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Sleep Architecture Parameters as a Putative Biomarker of Suicidal Ideation in Treatment-Resistant Depression

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Abstract

Background—Disturbed sleep may confer risk for suicidal behaviors. Polysomnographic (PSG) sleep parameters have not been systematically evaluated in association with suicidal ideation (SI) among individuals with treatment-resistant depression (TRD).

Methods—This secondary data analysis included 54 TRD individuals (N=30 with major depressive disorder (MDD) and N=24 with bipolar depression (BD)). PSG sleep parameters included Sleep Efficiency (SE), Total Sleep Time (TST), Wakefulness After Sleep Onset (WASO), REM percent/latency, and non-REM (NREM) Sleep Stages 1-4. The Hamilton Depression Rating Scale (HAM-D) was used to group participants according to presence or absence of SI. Sleep abnormalities were hypothesized among those with current SI. ANOVA analyses were conducted before (Model 1) and after adjusting for depression (Model 2) and diagnostic variables (Model 3).

Results—Significant differences in PSG parameters were observed in Model 1; those with SI had less NREM Stage 4 sleep ($p<.05$). After adjusting for central covariates, Models 2 and 3 revealed significantly less NREM Stage 4 sleep, lower SE ($P<.05$), and higher WASO ($P<.05$) among those with SI. BD participants with SI also had less NREM Stage 4 and more NREM Stage 1 sleep.

Limitations—1) a predominantly white sample; 2) exclusion of imminent suicide risk; 3) concomitant mood stabilizer use among BD patients; and 4) single-item SI assessment.

Conclusions—Independent of depression severity, SI was associated with less NREM Stage 4 sleep, and higher nocturnal wakefulness across diagnostic groups. Sleep may warrant further investigation in the pathogenesis of suicide risk, particularly in TRD, where risk may be heightened.

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Keywords

Sleep architecture; suicide risk; depression; bipolar disorder; treatment-resistance

Introduction

Worldwide, suicide accounts for nearly one million deaths annually and contributes significantly to global disease burden (World Health Organization (WHO), 2014). Given its overwhelming public health significance, suicide prevention has been named a national imperative by the Institute of Medicine (IOM), with calls to action to delineate evidence-based risk factors that advance suicide prevention (Institute of Medicine (IOM), 2002; Office of the Surgeon General National Action Alliance for Suicide Prevention, 2012). Despite unprecedented improvements in mental health awareness and global strategies for suicide prevention, however, suicide rates have remained alarmingly intractable over time and, in the United States, have recently increased (Centers for Disease Control and Prevention (CDC), 2014; Curtin et al., 2016; Griffiths et al., 2014; World Health Organization (WHO), 2013). This highlights the urgency to identify new risk factors and biomarkers that may enhance suicide surveillance and the development of novel therapeutic targets for suicide prevention (Chesney et al., 2014; Oquendo et al., 2014). Such efforts particularly hinge on identifying visible, modifiable risk factors for suicidal behaviors.

Sleep complaints are listed among the top 10 warning signs of suicide by the Substance Abuse and Mental Health Services Administration (SAMHSA) (National Mental Health Information Center, 2005), and research suggests that sleep disturbances may increase risk of suicide outcomes (Bernert and Joiner, 2007; Pigeon et al., 2012). Psychological autopsy studies indicate that over 90% of suicide decedents have at least one psychiatric condition—if not multiple medical conditions—at the time of death, with mood disorder diagnoses most commonly conferring risk (Bertolote et al., 2004; Cavanagh et al., 2003). Even so, preliminary research suggests that sleep complaints may be associated with risk for suicidal behaviors independent of affective episode or depressed mood and, in some cases, outperform risk associated with depressive symptoms (Bernert et al., 2005a; Bernert et al., 2014; Goldstein et al., 2008; Ribeiro et al., 2012; Sjostrom et al., 2009; Wong and Brower, 2012).

