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Pre-treatment insomnia as a predictor of single and combination antidepressant outcomes: a CO-MED report

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CONTRIBUTORS

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Abstract

Background—Most patients with major depressive disorder (MDD) report clinically significant sleep problems. Pre-treatment insomnia been associated with poorer treatment outcomes in some antidepressant trials, leading to suggestions that combined treatment regimens may be more successful in this subgroup. This study investigated this question using data from the CO-MED trial.

Methods—Adult outpatients with chronic and/or recurrent MDD were randomly assigned in 1:1:1 ratio to 28 weeks of single-blind, placebo-controlled antidepressant treatment with (1) escitalopram+placebo, (2) bupropion-sustained-release+escitalopram, or (3) venlafaxine-extended-release+mirtazapine. We compared baseline characteristics, tolerability, and treatment outcomes at 12 and 28 weeks for patients with and without pre-treatment insomnia.

Results—Of the 665 evaluable patients, the majority (88.3%) reported significant pre-treatment insomnia. Those with pre-treatment insomnia were more likely to be female (69.3% vs. 57.7%) and African-American (29.1% vs 11.8%). Those with pre-treatment insomnia symptoms reported higher rates of concurrent anxiety disorders, lower rates of alcohol and substance use disorders, and greater impairment in psychosocial functioning. The two groups did not differ in either tolerability or treatment outcomes among the three antidepressant treatments.

Conclusions—Insomnia symptoms, while common in patients with chronic/recurrent MDD, were not predictive of response, remission, or tolerability with either single or combined antidepressant medications.

Keywords

Major depressive disorder; Insomnia; Antidepressant

INTRODUCTION

Several studies indicate that most patients with major depressive disorder (MDD) experience sleep problems - most frequently difficulty falling asleep and/or waking frequently¹⁻³. Insomnia is a risk factor for both first-episode and recurrent depression, and it is also a core symptom of a major depressive episode^{2, 4}. In most cases, clinically significant insomnia either precedes the onset of MDD or occurs along with the onset of other depressive symptoms⁵. Insomnia within MDD has been associated with longer duration of depressive episodes, greater symptom severity, higher rates of comorbid anxiety, traumatic stress, and impulse-control disorders, higher levels of suicidal ideation, poorer quality of life, and worse physical and occupational functioning^{2, 6-12}

The impact of pre-treatment insomnia on clinical outcomes with different types of antidepressant medications is unclear. In an open-label study of 797 adult outpatients with nonpsychotic MDD who were treated with 8 weeks of bupropion-sustained release, no difference was observed in response rates based on pre-treatment insomnia¹³. Similarly, in

another study comparing the acute efficacy of three different antidepressant agents (fluoxetine, sertraline, and paroxetine), no difference in response was observed for depressed outpatients with- and without pre-treatment insomnia¹⁴. No difference in overall response rates was found for a sample of 309 children and adolescents with- and without pre-treatment insomnia who were treated with 10-20mg of fluoxetine for 8-9 weeks¹⁵. However, adolescent participants with pre-treatment insomnia showed a poorer response to fluoxetine, whereas child participants with pre-treatment insomnia showed higher response rates on the same medication regimen.

Several other studies have found worse outcomes for patients with pre-treatment insomnia symptoms. Lower response and remission rates were associated with pre-treatment and ongoing sleep disturbance in another study of 166 depressed adolescents treated for 12 weeks with sertraline, cognitive-behavioral therapy, or their combination¹⁶. In a recent study using a combined sample of 711 adults who participated in six different depression treatment trials, patients with baseline insomnia and/or objective sleep disturbances were less likely to reach remission when treated with antidepressant medications (imipramine, nortriptyline, fluoxetine, paroxetine, or bupropion) and/or psychotherapy (interpersonal therapy or cognitive behavioral therapy). Patients with three or more baseline sleep disturbances were approximately three times less likely to reach remission¹⁷. However, recent work by Manber and colleagues provides evidence that augmenting an antidepressant medication with a brief, symptom-focused, cognitive behavioral therapy for insomnia is promising for individuals with MDD and comorbid insomnia - in terms of alleviating both depression and insomnia^{7, 18}.

