A Comparison of Rates of Residual Insomnia Symptoms Following Pharmacotherapy or Cognitive-Behavioral Therapy for Major Depressive Disorder

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Objective: A number of pharmacologic studies have documented that insomnia is among the most commonly reported residual symptoms after remission from depression. Residual symptoms after remission are particularly relevant because these symptoms confer greater risk for subsequent depression. This study was the first to date to examine residual insomnia after cognitive-behavioral therapy (CBT) for depression and to compare CBT with pharmacotherapy for depression on residual insomnia rates.

Method: This naturalistic study examined rates of posttreatment insomnia complaints in patients (N = 94) who had been diagnosed with major depressive disorder (MDD), according to DSM-IV criteria, and who remitted from MDD after completing at least 20 weeks of either CBT or pharmacotherapy at an outpatient clinic specializing in mood disorders. Participants were randomly assigned to the treatment conditions, but only the data from those who completed treatment and remitted were analyzed. Primary outcome measure was the 17-item Hamilton Rating Scale for Depression. Data were collected from October 1, 1999, to September 23, 2003. Groups were compared using a χ^2 for nominal data.

Results: The rate of posttreatment insomnia was 22% for sleep-onset insomnia, 26% for sleep-maintenance insomnia, and 17% for early morning awakenings, and the rates did not statistically differ across the 2 treatment groups.

Conclusion: Although CBT and pharmacotherapy effectively addressed depression in these patients and addressed insomnia symptoms for many, there were a number of patients with residual insomnia. Whereas there appears to be no difference between CBT and pharmacotherapy with regard to rates of residual insomnia, the rates of such insomnia remaining after these treatments suggest that adjunctive sleep treatment to specifically address insomnia may be necessary for some MDD patients.

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Major depressive disorder (MDD) is a devastating condition that produces significant health care costs[1] and personal costs for millions worldwide. At a minimum, those who suffer from MDD experience heightened distress, fatigue, poor health, and lowered quality of life. The burden associated with MDD is compounded by its recurrent nature, as more than 80% of those who recover from an initial episode of depression will later experience multiple subsequent depressive episodes.[2] Whereas the costs and suffering associated with MDD in general are substantial, they are particularly noteworthy among the subgroup that present with concurrent insomnia problems, including sleep-onset insomnia, sleep-maintenance insomnia, or early morning awakenings. These concurrent insomnia symptoms enhance the risk for poorer response to depression therapy,[3] future relapse[4] or recurrence of MDD episodes,[5] and suicide.[6,7] Thus, the recognition and tracking of insomnia in the context of MDD seems particularly warranted.

Currently, both pharmacotherapy with various antidepressant medications and psychological interventions such as cognitive-behavioral therapy (CBT) are com-

monly used for MDD management, given their well-established efficacy for treating the range of symptoms associated with this condition. However, a sizable subgroup of MDD patients have less than optimal responses to these depression-focused therapies and are left with residual insomnia symptoms that represent a significant clinical concern. Residual insomnia symptoms, like those occurring coincident to an MDD episode, may cause MDD patients significant distress and complicate their recovery process. Insomnia symptoms have been found to increase risk for subsequent MDD.[8] Also, the variability of residual symptoms confers greater risk for relapse, and insomnia is among the most variable residual symptoms after depression treatment.[9] Given such observations, determining the rates of residual insomnia for commonly used MDD therapies seems an important pursuit in evaluating the overall effectiveness of the therapies. To date, there have been relatively few studies devoted to determining the residual insomnia rates found with MDD therapies. One study[10] found a moderately high residual insomnia rate (44%) among patients who showed remission of other MDD symptoms after treatment with fluoxetine. Another study[11] compared residual insomnia rates among patients treated with a form of psychotherapy (Cognitive Behavioral Analysis System of Psychotherapy [CBASP][12]) or nefazodone. Results of this study showed that those treated with CBASP had slightly higher rates of residual sleep-onset insomnia (38%) and much higher residual rates of early morning awakenings (22%) than those treated with the antidepressant medication nefazodone (sleep-onset insomnia = 31%; early morning awakenings = 12%). The rates of sleep-maintenance insomnia (30%) in the CBASP group were similar to those in the nefazodone group (28%).[11] CBASP is not as widely used or available as CBT, and because of reports of hepatic failures associated with nefazodone,[13–17] this agent is no longer readily prescribed for depression. Thus, it would be informative to have a comparison of CBT and commonly used antidepressants. Unfortunately, studies designed to determine residual insomnia rates following commonly used CBT interventions for depression or to compare residual insomnia rates following CBT and pharmacotherapy have yet to be conducted. As such, this study investigated rates of residual insomnia among MDD patients who showed remission of other depressive symptoms after they completed at least 20 weeks of CBT or pharmacotherapy.

