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Impact of psychotherapy on insomnia symptoms in patients with depression and multiple sclerosis

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Abstract The purpose of the study was to evaluate the prevalence of insomnia in multiple sclerosis patients with comorbid depression, associations between psychological symptoms, multiple sclerosis symptoms and insomnia, and to test effects of a 16-week protocol-based psychotherapy intervention for depression on insomnia symptoms. Participants with multiple sclerosis and depression ($n = 127$) were randomized to telephone administered cognitive behavioral therapy and telephone administered supportive emotion-focused therapy. Multiple sclerosis functional limitation was measured at baseline. Depression, insomnia, anxiety and quality of life were evaluated at pre treatment, mid treatment (8 weeks), and post treatment (16 weeks). Prevalence of insomnia $\geq$3 times per week was 78% at pre treatment and 43% at post treatment. Insomnia at baseline was associated with depression, multiple sclerosis related mood symptoms and anxiety. Middle of the night awakenings were associated with swallowing and speech problems. Improvements in insomnia were associated with improvement in depression and anxiety. Participants with residual insomnia were more likely to have major depressive disorder, greater multiple sclerosis severity, elevated anxiety and lower mental components of quality of life. Results demonstrate rates of insomnia in patients with comorbid multiple sclerosis and depression are higher than those reported in the general multiple sclerosis population and additional insomnia treatment is indicated beyond the treatment of comorbid psychological disorders.

Keywords Multiple sclerosis · Depression · Insomnia

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Multiple sclerosis is a chronic autoimmune demeylinating disease of the central nervous system. In the variable course and progression of symptoms in this disease, patients may experience episodic, chronic, or progressive symptoms including fatigue, pain, spasticity, loss of use of their arms and legs, loss of vision, impaired bowel and bladder function, and sexual problems. Prevalence of poor self-reported sleep quality as well as sleep disorders, such as insomnia and restless legs syndrome, is higher in patients with multiple sclerosis compared with the general population (Brass et al. 2009). This is attributable to multiple factors including pain and spasticity, medication side effects, as well as physical and emotional comorbidites such as depression. Several studies have reported more than half of patients with multiple sclerosis report poor sleep quality (Bamer et al. 2008; Tachibana et al. 1994). In addition to self-reported poor sleep quality, polysomnography demonstrates that patients with multiple sclerosis also have poorer objective sleep quality including more frequent arousals, greater wake after sleep onset, and poorer sleep efficiency (Attarian et al. 2004; Ferini-Strambi et al. 1994).

Sleep quality is particularly relevant in multiple sclerosis, as it is associated with greater disease severity, pain, and poorer mental and physical quality of life in patients with multiple sclerosis (Merlino et al. 2009). In addition, insomnia is one of the most prevalent sleep complaints in multiple sclerosis. Prior studies have reported that over half of patients with multiple sclerosis have difficulty initiating

and maintaining sleep, or early morning awakenings (Stanton et al. 2006; Tachibana et al. 1994). This is significantly higher than the rates in the general population, which are approximately 10–15% (Ancoli-Israel and Roth 1999).

The relationship between multiple sclerosis and insomnia is complicated by the high prevalence of mood and anxiety disorders. Insomnia symptoms are commonly associated with depression and anxiety, and thus may cause or exacerbate sleep disturbance in patients with multiple sclerosis (Ford and Kamerow 1989). Prevalence of significant depressive symptoms in multiple sclerosis has been reported as 41.8% with 25% meeting criteria for major depressive disorder (Chwastiak et al. 2002; Patten et al. 2003). One study in patients with multiple sclerosis found that those classified as poor sleepers on a standardized measure of sleep quality were more likely to have clinically elevated anxiety and depression (Merlino et al. 2009). Anxiety, which is correlated with depression in multiple sclerosis patients, is also associated with sleep disturbance (Brown et al. 2009; Bruce and Arnett 2008; Taylor et al. 2005). In longitudinal studies, there appears to be a different course in the relationship between depression, anxiety, and insomnia. Insomnia symptoms have been found to precede the onset of depression and recurrence of depressive disorders whereas insomnia symptoms occur concurrently or following anxiety (Chang et al. 1997; Pigeon et al. 2008). Recent research suggests that treating comorbid insomnia may enhance treatment response to antidepressants (Manber et al. 2008). Therefore, improvement in insomnia symptoms may contribute to quality of life and reduce risk for future depressive episodes. To date, no study has tested the results of treating depression on insomnia symptoms in patients with comorbid multiple sclerosis and depression.

