Distress improves after mindfulness training for progressive MS: a pilot randomised trial

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Abstract

Background. Mindfulness-based interventions have been shown to effectively reduce anxiety, depression and pain in patients with chronic physical illnesses. **Objectives.** We assessed the potential effectiveness and cost-effectiveness of a specially adapted Skype distant-delivered mindfulness intervention, designed to reduce distress for people affected by primary and secondary progressive MS. **Methods.** Forty participants were randomly assigned to the 8-week intervention (n=19) or a waiting-list control group (n=21). Participants completed standardised questionnaires to measure mood, impact of MS and symptom severity, quality of life and service costs at baseline, post-intervention and 3-month follow-up. **Results.** Distress scores were lower in the intervention group compared with the control group at post-intervention and follow-up ($p<0.05$), effect size -.64 post-intervention and -.94 at follow-up. Mean scores for pain, fatigue, anxiety, depression, impact of MS were reduced for the mindfulness group compared with control group at post-therapy and follow-up; effect sizes ranging from -.27 to -.99 post-intervention and -.29 to -1.12 at follow-up. There were no differences in quality-adjusted life years, but an 87.4% probability that the intervention saves on service costs and improves outcome. **Conclusions:** A mindfulness intervention delivered through Skype video conferences appears accessible, feasible and potentially effective and cost-effective for people with progressive MS.

INTRODUCTION

Multiple sclerosis (MS) affects 2.3 million people worldwide [1], including 127,000 people in the UK [2]. MS patients exhibit a higher prevalence of mood disorders relative to other medical [3] or neurological [4] conditions. Prevalence rates for depression and anxiety in MS are especially high [5].

These psychological sequelae may contribute to disease-related processes in MS [6]. Preliminary evidence suggests that reducing stress in MS results in reduction in new CNS lesions [7]. It therefore appears to be an important priority to make effective psychological therapies more readily available to people with MS.

To date very few psychological therapies for MS have differentiated between patients with relapsing-remitting (RR) MS and those with a progressive MS type [8]. Further, most of the new MS treatments focus on RRMS [9]. We address this imbalance by piloting an intervention that was developed for and with the help of patients with secondary progressive (SP) and primary progressive (PP) MS.

Mindfulness training can help people adjust to chronic illness [10]. Controlled trials on mindfulness in MS [11] showed that after the mindfulness training, patients reported improvements in quality of life, depression, fatigue [12, 13], standing and dynamic balance [13,14], and reduced fatigue and pain [15].

These results suggest that mindfulness is helpful in MS, but only one small study evaluated this methodology with patients with SPMS [14], two had small percentages (18%; 24%) of people with SPMS in their sample [12,13] and

none looked at people affected by PPMS. Further, the previous trials excluded patients with more severe symptoms and limited mobility. In this study, we included all levels of disease severity and disability.

The aims of this trial were:

1. To test trial processes to inform a phase III trial.

2. To evaluate the potential efficacy of the mindfulness intervention in terms of improvements in distress, depression, anxiety, impact of MS, pain and fatigue.

3. To assess the potential cost effectiveness of the mindfulness intervention.

METHODS

Study sample

We used a parallel group randomised control design. We recruited 40 participants across the UK. A pilot trial of at least 30 participants is adequate for obtaining estimates of the standard deviation of the outcome variable to determine sample size for an efficacy trial [16]. We recruited potential participants through adverts on the MS Society website and from National Health Service (NHS) MS centres across the UK.

Recruitment took place between December 2012 and May 2013. We administered the screening questionnaires via telephone. Inclusion criteria were diagnosis of PPMS or SPMS, internet access and some level of distress determined by a score of 3 or greater on the General Health Questionnaire; GHQ-12 [17]. This cut-off score was chosen following recommendations for

MS [18]. Exclusion criteria were severe cognitive impairment, as determined by a score of 20 or smaller on the Telephone Interview for Cognitive Status-Modified; TICS-M [19] and high suicide risk, as assessed by a score of 20 or greater on the Clinical Outcome of Routine Evaluation; CORE-10 [20]. Finally, people were excluded if they reported any serious psychological disorders (e.g. psychosis, substance abuse), severe hearing impairment, attending other psychological therapies or prior formal training in mindfulness.

Standard protocol approvals, registration and patient consents.

The study was approved by London City Road and Hampstead Research Ethics Committee (12/LO/1394) and registered at the Current Controlled Trials database (ISRCTN93263909). All participants completed written informed consent.