An appealing strategy for clinicians seeking to improve outcomes for depressed patients with insomnia symptoms is to select a treatment that can simultaneously impact sleep disturbances and depressive symptoms. Unfortunately antidepressant medications like selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) have been reported to worsen sleep architecture by lengthening sleep onset, reducing sleep efficiency, decreasing REM sleep and increasing wake time after sleep onset^{12, 19}. A recent meta-analysis suggests minimal differences between the SSRIs for improving insomnia symptoms²⁰. In contrast, sedating agents such as mirtazapine or trazodone may be useful for addressing insomnia symptoms in patients with MDD¹⁹⁻²². A randomized trial comparing outcomes for 294 patients with severe MDD treated with 8 weeks of either fluoxetine (20-40mg) or mirtazapine (15-60mg) found greater improvements in sleep-related symptoms for patients in the mirtazapine group²². These findings have led some researchers to suggest the strategy of augmenting first-line antidepressant treatment with hypnotic agents or sedating antidepressants with serotonin receptor agonist properties^{19, 23, 24}. Potential drawbacks to augmentation with sedating antidepressants such as mirtazapine are their tendency to contribute to weight gain and/or daytime sleepiness²⁵. Currently there is very little data evaluating the differential efficacy of single agent versus combined treatment regimens as a first-line treatment strategy for MDD patients with pre-treatment insomnia symptoms.

To address this knowledge gap, we investigated the prevalence of pre-treatment insomnia symptoms (i.e., trouble falling asleep, waking during the night, and/or waking before

necessary), differences in baseline demographic and clinical correlates (i.e., depressive symptom severity, atypical features, melancholic features, anxious features, suicidality, manic symptoms, medical and psychiatric comorbidity, psychosocial impairment, quality of life), antidepressant safety/tolerability, and treatment outcomes in a sample of chronically/recurrently depressed outpatients with and without pre-treatment insomnia when treated with a single agent or antidepressant combinations. Adult outpatients with chronic and/or recurrent MDD were randomly assigned to 28 weeks of single-blind, placebo-controlled antidepressant treatment with (1) escitalopram+placebo, (2) bupropion-sustained-release+escitalopram, or (3) venlafaxine-extended-release+mirtazapine.

METHOD

Study Overview

The rationale, design, and primary outcomes for the CO-MED trial have been described in detail by Rush and colleagues²⁶. In brief, CO-MED was a 7-month prospective, randomized, single-blind, multicenter, placebo-controlled trial that compared the efficacy of escitalopram monotherapy versus two types of antidepressant combinations as first-step treatment for chronic and/or recurrent MDD. Outpatients with non-psychotic MDD were recruited from six primary care and nine psychiatric care sites across the United States from March 2008 to September 2009. Outcomes were reported at 12 weeks and 28 weeks. The present study was undertaken to determine whether pre-treatment sleep disturbance was associated with differences in clinical characteristics and outcomes across the three treatment arms. The CO-MED study is registered at ClinicalTrials.gov under registration identification number NCT00590863.

Participants

Eligible participants were outpatients seeking treatment at the primary or specialty care site and planning to continue living in the area for the duration of the study. Participants were identified by their treating clinician and screened using each site's standard procedure. Clinical research coordinators recruited those who met criteria for chronic (current major depressive episode lasting for 2 years or more) or recurrent (having had at least one prior major depressive episode) MDD, as defined by a clinical interview and confirmed by the MINI International Neuropsychiatric Interview (MINI)²⁷. Additional inclusion criteria were scores of 16 or greater on the 17-item Hamilton Depression Rating Scale (HRSD)²⁸ and clinical acceptability of treatment with antidepressant medication combinations. Exclusion criteria included lifetime history of bipolar disorder, Axis I psychotic disorders, current psychotic symptoms, history of anorexia or bulimia, current primary diagnosis of obsessive compulsive disorder, current substance dependence, immediate need for psychiatric hospitalization, presence of an unstable general medical condition, any current medication or general medical condition contraindicated by study medications and, current or lifetime history of somatic antidepressant treatment (e.g., ECT). Potential participants were excluded if they were currently taking antipsychotic or anticonvulsant medications, mood stabilizers, central nervous system stimulants or any of the study drugs, or participating in depression-specific psychotherapy. See www.co-med.org for a full list of study exclusions.