This study presents secondary data analysis of a trial of telephone-administered psychotherapy for depression in multiple sclerosis (Mohr et al. 2005). The goals of this study were: (1) To determine the prevalence of insomnia in patients with multiple sclerosis and depression, (2) To evaluate the pretreatment correlation between insomnia, anxiety and multiple sclerosis symptoms, (3) To determine the effects of treatment for depression on insomnia symptoms (4) To determine treatment-related factors associated with improvement in insomnia, including improvement in depression and anxiety symptoms as well as treatment type. The present study analyzed insomnia outcomes resultant from two validated, protocol based (manualized) treatments for depression: telephone—administered cognitive behavioral therapy, which is a structured approach to treat depression through increasing behavioral activation and enhancing cognitive strategies for coping and telephone administered supportive emotion-focused therapy, a supportive and relationship-based approach to treating depression. We hypothesized that insomnia symptoms would improve with both treatments but there would be a greater improvement with cognitive behavioral therapy due to the more structured behavioral aspects of this treatment.

Methods

Participants

Participants were recruited from the Kaiser Permanente Medical Group of Northern California and regional chapters of the Multiple Sclerosis Society. The research protocol was approved by all participating institutions and all participants provided written informed consent. Eligibility criteria included (1) a diagnosis of multiple sclerosis confirmed by a neurologist, (2) functional limitation, which was defined as 3 out of 6 on Guy's Neurological Disability Scale (Sharrack and Hughes 1999), (3) Significant depressive symptoms, defined as $\geq$16 on the Beck Depression Inventory-II (Beck et al. 1996), and $\geq$14 on the Hamilton Depression Rating Scale (Hamilton 1960), (4) the ability to speak and read English, (5) age $\geq$18 years. Exclusion criteria included (1) dementia, (2) currently psychotherapy attendance, (3) disability that would prevent participation in assessment or treatment (e.g., reading or writing limitation), (4) severe psychopathology, including psychosis, current substance abuse, or plan or intent to commit suicide, (5) current multiple sclerosis exacerbation, and (6) use of medications that affect mood other than antidepressants (e.g., steroidal anti-inflammatory agents). Use of antidepressant medications was not exclusionary.

Procedure

A full description of the eligibility assessment and follow-up procedures is described elsewhere (Mohr et al. 2005). Briefly, potential participants were identified through the Kaiser Permanente Medical Group of Northern California patient database and subsequent to approval from their physicians, were sent a mailing asking them to return a pre-stamped postcard if they did not wish to be contacted further. Potential participants who did not return postcards were called 10 days later. During the phone calls, potential participants were provided with a brief description of the study and then asked to participate in a brief telephone screening to assess depressive symptoms and exclusionary criteria. Those who met initial screening criteria were invited to participate in a longer eligibility assessment involving a telephone interview and written questionnaires. Recruitment through the regional National Multiple Sclerosis Society was achieved through an announcement

in chapter newsletters. Assessments were conducted at baseline, mid treatment (week 8), and post treatment (week 16) by trained interviewers who were blinded to treatment assignment. Written self-report materials were mailed with pre-stamped and addressed envelopes and participants were paid $10–$50 per assessment, based on the length of assessment.

Measures

Depression and Anxiety: Current DSM-IV diagnoses of major depressive disorder were assessed using the Structured Clinical Interview for the DSM-IV (First et al. 1995) at baseline and post treatment. The reliability of the Structured Clinical Interview for the DSM-IV administered over the phone has been reported as 90–97% agreement with face-to-face assessments (Kobak et al. 1997; Ruskin et al. 1998; Simon et al. 1993). In random reliability checks, evaluators for this study had 100% reliability on major depressive disorder diagnoses in this study. Evaluator-rated depression severity was assessed using a telephone administered version of the Hamilton Depression Rating Scale (Hamilton 1960) at baseline, mid treatment, and post treatment. The telephone version of the Hamilton Depression Rating Scale used in this study was developed for the Medical Outcomes Study (Potts et al. 1990). In order to avoid overlap with insomnia ratings, Hamilton Depression Rating Scale scores for this study were calculated without the 3 insomnia items. Self-reported depression severity was measured by the Beck Depression Inventory-II (Beck et al. 1996). The Beck Depression Inventory-II was administered as self-report by mail at baseline, mid treatment and post treatment. Beck Depression Inventory-II scores were also calculated minus the insomnia item. The Hospital Anxiety and Depression Scale (HADS), Anxiety Subscale was administered to assess self-reported anxiety symptoms (Zigmond and Snaith 1983). This 7 items self-report measure assessed both physical and psychological anxiety symptoms including tension, worry, and restlessness. Items did not overlap with insomnia symptoms. Significant anxiety symptoms were defined at a HADS anxiety score $\geq$11.

