Insomnia, Suicidal Ideation, and Suicide Attempts in the Clinical Antipsychotic Trials of Intervention Effectiveness

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ABSTRACT

Objective: Insomnia occurs frequently in the clinical course of schizophrenia. There is a robust association between insomnia and suicide in other psychiatric disorders. Several previous studies found associations between insomnia and suicidal ideation, suicide attempt, and psychopathology in schizophrenia. We explored these associations in a cross-sectional study of a large sample of patients with schizophrenia.

Methods: In February 2020, we investigated relationships between current insomnia, suicidal ideation over the past 2 weeks, suicide attempt in the past 6 months (assessed by either the Calgary Depression Scale for Schizophrenia or self-report), and current psychopathology for subjects with baseline data from the Clinical Antipsychotic Trials of Intervention Effectiveness (*DSM-IV* schizophrenia trial conducted 2001–2004) using regression models.

Results: After controlling for multiple potential confounding factors, terminal insomnia was associated with significant, 2.7-fold increased odds of current suicidal ideation (OR = 2.7, 95% CI = 2.0–3.6, $P < .001$). Initial/middle insomnia was associated with a significant, 5.5-fold increased odds of suicide attempt in the past 6 months (OR = 5.5, 95% CI = 1.4–21.1, $P = .013$). Terminal insomnia was also a significant indicator of higher Positive and Negative Syndrome Scale total ($\beta = 0.12$, $P < .001$), positive subscale ($\beta = 0.11$, $P < .001$), and general psychopathology subscale ($\beta = 0.14$, $P < .001$) scores. There were no other significant associations between insomnia, suicidal thinking or behavior, and psychopathology.

Conclusions: Insomnia is associated with suicidal ideation, recent suicide attempt, and greater psychopathology in schizophrenia. Findings provide additional evidence that formal assessment of insomnia is relevant to the clinical care of patients with schizophrenia as an indicator of suicidal ideation and behavior, as well as symptom severity.

Trial Registration: ClinicalTrials.gov identifier: NCT00014001

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Insomnia occurs frequently throughout the clinical course of schizophrenia, in both medicated and unmedicated patients, with a prevalence of 23%–44% across several recent studies.[1–3] Multiple factors may contribute to this association, including dysfunctional and/or misaligned circadian rhythms.[4,5] There is evidence for sleep disturbances as well as abnormal sleep architecture and reduced spindles in early psychosis, and these aberrations may correlate with the severity of psychopathology.[6] A robust association exists between insomnia and suicidal thinking and behavior across multiple psychiatric conditions, including mood and anxiety disorders.[7,8] There is meta-analytic evidence for 2-fold increased odds of suicidal behaviors in psychiatric patients with versus without comorbid sleep disturbance.[7] However, these associations are relatively understudied in patients with schizophrenia. Nevertheless, suicide attempts and suicide death are common in patients with schizophrenia. A meta-analysis of observational studies found a 26.8% lifetime prevalence of suicide attempt[9] and another review found a 5% lifetime prevalence of suicide death[10] in patients with schizophrenia.

A small number of previous studies have directly investigated associations between insomnia and suicidal thinking and behavior in patients with schizophrenia. A retrospective analysis of 106 subjects during the psychosis prodrome found that sleep disturbance is associated with an increased prevalence of suicidal ideation but not suicide attempt.[11] A study of 110 patients with persecutory delusions in the context of non-affective psychosis found that insomnia, as measured by the Insomnia Severity Index (ISI), was significantly, positively correlated with the severity of suicidal ideation on the Columbia-Suicide Severity Rating Scale ($r = 0.10$, $P = .033$).[12] An 8-year, naturalistic study in 388 outpatients with schizophrenia spectrum disorders found a 19% prevalence of baseline insomnia (≥ 3 times per week in the past year).[13] In that study, baseline insomnia was associated with an almost 5-fold increased risk of suicide attempt over the follow-up period. In a study of 108 inpatients and outpatients with schizophrenia or schizoaffective disorder, we found that ISI scores were a significant indicator of Beck Scale for Suicide Ideation scores ($\beta = 0.27$), and patients with (versus without) severe insomnia were almost 15 times more likely to have a history of lifetime suicide attempt.[14]

