randomized controlled trial with 1:1 assignment to the group receiving telephone-counseling-based physical activity promotion versus a wait-list control group. Assessment of outcome variables occurred at baseline (before randomization), at 12 weeks postrandomization (primary outcome assessment point), and at 24 weeks postrandomization (assessment of maintenance effects, active treatment group only).

Participants and Setting

The study sample was composed of community-residing individuals with clinically definite MS. Participants were identified from a variety of sources, including (a) the Western Regional MS Center at the University of Washington; (b) the Neurology Clinic at the University of Washington; (c) advertisements and articles in local newspapers, MS newsletters, and web sites; (d) flyers sent to physiatrists' and neurologists' offices; (e) MS support groups in the Puget Sound region; (f) a large mailing sent to persons on the North American Research Consortium on MS and MS Association registries; and (g) two surveys of persons with MS, the methods of which are described elsewhere (Bamer, Cetin, Johnson, Gibbons, & Ehde, 2008). Potential participants typically called the study office to indicate they were interested in being screened. Those who indicated they were interested were screened by telephone for study eligibility.

Inclusion criteria for participants were (a) being between the ages of 18 and 70 years; (b) having a physician-confirmed diagnosis of MS; (c) having an Expanded Disability Severity Scale

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(EDSS; Kurtzke, 1983) score of 5.5 or less (able to walk without an assistive device for at least 100 m); (d) presence of significant depressive symptoms indicated by a score of 10 or more on the Patient Health Questionnaire–9 (PHQ-9; Kroenke, Spitzer, & Williams, 2001) or a response of 2 or more on Questions 1 (anhedonia item) or 2 (depressed mood item) on the PHQ–9; (e) diagnosis of major depressive disorder or dysthymia based on the Structured Clinical Interview for *DSM–IV* (SCID; First, Gibbon, Spitzer, & Williams, 2001) administered by phone; and (6) currently not meeting physical activity guidelines (exercising less than 150 min per week). Exclusion criteria were (a) having a cardiovascular, balance, or bone/joint problem that would make exercise unsafe according to the Physical Activity Readiness Questionnaire (PAR–Q; Thomas, Reading, & Shephard, 1992); (b) having extreme heat intolerance or experiencing Uhthoff effect (temporary blindness in people with MS triggered by increased core temperature); (c) receiving a prior diagnosis of schizophrenia, paranoid disorder, or bipolar disorder; (d) having active suicidal ideation; (e) having current alcohol dependence based on the substance dependence module of the SCID; and (f) being unable to complete forms without assistance. People on stable doses of antidepressant medications were not excluded in order to increase the generalizability of the findings and because we conceptualized physical activity as both a primary and adjunctive treatment for depression in this population. People with active suicidal intent or plan were contacted by a study psychologist for further assessment and referral for treatment, as needed.

Procedures

The institutional review board at the University of Washington approved the research study protocol. Potential participants eligible for the study at the initial telephone screening were invited to attend a baseline in-person visit at the medical center. Informed consent was obtained during this baseline visit prior to any further data collection. Participants were then asked to complete the self-report study measures. A research coordinator trained in administering the measures then administered the 7-Day Physical Activity Recall (7-Day PAR; Sallis et al., 1985), the Hamilton Rating Scale for Depression (HAM–D; Hamilton, 1960), and the SCID (First et al., 2001), The research coordinator (RW) was trained to conduct the SCID and HAM–D by an expert clinician rater and underwent repeated co-assessments with the expert until greater than 90% agreement was achieved at the item level for both instruments.

The randomization sequence was computer generated and blocked to yield equal allocation of every 50 participants without stratification. The first author prepared and sealed the opaque envelopes that contained condition assignments. Upon completion of the baseline assessment, participants met with the study counselor and underwent randomization. The study counselor would open the next consecutively numbered randomization envelope and inform the participant whether he or she was assigned to the intervention condition or the 3-month wait-list control condition.

Those randomized to the intervention condition immediately underwent an initial 40–60 min motivational interview and goal-setting session with the counselor. Those randomized to the control condition were informed that they would be contacted for a re-evaluation in 12 weeks and were then sent home. They were also informed that they would be provided the opportunity to receive the intervention after their 12-week outcome assessment.

For both groups, outcome assessments were conducted in person at the medical center by a trained research coordinator (RW) who was kept blind to participants' group assignments. Assessment of outcome variables occurred at baseline (before randomization), at 12 weeks postrandomization (primary outcome assessment point), and at 24 weeks postrandomization (assessment of maintenance effects for the active treatment group only).

