

Two Sides of the Same Coin: A Randomized Clinical Trial of the Unified Protocol for Addressing Depression and Anxiety in People With Multiple Sclerosis

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ABSTRACT

BACKGROUND: Depression and anxiety are common in people with multiple sclerosis (MS) and significantly impact disease symptomatology, coping, quality of life (QOL), and psychological well-being (PWB). Effective treatment of both is warranted and may be accomplished using a transdiagnostic intervention such as the Unified Protocol (UP). The purpose of this study was to conduct a pilot randomized controlled trial (Clinical Trials # NCT05953519) to determine the effectiveness of the UP in reducing depression and anxiety and the subsequent impact on MS symptomatology, coping, QOL, and PWB.

METHODS: Thirty people with MS and depression and/or anxiety were randomly assigned to a UP intervention (n = 12) or a control group (n = 18). Individuals in the intervention group completed a 12-week group virtual intervention. All completed baseline, posttreatment, and 3-month follow-up assessments. All study procedures were approved by the Kessler Foundation Institutional Review Board.

RESULTS: Following the intervention, significant reductions in depression, experiential avoidance, and fatigue were observed. Participants also demonstrated improvements in self-efficacy, coping (eg, benefit finding, social support), QOL (eg, flourishing), and PWB (eg, acceptance). These effects were maintained at the 3-month follow-up.

CONCLUSIONS: The UP intervention holds great promise in reducing mood symptoms in people with MS, as well as fatigue, one of the most detrimental symptoms associated with MS. The impact on coping, QOL, and PWB also suggests greater, long-standing effects on perspective, reframing, and coping, which are likely to have a greater impact overall for individuals with MS.

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Rates of emotional disorders (EDs) are high among people with multiple sclerosis (MS).¹⁻⁴ Both depression and anxiety impact individuals' MS symptoms (eg, fatigue), adherence, medical management, quality of life (QOL), and suicidal ideation.^{3, 5-12} Despite this, they often go untreated, and when treated, the focus is primarily on depression. Evidence for treating depression in MS is modest at best. A meta-analysis on cognitive behavioral therapy (CBT) interventions found moderate reductions when compared with treatment as usual.¹³ Subsequent meta-analysis in 2016 suggested that treatments were moderately effective when compared with an inactive comparator but not effective when compared with an active comparator. No improvement was found in 3 interventions that also assessed anxiety and in findings from an injection phobia study.¹⁴

In 2018, *Multiple Sclerosis Journal* published a Controversies in Multiple Sclerosis article that questioned whether anxiety was more important than depression in MS. Proponents for “no” contended that depression has long been “intertwined with the characteristics of the disease” and a known factor in worsening MS symptoms, poor QOL and disease management, and increased suicidal ideation.¹⁵ The counterargument to this was that anxiety, despite being less studied, is very common, with a large registry sample (N = 7786) reporting 54% incidence and evidence that anxiety has the same impact as depression.¹⁶

A 2019 study looked into the impact further and suggested that depression should take priority as it was associated with higher disability and lower employment.¹⁷ A year later, the lead author conducted a similar investigation and found anxiety to have a greater impact on MS symptomatology, well-being, and QOL.¹⁸ Previous investigations also suggested greater effects for anxiety with regard to being at risk for unemployment¹⁹ and having lower QOL early in the disease process.²⁰ This author and others have continued to recommend that attention should be paid to the role of anxiety in MS.^{16, 21} Given this, we sought to assess the Unified Protocol for the Transdiagnostic Treatment of Emotional Disorders (UP) that addresses both depression and anxiety for use in MS.

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PRACTICE POINTS



Depression and anxiety are highly prevalent among people with multiple sclerosis (MS) and detrimental to their health and well-being.

Transdiagnostic interventions, such as the Unified Protocol (UP), address both depression and anxiety and focus on the shared temperamental core of psychological disorders, which have been shown to impact functional outcomes as well.

Thus, the UP may hold great promise for not only treating emotional disorders but also improving symptoms, coping, psychological well-being, and quality of life of people with MS. ■

The UP is a contemporary CBT transdiagnostic treatment that targets the shared temperamental core of psychological disorders and is meant to help anyone struggling with managing their emotions, regardless of diagnosis.²² The focus on shared etiology and maintenance features is informed by advancements in psychopathology and emotion science²³⁻²⁵ and stands in slight contrast to traditional CBT protocols that tend to focus on a single domain or manifest symptoms.²⁶ The intervention can be conducted individually or in a group,^{27,28} typically over 12 weeks. It consists of 8 modules, of which 5 core modules address the fundamental components of CBT aimed at identifying one's emotional experiences and adverse reactions to them, namely thoughts, feelings (physical sensations), and behaviors. Two introductory sessions are aimed at understanding and tracking participants' emotions, reviewing participants' symptoms and how they interfere with daily life, providing a treatment rationale, enhancing motivation, and setting goals. From this, core modules are provided in sequential order. Following this, participants are encouraged to put what they have learned into practice and face their emotions while tracking their experiences in more objective ways. Finally, the last module consists of relapse prevention.²⁹

A meta-analysis in 2019 found large effect sizes for UP in reducing depression and anxiety,³⁰ and it has also been shown to result in improvements in transdiagnostic psychological symptoms, such as decreases in neuroticism and emotion or behavioral avoidance as well as increased positive affectivity and functional outcomes, including improvements in QOL and work functioning among the general population.³¹⁻³³ A meta-analysis of individuals with a medical condition found large effects as well.³⁴ Two of

these studies consisted of trials among people with MS^{35,36} in which significantly large effect sizes for decreasing depression and anxiety were found. Given this, we conducted a pilot randomized controlled trial (RCT) aimed at replicating this as well as examining other outcomes (eg, disease symptoms, coping) that are strongly associated with depression and anxiety in MS.