There is also a small literature on associations between sleep disturbance and suicide death in schizophrenia. A case-control study of 20 males with schizophrenia and suicide death and 20 living males treated at the same outpatient clinic found an almost 13-fold increase odds of insomnia in those patients who died by suicide.[15] A meta-analysis of 3 case-control studies (N = 176 total subjects) found a trend for an association between sleep disturbance and suicide death in schizophrenia (odds ratio [OR] = 1.99, 95% CI = 0.96–4.12).[16] A systematic review of risk factors for suicide in schizophrenia categorized insomnia as having a strong association with suicide.[10] Furthermore, insomnia may be associated with more violent suicide attempts. In a sample of 843 consecutive patients admitted to an

Clinical Points

- Insomnia is associated with current suicidal ideation, recent suicide attempt, and psychopathology in schizophrenia.
- Formal assessment of insomnia is relevant to the clinical care of patients with schizophrenia.

emergency department for psychiatric evaluation (17% with schizophrenia), those with insomnia who attempted suicide more frequently were more likely to use a violent method compared to other suicide attempters.[17]

Some evidence suggests associations between insomnia and the severity of psychopathology in schizophrenia. In our previous study, we also found that ISI scores were an indicator of higher levels of psychopathology, as measured by Positive and Negative Syndrome Scale (PANSS) total, positive, and general psychopathology subscale scores ($\beta = 0.32–0.40$ for each).[147] A longitudinal, pathway analysis in 29 subjects also found that insomnia was a predictor of later hallucinations and demonstrated a bidirectional relationship between insomnia and paranoia.[18] Regarding associations between insomnia and psychopathology outside of schizophrenia, there is evidence from both naturalistic and experimental studies that insomnia is associated with increased subclinical psychotic experiences.[19–22] A recent study in a large sample of 740 youth at clinical high risk for psychosis found that sleep problems were significantly, positively associated with attenuated psychotic symptom severity, including suspiciousness, perceptual abnormalities, and disorganized communication.[23] Two studies also found that insomnia was associated with greater impairments in quality of life in patients with schizophrenia.[1,24]

Given the relative paucity of studies on insomnia and suicidal thinking and behavior in schizophrenia, we attempted to replicate previous findings, as positive associations would underscore the importance of recognition and treatment of insomnia in these patients. In the present study, we examined associations between insomnia, suicidal ideation, suicide attempt, and psychopathology in a cross-sectional study of a well-characterized sample of patients with schizophrenia representing the largest sample to date. We hypothesized that the presence of insomnia would be associated with increased odds of current suicidal ideation, suicide attempt in the past 6 months, and greater levels of current psychopathology.

METHOD

Subjects and Procedures

Publicly available data were obtained from the CATIE schizophrenia trial (conducted January 2001–December 2004; ClinicalTrials.gov identifier NCT00014001), which is described elsewhere.[25] Briefly, 1,493 (medicated and unmedicated) patients with *DSM-IV* schizophrenia diagnosed by structured clinical interview at 57 US sites were randomized to one of 5 different antipsychotics for up to 18 months. The primary aim of the CATIE trial was to delineate differences in effectiveness of these treatments. The Augusta University institutional review board deemed the current study exempt.

In the present cross-sectional study, we investigated relationships between current insomnia, suicidal ideation over the past 2 weeks, suicide attempt in the past 6 months, and current psychopathology for subjects with available baseline data from the CATIE trial. Terminal insomnia at study baseline was assessed using the Calgary Depression Scale for Schizophrenia (CDSS; item 7, "EARLY WAKENING: Do you wake earlier in the morning than is normal for you? How many times per week does this happen?"). Initial and/or middle insomnia at study baseline was assessed by patient self-report in response to the question, "Trouble getting/staying asleep?" We dichotomized both of these variables as present/absent (yes/no). Suicidal ideation at study baseline was assessed using the CDSS (item 8, "SUICIDE: Have you felt that life wasn't worth living? Did you ever feel like ending it all? What did you think you might do? Did you actually try?"). A history of suicide attempt in the past 6 months was assessed by patient self-report. We also dichotomized both of these variables as present/absent (yes/no). Psychopathology was measured with the PANSS (total and subscale scores) at study baseline. Of note, the PANSS does not have an insomnia item or a suicide-specific item. We included all subjects in the CATIE trial with baseline CDSS scores. Data on age, race, sex, body mass index (BMI), smoking (cigarettes per day in the past week), CDSS total score, and alcohol and illicit drug use were also available.