Electroencephalograph (EEG) sleep parameters appear to predict rapid antidepressant treatment response, and have previously been proposed as a marker of synaptic plasticity within antidepressant treatment (Duncan et al., 2013a; Duncan et al., 2013b). Despite preliminary support for its utility as a possible biomarker of risk and treatment target, most studies investigating the link between sleep and suicide, to date, have evaluated subjective sleep disturbances, such as insomnia, nightmares, and poor sleep quality (Bernert et al., 2015). A search for objective, reliable biomarkers for elevated suicide risk has generated mixed results, underscoring the potential significance of sleep as a transdiagnostic marker and suicide risk factor (Ahmadpanah et al., 2015; Shakeri et al., 2015). Objective sleep measures, such as EEG sleep parameters, have not been systematically evaluated in relationship to elevated risk for suicidal symptoms and behaviors, and within bipolar (BD)

depression and major depressive disorder (MDD) in particular. Both disorders are associated with heightened risk of both all-cause and suicide mortality, with the standardized mortality ratio (SMR) for depression and bipolar 21 and 28 times higher than the general population (Chesney et al., 2014; Harris and Barraclough, 1997; Tondo et al., 2003). In addition, treatment-resistant depression (TRD) is associated with a host of adverse functional outcomes, including social and occupational impairment, functional disability, and reduced quality of life (Dunner et al., 2006; Papakostas et al., 2003). Such factors emphasize the need to identify new treatment targets that may critically inform the development of novel therapeutics in suicide prevention.

Both sleep disturbances and suicidal behaviors cut across psychiatric illnesses, pointing to their potential neurobiological importance in the pathogenesis of risk. Based on both scientific and clinical rationale, the present study investigated polysomnographic (PSG) sleep parameters in association with suicidal ideation (SI) among TRD patients with MDD or BD. SI is a risk factor for future suicide attempts, as well as risk for death by suicide (Lewinsohn et al., 1996; May et al., 2012). Based on previous findings from reports evaluating subjective sleep disturbances and current suicidal symptoms (Bernert et al., 2005b; McCall et al., 2010; Nadorff et al., 2011), we hypothesized that the presence of SI would significantly distinguish EEG sleep parameters among participants, with greater sleep architecture abnormalities expected among those endorsing current suicidal symptoms compared to those without.

Critical to this newly-emerging literature, a central methodological issue in the study of sleep and suicide risk has been a failure to control for severity of depression as a possible confounding factor. Given that sleep disturbances and suicidal symptoms are shared diagnostic criteria for MDD and BD, and because depression is among the strongest predictors of suicide risk, adjusting for the severity of depressive symptoms is considered crucial to establishing sleep disturbance as a valid, independent suicide risk factor (i.e., versus a mere correlate of depression). Extant studies that address this methodological issue suggest that subjective sleep disturbances serve as an evidence-based, independent risk factor for SI, suicide attempts, and suicide death (Bernert et al., 2015). However, no study has previously evaluated this relationship using objective sleep parameters within the context of TRD. Thus, the present study sought to investigate EEG-assessed sleep in association with current SI, adjusting for depression severity as a central covariate. We also aimed to examine this relationship by diagnostic subgroup. The present study was a secondary data analysis drawn from the pretreatment phase of a series of clinical trials evaluating the use of ketamine in TRD (Ibrahim et al., 2012; Zarate Jr et al., 2012).

Methods

Participants

Participants included 54 individuals who took part in a series of clinical trials (NCT00024635) evaluating the use of ketamine, an N-methyl-D-aspartate (NMDA) receptor antagonist, in TRD (Ibrahim et al., 2012; Zarate Jr et al., 2012). The current sleep study was conducted in the pretreatment phase of this trial, prior to ketamine infusion. Before enrolling in the study, participants aged 18-65, were assessed for a diagnosis of MDD or BD using the

Structured Clinical Interviews for the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) for Axis I Disorders (SCID-I)—patient version (First et al., 2002). All participants were experiencing a current major depressive episode (lasting > 4 weeks) and had previously not responded to at least two different antidepressants, as assessed by the Antidepressant Treatment History Form (ATHF) (Sackeim, 2001). BD patients were additionally required to not have responded to a prospective open trial of a mood stabilizer while at the NIMH (at least 4 weeks of therapeutic levels of either lithium or valproate [serum lithium, 0.6-1.2 mEq/L; or valproic acid, 50-125 µg/mL]). All patients had a Montgomery-Asberg Depression Rating Scale (MADRS) score of ≥ 20. Exclusion criteria included: (1) the presence of psychotic features, (2) a DSM-IV diagnosis of drug or alcohol abuse or dependence in the last 3 months, or (3) the presence of an unstable, serious, medical illness. Female subjects could not be pregnant or nursing. All participants were free of psychotropic medications (including benzodiazepines), or drugs with CNS effects, for at least 2 weeks prior to assessment (5 weeks for fluoxetine), with the exception of mood stabilizers among BD participants (n=18, lithium, n=6; depakote). Cigarette use was permitted during the trial, but alcohol use was not. Sleep disorders, such as sleep apnea or restless leg syndrome, were not exclusion criteria for study, unless participants were unable to withdraw from treatment (e.g. unable to stop use of CPAP). Participants were determined to be in good health, as determined by medical history, physical examination, blood labs, electrocardiogram (ECG), chest x-ray, urinalysis, and toxicology screening.