Randomisation

Randomisation took place once a cohort of ten patients had been consented, screened and baseline data collected. An independent service at the King's College Mental Health and Neuroscience Clinical Trials Unit (CTU) handled the randomisation, using fixed block sizes of two. This method ensured the researchers could not influence the order of allocation, preserving pre-randomisation allocation concealment. Each cohort of patients was randomised once the numbers recruited were sufficient to begin a group mindfulness course. On receiving the randomisation outcome from the CTU, AB notified participants of their group allocation. Those in the mindfulness group were offered a date for their first session. Participants in the waiting-list

group were discouraged from any new mindfulness related activities during the trial.

Blinding

The trial assessor (SW) was blind to treatment allocation. We used dummy codes in the data file, to ensure the statistician and health economists were blinded to treatment group allocation until they completed the main analyses. The nature of the intervention meant it was not feasible to keep the patients or clinical supervisors blind to treatment allocation.

Mindfulness intervention

The treatment phase took place between February 2013 and July 2013. We delivered the program in 8 hour-long sessions over an 8-week period via Skype video conferences. We restricted the number of participants up to 5 for each group based on Skype user guidance, which suggests the quality of videoconferences drops with more than this number [21]. Participants were sent a headset and webcam together with instructions of how to set up Skype. Participants could see each other and communicate as a group.

The format and manual for the mindfulness group, including length of sessions and individual mindfulness practices, were developed in partnership with patients with MS through initial experimental case studies. The content of the manual was adapted from the Mindfulness-Based Cognitive Therapy (MBCT) course book [22]. MBCT includes most of the mindfulness based stress reduction (MBSR) syllabus with additional cognitive therapy exercises. We adapted these cognitive exercises so that instead of exploring how

thoughts and feelings are linked and how this can lead to low mood, we discussed thoughts regarding having MS and how these thoughts are linked to anxiety and low mood. The eight chapters, one for each session, introduced key mindfulness concepts, addressed issues common to progressive MS, and described homework for the week ahead (see online supplementary material for content of each session). Each session started with a 10-minute mindfulness practice, followed by discussion of this practice and the homework practice of the previous week. Then new concepts (e.g. acceptance, relating to thoughts and self-compassion) were introduced. The mindfulness teacher asked open questions to facilitate a deeper understanding of the concepts. Formal teaching/psycho-education was kept to a minimum. A 5-10 minute mindfulness practice followed and finally homework for the next week was set.

Feedback from people with progressive MS who took part in the series of experimental case-studies (n=6, EDSS range=6.5-7.5) emphasised that we needed to account for compromised concentration, fatigue, mobility and problems with sitting in one posture during mindfulness home practices. We consequently shortened the daily home practice to 10-20 minutes and provided audio CDs produced specifically for this course (details in the supplement). We also adapted the type of standard mindfulness practices by removing mindful movement practice to accommodate patients with little or no mobility. This decision was based on discussions with neurologists, MS nurses and 2 people with secondary progressive MS, who expressed their concern that the inclusion of mindful movement could make the course unattractive to people with severe mobility problems. Guidance in the CD

practices reflected challenges of MS, such as lack of sensations or difficulties retaining a posture. Participants were encouraged to keep a diary of home practice, but, in fact, very few did record it.

Teaching standards and teacher's competence are important in mindfulness especially when working with vulnerable groups [23]. AB, a health psychologist, facilitated the courses. AB was supervised by PC, a clinical psychologist and expert mindfulness practitioner, who listened to session recordings to check fidelity of the intervention. AB and PC met weekly, and PC listened to excerpts of each and every session for supervision and fidelity purposes. Prior to the study AB, completed a recognised mindfulness teacher training course and ran supervised pilot mindfulness groups and one-to-one courses for people with MS.

Waiting-list / control

Participants allocated to the waiting-list group received the treatment they would normally expect within the NHS. People may receive a mix of clinical input and review from both primary and secondary care providers, according to individual health needs. Few patients routinely receive treatment for distress, for example according to a survey conducted by the MS Society [24], two thirds of people agreed that 'The NHS does not provide enough emotional support for MS'.

