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Pilot Intervention to Promote Tolerance for Uncertainty in Early Multiple Sclerosis

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Purpose/Objective: The ability to tolerate uncertainty about the future may be foundational to positive psychological adjustment. Conversely, intolerance of uncertainty (IU) has been shown to be a vulnerability factor for anxiety and depression. One stressor with a very high degree of uncertainty about the future is a new diagnosis of multiple sclerosis (MS). However, few psychological interventions in MS have directly targeted IU. ***Research Method/Design:*** Forty-eight participants with early MS and moderate levels of distress were randomized to receive either 6 sessions of a brief psychological intervention designed to improve the ability to tolerate uncertainty ($n = 23$) or treatment as usual (TAU; $n = 25$). Measures of mood, IU, and MS acceptance were administered at baseline and about 8 weeks later. Intervention effects were tested via linear regression controlling for baseline levels. ***Results:*** Participants were primarily Caucasian (85%) women (73%) and had lived with an MS diagnosis for an average of 376.3 days. Groups did not differ at baseline on most demographic or outcome variables. The intervention was well-tolerated, and most participants (82.6%) completed all 6 sessions and reported benefit. Postintervention, those in the intervention group demonstrated lower levels of IU and more MS acceptance relative to the TAU group. There was no effect of the intervention on global anxiety. Decreases in IU were associated with increases in MS acceptance ($r = -.63$). Effect sizes for these changes were moderate. ***Conclusions/Implications:*** These pilot results demonstrate that IU is responsive to a brief psychological intervention, and improvement with IU is associated with positive psychological outcomes.

Impact and Implications

People living with a recent diagnosis of multiple sclerosis (MS) are faced with a great deal of uncertainty about the future. The ability to tolerate this uncertainty is partly dispositional and is an important transdiagnostic protective factor for adjustment. Despite this, there are to date no published studies describing interventions designed to target intolerance of uncertainty (IU) in medical populations. This pilot study is the first to report on an intervention designed to specifically address IU in people recently diagnosed with MS. Findings from this study indicate that a six-session intervention can improve IU as well as acceptance of an MS diagnosis in individuals with early MS. The intervention was well tolerated by most participants. Psychological practitioners working with MS patients should consider the ways that a client's dispositional ability to tolerate uncertainty interacts with the unpredictability of the disease and consider IU as a key transdiagnostic treatment target in psychotherapy.

Keywords: uncertainty, multiple sclerosis, early MS

Introduction

Living with a progressive disease means learning to coexist with the unknowable, the unpredictable, and the uncontrollable. Decisions about how to manage health and illness inherently include accepting the presence of uncertainty (Sprague et al., 2013). This may be especially true for neurological conditions seen in medical rehabilitation, which are often typified by unpredictable trajectories of function, indistinct end points, and

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a progressive nature (Weinstein, 2011). Living with a chronic neurological condition such as epilepsy or multiple sclerosis (MS) means both managing the disease itself and also coping with chronic uncertainty about how function will change or affect quality of life over time (Barahmand & Haji, 2014; Buchanan et al., 2010).

As a psychological construct, uncertainty can be defined as a cognitive state occurring when one is unable to assign definite probabilistic values to future events (Tai-Seale, Stults, Zhang, & Shumway, 2012). Without such probabilities, the error of prediction goes up, decisions become more difficult, and the perceived consequences of making the wrong decision are magnified. Reducing uncertainty is, therefore, believed to be adaptive (Einstein, 2014) because when individuals are able to predict their environment, they perceive themselves as having greater control over potential outcomes (Bar-Anan, Wilson, & Gilbert, 2009). Given this, it is not surprising that human beings almost universally find states of uncertainty aversive (Carleton, 2012) and prefer to resolve uncertainty even if the more certain alternative is negative or unpleasant (Hsee & Ruan, 2016).

Despite this general human tendency to avoid uncertainty, there is now good evidence that some individuals are better able to cope with it than others. *Intolerance of uncertainty* (IU) is a personality construct described as "beliefs about the necessity of being certain, about the capacity to cope with unpredictable change, and about adequate functioning in situations that are inherently ambiguous" (Holaway, Heimberg, & Coles, 2006, p. 159; Obsessive Compulsive Working Group, 1997). IU is generally seen as dispositional or trait-like (Buhr & Dugas, 2002), although situation-specific IU has also been described in the literature (Mahoney & McEvoy, 2012b). People who are high in IU appear to struggle with ambiguous information, seeing it as more threatening or upsetting (Koerner & Dugas, 2008). IU may be seen as a vulnerability factor for worry and rumination (Yook, Kim, Suh, & Lee, 2010), especially when individuals who are high in IU are placed in situations with unpredictable but significant outcomes (Boswell, Thompson-Hollands, Farchione, & Barlow, 2013; Carleton et al., 2012; Koerner, Mejia, & Kusec, 2017).

High IU appears to be a central feature underlying anxiety disorders and depression (Gentes & Ruscio, 2011) and has been shown to predict anxiety and stress symptoms even after controlling for the effects of related confounds like age, gender, and depression (Bardeen, Fergus, & Orcutt, 2017; Dugas et al., 2007). In medical settings, high IU is associated with more worries about health and higher health anxiety. (Coutu et al., 2013; Rosen et al., 2010; Taha, Matheson, Cronin, & Anisman, 2014) People who are high in IU may attempt to reduce the uncertainty by gathering more information even when this is impossible or unproductive (e.g., via repetitive Internet searching for medical information; Fergus, 2013).