The study protocol was approved by the institutional review boards of the CO-MED National Coordinating Center (University of Texas Southwestern Medical Center, Dallas), the Data Coordinating Center (University of Pittsburgh), all participating clinical sites, and the Data Safety and Monitoring Board of the National Institutes of Health (Bethesda, MD). Participation was entirely voluntary and informed consent was taken prior to initiating study procedures. A full description of the protocol was given to each participant prior to obtaining written informed consent.

Definition of pre-treatment insomnia

The presence or absence of pre-treatment insomnia was determined based on responses to the 30-item Inventory of Depressive Symptomatology – Clinician-Rated (IDS-C)²⁹ at study intake. Three items from the IDS-C were used to evaluate the presence of 1) sleep onset insomnia (trouble falling asleep), 2) mid-nocturnal insomnia (waking during the night), and 3) early morning insomnia (waking before necessary) during the previous week⁷. Each item is rated from 0-3 on a Likert-type scale (higher scores indicate greater symptom severity). Participants who scored 2 on any of the three items were categorized as having pre-treatment insomnia. This method was selected due to ease of administration and previous work demonstrating substantial agreement between ratings of insomnia symptoms from the IDS and data from prospective sleep diaries³⁰. For the purposes of this analysis, those patients with scores of 2 or above were classified as having pre-treatment insomnia and those with scores below 2 were classified as not having pre-treatment insomnia. A cutoff score of 2 or greater has been widely used to denote clinically significant insomnia symptoms^{7, 30}.

Antidepressant treatment

Participants were stratified by clinical site and randomly assigned to three treatment groups using a web-based randomization system³¹. Random block sizes of three and six were used to minimize the probability of identifying the next treatment assignment. Dosing schedules were based on previous reports³²⁻³⁶ and doses were increased only in the context of acceptable side effects. Participants were withdrawn from the study if unacceptable or intolerable side effects occurred that could not be resolved with dose reduction or medication treatment of side effects. A 12-week acute study period was chosen for the primary analysis to ensure that maximal doses could be delivered for at least 4 weeks. This time frame also ensured that most participants whose depression could remit would do so without an excessively long trial and attrition could be minimized. Measurement-based care provided personally tailored and vigorous dosing³⁷⁻³⁹. Dosage adjustments were based on scores on the 16-item Quick Inventory of Depressive Symptomatology–Clinician-Rated (QIDS-C)⁴⁰ and patient report of side effect burden as measured by the Frequency, Intensity and Burden of Side Effects Rating (FIBSER)⁴¹ obtained at each visit. Treatment was guided by the CO-MED Operations Manual (available at www.co-med.org).

Bupropion-sustained release plus escitalopram

Bupropion-sustained release (150 mg/day) was started at baseline and increased to 300 mg/day at Week 1. Escitalopram began at 10 mg/day at Week 2. At Week 4, bupropion-sustained release was raised to 400 mg/day and/or escitalopram was raised to 20 mg/day if

the QIDS-C was >5 and side effects were acceptable. At Week 6 and beyond, doses were increased up to a maximum of bupropion-sustained release 400 mg/day (200 mg/day bid) and escitalopram 20 mg/day if the QIDS-C was >5 and side effects were acceptable.

Venlafaxine-extended release plus mirtazapine

Venlafaxine-extended release began at 37.5 mg/day for 3 days and then was raised to 75 mg/day. At Week 1, venlafaxine-extended release was raised to 150 mg/day. At Week 2, mirtazapine was added (15 mg/day). Thereafter, venlafaxine-extended release was raised to 225 mg/day and/or mirtazapine was increased to 30 mg/day at Week 4, mirtazapine was raised to 45 mg/day (maximum dose) at Week 6, and venlafaxine-extended release was raised to 300 mg/day (maximum dose) at Week 8 – all doses were increased only if the QIDS-C was >5 and side effects were acceptable.

Escitalopram plus placebo

Escitalopram began at one tablet (10 mg) per day to be increased to two tablets (20 mg) per day at 4 weeks and Pill placebo was started at Week 2 with the option to increase to two pills at Week 4; both doses were increased only if the QIDS-C was >5 and side effects were acceptable.

