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The effectiveness of the Mitchell Method Relaxation Technique for the treatment of fibromyalgia symptoms: a three-arm randomised controlled trial.(MS 2014-0734)

The effectiveness of the Mitchell Method Relaxation Technique for the treatment of fibromyalgia symptoms: a randomised controlled trial

Objective: To evaluate the effectiveness of the Mitchell Method Relaxation Technique (MMRT) in reducing symptoms of fibromyalgia. **Design:** A randomised controlled trial was used to compare the effectiveness of self-administered MMRT (n= 67) with attention control (n = 66) and usual care (n = 56) groups. **Main Outcome Measures:** Primary outcomes included self-reported fatigue, pain, and sleep. Secondary outcomes were daily functioning, quality of life, depression, and coping, anxiety and perceived stress. Outcomes were assessed at baseline, post-intervention (four weeks) and follow-up (eight weeks). **Results**: A significant combined improvement on outcomes ($p<.005$), specific significant effects for sleep problems ($d=0.29$, $p<.05$), sleep inadequacy ($d=0.20$, $p<.05$), and fatigue ($d=0.47$, $p<.05$) were present in the MMRT group. At the follow-up, fatigue did not differ to the post-intervention score ($p=.25$) indicating short-term sustainability of the effect. The effects on sleep problems and sleep inadequacy were not sustained. The pain levels decreased when the MMRT was practiced three times a week ($p<.001$). **Conclusion:** MMRT was effective in reducing pain, sleep problems, and fatigue. High rates of relative risk reduction for fatigue (37%) and pain (42.8%) suggest clinical significance.

Keywords: fibromyalgia; stress response; fatigue; sleep quality; pain; Randomised Controlled Trial.

Abbreviations:

PMR=Progressive Muscle Relaxation;

MMRT=Mitchell Method Relaxation Technique;

FIQR=Fibromyalgia Impact Questionnaire (Revised);

MOS=Medical Outcome Sleep Scale;

HADS-A=Hospital Anxiety and Depression Scale (Anxiety Subscale);

HADS-D=Hospital Anxiety and Depression Scale (Depression Subscale); PSS=Perceived Stress Scale;

VAS=Visual Analogue Scale;

HRQoL=Health-related Quality of Life.

Introduction

Fibromyalgia is a debilitating chronic condition, which is hallmarked by widespread pain, fatigue, sleep disturbance, and negative affect (Wolfe, Smythe, Yunus, Bennett, Bombardier, & Goldenberg, 1995). It is thought that 2 to 3% of the population experience this condition, although the prevalence rates are believed to be an underestimate (Bennett, Jone, Turk, Russell, & Matallana, 2007). The costs of health care for fibromyalgia are substantial (Berger, Dukes, & Oster, 2007). Currently, symptom management is the primary form of treatment, with pharmaceutical treatments commonly prescribed to reduce pain symptoms. Most medications, however, have adverse effects, which lead to the discontinuation of treatment, resulting in limited and non-sustained effect (Arnold, 2007). Multidisciplinary treatments, based on a biopsychological framework and aimed to address multi-domain symptoms of the condition, should form an important component of the treatment approach.

The MMRT is an auditory relaxation technique, practiced individually and in silence. MMRT focuses on the psychoneuroimmunological link between mind and body, and incorporates guided imagery, muscular relaxation and breathing exercises, and implies full engagement and autonomy (Mitchell, 1997). The stress-related posture is thought to increase muscle tension and influence the nervous and endocrine systems as well as to cause muscle stiffness and dystonic patterns (Mitchell, 1990). Mitchell (1990) suggested that this method causes postural realignment by reversing stress-related posture. Findings from a systematic review of mind-body treatments for fibromyalgia suggest that guided imagery and progressive muscle relaxation (PMR) are efficient techniques for the management of the symptoms of fibromyalgia (Baranowsky, 2009). These techniques have been associated with a moderate positive effect on quality of life and a spectrum of fibromyalgia symptoms in two trials (Baranowsky, 2009). The MMRT has been found to reduce the physiological stress response in healthy adults, indicated by heart rate measurements (Bell & Saltikov, 2000). MMRT is a technique that can be taught and self-applied and therefore is very likely to have a long-lasting sustained positive effect on outcome measures. Coherent combination of imagery, muscular relaxation and breathing addresses the management of symptoms associated with FM. It is, therefore, expected, that the MMRT will diminish features of the condition that contribute to fibromyalgia symptomatology.

Many relaxation therapies involve prolonged therapy sessions, some taking a minimum of 45 minutes, during which patients have to be immobile. Considering that fibromyalgia patients report switching between relaxation and movement as one of the strategies they use to cope with pain (Theadom, Cropley, Humphrey, 2007), long immobility during these sessions may induce pain and hamper the therapeutic effect. In contrast, MMRT sessions are short, and therefore, the technique is expected to be more effective at symptom management and also less onerous for patients. In addition, to make the therapy acceptable for participants, we chose to deliver the study online.

We propose that the MMRT will reduce fibromyalgia symptoms through its effect on the hypothesized underlying cause of the condition whilst the online delivery, self-application, and the short duration of each session reduce the burden on the fibromyalgia sufferers. In this RCT we examined the effectiveness of an online Mitchell Method Relaxation programme (Mitchell, 1997) in reducing fibromyalgia symptoms. The primary objective of this study was to evaluate the immediate effects of the MMRT on fibromyalgia symptoms and its short-term sustainability as well as to evaluate the dose-sensitive effect of the programme on health outcomes. The secondary objective was to identify its effects for subgroups of patients presenting with different co-morbidities, and to explore the mechanisms of the intervention. The third objective was to evaluate the clinical significance of the MMRT.

Method

Design

A three-arm randomised controlled trial (RCT) was used to evaluate the effectiveness of the MMRT in comparison to active control and usual care groups. The study was conducted in accordance with the CONSORT Statement for RCTs of Non-Pharmacologic Treatments (Boutron, Moher, Altman, Schulz, & Ravaud, 2008) and, where applicable, with the CONSORT 2010 Statement (Schulz, Altman, & Moher, 2010). The study was conducted online in England.

Participants and Recruitment Procedure

The study received ethical approval from the Faculty of Social Sciences, University of Surrey Ethics

Committee. Individuals diagnosed with fibromyalgia were approached online via regional support groups and 201 enrolled to participate in the study. Study participants gave their consent to take part in the current study via e-mail. To be eligible, participants had to meet the following criteria: aged between 18 to 80 years, have Internet access and to be diagnosed with fibromyalgia syndrome as outlined by American College of Rheumatology classification criteria of widespread pain persistent for at least 3 months and tenderness at a minimum of 11 of the 18 tender points (Wolfe et al, 1995). Additionally, participants had to satisfy the new preliminary diagnostic criteria for fibromyalgia (Wolfe, Clauw, Fitzcharles, Goldenberg, Katz, & Mease, 2010). Internet connectivity across Great Britain is now widespread, with approximately 83% having access to the Internet, and 73% of adults reporting use of the Internet every day. Internet connectivity is not confined to the more economically affluent groups (Office for National Statistics, 2013). Participants reporting severe psychiatric comorbidities, life-threatening conditions, substance abuse and pregnancy as well as recipients of any non-pharmaceutical treatment were excluded from the study. To detect a medium effect size, using MANOVA with power of $\beta=0.8$ and to account for 20% dropout rate, 67 participants were recruited for each group.

