Is Insomnia a Perpetuating Factor for Late-Life Depression in the IMPACT Cohort?

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Study Objectives: Insomnia and depressive disorders are significant health problems in the elderly. Persistent insomnia is a risk factor for the development of new-onset and recurrent major depressive disorder (MDD). Less clear is whether persistent insomnia may perpetuate MDD and/or dysthymia. The present longitudinal study examines the relationship of insomnia to the continuation of depression in the context of an intervention study in elderly subjects.

Design: Data were drawn from Project IMPACT, a multisite intervention study, which enrolled 1801 elderly patients with MDD and/or dysthymia. In the current study, subjects were assigned to an insomnia-status group (Persistent, Intermediate, and No Insomnia) based on insomnia scores at both baseline and 3-month time points. Logistic regressions were conducted to determine whether Persistent Insomnia was prospectively associated with increased risk of remaining depressed and/or achieving a less than 50% clinical improvement at 6 and at 12 months compared with the No Insomnia reference group. The Intermediate Insomnia group was compared with the other 2 groups to determine whether a dose-response relationship existed between insomnia type and subsequent depression.

Setting: Eighteen primary clinics in 5 states.

Participants: Older adults (60+) with depression.

Measurements and Results: Overall, patients with persistent insomnia were 1.8 to 3.5 times more likely to remain depressed, compared with patients with no insomnia. The findings were more robust in patients receiving usual care for depression than in patients receiving enhanced care. Findings were also more robust in subjects who had MDD as opposed to those with dysthymia alone.

Conclusions: These findings suggest that, in addition to being a risk factor for a depressive episode, persistent insomnia may serve to perpetuate the illness in some elderly patients and especially in those receiving standard care for depression in primary care settings. Enhanced depression care may partially mitigate the perpetuating effects of insomnia on depression.

Keywords: Insomnia, depression, elderly, treatment response, risk factor, primary care

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LATE-LIFE DEPRESSION AND INSOMNIA ARE SIGNIFICANT PUBLIC HEALTH ISSUES,[1] WITH AS MANY AS 42% OF OLDER ADULTS REPORTING TROUBLES associated with sleep.[2] A recent review of community and epidemiologic studies conducted exclusively in or including older-age cohorts (total n = 43,070) reported the prevalence of depression to be approximately 9% and that of insomnia to be approximately 17%.[3] The estimates were lower in studies with more stringent criteria, approximately 5% and 10% for depression and insomnia, respectively. Longitudinal studies that have evaluated depression and sleep in the elderly have found that insomnia confers an increased risk for depression.[4-7] As might be expected, it is not the only significant risk factor. A meta-analysis of studies in older adults found that recent bereavement, with an odds ratio (OR) of 3.3, was the largest risk factor for late-life depression and that sleep disturbance was second (OR 2.6).[8]

Nonetheless, insomnia has historically been considered a symptom, as opposed to a disorder. When it occurred with psychiatric illness, insomnia was viewed as a natural consequence of mood dysregulation in which sleep-onset insomnia and early-morning insomnia were considered the cardinal symptoms of anxiety and depression. As a symptom, insomnia was often viewed as a secondary phenomenon that would resolve with remission of, or recovery from, the parent disorder.

In recent years, this point of view has partially given way to the perspective that insomnia may exist as a primary disorder[9,10] and, when it occurs with psychiatric illnesses, it may be viewed as a comorbid condition.[9,11] This change in perspective has occurred owing to several considerations. First, to date, one longitudinal study has shown that insomnia symptoms worsen as patients with recurrent major depressive disorder (MDD) approach new-onset episodes of depression,[12] suggesting that insomnia may be a prodromal symptom of depression and may trigger or precipitate new episodes.