METHODS

The study was registered with ClinicalTrials.gov (NCT05953519), and all study methods and results are consistent with the Consolidated Standards of Reporting Trials guidelines.

Participants

Participants underwent screening for depression and anxiety. Inclusion criteria consisted of significant depression on the Beck Depression Inventory-Second Edition (cutoff score of 20 or higher)³⁷ and/or anxiety on the State-Trait Anxiety Inventory (cutoff of 1.25 SD above normative means),³⁸ a definitive diagnosis of MS, 18 years and older, English speaker, ability to provide informed consent, and access to the internet. The exclusion criteria were a history of any other neurological illness, current participation in another RCT, cognitive impairment that would affect the ability to fully participate in the group, inability to attend group sessions, and active participation in another formal clinical group or psychological therapy. Given the large effects previously found with the UP, a power analysis suggested that a sample size of 20 would be sufficient in order to obtain a power of 80% when utilizing a repeated-measures analysis of variance (ANOVA). It has also been suggested that a general rule of thumb for a pilot RCT is 12 participants per arm.³⁹ Given this, we sought a sample of 24. A total of 69 individuals were screened for the study, and 35 met the inclusion criteria (FIGURE 1).

Measures

Primary Outcomes

The Hospital Anxiety and Depression Scale⁴⁰ instrument was designed to measure anxiety and depression in a general medical population and is commonly used in MS.^{41,42} It consists of 14 items rated on a 4-point Likert scale. A cutoff of 8 has been suggested for the presence of minor depression or anxiety.⁴³ Cronbach α was 0.84 for anxiety and 0.64 for depression in the current sample.

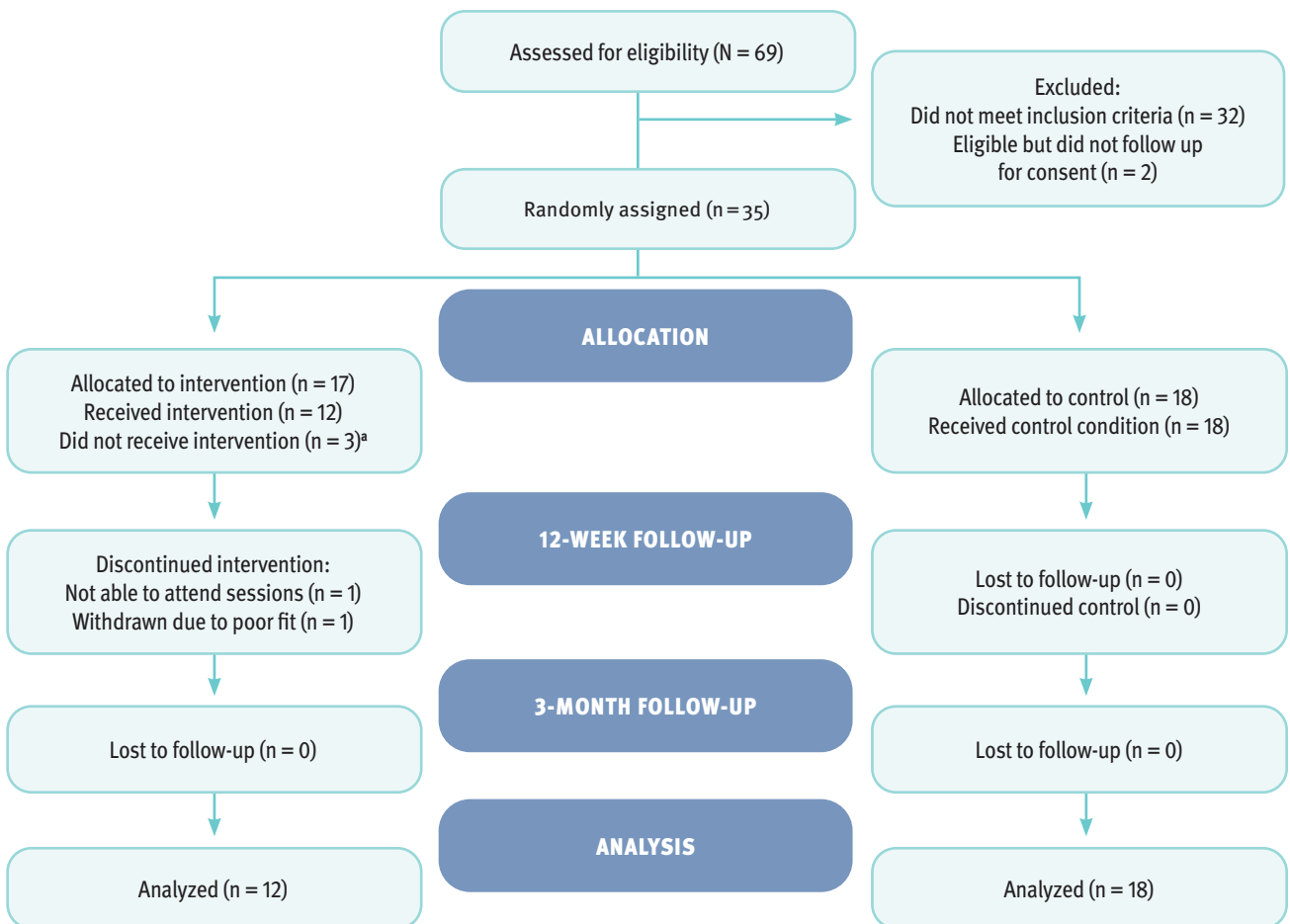
Positive and negative emotions were assessed by the Positive and Negative Affect Schedule,⁴⁴ a 20-item questionnaire rated on a 5-point Likert scale. It has also been used as a primary outcome measure in previous investigations of the UP among individuals with MS.^{35,36} Cronbach α was 0.85 for both the positive and negative subscales.