Measures

Demographic and clinical variables. At the baseline visit, background information was obtained from all participants, including demographics (age, race, ethnicity, marital status, employment status, educational level), self-reported weight and height for body mass index (BMI) calculation, date of MS diagnosis, and current medications (types and doses). Neurological status was assessed with a self-administered version of the EDSS (Bowen, Gibbons, Gianas, & Kraft, 2001), which is highly correlated with a standard physician-administered EDSS.

Manipulation check measure. Since the intervention was designed to operate via increased physical activity, we used the 7-Day PAR interview to assess intensity and duration of physical activity at baseline and 12 weeks (Sallis et al., 1985). The PAR is a valid measure of physical activity in adults with MS (Motl, McAuley, Snook, & Scott, 2006). The number of minutes spent in light, moderate, hard, and very hard physical activities are obtained for the past 7 days, multiplied by their respective metabolic equivalent of task values and summed to produce total energy expenditure in kilocalories per kilogram per week (kcal/kg/week).

Primary outcome measure. The primary outcome measure was the HAM–D (Hamilton, 1960), a widely used, semistructured interview composed of 17 items that assess depressive symptom severity. It was used to assess clinically significant response to treatment, as defined by at least a 50% decrease in the total score. This criterion is the primary metric for defining a clinically significant response to treatment in pharmacotherapy trials (Agency for Health Care Policy and Research [AHCPR] Depression Guideline Panel, 1993). The proportion of participants scoring a 7 or less on the HAM–D was used as an indicator of depressive episode remission (Frank et al., 1991).

Secondary outcome measures. Three additional measures served as secondary outcome measures of depression. The SCID major depression and dysthymia modules were readministered at 12 weeks to determine what proportion of the participants still met *Diagnostic and Statistical Manual of Mental Disorders* (4th ed.; *DSM–IV;* American Psychiatric Association, 1994) criteria for major depression or dysthymia at the end of the trial. The Hopkins Symptom Checklist (SCL–20; Derogatis, Lipman, Rickels, Uhlenhuth, & Covi, 1974) is a depression severity measure commonly used in clinical trials that has good reliability and validity and is sensitive to change over time (Derogatis et al., 1974; O'Connor et al., 2010). It was used to measure self-reported depressive symptom severity. To measure affect, we used the Positive and Negative Affect Scale (PANAS), a 20-item measure with 10 positive and 10 negative affect descriptors (Watson, Clark, & Tellegen, 1988). The two scales have been shown to be highly internally consistent and

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largely uncorrelated, with excellent convergent and discriminant validity and good sensitivity to change.

Side effects. Increasing physical activity could theoretically exacerbate symptoms of MS. Therefore, we used the MS-Related Symptom Checklist (Gulick, 1989) to determine whether the intervention resulted in worsening of 22 different symptoms such as weakness, spasms, balance problems, frequent urination, vision problems, numbness, or pain.

Study Conditions

Intervention condition. The counseling approach was based on MI, a client-centered and directive method for enhancing intrinsic motivation to change by exploring and resolving ambivalence (Miller & Rollnick, 2002). Key techniques include asking open questions to elicit motivation to change and commitment to change as well as reflective listening to build understanding and rapport. Affirmations and summaries highlight successes and reiterate reasons or ability to change. The MI counseling process is conceptualized as two phases, building motivation to change followed by negotiating goals and action planning (Miller & Rollnick, 2002).

The thrust of the intervention was to use MI to promote incremental increases in home- or community-based physical activity or exercise. During the first, in-person session, patients worked with the counselor to develop an activity program tailored to the participant's daily life, abilities, access to resources, and motivation. In this session, the counselor provided feedback about the participant's baseline physical activity levels, explored his or her readiness to change physical activity levels and barriers to increased physical activity. Finally, if appropriate, the counselor negotiated specific, realistic physical activity goals with the participant at the end of the first session. Those who were unsure of what activities they would like to participate in were provided with a menu of options including stretching and range-of-motion exercises, strengthening exercises, aerobic exercises, athletic activities, and lifestyle physical activities. The counselor used goal attainment scaling (Kiresuk, Lund, & Larsen, 1982) to elicit from the participant the frequency and duration of planned physical activities at the most likely outcome level (0), more than expected level (+1), much more than expected (+2), less than expected (–1), and much less than expected (–2). Goals and plans were written by the participant to take home, with assistance from the counselor if needed. After the initial session, the counselor wrote a short letter to the participant that summarized the goals and plans agreed upon in the session. The letters affirmed the participant's strengths and motivation and expressed confidence in his or her abilities to successfully accomplish their goals.