Second, antidepressants can exert their clinical effects without ameliorating the patients' insomnia complaints.[e.g.,13-16] For instance, in a fluoxetine trial, disturbed sleep and fatigue were the most common residual symptoms among depression remitters, (present in 44% and 38% of remitters, respectively).[15]

Disclosure Statement

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In a trial of nortriptyline, although depression remitters had significant decreases in mean sleep disturbance scores on the Pittsburgh Sleep Quality Index,[17] their mean score remained above the clinical cutoff and higher than that of healthy controls.[18] Third, similar findings have been observed in the cognitive behavioral treatment of depression.[19,20] For example, in two separate randomized trials comparing cognitive behavioral treatment for depression to antidepressant medication, approximately 50% of those with remitted depression had residual insomnia, and this was evenly distributed between intervention groups.[21,22] Fourth, in significant subsets of patients, insomnia becomes chronic, despite successful resolution of the psychiatric illness.[23-27] Fifth, Fava et al. recently reported that coadministration of eszopiclone with fluoxetine resulted in greater sleep improvements and antidepressant effects than fluoxetine alone.[28] Finally, there are a number of longitudinal studies showing that insomnia confers an increased risk for depression over time frames of between 6 months and 3 years.[4-6,12,29-36] There are also studies that show that insomnia can confer risk over periods that extend over decades.[7,37,38] In general, patients with persistent insomnia are approximately 3.5 times more likely to develop depression, as compared with subjects without insomnia complaints.

Despite a set of findings suggesting that insomnia is more than a symptom of depression, it does not completely rule out the possibility. Another interpretation of the above findings is that cognitive behavioral treatment for depression and a variety of antidepressant medication therapies improve sleep in a large number of patients.

It may be impossible to determine whether insomnia is purely a symptom or a marker of depression severity or if it is purely a separate disorder. More realistically, not all depressed individuals have an insomnia complaint, and, for a large percentage of depressed patients with an insomnia complaint, the insomnia does, in fact, resolve. It may be that, for some individuals, insomnia is simply a symptom that does not transition to a persistent comorbid insomnia. For others, insomnia does represent a comorbid condition that may or may not resolve without targeted intervention. One open question, therefore, is whether acutely depressed patients who already demonstrate persistent insomnia are more likely to remain depressed than patients with no insomnia complaints or than patients with only acute or mild insomnia. In the present study, we specifically evaluate the proposition that persistent insomnia may be a perpetuating factor for depression.

METHODS

Data were drawn from project IMPACT (Improving Mood-Promoting Access to Collaborative Treatment), a multisite randomized controlled trial of an enhanced care program for late-life depression in primary care that was found to significantly improve depression outcomes when compared with usual care.[39] Study protocols were approved by the institutional review boards of all 7 participating sites and the study coordinating center. For the current analysis, we used the prospective data collected at the study baseline, and at 3-, 6-, and 12-month time points.

Parent Sample

A total of 1801 elderly patients with depression from 18 primary care clinics were enrolled in the study. All participants completed a written informed consent form and a structured baseline interview conducted by trained lay interviewers according to structured format. Initial diagnoses of MDD were made using the Structured Clinical Interview for DSM-III-R (SCID),[7,40] which was also administered at the 6-month assessment. At each assessment (0, 3, 6, and 12 months), subjects were administered a battery of self-report questionnaires, including the 20 depression items from the Hopkins Symptom Checklist (HSCL-20).[41] Additional details regarding recruitment and sample aggregation may be found in Unützer et al.[42]

Participants were randomly assigned to a collaborative care management intervention program or to usual care at their regular primary care clinic. All patients were identified as having MDD and/or dysthymia, and all patients were made aware of the diagnosis. Patients in the intervention arm were assigned to a depression clinical specialist (typically a nurse trained in the intervention). In their initial visit with the specialist, a brief video and brochure about depression were viewed and discussed, and the patient engaged in a discussion of treatment options, including brief problem-solving therapy and/or antidepressant therapy. The specialist met regularly with treating physicians to discuss cases. Finally, if depression remission was not achieved, the patient was considered for a change in treatment approach and/or dosage and/or a psychiatric consultation. Patients assigned to the usual-care arm were informed of their diagnosis and encouraged to follow-up with their primary care providers. Patients in this arm (and their physicians) were allowed to use all primary care or specialty mental health services available to them apart from the depression-care specialist.