Health Outcomes and Measurements

Primary Outcome Measures

Pain Severity. To assess the severity of pain, a Visual Analogue Scale of Pain (VAS) was employed. VAS are widely used to assess pain in patients with fibromyalgia (Salaffi, Sarzi-Puttini, Ciapetti, & Atzeni, 2009). The scale was adapted for online use and transformed from a 10 cm scale into 1-10 point scale. Lower VAS scores indicate lower level of pain severity.

Sleep. The Medical Outcome Sleep Scale (Hays & Stewart, 1992) was employed to evaluate sleep quality. The MOS is a patient self-report sleep scale consisting of 12 items and is used to assess sleep across six domains: (1) sleep disturbance; (2) snoring; (3) awaking, due to shortness of breath or with a headache; (4) sleep adequacy; (5) somnolence; and (6), sleep quantity. The Sleep Problems Index summarizes responses using an abbreviated six-item index. This index contains questions from the sleep disturbance, sleep inadequacy, respiratory impairment, and somnolence domains, but not sleep quantity. Ten items of the

scale are scored using a six-point response scale, one item uses a five-point Likert scale, and sleep quantity is an open-ended question about the actual number of hours slept. Each subscale score and Sleep Problem Index range from a 0–100 scale and represents the percentage of a particular sleep domain; sleep quantity was recorded as 0–24 hours. Higher scores for the domains indicate worse sleep problems. The MOS has good construct validity and reliability when used with fibromyalgia patients (Cappelleri, Bushmakin, McDermott, Dukes, Sadosky, Charles, Petrie, & Martin, 2009). The Cronbach's α for each of the subscales was higher than .70 (Cappelleri, 2009).

Fatigue. Levels of fatigue were assessed using fatigue subscale of the Short Form-36 Health Survey (Ware & Kosinski, 2001). The subscale is a sensitive, valid and brief measure of fatigue and consists of 4 items: (1) 'Did you feel full of life?', (2) 'Did you have a lot of energy?', (3) 'Did you feel worn out?', & (4) 'Did you feel tired?'. The Likert scale for each item ranges from 1 ('none of the time') to 6 ('all of the time'). The total score represents the sum of the scores for all items and ranges from 4 to 24, with a greater score representing higher levels of fatigue. The SF-36 fatigue scale is highly correlated with multidimensional fatigue, as measured by Fatigue Symptom Inventory Scale, r=-0.68 to -0.77 (Brown, Kroenke, Theobald, & Wu, 2011).

Secondary Outcome Measures

The impact of Fibromyalgia. The Revised Fibromyalgia Impact Questionnaire (FIQR; Bennett, Friend, Jones, Ward, Han, & Ross, 2009) was administrated to assess the components of health that are affected by fibromyalgia. The FIQR consists of 10 items constituting 3 dimensions: (1) 'fibromyalgia symptoms', (2) 'function' and (3) 'overall impact'. The FIQR is an advanced measurement in comparison to FIQ (Burckhardt, Clark, & Bennett, 1991), as it includes symptoms of tenderness and dyscognition and does not have sex or race biased items. The FIQR has desirable discriminant validity (Luciano, Aguado, & Seranno-Blanco, 2013). The Cronbach's α value of the FIQR domains was higher than 0.80 (Bennet et al., 2009).

Depression (Dysphoria). To assess depression (dysphoria) the Depression subscale of the Hospital Anxiety and Depression Scale was employed (Zigmond, & Snaith, 1983). Evidence of the discriminant validity, reliability of the measure in people with fibromyalgia has been demonstrated (Pallant, & Tennant, 2007).

Anxiety. To assess the impact of treatment on the levels of negative affect, the anxiety subscale of the Hospital Anxiety and Depression Scale (Zigmond, & Snaith, 1983) was utilised. Greater score on HADS-A indicates lower anxiety levels.

Health-related Quality of Life. HRQoL was measured using SF-36 Health Survey (Ware & Kosinski, 2001). SF-36 has a desirable reliability and has been validated for clinical samples.

Coping. Coping difficulty and coping efficacy were assessed with two single items: 'how difficult was it to cope with symptoms for the past week?' and 'How satisfied are you with how you coped with symptoms during the past week?' respectively. The items are valid measures of coping efficacy and coping difficulty with good reliability (Lazarus, & Folkman, 1983).

Perceived Stress. The Perceived Stress Scale (PSS) was used to assess levels of perceived stress (Cohen, Kamarck, & Mermelstein, 1983). The PSS comprises of 10 items assessing the frequency of everyday stressful events and the perceived control of stressful event. PSS has been validated on a clinical sample of fibromyalgia patients. PSS construct and discriminant validity was reported. The scale has very good reliability, Cronbach's α=0.78 [Cohen, & Williamson, 1988).

To evaluate perceived effectiveness of the treatment intervention and the comparator, a Treatment Creditability Scale was utilised (Dunmore, 2001). The credibility scale asks participants to rate the logical approach of the treatment, the certainty that treatment will be successful and the degree of confidence with which to recommend the intervention to a friend. The items' scale ranges from 0 ('not at all') to 10 ('completely'). The measurement of the dose comprised of the single item inquiring the frequency with which the intervention was applied. The item's scale ranged from 1 ('every day') to 6 ('less than once a week'). To evaluate therapeutic effects of MMRT the assessment of outcome measures was performed three times: prior to the intervention treatment, immediately after a month of self-application, and at one-

month follow-up. At the baseline assessment participants reported the comorbidities and demographic characteristics.

Randomization

Participants were allocated to one of the three study conditions in blocks of 30 in a 1:1:1 ratio. An algorithm implemented within the RandNum and SysRand functions, provided by the SSIWEB software, produced the automated random allocation to one of the groups. Participants were then able to download their allocated instructions from the next page on the website. Participants in the experimental condition were able to download instructions for the MMRT intervention, the attention control group were asked to listen to a relaxation audio recording and usual care participants were instructed to close the questionnaire.

Treatments

The Mitchell Method Relaxation Technique (MMRT)

The intervention group received written instructions of the Mitchell Method Relaxation Technique (Mitchell, 1997) and a short (5 minutes 20 seconds) audio recording of the guided technique. Participants were asked to practice the MMRT by using the same audio recording every day for one month. When prepared and engaged, the participant sat at a desk or in a chair with a high back or laid on the floor. The participant was then given definite verbal orders (e.g. 'move and feel', 'stop', 'feel') to engage in a series of muscle relaxation exercises in the following sequence: arms, legs, body, head and face. Participants were not provided with training in discriminating between levels of muscle tension. Participants practiced muscle relaxation at their preferred level of tension to ensure autonomy – a key aspect of MMRT. After the completion of the exercise, participants engaged in deep breathing at a comfortable rate. Lastly, the participant performed an imagery task, recalling a pleasant occasion or concentrating on a pleasant repetitive sequence (e.g. song, prayer) for one minute.