The initial in-person session was followed by seven scheduled telephone counseling calls (Weeks 1, 2, 3, 4, 6, 8, and 10), each lasting about 30 min and a final in-person session lasting up to 60 min. All sessions were designed to promote motivation and commitment to the activity plan as well as monitoring progress toward goals, adjusting goals, and resolving barriers using the principles of MI. Participants were permitted self-initiated telephone contact with the counselor between sessions via a toll-free number. The counselor provided some direct assistance if desired by the participant, such as referrals to medical specialists, educational information, and resources such as Pilates or yoga videotapes for people to use on a trial basis. We used published resources to inform our advice regarding safe and effective MS-related exercise strategies (Petajan & White, 1999).

Training and fidelity. Three master's-level counselors delivered the intervention (two had a master's degree in social work and the other a master's degree in rehabilitation counseling). In preparation for the study, counselors completed a standard 2- to 3-day training program in MI and received additional training plus ongoing supervision from a clinical psychologist and experienced MI trainer (CHB). To assess MI treatment fidelity, we randomly selected 20% of the intervention sessions ($n = 65$) to be audio recorded and rated. Session recordings were coded by MI-trained staff and included behavior counts of key indicators of MI fidelity: open questions, closed questions, affirmations, reflections, and summaries as well as MI-inconsistent behaviors (arguing, confronting, and giving advice without permission; Miller & Rollnick, 2002). Subjective ratings were made of the therapist's MI spirit including warmth, understanding, and egalitarianism (from 1, *not at all,* to 7, *very much*). Overall occurrence of client-resistive behaviors was coded on the same 7-point scale. We report key indices of MI proficiency including percentage of open questions, reflections-to-questions ratio, frequency of MI-inconsistent behaviors, and ratings of MI spirit.

Control condition. The comparison group was defined as a wait-list control. Participants randomized to this group were offered treatment at the end of the 12-week trial. They were not provided with any specific depression treatments nor were they asked not to pursue depression treatment on their own during the 12-week trial.

Statistical Analyses

We conducted analyses using Stata Version 11 (StataCorp, 2009). Effectiveness of the randomization was assessed with Fisher's exact test for categorical variables and the Kruskal–Wallis test for continuous variables. The primary analyses were conducted under intention to treat (ITT). That is, the data were analyzed by the treatment group to which they had been assigned, whether they participated in or completed treatment. In addition, baseline values were carried forward for those missing posttreatment tests. This strategy was selected a priori but is an imperfect technique for addressing the impact of dropout, especially with differential dropout between treatment and wait-list control. To address this concern, we also estimated our HAM–D models using 20 multiple imputations for missing data. Our imputation model used baseline HAM–D score, physical activity, and antidepressant use. As an additional sensitivity analysis, we analyzed data using only the observed data. We evaluated intervention outcomes by the Wald test for the treatment indicator in a linear regression model, controlling for the preintervention score for that outcome.

Regarding power, the study was designed to randomize 108 participants and to have 80% power to detect a difference of at least 28 percentage points in the primary outcome (50% reduction in symptom severity) due to treatment ($\alpha = .05$, two-sided). With a final enrollment of 44 in treatment and 48 controls, we had approximately 30% power to detect the observed difference of 15 percentage points (34% and 19%, respectively) in the primary outcome and 80% power for a 0.59 *SD* difference in the secondary continuous outcomes. Among the completers, there was less than

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20% power for the observed difference of 13 percentage points in the primary outcome, and 80% power for a 0.63 *SD* difference in the secondary continuous outcomes.

Results

Participant Flow and Sample Characteristics

As depicted in Figure 1, 634 potential participants were screened, 276 declined to participate, 239 were excluded, and 119 consented. During the baseline assessment, an additional 13 persons were excluded because they did not meet *DSM–IV* criteria for MDD or dysthymia, and 14 were excluded because they were already meeting physical activity guidelines. Ninety-two participants were randomized: 44 into the treatment condition and 48 as wait-list controls. At 12 weeks, dropouts were greater in the control (19%) than in the treatment (5%) condition. At 24 weeks, maintenance data were obtained on 36 (82%) of those randomized to the treatment condition.