The Brief Experiential Avoidance Questionnaire⁴⁵ is a 15-item questionnaire rated on a 6-point Likert scale and is comprised of 6 subscales assessing experiential avoidance: behavioral avoidance, distress aversion, procrastination, distraction/suppression, repression/denial, and distress endurance. Cronbach α was 0.79.

Secondary Outcomes

Secondary outcomes consisted of 5 domains of interest to determine whether the UP intervention would have an impact. These

FIGURE 1. CONSORT Diagram for Unified Protocol Intervention



CONSORT, Consolidated Standards of Reporting Trials.

^aReasons: did not complete baseline assessment, n = 1; lost to follow-up before intervention started, n = 2.

included MS symptomatology, self-efficacy, coping, psychological well-being, and QOL.

The Modified Fatigue Impact Scale⁴⁶ consists of 21 items rated on a 5-point Likert scale. Its 3 subscales evaluate physical, cognitive, and psychosocial functioning. It was developed specifically for use in MS. For brevity, only the physical fatigue subscale was used. Cronbach α was 0.88.

The Pittsburgh Sleep Quality Index⁴⁷ ascertains sleep quality. The scale has 24 items rated by the individual and 5 items rated by a bed partner. Cronbach α was 0.66.

The Medical Outcomes Study Pain Effects Scale⁴⁸ assesses the experience and impact of pain and consists of 6 items rated on a 5-point Likert scale. The scale is part of the MS Quality of Life-54 inventory and validated for use in MS.⁴⁸ Cronbach α was 0.88.

The General Self-Efficacy Scale is a 10-item scale rated on a 4-point Likert scale and assesses perceived self-efficacy in coping with daily hassles and adaptation after experiencing stressful life events. Cronbach α was 0.84.

MS-specific self-efficacy was assessed by the University of Washington Self-Efficacy Scale, a measure made specifically for

individuals with MS.⁴⁹ The scale consists of 19 items rated on a 5-point Likert scale. Cronbach α was 0.93.

The Coping Orientation to Problems Experienced (COPE) Inventory⁵⁰ assesses different ways individuals respond to stress. It consists of 5 scales to measure problem-focused coping (active coping, planning, suppression of competing activities, restraint coping, seeking of instrumental social support) and 5 scales to measure emotion-focused coping (seeking of emotional social support, positive reinterpretation, acceptance, denial, turning to religion) as well as 3 less adaptive coping styles (focus on and venting of emotions, behavioral disengagement, mental disengagement). Three items measure alcohol and drug use, and 4 items assess the use of humor. Items are rated on a 4-point Likert scale. The majority (11 of 15) of the subscales had a Cronbach α of 0.70 or higher, with the highest being 0.98 for substance use. However, 4 subscales had α ranging from 0.27 to 0.60, with mental disengagement being the lowest, consistent with previous findings.⁵⁰

The Benefit Finding in Multiple Sclerosis Scale⁵¹ was developed to measure the perceived benefit of having MS. It consists

TABLE 1. Unified Protocol

	Session content	Assignments
Week 1: Introduction	Understanding emotional disorders and the importance of recording one's emotions	Progress record
Week 2: Module 1	Maintaining motivation and setting goals for treatment	Treatment goals and decisional balance
Week 3: Module 2	Understanding emotions and recognizing and tracking emotional responses	Three-component model and following your arc
Week 4: Module 3	Learning to observe your emotions and your reactions	Mindful emotion awareness form
Week 5: Module 4	Understanding thoughts	Practicing cognitive flexibility and downward arrow form
Week 6: Module 5	Understanding behaviors and avoiding your emotions and emotion-driven behaviors	Emotion-driven action tendencies, list of emotional behaviors form, and countering emotional behaviors form
Week 7: Module 6	Understanding and confronting physical sensations	Physical sensation test exercises and physical sensation test form
Week 8: Module 7	Putting it into practice: facing your emotions in the situations in which they occur	Emotion exposure hierarchy form and record of emotion exposure practice form
Weeks 9-11: Module 7	More putting it into practice	Week 11: Progress evaluation
Week 12: Module 8	Moving on from here: recognizing your accomplishments and looking to your future	Practice plan

Note: Modules in bold are core modules.

of 43 items rated on a 3-point Likert scale and is divided into 7 subscales: compassion/empathy, spiritual growth, mindfulness, new opportunities, lifestyle gains, family relations growth, and personal growth. Cronbach α was 0.94.

Resilience was assessed by the University of Washington Resilience Scale, which was developed for adults with chronic conditions and disabilities such as MS.⁵² It consists of 28 items rated on a 5-point Likert scale. Cronbach α was 0.88.

The Ryff Psychological Well-Being Scales were developed for the general population and consist of 6 subscales: positive relationships, autonomy, personal growth, purpose in life, environmental mastery, and self-acceptance.⁵³ Each subscale consists of 14 items rated on a 6-point Likert scale. Cronbach α ranged from 0.74 to 0.92, with all but one being 0.85 or higher.

Quality of life was assessed by the Satisfaction With Life Scale⁵⁴ and the Flourishing Scale.⁵⁵ Both are rated on a 7-point Likert scale. The first is a brief, 5-item measure assessing one's global cognitive judgment of satisfaction with one's life. It has been validated in many healthy and chronically ill populations.⁵⁶ Cronbach α was 0.90. The latter is an 8-item scale and measures perceived success in important areas of life such as relationships, self-esteem, purpose, and optimism. Cronbach α was 0.86.

Procedures

The study was a single-blind, parallel RCT completed over 3 study cohorts from May 2023 to August 2024. All procedures were approved by the Kessler Foundation Institutional Review Board, and informed consent was obtained from all participants.