METHOD

Study Design

This study employed a retrospective design with the study sample and dependent measures drawn from a larger clinical trial. The larger parent study used a randomized, split-plot, experimental design with 2 between-group cells (CBT and pharmacotherapy) and 2 within-group cells (baseline and posttreatment). Independent groups of MDD sufferers treated with either pharmacotherapy or CBT for depression comprised the parent study sample. These patients were randomly assigned to 1 of the 2 treatment conditions using computer software (Microsoft Access 2003; Microsoft Corporation, Redmond, Wash.). The overall study protocol was approved by the institutional review board at the Centre for Addiction and Mental Health (Toronto, Ontario, Canada). All participants provided written informed consent prior to any research activity.

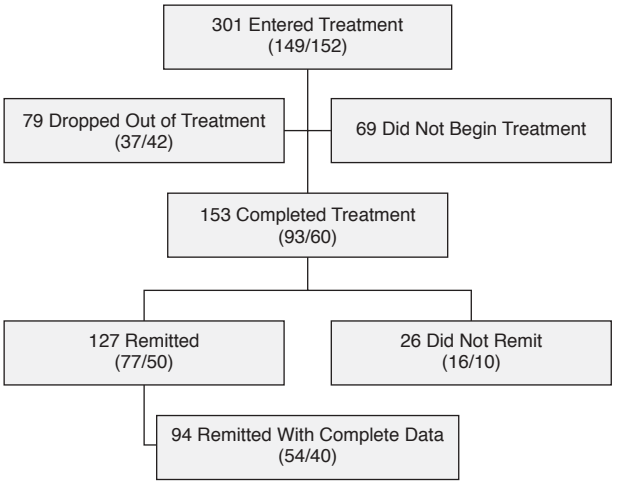
Participants

Participants for the present study were drawn from a larger trial examining the long-term prognosis of those with MDD treated with CBT or pharmacotherapy.[18] Those participating in the larger parent study were recruited through clinical referrals from the Mood and Anxiety Disorders Program at the Centre for Addiction and Mental Health or from media announcements. Study enrollment began on October 1, 1999, and the last posttreatment assessment was completed on September 23, 2003. Diagnostic eligibility for the study was determined using the Structured Clinical Interview for DSM-IV Axis I disorders.[19] Inclusion criteria were (1) diagnosis of MDD according to DSM-IV criteria, (2) age between 18 and 65 years, (3) minimum eighth-grade education, and (4) ability to read English and to provide informed consent. Exclusion criteria were (1) a current diagnosis of bipolar disorder, substance abuse disorder, schizophrenia, or borderline personality disorder; (2) a trial of electroconvulsive therapy within the past 6 months; and (3) a score of less than 12 on the Hamilton Rating Scale for Depression (HAM-D).[20] A total of 301 patients met selection criteria for the parent study, and 153 completed study procedures. To determine if there were residual insomnia complaints in those remitted from depression, only those who completed 20 weeks of therapy (either CBT or pharmacotherapy) and showed remission from depression (i.e., had a posttreatment HAM-D total score ≤ 7) were retained for analyses. In addition to a HAM-D score ≤ 7, remission was further defined, following consensus recommendations,[21] as reporting minimal symptoms for at least 12 weeks and no longer meeting DSM-IV diagnostic criteria for a major depressive episode on the Longitudinal Interval Follow-up Evaluation.[22] Ninety-four patients met these selection criteria and, thus, were chosen to serve as the study sample in the current investigation. Figure 1 depicts the study patient flow, and Table 1 shows the demographic characteristics of this sample.