The Attention Control

The attention control group received an audio recording of 'white noise' and steady sound of resting heart rate (60 beats per minute) - imitation of 'being in the womb'. Participants were instructed that regular

listening to the recording is deemed to initiate relaxation, increases sleep quality and reduces tension and stress, and subsequently reduces pain levels. Participants were asked to listen to the recording on a daily basis for one month. The length of recording was identical to the intervention. The mean total creditability score was not significantly different between participants who received the MMRT (M=6.02, SD=2.64) and participants who received the attention control treatment (M=5.30; SD=2.71), t (68) =1.10, p=.27), verifying the successful control for the placebo effect. Creditability score was not associated with health outcomes. Self-reports were employed to measure adherence to both, the MMRT and attention control, at post-intervention assessment and follow-up.

Waiting list control

Participants allocated to the waiting list group did not receive an active treatment and proceeded with usual care. All participants were offered the MMRT audio recording upon the completion of the study.

Study Flow

The flow chart (*figure 1*) presents process of the study, group allocation, excluded cases, and attrition rates. Dropouts resulted from the disregarding of e-mails, difficulty in contacting the participants, and withdrawals for personal reasons (i.e. holidays).

Intention-To-Treat Procedure

In accordance with the CONSORT statement for reporting randomised trials (Zwarenstein, Treweek, Gagnier, Altman, Tunis, Haynes, Gent, Oxman, & Moher, 2008), the statistical analysis was performed on the 'intention-to-treat' basis to avoid overestimation of clinical effectiveness and to control for bias introduced by participant dropout. All patients were included in the analysis, regardless of the treatment actually received and regardless of subsequent withdrawals or deviations from the protocol and loss to follow-up. Missing responses were imputed using multiple imputation procedure (Sterne, Carlin, Spratt, Royston, Kenward, Wood, & Carpenter, 2009). Linear regression analysis procedures were performed to determine the predictors of outcome variables. Co-morbidities, age, medication, and duration of the condition were significant predictors of baseline and post-treatment outcome measures. Therefore, to

preserve the naturally occurring trends in data the latter were stated as predictors in the linear regression model, used for multiple imputations. Due to reciprocal relationships between the outcome variables, all outcome measures were stated as predictors and used in the linear regression model for multiple imputations. The Rubin Rule of averaging on 5 sets of imputed data was performed to control for the uncertainty of the variance. Insignificant results of Little's test confirmed the assumption that data-values were missing at completely random (MACR) [χ^2 (756; 58) = 84.153, p=1]. Differences between means of the observed and imputed data were insignificant based on a 95% confidence level.

Participant's characteristics and randomization check

The age of participants ranged from 37 to 69 years. Participants were predominantly Caucasian (90%) and female (93.7%). The demographic characteristics are presented in Table 1. Frequencies of co-morbidities and gender distribution across groups are representative of the fibromyalgia population. To verify the randomisation and equal distribution of baseline characteristics between the three groups, the χ^2 test was performed on the categorical variables and MANOVA on the continuous variables. The groups did not differ in terms of distribution of males and females [χ^2 (2; 191) =.888, *p*=.642]. The frequencies of Restless Leg Syndrome [χ^2(2;191)=2.26, *p*=.323], Asthma [χ^2 (2;191)=2.52, *p*=.882], Chronic Fatigue Syndrome [χ^2(2;191)=816, *p*=.665], Sleep Apnoea [χ^2 (2;191)=4.48, *p*=.107] , depression and other co-morbidities [χ^2(2;191)=3.40, p=.183] were the same across the study groups. The three groups did not differ in terms of age [F(2; 191) =.834, *p*=.436] and diagnosis duration [F(1,191) = 2.76, *p* =.070]. Using Pillai's trace, MANOVA indicated, that at baseline, overall variances across all outcome measures was not significantly different across three study groups [V=.328, F (54; 326) =1.186, *p*=.187, β=.991]. However, follow-up univariate between-subjects ANOVA demonstrated the significant difference in the mean VAS pain score at the baseline [F (2; 188) =3.08, *p*=.05]. Post hoc multiple comparisons with Tukey's adjustment identified that the mean value of the baseline VAS pain score of the MMRT group (M=7.43, SD=1.68) was significantly higher than the mean value of the waiting list control group [(M=6.68; SD=1.42), *p*<.05]. The somnolence baseline scores significantly differed across the three groups [F (2; 188) =3.50, *p*<.05]. The mean baseline somnolence score of the MMRT group (M=55.19; SD=27.74) was significantly higher than the mean score for the control group (M=46.80; SD=33.86), *p*<.05). The baseline mean scores of FIQR, HRQoL, sleep dimensions, anxiety, dysphoria, perceived stress, coping efficacy and coping

difficulty did not differ across the groups.

Statistical Analysis

Evaluation of the immediate effects of the treatment

The researchers performed blinded analysis of the data. Two-tailed hypothesis tests were employed throughout the analysis. Between-subject MANCOVA was employed to test the differences between groups on the extent of change among outcome variables, after having adjusted for pre-intervention levels. MANCOVA, in contrast to several ANOVAs, accounts for multivariate relationships between pain, sleep, fatigue, and other outcomes. Using Levine's Test of Equality of Error Variance, the assumption of homogeneity of variance was supported, indicating the robust multivariate analysis. The baseline measures for all outcomes were included as covariates due to significant differences in baseline VAS score and somnolence scores across groups and its reciprocal relationships with other primary and secondary outcome measures. Age, medication, co-morbidities, and diagnosis duration were included as covariates, to control for its predictive value identified at the preliminary analysis. To provide accurate estimates of the effect sizes for the population Cohen's *d*s were calculated. MANCOVA was followed up with discriminant function analysis to test the differences between study conditions and to explore the covariance between changes in outcome variables.

Evaluation of the sustained effects of the treatment

A treatment (MMRT, Attention Comparator, Control Group), by time (baseline, post-intervention, one month follow-up) Mixed-Subject MANOVA was conducted to evaluate the effect of the intervention against the attention group and the waiting list control group. Due to the significant results of Mauchley's test and the violated assumption of sphericity for sleep inadequacy scores [χ^2 (2) =30.3, p<.001], sleep problems scores [χ^2 (2) =22.87, p<.001] and fatigue scores [χ^2 (2) =1.81, p<.05] the Greenhouse–Geisser corrected values are presented. The differences between the groups are assessed by planned comparisons and differences across time are assessed using Bonferroni adjustments.

Evaluation of effects for subgroups, dose-sensitive effects and mechanisms of the treatment

Bootstrapping method of simple moderation analysis was performed (Hayes, 2009; 2012; 2013) to test for moderating effect of comorbidity (i.e. RLS) on the effectiveness of the MMRT and the conditional effect of the MMRT at a value of dose. A presence of comorbidity was coded as 1 and its absence was coded as 0. Multiple mediation analysis (Preacher & Hayes, 2008) to test for the indirect effects of the intervening variables was performed.

The clinical significance of the treatment

The clinical significance of the treatment is presented by taking into account: the Absolute Risk Reduction (ARR), Relative Risk Reduction (RRR), Number Needed to Treat (NNT), Cohen's U_3, and Probability of the Superiority. The ARR is an arithmetic difference between experimental group and the control group in percentages of participants who displayed the reduction in the outcome scores after the treatment. The RRR is based on the relative percentage of participants who benefited in terms of each outcome in comparison to control groups. NNT was calculated using the following formula: 1÷ Ö (Cohen's *d*−1÷(*CGP*))−*CGP*, where Ö is the cumulative distribution function of the standard normal distribution; CGP is the control group's percentage of people displaying symptom reduction in the control group; and *ä* - the population Cohen's *d*. U_3 was calculated by multiplying cumulative distribution function (Ö) by Cohen's *d*. Probability of the Superiority was calculated using the following formula: Ö(Cohen's *d* ÷√2).