Procedures

Participants were invited to take part in an EEG sleep study at the NIMH, conducted within the pretreatment period of a larger investigation studying ketamine as a maintenance treatment in TRD; results of this study have been reported elsewhere (Duncan et al., 2013a). Participants who met inclusion criteria were admitted to the NIMH Mood and Anxiety Disorders Research Program in Bethesda, MD. This study was approved by the Combined Central Nervous System (CNS) Institutional Review Board of the National Institutes of Health (NIH). All subjects provided written informed consent before entry into the study and were assigned a clinical research advocate from the NIMH Human Subjects Protection Unit to monitor the consent process and research participation.

The ATHF was used to assess treatment history as well as history of treatment non-response according to standard criteria within pharmacotherapy clinical trials (Fava, 2003; Sackeim, 2001). Responses to this form were used to evaluate TRD classification for study inclusion criteria. History of non-response to at least two adequate antidepressant trials was required for inclusion and enrollment in the present study.

Total scores on the Hamilton Depression Rating Scale (HAM-D) (Hamilton, 1960), a 17-item, clinician-administered measure, were used to assess depressive symptoms. Scores are summed to provide an overall index of depression severity (Hamilton, 1960). The HAM-D has been shown to be a valid and reliable assessment, used extensively as an outcome measure in depression clinical trials (Gorlyn et al., 2014; Knesevich et al., 1977; Kramer et al., 2014; Raison et al., 2013).

Current SI symptoms were assessed using the HAM-D, Item 3 (HAM-D3) (Hamilton, 1960). For suicidal symptom ratings on this measure, scores range from 0 to 4 (0 = symptom absent, 1 = feels life is not worth living, 2 = wishes he/she were dead or any thoughts of possible death to self, 3 = ideas or gestures of suicide, and 4 = attempts at suicide). Participants were subsequently grouped according to endorsement of presence (HAM-D3 score > 1) versus absence (HAM-D3 score = 0) of SI symptoms. This method (i.e., categorizing risk by presence (non-zero score) or absence of SI symptoms) has been used previously to distinguish those at elevated risk for suicide (Alexopoulos et al., 1999; Desseilles et al., 2012; Sabo et al., 1991; Trajkovic et al., 2011), including in the STAR*D study (Claassen et al., 2007; Zisook et al., 2009); wherein 63% of those with MDD reported mild SI.

Sleep Parameters—Following a one-night adaptation, whole-night EEG sleep recordings were assessed. The current sleep study required that participants not nap during the 3 days prior to PSG assessment, which was monitored by nursing staff. Two EEGs (C3/A2 and C4/A1), two electrooculograms, and one submental electromyogram, were recorded using a Nihon-Kohden system (Neurofax Sleep v. 05-50; Nihon Kohden Corporation, Japan) and Polysmith Acquisition and Review software (v. 4.0.25.0) with a 200 Hz sampling rate. Sleep EEGs were visually scored by reviewers in 30-second epochs according to established criteria (Rechtschaffen and Kales, 1968). Reviewers were blind to participant and night of the study. The following PSG sleep indices were assessed as primary parameters: *sleep efficiency* (SE; percent of time spent awake/time spent in bed), *rapid eye movement (REM) latency* (REM latency; minutes from sleep onset to REM onset), *wakefulness after sleep onset* (WASO; minutes awake following sleep onset for the duration of the sleep period), *total sleep time* (TST; sleep duration, in hours), *percent of REM sleep* (REM %; time spent in this sleep stage, as a percentage), and *duration of non-rapid eye movement* (NREM) Stages 1-4 (NREM Stages 1-4; minutes spent in each NREM sleep stage).