Primary Measure

The 17-item HAM-D was administered to patients at pretreatment and posttreatment. The HAM-D contains

Figure 1. Patient Flow for Depression and Insomnia Study[a]



[a]Sample size shown as total sample; CBT/pharmacotherapy breakdown shown in parentheses.
Abbreviation: CBT = cognitive-behavioral therapy.

Table 1. Demographic Characteristics and Depression History of Patient Sample

Variable	CBT (N = 54)	Pharmacotherapy (N = 40)	Total (N = 94)
Gender			
Male, N (%)	22 (41)	15 (38)	37 (39)
Female, N (%)	32 (59)	25 (63)	57 (61)
Age at first interview			
Age range, y	21–66	20–64	20–66
Mean (SD) age, y	36.7 (9.7)	39.7 (11.2)	37.9 (10.4)
Ethnicity/race			
White, N (%)	44 (81)	31 (78)	75 (80)
African/West Indian, N (%)	2 (4)	3 (8)	5 (5)
Asian, N (%)	3 (6)	2 (5)	5 (5)
Other, N (%)	5 (9)	4 (10)	9 (10)
Depression history			
Pretreatment HAM-D-17 score, mean (SD)	19.2 (3.5)	18.3 (4.6)	18.9 (4.0)
First episode (no previous episodes), N (%)	9 (17)	6 (15)	15 (16)
Recurrent, N (%)	41 (76)	30 (75)	71 (76)
3 or more episodes, N (%)	38 (70)	28 (70)	66 (70)
Current use of sleep medication, N (%)	2 (4)	2 (5)	4 (4)

Abbreviations: CBT = cognitive-behavioral therapy, HAM-D-17 = 17-item Hamilton Rating Scale for Depression.

items that query the presence of sleep-onset insomnia, sleep-maintenance insomnia, or early morning awakenings. A nonzero response on the sleep-onset insomnia item connotes a sleep-onset latency greater than 30 minutes occurring at least 2 days per week. Likewise, a score of 1 or greater on the sleep-maintenance insomnia item indicates sleep-maintenance problems/restless sleep occurring a minimum of 2 days per week, and a nonzero response on the early morning awakening item denotes significant early morning awakenings. The HAM-D is a validated depression measure,[23,24] with demonstrated utility for detecting insomnia symptoms in depression.[25]

Treatment Procedures

Patients in the pharmacotherapy condition were treated with antidepressant medications for a period of 6 months. There were 4 study psychiatrists (3 male, 1 female) with considerable expertise (8–25 years) in the pharmacologic treatment of MDD. Choice of medication was naturalistic and based on the treating psychiatrist's clinical judgment. Patients who failed to respond to their first antidepressant medication were allowed to discontinue and start on a second. If they failed both trials, they were removed from the study and offered alternative care in the depression clinic at the Centre for Addiction and Mental Health. Pharmacotherapy sessions were 20 minutes in duration and followed recommendations for clinical management.[26] They emphasized both medication management (education, dosage adjustment, dosage scheduling, and side effects) and clinical management (discussion of functionality, support, and limited advice). Psychotherapeutic strategies utilized in CBT[27] were prohibited. Patients attended approximately 10 to 13 sessions with their study psychiatrist over a 26-week period and were maintained on antidepressant medication during that time.

Following the protocol developed by Beck et al.,[27] patients in the CBT condition received a course of 20 individual weekly sessions of CBT, which spanned 22 to 24 weeks. Sessions were 50 minutes in length. Treatment was provided by a single therapist throughout the trial. Therapists were 1 (male) licensed clinical psychologist (a member of the Academy of Cognitive Therapy) and 7 master's-level staff (2 male, 5 female) with extensive experience conducting CBT (5–15 years). Treatment fidelity was assessed using the Cognitive Therapy Rating Scale[28] to rate 18 audiotapes (early, middle, and late sessions) from 6 randomly chosen patients. There are 11 items with possible scores of 0 to 6 for each item; thus, the range of possible scores is 0 to 66. The scores for the therapists evaluated by our 2 raters ranged from 38 to 54. The mean ratings for the 2 raters across all tapes were high (46.94 and 47.35), and the level of interrater agreement was good (intraclass correlation coefficient = 0.826).

