Insomnia in Patients With Depression: *A STAR*D Report*

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ABSTRACT

Introduction: Insomnia symptoms, which are common in depression, have a significant impact on function and quality of life. However, little is known about the prevalence and associated features of insomnia symptoms in representative treatment-seeking patients with depression.

Methods: Data from the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial were analyzed. STAR*D recruited 3,743 adult outpatients diagnosed with nonpsychotic major depressive disorder (MDD) from primary (n=18) and psychiatric care (n=23) clinics across the United States. Baseline sociodemographic and clinical features were compared between those with insomnia symptoms (84.7%) and those without (15.3%).

Results: The most common presentation was the simultaneous presence of sleep onset, mid-nocturnal, and early morning insomnia symptoms (27.1%). Of these three types of insomnia symptoms, mid-nocturnal insomnia symptoms were the most commonly found alone (13.5%) and in combination with one or more other types (82.3%). Insomnia symptoms were associated with several indicators of a more severe depressive illness. Only a small proportion of participants with insomnia symptoms were receiving treatment for sleep disturbances at study initiation, and the vast majority of those receiving treatment still reported having insomnia symptoms.

Conclusion: In outpatients who seek treatment for nonpsychotic MDD in typical clinical settings, insomnia symptoms are very common, undertreated, and indicative of a more severe depression.

CNS Spectr. 2010;15(6):394-404.

FOCUS POINTS

- In patients with depression, insomnia is underrecognized and undertreated.
- Insomnia was more commonly reported in depressed patients who were older, African-American, unemployed, single or divorced.
- Insomnia symptoms were associated with an increased burden of depressive illness, including greater depressive symptom severity, anxious features, more concurrent medical comorbidities and psychiatric diagnoses, a reduced quality of life, and worse physical functioning.

INTRODUCTION

Major depressive disorder (MDD), an often chronic or recurrent illness, is associated with significant mortality and morbidity.[1-2] A leading cause of psychosocial dysfunction,[3] MDD results in increased health service utilization and cost, and contributes to the development of several chronic medical illnesses such as heart disease[4] and diabetes.[5]

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Symptoms of insomnia occur in approximately one third of individuals with mental illness[6] and may be a major contributor to the disability associated with depression.[7] Insomnia is one of the most prevalent symptoms of depression,[8] and it is a diagnostically important symptom of depression.[9] Approximately 80% of psychiatric inpatients and 70% of psychiatric outpatients with MDD report problems initiating or maintaining sleep.[10] Further, the clinical impact of insomnia is substantial since insomnia symptoms are associated with an increased risk for depression recurrence,[11] failure to respond to antidepressant medication,[12] poor quality of life in depressed patients,[13] increased risk of suicidality,[14] active suicidal ideation, specific plans for suicide, and previous suicide attempts.[15] In addition, symptoms of chronic insomnia are a forerunner of MDD in many individuals.[6] Having insomnia symptoms as a young adult has been found to be associated with having depression through midlife.[16]

Prior studies on the sociodemographic determinants of insomnia symptoms have consistently reported an increased prevalence of insomnia symptoms in women,[6,17-19] the elderly,[18,19] and individuals who are separated, divorced, widows/widowers,[6,19] or are unemployed.[17,20] A higher prevalence has been found in individuals with lower income[19] or lower education,[18] but a multivariate analysis failed to identify these as individual risk factors for insomnia symptoms.[6] The risk of insomnia symptoms has been found to be highest in retirees, followed by homemakers, a finding that is not generalizable to all employment or unemployment relationships of insomnia symptoms. Other factors associated with insomnia symptoms include lifestyle, psychoactive substance abuse or withdrawal, mental disorders, medical disorders, breathing disorders during sleep, restless legs syndrome, and other related conditions. However, it is difficult to compare studies and study results as there is no uniform classification or definition for insomnia symptoms in current use.[6]

Despite the clinical importance of insomnia symptoms, little is known about the prevalence and features associated with insomnia symptoms in patients with MDD who are seeking treatment in representative clinic settings (eg, primary or psychiatric clinics in the private or public sector). This hypothesis-generating study was conducted to define the prevalence and types of insomnia symptoms found in a large sample of self-referred representative outpatients who have nonpsychotic MDD; in addition, it sought to determine whether any sociodemographic or clinical characteristics are associated with the presence of insomnia symptoms. The analyzed study sample consisted of clinic-referred patients enrolled into the Sequenced Treatment Alternatives to Relieve Depression (STAR*D)[21] study, which used broadly inclusive eligibility criteria in recruiting outpatients who were seeking treatment in primary or psychiatric care. Thus, the study results are generalizable to most depressed outpatients being treated for MDD in the United States.

METHODS

Study Description

The rationale and design of the STAR*D study are described elsewhere.[21,22] STAR*D was designed to prospectively define which treatments are most effective for outpatients with nonpsychotic MDD who have an unsatisfactory clinical outcome to an initial treatment and, if necessary, to identify subsequent treatment(s). The study was conducted at 18 primary care settings and 23 psychiatric care settings across the US that provided care in either the public or private sector.