Fortunately, research in this area has shown that though IU is trait-like, it is also modifiable and can respond to intervention (Dugas & Ladouceur, 2000). In fact, a number of trials investigating CBT, mindfulness, and other interventions for anxiety disorders have found that changes in IU may emerge as a secondary effect of treatment and are associated with subsequent reductions in worry and distress (Bomyea et al., 2015; Boswell et al., 2013; Carleton, 2012; Kim, Lee, Kim, Choi, & Lee, 2016; Koerner et al., 2017; Mahoney & McEvoy, 2012a; Talkovsky & Norton, 2016).

One medical condition that requires patients to cope with a great deal of uncertainty is MS, which is a progressive, demyelinating disease of the central nervous system. Because of many recent advances in management and treatment of MS (Reich, Lucchinetti, & Calabresi, 2018), physicians are now able to make general prognoses about disease course based on certain medical and personal demographics (e.g., age and gender; Miller, 2011). However, the pathogenesis of MS remains incompletely understood, and the disability trajectory of the disease is difficult to predict. There are multiple MS disease courses, but all are characterized by unpredictability both in terms of symptoms (i.e., what they are and how and when they will emerge) and progression (i.e., the point at which functional declines will limit independence; Reich et al., 2018).

Alongside learning to cope with the symptoms of MS, individuals with this condition must also learn to live in a chronic state of uncertainty. The ability to tolerate this uncertainty has been described as central to quality of life in MS (Alschuler & Beier, 2015; Giammanco et al., 2014), and individuals with MS report that learning to live with uncertainty is among the most significant challenges they face (Simmons, 2010). High levels of IU may be especially impactful for individuals early in the MS course as this period requires active adjustment to a new chronic health problem with an uncertain prognosis (Giordano et al., 2011; Janssens et al., 2003).

Given the central importance of tolerating uncertainty in adjusting to an MS diagnosis, interventions that reduce IU and enhance coping with uncertainty are warranted. However, the majority of care early after an MS diagnosis focuses on patient education and disease management (Rintell, Frankel, Minden, & Glanz, 2012; Solari et al., 2010) rather than on providing skills to manage worry about an uncertain future. Interventions to promote psychological health in MS are numerous and effective but tend to focus on specific physical and mental health comorbidities (e.g., fatigue, sleep, depression, or anxiety) and not on coping with the uncertainty of the disease itself. Therefore, there is an apparent need for the development of an intervention for individuals with MS that includes IU as a central feature (Alschuler & Beier, 2015), particularly in the active adjustment phase postdiagnosis.

The purpose of the present study was to address this need by developing and testing a brief intervention designed to improve the ability to tolerate uncertainty and to improve MS acceptance in a group of individuals in the early phases of MS. Consistent with the pilot stage of research, a primary purpose of this project was to evaluate satisfaction, acceptability, and adherence to the intervention. We also sought to conduct a preliminary assessment of the effectiveness of the intervention. We hypothesized that a brief, six-session intervention that focused on ways to manage uncertainty and uncertainty-associated distress would lead to improved ability to tolerate uncertainty, higher levels of MS acceptance, and lower levels of global anxiety relative to treatment as usual (TAU). We further hypothesized that intervention-related improvements in the ability to tolerate uncertainty would be associated with improvements in MS acceptance and global anxiety.

Method

Participants

Participants were 48 patients in a multidisciplinary MS specialty clinic in the Pacific Northwest who were recruited over a 6-month period through physician referral, fliers posted in the clinic, and/or having participated in prior research studies and indicating an interest in being contacted for relevant future research. To enroll in the study, participants were required to (a) have a physician-confirmed diagnosis of MS or clinically isolated syndrome (CIS; a single episode of MS-like symptoms), using the revised McDonald criteria (Polman et al., 2011); (b) be diagnosed within the past 36 months (Kiropoulos, Kilpatrick, Holmes, & Threader, 2016); (c) have at least moderate psychological distress (on the basis of scoring >10 on the Generalized Anxiety Disorder scale [GAD-7] or the Patient Health Questionnaire [PHQ-9]); and (d) be able to read, speak, and understand English. The protocol was approved by the Institutional Review Board at the University of Washington.

Procedures

A total of 67 individuals contacted the research study assistant. Two of the individuals declined to participate in the study after learning more details. The research study assistant then performed an initial screening for inclusion/exclusion criteria with the remaining 65 individuals. Of these individuals, 53 met eligibility based on measures of distress, and 12 did not. Those who did not meet eligibility criteria were offered a list of resources for MS. After screening, five individuals could not be contacted by study staff after four attempts. Therefore, the final sample for this study included 48 participants.

Once enrolled, participants were assigned a number and sent a link to complete the baseline survey (described below) via a secure, cloud-based survey system maintained by the University of Washington. The participant number was then randomized to either the intervention or TAU condition via an online randomizer. After completing the baseline survey, participants were notified of their group assignment and were told to expect contact from the study clinician to schedule the first appointment or were assigned to TAU and told they should continue to conduct their lives as they normally would.

Participants were asked to complete the postintervention survey eight weeks after the baseline survey. This timeframe was selected to allow participants enrolled in the intervention to complete the six weekly sessions and to accommodate any difficulties in scheduling. Any missing data were followed by a call from the study research assistant for clarification. In response, participants would either provide the missing data or indicate they were unsure and/or preferred not to answer the question.

Treatment Conditions

IU intervention. The intervention used in this trial was created by the study authors and is based on basic principles from existing cognitive–behavioral and acceptance-based psychotherapies. The intervention is focused on understanding the difference between the aspects of MS that are knowable versus unknowable, understanding those aspects that can and cannot be controlled, learning to tolerate not knowing exactly what the future will hold, setting personal goals for accepting MS despite uncertainty, practicing mindfulness, and finding ways to live in conjunction with personal values despite uncertainty about the future. An abbreviated outline of the treatment is presented in Table 1.