Statistical Analysis

Data were analyzed in February 2020 with SPSS version 26 (SPSS, Inc; Chicago, Illinois). Descriptive statistics (means, standard deviations, and proportions) were calculated for demographic and clinical variables. A 1-sample Kolmogorov-Smirnov test was used to examine each variable for normality. Age, smoking, BMI, CDSS total score, and PANSS total and subscale scores were all non-normally distributed. We first made the following comparisons using a χ^2 test, 2-sided: (1) terminal insomnia and current suicidal ideation, (2) terminal insomnia and suicide attempt in the past 6 months, (3) initial/middle insomnia and current suicidal ideation, and (4) current initial/middle insomnia and suicide attempt in the past 6 months. We then investigated the association between insomnia and suicidal thinking and behavior using logistic regression models. The assumptions of logistic regression were met. Age, sex, race, smoking, BMI, alcohol and drug use, and PANSS total score were considered as potential confounding and/or moderating factors.

We then investigated relationships between insomnia and psychopathology. We first calculated bivariate correlations (Spearman ρ) between baseline PANSS total and positive, negative, and general subscale scores and initial/middle and terminal insomnia. For any bivariate correlations with $P < .10$, we investigated these associations in linear regression

Table 1. Demographic and Clinical Characteristics of the Study Sample

Variable	Initial/middle insomnia at baseline: Yes (n = 268), mean (SD)	Initial/middle insomnia at baseline: No (n = 330), mean (SD)	*P* value[a]	Terminal insomnia at baseline: Yes (n = 381), mean (SD)	Terminal insomnia at baseline: No (n = 1,057), mean (SD)	*P* value[a]
Age, y	37.8 (12.1)	39.4 (11.5)	.11	40.8 (11.0)	40.5 (11.2)	.67
Smoking, cigarettes/d	12.9 (14.0)	11.8 (15.8)	.09	12.1 (14.2)	12.6 (14.5)	.42
BMI	29.6 (7.1)	29.4 (6.7)	.69	30.2 (7.2)	29.7 (7.0)	.12
CDSS total score[b]	4.5 (4.4)	4.3 (4.1)	.68	7.9 (4.4)	3.3 (3.7)	< .01
PANSS total[b]	77.6 (17.9)	75.8 (19.0)	.25	79.1 (17.5)	74.4 (17.4)	< .01
PANSS positive[b]	18.8 (5.5)	18.1 (5.9)	.15	19.5 (5.8)	18.1 (5.5)	< .01
PANSS negative[b]	20.6 (6.7)	20.8 (6.8)	.67	20.5 (6.0)	20.1 (6.6)	.39
PANSS general[b]	38.2 (9.4)	36.9 (9.4)	.09	39.2 (9.3)	36.2 (9.1)	< .01
	n (%)	n (%)		n (%)	n (%)	
Sex			.92			< .01
Male	201 (75.0)	249 (75.5)		258 (67.7)	813 (76.9)	
Female	67 (25.0)	81 (24.5)		123 (32.3)	244 (23.1)	
Race			< .01			.32
African descent	200 (74.6)	197 (59.7)		216 (56.7)	652 (61.7)	
Caucasian	58 (21.6)	110 (33.3)		146 (38.3)	355 (33.6)	
Hispanic	2 (0.7)	5 (1.5)		9 (2.4)	18 (1.7)	
South Asian	7 (2.6)	15 (4.5)		7 (1.8)	27 (2.6)	
Other	1 (0.4)	3 (0.9)		3 (0.8)	5 (0.5)	
Alcohol use			< .01			.96
Abstinent	159 (59.3)	203 (61.7)		246 (64.6)	684 (64.9)	
Use without impairment	82 (30.6)	114 (34.7)		107 (28.1)	289 (27.4)	
Abuse or dependence	27 (10.1)	12 (3.6)		28 (7.3)	81 (7.7)	
Drug use			.06			.67
Abstinent	190 (70.9)	260 (79.0)		286 (75.1)	803 (76.2)	
Use without impairment	45 (16.8)	43 (13.1)		54 (14.2)	154 (14.6)	
Abuse or dependence	33 (12.3)	26 (7.9)		41 (10.8)	97 (9.2)	