The STAR*D protocol was developed in accordance with the principles of the Declaration of Helsinki, and it was approved and monitored by the National Coordinating Center (University Of Texas Southwestern Medical Center, Dallas, TX), the Data Coordinating Center (University of Pittsburgh Epidemiology Data Center, Pittsburgh, PA), the institutional review boards at the 14 regional centers and at each clinical site, and the Data Safety and Monitoring Board of the National Institute of Mental Health. All risks, benefits, and adverse events associated with STAR*D participation were explained to participants, who provided written informed consent prior to study entry. Eligible and consenting participants were enrolled into the first level of the STAR*D study and began treatment with the selective serotonin reuptake inhibitor (SSRI) citalopram.

Study Participants

From July 2001 through April 2004, STAR*D enrolled 4,041 treatment-seeking outpatients

18–75 years of age who had a diagnosis of nonpsychotic MDD established by the participants' treating clinicians and confirmed by a checklist using *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition[23] criteria. Recruitment via advertisement was proscribed. Minimal exclusion criteria and broad inclusion criteria that allowed a majority of axis I and axis III disorders were used to enroll a sample representative of patients seeking treatment in typical clinic settings. Outpatients with a baseline 17-item Hamilton Rating Scale for Depression ($HRSD_{17}$)[24] score ≥14 (gathered by trained and certified clinical research coordinators [CRCs] at the clinical sites) were eligible if their clinicians determined that outpatient treatment with an antidepressant was both safe and indicated. Concomitant medications for current general medical conditions (GMCs) or associated symptoms of depression were allowed for anxiety (eg, lorazepam) and sleep (any sedative-hypnotics as well as trazodone ≤200 mg), as were medications for sexual side effects. Patients were excluded if they had bipolar or psychotic disorders, obsessive-compulsive or eating disorders (only if it was the primary diagnosis), GMCs contraindicating the use of protocol medications in the first two treatment steps, substance dependence (only if it required inpatient detoxification), or a clear history of non-response or intolerance (in the current major depressive episode) to any protocol antidepressant in the first two treatment steps. Patients were also excluded if they were breastfeeding, pregnant, or intending to become pregnant in the nine months subsequent to study entry.

Assessments

At the baseline clinic visit, CRCs gathered participants' self-reported prior personal and family histories, as well as sociodemographic and clinical information. At this visit, CRCs also gathered information regarding any non-study medications (including hypnotics) being taken by the participant, including dose and reason for taking the medication. Participants completed the self-report Psychiatric Diagnostic Screening Questionnaire[25,26] to estimate the presence of 11 potential concurrent axis I (psychiatric) disorders. CRCs obtained an initial $HRSD_{17}$, 16-item Quick Inventory of Depressive Symptomatology–clinician-rated, and the Quick Inventory of Depressive Symptomatology self-report ($QIDS\text{-}SR_{16}$)[27,28] to assess depressive symptom severity, as well as the clinician assessment of whether the participant was currently at risk of suicide. The CRCs also completed the 14-item Cumulative Illness Rating Scale (CIRS)[29] to gauge the severity/morbidity of GMCs relevant to different organ systems. Each of the 14 CIRS illness categories was scored 0 (no problem) to 4 (extremely severe, immediate treatment required, end organ failure, or severe impairment in function). The CIRS was scored as total score, which is the number of GMC categories endorsed (0–13 excluding the psychiatric illness category) multiplied by the severity index (the average severity of the categories endorsed).

Within 72 hours of the baseline visit, research outcomes assessors (not located at any clinical site and masked to treatment) conducted a telephone interview with the participant to gather the 30-item Inventory of Depressive Symptomatology–Clinician-rated ($IDS\text{-}C_{30}$)[28] and the $HRSD_{17}$ to assess depressive symptom severity. Responses to the $IDS\text{-}C_{30}$ and the $HRSD_{17}$ were used to estimate the presence of atypical and anxious features. Also within 72 hours of the baseline visit, an interactive voice response system[30,31] collected the 12-item Short Form Health Survey (SF-12)[32] (perceived physical functioning or SF-Physical, and mental health functioning or SF-Mental), the 16-item Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q),[33] and the Work and Social Adjustment Scale (WSAS).[34]

Definition of Insomnia Symptoms

Since STAR*D was a depression study rather than a sleep study, participants did not undergo polysomnography. Insomnia symptoms were defined using the three insomnia items on the $IDS\text{-}C_{30}$, which describe the participant's condition over the prior 7 days. One item each addresses symptoms of sleep onset insomnia (trouble falling asleep), mid-nocturnal insomnia (waking during the night), and early morning insomnia (waking before necessary). Each item is scored on a scale of 0–3, (higher scores indicate greater symptom severity) (Table 1). A score ≥2 on an item indicated the presence of that specific type of insomnia symptoms. A score ≥2 on any of these three items indicated the presence of "any insomnia symptoms." A combination of any (or none) of the three types of insomnia symptoms was possible. The cutoff point of 2 or above was chosen. This score is commonly used in studies as the cutoff point to indicate the presence of an insomnia

symptom type,[35] although the mid-nocturnal item may lack specificity as there is a potential overlap between the determinants of the score.