Although this intervention includes a novel focus on uncertainty, the authors do not claim credit for inventing the various elements it contains. Our intervention relied on techniques and applications that are widely available and commonly used by rehabilitation psychologists. For example, the focus on cognitive defusion, mindfulness, and acceptance are similar to concepts central to acceptance and commitment therapy (ACT), which has been shown to improve acceptance (Nordin & Rorsman, 2012) and adjustment (Pakenham & Fleming, 2011) in pilot trials of individuals with MS. However, these trials did not directly focus on IU or the medical uncertainty associated with the disease. Similarly, addressing cognitions relating to uncertainty and the need for predictability is similar to CBT approaches that target IU in generalized anxiety disorder (GAD), especially those developed by Dugas, Robichaud, and colleagues (Dugas et al., 2010; Robichaud, 2013; van der Heiden, Muris, & van der Molen, 2012). These approaches generally include self-monitoring, education regarding uncertainty, thought awareness, and discussion of core fears and have demonstrated efficacy in reducing distress in people with GAD (Dugas & Ladouceur, 2000; Gosselin, Ladouceur, Morin, Dugas, & Baillargeon, 2006).

Our intervention also differed from existing approaches in some key ways. Traditional CBT approaches like the ones above typically include several therapeutic elements of which tolerance for uncertainty is only one. In our intervention, uncertainty was a central feature of each session of the intervention. Similarly, most existing approaches focus on reducing symptoms such as anxiety and depression whereas in this intervention anxiety and depression were never overtly discussed and were not identified treatment targets. Our approach also focused on cognitive defusion and thought acceptance strategies over traditional thought-challenging exercises, making it much more like ACT than traditional cognitive therapy. Although there are treatment protocols to target IU in GAD (Dugas et al., 2010; Robichaud, 2013; van der Heiden et al., 2012), there are practical limitations to implementing these in a medical rehabilitation setting, such as the long course of individual, in-person treatments typical in those approaches (e.g., 12 to 16 sessions; Dugas et al., 2010; Robichaud, 2013; van der Heiden, et al., 2012). To improve accessibility and participation, our intervention was limited to six sessions, and participants chose whether they wanted to participate in-person, by telephone, or by a combination of in-person and telephone visits. Finally, existing interventions that specifically include tolerance of uncertainty (Dugas et al., 2010; Robichaud, 2013; van der Heiden et al., 2012) were designed for use in people with clinical anxiety disorders such as GAD and not for those experiencing more normative uncertainty associated with a medical condition such as MS. Our intervention was specifically designed by providers with experience in early MS and tailored to this population in terms of both content (e.g., containing examples based in MS symptoms) and structure (e.g., designed to be brief and accessible remotely for working-age individuals).

Treatment as usual (TAU). Participants in the TAU comparison did not receive contact with a study clinician and were asked

Table 1
Intervention Outline

Session	Topic area	Content	At home activities
1	Introduction to the intervention and to uncertainty	1. Intro to treatment, goals and structure 2. What is "uncertainty"? What is "uncertainty anxiety?" 3. Introducing the "coping line" (ranging from over-control to avoidance behaviors)	Worksheet: "The Crystal Ball"—What 3 things about your future with MS do you most want to know? How much distress does not knowing cause you?
2	Mindfulness/thought awareness	1. Understanding the difference between thoughts and feelings 2. Introduction to mindfulness meditation as a tool for nonjudgmental awareness of uncertainty related thoughts and reactions 3. How to notice when you are distressed by uncertainty	Mindfulness meditation practice—Mindfully noticing thoughts and feelings about MS Mindfully noticing "uncertainty anxiety"
3	Managing the need for control	1. Knowing the difference between the controllable and uncontrollable aspects of MS 2. Understanding when one is trying to control the uncontrollable 3. Intro to two common "over-control" strategies – rumination and catastrophizing – and how to avoid them 4. Strategies to manage overcontrol strategies as attempts to reduce uncertainty	Worksheet: Separating oneself from one's worries about MS
4	Acceptance & Integration	1. What is "acceptance"? What does that mean in MS? 2. Acceptance as integration of MS as one aspects of a person's life, not the only or defining aspect of life 3. How to sit comfortably with not knowing exactly how the future will unfold 4. Discussion of the relationship between tolerating uncertainty and MS acceptance	Worksheet: Understanding the aspects of MS that cannot be predicted or changed, and how to accept them
5	Living with Values	1. What are life "values?" 2. The difference between "values," "goals" and "choices" 3. Understanding that uncertainty can affect how you approach goals, but not core values 4. Discussion of how a struggle for certainty is energy taken away from living in conjunction with values 5. Discussion of personal values and how to honor them even with MS	Worksheet: Identifying personal values in 8 domains (Family life, work life, community life, etc.); How are these affected by MS?
6	Wrap up and Maintenance Planning	1. Review of skills, techniques and ideas from treatment 2. Discussion of strategies for maintenance of those skills 3. "Relapse" prevention planning (i.e., how to mobilize skills for managing uncertainty if/when worry about the unknowable returns)	Worksheet: Revisiting exercise from Session 1 ("The Crystal Ball"). How much distress do these questions about the future now cause you?

to continue with their lives as they normally would. In describing the TAU condition to participants, we provided clear information and were consistent with recommended language (Watts, Turnell, Kladnitski, Newby, & Andrews, 2015). Participants in the TAU could take part in other nonstudy interventions as they normally would.

It is important to note that as a control condition, TAU is designed to account only for the effects of time and repeated testing on outcomes. It essentially asks the following: Is this treatment better than nothing? TAU is, therefore, limited in that it does not control for the effect of therapist attention, contact, or other threats to validity. However, in selecting this comparison condition we considered the importance of matching the phase of research to the control group (Mohr et al., 2009). Given the primary purpose of the trial was to develop a treatment, establish treatment parameters, and explore potential effects, a small sample size and no-treatment comparison was considered acceptable to balance innovation with scientific control (Bowen et al., 2009; Mohr et al., 2009). TAU comparisons have been used in other pilot trials of psychological interventions for early MS (Kiropoulos et al., 2016).