Statistical Analysis

Spearman correlations were employed to descriptively assess relationships between SI and PSG parameters, where the full range of ideation score was used. An Analysis of Variance (ANOVA) framework was used to test hypothesized main effects, in which mean differences in PSG sleep parameters were expected according to the presence or absence of current SI symptoms. Three separate models were used to evaluate the association between sleep parameters and SI, both before and after adjusting for central diagnostic and depression covariates. *Model 1* assessed symptom relationships before adjusting for central covariates; *Model 2* assessed the impact of depressive symptoms as a covariate with sleep parameters; and *Model 3* added diagnosis (BD or MDD) as a factor. IBM SPSS software, Version 22.0.0.2 was used for all analyses. Significance was evaluated at $p < 0.05$, using two-tailed tests.

Statistical Analysis—Model 1—HAM-D3 constituted the independent grouping variable (1 = yes, 0 = no), representing the presence or absence of HAM-D-assessed SI. PSG sleep parameters constituted the dependent measures in separate ANOVA tests, which

included SE, REM latency, WASO, TST, REM %, and time spent in NREM Sleep Stages 1-4. Model 1 assessed symptom relationships before adjusting for central covariates.

Statistical Analysis—Model 2—Sleep parameters were next assessed in separate models to evaluate the impact of depression as a central covariate. To evaluate sleep parameters according to the presence of current SI, the same variable structure above was used. Using an ANCOVA framework to evaluate how the association between current suicidal symptoms and PSG parameters may vary by severity of depression, adjusted HAM-D total score was added as a central covariate in Model 2. Consistent with past studies, overlapping sleep and suicidal items (items 3, 4, 5, and 6) were removed from the calculation of the HAM-D total score to avoid collinearity effects (Bernert et al., 2014; Smith et al., 2004; Wong and Brower, 2012). To prevent confusion from the HAM-D total, this variable will be referred to as the HAM-D-Adjusted (HAM-DA) total.

Statistical Analysis—Model 3—In the third model, diagnosis (BD or MDD) was added as a factor, and the interaction term was included to evaluate how the relationship between current SI symptoms (their presence or absence) and PSG parameters may vary by diagnostic subgroups. The main effect of HAM-DA was included in the model.

Results

Sample characteristics for the 54 participants are presented in Table 1. All subjects had a confirmed clinical diagnosis of TRD MDD ($n = 30$) or BD ($n = 24$). During a brief intake assessment, a large proportion of participants endorsed a history of past suicide attempts and previous psychiatric hospitalizations, as well as a family history of suicide, mood disorder diagnoses, and alcohol dependence. The average age of onset and length of illness reflected a more severe course, consistent with TRD criteria.

Table 2 presents descriptive statistics for primary variables. As expected, HAM-D total scores revealed depressive symptoms in the moderate to severe clinical range. For PSG parameters, means indicated reduced sleep duration across the sample, along with increased nocturnal wakefulness as evidenced by higher WASO and reduced time in REM and NREM Sleep Stages 3 and 4. In comparison, results revealed mean SE statistics within the normal range, yet short sleep overall ($M = 6.07$ hours TST). Comparable findings were observed for time spent in NREM Sleep Stages 1 and 2. For HAM-D Item 3, endorsement of current SI was present in 57% of the sample ($n = 31$). Inter-item correlations between PSG variables, depressive symptoms, and SI revealed significant symptom relationships between variables; an inter-correlation matrix is presented in Table 3.

Analyses of main effects revealed partial support for study hypotheses. In *Model 1*, sleep parameters were first evaluated in association with suicide risk, unadjusted for diagnosis or severity of depression. Results revealed a significant mean difference for only one sleep index: less NREM Stage 4 sleep was observed among those endorsing current SI ($p < .05$) compared to those without SI. *Model 2*, which controlled for the severity of depression, revealed similar findings. Participants endorsing SI (as assessed via the HAM-D3) displayed significantly less NREM Stage 4 sleep and SE. *Model 3*, which added diagnosis as a second

factor, found that the presence of SI was associated with significantly less time spent in NREM Stage 4 sleep, more WASO, and significantly less SE ($p < .05$; see Table 4).