Insomnia was measured by 3 items on the Hamilton Depression Rating Scale: early insomnia, middle insomnia, and late insomnia. Items were scored from 0 (not at all) to 2 (significant insomnia $\geq$3 days per week). In analyses of insomnia as a continuous variable, these items were summed to create an insomnia total score. Insomnia sub scores for early, middle, and late were also explored. In categorical analyses, presence of insomnia was defined as a score of 2 on at least one insomnia item. A score of 2 on early insomnia was defined as difficulty initiating sleep for $\geq$30 min 3 or more days per week for early insomnia. A score of 2 on middle insomnia was defined as middle of the night awakenings with wake after sleep onset $\geq$3 days per week for middle insomnia. A score of 2 on late insomnia was defined as early awakening and getting out of bed for $\geq$30 min on $\geq$3 days per week for late insomnia. The Hamilton Depression Rating Scale insomnia items have been validated with sleep diaries in depressed participants (Manber et al. 2005).

Multiple sclerosis—related functional limitation was measured using The Guy's Neurological Disability Scale which was telephone administered (Sharrack and Hughes 1999). This structured interview assesses 11 basic areas of function (e.g., limb function, vision) and produces a total score that is highly related to objective measures of functional impairment based on neurological exam ($r = .81$) (Sharrack and Hughes 1999).

Quality of life was measured by the SF (36) Questionnaire (Ware et al. 1993). This 36 item questionnaire assesses 8 domains of quality of life: physical function, role-physical, bodily pain, general health, vitality, social functioning, role-emotional, and mental health. A mental health and physical health composite score were also calculated.

A brief screening of cognitive function was performed to determine eligibility criteria using a battery of telephone administered neuropsychological tests including Digit Span (Wechsler 1997), The California Verbal Learning Test (Delis et al. 1987), The Controlled Oral Word Association Test-FAS version (Lezak 2004), and the Similarities test from the Wechsler Adult Intelligence Scale, third edition (Wechsler, 1997). Participants who scored below the fifth percentile on any scale were determined to have dementia and excluded from the study.

Treatments and clinicians

Participants were randomized to one of two 16-week telephone administered psychotherapies, cognitive behavioral therapy and supportive emotion-focused therapy. Sessions were 50 min in duration and occurred weekly. Randomization was stratified based on current major depressive disorder diagnosis and use of antidepressant medication. All treatments were administered by doctoral level psychologists with 1–5 years of post degree experience. Psychologists were selected based on expertise and nested in treatment arm to avoid bias based on theoretical orientation. All 5 therapists in the cognitive behavioral therapy treatment arm were trained in cognitive behavioral therapy and reported this as their primary treatment modality. The 4 therapists in the supportive emotion-focused therapy arm all reported a strong belief that the therapeutic relationship is the principal vehicle for change in psychotherapy. The telephone administered cognitive behavioral therapy treatment was based on cognitive

behavioral therapy for depression (Beck 1995) with content added for multiple sclerosis and used a workbook as a guide through treatment (Mohr 2010a, b). The goal of treatment was to teach participants skills to manage cognitions and behaviors that contribute to depression and improve skills in managing stressful life events and interpersonal difficulties. Supportive emotion-focused therapy was adapted from a manual from Greenberg and colleagues for process-experiential psychotherapy (Greenberg et al. 1993). Goal of this treatment was increasing participants' level of experiencing their internal world. Therapeutic tasks included maintaining attention on empathic attunement, developing the therapeutic bond, and facilitating direct expression of present emotional experience and current needs. Thus, supportive emotion-focused therapy controlled for non-specific factors associated with cognitive behavioral therapy, including dosage, the therapeutic relationship, use of a psychotherapy treatment manual with a coherent theoretical justification and clearly described procedures, and individualized application of the treatment model.

Data analysis

Analyses were conducted in an intention-to-treat basis. Data were analyzed using SAS (v. 9.2 SAS Corporation, Cary, NC). Analyses compared baseline demographics between treatment groups using *t*-test for continuous data and χ^2 for categorical variables. Bivariate correlations were used to evaluate associations between insomnia, depression, anxiety and multiple sclerosis symptoms. Finally, mixed modeling using Proc Mixed was used to test improvements in depression on the (Hamilton Depression Rating Scale and the Beck Depression Inventory-II), anxiety, and treatment type as predictors of improvements in insomnia symptoms over time. Missing data in mixed models ($n = 1$ pretreatment and $n = 6$ post treatment) was ignored under the assumption it was missing completely at random. Statistical significance was defined as $P < .05$ in two-tailed tests.