Measures

Demographic and medical factors. Participants completed measures of medical and demographic information. These included age, race/ethnicity, sex/gender, income and education, number of physician and emergency department visits, current

medications, duration of symptoms, and MS type. Severity of functional disability was measured via the 10-item version of the PROMIS Physical Function Short Form (Jensen et al., 2015), a scale that assesses limitations in activities of daily living due to physical health. This scale has been validated in people with MS (Amtmann, Bamer, Kim, Chung, & Salem, 2018).

Acceptability and adherence. To measure acceptability, participants were asked to report on both perceived benefit from the intervention as well as global satisfaction with the intervention. Perceived benefit was assessed via a two-item, in-house treatment benefit scale. This scale asked participants to report the extent that they, "benefitted from the treatment you received" (five response options, ranging from *no benefit* to *extreme benefit*) and whether they felt they experienced any, "negative effects from the treatment" (five response options, ranging from *no negative side effects* to *extreme negative effects*). For both questions, participants were also asked to record specific ways they benefitted and/or specific negative effects they experienced.

To measure overall satisfaction, participants completed a single item that asked, "How satisfied were you overall with the study treatment?" (five response options, ranging from very *dissatisfied* to *very satisfied*). Participants were then asked to record the primary reasons they felt satisfied or dissatisfied. Single-item evaluations of patient satisfaction such as these are common in the medical literature (Lloyd, Jenkinson, Hadi, Gibbons, & Fitzpatrick, 2014; Pleil et al., 2005). Adherence was assessed on the basis of number and percentage of total sessions completed an intent-to-treat approach, in which anyone randomized to treatment was included regardless of actual participation.

IU. IU was measured using the Intolerance of Uncertainty Scale (Buhr & Dugas, 2002), whose 27 items relate to the idea that uncertainty is unacceptable, leads to frustration, and creates an inability to take action. This scale has demonstrated strong psychometric characteristics (Buhr & Dugas, 2002) including in the present sample (n = 48, Cronbach's α = .95).

MS acceptance. MS acceptance was measured with the Acceptance of Chronic Health Conditions, MS version (ACHC-MS; Stuifbergen, Becker, Blozis, & Beal, 2008). This scale asks about the degree to which a person views MS as one of many personal characteristics and not necessarily the central or defining characteristic. Statements include "I can't conquer MS but I can adapt to it" and "I think of MS as just part of who I am." The ACHC-MS Scale consists of 10 items scored on a five-category Likert rating scale, ranging from (1) *strongly agree* to (5) *strongly disagree*. The scale has demonstrated adequate psychometric properties in people with MS (Stuifbergen et al., 2008) using both the 10-item scale and shorter versions (Forslin, Kottorp, Kierkegaard, & Johansson, 2016). The present sample demonstrated acceptable internal reliability on this scale (Cronbach's α = .85).

Global anxiety. Global anxiety was assessed using the seven-item GAD-7 (Spitzer, Kroenke, Williams, & Lowe, 2006), which is a widely used self-report measure developed to screen for clinically significant anxiety. Participants rate the presence of symptoms on a three-point scale as occurring during the last 2 weeks (0) *not at all*, (1) *several days*, or (2) *more than half the days*. Items are summed to create a symptom severity score ranging from 0 to 14. This scale has demonstrated good psychometric properties in people with MS (Terrill, Hartoonian, Beier, Salem, & Alschuler, 2015) and has been recommended as a screening measure specifically in this population.

Analytic Plan

For all analyses, we used an intent-to-treat (ITT) approach. Missing data at the individual-item level was imputed with mean scores for scales in which fewer than 10% of answers were missing. If more than 10% were missing, the scale was not included in the analyses.

We first computed descriptive statistics to characterize the sample in terms of demographic and medical factors as well as level of functional disability. To describe acceptability, we calculated means and standard variation for perceived benefit and perceived satisfaction among those who completed the active intervention. We also calculated adherence rates in terms of number of sessions attended out of six.

Before testing intervention effectiveness, we determined whether randomization was successful in producing two similar groups for comparison. We did this by comparing TAU and intervention groups on a range of demographic and outcome variables using t tests or chi-square tests (for continuous or categorical variables, respectively). If a variable differed at baseline between the TAU and intervention groups and that variable was also correlated with prepost change in a key outcome (IU, anxiety, or MS acceptance), we planned to include it as a control variable in subsequent analyses.

After testing randomization, we tested intervention effects. This was done with three linear regression analyses, one for each primary outcome (IU, MS acceptance, and global anxiety). For each regression, we included the baseline score for the outcome in block one along with any potential control variables (identified via the procedure above). In block two, we entered group assignment (intervention or TAU, dummy coded). This residualized change approach is appropriate for prepost randomized designs (Castro-Schilo & Grimm, 2018; Choi & Bohman, 2007) and allowed us to describe the effect of the intervention on the postoutcome after controlling for baseline levels.

To aid in clinical interpretation, we followed significant intervention effects in the regression with a simple pre to post paired-sample t test for the intervention and TAU groups and calculated repeated measures Cohen's d effect sizes for these changes. Although this post hoc t test approach is not strictly necessary given significance of the regression equation, we thought it may provide more useful descriptive information to clinicians by demonstrating the change from baseline to postoutcome was statistically significant using a common parametric approach. To determine if changes in IU were associated with changes in other variables, we created a prepost change score for the other key outcomes (anxiety and MS acceptance) and correlated them using Pearson's r.