Results

Immediate effects of the MMRT

MANCOVA, using Pillai's trace, identified a significant groups and pre-post interaction across all outcomes [V=.511, F (56; 266) =1.631, $p<.005$, $\eta^2=.256$]. Summary of mean scores before and after the intervention, together with effect sizes at 95% confidence level for all variables are presented in Table 2. Separate univariate ANCOVAs on the outcome variables revealed significant difference across the groups in mean changes of sleep problems [$F(2;159)=3.70$, $p<.05$, $\eta p^2=.044$], sleep inadequacy [$F(2;159)=3.09$, $p=.048$, $\eta p^2=.037$], anxiety [$F(2;159)=3.22$, $p<.05$, $\eta p^2=.039$], and fatigue [$F(2;159)=4.633$, $p<.05$, $\eta p^2=.055$]. The confidence intervals of effect sizes on the primary outcomes are presented in Table 3.

The mean pre-post change of perceives stress score (PSS) did not significantly differ across three study arms [F (2; 159) =2.27, p=.11, ηp^2=.027]. Similarly, the treatment effects on sleep disturbance [F (2; 156) =.924, p=.39, ηp^2=.011] and sleep initiation [F (1; 159) =2.15, p=.12, ηp^2=.026] were insignificant. The mean changes of the VAS score across three groups did not significantly vary [F (2; 159) =.536, p=.592, ηp^2=.007]. Univariate ANCOVAs did not detect significant differences between the study groups in mean pre-post changes of the secondary outcome variables (Table 2).

MANCOVA was followed-up with one way between-subject analysis of variance of fatigue, anxiety, sleep problems, sleep inadequacy, controlling for baseline measurements, age, medication, duration of diagnosis and comorbidities. Planned contrasts revealed that the average pre-post change of fatigue score in the MMRT was significantly different from the mean change of the score in the control [t (160) =2.16, p<.05], and attention comparator [t (160) =6.32, p<.05] groups. The attention comparator group's pre-post change in fatigue score was not significantly different from the mean of the control group [t (160) =-.223, p=.823]. The mean pre-post change in levels of anxiety for the attention comparator group was significantly higher than the mean for the wait-list control group [t (160) =2.50, p<.05]. However, the anxiety levels in the main intervention group did not significantly drop in comparison to the control group [t (160) =.885, p=.38]. Sleep inadequacy was significantly reduced for MMRT group when comparing to waiting list control group, [t (160) =-2.56, p=.01], but did not significantly differ from the attention comparator group [t (160) =6.97, p=.188]. Sleep problems were reduced after the MMRT significantly more than in attention control [t (160) =8.37, p<.01], and waiting list groups [t (160) =2.36, p<.02].

MANCOVA was additionally followed up with discriminant function analysis to explore whether the MMRT group membership significantly predicted the pre-post intervention change across outcomes. The first discriminant function explained 63.4% of the variance (canonical r^2=.25). Change in scores on sleep inadequacy (r=.377), sleep problems (r=.491) and fatigue (r=.456) loaded significantly high on the first function. The first discriminant function significantly differentiated the MMRT group from the attention comparator and control groups, [Λ=.807, $\chi^2(12)$= 39.72, p<.001]. The second function explained 36.6 % of variance (canonical r^2=.277) and was correlated with pre-post change in anxiety levels (r=.30). The second function significantly differentiated control group from both active groups, [Λ=.923, χ^2 (5) =14.79, p<.01]. Therefore, the MMRT group demonstrated significantly greater reduction of fatigue, sleep

problems and sleep inadequacy scores relative to the control and usual care groups. Whilst, the active control's group mean pre-post change in anxiety was significantly different to usual care.

Effects of the MMRT at one-month follow-up

Mixed Subject MANOVA indicated the significant effect of time on all outcome measures within the entire cohort [V=.959, F (2; 137) =62.02, $p<.001$, $\eta^2= .059$]. Overall, the outcome measures significantly differed across the three study arms over time [V=.735, F (2; 276) =1.54, $p<.005$, $\eta^2=.368$]. However, the effect of attention comparator group on the anxiety levels was not sustained at the follow-up [F (4; 376) =1.61, $p=.171$].

Sleep Inadequacy

Mean scores of sleep inadequacy at three time points were significantly different across the groups [F (3.81; 376) =2.895, $p<.05$]. The planned contrast comparison indicated significant difference between post-intervention mean scores and the follow-up mean scores [F (2; 376) =4.89, $p<.01$]. However, the mean scores at one-month follow-up did not differ from the score assessed at the baseline [F (2; 376) =673, $p=.512$]. The latter suggests that the effect of the intervention on sleep inadequacy did not sustain at the follow-up.

Sleep Problems

Mean scores of sleep problems (MOS) significantly varied across assessment points between the groups [F (3.59; 376) =2.79, $p<.05$, $\eta^2= .030$]. Within subject contrasts indicated significant difference between mean scores at baseline and post-intervention [F (2; 376) =2.83, $p<.05$]. However, the follow-up mean score of the MMRT group (M=51.11; SD=13.16) was significantly higher than the post-intervention mean score (M=46.46 SD=14.16), [F (2; 376) =4.50, $p<.05$]. Therefore indicating, that sleep problems score regressed to the baseline score.

Fatigue

There was a significant interaction between the groups and time [F (3.81; 376) = 2.812, $p<.05$, $\eta p^2=.033$].

Planned within-subject contrasts with Bonferroni adjustment showed that the follow-up MMRT fatigue score was significantly lower than baseline scores [F (2;356)=3.182, p<.05], however, did not differ from the fatigue levels as measured immediately after the intervention [F(2;356)=1.415, p=.246], indicating the sustained effect of MMRT on fatigue levels.

Dose-sensitive effects of the MMRT

The mean value of dosage was 3.5 (SD=1.27), which corresponds to 5 sessions a week. A significant dose-conditioned effect of the intervention on the VAS score was observed [R=.24, F (3; 132) =3.44, p<.05; interaction B=-.72, t=-2.97, p<.005]. At the value of dose = 4.77, which corresponds to 3 sessions a week, [t (049) = 2.10, p<.05]. The VAS score was significantly reduced by .55 when the technique was practiced at least 3 times a week. The mean pre-post changes in VAS scores at a value of dose are presented in *figure 2*. Dose of the intervention did not have a moderating effect on any other outcome variables. The dose was significantly reduced by a value of 3.37 at the follow-up assessment [t(190)=36.37, p<.001; CI: 3.18; 3.55].

MMRT effects for clinical subgroups

Restless Leg Syndrome (RLS) did not have a significant moderating effect on pre-post change in sleep inadequacy, sleep problems and fatigue as evaluated by bootstrapped moderated mediation model [R=.11, p=.97; interaction B=6.19, t(.48)=1.29, p=.20]. The independent t-test identified significant difference [t (65) =-2.08, p<.05] between mean pre-post changes in sleep problems score for the participants' with co-morbid RLS (M=7.20; SD=18.19) and those without the co-morbidity (M=- 6.6; SD=21.49). Similar results were observed in coping difficulty [t (65) =2.40, p<.05]. Participants with RLS co-morbidity experienced small increase in coping difficulty (M=.14, SD=.21), whereas participants without comorbid RLS displayed decrease in coping difficulty (M=-.81; SD=1.39). The effects however, were not significant when compared to the control groups. Frequencies of other comorbidities were too low to conduct the moderation analysis.