Study Sample

Subjects

The original sample (n = 1801) of subjects meeting SCID criteria for MDD and/or dysthymia had a mean age of 71.2 (± 7.5) years; 77% were white/non-Hispanic, and 65% were women. Of these, 17 were excluded for completely missing data at 6 months, and a total of 27 were excluded at 12 months. Additional analyses were conducted excluding a subset of 544 subjects with dysthymia only (i.e., no MDD) at baseline.

Sample Categorization for Insomnia Status

Following the methodologic precedent set by Ford and Kamerow[29] and used by other investigators,[e.g.,30] insomnia status was categorized on the basis of item responses pertaining to insomnia on the HSCL. Recent 3 empiric support exists for the validity of single-item sleep measures derived from depression scales.[43]

In specific, the 3 HSCL questions are related to the degree of complaint associated with "trouble falling asleep," (Item #7) "early morning awakening," (Item #8), and "restless or disturbed sleep" (Item #9) for the month prior to the interview. Scores from these items (which ranged from 0-4) were summed

Table 1—Demographic and Clinical Characteristics at Study Intake Comparing the Parent Sample to the Primary Study Sample and Comparing Persistent Insomnia to no Insomnia Status

Variable	Parent sample (n = 1801)	Study sample (n = 500)	Persistent insomnia (n = 207)	No insomnia (n = 293)	P value
Age, y, mean (SD)	71.2 (7.5)	71.1 (7.4)	70.0 (7.0)	72.1 (7.6)	0.001
Female sex, no. (%)	65%	326 (65)	134 (65)	192 (66)	0.86
Ethnic minority, no. (%)	23%	112 (22)	56 (27)	56 (19)	0.05
Married, no. (%)	46%	229 (46)	94 (45)	135 (46)	0.78
High-school graduate, no. (%)	79%	412 (81)	168 (81)	244 (83)	0.32
Enhanced-care arm, no. (%)	50%	252 (50)	92 (44)	160 (54)	0.02
Depression score, mean (SD)	1.7 (0.6)	1.6 (0.6)	1.9 (0.6)	1.4 (0.6)	< 0.001
Comorbid medical illnesses, no. (mean)	3.6 (1.9)	3.7 (2.0)	4.1 (2.1)	3.4 (1.8)	0.001
Alcohol problem, no. (%)	65 (3)	25 (5)	12 (6)	15 (4)	0.72
PTSD history, no. (%)	193 (11)	42 (8)	22 (11)	20 (7)	0.13
Using antidepressant, no. (%)	771 (43)	228 (46)	91 (46)	148 (45)	0.91

Test statistics were t-tests for continuous data and χ^2 for categorical data. PTSD refers to posttraumatic stress disorder.
*There were no group difference between the parent sample and the study sample. P values represent values for group differences between the persistent insomnia group and the no insomnia group.

(possible range 0-12) and then averaged to arrive at an insomnia score with a possible range of 0 to 4.

Subjects with a mean insomnia score of 1.0 or less at both baseline and 3 months were defined as having "No Insomnia" (n = 293); subjects scoring 2.5 or higher at both time points were defined as having "Persistent Insomnia" (n = 207). These cutoffs were chosen in order to strike a balance between each group's sample size and sample purity. More stringent cutoffs led to increasingly small group sizes, whereas less stringent cutoffs were felt to dilute both groups with subjects who may have had transient or modest insomnia. One alternative would be to choose a reasonable clinical cutoff and dichotomize the entire sample. Instead, a No Insomnia and a Persistent Insomnia group were aggregated per the above criteria, whereas all other subjects were defined as "Intermediate Insomnia" (n = 1301); these were excluded from the primary analyses but entered into secondary analyses, which allowed a dose-response relationship to be assessed.

In addition, further analyses were undertaken in a more restricted sample with insomnia status determined on the basis of having insomnia (n = 107) or no insomnia (n = 282) across 3 consecutive time points (0,3, and 6 months), with 1412 subjects falling into the intermediate category.