Data Analysis

These analyses aimed to identify differences in baseline sociodemographic and clinical characteristics between the "any insomnia symptoms" and "no insomnia symptoms" groups. Summary statistics of the sociodemographic and clinical characteristics are presented for the analyzable sample. Data are presented as means (standard deviation [SD]), median (range), or percentages. Group comparisons were made between those with and without co-occurring insomnia symptoms. For categorical variables, group percentages were calculated and chi-square tests performed. For continuous variables, means and standard deviations were calculated. T-tests were performed to statistically compare the two groups. To clarify the association between insomnia symptoms and increased depression symptom severity, the authors ran a Spearman Correlation between the sum of the three insomnia IDS-C_{30} items and the sum of the 27 non-insomnia-related IDS-C_{30} items. Since this study is an exploratory analysis, a strict threshold for statistical significance of $P<.05$ is not as important as when testing a specific hypothesis. Given the number of comparisons, there is a chance of identifying a large number of statistically significant findings. Therefore, to reduce the chance of this, a more conservative threshold of $P<.01$ to identify significant findings was used.

TABLE 1.
Definition of Insomnia Symptoms

Any Insomnia Symptoms is defined as "Yes" if any of the following IDS-C_{30} items is ≥2:

1. Sleep Onset Insomnia Symptoms
   - 0=Never takes >30 minutes to fall asleep
   - 1=Takes ≤30 minutes to fall asleep
   - 2=Takes ≤30 minutes to fall asleep, more than half the time
   - 3=Takes >60 minutes to fall asleep, more than half the time
2. Mid-Nocturnal Insomnia Symptoms
   - 0=Does not wake up at night
   - 1=Restless, light sleep with few awakenings
   - 2=Wakes up at least once a night, but goes back to sleep easily
   - 3=Awakens more than once a night and stays awake for ≥20 minutes, more than half the time
3. Early Morning Insomnia Symptoms
   - 0=Less than half the time, awakens ≤30 minutes before necessary
   - 1=More than half the time, awakens ≥30 minutes before necessary
   - 2=Awakens ≥1 hour before necessary, more than half the time
   - 3=Awakens ≥2 hours before necessary, more than half the time

IDS-C_{30}=30-item Inventory of Depressive Symptomatology–clinician-rated.

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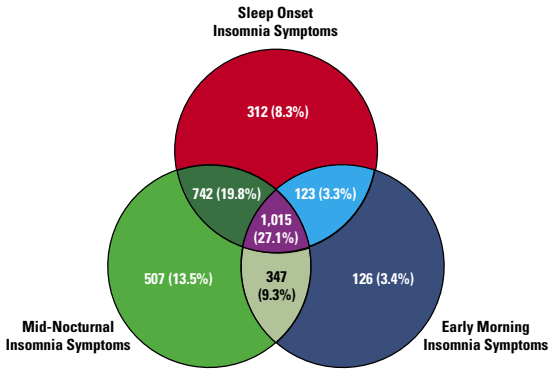
RESULTS

Of the 4,041 participants enrolled in STAR*D, 3,743 completed all sleep items on the IDS-C_{30} and were included in these analyses. Those not included did not significantly differ from those included by severity of baseline depression, number of GMCs, or most other parameters. The group with missing data did have a slightly lower median SF-12 physical score (49.3 versus 51.8, $P=.0200$), and they were less likely to be taking hypnotics at presentation (18.6% versus 24.9%, $P=.0154$).

Sociodemographic and Clinical Characteristics

Of the evaluable sample, 84.7% (3,172/3,743) presented with some type of insomnia symptoms. Mid-nocturnal insomnia symptoms were the most common of the three types (Figure). It

FIGURE.
Baseline insomnia symptoms diagram



Note: patients with no insomnia symptoms=571 (15.3%).

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was the most common to be reported alone (not in combination with another type) (13.5%) as well as the most common overall, being a part of 82.3% of the insomnia symptom presentations (including alone and in combination with one or both of the other types). The most common presentation by far, among all the possible combinations, was having all three types of insomnia symptoms (27.1%).

Those with any insomnia symptoms, as compared to those with no insomnia symptoms, were older, had slightly fewer years of schooling, and earned less monthly income (Table 2). Further, those with insomnia symptoms were significantly more likely to be seen in a primary care setting, and more likely to be African American, divorced, unemployed, or receiving public insurance. Participants with insomnia symptoms were substantially more likely than those without such symptoms to be on a hypnotic at the time of enrollment (27.1% versus 12.5%), yet in a very high percentage of cases the treatment was not effective. In fact, of the 931 participants with depression who were receiving hypnotics at enrollment, 860 (92.3%) still reported symptoms of insomnia.

Clinically, participants with insomnia symptoms presented with greater depressive symptom severity, whether measured by the interviewer-administered $HRSD_{17}$ or IDS-C_{30} scales, or by the self-report QIDS-SR_{16}. This difference remained even when the insomnia items were not included in the total score (Table 3). The Spearman Correlation between the sum of the three insomnia IDS-C_{30} items and the sum of the 27 non-insomnia IDS-C_{30} items found that greater levels of insomnia symptoms do indeed correlate with greater depression severity ($P<.0001$). Other clinically meaningful differences were also apparent. Participants with insomnia symptoms were significantly more likely to have anxious features or have a family history of alcohol abuse. Of note, participants with insomnia symptoms were no more likely to have current suicide risk.