Results

Baseline characteristics

Data were available for 127 participants (65 were randomized to the supportive emotion-focused therapy and 62 were randomized to the cognitive behavioral therapy groups). Of the 7 participants who dropped out of the study, all but 2 participants (one from each group) agreed to continue with assessments. Baseline participant characteristics are listed in Table 1. Approximately half of the sample was on disability. Participants were predominantly middle aged, female, and White. The majority of the sample reported having a relapsing form of multiple sclerosis ($n = 113$, 89%) and a small portion reported primary progressive multiple sclerosis ($n = 13$, 10%). Only one participant did not report a multiple sclerosis type. There was a wide range of multiple sclerosis—related functional limitation reported on Guy's Neurological Disability Scale but most scores were in the mild to moderate range (range = 10–37, $M = 23.37$, SD = 6.25). The majority of participants reported having relapsing/remitting multiple sclerosis ($n = 112$, 88%). The majority ($n = 89$, 70%) met criteria for major depressive disorder at baseline and nearly

Table 1 Baseline participant characteristics

	Cognitive behavioral therapy ($n = 62$) *n* (%) or *M* (SD)	Supportive emotion-focused therapy ($n = 65$) *n* (%) or *M* (SD)
Age	48.6 (9.6)	47.6 (10.1)
% Female	51 (75.8)	48 (78.5)
% White	58 (93.5)	56 (86.2)
Employment		
% Employed	17 (25.8)	17 (26.2)
% Disability	32 (51.6)	32 (56.9)
Guy's Neurological Disability Scale Total Score	23.9 (5.8)	22.9 (6.7)
% Major depressive disorder	46 (72.6)	43 (67.7)
Beck Depression Inventory-II	26.7 (8.1)	28.4 (7.9)
Hamilton Depression Rating Scale	21.4 (3.9)	21.7 (3.5)
Hospital Anxiety and Depression Scale, Anxiety Scale	21.4 (3.9)	10.6 (3.6)
Hospital Anxiety and Depression Scale Anxiety score $\geq$11	29 (47.7)	31 (46.8)

half ($n = 60$, 47%) reported clinically significant anxiety. There were no significant differences between treatment groups among baseline values.

Prevalence of insomnia

Pre and post treatment prevalence of insomnia symptoms is listed in Table 2. At baseline, 78% ($n = 98$) reported insomnia of any type ≥3 times per week. This declined to 43% ($n = 53$) at post treatment. At both time points early insomnia and middle insomnia were more common than late insomnia.

Correlations of Insomnia with Depression, Anxiety, multiple sclerosis symptoms, and Quality of Life Correlations between insomnia, depression, anxiety, multiple sclerosis symptoms and quality of life at baseline are listed in Table 3. The insomnia total score and middle insomnia were positively correlated with the Hamilton Depression Rating Scale score ($P < .05$ for total insomnia and $P < .01$ for middle insomnia). Anxiety was positively associated with total insomnia ($P < .05$) and early insomnia ($P < .05$). There were few correlations between multiple sclerosis symptoms and insomnia. Among areas of functional limitation, total insomnia was positively correlated with multiple sclerosis related mood symptoms ($P < .05$) and middle insomnia was positively correlated with swallowing problems ($P < .05$) and speech problems ($P < .05$). The general health component of the quality of life measure was correlated with early insomnia ($P < .05$) but insomnia was not related to the mental health or physical health component scores.

Predictors of insomnia improvement

First, two measures of depression (interview based and self-report) were tested in separate models as predictors of change in insomnia treatment. Models with depression and anxiety predicting change in insomnia are listed in Table 4. Results were concordant for both depression measures for total insomnia and early insomnia. Higher depression at baseline and greater improvement in depressive symptoms over time were associated with a greater improvement in the total insomnia score ($P < .01$ for the Hamilton Depression Rating Scale and $P < .05$ for the Beck Depression Inventory-II) and early insomnia ($P < .01$ for the Hamilton Depression Rating Scale and $P < .05$ for the Beck Depression Inventory-II). There was a trend for a change in depression by time interaction in middle insomnia for the Hamilton Depression Rating Scale only ($P = .06$). Higher baseline Hamilton Depression Rating Scale scores were associated with greater improvements in middle insomnia ($P < .0001$) and higher baseline Beck Depression Inventory-II scores were associated with greater improvement in late insomnia ($P < .05$).