Results

Demographic and Descriptive Variables

Participants enrolled in the study (N = 48) were primarily Caucasian (85%) women (73%), who were diagnosed with MS or CIS for an average of 376 days (with a range of nine to 1,033

days). The sample was well educated with 88% of participants holding a technical, associate's, bachelor's, or other advanced degree. The average age for the sample was 37.9 years (SD = 10.9). Overall, these sample characteristics are consistent with the demographics of individuals with early MS in the United States (Federation, 2013). Demographics of this sample are presented in Table 2.

Regarding level of functional disability, the mean score on the PROMIS Physical Function scale was 40.9 (SD = 7.6) on a raw scale ranging from 10 (total limitations in activities of daily living) to 50 (no limitations). Because all PROMIS scales are designed to be converted to a t-score metric for comparison to a large national normative data, we determined that participants in our sample reported a level of physical disability that was less than one half of one standard deviation from the general U.S. population (t = 45.5; SD = 8.6). This is consistent with mild levels of physical impairment (Amtmann et al., 2018) and is representative of early MS, where the disease does not typically create significant limitations in function.

A total of 23 participants were randomized to the intervention group, and 25 were randomized to TAU. Of these, three participants did not complete their post-assessments (two in the intervention group and one in TAU). The two intervention group participants who were lost to follow-up completed the first session of treatment and then withdrew from the study. The individual assigned to TAU who did not complete the post-assessment was lost to follow-up and could not be contacted. Their baseline scores were included in all analyses. In terms of participation, 14 individuals (61%) elected to do the intervention by telephone, five participants (22%) by in-person visits, and the remaining four participants (17%) by a mix of telephone and in-person visits.

Adherence and Acceptability

Regarding adherence, a majority of participants randomized to the intervention completed all six sessions (19/23 or 82.6%). Of the remaining four participants, one actively withdrew from treatment after three sessions but still elected to complete the post-assessment. Two completed one session but were lost to contact (i.e., they could not be reached and did not complete the post-assessment). One individual was randomized to treatment and completed both pre- and post-assessments but did not attend any treatment sessions. Taken together, the average number of sessions completed was 5.2 (SD = 1.9).

Regarding acceptability, most participants reported benefitting from the intervention with 85.6% reporting at least "some benefit" and 67% reporting "a lot" or "extreme benefit," (Range = 1–5, M = 3.67, SD = 1.1). As expected, most participants (17 or 81%) reported no negative effects associated with the intervention (Range = 1–5, M = 1.33, SD = .80). Of the remaining four (19%), two individuals appeared to have misunderstood the question (i.e., "How much do you think you had negative effects from the treatment you received?") and replied in terms of their overall MS treatment, listing difficulties in taking oral medications and pain at injection sites. The remaining two included one individual who felt that the intervention caused more initial anxiety "that soon passed," and another who felt that the intervention had too great a focus on "negative thinking." Overall satisfaction with the intervention was 3.1 (SD = 1.2) on a 0 to 4 scale, and 71.4% of participants described being either *satisfied* or *very satisfied*.

Of course, not all participants reported satisfaction or benefit from the intervention. Three participants reported no or only a little benefit. One participant (the one who expressed experiencing negative effects of the intervention and chose to withdraw after three sessions) was generally not happy with the intervention. This

Table 2
Demographics by Study Condition

Variable	Total	Intervention	TAU
	n or *M* (*SD*)	*n* or *M* (*SD*)	*n* or *M* (*SD*)
Sample size	48	23	25
Sex			
Female	35 (73)	16 (70)	19 (76)
Male	13 (27)	7 (30)	6 (24)
Marital status*			
Married/Cohabitating	28 (58)	17 (74)	11 (44)
Not married/Cohabitating	20 (42)	6 (26)	14 (56)
Race/ethnicity			
White	41 (85)	21 (91)	20 (80)
Black or African American	1 (2)		1 (4)
Multiracial	6 (13)	2 (9)	4 (16)
Hispanic, Latino, or Spanish	3 (6)		3 (12)
Education level			
College	42 (88)	19 (83)	23 (92)
No college	6 (12)	4 (17)	2 (8)
Employment status			
Employed	32 (67)	13 (57)	19 (76)
Not employed	16 (33)	10 (43)	6 (24)
Age	37.90 ± 10.90	39.61 ± 10.99	35.92 ± 10.56
PROMIS Physical Function	45.47 ± 8.55	44.57 ± 7.47	46.30 ± 9.51

* Significant difference ($p < .05$) between intervention and TAU via chi-square/independent samples t test.

participant felt that the intervention should have been more focused on positivity and active coping rather than management of uncertainty or anxiety. This participant suggested that the intervention, "Make people think of two positive thoughts after each exercise [and] don't have them end on negative thoughts. Encourage thought rebounding to positivity." The same participant felt that the intervention, "instigates dwelling and depression instead of helpful rescue thoughts."

When asked to describe the primary reasons for satisfaction or benefit, participants described an increased ability to acknowledge and accept their distressing cognitions about the uncertainty of MS. One participant reported, "I feel more able to experience negative feelings and thoughts, especially about MS and am not afraid of being consumed by them." Another participant expressed a similar perspective: "Knowing it's okay to have the thoughts I have about MS but at the same time not allowing the thoughts to be any more than that—a thought that probably cannot be answered and won't in this life, and it's ok and to just let the thought go . . . and float on to move on." Finally, one participant shared, "I'm able to look at my health struggles with a new perspective: One that doesn't judge, which helps keep my anxiety lower." The participant who chose to withdraw endorsed some positive as well as negative effects of the intervention. For example, this participant commented, "I learned some coping methods and ways to talk myself back into the moment when I'm stressing out."