The average age of participants was 48 years old, and the range was 29 through 64 years. The majority of participants (74%) reported having been diagnosed with a relapsing–remitting subtype of MS, 14% had secondary progressive, 3% had primary progressive, 1% had progressive relapsing, 5% had unknown subtype, and 2% had missing subtype data. The participant sample was 86% female and 53% married or cohabiting; 49% had at least a 4-year college degree. Whites constituted 92% of the sample, 2% were Native American, and approximately 5% were African American, Hispanic/Latino, multiracial, or other. About two thirds of both groups were overweight or obese per BMI (69% in treatment, 63% in control).

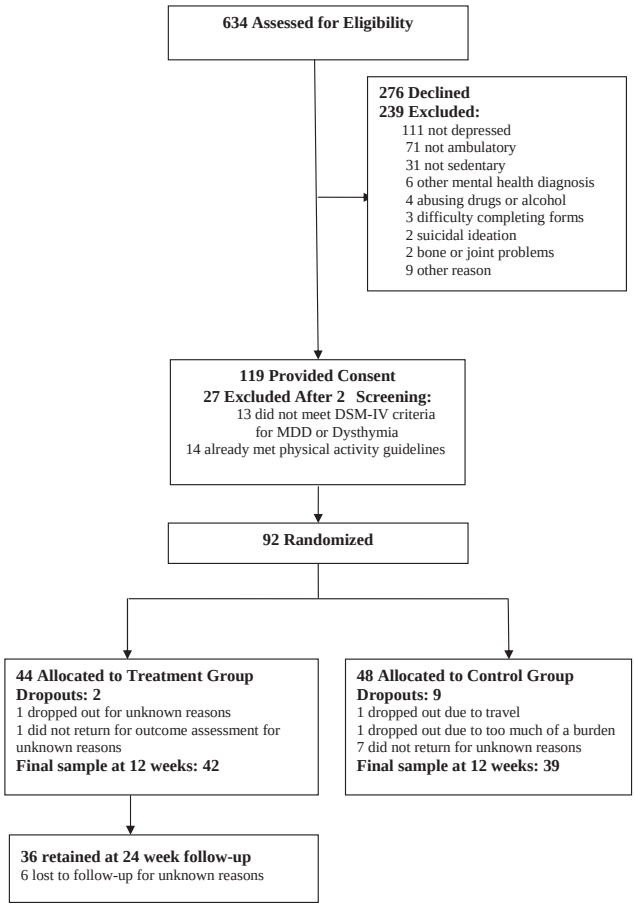


Figure 1. Participant flow through the study.

Randomization Effectiveness

We compared the two randomized groups on baseline characteristics to judge the effectiveness of the randomization (Table 1). The treatment and control groups did not differ on age, sex ratio, education, race/ethnicity, marital status, years since diagnosis, percentage with the relapsing–remitting type of MS, or BMI category. Groups also were equivalent on most of the outcome measures at baseline. However, the treatment group was observed to have significantly greater baseline depression severity on the HAM–D. Therefore, we conducted principal outcome analyses both controlling and not controlling for baseline HAM–D scores. Controlling for baseline HAM–D scores did not influence outcome analyses. Therefore, we present results without controlling for baseline HAM–D.

Manipulation Check

With baseline energy expenditure controlled, the treatment group reported significantly greater energy expenditure at 12 weeks than controls (see Table 2). However, the between-groups differences were modest. The physical activities most frequently reported were walking ($n = 38$), weight lifting ($n = 8$), yoga ($n = 7$), stationary bicycling ($n = 5$), swimming/water exercises ($n = 5$), and physical therapy ($n = 4$).

Primary Outcome

There was a nonsignificant trend toward a greater response rate in the treatment group compared with controls. Among the treatment group, 15 (34%) demonstrated at least a 50% decrease in HAM–D score from baseline to 12 weeks versus nine (19%) among the controls (Fisher's exact $p = .10$). There was no significant difference in remission rate (12-week HAM–D < 8) between the treatment group ($n = 13$; 30%) and the control group ($n = 11$; 23%). Based on the response rate, the number of persons who would need to be treated in order for one additional person to respond (NNT) compared with controls was 6.5. The NNT to have one more person remit was 15.1.

Secondary Outcomes

In contrast, when we examined the effects of the intervention using the HAM–D as a continuous measure, regression analyses showed that the intervention group reported a significantly lower posttreatment depression severity than did controls, after the baseline HAM–D was controlled (Table 2). Follow-up regressions showed that the effect of treatment condition was not confounded by age, sex, antidepressant use, baseline physical activity, or baseline MS-related symptoms. Mean change in HAM–D scores from baseline to posttreatment was –6.5 (*SD* 5.9) in the treatment group versus –1.1 (*SD* 5.5) among controls. The effect size was –1.2, a large effect according to Cohen (Cohen, 1988).