Higher baseline anxiety and greater improvement in anxiety over time (HADS by time interaction) were associated greater improvement in the total insomnia score

Table 2 Insomnia prevalence greater than or equal to 3 times per week

	Insomnia symptoms *n* (%)[a]			
	Any insomnia	Early	Middle	Late
Baseline	98 (77.8)	60 (47.6)	64 (50.8)	29 (15.9)
Post treatment	53 (43.4)	36 (29.5)	29 (23.8)	11 (9.0)

[a] Percentages vary slightly between assessments due to missing data ($n = 1$ at baseline and $n = 6$ at post treatment)

Table 3 Correlations with insomnia symptoms at baseline ($n = 126$)

	Insomnia symptoms			
	Total insomnia	Early	Middle	Late
Depression[†]				
Hamilton Depression Rating Scale	.23*	.06	.28**	.09
Beck Depression Inventory-II	.07	.07	.01	.05
Anxiety				
Hospital Anxiety and Depression Scale, Anxiety Scale	.22*	.21*	.10	.06
MS-Symptoms				
Functional limitation total	.13	.05	.09	.11
Cognitive	.07	.08	.08	−.04
Mood	.21*	.14	.16	.00
Visual	−.02	−.05	.00	.03
Speech	.15	.10	.18*	−.00
Swallowing	.10	−.03	.22*	.00
Upper limb	−.01	−.10	−.00	.11
Lower limb	−.10	−.15	−.12	.10
Sexual	.06	.14	−.00	−.05
Bladder	.04	−.03	.03	.09
Bowel	.03	.06	−.05	.03
Fatigue	.05	−.04	.02	.12
Quality of life				
Physical function	−.09	−.05	.03	−.14
Role-physical	.06	.06	.10	−.03
Bodily pain	−.14	−.12	−.02	−.12
General health	−.21*	.08	−.03	−.10
Vitality	−.02	.02	−.01	−.01
Social functioning	.01	.11	−.17	−.03
Role emotional	−.10	.04	.00	−.04
Mental health	−.09	.02	.04	−.02
Mental component score	−.08	−.05	.06	.02
Physical component score	−.09	−.09	.05	−.12

* $P < .05$; ** $P < .01$, [†] Depression scores are calculated minus insomnia items

Table 4 Mixed models predicting improvement in total insomnia score, early, middle, and late insomnia

Variable	Estimate	Standard Error	*P*
Insomnia Total Score			
Intercept	−.23	.65	.73
Time	−.27	.15	.07
Therapy group	−.15	.27	.58
Baseline Hamilton Depression Rating Scale	**.17**	**.03**	**<.0001**
Change in Hamilton Depression Rating Scale	.03	.02	.26
Therapy group × time	.09	.17	.59
Change in Hamilton Depression Rating Scale × time	**.05**	**0.02**	**<.01**
Early insomnia			
Intercept	−2.52	.95	<.01
Time	−.03	.19	.86
Therapy group	−.23	.37	.53
Baseline Hamilton Depression Rating Scale	**.14**	**.05**	**<.01**
Change in Hamilton Depression Rating Scale	.02	.03	.45
Therapy group × time	.14	.24	.56
Change in Hamilton Depression Rating Scale × time	**.07**	**.02**	**<.001**
Middle insomnia			
Intercept	−4.43	1.07	<.0001
Time	−.37	.22	.09
Therapy group	−.25	.39	.51
Baseline Hamilton Depression Rating Scale	**.24**	**.06**	**<.0001**
Change in Hamilton Depression Rating Scale	−.002	.03	.95
Therapy group × time	−.13	.29	.65
Change in Hamilton Depression Rating Scale × time	.04	.02	.05
Late insomnia			
Intercept	−3.42	1.12	<.01
Time	−.15	.42	.71
Therapy group	.30	.51	.56
Baseline Hamilton Depression Rating Scale	.09	.05	.09
Change in Hamilton Depression Rating Scale	.04	.06	.47
Therapy group × time	.12	.43	.78
Change in Hamilton Depression Rating Scale × time	.03	.04	.54
Insomnia Total Score			
Intercept	1.89	.44	<.0001
Time	**−.33**	**.14**	**<.05**
Therapy group	−.12	.28	.68
Baseline Beck Depression Inventory-II	**.04**	**.02**	**<.05**
Change in Beck Depression Inventory-II	.01	.01	.68
Therapy group × time	−.06	.17	.71
Change in Beck Depression Inventory-II × time	**.02**	**.01**	**<.05**
Early insomnia			
Intercept	−1.25	.57	<.05
Time	−.15	.18	.38
Therapy group	−.24	.36	.51
Baseline Beck Depression Inventory-II	**.05**	**.02**	**<.05**
Change in Beck Depression Inventory-II	.01	.02	.59
Therapy group × time	−.08	.23	.75
Change in Beck Depression Inventory-II × time	**.02**	**.01**	**<.05**
Middle insomnia			
Intercept	−.80	.54	.14
Time	**−.49**	**.21**	**<.05**
Therapy group	−.09	.35	.79
Baseline Beck Depression Inventory-II	.03	.02	.08
Change in Beck Depression Inventory-II	.003	.02	.86
Therapy group × time	−.27	.26	.31
Change in Beck Depression Inventory-II × time	.005	.01	.70
Late insomnia			
Intercept	−3.31	.77	<.0001
Time	−.13	.40	.75
Therapy group	.48	.50	.34
Baseline Beck Depression Inventory-II	**.05**	**.02**	**<.05**
Change in Beck Depression Inventory-II	.004	.03	.90
Therapy group × time	−.06	.42	.88
Change in Beck Depression Inventory-II × time	.02	.02	.44
Insomnia Total Score			
Intercept	1.58	.36	<.0001
Time	**−.35**	**.13**	**<.01**
Therapy group	−.18	.27	.50
Baseline Hospital Anxiety and Depression Scale, Anxiety Subscale	**.11**	**.03**	**<.01**
Change in Hospital Anxiety and Depression Scale, Anxiety Subscale	−.02	.04	.62
Therapy group × time	−.03	.17	.85