Participants also reported benefits from a focus on values-based living. For example, one participant said, "I also found thinking about values as opposed to goals was helpful to see that I can continue to live according to these values despite any limitations that MS symptoms might cause." Participants also generally appreciated the length and flexibility of the intervention format: "[This is a] concise, precise, and effective way to learn to cope with the ups and downs or the constant putting out fires I have to do when coping with my MS." Overall, the intervention was well-received, and participants reported levels of satisfaction and benefit consistent with other novel psychotherapeutic interventions in MS.

Treatment Effectiveness

Randomization check. To determine if randomization was successful, we compared the intervention and TAU groups at baseline using *t* tests and chi-square tests on a range of medical, demographic, and study outcome variables. The intervention and TAU groups did not significantly vary at baseline by sex (69.6% vs. 75% women; $\chi^2 = .251$, $p = .75$), by income bracket ($\chi^2 = 1.73$, $p = .63$), or by age (35.9 vs. 40.1, $t = -1.32$, $p = .19$). Regarding medical factors, the groups did not differ by days since diagnosis (422.9 vs. 333.5; $t(46) = -1.22$, $p = .23$) by severity of any of 21 common MS symptoms ranked 0–10 in severity (including fatigue, spasms, numbness, weakness, heat sensitivity, or pain; all ps $>.10$), or by severity of functional disability (PROMIS Physical Function, 41.2 vs. 40.6; $t = .28$, $p = .78$). The groups also did not differ at baseline on the study outcome variables: IU (57.4 vs. 64.7, $t = 1.1$, $p = .28$), MS acceptance (31.6 vs. 29.5, $t = -.96$, $p = .34$), or GAD-7 score (7.3 vs. 9.7, $t = 1.4$, $p = .16$).

The groups did differ on time between surveys, which was 66.1 day for those in the intervention group and 44.8 days for those in TAU ($t = -4.8$, $p < .001$). This result was likely because for those in TAU, the post-assessment was scheduled at 8-weeks post baseline whereas for the intervention group, the post-assessment could not be completed until the final intervention session was completed. Scheduling issues for some participants in the IU intervention led to a slightly longer study duration for this group. However, study duration was not associated with baseline to postchanges in key outcomes (IU, MS Acceptance, or GAD-7; all ps $>.25$). Participants in the TAU group were also less likely to be married or living with a partner (44% vs. 74% in the intervention group; $\chi^2 = 4.03$, $p < .05$). This difference in marital status was not significantly associated with change in study outcomes.

Based on randomization testing, no additional demographic or medical variables met our criteria for inclusion as controls (i.e., none differed by group and were associated with the outcome). We therefore did not include control variables in our effectiveness testing.

Assumptions testing. Univariate normality was established for baseline and postscores on all three outcome measures with no distribution having skewness $> .75$ or kurtosis $> .86$. There were no outliers (>3 standard deviations above the mean) for any measure. Homoscedasticity was established through examination of Q-Q plots, which were linear and fell near the 45-degree reference line.

Intervention effects. The regression model predicting IU was significant, $F(2, 41) = 45.3$, $p < .001$, and accounted for 69% of the variance in post-IU scores. The intervention term added a statistically significant amount of variance to the model after controlling for baseline levels of IU ($\beta = -.19$; $r^2\Delta = .03$; $F\Delta = 4.4$, $p = .04$).

The same model predicting MS acceptance was significant, $F(2, 42) = 25.5$, $p < .001$, and accounted for 55% of the total variance. The intervention term was statistically significant after controlling for baseline levels of MS acceptance ($\beta = .38$; $r^2\Delta = .15$; $F\Delta = 13.5$, $p < .001$).

Finally, the overall regression model predicting global anxiety at the post-assessment (GAD-7 total score) was significant, $F(2, 42) = 20.2$; $p < .001$, and accounted for 49% of the total variance. However, the intervention term was not significant ($\beta = -.15$; $r^2\Delta = .02$; $F\Delta = 1.8$, $p = .18$).

To aid in interpretation, the means of the study outcomes by treatment condition are presented in Figure 1. Paired samples *t* tests demonstrated that for the intervention group IU decreased significantly ($t = -2.76$, $p < .01$), and MS acceptance increased significantly ($t = 3.66$, $p < .01$) with effect sizes in the moderate range (IU: $d = .60$; MS acceptance: $d = .80$). However, for those in the TAU group, these variables did not change across time (all ps $> .45$). Therefore, at post-assessment the intervention and TAU groups were significantly different in both IU ($t = 2.1$, $p < .05$; MS acceptance: $t = 3.5$, $p < .001$).

Regarding Hypothesis 2, Pearson's product moment correlations among change scores (post-assessment minus baseline scores) suggested that change in IU was associated with both change in MS acceptance ($r = -.63$, $p < .01$) and change in global anxiety ($r = .54$, $p < .05$). Improvements in ability to tolerate uncertainty were associated with decreases in global anxiety and increases in MS acceptance.