[a]*P* values for continuous variables are from either Student *t* test, 2-sided, or Mann-Whitney *U* test. *P* values for categorical variables are from χ^2 test.
[b]Possible ranges for scores for these rating instruments are as follows: CDSS total score 0–27, PANSS total score 30–210, PANSS positive score 7–49, PANSS negative score 7–49, PANSS general score 16–112.
Abbreviations: BMI = body mass index, CDSS = Calgary Depression Scale for Schizophrenia, PANSS = Positive and Negative Syndrome Scale.

models, controlling for potential confounding effects of age, sex, race, smoking, BMI, and alcohol and drug use.

RESULTS

The total number of subjects in the CATIE trial was 1,450. The demographic and clinical characteristics of the study sample are presented in Table 1. 1,438 subjects had CDSS data on terminal insomnia, and approximately 600 subjects had data on initial/middle insomnia and suicide attempt in the past 6 months. The reasons for missing data on initial/middle insomnia and suicide attempt were not specified. Subjects with data on suicide attempt were significantly younger (38.9 versus 41.8 years) and had significantly higher PANSS negative symptom scores (20.7 versus 19.8) but otherwise did not differ on any demographic or clinical variables, including CDSS total score or the prevalence of terminal insomnia or current suicidal ideation on the CDSS. Subjects with (versus without) terminal insomnia had significantly higher CDSS total scores with a large effect size (Cohen $d = 1.13$) and significantly higher PANSS total scores with a small-to-medium effect size (Cohen $d = 0.27$) (see also Table 1). In the study sample, the prevalence of initial/middle insomnia was 45%, and the prevalence of terminal insomnia was 27%. The prevalence of suicidal ideation was 18%, and 3% of subjects reported a suicide attempt in the past 6 months.

Current Insomnia and Suicidal Ideation

There was an increased prevalence of current suicidal ideation in patients with versus without terminal insomnia (29.7% versus 13.2%, $\chi^2 = 52.8$, $P < .001$), as well as in patients with versus without initial/middle insomnia (19.8% versus 13.0%, $\chi^2 = 5.0$, $P = .033$). In a logistic regression model, after controlling for potential confounding factors, terminal insomnia was associated with significant, 2.7-fold increased odds of current suicidal ideation (OR = 2.7, 95% CI = 2.0–3.6, $P < .001$; see Table 2). However, in a logistic regression model, after controlling for potential confounding factors, the association between initial/middle insomnia and current suicidal ideation was not significant (see Table 2). The pattern of findings was unchanged in a post hoc analysis of inpatient versus outpatient status at study baseline (data not shown).

Current Insomnia and Recent Suicide Attempt

There was an increased prevalence of suicide attempt in the past 6 months in patients with versus without initial/middle insomnia (5.8% versus 1.2%, $\chi^2 = 9.4$, $P = .004$). By contrast, there was not a significant increased prevalence of

Table 2. Logistic Regression Models of Insomnia as an Indicator of Suicidality

		Final logistic regression model[a]				
Dependent variable	Indicator	R^2	*F*	VIF	OR (95% CI)	*P* value
Baseline suicidal ideation (CDSS item 8)	Baseline terminal insomnia (CDSS item 7)	0.08	12.60	1.03	2.65 (1.97–3.57)	<.001
	Age				0.99 (0.97–1.00)	.026
	Race (Caucasian vs African descent)				0.65 (0.47–0.89)	.010
	PANSS total score				1.02 (1.02–1.03)	<.001
Suicide attempt in past 6 mo (subject self-report)	Baseline terminal insomnia (CDSS item 7)	0.03	1.26	1.03	1.11 (0.35–3.45)	.864
Baseline suicidal ideation (CDSS item 8)	Baseline initial/middle insomnia (Subject self-report)	0.07	3.48	1.04	1.37 (0.85–2.20)	.198
Suicide attempt in past 6 mo (subject self-report)	Baseline initial/middle insomnia (Subject self-report)	0.04	2.04	1.04	5.49 (1.43–21.09)	.013
	Sex				3.22 (1.05–9.94)	.042

[a]After adjustment for confounders.
Abbreviations: CDSS = Calgary Depression Scale for Schizophrenia, OR = odds ratio, PANSS = Positive and Negative Syndrome Scale, VIF = variance inflation factor.