Sample Categorization for Depression Status

As was undertaken in the original IMPACT study,[39] 3 measures of depression were employed. First, the 6-month SCID assessment was used to categorize subjects as Remitted or Un-Remitted at 6 months (note that the SCID was not administered at 12 months). Second, the 20-item HSCL depression score was recalculated absent the 3 sleep items and then divided by 17 to arrive at a revised mean HSCL score with a possible range of 0 to 4. As was done in the parent study, subjects scoring a mean of less than 0.5 on the resulting HSCL score at 6 months were defined as "Remitted" and those scoring 0.5 or greater were defined as "Un-Remitted." The same procedure was used to identify remission status at 12 months. Third, clinical improvement was defined as a 50% or greater reduction in the HSCL score (absent sleep items) from baseline to the 6-month assessment, with the groups classified as "Improved" or "Not Improved." Again, the same procedure was used to identify improvement status at 12 months (percentage of HSCL reduction from baseline to 12-month assessment).

Statistical Considerations

Data Management

The parent IMPACT study used a multiple imputation technique for missing data. Rates of missing data ranged from 0% to 2% at the item level. The results across 5 imputed data sets were combined by averaging, and standard errors were adjusted to reflect both within-imputation variability and between-imputation variability. Additional details of the imputation techniques are available elsewhere.[44] The resulting dataset was used as a starting point for the current study in which preliminary analyses were conducted using SPSS 15.0 (SPSS, Inc., Chicago, IL), whereas all outcome analyses were performed using SAS 9.1 (SAS Institute Inc., Cary, NC).

Insomnia Group Characteristics

Demographic characteristics of the Persistent Insomnia and No Insomnia groups were compared using t-tests for continuous variables (e.g., age) and were assessed using contingency analyses for categorical variables (e.g., sex). As displayed in Table 1, the groups did not differ with respect to race, sex, education, or marital status. They also did not differ with respect to clinical characteristics, including alcohol use, history of posttraumatic stress disorder, and antidepressant use. The groups did differ with respect to baseline severity of depression, the number of chronic illnesses at baseline, and the proportions of each group randomized to the IMPACT intervention versus care as usual. These 3 baseline differences are controlled for in all analyses. Depression severity (0-4.0) was stratified into

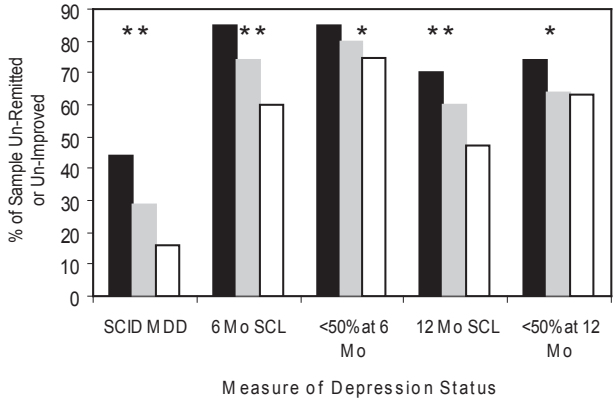

Figure 1—Dose-Response Relationship of Insomnia Status Across Depression Outcomes. The Persistent Insomnia, Intermediate Insomnia and No Insomnia groups are represented by the black, grey, and white bars, respectively. The measures of depression are defined as: SCID MDD (Structured Clinical Interview for DSM-III-R diagnosis of major depressive disorder at 6 months); 6 Mo SCL (scoring above the depression cutoff on the 17-item version of the Hopkins Symptom Checklist [HSCL] at 6 months); < 50% at 6 Mo (a less than 50% improvement on the 17-item version of the HSCL from baseline to 6 months); 12 Mo SCL (scoring above the depression cutoff on the 17-item version of the HSCL at 12 months); and < 50% at 12 Mo (a less than 50% improvement on the 17-item version of the HSCL from baseline to 6 months). For each measure of depression, χ^2 analyses conducted where * denotes $P < 0.05$ and ** denotes $P < 0.001$.

3 equal-sized strata, and chronic illness (0-11) into strata of 0 to 2, 3 to 4, and 5+ illnesses. In addition, age was significantly lower in the Persistent Insomnia group (70.0 versus 72.1 years), but age was not correlated with mean sleep scores, individual sleep item scores, change in sleep scores from baseline to 3 months, or total HSCL scores (minus sleep items) at 6 or 12 months and was therefore not included as a control variable. Instead, a propensity score was calculated and added as a control variable to adjust for a number of baseline variables (described in more detail below).