Statistical Analysis

Statistical Package for the Social Sciences (SPSS) software for Windows, Version 10.0 (SPSS Inc., Chicago, Ill.), was used to conduct study analyses. A nonparametric χ^2 analysis was conducted to assess whether there were differences between the 2 therapies (CBT vs. pharmacotherapy) at posttreatment and to provide rates of residual insomnia symptoms.

Table 2. Pretreatment and Posttreatment Insomnia Complaints in Those Completing Treatment and Remitting From Depression (HAM-D-17 score ≤ 7)[a]

Variable	CBT With Baseline Sleep Problem (N = 47)[b]	All CBT Study Patients (N = 54)[c]	Pharmacotherapy With Baseline Sleep Problem (N = 36)[b]	All Pharmacotherapy Study Patients (N = 40)[c]	Total With Baseline Sleep Problem (N = 83)	Total Study Patients (N = 94)
Sleep-onset insomnia						
Pretreatment	30 (64)	30 (56)	25 (69)	25 (63)	55 (66)	55 (59)
Posttreatment	11 (23)	13 (24)	8 (22)	8 (20)	19 (23)	21 (22)
Sleep-maintenance insomnia						
Pretreatment	36 (77)	36 (67)	31 (86)	31 (78)	67 (81)	67 (71)
Posttreatment	13 (28)	14 (26)	9 (25)	10 (25)	9 (11)	24 (26)
Early morning awakenings						
Pretreatment	23 (49)	23 (43)	18 (50)	24 (60)	41 (49)	47 (50)
Posttreatment	8 (17)	8 (15)	8 (22)	8 (20)	16 (19)	16 (17)
Any sleep problem						
Pretreatment	47 (100)	47 (87)	36 (100)	36 (90)	83 (100)	83 (88)
Posttreatment	24 (51)	27 (50)	20 (56)	21 (53)	44 (53)	48 (51)

[a]All data shown as N (%).
[b]Number of patients by treatment condition who had a sleep problem at pretreatment.
[c]Number of patients by treatment condition irrespective of whether they had a pretreatment sleep problem.
Abbreviations: CBT = cognitive-behavioral therapy, HAM-D-17 = 17-item Hamilton Rating Scale for Depression.

RESULTS

At pretreatment, there were 55 patients (59%) who endorsed sleep-onset difficulty, 67 (71%) who reported sleep-maintenance problems, and 47 (50%) who had a complaint of early morning awakenings on the HAM-D. At posttreatment, HAM-D responses showed that 21 (22%) were complaining of sleep-onset insomnia, 24 (26%) reported sleep-maintenance insomnia, and 16 (17%) reported early morning awakenings. The overall rate (i.e., having sleep-onset insomnia or sleep-maintenance insomnia or early morning awakenings) at posttreatment was 51%. Table 2 contains the group rates at pretreatment and posttreatment for all 3 types of insomnia symptoms.

A crosstab procedure in SPSS was used to assess whether the type of depression treatment received (CBT vs. pharmacotherapy) produced differential proportions of sleep-onset insomnia or sleep-maintenance insomnia at posttreatment. We also used the same procedure to ensure the groups did not differ in their proportions of insomnia sufferers at pretreatment. The variables were nominal (0 = no insomnia, 1 = insomnia); thus, a nonparametric procedure was used. A χ^2 test of independence was calculated to assess the association between therapy and posttreatment sleep status. Our comparisons of the pharmacotherapy and CBT groups on their pretreatment levels of sleep-onset insomnia ($\chi^2 = 0.46$, $p = .50$), sleep-maintenance insomnia ($\chi^2 = 1.32$, $p = .64$), and early morning awakenings ($\chi^2 = 2.79$, $p = .10$) showed no statistically significant differences. Likewise, the groups did not differ statistically at posttreatment on sleep-onset insomnia ($\chi^2 = 0.22$, $p = .64$), sleep-maintenance insomnia ($\chi^2 = 0.01$, $p = .92$), or early morning awakenings ($\chi^2 = 0.44$, $p = .51$). Thus, rates of insomnia in the 2 therapy groups were not statistically different at pretreatment or posttreatment.