Using a computer-generated sequence, participants were randomly assigned to either the intervention or control condition. Assessors were blinded to the participants' assignments. Participants in the UP intervention completed a 12-week, virtual group UP intervention and attended one 90-minute session per week via Zoom Health. Prior to weeks 3 and 12, participants met with the facilitator for an individual 30- to 45-minute session to discuss personal treatment goals. All sessions were facilitated following the UP manual, and treatment fidelity was assessed by a UP expert trainer (J.B.). Between sessions, participants were asked to complete the Overall Anxiety Severity and Impairment Scale, the Overall Depression Severity and Impairment Scale, the Positive Emotion Scale, and the Other Emotion Scale as well as a series of assignments that reflected on their weekly experiences and applied session content (TABLE 1).

The control condition received treatment as usual. All participants completed an online survey after the initial 12 weeks and again at 3 months.

To examine between-group differences, we tested a series of repeated-measure ANOVAs. We elected not to apply an α adjustment for multiple comparisons given the pilot nature of this RCT and its associated small sample size. In addition to model parameters, we report η^2 effect sizes, where values of approximately 0.01 are interpreted as small effects, values of approximately 0.06 are interpreted as medium effects, and values of approximately 0.14 or higher are interpreted as large effects.⁵⁷ With the exception of the COPE substance use subscale (kurtosis=7.77), all variables met normality assumptions.⁵⁸ In addition to

TABLE 2. Group Characteristics

	Treatment (n = 12) ^a	Control (n = 18) ^a	t or χ^2
Age, y (range, 22-67)	48.08 (12.94)	46.89 (11.60)	$t_{(28)} = -.264$ to .794
Sex	2M/10F	1M/17F	$\chi^2 = .988$, .320
Education, y (range, 12-20)	14.50 (2.11)	15.89 (2.32)	$t_{(28)} = 1.66$, .108
Disease course	11 RR/1 PROG	12 RR/6 PROG	$\chi^2 = 2.52$, .113
Disease duration, y (range, 1-36)	10.67 (8.99)	17.17 (11.04)	$t_{(28)} = 1.70$, .101
HADS depression	9.42 (1.88)	9.67 (3.69)	$t_{(28)} = .216$, .831
HADS anxiety	11.75 (6.17)	11.28 (3.63)	$t_{(28)} = -.265$ to .793
Ever therapy for depression	9 (75%)	14 (78%)	$\chi^2 = .031$, .860
Ever therapy for anxiety	7 (58%)	10 (56%)	$\chi^2 = .023$, .880
Ever medication for depression	11 (92%)	11 (61%)	$\chi^2 = 3.44$, .064
Ever medication for anxiety	7 (58%)	9 (50%)	$\chi^2 = .201$, .654

HADS, Hospital Anxiety and Depression Scale; PROG, progressive multiple sclerosis; RR, relapsing-remitting multiple sclerosis.

^aData is mean (SD) or frequency.

repeated-measure ANOVAs, we descriptively examined rates of clinical elevation in depression and anxiety within and between groups up to the 3-month follow-up, based on the established cut-offs on the Hospital Anxiety and Depression Scale.

RESULTS

Thirty people with MS who met the criteria for depression (n = 3), anxiety (n = 2), or Comorbid Anxiety Disorder (n = 25) were randomly assigned into the treatment (n = 12) or control condition (n = 18). There were no differences between the 2 groups on age, sex, education, disease course, disease duration, or severity of depression or anxiety. There were no differences in past treatment for depression or anxiety (TABLE 2).

The treatment group experienced significant reductions in depression and experiential avoidance immediately following the 12-week intervention and at the 3-month follow-up. Significant reductions in fatigue and improvements in general self-efficacy, environmental mastery, coping (ie, benefit finding and instrumental social support), QOL (ie, flourishing), and psychological well-being (PWB; ie, positive relationships with others and self-acceptance) were also observed (TABLE S1, FIGURE 2). No significant effects were found for anxiety, positive or negative affect, sleep disturbance, pain, or MS self-efficacy.

The rates of clinically significant depression and anxiety were more significantly reduced in the treatment group than in the control group. Prior to treatment, the rates for depression were 72% and 83% for the control and treatment groups, respectively. Immediately following the UP intervention, the treatment group rate sharply declined to 8% and then rose slightly to 33% at the 3-month follow-up. In contrast, the rate of depression among the control group remained steady (67%; FIGURE S1). Rates of clinically elevated anxiety demonstrated a similar pattern, with rates at baseline of 83% and 67% for the control and the treatment groups, respectively. In the treatment group, rates of anxiety decreased slightly to 58% immediately following the intervention

and then decreased even more to 33% at the 3-month follow-up. For the control group, the rate of anxiety was 56% at the 12-week survey and 67% at the 3-month follow-up (FIGURE S2).

DISCUSSION

The primary outcome of this study was whether the UP affected rates of anxiety and depression among people with MS. Our secondary outcomes, perhaps the more important part of our work, were its effects on MS symptoms, coping, PWB, and QOL.

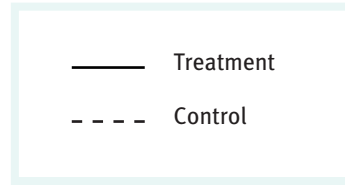
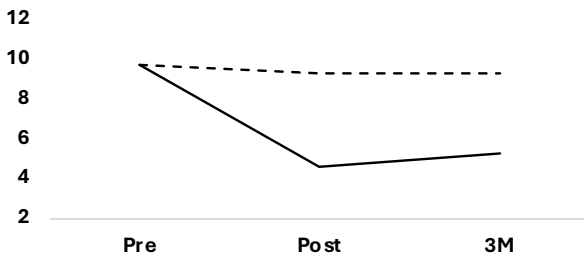
Individuals in the treatment group demonstrated improvements in depressive symptoms, experiential avoidance, fatigue, PWB, QOL, and coping. Consistent with empirical support for the durability of UP effects in general mental health contexts,²⁶ these effects were maintained over a 3-month period. Effects were greatest ($\eta^2 \geq 0.14$) for depression, fatigue, aspects of coping and PWB, and experiential avoidance.