An interaction between SI and diagnosis for NREM Stage 1 sleep in *Model 3* was significant ($F_{1,49} = 7.97$, $p = .007$). Specifically, post-hoc tests suggested that individuals with BD who endorsed current SI had significantly more NREM Stage 1 sleep minutes than BD participants without current SI ($p = .02$). No significant difference was noted in this sleep stage among MDD participants ($p = .19$). A significant interaction was also revealed for NREM Stage 4 sleep ($F_{1,49} = 9.01$, $p = .004$; see Figure 1). Compared to those without current SI, BD participants with SI spent significantly fewer minutes in NREM Stage 4 sleep ($p < .001$), whereas no such difference was observed among MDD participants ($p = .92$). Effect sizes appeared more pronounced among those with BD. For example, for the full sample, the observed effect size for SI to NREM Stage 1 sleep, NREM Stage 4 sleep, WASO, and SE were $d = 0.28, 0.85, 0.60$, and 0.65 , respectively; whereas within BD, effect sizes were $d = 0.71, 1.13, 0.74$, and 0.73 . In general, both SI groups spent less time in NREM Stage 4 sleep (i.e., low TST), particularly MDD participants. No other interactions were significant.

Post-Hoc Analyses

In a post-hoc analysis, HAM-D insomnia items were added together, and Spearman correlations were run to evaluate their correspondence with PSG measures. As expected, lower insomnia was significantly associated with greater sleep efficiency, REM Time, REM %, Stage 2 Time, Stage 2 %, TST, and lower WASO ($p < .05$). No other variables were significantly correlated with the total insomnia score. Demographic variables of gender ($r = -.43$, $p < .05$), but not age ($r = -.12$, $p > .05$), correlated with Stage 4, wherein males showed less time spent in this particular sleep stage. However, adding gender, as well as HAM-D insomnia items, as a covariate did not eliminate group differences from the initial models.

Discussion

To our knowledge, this study is the first to evaluate SI in the context of an objective assessment of sleep within a TRD sample with BD or MDD. We found that current SI was associated with sleep architecture abnormalities, including less NREM Stage 4 sleep and higher nocturnal wakefulness, compared to participants who did not currently endorse SI. Across both diagnostic groups, participants demonstrated considerable clinical severity (see Table 1) and sleep disruption compared with age-stratified findings from nonclinical populations and normative sleep studies (Ohayon et al., 2004). Specifically, average PSG sleep parameters reflected fragmented sleep and reduced sleep duration (e.g., TST of only 6 hours), substantial wakefulness following sleep onset, and reduced time spent in the deeper stages of sleep, such as NREM Stage 4. Such results provide new PSG data that describe sleep parameters among TRD participants, underscoring the potential need for sleep treatment in this population.

Results suggested that sleep architecture abnormalities were greatest in TRD participants who endorsed current SI compared to those without such symptoms. Less time spent in NREM Stage 4 sleep was evident across the full sample, but particularly apparent among those endorsing current suicidal symptoms. Importantly, this finding was observed even after

adjusting for depressive symptoms as a central covariate—a perhaps too-stringent test, but one which converges with recent subjective reports (Bernert et al., 2015). This finding distinguishes PSG sleep parameters as a putative biomarker of risk for current SI—independent of depressed mood—and builds on the subjective sleep literature identifying such complaints as evidence-based risk factors for suicide (Bernert et al., 2015). Last, significant differences were observed by diagnostic subgroup. For example, after accounting for depression and central diagnostic covariates, current suicidal symptoms were tied to less time spent in the deeper stages of sleep, such as NREM Stage 4, and more time spent in lighter sleep stages, such as NREM Stage 1. However, this effect appeared more pronounced among those with BD, with slightly larger effect sizes observed for this subgroup.

While preliminary, our findings are consistent with recent clinical and nonclinical investigations of subjective sleep disturbances, indicating sleep problems as an empirical risk factor for SI, suicide attempts, and suicide death, even after adjusting for severity of depression (for a review, see (Bernert et al., 2015). By comparison, of sixteen total studies that have evaluated PSG and suicide risk, only one included depression severity as a covariate (Keshavan et al., 1994). To our knowledge, this study is the first to evaluate PSG and current suicidal ideation covarying for depression severity among a TRD sample. This extends past research by using an objective index of sleep, evaluated among a group at considerably heightened risk. Given a lack of correspondence observed in past reports between objective and subjective sleep assessments (Bianchi et al., 2013; Dorsey and Bootzin, 1997; Frankel et al., 1976; Vanable et al., 2000; Zucconi et al., 1996), our findings emphasize the potential importance of objectively-evaluated differences in sleep parameters among those experiencing current SI. Further research, evaluating whether this may reflect underlying pathophysiological differences among those at risk for SI, in comparison with other important risk factors for suicide (Pompili et al., 2013b; Ribeiro et al., 2012), is recommended.