Baseline Depressive Symptoms

To determine whether any specific baseline depressive symptoms were associated with the presence of insomnia symptoms, the authors examined the individual IDS-C_{30} items (minus the insomnia items) and adjusted the analysis for the effect of baseline characteristics that

TABLE 2.
Definition of Insomnia Symptoms

	Any Insomnia Symptoms		
Demographic	***No (%) N=571***	***Yes (%) N=3,172***	***P Value***
Setting			.0074
Primary care	33.4	39.4	
Specialty care	66.6	60.6	
Race*			<.0001
White	82.3	74.7	
African American	10.3	18.6	
Other	7.4	6.7	
Ethnicity: Hispanic			.4118
No	88.6	87.4	
Yes	11.4	12.6	
Sex			.2763
Male	39.1	36.7	
Female	60.9	63.3	
Marital status†			<.0001
Never married	38.5	28.4	
Married	43.1	41.5	
Divorced	16.1	27.1	
Widowed	2.3	3.1	
Employment status‡			<.0001
Employed	67.3	55.3	
Unemployed	28.2	38.6	
Retired	4.6	6.1	
Insurance status§			.0080
Private insurance	57.7	51.2	
Public insurance	10.8	14.7	
No insurance	31.5	34.1	
On hypnotic	12.5	27.1	<.0001
	Mean (SD)	Mean (SD)	
Age (years)	37.3 (13.6)	41.1 (13.1)	<.0001
Years of schooling	14.2 (3.4)	13.3 (3.2)	<.0001
Income ($/month)	2,691 (3,104)	2,371 (3,149)	.0002

Note: All pairwise comparisons below use the Bonferroni multiple comparison adjustment.

* *White* is significantly different from *African American* ($P<.0001$); *White* is not significantly different from *Other* ($P=.9281$); and *African American* is significantly different from *Other* ($P=.0018$). Significance was indicated by Bonferroni corrected α value=.0167.

† *Never married* is significantly different from *Married* ($P=.0088$); *Never married* is significantly different from *Divorced* ($P<.0001$); *Never married* is not significantly different from *Widowed* ($P=.0453$); *Married* is significantly different from *Divorced* ($P<.0001$); *Married* is not significantly different from *Widowed* ($P=.2685$); and *Divorced* is not significantly different from *Widowed* ($P=.4782$). Significance was indicated by a Bonferroni corrected α value=.0125.

‡ *Employed* is significantly different from *Unemployed* ($P<.0001$); *Employed* is not significantly different from *Retired* ($P=.0250$); and *Unemployed* is not significantly different from *Retired* ($P=.0930$). Significance was indicated by a Bonferroni corrected α value =.0167.

§ *Private insurance* is significantly different from *Public insurance* ($P=.0044$); *Private insurance* is not significantly different from *No insurance* ($P=.0557$); and *Public insurance* is not significantly different from *No insurance* ($P=.1481$).

SD=standard deviation.

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were not equally distributed across the insomnia symptom/no insomnia symptom groups. At baseline, participants with insomnia symptoms were significantly more likely to report hypersomnia, decreased appetite, a negative future outlook, and sympathetic arousal (the latter defined by the IDS-C_{30} as the presence of palpitations, tremors, blurred vision, tinnitus or increased sweating, dyspnea, hot and cold flashes, and/or chest pain) (Table 4).

Concurrent Psychiatric Diagnoses

Participants with insomnia symptoms were significantly more likely to have at least one comorbid psychiatric diagnosis (Table 5). Most anxiety disorders were significantly more likely to be present in participants with insomnia symptoms. Those with insomnia symptoms were more than twice as likely to have generalized anxiety disorder, panic disorder, posttraumatic stress disorder, agoraphobia, somatoform disorder, or hypochondriasis. They were also more likely to have a greater number of psychiatric comorbidities.

TABLE 3.
Baseline Clinical Characteristics Associated With Any Insomnia Symptoms

	Any Insomnia Symptoms		
Demographic	*No N=571 Mean (SD)*	*Yes N=3,172 Mean (SD)*	*P Value*
$HRSD_{17}$ (without insomnia items)	13.5 (5.0)	17.1 (5.4)	<.0001
IDS-C_{30} (without insomnia items)	26.1 (10.1)	31.6 (10.1)	<.0001
QIDS-SR_{16} (without insomnia items)	12.4 (4.2)	13.6 (4.2)	<.0001
	%	%	
Family history of depression	56.0	55.0	.6544
Family history of alcohol abuse	34.9	41.6	.0028
Family history of drug abuse	19.9	24.1	.0309
Family history of suicide	3.3	3.6	.7957
Attempted suicide	13.3	17.2	.0214
Present suicide risk	3.1	2.6	.4989
Age at onset			
≤18 years	45.8	40.8	
>18 years	54.2	59.3	
Atypical features	17.9	16.8	.5386
Anxious features	23.0	49.8	<.0001
Chronic depression	24.0	25.5	.4346
Recurrent depression	71.8	74.3	.2227

SD=standard deviation; $HRSD_{17}$=17-item Hamilton Rating Scale for Depression; IDS-C_{30}=30-item Inventory of Depressive Symptomatology–clinician-rated; QIDS-SR_{16}=16-item Quick Inventory of Depressive Symptomatology–self-Rated.