Measurements

Participants completed online questionnaires at baseline (prior to randomisation), post-intervention and 3-month follow-up. Assessments occurred between January 2013 and October 2013. The blind assessor (SW) notified participants by email when questionnaires were due. Where participants had failed to complete the questionnaires a week later, SW phoned them to ensure that they had received the email and that they were not encountering any technical difficulties. Qualitative interviews (n=15) were conducted with people who took part in the mindfulness groups on their experiences of the intervention. These will be reported in detail elsewhere.

Demographics and MS data

The baseline questionnaire included demographic information, such as ethnicity, age, gender, marital status, education and details about MS. The self-reported Expanded Disability Status Scale (EDSS) [25] was used to measure MS severity. EDSS includes items on mobility, strength, co-ordination, sensation, bladder, vision, speech, swallowing and cognition. EDSS scores can range from 0 (no neurological impairment) to 10 (death from MS).

Primary outcome:

The General Health Questionnaire, GHQ [17] is designed to measure general levels of distress. The GHQ is uncontaminated by the experience of MS-related somatic symptoms and is the most treatment responsive measure of psychological distress in MS [26]. Higher scores on this scale represent high distress.

Secondary outcomes:

Hospital Anxiety and Depression Scale; HADS [27]. This scale assesses the symptoms of anxiety and depression in both secondary and primary care patients [28]. Higher scores on this scale represent high anxiety and depression.

Multiple Sclerosis Impact Scale; MSIS-29 [29]. MSIS-29 measures the physical, and the psychological impact of MS. MSIS-29 subscales have shown good variability, small floor and ceiling effects, high internal consistency and high test-retest reliability [29]. Higher scores on this scale represent high impact.

Pain intensity was assessed with a numerical rating scale [30] (scaled from 0 to 10) addressing the average pain, which is associated with MS according to the patient's point of view. Thereby, 0 represents no pain and 10 the most painful sensation imaginable.

Fatigue Severity Scale, FSS [31], assesses the impact of fatigue in the daily living of patients with three items related to physical impact, three items to the psychological environment and the remaining three are more generic. Higher scores on this scale represent high fatigue.

Service use and costs were measured using an adapted version of the Client Service Receipt Inventory; CSRI [32]. This self-report measure recorded data on hospital, community health and social care services, and informal (unpaid) care from friends and relatives. The CSRI is always adapted for each study in which it is used. The format remains the same but the services included relate

to the illness in question. Also, the CSRI period was chosen to cover the entire follow-up.

EuroQol; EQ-5D [33] considers mobility, self-care, usual activities, pain/discomfort and anxiety/depression and was used to generate Quality Adjusted Life Years, QALYs, [34], using the area-under-the-curve method.

Data analysis plan

Outcome analysis was conducted using Stata 12.1. To compare group demographic and clinical characteristics at baseline we used a binomial test for equal proportions between groups for categorical variables and an independent t-test for equal means between groups for continuous variables. We conducted all group comparisons on an intention-to-treat basis where we analysed participants in the group to which they were randomised. Treatment effects on the primary and secondary outcomes were estimated using linear mixed modelling where the outcome variables at the two post-intervention time points were the dependent variable. Baseline values of the outcome variable, time (post-intervention, follow-up), and group (mindfulness or waiting-list) were included as covariates. In addition, time*group interaction terms were included to allow treatment effects to vary across the post-therapy and 3-month follow-up assessments. Subject-varying random intercepts and slopes of time were included, in order to account for correlation between measures taken on the same individual at various time-points. We explored the effect of informative missingness processes by means of a formal sensitivity analysis [35]. Missing baseline covariates were handled using the missing indicator method [36]. This involves imputing missing values with the

mean of the observed values and including variables for missingness for each variable with missing data in the model dummy.

For the cost-effectiveness analysis, intervention costs were estimated using a bottom-up micro-costing approach of the resources and time spent by professionals providing the mindfulness sessions. Costs of other health and social care services used by participants were derived by multiplying the number of units (admission days, consultations, etc.) by their unit cost, taken from relevant publications [37]. Unit costs for the financial year 2012/13 were applied to individual services reported.

We made cost comparisons between the two groups using bootstrapping methods to account for non-normality in the data distribution. Service cost data were combined with a change in the primary outcome measures (GHQ scores) and quality-adjusted life years (QALYs), generated from the EQ-5D to assess the cost-effectiveness. Incremental cost-effectiveness ratios were constructed. Uncertainty around these was explored using non-parametric bootstrapping with 1000 resamples to produce a joint distribution of incremental costs and effects for the two groups.