Depression Outcomes

Common OR estimates with 95% confidence intervals (CI) for both Un-Remitted depression and for achieving less than a 50% improvement in depression severity were calculated at both 6 months and 12 months for the Persistent Insomnia group, with No Insomnia as the reference group in a series of logistic regressions. This was done when insomnia status was defined by 2 time points (baseline and 3 months) and by 3 time points (baseline, 3 months, and 6 months). As indicated above, adjusted ORs controlled for baseline differences on depression severity, medical burden, and intervention arm.

In addition, because subjects were not randomly assigned to Insomnia Status groups, the above covariates might not adequately adjust for potential differences between these 2 insomnia-status groups. In order to adjust for the effects of those variables, we used propensity scores to address the issue of potential selection bias.[45,46] A logistic regression model was run with Persistent Insomnia as the dependent variable (yes/no) and all baseline characteristics that might be associated with the Persistent Insomnia as the independent variables. The independent variables included age, sex, ethnicity, education, marital status, alcohol screening score (CAGE), use of antidepressants, NEO score, number of chronic conditions, posttraumatic stress disorder, quality of life, 17-item HSCL score, and the 3 items of the Sheehan Disability Scale. The predicted probabilities derived from the logistic-regression model were the propensity scores. In the multiple logistic regression models in which we evaluated the adjusted effect of persistent insomnia on the 6-and 12-month depression outcomes, we included the propensity scores as a covariate in addition to the categorized depression severity (by strata), the number of chronic conditions at baseline (by strata), and assigned intervention arm (enhanced care vs usual care) to further adjust for the likelihood of a patient having persistent insomnia.

In order to assess the effect of intervention arm on outcomes, the enhanced-care arm and the usual-care arm were also analyzed separately. In order to assess whether subjects with baseline MDD differed from those with dysthymia-only at baseline, the entire set of analyses was repeated in this smaller sample. Finally, in order to assess whether there was any dose-response relationship with respect to insomnia severity, we report a simple χ^2 analysis of Insomnia status (Persistent, Intermediate, and No Insomnia) and the depression outcomes at 6 and 12 months.

RESULTS

Primary Outcomes

As assessed by the SCID at 6 months and the HSCL at both 6 and 12 months, subjects with Persistent Insomnia were more likely to exhibit Un-Remitted depression and less than 50% improvement on the HSCL, in contrast to the No Insomnia reference group on 5 of the 7 measures of depression. As presented in Table 2, adjusted ORs ranged from 1.8 to 3.5. These outcomes were more robust when the sample was restricted by excluding subjects who were dysthymic only (i.e., did not have MDD). In this MDD sample, Persistent Insomnia was a significant predictor in 6 of 7 the models, with adjusted ORs ranging from 2.5 to 5.9.

Effect of Intervention Arm

When the entire sample was analyzed, intervention arm was a significant predictor in all models when entered as an independent variable. We then ran all models with an interaction variable (between Persistent Insomnia and Intervention), but the interaction variable was not a significant predictor in any of the models. We then removed both the interaction term and the intervention variable from each model in order to reanalyze data by intervention arm. As presented in Table 2, the findings with respect to persistent insomnia were more robust in the usual-care group (and less robust in the enhanced-care group).

Dose-Response Relationship

χ^2 analyses revealed significant associations between "insomnia dose" (Persistent, Intermediate, or No Insomnia) and

Table 2—Adjusted Odds Ratio Estimates of Variables Predicting Depression Status at 6 and 12 Months