A dosing model from a consensus depression work group[29] was employed; thus, study patients may have had 1 or 2 trials of different medications. Given the modest group size for pharmacotherapy (N = 40), separate analyses were not conducted for each study drug. However, Table 3 contains the rates of residual sleep problems for each of the study drugs. The medications in the table represent the final medication patients were taking when they were determined to be remitted at the posttreatment assessment.

DISCUSSION

Both pharmacotherapy and CBT effectively decreased sleep complaints in many remitted patients. The rates for pretreatment sleep complaints were as high as 71% (i.e., for sleep-maintenance insomnia), which is consistent with previously reported sleep-disturbance rates,[30] and after remission from depression, insomnia symptom rates decreased by more than one half. Although many depression treatment responders reported no insomnia complaints at posttreatment, there were a number of patients who reported residual insomnia symptoms after remission. Interestingly, rates of residual insomnia symptoms for pharmacotherapy and CBT did not differ significantly. These findings suggest that conventional depression therapies fail to address insomnia symptoms in a number of patients and that there is no apparent advantage of pharmacologic therapy over CBT with respect to sleep improvement.

There were higher rates of residual sleep-maintenance insomnia than sleep-onset insomnia or early morning awakenings, although there were also higher rates of sleep-maintenance insomnia than the other 2 insomnia subtypes

Table 3. Residual Sleep Problems by Study Medication at Time of Posttreatment Assessment and Determination of Remission[a]

Medication at Posttreatment	Residual Sleep-Onset Problems	Residual Sleep-Maintenance Problems	Residual Early Morning Awakening Problems	Any Residual Sleep Problems	No Residual Sleep Problems
Citalopram, 10–30 mg/d (N = 9)	3 (33)	1 (11)	4 (44)	7 (78)	2 (22)
Venlafaxine, 37.5–150 mg/d (N = 8)	2 (25)	4 (50)	3 (38)	4 (50)	4 (50)
Paroxetine, 20 mg/d (N = 5)	2 (40)	1 (20)	0 (0)	3 (60)	2 (40)
Fluoxetine, 20 mg/d (N = 1)	0 (0)	1 (100)	0 (0)	1 (100)	0 (0)
Nefazodone, 100 mg/d (N = 1)	0 (0)	0 (0)	0 (0)	0 (0)	1 (100)
Bupropion, 100–150 mg/d (N = 16)	2 (13)	4 (25)	3 (19)	7 (44)	9 (56)

[a]All data are shown as N (%) within medication group (e.g., 3 of 9 participants taking citalopram reported posttreatment sleep-onset problems); study participants could have more than 1 sleep problem.

at baseline. The findings in this study were similar to those reported in a previous study comparing residual insomnia in treatment with CBASP and nefazodone.[11] In the current study, we found slightly lower residual rates of sleep-onset insomnia complaints for CBT and pharmacotherapy than were noted by Manber et al.[11] subsequent to treatment with CBASP and nefazodone. The rates of residual sleep-maintenance insomnia complaints were comparable between the Manber et al.[11] study and the current study. Lastly, the rate of residual early morning awakenings was lower for CBT than CBASP, and nefazodone had a lower residual rate than the medications used in this study.[11] The overall residual insomnia rate for pharmacotherapy in the current study (53%) was slightly higher than the 44% rate reported for a previous study with fluoxetine.[10] Overall, the present results were comparable with previous studies. Differences between the rates in these studies may be attributable to the different sleep indices used (sleep diary vs. HAM-D sleep items), the fact that the therapies were different, and that more stringent criteria were used in this study to define remission from depression.

Although rates of posttreatment sleep disturbance between 17% and 26% are somewhat encouraging, especially given that the pretreatment insomnia rate was as high as 71%, there remains some cause for concern. The most important reason is the well-documented relationship between residual symptoms and subsequent depression. The presence of residual symptoms after depression treatment is predictive of future episodes of depression.[31,32] In addition, the rate across insomnia subtypes at posttreatment (i.e., reporting any insomnia symptom) was quite high (51%). It remains unknown how many have clinically significant insomnia, but clinically significant insomnia is important because it has enormous associated economic and personal costs[33–35] and tends to be chronic[36]; thus, it warrants treatment. The fact that the insomnia persists after remission from depression also may be suggestive that this group is suffering from an untreated primary or comorbid sleep disorder (i.e., insomnia). Further study is needed in this area and is beyond the scope of the present investigation.