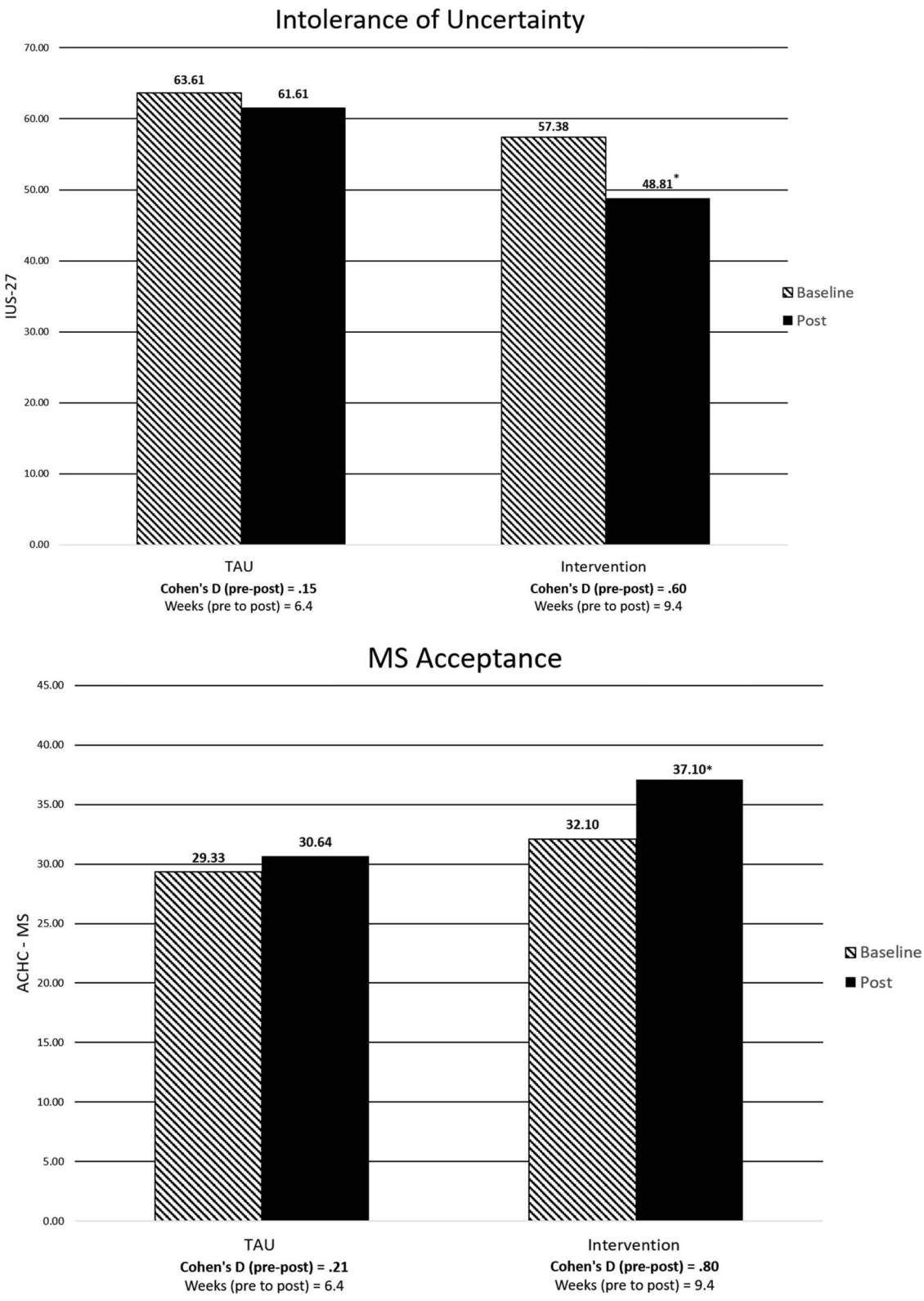

Figure 1. Pre-post change in intolerance of uncertainty and MS acceptance by treatment group.

Discussion

The present study developed and tested an intervention designed to improve ability to tolerate uncertainty in a group of individuals less than three years from a new diagnosis of MS. The target construct (IU) was selected based on the premise that improvements in IU would be foundational to positively impacting critical psychological and well-being outcomes, such as anxiety and quality of life, for this population (Alschuler & Beier, 2015). The intervention was generally acceptable to participants and was associated with high levels of perceived benefit and satisfaction and few negative effects. As hypothesized, this intervention also yielded positive effects on IU and MS acceptance relative to a TAU group.

In many ways, the selection of IU as a target represents an inverse of classic interventions. Such interventions typically prioritize distress (e.g., anxiety) and identify constructs that may contribute to that difficulty, such as physiological activation and cognitive appraisals. For example, in the traditional CBT model, anxiety is the key target, and other positive effects (including greater tolerance for uncertainty) may occur incidentally during treatment. In comparison, the intervention we developed and tested directly and overtly targeted IU, and discussion of uncertainty and the stress it caused was core to the intervention. Although downstream effects on anxiety were measured, anxiety was not a direct focus of the intervention.

There are numerous potential benefits of this type of approach. First, IU is a cross-diagnostic issue, and it could be argued that IU is more central to coping with MS than a resulting psychiatric condition or effect. Second, a robust intervention with universal application may allow for a more efficient approach to providing treatment for MS patients. The concept of a universal treatment approach is not new to psychology. For example, the well-known unified protocol (UP) has been established as a singular, universal approach to treatment of mood disorders (Barlow et al., 2017). Purported benefits of the UP include the possibility for clinicians to have expertise in a single intervention to treat multiple problems as opposed to expertise in multiple interventions. The same principle may hold for this study's intervention.

To our knowledge, only one other trial has been conducted using an intervention focused exclusively on improving IU. Recently, Hebert and colleagues (Hebert & Dugas, 2018) reported on an IU intervention based on behavioral experimentation. In a case replication series, seven French-speaking individuals with GAD completed the 12-session intervention, which focused on identifying and testing relevant personal beliefs about uncertainty via predetermined behavioral experiments. This behavioral approach was effective at reducing rates of GAD in this sample and supports the idea that one can reduce GAD symptoms by exclusively targeting IU. Although our own intervention focused more on radical acceptance of uncertainty and on cognitive defusion strategies (rather than on behavioral experimentation to challenge beliefs about uncertainty) and focused more narrowly on the uncertainty associated with a medical condition, the underlying intent of both interventions were similar, supporting the applicability of this concept across populations.