The observed effects for depression are consistent with previous findings of the UP among people with MS. The consistency in such significant effects is extremely promising, particularly considering previous suggestions that treatment of depression in MS is modest at best. Further evaluation of the effectiveness of UP in ameliorating depression in MS when compared with active comparator treatment is warranted and the next logical step.

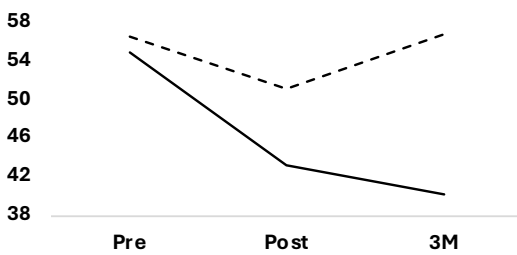
The finding that fatigue was greatly reduced following participation in the UP intervention is consistent with the assertion that MS symptoms are greatly worsened by depression and anxiety. MS-related fatigue is construed as primary or secondary. Although the former is related to the centrally mediated process of the disease, secondary fatigue is attributed to a host of factors that accompany MS (eg, depression, sleep disturbance, medication adverse effects).⁵⁹ Provided this, it has been proposed and shown that treatment of these factors results in reductions in fatigue.^{6,60} This was certainly the case following the UP intervention. The associated improvement in fatigue may also be attributed to the improvements in self-efficacy. Previously, reductions

FIGURE 2. Changes in Participant Outcomes

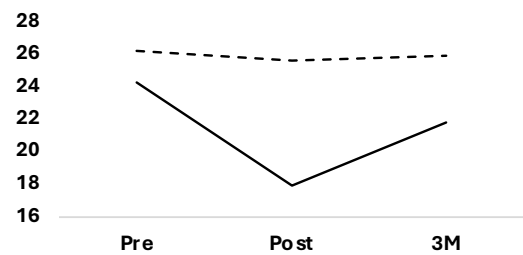
Depression



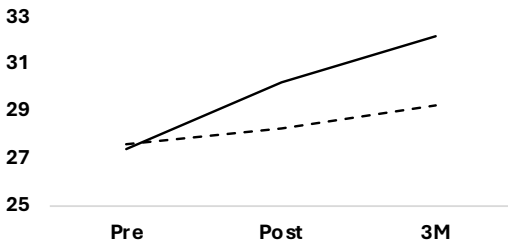
Experiential avoidance



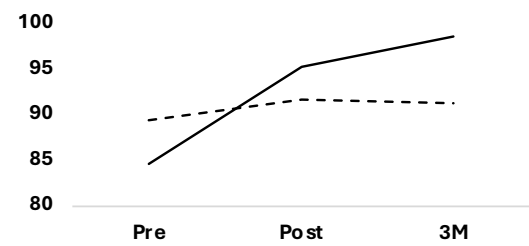
Fatigue



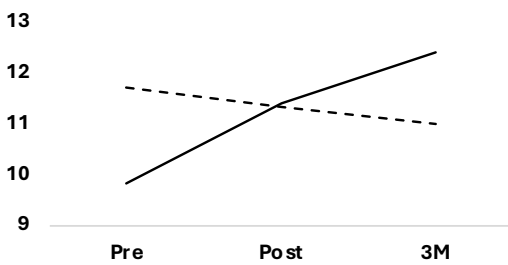
Self-efficacy



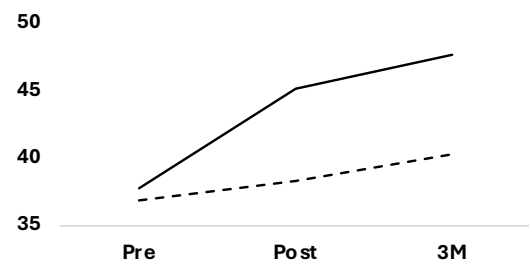
Benefit finding



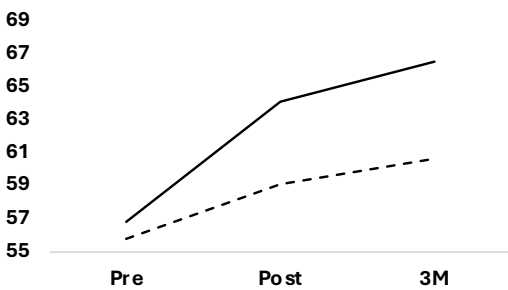
Instrumental social support



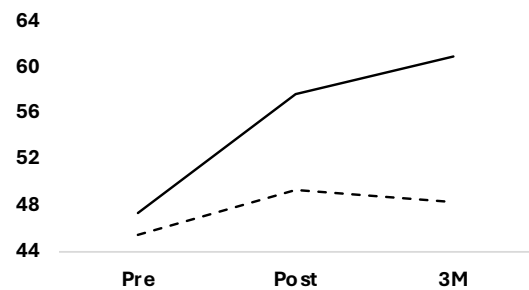
Flourishing



Personal relationships with others



Self-acceptance



3M, 3 months after the intervention; Post, after the intervention; Pre, before the intervention.

in fatigue and increases in self-efficacy were found following a CBT fatigue management program in which the main goal was to normalize fatigue experiences and learn helpful ways to think about fatigue.⁶¹ This is similar to the objectives of UP. Although aimed at addressing emotions and one's responses to and thoughts about them, it may be that the intervention simultaneously had an impact on the way individuals thought about their fatigue and how best to manage and cope with it. In general, CBT interventions that address maladaptive thoughts and behaviors and provide fatigue-specific skill-building exercises have shown the most promise.⁶² The ability of the UP intervention to influence both depression and fatigue so greatly is noteworthy given that they are the 2 most detrimental symptoms associated with MS.