The mechanism of the MMRT

The mediating roles of sleep problems and sleep inadequacy were tested. The total effect of the MMRT and the indirect factors explained 34.4% of the change in the variance of fatigue, and sleep inadequacy, and sleep problems, explained 14.7% of the unique variance in fatigue change [R=.344, R^2=.118, F(3;187)=8.37, p<.001]. However, only sleep problems had a significant mediating effect on fatigue (figure. 3). No other significant mediators were identified.

The clinical significance of the MMRT

Table 4 presents Absolute Risk Reduction (ARR), Relative Risk Reduction (RRR), and Number Needed to Treat (NNT) for the MMRT group comparatively to the waiting list control group. As indicated by Cohen's U_3, the 70.54% of the individuals who received MMRT had greater reduction in pain severity than the mean reduction rate in usual care group. The percentages for sleep inadequacy; sleep problems, and fatigue are given in Table 4. Given overall improvement in both control and treatment groups, the probabilities of a person selected at random from the MMRT group having a larger reduction in pain severity (64.87%) fatigue (63.02%), sleep problems (58.12%), and sleep inadequacy (55.62%) than a person selected at random from the control group, are relatively large.

Discussion

This is the first study to evaluate the effectiveness of the Mitchell Method Relaxation Technique in reducing symptoms associated with fibromyalgia. The results showed a dose-response effect on pain levels, moderate sustained effect on fatigue, and short-term positive effect on sleep quality. Thus, the MMRT is effective at reducing fatigue, sleep problems, and in particular, sleep inadequacy for people with fibromyalgia. Furthermore, the technique effectively reduces pain severity, if practiced at least 3 times a week. However, practicing the MMRT did not improve functioning, depression (dysphoria), HRQoL or coping with the condition.

Fatigue and poor sleep emerge as the most prominent problems of fibromyalgia experience and have been reported by patients as being more detrimental than pain (Bennet et al., 2007) yet, treatments targeting fatigue and sleep in patients with fibromyalgia are in shortage (Cropley & Theadom, 2008). Although

existing mind-body interventions decreased pain levels, improved mood and functioning in short-term did not result in improved sleep quality or decreased fatigue levels (Theadom et al., 2015). Whilst the MMRT significantly attenuated sleep problems and fatigue prevalent in fibromyalgia. Furthermore, the positive effect of the MMRT on fatigue persisted a month later. Therefore, the MMRT is a favourable symptom management aid for fibromyalgia-related fatigue and sleep problems compared to other existing mind-body therapies.

The results revealed that improvement in sleep quality significantly accounted for the reduction in fatigue levels induced by the MMRT. The latter is in line with the evidence supporting the moderating role of poor sleep in fatigue (Nicassio et al., 2002). In conjunction with insignificant mediating effect of pain on fatigue levels, this points out the primary causal role of sleep problems in fibromyalgia-related fatigue.

Identification of subgroups of patients is an important factor of the treatments' effectiveness particularly for patients with fibromyalgia (Adams & Sims, 2005). We used the bootstrapped method in the present study to evaluate the moderating role of comorbid RLS on the MMRT effect. The effectiveness of the MMRT for the subgroup of patients displaying RLS co-morbidity was however not supported. Thus, the effects of the MMRT, as well as effects of other treatments, for different clinical subgroups of fibromyalgia patients should be investigated in studies with a larger sample size. The presence of RLS causes sleep difficulties (Allen, Walters, Montplaisir, Hening, Myers, Bell, & Ferini-Strambi, 2005), in addition to the normal sleep problems accompanying fibromyalgia, and thus, conflicts with the MMRT's effects on sleep. This suggests a need for specific symptom management for patients with comorbid dystonic patterns.

Future studies of the effectiveness of the MMRT are urged to assess the long-term effects. The long-term effect is not reflected in the current study, due to the reduced adherence to the intervention as assessed at the one-month follow-up. The MMRT can be easily learned and self-applied, and therefore likely to have long-term therapeutic effects with sustained practice. Perhaps educating patients of the benefits of continuing with the technique would increase adherence and practice long-term. The issue of treatment adherence should be addressed by future research in order to increase the sustainability of the MMRT's corrective effect on fibromyalgia symptoms.

The intervention was self-applied and delivered online, and this may have contributed to the dropout rate, and perhaps this could have been reduced if there was regular contact with a health professional. It is expected that MMRT will have a greater sustained effect on health outcomes if implemented in clinical settings or under therapist's supervision. In addition, the limitations of the study include self-reported measures of compliance, which could be overcome by direct observations in clinical settings. On the other hand, the online delivery, self-application and minimal intrusion throughout the study, provides evidence of the MMRT effectiveness in real world settings, thus increasing the ecological validity of the findings. In addition, patients with fibromyalgia may prefer interventions that they can practice at home, and this would increase their perceptions of control over their condition, and also will help to avoid the necessary travel to the clinic, which patients could find challenging. Furthermore, the nature of the technique and the session's short duration accommodate for the patients' need to shift between movement and immobility. Comparative studies are required to determine the constructive modes of delivery and duration of sessions.

Several measures were taken to obtain an objective assessment of the technique. The study included a representative homogeneous sample of fibromyalgia patients. The selection bias was eliminated by randomisation procedure. Furthermore, the blinding of the assessors of the outcomes was performed. Additionally, the potential biases introduced by the high attrition rates were reduced through the employment of intention-to-treat analysis. The significantly greater improvement of the MMRT group in comparison to attention control group, as indicated by the discriminant function analysis, supports the specific effect of the intervention and accounts for the unspecified placebo effect. The rigorous method of this study helps to ascertain objective evaluation of the MMRT effectiveness.

The MMRT fulfils few of the criteria for clinical significance. Firstly, The MMRT effect on pain and fatigue was relatively large, 42.84% and 37%, respectively. Secondly, the estimate of the Number Needed to Treat (NNT) is 4.74 for pain and 5.38 for fatigue. The NNT of 2-5 is considered indicative of the clinically effective treatment in pharmaceutical research (Cook & Sackett, 1998). Furthermore, none of the study participants reported adverse effects of the treatment. Stringent control for biases as well as a relatively small NNT, large magnitude of the effects and absence of health hazards advocate the clinical importance of the MMRT for fatigue and pain levels attenuation.

In summary, the Mitchell Method Relaxation Technique attenuates sleep inadequacy, sleep problems, and subsequently fatigue, and pain in patients with fibromyalgia. This symptom management does not require substantial effort and commitment. The technique, therefore, is a feasible and cost-effective management of fibromyalgia symptoms in patients without comorbid RLS. This study highlights the role of effective management of sleep problems in the fibromyalgia treatment approach. The absence of adverse effects, rigorous methods of evaluation and the supported effectiveness in symptoms management, signify the MMRT as an adjuvant treatment for the individuals diagnosed with fibromyalgia.

References

Adams, N., & Sims, J. (2005). Rehabilitation Approaches in fibromyalgia. *Disability and Rehabilitation, 12,* 711-723.