Medication blinding

The first medication given in each treatment group was given open label (both participant and study personnel unblinded), while each second medication was single-blinded (participant only). In the escitalopram plus placebo group, the placebo was blinded; in the bupropion-sustained release plus escitalopram group, escitalopram was blinded; and in the venlafaxine-extended release plus mirtazapine group, mirtazapine was blinded. Participants remained blinded to the second study medication during both the acute and continuation phases of the study. The study coordinators and physicians were not blinded to maximize safety and to allow physicians to make informed flexible dosing decisions. In emergencies requiring treatment by a physician outside of the study team, the study coordinator informed the emergency physician about the medications taken by the patient. If the participant inadvertently learned of the masked study medication, a protocol deviation was recorded and the patient remained in the study. There is no data to suggest that un-blinding impacted the study results.

Baseline characteristics

Socio-demographic and clinical characteristics were gathered at baseline for all participants. The 16-item Quick Inventory of Depressive Symptomatology – Self-Rated (QIDS-SR)^{29, 40} was used to evaluate severity of depressive symptoms, but three items pertaining to sleep were omitted from the total score for the present analyses. Insomnia, atypical features, and melancholic features were assessed using the 30-item IDS-C²⁹. Anxious features were assessed using the HRSD²⁸. Risk of suicidal thoughts, plans, and behaviors were measured using the Concise Health Risk Tracking – Self-Rated (CHRT-SR)⁴² and Concise Associated Symptoms Tracking– Self-Rated (CAST-SR)⁴³ scales. Manic symptoms were assessed using the Altman Self-Rated Mania Scale (ASRMS)⁴⁴. The Psychiatric Diagnostic

Screening Questionnaire (PDSQ)^{45, 46} was used to assess comorbid Axis I psychiatric disorders and the Self-administered Comorbidity Questionnaire (SCQ)⁴⁷ was used to assess comorbid medical conditions. The Work and Social Adjustment Scale (WSAS)⁴⁸ and the Quality of Life Inventory (QOLI)⁴⁹ were used to measure psychosocial impairment and quality of life.

Dosing, tolerability, and side effects

The QIDS-SR was collected at baseline and at each clinic visit along with the WSAS, QOLI, and Frequency, Intensity and Burden of Side Effects Rating (FIBSER)⁴¹. Additional measures included open label and blinded medication dose, presence of serious adverse events, and the Systematic Assessment for Treatment Emergent Events-Systematic Inquiry (SAFTEE-SI)⁵⁰. These same measures were collected throughout the continuation phase.

Treatment outcomes

The primary treatment outcome of symptom remission was determined based on the final two consecutive QIDS-SR scores (with the three insomnia items omitted) during the 12-week acute trial. To ensure that remission status was not falsely assigned due to one week of reduced symptom severity, one of these ratings had to be less than 5, and the other had to be less than 7. For participants who exited prior to 12 weeks, the score from their last study visit was used to determine remission status. Participants who exited before completing any post-baseline visits were deemed not remitted for the purposes of all analyses. Treatment response was defined as a 50% or greater reduction in QIDS-SR score (with insomnia items omitted) from baseline to study exit. Response and remission at Week 28 were determined following a similar algorithm. Secondary outcomes included early termination, side-effect burden measured by the FIBSER, detailed side effects measured by the SAFTEE-SI, psychosocial functioning as measured by the WSAS, and quality of life measured by the QOLI.

Analyses

Descriptive statistics, including measures of central tendency and dispersion, were computed for continuous data. Frequency distributions were estimated for categorical data. To examine the association of pre-treatment insomnia with participant demographic and clinical characteristics, we used chi square/Fisher's exact test for categorical variables and t-tests/Kruskal-Wallis tests for continuous variables. Regression models with pre-treatment insomnia as an independent variable were used to examine response, remission, and side effect burden. Logistic regression models were computed for binary data and cumulative logistic regression models were computed for non-binary data. A treatment by pre-treatment insomnia term was computed to examine differences in outcome between the three treatment conditions for those with pre-treatment insomnia compared to those without. Outcome analyses were also conducted with adjustment for baseline characteristics that were not balanced between the two groups – treatment, race, PDSQ substance abuse, CAST Mania, and WSAS. To control for the overall type I error rate, we employed a significance criterion of 0.025 for all comparisons.