Although our intervention was designed to improve IU, we were also interested in the extent to which participants became more accepting of their MS diagnosis as a result of the intervention. Results of the trial were positive, and improvements in MS acceptance were associated with improvements in tolerance for uncertainty. In fact, the effects for improving MS acceptance were slightly larger than those for IU. Future research is needed to better understand the mechanisms by which these constructs were impacted, but hypothetical mechanisms are apparent. A central element of the study was to address cognitions about certainty and, perhaps more importantly, to promote the perspective that one can live well despite uncertainty and uncertainty-related cognitions. Consistent with principles of acceptance and commitment therapy, this theme was supported by the idea that an unpleasant scenario (i.e., the presence of uncertainty) does not have to be fixed or resolved prior to moving forward with one's life; rather, the goal is to be able to coexist with its presence and stay focused on living consistent with one's values. We believe that the reluctance to live with uncertainty is a barrier to acceptance for many individuals with MS. Consistent with acceptance research at large, being able to "accept MS" means accepting the challenges that come with it. One of these challenges is surely living with the constant specter of the unpredictable loss of function.

One notable strength of this study is the application of a psychosocial intervention to individuals recently diagnosed with MS. In early MS, symptoms typically develop slowly, and most individuals report experiencing symptoms for years before diagnosis. A period of relatively mild and stable symptoms typically emerges in the early course. For these reasons, in the MS research literature, the terms "newly" or "recently" diagnosed are often used to describe a wide range of time frames, including individuals up to 5 years after diagnosis (Kiropoulos et al., 2016). To our knowledge, our small sample represents the most recently diagnosed group of individuals with MS participating in a psychosocial intervention trial in the published literature. Most participants were within six months of diagnosis with a mean of around 12 months.

We targeted this time period with the idea that this is a critical period of adjustment (Rintell et al., 2012). Intuitively, we believe that there is extra value to promoting healthy coping at this stage. Early adjustment is a flexible period of learning during which a person's perspective may be particularly malleable. By optimizing coping at this early stage, patients may find themselves on a "better" or "healthier" coping trajectory for the long term. We were initially concerned that this period would also be a time when individuals face numerous competing demands that may detract from their ability to participate in this type of intervention. However, we discovered this was not the case, and there was good interest, engagement, and positive outcomes for most participants.

Last, we designed this intervention with accessibility in mind and found this did not compromise the impact of the intervention. Accessibility was targeted in two ways. First, we developed a brief intervention (six sessions), understanding that individuals at this stage of the disease have numerous competing demands across both medical and nonmedical domains. For example, individuals with early MS tend to be in their 20s or 30s, may have young children, and often continue to work. Second, we included an option to deliver the intervention by telephone to overcome any barriers to participation in the study. Consistent with other studies of telephone-delivered interventions (Ehde et al., 2015; Mohr et al., 2000), we were able to demonstrate a positive effect and endorse the concept of delivering a high-quality psychotherapeutic intervention remotely.

This study was preliminary and has some significant limitations. Most importantly, this was a pilot intervention with a relatively small sample. Although our sample of 48 individuals exceeds typical recommendations for pilot research (Lancaster, Dodd, & Williamson, 2004), small samples are inherently unstable, and our findings certainly require replication with a larger and more diverse group. Second, we relied on a quasi-experimental design. Although randomized, neither the therapist nor the participants could be blinded to treatment condition. The comparator was a no treatment control group (TAU). Although TAU may be an appropriate comparator for certain pilot RCTs (Reynolds et al., 2001) it is designed only to counteract the effects of time and repeated testing. Thus, there is always the possibility that intervention effects were driven by nonspecific or placebo factors including patient expectancies and therapist attention rather than by the treatment per se. Participants were explicitly told that their interventionist would never see their individual level data, and outcome data were collected online through a de-identified database. However, we do not know if factors such as social desirability influenced results differently between TAU and treatment groups.

Although there is general agreement in the literature that IU is a core feature of worry and anxiety for some individuals, it remains to be seen whether directly targeting this variable offers any incremental benefit over traditional approaches focusing on symptom reduction. Given that certain forms of CBT may also indirectly affect tolerance for uncertainty (Newby et al., 2018; Talkovsky & Norton, 2018), future work should involve direct comparisons of IU-focused interventions with these more general CBT approaches. It may be that these therapies achieve similar outcomes through different mechanisms or that they are differently helpful for patients based on their level of IU, goals, and preferences for treatment. It may be that there is no incremental benefit to targeting IU above other anxiety-related constructs, which would be important information for treatment development. This is simply not known and cannot be inferred from these pilot data.

Another limitation of our study was the limited time frame for assessment. An underlying goal of this intervention was to help individuals get on a positive coping trajectory that optimizes function and quality of life over the duration of their MS. As a brief pilot without a long-term follow-up, we were unable to assess the extent to which this was accomplished. We can state with confidence that the intervention improved an individual's current level of functioning, but a study with a more distant follow-up would be required to determine whether it makes a difference long term. Related to timeframe is the fact that our two groups differed in terms of weeks between assessments (6.4 for TAU and 9.4 for the intervention). This was an unintended consequence of scheduling, which unfortunately did not properly account for the greater likelihood of delay in people completing six sessions of an intervention relative to those in TAU. Although this difference did not substantially impact results, it is worth noting. Measures of social function or overall quality of life will also help to determine if the intervention makes a lasting improvement outside of improving self-report psychological constructs.

Despite these limitations, the present study provides preliminary evidence that an intervention developed to specifically target ability to tolerate uncertainty can improve IU and MS acceptance in individuals with early MS. The intervention is a novel method of addressing an issue that is central to living with MS (Simmons, 2010) and could be applied widely to positively impact patients who present with a variety of mood and quality of life-related concerns. These results support the need for ongoing research in this area, including larger trials against active interventions and with longer-term follow-up.

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