Allen, R.P., Walters A.S., Montplaisir J., Hening W., Myers, A., Bell, T.J., Ferini-Strambi L.(2005). Restless leg syndrome prevalence and impact: REST general population study. Archive Intern Medicine,13(165),1286-92.

Arnold, L. (2007). Duloxetine and Other Antidepressants in the Treatment of Patients with Fibromyalgia. *Sleep Medicine 8 (s2),* 63-74. DOI: 10.1111/j.1526-4637.2006.00178.x

Baranowsky, J. (2009). Qualitative systemic review of randomized controlled trials on complementary and alternative medicine treatments in Fibromyalgia. *Rheumatology International, 30,* 1–21.

Bell, J., A., & Saltikov, J., B. (2000). Mitchell's Relaxation Technique: Is It Effective? *Physiotherapy, 86,* 473-478.

Bennett, R.M., Friend, R., Jones, K., D., Ward, R.,Han, B.K., Ross, R.L. (2009). The Revised Fibromyalgia Impact Questionnaire (FIQR): validation and psychometric properties. *Arthritis Research & Therapy, 11,* R120 doi:10.1186/ar2783.

Bennett, R.M., Jone, J., Turk, D., Russell, I., & Matallana, L. (2007). An Internet survey of 2,596 people with fibromyalgia. *BMC Musculoskeletal Disorders, 8 (27),* doi:10.1186/1471-2474-8-27

Berger, A., Dukes, E., & Oster, G. (2007). Characteristics and healthcare costs of patients with fibromyalgia syndrome. *International Journal of Clinical Practice, 61,* 1498-1508.

Boutron, I., Moher, D., Altman, D.G., Schulz, K., Ravaud, P. (2008). Methods and Processes of the CONSORT Group: Example of an Extension for Trials Assessing Nonpharmacologic Treatments.

Annals of Internal Medicine. W60-W67. Retrived from: http://www.consort-statement.org/extensions/interventions/non-pharmacologic-treatment-interventions/

Brown, L.F., Kroenke K., Theobald, D.E., Wu, J. (2011). Comparison of SF-36 vitality scale and Fatigue Symptom Inventory in assessing cancer-related fatigue. *Support Cancer, 19(8),* 1255-9. doi: 10.1007/s00520-011-1148-2.

Burckhardt, C.S., Clark, S.R., & Bennett, R.M. (1991). The Fibromyalgia Impact Questionnaire: development and validation. *Journal of Rheumatology, 18,* 728-33.

Cappelleri, J., C., Bushmakin, A. G., McDermott, A. M., Dukes, E., Sadosky A., Charles D. Petrie, C., D., Martin, S. (2009). Measurement properties of the Medical Outcomes Study Sleep Scale in patients with fibromyalgia. *Sleep Medicine, 10 (7),* 766–770.

Cohen, S., Kamarck, T., & Mermelstein, R. (1983). A global measure of perceived stress. *Journal of Health and Social Behavior, 24,* 386-396.

Cook, R.J., & Sackett, D.L. (1998). The number needed to treat: a clinically useful measure of treatment effect. *British Medical Journal, 310,* 452-4.

Cropley, M., & Theadom A. (2008). Sleep disturbance in fibromyalgia syndrome. *Future Rheumatology, 3,* 533-535.

Dunmore, 2001- C-scale in Ehlers, A., Clark, D., Hackmann, (2003). A Randomized Controlled Trial of Cognitive Therapy, a Self-help Booklet, and Repeated Assessments as Early Interventions for Posttraumatic Stress Disorder, *Arch Gen Psychiatry, 60(10),* 1024-1032.

Hayes, A. (2009). Beyond Baron and Kenny: Statistical Mediation Analysis in the New Millennium. *Communication Monographs, 76,* 408-420.

Hayes, A. (2013). *Introduction to Mediation, Moderation, and Conditional Process Analysis: A Regression-Based Approach.* New York: Guildford Press.

Hayes, A. F. (2012). PROCESS: A versatile computational tool for observed variable mediation, moderation, and conditional process modelling [White paper]. Retrieved from http://www.afhayes.com/public/process2012.pdf

Hays, R. D., & Stewart, A. L. (1992). Sleep measures. In A. L. Stewart & J. E. Ware (eds.), Measuring functioning and well-being: The Medical Outcomes Study approach (pp. 235-259), Durham, NC: Duke University Press. *Immunity, 22,* 668–675.

Lazarus, R.S., & Folkman, S. (1984). *Stress, appraisal, and coping.* New York: Springer.

Luciano, J., Aguado, J., & Seranno-Blanco, A. (2013). Dimensionality, reliability and validity of the Revised Fibromyalgia Impact Questionnaire (FIQR). *The American College of Rheumatology, 65,* 2-26.

Mitchell, L (1977). *Simple Relaxation: The Mitchell method for easing tension*. Frome and London: Butler and Tanner, 15-23, 40-112.

Moher, D., Schulz, K.F. & Altman, D.G. for the CONSORT group, 2001. The CONSORT statement: Revised recommendations for improving the quality of reports of parallel-group randomized trials. *Annuals of Internal Medicine, 134,* 657-662.

Nicassio, P.M., Moxham, E. Schumand, C. & Gevirtza, R. (2002), The contribution of pain, reported sleep quality, and depressive symptoms to fatigue in fibromyalgia. *Pain, 100,* 271-279.

Office for National Statistics (2013). *Internet access—Households and individuals, 2013. http://www.ons.gov.uk/ons/rel/rdit2/internet-access---households-and-individuals/2013/stb-ia-2013.html.*

Pallant, J., Tennant, A. (2007). An introduction to the Rasch measurement model: An example using the Hospital Anxiety and Depression Scale (HADS). *British Journal of Clinical Psychology, 46(1),* 1-18.

Preacher, K. J., & Hayes, A. F. (2008). Asymptotic and resampling strategies for assessing and comparing indirect effects in multiple mediator models. *Behavior Research Methods, 40,* 879-891.

Salaffi F, Sarzi-Puttini P, Ciapetti A, Atzeni F. (2009). Assessment instruments for patients with fibromyalgia: Properties, applications and interpretation. *Clinical Experimental Rheumatology, 27(5;S56),* 92-105.

Schulz, K.F., Altman, D.G., Moher, D., CONSORT Group. (2010). CONSORT 2010 Statement: Updated Guidelines for Reporting Parallel Group Randomised Trials. *PLoS Med 7(3): e1000251.* doi:10.1371/journal.pmed.1000251

Sterne, J., Carlin, J., Spratt, M.,Royston, P., Kenward, G., Wood, A., Carpenter, J. (2009). Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls, *British Medical Journal, 338 (b2393),* 1-35.

Theadom, A., Cropley, M., Humphrey, K. (2007). Exploring the role of sleep and coping in quality of life in fibromyalgia. *Journal of Psychosomatic Research, 62,* 145– 151.

Theadom, A., Cropley, M., Smith, H. E., Feigin, V. L., & McPherson, K. (2015). Mind and body therapy for fibromyalgia. The Cochrane Database of Systematic Reviews, 4, CD001980. http://doi.org/10.1002/14651858.CD001980.pub3

Ware, J. E., & Kosinski, M. (2001). *SF-36 physical & mental health summary scales: a manual for users of version 1*. Quality Metric Inc.