RESULTS

A total of 835 participants were assessed for eligibility, 734 (87.9%) signed consent to be screened, and 665 (90.6%) were deemed eligible and randomly assigned to one of the three treatment groups. Of these, 587 (88.3%) met the definition for pre-treatment insomnia (Figure 1). The most frequent type of insomnia was a combination of sleep-onset, mid-nocturnal, and early-morning insomnia.

Baseline characteristics

Analysis of baseline data indicated a small number of socio-demographic differences (Table 1). Participants in the insomnia group were more likely to be female (69.3% vs. 57.7%) and African-American (29.1% vs 11.8%). No significant differences were found for age, years of education, employment status, or monthly household income. Examination of baseline clinical characteristics indicated significant differences with respect to baseline insomnia symptom severity, comorbid psychiatric conditions, and psychosocial functioning. As expected based on our grouping algorithm, those in the pre-treatment insomnia symptoms group reported significantly greater baseline insomnia symptoms on the QIDS-SR. Participants with pre-treatment insomnia symptoms were more likely to screen positive for comorbid anxiety disorders, including generalized anxiety disorder (21.1% vs. 9.0%), panic disorder (10.7% vs. 2.6%), and agoraphobia (11.4% vs. 2.6%). However, they were less likely to screen positive for substance use disorders, including alcohol abuse (8.9% vs. 19.5%) and substance abuse (11.9% vs. 22.1%). Participants in the pre-treatment insomnia symptoms group reported significantly greater impairment in social and occupational functioning. No differences were found with respect to anxious, melancholic, or atypical features, suicidality, comorbid medical conditions, or physical health status (Table 1).

Dosing, tolerability, and side effects

There were no significant differences in treatment duration or medication dosing (Supplementary Table 1). Results from unadjusted and adjusted analyses showed no statistically significant differences in rates of adverse events or side effects at either 12 or 28 weeks (Supplementary Table 2).

Treatment outcomes

The pre-treatment insomnia group had lower overall rates of response (51.2% vs 57.1%, Unadjusted OR = 0.946, Adjusted OR = 1.085) and remission at week 12 (37.6% vs 44.9%, Unadjusted OR = 0.824, Adjusted OR = 1.037), but these differences were not statistically significant (Supplementary Table 2). The same pattern was found for week 28 response (57.5% vs 64.9%, Unadjusted OR = 0.884, Adjusted OR = 0.940) and remission (44.5% vs 47.4%, Unadjusted OR = 1.022, Adjusted OR = 1.227) (Supplementary Table 2).

Participants without pre-treatment insomnia who were treated with escitalopram plus placebo (69.6%) had the highest response rates at 12 weeks and those without pre-treatment insomnia who were treated with venlafaxine sustained release plus mirtazapine had the highest response rates at 28 weeks (69.6%). However, no statistically significant interactions

were found for treatment response by pre-treatment insomnia and treatment group (Supplementary Table 3).

The highest remission rates were found for participants with pre-treatment insomnia when treated with escitalopram plus placebo at both 12 weeks (48.4%) and 28 weeks (54.8%). In contrast, participants without pre-treatment insomnia showed the highest remission rates when treated with bupropion plus escitalopram at both 12 weeks (45.8%) and 28 weeks (54.2%). However, no statistically significant interactions were found for remission rates by pre-treatment insomnia and treatment group at either 12 or 28 weeks (Supplementary Table 3).

DISCUSSION

This study used data from the single-blind CO-MED trial to examine the relative efficacy and tolerability of single agent or combined antidepressant treatment regimens in depressed outpatients with and without pre-treatment insomnia symptoms. Previous studies of single agent antidepressant therapies have painted a mixed picture regarding the impact of baseline insomnia on treatment outcomes. This study is the first to examine the impact of pre-treatment insomnia on outcomes for combined antidepressant treatment (either bupropion-sustained release + escitalopram or venlafaxine-extended release + mirtazapine) as compared to treatment with a single antidepressant agent (escitalopram + placebo). The rationale for enhanced efficacy of medication combinations as first-step treatment for subgroups of depressed individuals includes the potential for impacting a wider range of neurotransmitter and neuromodulator systems at the outset of treatment, a possible synergistic effect of two medications working together, and a more rapid treatment response²⁶.