RESULTS

Sample selection and attrition

The flow of participants through the trial is presented in Figure 1. Of the 165 information packs that were sent out to the recruitment sites across the UK, 115 people expressed interest in participating, and 93 agreed to be assessed for eligibility. Fifty were excluded, and three declined to be randomised.

Insert Figure 1 here

Of the 40 randomised participants, 17 (42%) had PPMS, and 23 (57.5%) had SPMS. The overall sample was 55% female, predominantly white British (90%), with a mean age of 52.7 years (SD=9.5), with the majority married or cohabiting (77.5%). Median time since diagnosis was 12.0 years (range=1-38).The mean neurological disability score (EDSS) was 6.5 (SD=1.5), which indicates a transition from being ambulant with an assistive device to requiring a wheelchair. Previous mindfulness studies in MS had all cut-off at EDSS score of 6 [11]. The groups were well matched for gender, age, marital status, education, EDSS scores, distress scores and time since diagnosis. However, the intervention group had fewer people with PPMS than the control group. We controlled for MS type in the intention-to-treat analysis to account for potential confounding due to the imbalance in MS type. The demographic and illness characteristics across the groups are presented in Table 1.

Insert table 1 here

Testing Trial Procedures

Suitability of eligibility criteria

Of the 50 people expressing interest in the study but excluded, 34 (68%) had GHQs below the requisite criteria, 3 (6%) had a high CORE score and 1 (2%) had a low TICS score. Twelve further individuals were ineligible for reasons including no access to a computer (8%), a diagnosis of RRMS (14%), and a hearing impairment (2%).

Retention rates

Eighteen of the 19 participants completed the mindfulness intervention. One participant dropped out after the first session due to changes in personal circumstances but continued to complete the study questionnaires. The remaining 18 participants continued participating in the mindfulness course until the end of the intervention. All the participants attended 4 or more of the 8 mindfulness sessions and 14 (73.7%) attended 6 or more sessions**.** Reasons for not attending included: medical appointments, planned holidays, pain/ fatigue and technical problems, e.g. computer virus, stolen computer, problems with audio. In the waiting-list group, 2 participants (9.5%) at post-intervention and 3 (14.3%) at 3-month follow-up failed to complete the questionnaire. In the mindfulness group, 2 participants (10.5%) did not complete the post-intervention questionnaires and 4 participants (21%) the 3-month follow-up questionnaires.

Potential Efficacy

Primary outcome

The mean and standard deviations at baseline, end of the intervention, and 3-month follow-up for all outcomes are presented in Table 2. Table 3 provides the estimates for the treatment effect on the outcome variable in the original units of the scale (estimate column) and as a standardised effect size Cohen's d (effect size column). Mean GHQ scores were lower in the mindfulness group compared to waiting-list group at both the post-intervention and 3-month follow-up. Both differences related to large effect sizes and were statistically significant at the 5% level. The effect size for post-intervention

was -.64, a medium to large effect, and the 3-month effects size was -.94, a large effect.

Descriptive statistics for primary, secondary and process outcomes

Secondary outcomes

Mean HADS depression, HADS anxiety, MSIS psychological and MSIS physical scores, pain and fatigue were reduced for the mindfulness group compared to waiting-list at both post-intervention and 3-month follow-up (Tables 2 and 3). For variables capturing psychological distress (HADS depression, HADS anxiety, and MSIS psychological) the magnitude of the difference tended to be medium to large and was significant for all at both post-intervention and 3-month follow-up, except anxiety post-therapy. Pain, fatigue and MSIS physical showed small to medium effect sizes, but these were non-significant, except for MSIS physical post-therapy and pain at three months.

Insert tables 2 & 3 here

Service use

Both formal service and informal care costs were lower for the mindfulness group. Whilst hospital and social care costs were similar at baseline, by the 3-month follow-up, the waiting-list group had substantially higher costs. This difference is explained by the high inpatient costs, which accounted for more than two-thirds of the health and social care cost for this group. However, this difference was not statistically significant (mean difference= -£720, 95% CI -

£2636 to £1196). Similarly, informal care costs were higher for the waiting-list group. It is worth noting that although the total costs were not particularly different at baseline (control group: £3703 versus mindfulness group: £3080), the difference had widened at 20-week follow-up, but was not statistically significant (mean difference -£2285, 95%CI -5003 to 579).