Model	Entire Sample				Enhanced Care Arm		Usual Care Arm	
Measure of DV	β	SE	P	Adjusted OR	P	Adjusted OR	P	Adjusted OR
IVs in Model				(95% CI)		(95% CI)		(95% CI)
1 SCID MDD at 6 Mo								
Persistent Insomnia (2x)	1.02	0.25	< 0.0001	2.77 (1.7-4.5)	0.055	2.13 (.98-4.6)	< 0.0001	3.61 (1.8-7.2)
Intervention arm	-0.58	0.23	0.010	0.56 (0.4-0.9)	-	-	-	-
SCL17 (strata 2 vs 1)	0.32	0.32	0.322	1.37 (0.7-2.6)	0.515	1.38 (0.5-3.6)	0.189	1.72 (0.8-3.8)
SCL17 (strata 3 vs 1)	0.63	0.41	0.124	1.88 (0.8-4.2)	0.023	4.39 (1.2-15.0)	0.176	1.89 (0.8-4.7)
No. diseases (2 vs 1)	0.10	0.30	0.729	1.11 (0.6-2.0)	0.429	1.45 (0.6-3.7)	0.950	1.03 (0.5-2.3)
No. diseases (3 vs 1)	0.53	0.31	0.092	1.69 (0.9-3.1)	0.003	4.43 (1.7-11.7)	0.975	0.99 (0.4-2.2)
Propensity score	0.88	0.76	0.244	2.40 (0.5-10.6)	0.478	0.45 (0.1-4.1)	0.139	3.30 (0.7-16.0)
2 SCL Un-Remitted at 6 Mo			#		#			
Persistent Insomnia (2x)	1.04	0.27	< 0.0001	2.83 (1.7-4.8)	0.127	1.74 (0.9-3.6)	< 0.0001	4.65 (2.0-10.7)
3 < 50% improved at 6 Mo								
Persistent Insomnia (2x)	1.13	0.23	< 0.0001	3.09 (2.0-4.9)	0.054	1.87 (0.99-3.5)	< 0.0001	5.26 (2.5-10.8)
4 SCL Un-Remitted at 12 Mo			#				#	
Persistent Insomnia (2x)	0.12	0.28	0.670	1.13 (0.6-2.0)	0.258	0.65 (0.3-1.4)	0.113	2.19 (0.8-5.8)
5 < 50% improved at 12 Mo								
Persistent Insomnia (2x)	0.57	0.24	0.018	1.78 (1.1-2.9)	0.574	1.20 (0.6-2.3)	0.008	2.89 (1.3-6.3)
6 SCL Un-Remitted at 12 Mo			#		#		#	
Persistent Insomnia (3x)	0.59	0.42	0.166	1.81 (0.8-4.2)	0.893	0.92 (0.3-2.8)	0.042	5.56 (1.1-29.1)
7 < 50% improved at 12 Mo								
Persistent Insomnia (3x)	1.24	0.35	< 0.0001	3.47 (1.7-6.9)	0.028	2.91 (1.1-7.5)	0.009	4.55 (1.5-14.1)

In models 1-5, insomnia status is consistent across 2 time points (2x): baseline and 3 months (No Insomnia is the reference group); whereas, in models 6-7, insomnia status is consistent across 3 time points (3x): baseline, 3 months, and 6 months. In models 2-7, the same variables as in Model 1 were entered, but only the values for Persistent Insomnia are displayed. Besides intervention arm, no other variables significantly predicted depression status except for Symptom Checklist (SCL) strata 2 vs. SCL strata 1 (denoted by #). DV refers to Dependent Variable; IV, Independent Variables; SCID, Structured Clinical Interview for DSM-III-R; OR, odds ratio; CI, confidence interval.

depression status. At the 6-month time point, SCID-assessed MDD remained in 44% of subjects with Persistent Insomnia, 29% of those with Intermediate Insomnia, and 16% of those with No Insomnia ($P < 0.001$). Figure 1 graphically depicts these findings and those from the other measures of depression status; all analyses were significant at $P < 0.05$.

Posthoc Descriptive Results

In order to place insomnia within a context of other symptom clusters of depression, we provide some simple descriptive statistics. For the entire parent sample (n = 1801), mean HSCL scores for each of the 9 depression-symptom clusters at baseline are displayed in Figure 2a (0-4.0 range possible). As can be seen, insomnia had the fourth-highest mean baseline value and the largest standard deviation. In terms of persistent symptom clusters (with persistence defined as a mean symptom score of 2.5 or greater at both baseline and 3 months), Persistent Insomnia was observed in 11.6% of the parent sample, which is fifth of the 9 symptom clusters (see Figure 2b). Finally, we wondered whether any particular persistent symptom would occur in the absence of other persistent symptoms (or in the presence of multiple other persistent symptoms). Figure 2c shows, for each persistent symptom cluster, how many other persistent symptoms co-occur. The number of other persistent symptoms ranged from 1.4 to 3.9 additional persistent symptoms. Persistent Insomnia is associated with the second-smallest number of persistent symptoms (1.9) and, when present, Persistent Insomnia is most often associated with persistent fatigue (57% of the time).