Our results indicated no significant differences with respect to treatment duration, dosage, side effects, or treatment outcomes based on pre-treatment insomnia. We did not find significant evidence for differential efficacy of the three treatment regimens, despite suggestions that the addition of sedating agents such as mirtazapine may be useful for improving outcomes for patients experiencing insomnia within MDD²⁵. In fact, a larger proportion of insomnia patients reached remission when treated with escitalopram alone, suggesting that a single antidepressant agent may still be the most appropriate first line treatment for chronically/recurrently depressed individuals with pre-treatment insomnia.

The impact of pre-treatment insomnia on treatment outcomes deserves attention from psychiatrists and primary care physicians, since the vast majority of depressed individuals will suffer from some form of sleep disturbance^{1, 7, 19, 51}. In our sample of treatment-seeking patients with chronic and/or recurrent MDD, nearly 90% reported at least one symptom of insomnia at baseline and roughly two-thirds of participants with pre-treatment insomnia reported sleep disturbances in either two or three of the areas assessed (i.e., sleep onset insomnia, mid-nocturnal insomnia, and early morning insomnia). This finding is strikingly similar to the rates reported in other treatment studies that used clinician ratings to evaluate insomnia symptoms⁷ and to those using objective sleep measures¹⁷.

Also in line with previous research, we found significant differences in the baseline socio-demographic and clinical characteristics of patients with and without pre-treatment insomnia^{2, 7, 52}. Participants with pre-treatment insomnia were more likely to be female and African-American. They reported higher rates of comorbid anxiety disorders and greater functional impairment relative to participants without pre-treatment insomnia symptoms. In contrast to some previous research⁷, we did not find higher rates of comorbid medical conditions in participants with pre-treatment insomnia.

Strengths of this study include large sample size, comprehensive assessments, and the use of measurement-based care. However, this was a secondary analysis of data from the CO-MED trial and some limitations must be considered. Because the CO-MED trial was not designed as a sleep study, we used clinician-rated insomnia symptoms to define the presence or absence of pre-treatment insomnia, rather than employing objective sleep measures such as polysomnography. While laboratory based sleep studies are preferred by those working in sleep medicine, clinician interviews remain the standard practice for assessing insomnia in the majority of outpatient psychiatric clinics. For this reason, our methods may actually increase the generalizability of results to those patients with chronic/recurrent MDD seen in outpatient psychiatry settings. As evidence for the validity of our insomnia classification, patients in the pre-treatment insomnia group reported significantly greater levels of sleep disturbance on the CAST-SR scale.

The CO-MED trial enrolled adult outpatients with moderate-to-severe chronic and/or recurrent MDD, which may limit generalizability to the larger population of depressed individuals. Our results may not be applicable to children or adolescents, psychiatric inpatients, outpatients with minor depression, or those with less persistent depressive episodes. We also excluded patients who had MDD with psychotic features and those with comorbid eating disorders, obsessive compulsive disorder, substance dependence, and serious medical or psychiatric problems that required hospitalization.

An additional limitation of secondary analysis is that we did not power the study specifically for subgroup analyses. Since there were a relatively small number of participants without pre-treatment insomnia, it is likely that there was insufficient statistical power to detect meaningful differences between the two groups. For example, overall rates of response and remission were lower in the pre-treatment insomnia group, but these differences were not statistically significant, suggesting that we had limited power to detect small effect size differences.

While the CO-MED trial provides significant new information regarding the efficacy of combined antidepressant treatment for depressed patients with insomnia, the antidepressant combinations we studied were not chosen specifically for their presumed impact on sleep difficulties. Of the treatment regimens studied here, the combination of venlafaxine (an activating SNRI which may increase sleep problems) and mirtazapine (a tetracyclic antidepressant with sleep promoting properties) is the most similar to the type of combination antidepressant treatment strategy used by clinicians seeking to address insomnia that occurs within a major depressive episode. We did not find a benefit of this combination relative to escitalopram monotherapy and it is possible that the activating

effects of venlafaxine worked to counteract the sedating properties of mirtazapine. It is also possible that the mirtazapine dosing was too low to realize any sleep-promoting effects when combined with venlafaxine.