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Table 1
Baseline Characteristics and Effectiveness of Randomization

Baseline characteristic	Treatment (n = 44)		Control (n = 48)		Test[a]
	N (%)	Mean (*SD*)	N (%)	Mean (*SD*)	
Age (years)		47.1 (8.9)		49.7 (7.9)	$\chi^2(1) = 2.10$, $p = .15$
Female	39 (89)		40 (83)		$p = .56$
Education					$p = .61$
High school or less	10 (23)		9 (19)		
Community college	15 (34)		13 (27)		
Bachelor's degree or higher	19 (43)		26 (54)		
White (not Hispanic)	42 (95)		43 (90)		$p = .44$
Married or cohabitating	13 (30)		18 (38)		$p = .51$
Duration of multiple sclerosis		9.4 (7.1)		11.7 (8.3)	$\chi^2(1) = 1.75$, $p = .19$
Relapsing–remitting multiple sclerosis	32 (76)		36 (75)		$p = 1.00$
Body mass index category					$p = .64$
<25	13 (31)		18 (38)		
From 25 to <30	9 (21)		12 (25)		
30+	20 (48)		18 (38)		
7-Day PAR (kcal/kg/week)		223.5 (8.2)		222.6 (6.9)	$\chi^2(1) = 0.03$, $p = .84$
SCID					
Major depressive disorder	40 (91)		43 (90)		$p = 1.00$
Dysthymia	4 (9)		5 (10)		
HAM–D		17.7 (4.9)		15.5 (4.6)	$\chi^2(1) = 4.80$, $p = .03$
SCL–20		2.1 (0.6)		2.0 (0.5)	$\chi^2(1) = 0.70$, $p = .40$
Using antidepressants	22 (50)		17 (35)		$p = .21$
MS-Related Symptom Checklist		45.3 (18.0)		48.0 (14.4)	$\chi^2(1) = 0.18$, $p = .68$

Note. 7-Day PAR (kcal/kg/week) = 7-Day Physical Activity Recall (energy expenditure in kilocalories per kilogram per week); SCID = Structured Clinical Interview for *DSM–IV*; HAM–D = Hamilton Depression Rating Scale; SCL–20 = Hopkins Symptom Checklist; MS = multiple sclerosis.
[a] Fisher's exact test for categorical variables; Kruskal–Wallis for continuous variables.

Similar findings emerged from the self-report and diagnostic measures (see Table 2). Based on the SCL–20, participants in the treatment group reported significantly lower depression severity at the end of treatment compared with controls, after baseline values were controlled. Relative to control participants, those in the treated condition reported significantly greater positive affect and significantly less negative affect on the PANAS at the end of treatment. In the treatment group, a significantly larger fraction (59%) no longer met *DSM IV* criteria for MDD or dysthymia at the end of treatment versus 27% among controls (Fisher's exact p = .0029).

The foregoing analyses were based on intent to treat. We conducted a sensitivity analysis of only completers. The results were nearly identical and therefore are not shown. For both our primary outcome, a 50% reduction in HAM–D scores, and for a HAM–D score of less than 8, the differences were not statistically significant under ITT or a completers' analysis, and they remained nonsignificant under the multiple imputation model. For the HAM–D as a continuous outcome, the treatment effect was attenuated but still statistically significant, $t(88) = -2.78$, $p = .007$.

Maintenance of Treatment Effect

At 24 weeks, the participants in the treatment group maintained the same mean HAM–D score (11.4 ± 7.0) as they did at the end of treatment (10.6 ± 5.7) and remained as physically active, reporting average energy expenditure of 228.8 (9.1) kcal/kg/week at 24 weeks compared with 229.0 (10.1) kcal/kg/week at 12 weeks.

Table 2
Posttest Data Based on Intent to Treat

Outcome	Treatment (n = 44) Mean (*SD*)	Control (n = 48) Mean (*SD*)	Wald test[a]
7-Day PAR (kcal/kg/week)	228.5 (9.9)	224.4 (9.2)	$t(88) = 2.29$, $p = .0245$
HAM–D	11.2 (6.2)	14.2 (6.6)	$t(88) = -3.99$, $p = .0001$
SCL–20	27.6 (15.8)	35.2 (13.8)	$t(89) = -3.17$, $p = .0021$
PANAS Positive Affect	28.4 (9.2)	24.5 (6.6)	$t(89) = 3.35$, $p = .0012$
PANAS Negative Affect	20.1 (8.0)	23.6 (7.4)	$t(89) = -3.84$, $p = .0002$
MS-Related Symptom Checklist	36.2 (18.5)	45.3 (16.9)	$t(89) = -2.62$, $p = .0104$

Note. 7-Day PAR (kcal/kg/week) = 7-Day Physical Activity Recall (energy expenditure in kilocalories per kilogram per week); HAM–D = Hamilton Depression Rating Scale; SCL–20 = Hopkins Symptom Checklist; PANAS = Positive and Negative Affect Schedule.
[a] Wald test for treatment in a linear regression model controlling for the preintervention score for that outcome.