QALYs accrued were greater in the waiting-list control group (see EQ5D Table 2), but this was largely due to a large baseline difference. When we control for baseline utility, the QALY difference is close to zero (-0.006, 95% CI -0.039 to 0.027). This, along with the cost savings for the mindfulness group, means that the latter has more than a 90% chance of being the most cost-effective option at a threshold of £20,000.

Figure 2 is a scatterplot representing the bootstrapped societal costs-effects (GHQ) pairs for mindfulness compared to waiting-list (TAU). A great proportion (87.4%) of the scatter points lie in the south-east quadrant, showing that mindfulness is associated with lower costs, and better GHQ score, compared to the waiting-list group, therefore making it dominant. This indicates an 87.4% probability that the intervention saves money and improves outcomes.

Insert Figure 2 here

DISCUSSION

The study suggests that a Skype delivered mindfulness intervention, adapted specifically for people with progressive MS, is feasible in terms of participants' willingness to be screened for and enter a randomised controlled trial, and

complete the intervention and assessments. The mindfulness intervention showed positive effects for people with progressive MS. Specifically, distress, as measured by GHQ, was lower in the mindfulness group compared to waiting-list group at the end of the intervention, and the effects remained at the 3-month follow-up. The effect size increased from a medium at the end of intervention to large effect at follow-up. Pain, fatigue, anxiety, depression and psychological and physical impact of MS were also reduced in the mindfulness group compared to waiting-list group both post-intervention and at 3-month follow-up. The largest effects were for the mood variables.

Our findings also indicate lower total costs (health, social and informal care) for the mindfulness group compared to the waiting-list group, but these differences were not statistically significant. For both groups, informal care costs contribute a considerably higher proportion to the total costs compared to health and social care, which is not unusual for MS patients [38]. Although the observed differences in costs QALYs are not statistically significant, the large cost differences and effects on outcome mean that there was a high probability that the intervention was cost-effective.

There were no significant differences in QALY's between the groups using EQ-5D. This could be attributed to the short follow-up period or the non-responsiveness of the EQ-5D in people with progressive MS. Three of the five items focus on physical abilities that are unlikely to change in progressive disease. Previous work indicates issues with all the five domains of the EQ-5D [39]. The absence of questions related to cognition and fatigue which are often major issues in people with progressive MS have also been queried [40,41].

Several previous trials of mindfulness interventions have shown benefits upon psychological well-being in people with chronic conditions [10]. This pilot trial looked specifically at reducing distress, anxiety and depression for people with progressive MS as very few psychological interventions have focused specifically on this group of patients with MS [9]. The shorter duration of each session and the daily homework practice meant that the mindfulness course might be more accessible and manageable to this group of patients. In fact, no dose response has been found between in-class hours and effect size [42] and shortened mindfulness practice has been successful before, for example in people with psychosis [43], anxiety, depression [44] and health-care staff [45].

Further, traditional mindfulness programs all include mindful movement. We removed this practice based on feedback from people with progressive MS involved in the adaptation of the intervention and instead we used a general mindfulness practice that people could do when sitting. This made sure our intervention was applicable even for people with severe mobility limitations. Our study also suggests that people with limited physical function can benefit from mindfulness practices, even without the mindful movement practice. However it is difficult to determine the actual effect of removing the mindful movement from the practices. According to a recent meta-analysis different meditation styles and traditions are characterized by different patterns of neural activation [46].

Limitations of this pilot study should be noted. First, mindfulness as a process was not measured. Observed benefits cannot be directly attributed to increased mindfulness. Second, there was no active control group; a full trial,

with an active control, is needed to control for nonspecific therapy effects. Third, one mindfulness teacher delivered all the mindfulness courses. Fourth, some participants questioned the adequacy for screening purposes (though not outcome assessment) of the GHQ response metric that asks respondents to compare their recent health with how it is 'usually'. For many participants 'same as usual' (scored 0) can mean experiencing high levels of distress, if this is seen as a long-term problem. Fifth, psychological outcome measures were based on patients self-report, and so these measures were dependent on participants' willingness to report any difficulties. Finally, a larger trial can further examine the efficacy of the intervention.

To conclude, this is the first study to show that delivering mindfulness to small groups via Skype is likely to be an effective treatment for distress in progressive MS. Further, a web-based training can be an accessible and flexible way to reach people across the country. The current study is the first to show that this adapted treatment approach is likely to be cost effective. The present study had a good recruitment rate, uptake and retention, suggesting a basis for further investigation in a larger scale study.

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