Table 3. Linear Regression Models of Insomnia as a Predictor of Psychopathology

		Final linear regression model[a]				
Indicator	Dependent variable	R^2	*F*	VIF	β	*P* value
Baseline terminal insomnia (CDSS item 7)	Baseline PANSS total score	0.03	5.89	1.01	0.120	<.001
	Baseline PANSS positive score	0.04	6.19		0.107	<.001
	Baseline PANSS negative score	0.02	3.95		0.048	.074
	Baseline PANSS general score	0.04	6.86		0.139	<.001
Baseline initial/middle insomnia (subject self-report)	Baseline PANSS total score	0.03	1.81	1.04	0.047	.266
	Baseline PANSS positive score	0.03	1.86		0.062	.141
	Baseline PANSS negative score	0.04	2.80		0.005	.909
	Baseline PANSS general score	0.03	2.09		0.062	.143

[a]After adjustment for confounders.
Abbreviations: CDSS = Calgary Depression Scale for Schizophrenia, PANSS = Positive and Negative Syndrome Scale, VIF = variance inflation factor.

suicide attempt in the past 6 months in patients with versus without terminal insomnia (4.6% versus 2.5%, $\chi^2 = 1.8$, $P = .178$). In a logistic regression model, after controlling for potential confounding factors, initial/middle insomnia was associated with significant, 5.5-fold increased odds of suicide attempt in the past 6 months (OR = 5.5, 95% CI = 1.4–21.1, $P = .013$; see Table 2). By contrast, in a logistic regression model, after controlling for potential confounding factors, terminal insomnia was not associated with increased odds of suicide attempt in the past 6 months (see Table 2). The pattern of findings was unchanged in a post hoc analysis of inpatient versus outpatient status at study baseline (data not shown).

Current Insomnia and Psychopathology

Terminal insomnia was significantly, positively correlated with PANSS total (ρ = 0.11), positive subscale (ρ = 0.10), and general psychopathology subscale (ρ = 0.13; $P < .001$ for each) but not negative subscale (ρ = 0.02, $P = .391$) scores. By contrast, initial/middle insomnia was not correlated with PANSS total or subscale scores ($P > .05$ for each). As shown in Table 3, in linear regression models, after controlling for potential confounding factors, terminal insomnia remained a significant indicator of higher PANSS total (β = 0.12, $P < .001$), positive subscale (β = 0.11, $P < .001$), and general subscale (β = 0.14, $P < .001$) scores, but initial/middle insomnia was not associated with psychopathology. The pattern of findings was unchanged in a post hoc analysis of inpatient versus outpatient status at study baseline (data not shown).

Given these associations, in post hoc analyses, we also investigated associations between terminal insomnia and individual PANSS items. In linear regression analyses, after controlling for potential confounding factors, terminal insomnia was associated with significantly greater levels of delusions, hallucinations, suspiciousness, hostility, somatic concerns, anxiety, guilt, tension, depression, disorientation, and active social avoidance ($P < .01$ for each). The strength of these associations with most individual PANSS items was small (β = 0.08–0.12), although somewhat larger effects were seen for anxiety (β = 0.18) and depression (β = 0.24). Concordantly, terminal insomnia was also significantly, positively correlated with the CDSS total score (ρ = 0.46; $P < .001$).