Along these lines, a recent latent class analysis in a large study of adolescents (N=12,395) identified subjective sleep disturbances as one feature of a newly-identified “invisible risk” category for suicidal behaviors (Carli et al., 2014). Those with reduced sleep and high sedentary behaviors showed equivalent rates of depression, anxiety, and risk for SI and suicide attempts, relative to the “high risk” group. Such risk was not otherwise evident in other areas of functioning, and observed despite the absence of more traditional risk factors associated with this “high risk” grouping (e.g., substance use). Although conducted among youth versus adults, this converges with our findings to support future evaluation of sleep as a potential underlying neurobiological factor in suicide prevention.

To date, few known reports have evaluated EEG sleep parameters in relation to suicidal ideation. In contrast to the results of the present study, two studies reported differences in REM sleep parameters (e.g., reduced REM, more phasic REM) among those with current SI and among those with a history of past suicide attempts; although this may be due to distinct differences in design and sample methodology. Specifically, one report focused exclusively on women, yet failed to adjust for depression (Agargun and Cartwright, 2003). Whereas the other investigation controlled for depression, yet evaluated EEG in association with past suicide attempts among those with psychotic depression (Agargun and Cartwright, 2003;

Keshavan et al., 1994)—a diagnosis that served as a basis for exclusion in the present study. A central goal of the current study was to therefore evaluate PSG parameters in association with current SI, adjusting for depression as a central covariate. Methodologically, this is considered fundamental to establishing evidence-based risk factor for suicide, given the importance of depression in suicide. Results indicated initial support for this test. However, these appeared limited to SE, WASO, and NREM Stage 4 PSG sleep parameters, indicating greater nocturnal wakefulness, sleep fragmentation, and restricted time spent in SWS, as well as more time spent in the lighter stages of sleep among those with current SI.

According to inter-item correlations and the specificity of the current findings, SE and WASO were highly correlated, suggesting that risk may be conferred as a function of nocturnal wakefulness. In contrast, NREM Stage 4 sleep was not highly correlated with other sleep variables, yet significantly associated with SI across all three models. This may suggest greater specificity of effects regarding NREM Stage 4 sleep on SI (i.e. relative to SE and WASO, which appeared more distinct to model tests or diagnostic categories). Such findings may highlight future areas of study to inform the way in which risk is conferred, and whether this may occur directly or indirectly, through other sleep variables or co-occurring risk factors. Replication is warranted, to address these questions, among both TRD samples and those with less severe, non-treatment-refractory depression.

Regarding clinical significance, sleep disturbances are overrepresented among mood disorders, unlikely to resolve with efficacious psychotherapy and pharmacological treatments, and predict poor prognostic outcomes for these disorders (Carney et al., 2011; Troxel et al., 2012). This includes increased risk of recurrence for future depressive episodes (Karp et al., 2004; Ng et al., 2015) and, for BD patients, decreased treatment adherence and increased rates of relapse (Kupfer, 2005). Given our results, and prior research demonstrating that insomnia is associated with high-lethality suicide attempts in an emergency department sample (Pompili et al., 2013a), our findings provide rationale for developing a sleep-focused intervention for suicidal behaviors among high-risk populations. Because sleep complaints and suicide risk cut across psychiatric illnesses, future research may benefit from evaluating sleep as a shared neurobiological factor to inform mechanisms of risk. Previous studies report that specific elements of EEG slow wave sleep (e.g. slow wave amplitude and slope) may serve as central biomarkers of synaptic plasticity and predict ketamine-induced rapid antidepressant treatment effects, as well as associations with brain derived neurotrophic factor (BDNF) (Duncan et al., 2013a; Duncan et al., 2013b). In this way, sleep may warrant additional investigation as a potential biomarker in the pathogenesis of risk for suicide outcomes.