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Concurrent General Medical Conditions and Quality of Life

Participants with insomnia symptoms tended to have more general medical comorbidity (Table 6), with a greater CIRS total score. They also had significantly worse physical functioning as measured by the SF-12, and poorer quality of life as measured by the Q-LES-Q and WSAS.

DISCUSSION

In this broadly representative sample of clinic-referred outpatients with nonpsychotic MDD, insomnia symptoms were extremely common. Mid-nocturnal insomnia symptoms were the most prevalent type of insomnia symptoms, whether found alone or in combination with sleep onset and/or early morning insomnia symptoms. This result is consistent with findings from selective clinical trials of MDD.[36,37] Mid-nocturnal insomnia symptoms have also been found to be the most common residual type of insomnia symptoms following treatment for MDD.[37] Mid-nocturnal insomnia symptoms, in particular, may carry special clinical importance, as a lower severity of mid-nocturnal insomnia symptoms at baseline has been associated with a greater likelihood of improved mood after treatment.[38]

Certain sociodemographic characteristics helped distinguish participants with depression who have insomnia symptoms from those who do not. Participants with symptoms of insomnia were significantly more likely to be African American, which is consistent with the limited data on racial differences in insomnia symptoms in MDD and suggests a distinct sleep profile with greater chronic sleep arousal for African Americans.[39] Insomnia symptoms were also associated with greater age and substantial acute stressors, including divorce and unemployment, which is consistent with findings from epidemiologic studies.[40]

The presence of insomnia symptoms was associated with a greater illness burden, including greater depressive severity and likelihood of anxious features, more concurrent psychiatric or general medical illness, and poorer quality of life. These associations remained even after the sleep disturbance items were controlled for. These findings are consistent with those of prior studies in more selected clinical populations.[14,41,42] Previous studies have also found that greater degree of concurrent psychiatric and medical illness and a reduced quality of life were associated with treatment-resistant depression.[43,44] This further emphasizes the key role of insomnia symptoms as a predictor of a harder-to-treat depressive illness.

No significant association was found between insomnia and the presence of atypical symptoms (which may or may not include hypersomnia as a symptom). Approximately 17% of participants with insomnia had atypical symptoms, while ~18% of those without insomnia had atypical symptoms. These findings are consistent with the notion that the presence of insomnia

TABLE 4.
Baseline Depressive Symptoms Associated With Any Insomnia Symptoms

	Any Insomnia Symptoms				
IDS-C_{30} items	*No N=571 (Mean)*	*Yes N=3,172 (Mean)*	*Unadjusted P Value*	*Odds Ratio**	*Adjusted P Value**
Hypersomnia	43.6	21.3	<.0001	.35	<.0001
Mood (sad)	94.6	97.8	<.0001	1.13	.6360
Mood (irritable)	73.9	82.8	<.0001	1.23	.0745
Mood (anxious)	71.1	83.7	<.0001	1.29	.0233
Mood reactivity	63.2	75.1	<.0001	1.16	.1714
Quality of mood	72.7	75.2	.1991	.91	.3627
Appetite decreased	30.2	47.6	<.0001	1.53	<.0001
Appetite increased	22.7	21.7	.6069	.90	.3541
Weight decrease	20.7	32.5	<.0001	1.35	.0102
Weight increase	23.1	23.0	.9660	.89	.3029
Concentration	84.6	91.2	<.0001	1.08	.5884
Outlook (self)	79.5	81.2	.3327	.73	.0140
Outlook (future)	76.1	77.1	.5962	.64	.0003
Suicidal ideation	39.9	49.6	<.0001	.99	.9136
Involvement	78.6	86.5	<.0001	.92	.5132
Energy	82.8	91.1	<.0001	1.15	.3223
Pleasure	61.0	73.2	<.0001	1.06	.6141
Sexual interest	58.7	64.9	.0043	.80	.0305
Psychomotor slowing	54.6	64.3	<.0001	.90	.2858
Psychomotor agitation	51.4	64.3	<.0001	1.24	.0277
Somatic complaints	67.4	78.4	<.0001	1.17	.1366
Sympathetic arousal	51.5	71.2	<.0001	1.38	.0015
Panic	23.8	40.9	<.0001	1.29	.0305
Gastrointestinal	30.9	44.4	<.0001	1.23	.0424
Interpersonal sensitivity	56.9	61.6	.0340	.85	.1320
Leaden paralysis	36.8	45.9	<.0001	.85	.1258

* Adjusted for age, anxious depression, baseline severity of depression (IDS-C_{30} without insomnia items).
IDS-C_{30}=30-item Inventory of Depressive Symptomatology–clinician-rated.