DISCUSSION

We found that insomnia was a common symptom in a large cross-sectional study of patients with schizophrenia. After controlling for potential confounders, (*a*) terminal insomnia was associated with significant increased odds of current suicidal ideation, (*b*) initial/middle insomnia was also associated with a significant increased odds of suicide attempt in the past 6 months, and (*c*) terminal insomnia was also a

significant indicator of higher total, positive, and general psychopathology, most notably anxiety and depression, although the strength of these associations was small (β = 0.11–0.14). Taken together, these findings are broadly consistent with previous associations between insomnia and suicidal thinking and behavior in schizophrenia.[12,13,17] We found that initial/middle insomnia was associated with 5.5-fold increased odds of suicide attempt in the past 6 months. To put this association in context, a large meta-analysis of risk factors for suicide attempt in patients with schizophrenia found the following significant associations: history of depression (OR = 4.1), hopelessness (OR = 2.2), family history of suicide (OR = 1.8), and history of alcohol use (OR = 1.7).[26]

Strengths of the present study include the largest sample to date, including a high proportion of subjects of African descent, to investigate cross-sectional relationships between insomnia and suicidal thinking and behavior and the consideration of multiple potential confounding factors. We found a 27% prevalence of terminal insomnia and a 45% prevalence of initial/middle insomnia, which are consistent with estimates from several recent studies in patients with schizophrenia.[1–3] Subjects with versus without terminal insomnia were significantly more likely to be female (32.3% versus 23.1%), which is consistent with adiagnostic meta-analytic data.[27] We also replicated our previous finding of an association between current insomnia and suicidal ideation and psychopathology in schizophrenia. Our findings contribute to a growing literature regarding associations between insomnia and suicidal thinking and behavior in schizophrenia.

Study limitations include the self-reported measures of insomnia and suicidal thinking and behavior, and non-standardized antipsychotic treatment prior to entry into the CATIE trial. We controlled for PANSS total score in the primary analyses, suggesting the associations between insomnia and suicidal thinking and behavior were not driven by illness acuity. The pattern of findings was unchanged in a post hoc analysis of inpatient versus outpatient status at study baseline. Although the CDSS items for terminal insomnia and suicidal ideation are scored on a 4-point Likert scale (absent, mild, moderate, severe), we dichotomized these measures as yes/no variables (1) for consistency with the other self-report measures (initial/middle insomnia and suicide attempt in the past 6 months) and (2) because small numbers of subjects with moderate and severe ratings delimited comparisons across a larger number of categories. Another limitation is the absence of available longitudinal data on insomnia in the CATIE trial, which also precludes the ability to make inferences regarding the temporality of observed associations. Future large, longitudinal studies are needed to disentangle these associations. These studies should also assess for comorbid sleep disorders (eg, obstructive sleep apnea). Although the CATIE trial was designed as an effectiveness trial with broad inclusion criteria to increase generalizability, subjects may not be fully representative of the general patient population with schizophrenia. Data were not available on schizophrenia subtypes in the CATIE trial, although it is plausible that associations between insomnia and suicidal thinking and behavior may vary by illness subtype. A review of risk factors for suicide in schizophrenia found strong associations with increased positive symptoms, particularly auditory hallucinations and delusions, and low negative symptoms.[10] These findings are consistent with evidence for lower suicide risk in patients with primary, enduring negative symptoms.[28] This raises the possibility of increased risk for suicidal thinking and behavior in patients with paranoid schizophrenia and insomnia, compared to other schizophrenia subtypes.

A number of different psychological and physiological mechanisms that may mediate the association between insomnia and suicide in psychiatric disorders have been proposed, including cognitive distortions and dysfunction, serotonergic dysfunction, hyperarousal, and hypothalamic-pituitary-adrenal (HPA) axis dysfunction.[29–31] These mechanisms are potentially relevant to patients with schizophrenia. For example, positive symptoms may interfere with sleep, and patients may have associated cognitive distortions.[32] Schizophrenia (and clinical high risk for psychosis) is also associated with misalignment of circadian rhythms in sleep-wake and melatonin cycles, which may contribute to insomnia.[4,5,33] Circadian clock gene expression is also altered in patients with schizophrenia.[34] Thus, mechanistic studies in this area are also warranted.

Previous studies of suicidal thinking and behavior in schizophrenia did not focus on associations with the phase of insomnia (ie, initial versus middle versus terminal). Outside of schizophrenia, one study[35] found that adults with melancholic depression and suicide attempt during the current episode had higher rates of middle and terminal insomnia than those who never attempted suicide. Another study[36] in adolescents found that terminal insomnia was a significant predictor of current suicidal ideation. A study by Del-Monte and Graziani[37] showed the importance of different types of suicidal thoughts (eg, anticipatory, relief-oriented, and permissive beliefs) and how they relate to suicidal behavior. These different kinds of thoughts could be related differently to phases of insomnia. Characterization of suicidal thoughts in patients with insomnia and schizophrenia could inform potential treatment approaches for these patients (eg, cognitive-behavioral therapy for insomnia). Thus, future studies should consider associations between phase of insomnia and suicidal thinking and behavior in schizophrenia, as well as specific types of suicidal thoughts.