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Side Effects

The two groups were compared on MS-related side effects at the end of the trial to determine whether participating in a self-directed physical activity program caused symptoms to worsen. Those in the treatment group reported significantly less MS-related side effects compared with controls, after baseline MS-related symptoms were controlled (Table 2).

Physical Activity as a Mediator of Depression Improvement

Change in HAM–D and change in energy expenditure (kcal/kg/week) were modestly positively correlated ($\rho = -0.28$; $p = .009$). However, controlling for change in energy expenditure, the treatment effect would be –4.2 points with no change in kcal/kg/week, and −4.8 points with a 4-point change in kcal/kg/week. Change in kcal/kg/week was not statistically significant in this model.

Treatment Fidelity and Dose

Overall fidelity to MI-consistent behaviors and spirit was good—72% of questions were open rather than closed, and the ratio of reflections to questions was 2.9:1. Both of these indices exceeded standards for MI competency (Moyers, Martin, Manuel, & Miller, n.d.). The mean (SD) frequency of observed therapist behaviors that were MI inconsistent was 0.26 (0.57) per session. The mean (SD) frequency of observed client-resistive behavior was similarly rare, 0.28 (0.76) occurrences per session. Ratings of MI spirit were satisfactory (means 5.73–5.88; range 4–7). The average number of sessions completed was 6.9 (1.7), and 86.4% of the participants received at least six sessions. The average (SD) time spent in counseling sessions was 138 (59) minutes.

Discussion

The results of this study represent a novel and promising approach to depression treatment in people with MS. Our primary hypothesis was that the intervention group would demonstrate a significantly greater treatment response rate (at least a 50% reduction in initial depression severity) compared with the wait-list control group. Although the intervention did not meet this rigorous test of clinical significance, when the HAM–D was analyzed as a continuous measure, the experimental group was observed to have significantly lower postintervention depression severity than the wait-list controls. This statistically significant treatment effect was confirmed with the postintervention SCL–20, a self-report measure of depression severity. Additionally, a significantly greater percentage of the treatment group no longer met criteria for major depression or dysthymia after treatment (59% vs. 27% in the control group). The treatment effect was sustained through 12 weeks after the end of treatment. The effect of the intervention was not confounded by age, sex, antidepressant use, baseline level of physical activity, or baseline MS symptoms. The effect-size was large (–1.2), and the number needed to treat to achieve one additional response was 6.5. Finally, the effect size achieved in this study compares favorably with the average effect size reported in meta-analyses of cognitive–behavioral therapy for depression (0.87; Gloaguen, Cottraux, Cucherat, & Blackburn, 1998) and exercise for depression (0.40–0.82; Krogh, Nordentoft, Sterne, & Lawlor, 2011; Mead et al., 2009), though the response rate, remission rate, and magnitude of change in HAM–D scores are somewhat modest compared with those in randomized controlled trials of other forms of treatment for major depression in people with MS (see Table 3). Follow-up studies are needed to replicate these findings to compare the intervention to more rigorous control conditions and determine which persons are most likely to benefit from this approach. Research should also investigate the longer term outcomes of physical activity interventions as well as how to implement this type of intervention into standard practice.