The effects seen with coping, particularly benefit finding, and social support speak to the presumed underlying mechanisms of UP and how the program may lead to reductions in EDs. Social support is one of the leading predictors of depression and anxiety in MS.^{18,63,64} It is possible that the observed increase in utilization of instrumental social support, whether experienced through the group directly or in a participant's life, subsequently reduced feelings of depression. One question is whether individual treatment with UP would yield similar results. If not, findings would suggest that the UP group format is more beneficial. The effect for benefit finding and the lack of findings for the other coping styles more generally are exciting as well and may be reflective of a participant's change in perspective. The premise of benefit finding is identifying meaningful aspects of life when contending with a challenging circumstance or illness. Although defined as coping, it is less a coping style and more of a changed approach to life and a shift in perspective and meaning. Another study's findings showed that benefit finding increased following treatment of depression in MS.⁶⁵

The effects observed for experiential avoidance are important and relate to the most pressing question the study results generated: Why was there no effect for anxiety? Although anxiety was a primary outcome variable, we included a measure of experiential avoidance for an important reason. Experiential avoidance is defined as the reluctance to remain in contact with distressing feelings or an attempt to control or avoid them. These behaviors can exacerbate distress and/or limit one's behaviors, further contributing to increased anxiety.⁶⁶ It has recently been shown that experiential avoidance is linked to both depression and anxiety among individuals with MS.⁶⁷ Confronting this avoidance is a major component of the UP intervention. Contemporary CBT, including the UP, emphasizes the natural function of so-called *negatively valenced emotions*, such as anxiety, and focuses more on engaging with the world in the presence of anxiety. Conversely, it is less focused on reducing anxiety as a primary treatment aim. In this regard, the significant reduction in avoidance and the increase in one's ability to confront and stay with one's anxiety are more important than a reduction in anxiety. The proximal goal is not to eliminate anxiety; at a basic level, some frequency of state anxiety associated with uncertainty regarding future events may be unavoidable for many people with MS. Therefore, the message is to engage with one's life despite the understandable discomfort of this uncertainty.

With this said, previous investigations of the UP among people with MS found larger effects for reducing anxiety. In our study, 83% of the people in the control group reported significant depression at onset; this rate declined to 56% at 12 weeks. The changes in mean scores for the controls in the 2 prior studies that had larger effect sizes were 0.41 and 0.71 compared with 1.89 in our study.^{35,36} This suggests that the present control group demonstrated a decline in anxiety that was not significantly different from the 3.42 mean difference in the treatment group. Nonetheless, the significant reduction in avoidance is more reflective of the nature of the intervention as it pertains to ameliorating the effects of anxiety in general. This pattern is consistent with findings for the use of UP group intervention in residential treatment settings for eating disorders, where the magnitude of reductions in experiential avoidance and anxiety sensitivity is larger than the reduction in anxiety symptoms.⁶⁸

Some limitations should be acknowledged. The present investigation was single-blind, with the control group not receiving any intervention. In addition, given the nature of this early comparative trial, we did not correct for potential α inflation given the number of unique inferential tests. The inclusion of follow-up observation is a strength, yet the integration of additional within-treatment assessments would provide more information about the timing and nature of changes at the individual and group levels. Finally, the small number of groups and facilitators prevented us from examining nested-level effects and differences.

CONCLUSIONS

Taken together, the present study's findings suggest that the UP holds tremendous promise in ameliorating EDs in people with MS. Further studies are warranted in which a larger, more balanced, diverse sample is included and the UP intervention is compared with an active comparator. ■

Data Availability: The data that support the findings of this study are available from the corresponding author (L.S.) upon reasonable request.

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Conflicts of Interest: The authors declare no relevant conflicts of interest.

Previous Presentation: Findings were previously presented at the 38th Annual Meeting of the Consortium of Multiple Sclerosis Centers; May 29-June 1, 2024; Nashville, TN.

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TABLE S1. Group Comparisons of the Primary and Secondary Outcomes