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is not related to the likelihood of having atypical depression, which does not conflict with the findings of other studies.

No significant association was found between past suicide attempts and the presence of insomnia symptoms, a finding that contrasts with those of several earlier studies.[15,45] This difference may be due to use of the suicide questions of the IDS-C_{30} to determine the presence/absence of insomnia symptoms rather than a specific suicide scale or sleep habit questionnaire as that utilized by Chellappa and colleagues.[15] Further, the current study excluded patients at high risk of suicide. Thus, the sample had a lower risk of suicide compared to the study by Agargun and colleagues,[45] which enrolled only patients with a suicide attempt during their current major depressive episode.

Interestingly, of the STAR*D participants who had insomnia symptoms at study initiation, only a low proportion were receiving a hypnotic (27%). This low percentage is consistent with literature reports on the under-recognition and under-treatment of insomnia symptoms, whether the sample is an epidemiologic sample,[46,47] is from a primary care setting,[48] or is from a psychiatric care setting.[49] This finding is also consistent with the view that standard clinical assessments of insomnia symptoms in real practice are rather inadequate,[50] which may result in lesser attention being paid to insomnia symptoms. Certainly, insomnia symptoms had been under-recognized in patients enrolled into STAR*D. Unfortunately, whether those treated were under-treated could not be determined, as the current study did not uniformly gather information regarding the specific hypnotic medication prescribed for sleep or its dosage.

Insomnia symptoms are persistent and difficult-to-treat, even following an adequate treatment of depression.[37,51-54] The persistence of insomnia symptoms and the difficulty in treating them was confirmed by the current finding that of STAR*D participants who were receiving hypnotics at study initiation, the majority (92%) still reported having insomnia symptoms in the prior week. This finding reinforces the view that insomnia symptoms should be aggressively treated in patients with MDD. It would also be

TABLE 5.
Association of Baseline Psychiatric Comorbidity With Any Insomnia Symptoms

	Any Insomnia Symptoms		
PDSQ item	*No (%) N=571*	*Yes (%) N=3,172*	*P Value*
Generalized anxiety disorder	10.8	22.9	<.0001
OCD	10.4	14.3	.0144
Panic	5.1	13.0	<.0001
Social phobia	29.0	28.9	.9403
PTSD	9.3	19.5	<.0001
Agoraphobia	5.3	11.8	<.0001
Alcohol abuse	9.9	11.9	.1679
Drug abuse	7.8	7.3	.7191
Somatoform	0.5	2.6	.0064
Hypochondriasis	1.9	4.6	.0049
Bulimia	10.4	12.7	.1292
PDSQ Count			<.0001
0	59.3	43.4	
1	20.8	26.5	
2	12.1	13.6	
3	5.1	7.1	
≥4	2.6	9.4	

PDSQ=Psychiatric Diagnostic Screening Questionnaire; OCD=obsessive-compulsive disorder; PTSD=posttraumatic stress disorder.

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TABLE 6.
Baseline Medical Comorbidity, Quality of Life, and Functioning Measures Associated With Any Insomnia Symptoms

	Any Insomnia Symptoms		
Clinical Feature	*No N=571 Mean (SD)*	*Yes N=3,172 Mean (SD)*	*P Value*
CIRS			
Total score	3.2 (3.4)	4.4 (3.7)	<.0001
Categories endorsed	2.3 (2.0)	3.1 (2.3)	<.0001
Severity index	1.1 (0.7)	1.2 (0.6)	<.0001
SF-12			
Physical	52.9 (10.9)	48.8 (12.0)	<.0001
Mental	27.2 (8.8)	26.5 (8.6)	.1126
Quality of Life			
Q-LES-Q	45.9 (14.9)	40.9 (15.1)	<.0001
WSAS	21.5 (9.1)	23.9 (9.2)	<.0001

SD=standard deviation; CIRS=Cumulative Illness Rating Scale; SF-12=12-item Short Form Health Survey; Q-LES-Q=Quality of Life Enjoyment and Satisfaction Questionnaire; WSAS=Work and Social Adjustment Scale.

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beneficial for studies to focus on finding more effective treatments for insomnia symptoms in patients with MDD. It should be noted that data were not gathered regarding how hypnotics were taken. It is likely that at least some participants were taking hypnotics as needed rather than on a regular basis. It is possible that the hypnotics would be less effective if taken as needed rather than on a regular basis. It is also possible that participants may report their sleep as poor even when the prescribed hypnotics are effective, due to comorbidities or medical reasons that could adversely affect sleep despite an effective hypnotic.

Two recent studies have shown that MDD patients who were receiving treatment with an SSRI received significantly greater improvement of insomnia symptoms with concomitant hypnotic treatment with either eszopiclone[55] or zolpidem extended-release[56] compared to concomitant placebo. Also, in a recent study of 30 individuals with comorbid MDD and insomnia (per *DSM-IV-TR* criteria), Manber and colleagues[58] found that patients randomized to escitalopram and seven individual therapy sessions of cognitive-behavioral therapy (CBT) for insomnia had a significantly greater rate of remission of depression than those randomized to the control treatment of escitalopram and seven individual therapy sessions of quasi-desensitization. Manber and colleagues[57] concluded that the augmentation of treatment with brief symptom-focused CBT for insomnia symptoms in individuals who have MDD and comorbid insomnia symptoms is promising for the alleviation of both depression and insomnia symptoms.