The use of telephone delivery and physical activity as a treatment for depression has several advantages in this population where undertreatment of depression is the norm (Feinstein, 2002; Mohr et al., 2006). Telephone-delivered interventions can help overcome common barriers to depression treatment such as geographic distance, transportation, inconvenience, time requirements, stigma, and fear of embarrassment (Collins et al., 2004). Based on our prior survey data (Blake et al., 2002) as well as evidence from this study demonstrating no adverse effects, low dropout rate (4.5%), and high treatment adherence, the intervention appears safe, acceptable, tolerable, and feasible. Physical activity interventions are especially compelling in people with MS because of the potential to generate other health benefits (Petajan et al., 1996). Nearly half of the participants were already on antidepressant medications, and the effect of the intervention on depression severity remained significant when we controlled for medication status. Therefore, the intervention could be used alone or as a means of augmenting standard antidepressant treatment (Trivedi et al., 2011). Our finding of significantly lower MS-related symptoms (side effects) in the treatment condition versus the control condition is consistent with the general health benefits of physical activity in this population (Petajan et al., 1996). Although we did not perform a formal cost analysis, the intervention is efficient, requiring an average of 138 min of counselor contact time. Assuming a cost of $50 per hour for a master's-level clinician, the cost of the intervention would be approximately $115 per subject and up to $275 for those who received the maximum dose planned. Consequently, interventions of this type may have greater potential for adoption in real-world settings compared with typical interventions that are in person, clinic based, and resource intensive. Comparative research is needed into the cost-effectiveness of in-person versus telephone and physical activity versus other standard interventions for depression in people with MS.

While the results of this study require replication, we can describe some of the potential clinical implications and suggestions for future research. Training in MI was required to implement this intervention, but neither the therapists nor the supervisor had training in exercise science. Participants typically had experience with exercise regimens or other types of physical activity that were safe and feasible for them to engage in. In this study, master's-level counselors delivered the intervention under the supervision of a psychologist with expertise in MS and MI. Whether the intervention could be carried out successfully by others (e.g., nurses, physical therapists, or paraprofessionals) or without the use of MI or without expert supervision is uncertain pending further research. Telephone-based interventions overcome numerous barriers to treatment, especially for persons with disabilities. How-

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Table 3
Randomized Controlled Treatment Trials for Major Depression in People With Multiple Sclerosis

Author (year)	Treatment condition	Pre–HAM–D score	Post–HAM–D score	Change in HAM–D score	Response rate (%)	Remission rate (%)	No longer met MDD criteria (%)	Comments
Mohr et al., 2001	CBT (n = 20)	21.0	12.4	−8.6	50		40	16-week treatment; quasi-random assignment; raters not masked to group assignment. Drop-out rates: 5% in CBT, 29% in sertraline, & 18% in SEG.
	Sertraline (n = 21)	20.5	13.9	−6.6	24		38	
	SEG (n = 22)	20.5	15.7	−4.8	14		9	
Mohr et al. (2005)	TCBT (n = 62)	21.3	12.0	−9.3			87[a]	Only 69%–72% of participants had MDD at baseline.[a] The treatment phase was 16 weeks. Both groups improved significantly with greater improvement on the HAM–D and % with MDD among TCBT vs. EFT. Drop-out rate: 5% in TCBT & 6% in EFT.
	EFT (n = 65)	21.7	14.8	−6.9			71[a]	
Ehde et al., (2008)	Paroxetine (n = 22)	17.2	9.4	−7.8	57	48	87	Nonsignificant differences between treatment groups on all outcomes by ITT; nonsignificant trend for completers on paroxetine to have a higher response rate than those on placebo (78.6% vs. 42.1%). Drop-out rate: 23% in paroxetine group & 0 in control group.
	Placebo (n = 20)	19.0	11.4	−7.6	40	25	74	
Current study	TELEPAC (n = 44)	17.7	11.2	−6.5	38	30	59	12-week treatment phase; individualized home-based physical activity program. Drop-out rate: 5% in TELE & 19% in WLC.
	WLC (n = 48)	15.5	14.2	−1.3	21	23	27	

Note. HAM–D = Hamilton Depression Rating Scale; MDD = major depressive disorder; CBT = cognitive–behavior therapy; SEG = supportive expressive group; TCBT = telephone CBT; EFT = emotion-focused therapy; ITT = intent to treat; TELEPAC = telephone-based physical activity counseling; WLC = wait-list control.
[a] All analyses based on intent-to-treat.

ever, telephone counseling is also fraught with questions about confidentiality, professional liability, safety, and reimbursement—questions that are important to consider prior to implementation but are beyond the scope of this article.

Several limitations of the study should be discussed. The study included people with MS who were able to ambulate, had mild to moderate major depression, and did not report suicidal ideation with intent or plan. Therefore, the appropriateness of this intervention for people with greater MS-related disability, more severe depression, or increased suicidal risk is uncertain. We utilized only one subjective measure of physical activity. Although self-report measures of physical activity have been found to be valid in people with MS (Motl et al., 2006), future research should use objective measures of physical activity such as accelerometers to complement self-report measures.