Table 4 continued

Variable	Estimate	Standard Error	*P*
Change in Hospital Anxiety and Depression Scale, Anxiety Subscale × time	**.05**	**.02**	**<.05**
Early Insomnia			
Intercept	−1.71	.52	<.01
Time	−.19	.16	.24
Therapy group	−.31	.37	.40
Baseline Hospital Anxiety and Depression Scale, Anxiety Subscale	**.16**	**.05**	**<.01**
Change in Hospital Anxiety and Depression Scale, Anxiety Subscale	.008	.05	.88
Therapy group × time	−.03	.24	.91
Change in Hospital Anxiety and Depression Scale, Anxiety Subscale × time	**.07**	**.03**	**<.05**
Middle insomnia			
Intercept	−1.16	.53	<.05
Time	**−.56**	**.21**	**<.01**
Therapy group	−.11	.36	.77
Baseline Hospital Anxiety and Depression Scale, Anxiety Subscale	**.12**	**.05**	**<.05**
Change in HADS	.01	.05	.77
Therapy group × time	−.30	.27	.26
Change in Hospital Anxiety and Depression Scale, Anxiety Subscale × time	−.004	.03	.90
Late insomnia			
Intercept	−3.06	.70	<.0001
Time	.01	.35	.98
Therapy group	.28	.51	.58
Baseline Hospital Anxiety and Depression Scale, Anxiety Subscale	.08	.06	.15
Change in Hospital Anxiety and Depression Scale, Anxiety Subscale	−.08	.07	.27
Therapy group × time	.06	.41	.88
Change in Hospital Anxiety and Depression Scale, Anxiety Subscale × time	**.11**	**.05**	**<.05**

Bolded values indicate $P < .05$

($P < .001$, $P < .05$, respectively) and early insomnia ($P < .05$, and $P < .001$, respectively). Higher baseline insomnia was also associated with greater change in middle insomnia ($P < .05$) and change in anxiety over time was associated with greater improvement in late insomnia ($P < .05$). In all models, treatment type (cognitive behavioral therapy vs. supportive emotion-focused therapy) and the treatment type by time interaction was not significant (Fig. 1).