Also off note is the fact that CO-MED did not include a combination strategy consisting of an antidepressant agent and a hypnotic agent. This may be a more common strategy in routine clinical practice and it may prove to be more effective combined strategy for treating insomnia within MDD⁵³. Future studies comparing these two types of combination strategies would be helpful to assist clinicians deciding between single agent and combined antidepressant treatments for patients who present with pre-treatment insomnia.

These limitations notwithstanding, this study provides additional information regarding the usefulness of combination antidepressant treatment regimens for depressed patients with insomnia. Despite some previous work indicating worse treatment outcomes for this subset of depressed individuals, our results indicate that outpatients with chronic or recurrent depression and insomnia respond as well as those without insomnia when treated with either single agent or combination antidepressant strategies. Although not statistically significant, response and remission rates were slightly higher for insomnia patients when treated with escitalopram alone. Given the added complexity inherent in using a combined medication strategy, first line treatment with a single SSRI may be the most appropriate choice for patients presenting with insomnia at baseline. These findings deserve clinical attention since insomnia is a highly prevalent complaint among patients with chronic and/or recurrent MDD.

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Highlights

- We examine the impact of pre-treatment insomnia on response to single and combination anti-depressant treatment in a sample of patients with chronic/recurrent MDD
- We explore demographic and illness related correlates of pre-treatment insomnia status in a sample of patients with chronic/recurrent MDD
- Results indicate no significant differences in treatment response for those with and without pre-treatment insomnia symptoms
- Patients with pre-treatment insomnia were more likely to be female and African American. They had higher rates of concurrent anxiety disorders, lower rates of alcohol abuse and substance abuse, and greater impairment in psychosocial functioning.

Figure 1.
CO-MED enrollment flow chart

Table 1

Baseline socio-demographic, clinical, and comorbidity measures by pre-treatment insomnia.

Measure	Pre-treatment Insomnia				Analysis	
	Yes (N=587)		No (N=78)		Test statistic	p
	n	%	n	%		
Gender					$\chi^2(1)=4.2873$	0.04
Male	180	30.7	33	42.3		
Female	407	69.3	45	57.7		
Racial background					$\chi^2(2)=10.674$	<0.01
Caucasian	368	64.9	63	82.9		
African American	165	29.1	9	11.8		
Other	34	6.0	4	5.3		
Hispanic ethnicity	87	14.8	14	17.9	$\chi^2(1)=0.5228$	0.47
Employed	284	48.4	47	60.3	$\chi^2(1)=3.8836$	0.05
Clinical setting					$\chi^2(1)=1.2225$	0.27
Primary	310	52.8	36	46.2		
Specialty	277	47.2	42	53.8		
Current episode duration 2+ years	319	54.5	49	62.8	$\chi^2(1)=1.9154$	0.17
Chronic/recurrent depression					$\chi^2(2)=1.9497$	0.38
Chronic only	126	21.5	20	25.6		
Recurrent only	266	45.5	29	37.2		
Both	193	33.0	29	37.2		
QIDS-SR (insomnia items omitted)					$\chi^2(3)=5.03$	0.17
0-10 None/Mild	138	24.3	24	31.2		
11-15 Moderate	247	43.4	26	33.8		
16-20 Severe	160	28.1	26	33.8		
21-27 Very severe	24	4.2	1	1.3		
Anxious features	440	75.0	57	73.1	$\chi^2(1)=0.129$	0.72
Atypical features	85	14.5	18	23.1	$\chi^2(1)=3.8871$	0.04
Melancholic features	116	21.7	8	11.3	$\chi^2(1)=4.2039$	0.05
Lifetime severity of suicidality					(P)<0.0001	0.66
None	177	31.1	21	28.4		
Thoughts of dying	157	27.6	20	27.0		
Suicidal thoughts	88	15.5	10	13.5		
Specific method	50	8.8	9	12.2		
Plan/gesture	32	5.6	6	8.1		
Preparation	11	1.9	3	4.1		
Attempt	54	9.5	5	6.8		
PDSQ psychiatric comorbidity						
Agoraphobia	67	11.4	2	2.6	$\chi^2(1)=5.7987$	0.02
Alcohol abuse	52	8.9	15	19.5	$\chi^2(1)=8.4655$	<0.01