DISCUSSION

In the present study, after adjusting for baseline differences, it was found that depressed older primary care patients with persistent insomnia were more likely to remain depressed or fail to achieve a benchmark of clinically significant improvement, as compared with subjects with no insomnia. These results are in keeping with prior longitudinal studies that indicated that insomnia was a risk factor for both first and recurrent episodes of major depression. The present study adds to this body of literature by providing evidence that insomnia may also serve to perpetuate depression.

The finding that this risk was higher in the usual-care group, suggests that enhanced depression may partially mitigate the perpetuating effects of insomnia on depression. In addition, the finding that, as insomnia moves from not present to acutely or moderately present to persistently present, the prevalence of ongoing depression increases in a dose-response fashion is an expected outcome especially if persistent insomnia is different than insomnia as a symptom. The fact that the primary findings were more robust in the MDD population, than in those with dysthymia alone, is less straightforward. This is perhaps owing to underlying differences in these clinical entities. Finally, comparing insomnia to other depressive symptoms provides some interesting, albeit inconclusive, data. Insomnia is no more or less prevalent than other symptoms either at baseline or when the symptoms are classified as persistent by meeting the same criteria across 2 consecutive time points, yet, when it does present as a persistent symptom, it is less often part of a larger

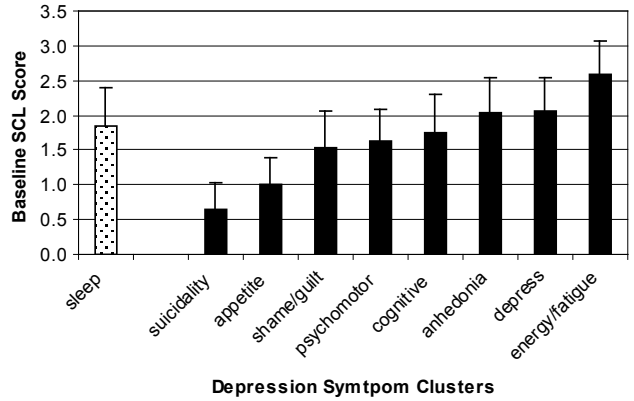

Figure 2a— Mean Symptom Score at Baseline. Mean symptom cluster scores of the parent sample (n = 1801) at baseline with a possible range of 0 to 4.0.

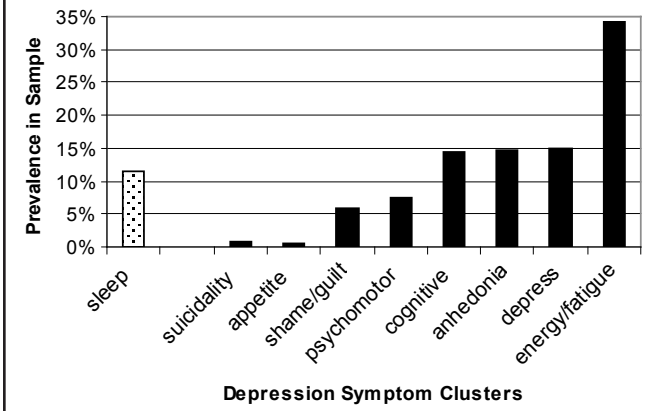

Figure 2b— Prevalence of Persistent Symptom. Percentage of the parent sample that exhibited an elevated symptom score at both baseline and the 3-month time point.