Since the current study used broadly inclusive criteria to recruit a very large sample from both primary care and psychiatric care settings, the findings are likely to be widely generalizable to typical treatment-seeking clinic outpatients. The prevalence rate of insomnia symptoms (>84%) was consistent with prior reports of insomnia symptoms being present in nearly all patients with depression in clinical[49] and epidemiologic populations.[10] Unfortunately, the findings may not be generalizable to research-respondent patients with insomnia symptoms, as differences have been found between such patients and those seeking treatment for insomnia symptoms in a clinic setting. Stepanski and colleagues[58] compared 50 individuals with insomnia symptoms who were recruited via newspaper advertisements for psychopharmacologic trials to 50 patients seeking treatment for insomnia symptoms at a sleep center. They reported no differences in sleep parameters, but found that physician-referred patients had significantly higher scores on psychometric measures (Minnesota Multiphasic Personality Inventory [MMPI]) and higher daytime alertness. Scores on the MMPI scales for hypochondriasis, depression, hysteria, and psychasthenia were significantly higher in the physician-referred group. It should be noted that the study by Stepanski and colleagues[58] did not consist of patients with depression, but focused solely on patients with insomnia. However, the comparison between treatment-seeking and research-respondent patients with insomnia remains relevant with regard to the generalizability of the current findings.

Limitations of the current study include the unavailability of the specific dosage of hypnotic medications prescribed for sleep. While dosage information was gathered, no information was available to confirm that the medication was, in fact, being taken as prescribed. Consequently, whether an adequate trial of the hypnotic was provided, was unable to be determined. However, the proportion of participants with insomnia symptoms who received any hypnotic was low; thus, these results likely under-estimate the problem of under-recognition and treatment. Second, three items from the IDS-C_{30} were used as a sleep measure rather than using a more extensive validated measure of insomnia symptoms (such as polysomnography), a brief sleep assessment questionnaire feasible for administration in an effectiveness study, or a sleep diary. The analysis of insomnia symptoms was not the original aim of the study and such methods are not cost-effective in an effectiveness study. Third, the IDS-C_{30} item used to identify mid-nocturnal insomnia symptoms has low specificity due to potential overlap between determinants of the score (Table 1). For example, a participant who is restless, has multiple awakenings, and has difficulty returning to sleep could possibly answer with response #1 or #3. This could be used as an indicator that the cutoff for identifying mid-nocturnal insomnia symptoms should be a score of 3 on this item. However, it seems unlikely that this low specificity would have affected the results. Only

20.4% of participants reported a score of 2 on this item and the majority of them likely also reported another type of insomnia symptom as well; this means these patients still would have been included in the "any insomnia symptoms" group; 80.6% (2,104/2,611) of participants subcategorized into the mid-nocturnal insomnia symptoms group also reported symptoms of either sleep onset or early morning insomnia, or both. If a score of 3 on this item had been used as a cutoff for determining the presence of mid-nocturnal insomnia symptoms, the prevalence of any insomnia symptoms in this sample would reduce from 84.7% (3,172/3,743) to 76.5% (2,865/3,743). Despite these limitations regarding the measurement of insomnia symptoms, the prevalence rates from correspond to rates reported in studies of clinical populations that used more extensive sleep diaries.[59] In addition, the IDS-C_{30} has been shown to be a valid measure of insomnia symptom severity that is in substantial agreement with more comprehensive sleep diary data.[35]

Finally, the study results showed a number of statistically significant, but clinically small differences between the insomnia symptoms/no insomnia symptoms groups. This was a function of the large sample size.

CONCLUSION

In this hypothesis-generating study, insomnia symptoms were found to be common, clinically-relevant, underrecognized and undertreated in patients with MDD. They were also persistent even when treated, which is important given that the persistence of insomnia symptoms has been associated with treatment-resistant depression. Mid-nocturnal insomnia symptoms were the most common of the three types, and the most common presentation was the presence of all three types. Sociodemographic characteristics associated with the presence of insomnia symptoms included being African American, being older, and the presence of several substantial acute stressors. Insomnia symptoms were associated with several indicators of a more severe depressive illness. Although few question the need to treat either primary insomnia symptoms or MDD, there is no consensus on whether and how to treat insomnia symptoms when they co-occur with MDD. Future research must focus on determining how to best identify insomnia symptoms and measure their responsiveness to an intervention in patients with MDD, and on how to select the most effective MDD intervention based on associated insomnia symptoms. ***CNS***