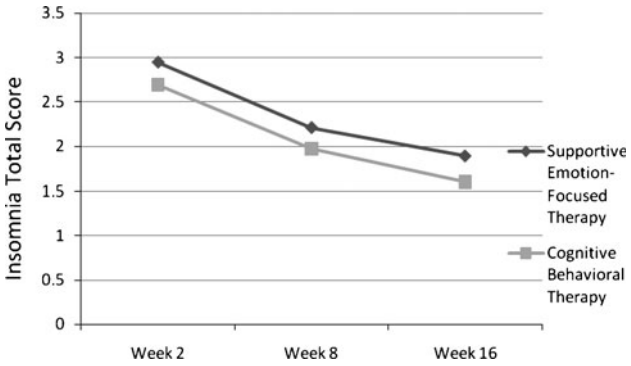

Fig. 1 Change in insomnia total score over time by psychotherapy group

Associations with insomnia at post treatment

At the end of treatment, 27% ($n = 35$) continued to meet criteria for major depressive disorder and 21% ($n = 26$) had elevated anxiety symptoms. In univariate regression models, higher multiple sclerosis-related functional limitation ($B = .06$, SE $= .02$, $P < .01$), higher depression on the Hamilton Depression Rating Scale ($B = .13$, SE $= .02$, $P < .01$) and higher anxiety scores ($B = .10$, SE $= .03$, $P < .01$) were associated with higher post treatment insomnia symptoms. Insomnia at post treatment was also associated with a lower mental composite quality of life score on the SF-36 ($B = -1.66$, SE $= .54$, $P < .05$). Insomnia at post treatment was not associated with the physical health composite score. When depression and anxiety were included in a multivariate model, with age and gender, only post treatment depression independently predicted post treatment insomnia ($R^2_\Delta = .17$, $P < .0001$). In logistic regression models, having insomnia at post treatment was associated with an increased risk of meeting criteria for major depressive disorder (OR $= 5.80$, $P < .0001$) and increased risk of elevated anxiety scores (OR $= 3.18$, $P < .05$). In addition, a significant number of participants without major depressive disorder continued to report significant insomnia symptoms at post treatment ($n = 30$, 33% of participants without major depressive disorder, and $n = 35$, 37% of participants without elevated anxiety had persistent insomnia).

Discussion

This study evaluated the prevalence of insomnia symptoms, associations between insomnia with mood and

disease characteristics and response of insomnia symptoms to psychotherapy for depression in patients with multiple sclerosis and depression. Results demonstrate that patients with comorbid multiple sclerosis and depression have levels of insomnia symptoms above and beyond that reported of the overall multiple sclerosis population but on par with other samples of patient with major depressive disorder, with over 77% of the sample reporting clinically significant insomnia symptoms (difficulty initiating sleep, maintaining sleep, or early morning awakenings $\geq$3 days per week). In a study that used a diary based measure of sleep in a sample of patients with multiple sclerosis who were not selected on depression, 42% reported difficulty initiating sleep, 53% reported extended awakenings, 58% reported waking and being unable to return to sleep $\geq$2 times per week, (Stanton et al. 2006). However, the rates of insomnia found in our sample are comparable to prevalence of insomnia symptoms in patients with major depressive disorder enrolled in the STAR*D trial, which found that 84.7% of the 3,743 participants reported at least one symptom of insomnia on the Hamilton Depression Rating Scale baseline (Sunderajan et al. 2010).

We found that the severity of insomnia was correlated with interviewer rated depressive symptoms on the Hamilton Depression Rating Scale but not with self report depression on the Beck Depression Inventory-II. This may reflect method variance as well as the high base rates of insomnia and depression, which contribute to restricted range. In addition, the items of the Hamilton Depression Rating Scale focus more on the somatic symptoms that are often related to anxiety, whereas the Beck Depression Inventory-II focuses more on the cognitive symptoms of depression. Insomnia symptoms at baseline were also not associated with the majority of quality of life and multiple sclerosis symptoms at baseline, including bowel and bladder symptoms, fatigue, and weakness in the limbs. Among the multiple sclerosis symptoms, only speech and swallowing difficulties were correlated with middle of the night awakenings and mood symptoms were associated with the total insomnia score. The correlation between difficulty swallowing, speech problems and insomnia may suggest that those with the most severe multiple sclerosis symptoms, may also have more severe sleep disturbance due to greater overall disease severity, such as weakness in the upper airway (De Pauw et al. 2002). Bulbar dysfunction in multiple sclerosis may contribute to both arousals during sleep as well as dysphagia (Autret et al. 2001; Howard et al. 1992; Thomas and Wiles 1999). We also found that patients with the most severe multiple sclerosis symptoms at baseline were more likely to have higher insomnia symptoms post treatment. It is possible that insomnia symptoms due to depression would be likely to remit with improvement in depression whereas insomnia associated with multiple sclerosis severity would not improve with depression treatment.

In evaluating the course of insomnia symptoms with depression treatment, we found that insomnia improved significantly, from over 3/4ths of the participants at baseline to less than half of participants. The post treatment rates of insomnia were similar to those of other reports of sleep disturbance in multiple sclerosis samples (Stanton et al. 2006; Tachibana et al. 1994). However, the rates of residual insomnia were higher than reported in depression remitters in non- multiple sclerosis samples (Carney et al. 2007; Nierenberg et al. 2010). The greatest improvement in insomnia was seen in those with the greatest improvement in symptoms of depression and anxiety. Specifically, sleep onset insomnia complaints were the most responsive to changes in depression and anxiety. When evaluated alone, middle of the night awakenings and early morning awakenings were not associated with improvement in depression and anxiety symptoms. Although it has been reported that insomnia symptoms precede the development of depression, this study appears to reflect improvement of insomnia as a result of depression and anxiety improvement (Chang et al. 1997). The design of this study makes it impossible to determine if insomnia symptoms preceded the development of depression or anxiety.