This study also highlights the importance of considering residual symptoms as a potential factor in recurrence after depression treatments. Most of the sample had recurrent depression and had had at least 3 episodes of depression in the past. Given that residual insomnia is predictive of future depressive episodes[8] and that the risk for depression is substantially increased in those with multiple past episodes,[2] the sample described here can be reasonably considered to be at very high risk for future depression. Several studies have also suggested that groups with comorbid insomnia and depression are at higher risk for suicide.[6,37] More research focus on sleep as a risk factor and more sleep-treatment studies in such patients are important to understand and better manage these complex clinical cases.

Unfortunately, this study lacked the sample size to compare rates of residual insomnia across the specific drugs. Thus, the findings must be interpreted cautiously, as rates of residual insomnia may vary by antidepressant medication type. The rates across medications varied according to the type of insomnia. The rates of overall sleep disturbance (i.e., any sleep problem at posttreatment) were highest for the selective serotonin reuptake inhibitors citalopram and paroxetine. It remains to be seen whether particular antidepressants are more effective at eliminating 1 type of residual insomnia complaint over another. Because of the small sample size for each medication, definitive statements about specific medications producing differential rates of residual insomnia will have to be investigated in future studies. However, these findings appear commensurate with reports of residual sleep problems with multiple other medication types (e.g., fluoxetine, reboxetine, imipramine, nefazodone).[9–11,38] Nonetheless, it should be noted that this was a naturalistic study, and the results that pertain to specific medications should be considered with the caveat that the medications listed are the medications that led to the remission only. What effects, if any, prior medications may have had on the rates reported remain unknown.

This study is limited by its use of single sleep items taken from the HAM-D rather than use of a validated in-

somnia screening instrument. Future studies employing a well-validated insomnia screening method, whether prospective (sleep logs), retrospective (self-report insomnia questionnaire), or objective (e.g., polysomnography), could provide more precise rates of baseline and posttreatment insomnia. However, the residual insomnia rates in this study were comparable with those reported using sleep diaries at posttreatment in a previous study.[11] In addition, a study comparing sleep-diary estimates with HAM-D sleep items provides some support for the use of the HAM-D as an index of sleep disturbance in those with depression.[25] Future studies could improve upon the present study by including a measure of clinical significance and by characterizing the sample in terms of diagnostic criteria for insomnia using validated diagnostic measures/procedures. Similarly, by not formally assessing sleep disorders at pretreatment, it remains unknown whether some of these patients are suffering from an occult sleep disorder such as sleep apnea. An additional limitation is the absence of a placebo or control group for comparison. Lastly, whereas the original intent-to-treat sample was randomized to treatment, the sample examined in the current study was selected based on specific criteria (i.e., completing treatment and remitting) and thus was not a random sample. This means that those who completed the study and remitted from depression in the CBT group could have different differential characteristics from those who completed and remitted in the pharmacotherapy group.

Nonetheless, this study is the first comparison of residual insomnia rates after CBT and pharmacotherapy depression treatment. The results are generally positive for patients treated with conventional depression therapies and suggest no benefit for 1 depression therapy over another (e.g., CBT vs. pharmacotherapy). However, they also indicate that there is room for improvement in managing some patients with insomnia. The possibility that some of these patients are suffering primarily from a sleep disorder with accompanying mood symptoms or that they are suffering from comorbid but independent disorders such as primary insomnia and MDD warrants future investigation. Preliminary evidence suggests that treating the insomnia in addition to the depression has a positive impact on the course of the depression.[39] That line of research notwithstanding, the present findings are important given the increased risk that residual insomnia confers for later depression.

Drug names: bupropion (Wellbutrin and others), citalopram (Celexa and others), fluoxetine (Prozac and others), imipramine (Tofranil and others), paroxetine (Paxil, Pexeva, and others), venlafaxine (Effexor and others).

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