A recent online survey of clinicians found that although sleep disturbances are commonly reported in patients with schizophrenia, < 20% of clinicians formally assessed these symptoms. Future studies should also employ standard instruments in the assessment of insomnia (eg, ISI[38]) and circadian rhythm dysfunction (eg, Morningness-Eveningness Questionnaire[39]), which are brief and easily administered, increasing their relevance to clinical practice.

Given associations with greater levels of psychopathology, the present findings also suggest that insomnia may represent an important treatment target in schizophrenia, just as early evidence suggests that treatment of insomnia may help resolve suicidal ideation in patients with major depressive disorder.[40] We found that terminal insomnia was significantly positively correlated with PANSS anxiety, as well as depression as measured by both the PANSS and CDSS. Given evidence for a role of the stress system, including HPA axis dysfunction, in anxiety and depression, our findings also underscore the need for recognition and treatment of these symptoms in patients with schizophrenia.[41] We note that the strength of associations between insomnia and psychopathology was modest and warrants replication in other samples.

There is some evidence for pharmacologic and nonpharmacologic treatments for insomnia in patients with schizophrenia, including sedating antipsychotics, melatonin, eszopiclone, and cognitive-behavioral therapy for insomnia.[42,43] There is evidence that treatment with first- and second-generation antipsychotics is associated with improvements in sleep time, efficiency, and quality.[44,45] There is also evidence that long-term (>1 year) clozapine monotherapy is associated with stabilization of rest-activity cycles.[46] Interestingly, in the International Suicide Prevention Trial (InterSePT) of high-risk patients with schizophrenia, there were significantly fewer suicide-related outcomes in patients treated with clozapine versus olanzapine, and insomnia was significantly less likely to be reported as an adverse effect in patients treated with clozapine.[47] Whether beneficial effects on insomnia contribute to the antisuicidal properties of clozapine warrants further investigation. Subjects in this phase of the CATIE trial were not treated with clozapine. There is also evidence that long-acting injectable antipsychotics may moderate a number of key risk factors for suicide in schizophrenia, including adherence, psychopathology (eg, command hallucinations, agitation, or motor restlessness), and illness relapse, thereby mitigating risk.[48] Interestingly, higher levels of insomnia before antipsychotic withdrawal predict worsening psychopathology following antipsychotic discontinuation.[49] This represents an important potential issue given the high prevalence of medication nonadherence in schizophrenia and demonstrates a possible advantage of long-acting injectable antipsychotics. There is evidence for the efficacy of cognitive-behavioral therapy for insomnia in schizophrenia.[50–53] A small, randomized trial found that adjunctive eszopiclone was associated with significant improvements in insomnia and cognition in schizophrenia but was not associated with improvements in psychiatric symptoms, although subjects were clinically stable at study baseline.[54] In addition to non-standardized antipsychotic treatment prior to study entry, another important consideration is potential changes in patterns of pharmacologic treatment of schizophrenia, including potential increased use of adjunctive treatments for insomnia, long-acting injectable antipsychotics, and clozapine, since the period of enrollment for the CATIE trial (2001–2004). It would be interesting to investigate effects of these changes on both insomnia and suicidal thinking and behavior in patients with schizophrenia.

Our findings provide additional evidence that formal assessment of insomnia is relevant to the clinical care of patients with schizophrenia as an indicator of suicidal thinking and behavior, as well as symptom severity. More broadly, the findings underscore the need for comprehensive suicide risk assessment in patients with schizophrenia, including identification and vigilant monitoring of risk factors, treatment of affective symptoms and substance use comorbidity, and promotion of treatment adherence.[10,15]

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Editor's Note: We encourage authors to submit papers for consideration as a part of our Focus on Suicide section. Please contact Philippe Courtet, MD, PhD, at pcourtet@psychiatrist.com.