Contrary to our expectations, there was no difference between the two psychotherapies—cognitive behavioral therapy and supportive emotion-focused therapy for improvement in insomnia symptoms. This result may be due to the fact that neither psychotherapy specifically addressed sleep related thoughts and behaviors, such as sleep restriction therapy, stimulus control therapy, and sleep hygiene to improve sleep latency, sleep efficiency and sleep quality (Morgenthaler et al. 2006). There is some evidence suggesting that increasing daytime activity alone may have a significant impact on sleep. An multidisciplinary "energy conservation program" in patients with multiple sclerosis improved physical and mental fatigue, depression, and sleep quality (Sauter et al. 2008). In addition, participants significantly reduced their average time in bed from 8 h 36 min to 8 h 6 min post treatment, which is consistent with techniques to improve sleep consolidation used in treating insomnia.

This study demonstrates that having residual insomnia symptoms after psychotherapy for depression may be an important indicator of residual mood disturbance after psychotherapy. Participants with persistent insomnia after psychotherapy for depression were nearly six times more likely to continue to meet criteria major depressive disorder at post treatment and over 3 times more likely to continue to have clinically elevated anxiety. Post treatment insomnia was also correlated with lower quality of life, particularly in the mental health domain. Despite the improvements in

depression and insomnia in this study, a high number of participants without major depressive disorder at post treatment continued to report clinically significant insomnia symptoms (33% of those without depression). The high prevalence of residual insomnia symptoms is likely to be due to the multifactoral nature of insomnia in multiple sclerosis. The intervention was focused on addressing depression, therefore insomnia due to restless legs, pain or bladder symptoms would not be expected to improve with depression.

Given the high rates of insomnia symptoms and other sleep disorders in patients with multiple sclerosis, results of this study demonstrate the utility of sleep disorders screening and interventions to improve quality of life and possibly additional outcomes for patients with multiple sclerosis. There is evidence that cognitive and behavioral interventions for insomnia are effective in improving insomnia comorbid with other medical conditions, including osteoarthritis, coronary artery disease, and chronic obstructive pulmonary disease (Rybarczyk et al. 2005). In addition, recent evidence suggests that cognitive behavioral therapy for insomnia may improve response to antidepressant medications in patients with depression (Manber et al. 2008).

Results of this study are limited by measurement of insomnia from a depression interview, rather than measures more specific to sleep (e.g., sleep times, sleep quality, restless legs) Therefore, we were not able to determine the cause of insomnia or the aspects of insomnia that improved with treatment of depression. Our measurement also did not take into account daytime dysfunction related to sleep, therefore it was an assessment of insomnia symptoms rather than the disorder of insomnia as defined by the International Classification of Sleep Disorders Second Edition (International Classification of Sleep Disorders, Second Edition: Diagnostic and Coding Manual 2005). There also was no treatment specifically provided to target sleep symptoms in either psychotherapy group. There was no placebo or no-treatment control condition in this study. Thus, while we believe it is unlikely, it is possible that these results reflect the natural history of the symptoms reported.

In conclusion, this study demonstrates high prevalence of insomnia in patients with both multiple sclerosis and depression. Insomnia symptoms, particularly sleep onset insomnia, improved with psychotherapy for depression, with the greatest improvement seen in those with most improvement in their depression and anxiety. However, a considerable percentage of participants continued to experience insomnia despite remission of major depressive disorder and low symptoms of anxiety. This is an important finding because residual insomnia was predictive of continued psychiatric morbidity and poorer quality of life. These results suggest that treatment of depression and anxiety has the potential to greatly improve insomnia in multiple sclerosis but may not be sufficient to address the heterogeneous etiology of insomnia in many multiple sclerosis patients. Due to the multiple psychological, physiological, and behavioral factors that cause insomnia in multiple sclerosis, a multi-faceted intervention addressing each of the relevant factors is likely to be necessary in the treatment of insomnia in patients with multiple sclerosis, including screening for other primary sleep disorders (e.g., obstructive sleep apnea and restless legs syndrome), the management of depression and anxiety as well as pain management.

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