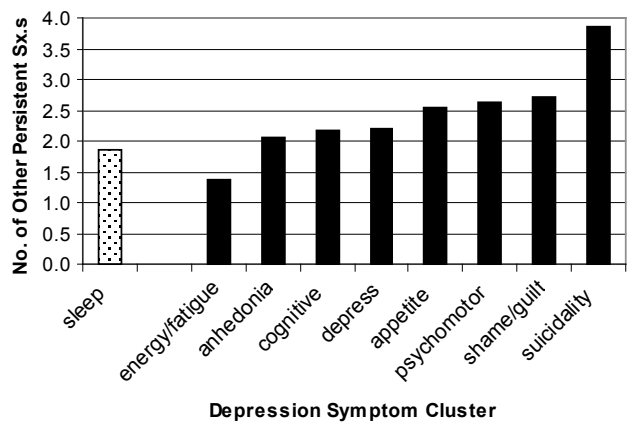

Figure 2c— Co-occurring Persistent Symptoms. For each individual symptom, the bar represents the mean number of other persistent symptoms that are co-occurring. For example, subjects with persistent insomnia had a mean of 1.9 co-occurring persistent depressive symptoms.

set of persistent symptoms than are other symptom clusters. Certainly this may be because depression presents across time with a changing array of persistent symptoms. Nonetheless, if persistent insomnia were merely a marker for more entrenched or more severe depression, one would expect it to occur more regularly with other persistent depressive symptoms. Overall, the set of findings from this study support the hypothesis that insomnia may serve as a perpetuating factor in depression.

What these data do not unequivocally tell us is whether insomnia that presents with depression is a symptom or a comorbid disorder. Although we have primarily argued for the latter perspective, it is more likely, as noted in the introduction, that insomnia is simply a symptom in some cases and clearly a disorder requiring its own treatment focus in other cases. In the absence of a definitive causal study, it will take a continued amalgamation of varying kinds of evidence to make a causal claim with respect to insomnia perpetuating the course of depression. The findings from the current study do begin to build the case that persistent insomnia (as defined in this study) may blunt treatment response and serves as a barrier to remission from depression in a particular population and that this is especially true in older patients receiving standard primary care-based treatment of depression.

This study has some of the same limitations that are true of the epidemiologic studies that preceded it. First, the measure used consisted of 3 sleep-related items as opposed to a validated insomnia instrument, though the use of item measures has recently been validated as an index of insomnia.[43] Second, removing the 3 sleep items from the HSCL to assess clinical status and depression severity created an unvalidated index of depression. Third, the time between measurements (3-6 months) only allows for an approximation of acute versus persistent insomnia, as the HSCL asks for answers to be tied to the prior month; by default this does not allow us to adequately characterize the difference among what may be transient, recurrent, or persistent insomnia. Similarly, the instruments used are retrospective and subjective for the prior month (as opposed to a daily sleep diary that provides such data much more proximally). Fourth, we were unable to control for type and number of medications used, including antidepressant type. Finally, our data do not speak to the issue of whether the effects observed in this study generalize to other age cohorts.

In order to further evaluate the proposition that insomnia serves to perpetuate depression, several lines of research are possible. First, a large-scale longitudinal study using full, validated insomnia instruments with monthly time points could be deployed to replicate and extend the present findings. Second, intervention trials (both pharmacologic and behavioral) may be conducted that treat persistent insomnia in either current or remitted depression to assess whether this improves depression or delays or aborts recurrent episodes of depression. There are 2 uncontrolled studies that have shown that patients presenting with insomnia and depression who completed a course of cognitive behavioral therapy for insomnia had improvements in both sleep and depression.[47,48] Controlled trials are needed to replicate these preliminary findings. Third, an intervention model could be used to determine whether adjunctive treatment for insomnia (in addition to standard treatment for depression) affects the clinical course of MDD. To date, 1 such study has shown that patients treated concomitantly with fluoxetine and eszopiclone exhibited less illness severity over the course of an 8-week intervention and a faster time to recovery than subjects treated with fluoxetine on-

ly.[21] If replicated and extended to include other adjuvant interventions (e.g., cognitive behavioral therapy) such data would test the perspective that persistent insomnia is a comorbid condition that, when untreated, prolongs illness and, when treated, hastens recovery. If possible, it would also be helpful to determine if there are levels of insomnia severity and/or duration that are empiric thresholds for chronicity that seems to be a risk for ongoing depression. Similarly, data that could establish the patient characteristics for insomnia that does versus does not resolve when depression ameliorates could help guide clinical decision-making during the course of depression.

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