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Faculty Disclosures: Dr. Sunderajan has received grant/research support from Bristol-Myers Squibb, Eli Lilly, and Takeda. Dr. Gaynes has received grant/research support from the Agency for Healthcare Research and Quality, Bristol-Myers Squibb, the National Institute of Mental Health (NIMH), Novartis, and M-3 Corporation; and has performed as an advisor for Bristol-Myers Squibb. Dr. Wisniewski is consultant to Bristol-Myers Squibb, Case Western University, Cyberonics, and ImaRx Therapeutics. Ms. Miyahara reports no affiliation with or financial interest in any organization that may pose a conflict of interest. Dr. Fava is a consultant/advisor to Abbott, Amarin, Aspect Medical Systems, AstraZeneca, Auspex, Bayer AG, Best Practice Project Management, Biovail, BrainCells, Bristol-Myers Squibb, Cephalon, Clinical Trials Solutions, CNS Response, Compellis, Cypress, Dov, Eli Lilly, EPIX, Fabre-Kramer, Forest Pharmaceuticals, GlaxoSmithKline, Grunenthal GmBH, Janssen, Jazz, Johnson & Johnson, Knoll, Labopharm, Lore, Lundbeck, MedAvante, Merck, Methylation Sciences, Neuronetics, Novartis, Nutrition 21, Organon, Pamlab, Pfizer, PharmaStar, Pharmavite, Precision Human Biolaboratory, Roche, sanofi-aventis, Sepracor, Solvay, Somaxon, Somerset, Synthelabo, Takeda, Tetragenex, Transcept, Vanda, and Wyeth; is on the speaker's bureus of Advanced Meeting Partners, the American Psychiatric Association, AstraZeneca, Boehringer-Ingelheim, Bristol-Myers Squibb, Cephalon, Eli Lilly, Forest Pharmaceuticals, GlaxoSmithKline, Imedex, Novartis, Organon, Pfizer, PharmaStar, MGH Psychiatry Academy/ Primedia and Reed-Elsevier, UBC, and Wyeth; has received research support from Abbott, Alkermes, Aspect Medical Systems, AstraZeneca, Bristol-Myers Squibb, Cephalon, Eli Lilly, Forest Pharmaceuticals, Ganeden, GlaxoSmithKline, Johnson & Johnson, Lichtwer Pharma GmbH, Lorex, National Alliance for Research in Schizophrenia and Depression (NARSAD), National Center for Complementary and Alternative Medicine, National Institute on Drug Abuse (NIDA), the NIMH, Novartis, Organon, Pamlab, Pfizer, Pharmavite, Roche, sanofi-aventis, Shire, Solvay, Synthelabo, and Wyeth; owns equity in Compellis; receives copyright royalties for the MGH CPFQ, SFI, ATRQ, DESS, and SAFER instruments; and has submitted patent applications for SPCD and for a combination of azapirone and bupropion in major depressive disorder. Dr. Akingbala reports no affiliation with or financial interest in any organization that may pose a conflict of interest. Ms. DeVeaugh-Geiss receives grant/research support from M-3 Corporation and the NIMH; owns equity in GlaxoSmithKline; and her husband owns Brainstorms CNS, LLC. Dr. Rush is a consultant/advisor to Advanced Neuromodulation Systems, AstraZeneca, Best Practice Project Management, Bristol-Myers Squibb, Cyberonics, Forest Pharmaceuticals, Gerson Lehman Group, GlaxoSmithKline, Jazz, Magellan Health Services, Merck, Neuronetics, Novartis, Ono, Organon, Otsuka, Pamlab, Pfizer, Transcept, The Urban Institute, and Wyeth; is on the speaker's bureaus of Cyberonics, Forest Pharmaceuticals, and GlaxoSmithKline; receives grant/research support from the NIMH and the Stanley Medical Research Institute; owns equity in Pfizer; receives royalties from Guilford Publications and Healthcare Technology Systems; and receives a stipend from the Society of Biological Psychiatry for his role as treasurer. Dr. Trivedi is a consultant/advisor to and on the speaker's bureaus of Abbott, Abdi Brahim' Akzo, AstraZeneca, Bristol-Myers Squibb, Cephalon, Eli Lilly, Fabre-Kramer, Forest Pharmaceuticals, GlaxoSmithKline, Janssen, Products LP, Johnson & Johnson, Meade Johnson, Neuronetics, Parke-Davis, Pfizer, Sepracor, VantagePoint, and Wyeth; and receives grant/research support from Agency for Healthcare Research and Quality, Corcept, Cyberonics, Merck, the NIDA, the NIMH, NARSAD, Novartis, Pharmacia & Upjohn, Predix, Solvay, and Targacept.

Funding/Support: This project was funded with Federal funds from the NIMH, National Institutes of Health, under contract N01MH90003 to UT Southwestern Medical Center at Dallas (P.I.: A.J. Rush). The content of this publication does not necessarily reflect the views or policies of the Department of Health and Human Services, nor does mention of trade names, commercial products, or organizations imply endorsement by the US government. This work was independent of the funders (ie, the funders had no involvement in the collection, analysis, and interpretation of data; writing of this report; or the decision to submit the article).

Acknowledgment: The authors would like to thank the STAR*D investigators for their help in making this large and complex multicenter study possible and for generating the data for this report, Jon Kilner, MS, MA (Pittsburgh, Pennsylvania) for editorial support, and e.Solution (Dallas, Texas) for secretarial support.

Submitted for publication: September 16, 2009; Accepted for publication: March 29, 2010.

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