		Baseline	Immediate	3 months	F, P value	n ²
Primary outcomes, mean (SD)						
HADS depression^a	I	9.42 (1.88)	4.58 (3.03)	5.25 (4.05)	$F_{(2,56)}=6.43, P=.003$.19
	C	9.67 (3.69)	9.28 (4.34)	9.28 (4.50)		
HADS anxiety^a	I	11.75 (6.17)	8.33 (5.91)	6.67 (4.56)	$F_{(1,45,56)}=1.55, P=.226$.05
	C	11.28 (3.63)	9.39 (4.03)	9.28 (4.75)		
PANAS positive affect^b	I	23.00 (5.81)	29.92 (6.43)	29.92 (9.07)	$F_{(2,56)}=.446, P=.642$.02
	C	19.06 (4.61)	24.11 (7.45)	23.00 (7.15)		
PANAS negative affect^b	I	25.67 (10.44)	21.67 (8.04)	19.83 (7.47)	$F_{(2,56)}=.413, P=.663$.02
	C	27.39 (6.18)	24.72 (8.01)	24.61 (8.60)		
BEAQ^a	I	54.83 (15.04)	43.17 (13.49)	40.25 (12.86)	$F_{(1,46,56)}=4.68, P=.024$.14
	C	56.50 (9.04)	51.17 (11.15)	56.78 (13.72)		
Secondary outcomes, mean (SD)						
MFIS physical fatigue^a	I	24.33 (5.00)	17.92 (7.24)	21.83 (7.00)	$F_{(2,56)}=4.07, P=.022$.13
	C	26.28 (5.65)	25.67 (6.33)	25.94 (7.23)		
PSQI^a	I	10.83 (3.97)	10.50 (3.83)	8.33 (3.23)	$F_{(2,56)}=1.33, P=.272$.05
	C	11.35 (3.94)	10.29 (3.20)	10.06 (4.42)		
PES^a	I	17.83 (5.20)	14.92 (4.14)	17.67 (6.62)	$F_{(2,56)}=0.009, P=.991$.00
	C	19.50 (6.46)	16.78 (6.09)	19.22 (6.24)		
GSES^b	I	27.42 (3.65)	30.25 (2.83)	32.25 (3.89)	$F_{(2,56)}=3.72, P=.030$.12
	C	27.61 (4.57)	28.33 (4.26)	29.28 (4.10)		
DMSES^b	I	48.75 (12.82)	54.92 (10.01)	58.50 (12.98)	$F_{(2,56)}=0.514, P=.601$.02
	C	43.39 (9.86)	46.67 (12.43)	47.78 (14.48)		
COPE active coping^c	I	10.42 (2.47)	11.08 (2.23)	11.58 (2.31)	$F_{(1,70,56)}=.253, P=.742$.01
	C	10.61 (3.16)	11.22 (2.34)	11.22 (2.46)		
COPE planning^c	I	11.17 (2.52)	12.17 (3.13)	13.08 (2.81)	$F_{(2,56)}=.802, P=.454$.03
	C	10.61 (3.70)	11.56 (2.91)	11.56 (3.35)		
COPE suppression of competing activities^c	I	9.92 (2.64)	10.17 (1.19)	10.58 (2.87)	$F_{(2,56)}=.004, P=.996$.00
	C	9.72 (2.74)	9.89 (2.27)	10.39 (2.80)		
COPE restraint^c	I	8.58 (2.07)	8.83 (2.37)	9.33 (1.72)	$F_{(2,56)}=.014, P=.986$.00
	C	9.00 (2.06)	9.39 (2.06)	9.78 (2.21)		
COPE instrumental social support^c	I	9.83 (4.06)	11.42 (3.37)	12.42 (2.81)	$F_{(2,56)}=6.75, P=.002$	0.19
	C	11.72 (3.21)	11.33 (3.73)	11.00 (3.88)		
COPE positive reinterpretation and growth^c	I	10.17 (2.48)	12.50 (2.32)	13.08 (2.61)	$F_{(2,56)}=2.14, P=.127$.07
	C	10.78 (3.26)	11.39 (2.57)	11.89 (2.95)		
COPE acceptance^c	I	10.00 (2.41)	12.00 (1.28)	11.50 (2.15)	$F_{(2,56)}=1.87, P=.163$.06
	C	10.17 (2.79)	10.44 (2.36)	11.67 (2.22)		
COPE denial^c	I	6.33 (2.87)	5.33 (2.15)	5.75 (2.30)	$F_{(1,69,56)}=1.15, P=.319$.04
	C	6.06 (2.01)	6.22 (2.62)	5.44 (2.23)		
COPE turning to religion^c	I	9.58 (5.14)	9.58 (5.07)	9.75 (5.10)	$F_{(1,77,56)}=.021, P=.969$.00
	C	9.56 (4.80)	9.39 (5.45)	9.61 (5.34)		
COPE emotional social support^c	I	8.58 (3.68)	10.25 (3.17)	10.42 (4.03)	$F_{(2,56)}=1.73, P=.186$.06
	C	10.44 (3.45)	11.00 (3.94)	10.28 (4.21)		

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Continued

COPE venting emotions^c	I	9.33 (3.17)	9.33 (1.67)	9.00 (2.56)	$F_{(2,56)}=1.45, P=.644$.02
	C	11.67 (2.95)	12.00 (2.20)	12.22 (2.86)		
COPE behavioral disengagement^c	I	6.50 (2.24)	6.33 (2.23)	6.33 (1.37)	$F_{(2,56)}=.042, P=.959$.00
	C	8.39 (2.00)	8.00 (2.57)	8.00 (2.14)		
COPE mental disengagement^c	I	10.83 (2.29)	9.91 (2.31)	9.67 (2.71)	$F_{(2,56)}=.249, P=.780$.01
	C	11.11 (2.68)	10.17 (2.66)	9.33 (1.61)		
COPE substance use^c	I	5.25 (3.28)	4.92 (2.23)	4.92 (2.39)	$F_{(2,56)}=.672, P=.515$.02
	C	5.17 (1.86)	5.28 (2.32)	4.50 (1.29)		
COPE humor^c	I	8.92 (3.53)	9.83 (3.35)	10.17 (3.95)	$F_{(2,56)}=.533, P=.590$.02
	C	8.72 (4.25)	8.72 (3.71)	8.83 (4.08)		
BFIMSS total score^b	I	84.58 (14.42)	95.33 (16.52)	98.58 (16.03)	$F_{(2,56)}=5.07, P=.009$.15
	C	89.44 (17.38)	91.72 (16.58)	91.33 (16.47)		
UWRS^b	I	23.92 (5.11)	27.00 (5.13)	28.33 (6.12)	$F_{(1,69,56)}=3.20, P=.058$.10
	C	23.67 (5.99)	23.17 (5.48)	23.11 (6.74)		
Ryff autonomy^b	I	66.33 (10.54)	69.00 (12.58)	69.92 (10.09)	$F_{(2,56)}=.387, P=.681$.01
	C	59.33 (15.68)	60.44 (13.94)	63.61 (12.49)		
Ryff environmental mastery^b	I	49.83 (10.96)	58.42 (10.83)	61.00 (11.65)	$F_{(2,56)}=5.84, P=.005$.17
	C	45.06 (10.01)	48.50 (9.58)	46.72 (11.18)		
Ryff personal growth^b	I	66.67 (10.89)	71.50 (10.83)	73.50 (8.64)	$F_{(2,56)}=1.00, P=.373$.04
	C	62.89 (12.32)	66.67 (10.87)	66.11 (12.80)		
Ryff positive relations with others^b	I	56.83 (15.45)	64.17 (13.62)	66.58 (12.71)	$F_{(1,49,56)}=4.47, P=.027$.14
	C	55.83 (11.38)	59.17 (12.59)	56.72 (13.77)		
Ryff purpose in life^b	I	55.17 (14.06)	62.75 (10.41)	66.83 (10.99)	$F_{(2,56)}=2.23, P=.117$.07
	C	51.83 (13.46)	55.50 (11.08)	56.22 (11.43)		
Ryff self-acceptance^b	I	47.42 (14.84)	57.75 (12.80)	61.00 (13.84)	$F_{(2,56)}=3.69, P=.031$.12
	C	45.56 (16.00)	49.39 (15.23)	48.33 (17.12)		
SWLS^b	I	16.58 (4.83)	22.75 (5.61)	23.08 (5.33)	$F_{(1,79,56)}=1.76, P=.185$.06
	C	15.56 (8.38)	18.22 (8.34)	18.22 (8.12)		
FS^b	I	37.75 (8.00)	45.17 (9.85)	47.67 (5.76)	$F_{(2,56)}=3.99, P=.024$.13
	C	36.89 (10.33)	38.33 (10.32)	40.28 (10.39)		