Measure	Pre-treatment Insomnia				Analysis	
	Yes (N=587)		No (N=78)		Test statistic	p
	n	%	n	%		
Bulimia	71	12.1	7	9.0	$\chi^2(1)=0.6478$	0.42
Drug abuse	28	4.8	7	9.0	(P)=0.0612	0.17
Generalized anxiety disorder	124	21.1	7	9.0	$\chi^2(1)=6.4253$	0.01
Hypochondriasis	27	4.6	2	2.6	(P)=0.1922	0.56
Obsessive-compulsive disorder	73	12.4	6	7.7	$\chi^2(1)=1.4801$	0.22
Panic disorder	63	10.7	2	2.6	$\chi^2(1)=5.2092$	0.02
Post-traumatic stress disorder	75	12.8	6	7.7	$\chi^2(1)=1.664$	0.20
Social anxiety disorder	160	27.3	18	23.1	$\chi^2(1)=0.6138$	0.43
Somatoform disorder	21	3.6			(P)=0.0697	0.16
Substance abuse	70	11.9	17	22.1	$\chi^2(1)=6.1628$	0.01
SCQ medical comorbidity					$\chi^2(3)=4.2419$	0.24
Back pain	99	16.9	13	16.7	$\chi^2(1)=0.0025$	0.96
Diabetes	68	11.6	6	7.7	$\chi^2(1)=1.0546$	0.30
Heart disease	32	5.5	8	10.3	(P)=0.0491	0.12
Neuropsychological disease	17	2.9	1	1.3	(P)=0.2527	0.71
	M	SD	M	SD		
Age (years)	42.7	13.0	42.5	12.7	$t(663)= 0.18 $	0.86
Education (years)	13.8	3.0	13.8	2.4	$t(105.0)= 0.18 $	0.86
Monthly household income (\$)	2617	5237	3157	6208	$\chi^2(1)=1.7053$	0.19
Age at first episode	24.3	14.2	22.0	12.9	$\chi^2(1)=1.4706$	0.23
Years since first episode	18.5	13.5	20.4	14.4	$\chi^2(1)=1.1591$	0.28
N prior episodes	8.7	19.6	11.2	22.0	$\chi^2(1)=1.3397$	0.24
N prior antidepressants	1.5	1.7	1.5	1.7	$\chi^2(1)=0.0002$	0.99
N concomitant medications	3.1	2.9	2.5	2.3	$\chi^2(1)=4.4232$	0.04
Current episode duration (months)	62.7	106	54.3	91.6	$\chi^2(1)=0.1376$	0.71
QIDS-SR (insomnia items omitted)	13.4	4.27	12.9	4.54	$t(644)=0.94$	0.35
QIDS-SR Insomnia items	5.90	2.27	2.23	2.03	$U(1)=119$	<0.01
ASRMS (insomnia item omitted)	1.03	1.79	1.28	1.70	$U(1)=2.54$	0.12
CAST-SR Irritability	12.4	3.8	12.2	3.9	$t(662)=0.39$	0.70
CAST-SR Anxiety	6.3	2.9	5.8	3.2	$t(662)=1.39$	0.17
CAST-SR Mania	3.5	2.8	4.1	3.0	$U(1)=2.26$	0.14
CAST-SR Insomnia	5.4	2.1	2.4	1.9	$U(1)=98.4$	<0.01
CAST-SR Panic	2.7	2.2	2.2	2.0	$U(1)=3.20$	0.08
CHRT-SR Total	9.9	5.4	9.7	4.6	$t(662)= 0.31 $	0.76
QOLI	-1.2	1.9	-1.1	1.7	$t(659)=0.68$	0.50
WSAS	27.2	8.8	24.8	8.7	$t(662)=2.30$	0.02

ABBREVIATIONS: ASRMS Altman Self-Rated Mania Scale; CAST-SR Concise Associated Symptoms Tracking – Self-Rated; CHRT-SR Concise Health Risk Tracking – Self-Rated; PDSQ Psychiatric Diagnostic Screening Questionnaire; QIDS-SR Quick Inventory of Depressive

Symptomatology – Self-Rated; QOLI Quality of Life Inventory; SCQ Self-administered Comorbidity Questionnaire; WSAS Work and Social Adjustment Scale.

NOTE: Chi-square for continuous measures indicates Kruskal-Wallis test

NOTE: A bold p-value indicates statistical significance.

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