Wolfe F., Clauw D.J., Fitzcharles, M.A., Goldenberg, D.L., Katz, R.S., Mease, P. (2010). The American College of Rheumatology preliminary diagnostic criteria for fibromyalgia and measurement of symptom severity. *Arthritis Care Research, 62,* 600–10.

Wolfe, F., Smythe, H.A., Yunus, M.B., Bennett, R.M., Bombardier, C., & Goldenberg, D.L. (1995). The American College of Rheumatology. Criteria for the classification of fibromyalgia. Report of the Multicenter Criteria Committee. *Arthritis Rheumatology ,33,* 160–172.

Zigmond, A. S., & Snaith, R. P. (1983). The hospital anxiety and depression scale. *Acta Psychiatrica Scandinavica, 67,* 361–370.

Zwarenstein, M., Treweek, S., Gagnier, J., & Altman, G. Tunis, S., Haynes, B., Gent, M., Oxman A., D., David Moher, D. (2008). Improving the reporting of the Pragmatic Trals: an Extension of the CONSORT Statement. *British Medical Journal, 337,* 1-8. doi: http://dx.doi.org/10.1136/bmj.a2390.

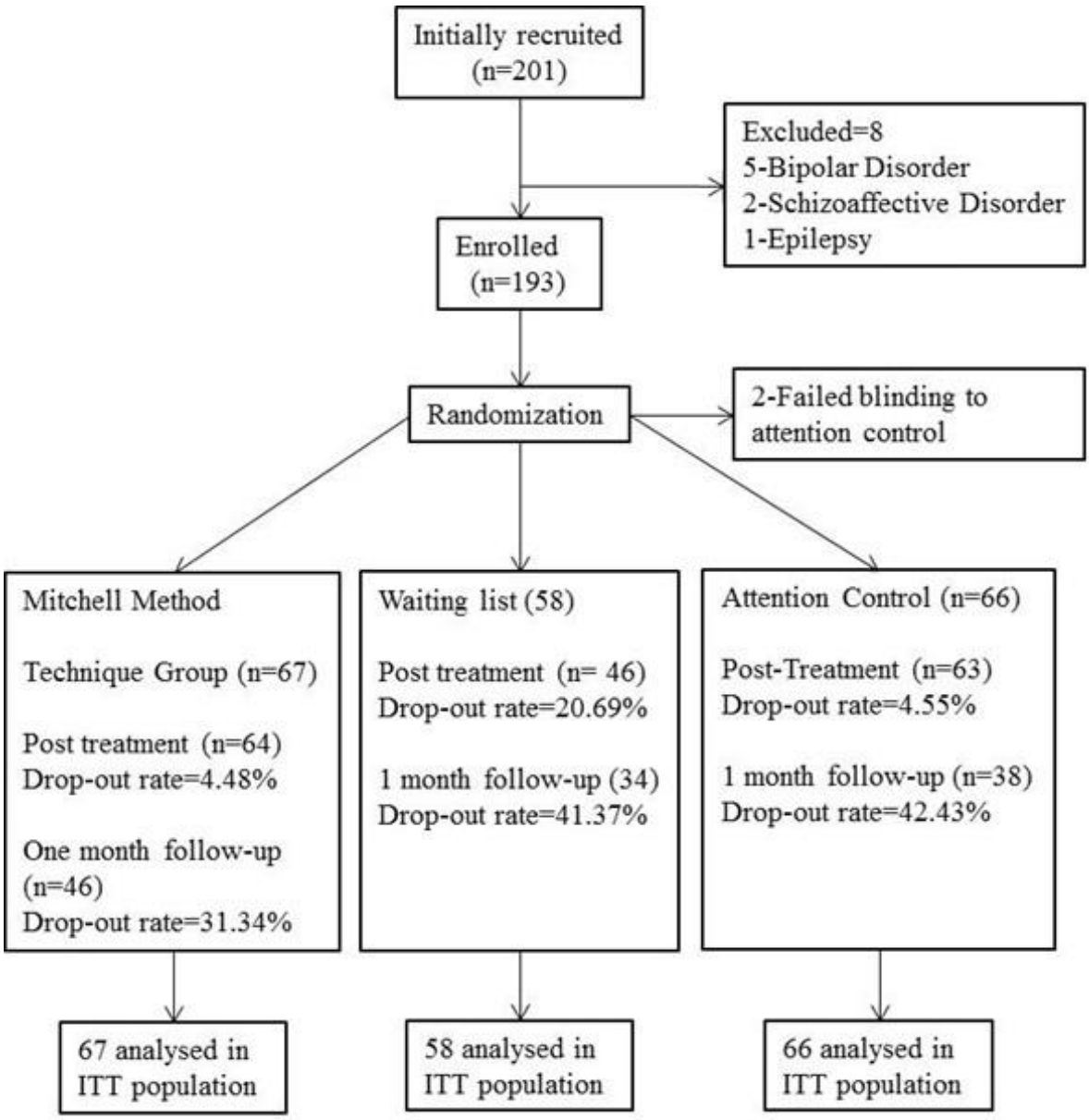

Figure 1. Participants flow chart according to the revised CONSORT statement (2001).

Figure 2. Dose-conditioned mean pre-post change of VAS score.