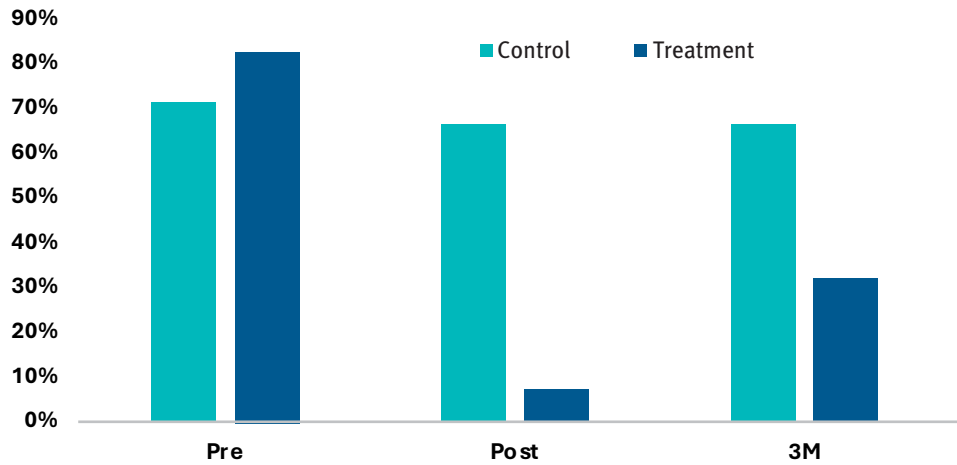
BEAQ, Brief Experiential Avoidance Questionnaire; BFIMSS, Benefit Finding in Multiple Sclerosis Scale; C, control arm; COPE, Coping Orientation to Problems Experienced Inventory; DMSES, University of Washington Disease Management and Self-Efficacy Scale; FS, Flourishing Scale; GSES, General Self-Efficacy Scale; HADS, Hospital Anxiety and Depression Scale; I, intervention arm; MFIS, Modified Fatigue Impact Scale; PANAS, Positive and Negative Affect Schedule; PES, Medical Outcomes Study Pain Effects Scale; PSQI, Pittsburgh Sleep Quality Index; Ryff, Ryff Psychological Well-Being Scales; SWLS, Satisfaction With Life Scale; UWRS, University of Washington Resilience Scale.

^aLower scores indicate better functioning.

^bHigher scores indicate better functioning.

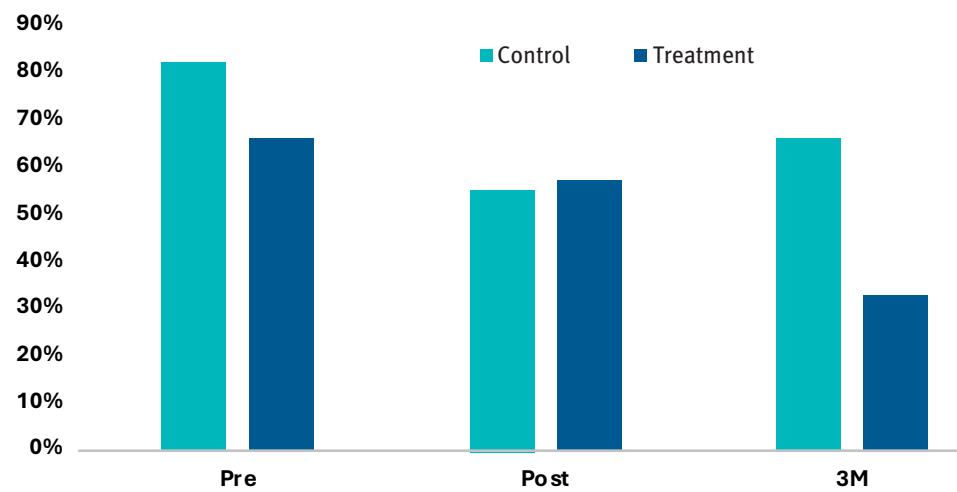
^cHigher scores indicate greater use of coping mechanism.

FIGURE S1. Participants Meeting Cutoff for Depression



3M, 3-month follow-up; Post, after intervention; Pre, before intervention.

FIGURE S2. Participants Meeting Cutoff for Anxiety



3M, 3 months after intervention; Post, after intervention; Pre, before intervention.