The effect of the intervention on physical activity was weak. At the end of the trial, no one reported enough physical activity to meet public health guidelines—that is, at least 450 kcal/kg/week, which corresponds to about 30 min of moderately intense physical activity at least 5 days per week or 20 min of vigorous physical activity at least 3 days per week (Haskell et al., 2007). Prior research indicates that there is a dose–response relationship between the intensity and duration of physical activity and recovery from depression (Dunn, Trivedi, Kampert, Clark, & Chambliss, 2005). As a result, the effects of this type of intervention on depression may be more powerful if the telephone counseling is designed to achieve physical activity frequency, intensity, and duration that meet public health guidelines. When this trial was designed, no clear evidence for a dose–response relationship existed, and participants were simply counseled to become more active. Given our present knowledge, it may be useful to include dose–response information in the context of the MI. In addition, it may be more effective to focus the MI on having the participant choose from several evidence-based strategies for becoming more physically active such as goal setting, self-monitoring, contracting, cuing, and using self-rewards (Conn, Hafdahl, Brown, & Brown, 2008). In this trial, master's-level counselors delivered the intervention. It is not known if this intervention would have been more effective in increasing physical activity if the intervention had been delivered by interventionists with more expertise in physical activity, such as physical therapists. Future research could utilize counselors with formal training in exercise physiology, physical therapy, or related disciplines.

Certain weaknesses in the study design should be addressed in future research. The study design did not include an attention control group. Therefore, we are unable to determine the degree to which the effects of the intervention on physical activity and depression severity are attributable to the nonspecific effects of therapist attention or the specific effects of the counseling employed. The control group was offered the intervention after the 12-week assessment; therefore, we are not able to compare outcomes between the two groups at 24 weeks. Randomization allocation via numbered, sealed envelopes can be subverted. Randomization by other methods such as via e-mail from the study biostatistician should be considered. We relied on a valid self-report to measure of physical activity, whereas future studies should consider combining both self-report and objective data (e.g., accelerometer recordings) to produce a more valid estimate of community-based physical activity (Motl et al., 2006).

There was no evidence to support the hypothesized mechanism of action. Increased physical activity did not mediate the effect of the intervention on depression severity. We suspect that this may be due to the limited gains subjects made in physical activity overall. However, there are numerous pathways by which a physical activity intervention could impact depression severity (Brosse et al., 2002). Exercise is thought to increase monoamine levels and levels of their precursor molecules. Exercise is also associated with a dampening of the hypothalamic–pituitary–adrenal axis response to stress. Exercise may improve depression-related self-evaluations such as self-esteem, self-efficacy, body image, and self-worth. Exercise may represent a form of behavioral activation. Exercise may interrupt rumination and provide distraction from negative emotions. Future research should include an examination of these and other potential exercise-related mediator variables to provide direction for subsequent intervention research.

The use of the HAM–D merits discussion. While the HAM–D remains the most widely used primary outcome measure for depression trials, its status as the "gold standard" has been challenged on psychometric grounds (Bagby, Ryder, Schuller, & Marshall, 2004). The HAM–D is considered adequate in terms of traditional psychometric properties (internal consistency, reliability, and convergent and discriminant validity), but it is not unidimensional, and it contains items relatively insensitive to change (Bagby et al., 2004). Rasch analysis has been used to identify shorter, unidimensional item subsets that are sensitive to change (Ruhé, Dekker, Peen, Holman, & de Jonghe, 2005). However, these measures do not include all *DSM–IV* symptoms of depression, and using one would limit the comparability of this study to other similar trials. Finally, our use of a 50% reduction in the HAM–D as the primary outcome may have been overly conservative given that the trial represented an augmentation intervention for 50% of the intervention group and 35% of the control group.

In conclusion, the results of this study extend previous research in at least two important ways. First, this study demonstrates that the antidepressant effects of physical-activity-based interventions may be generalizable to people who have major depression in the context of MS. In fact, people with MS may represent a particularly promising group in which to study physical activity and depression because factors related to depression such as inactivity and fatigue are especially common in this disease group (White & Dressendorfer, 2004). MS-related fatigue and inactivity can create a downward spiral of deconditioning, greater fatigue, and lower activity potentially contributing to the high prevalence of major depression in this population. Therefore, physical activity may be an especially effective way of reversing these dysfunctional trends and improving overall functioning in this population. Second, the study suggests that telephone counseling based on MI may have potential as a means of delivering physical activity promotion interventions in people with MS. Telephone-delivered interventions like this one could overcome some of the barriers to specialty care faced by people with MS and extend the benefits of increased physical activity to a larger fraction of the population with MS.

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