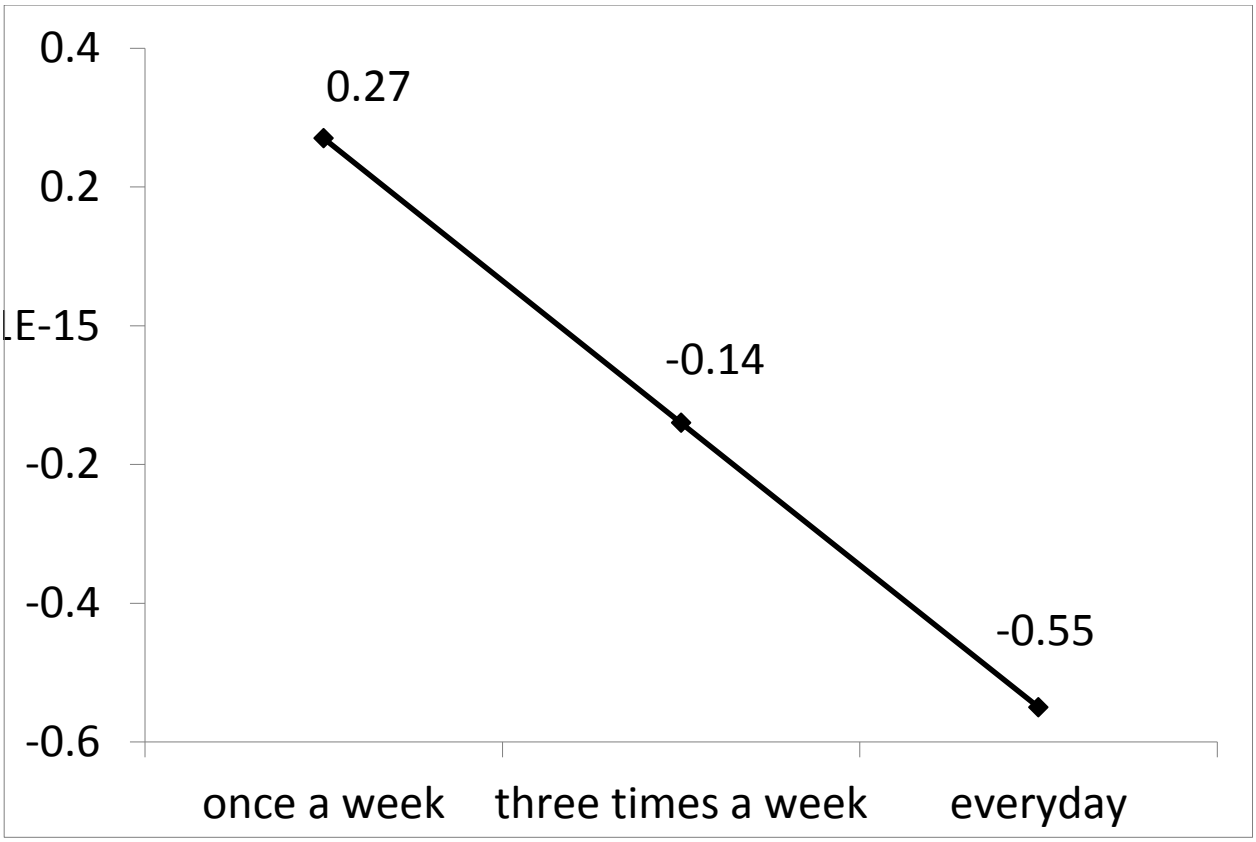

Figure 3. The MMRT mechanism, being tested on the basis of the multiple mediator model (Preacher, & Hayes, 2008).

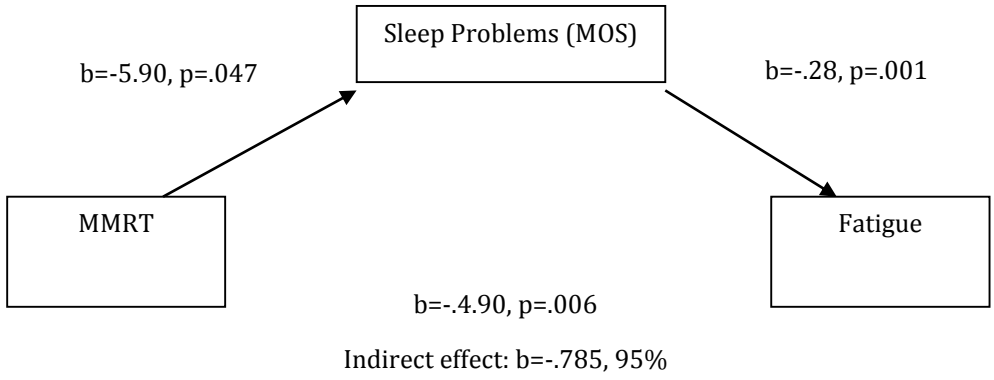

Table 1. Baseline characteristics of the three study groups

	MMRT	**Attention Control**	**Waiting List**
Age	48.10 ±11.08	50.46±10.75	48.95±10.13
Gender	63 Females 4 males	63 Females 3 males	53 Females 5 males
Diagnosis duration (years)	11.61±6.99	14.09±9.56	10.97±6.77
Restless Leg Syndrome	17.9%	24.2%	13.8%
Asthma	9%	6.9%	9.1%
Chronic Fatigue Syndrome	3%	4.5%	1.7%
Sleep Apnea	6%	0%	6.9%
Depression	10.4%	9.1%	6.9%
Other co-morbidities	68.7%	54.5%	67.2%

Table 2. Means and standard deviations for all variables per group at baseline (pre) and at the end of the intervention (post).

	MMRT (N=67)		**Attention Control (N=66)**		**Waiting List (N=58)**				
	Pre	***Post***	***Pre***	***Post***	***Pre***	***Post***	***Par.η²***	***d***	***p***
VAS	7.44±1.69	7.03±1.81	7.26±1.74	7.26±2.03	6.70±1.42	6.87±1.69	.017	0.54	.59
Sleep problems index	49.50±16.88	46.46±14.16	50.48±18.44	54.40±18.76	54.86±15.10	55.73±14.71	.044	0.29	.03
Sleep initiation	3.33±0.17	3.00±0.20	2.90±0.17	2.94±0.17	3.26±1.80	3.31±1.90	.026	0.22	.12
Sleep disturbance	38.05±2.32	42.16±2.89	37.4±2.60	37.70±2.48	41.77±2.51	42.22±2.72	.011	0.16	.39
Sleep inadequacy	85.53±20.89	76.57±20.89	87.03±20.14	87.28±25.76	87.96±17.50	89.63±25.19	.037	0.20	.05
Sleep quantity	5.95±0.22	6.00±0.18	6.18±0.22	5.96±0.15	6.16±0.25	5.89±0.26	.001	0.28	.70
Fatigue (SF-36)	20.47±17.09	18.73±15.87	15.45±16.23	19.09±11.89	16.98±17.04	20.88±15.35	.055	0.47	.01
PSS	22.64±0.95	18.89±0.89	23.40±0.94	20.67±0.80	23.10±0.82	19.98±0.86	.027	0.10	.11
HADS-A*	9.72±3.56	10.00±4.09	9.61±3.38	10.50±3.96	10.28±2.97	9.73±3.33	.039	0.07	.04
HADS-D	10.40±0.27	10.40±0.46	9.62±0.26	9.73±4.60	10.06±0.31	10.50±0.40	.015	0.17	.30
HRQoL	29.80±17.27	31.20±19.45	32.37±21.78	29.21±22.67	29.84±18.87	26.50±20.48	.012	0.01	.157

FIQR	68.09±20.03	68.79±16.90	69.83±20.67	68.72±17.88	65.50±16.10	66.10±15.34	.001	0.24	.708
Coping difficulty	3.54±1.00	3.47±0.96	3.65±1.05	5.21±3.48	3.35±0.94	3.29±1.00	.013	0.56	.148
Coping efficacy	3.30±1.17	2.49±9.33	3.20±1.13	2.37±0.87	2.98±1.00	2.41±1.00	.019	0.33	.075

Note: Greater score on HADS-A indicates lower anxiety levels. Greater scores for all other variables correspond to higher levels of the outcomes. Cohen's *d* reflects difference between mean pre-post changes of MMRT and waiting list groups divided by pooled standard deviations. P values represent between groups difference of within-group mean pre-post change, controlling for baseline outcome measures and characteristics using MANCOVA.

Table 3. The estimation of the mean pre-post change in the scores (95 % CI).

	MMRT	Attention Control
Sleep problems index	[-14.13;-0.99]	[-5.98;7.05]
Sleep inadequacy	[-24.01; -2.75]	[-17.33;3.75]
Fatigue	[-15.98;-2.34]	[-6.78;6.07]

Table 4. Clinical significance of the MMRT for fatigue, sleep problems, sleep inadequacy, and pain comparing to waiting list (WL).

	ARR (%)	RRR (%)	NNT	U_3 (%)	Probability of superiority (%)
SF-36 Fatigue	15.3	37	5.38	68.08	63.02
Sleep Problems	15.4	26.7	9	61.41	58.12
Sleep Inadequacy	3.6	4.9	16.34	57.93	55.62
VAS	14.77	42.84	4.74	70.54	64.87