Several limitations in the present study should be noted. First, a single item constituted our primary assessment of SI symptoms. Although this approach has reliably distinguished those at risk for suicide in previous studies (Alexopoulos et al., 1999; Sabo et al., 1991; Zisook et al., 2009) (Lewinsohn et al., 1996; May et al., 2012)—replication using a validated assessment of suicidal symptoms is necessary. Given that, similar to most clinical trials, imminent risk for suicide was an exclusion criterion in the present study, future studies are needed to evaluate PSG parameters among individuals at acute risk for suicide, such as within emergency settings. Next, individuals with BD were receiving mood stabilizers,

which could have contributed to differences in sleep. This is unlikely to account for our findings for several reasons. First, such medication use would be expected to result in key differences in overall sleep parameters rather than changes specific to SI, as observed here. Second, mood stabilizers, including lithium are associated with *increased* rather than decreased time spent in SWS (Friston et al., 1989; Harding et al., 1985; Harvey, 2008; Kupfer et al., 1974), yet we observed the opposite in the present study. Future studies, among larger, medication-free samples of patients with TRD are nonetheless needed to confirm effects and guide further research. An additional constraint is this study's cross-sectional design, which prevents assessment of the directionality of the findings. Longitudinal research is recommended. Finally, sleep disorders, such as obstructive sleep apnea, did not serve as a basis for exclusion in this study, which is a suggested focus for future research.

Despite such constraints, this study possesses several notable strengths, including systematic and objective evaluation of sleep among a highly treatment-refractory group. Current SI symptoms, proximal to sleep assessment, is an additional strength. Previous PSG studies evaluating suicide risk focused on assessment of past or recent (>1 year) suicidal thoughts (Agargun and Cartwright, 2003; Bernert et al., 2015) versus current SI, as examined here. Next, depression severity was a central covariate in this study, which was likewise conducted within a controlled, drug-free clinical research setting. Next, this report is unique in its evaluation of TRD patients with unipolar or bipolar depression. Given preliminary findings that appeared distinct by diagnosis, this may guide future research—particularly in view of the well-established literature on dysregulated sleep and its relevance to relapse and antidepressant treatment response (Frank et al., 2000). Finally, our findings may be notable given the level of sleep disturbance observed across TRD participants in general, and observation that suicidal symptoms predicted key differences in EEG parameters despite this.

Conclusion

In sum, we found significant differences in sleep architecture among TRD participants with current SI versus those without, with decreased NREM Stage 4 sleep observed across the full sample in association with risk. Several sleep parameters (higher WASO and NREM Stage 1 sleep, and lower SE) were furthermore predicted by diagnostic subgroup. These findings were observed after adjusting for the severity of depression, suggesting that EEG sleep parameters may be a potential biomarker of current SI. Given recent emphasis on the assessment of biomarkers to guide risk prediction and a biosignature for suicide (Oquendo et al., 2014), our findings highlight the potential importance of sleep as a proposed neurobiological factor that may provide insights into the pathogenesis of risk. Given that sleep disturbances are visible in the weeks and months preceding suicide death (Goldstein et al., 2008), yet highly treatable (Morin et al., 2009), we recommend replication and further study of sleep as a putative biomarker and therapeutic target in suicide prevention.

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Highlights

- Suicidal ideation in treatment-resistant depression is linked with less deep sleep.
- The same group had increased nocturnal wakefulness and decreased sleep efficiency.
- Effect sizes were greater for those with bipolar than major depressive disorder.
- Sleep architecture may be a key putative biomarker in suicide prevention.

Figure 1.

Stage 4 Interaction. Interaction for non rapid eye movement (NREM) Stage 4 sleep in minutes (min) according to presence of current suicidal ideation (SI) or absence of suicidal ideation symptoms (non-SI) among patients with bipolar disorder (BD) or major depressive disorder (MDD).

Table 1

Sample Characteristics

	Full	MDD	BD
	(N = 54)	(n = 30)	(n = 24)
Demographic Information			
<i>Age</i>	46.1 (12.5)	47.4 (13.3)	44.4 (11.6)
<i>Gender (Female) %</i>	50.0	33.3	70.7
<i>Education Level (College) %</i>	46.3	56.7	33.3
Clinical Severity			
<i>Past Suicide Attempt %</i>	40.7	36.7	45.8
<i>Family History of:</i>			
<i>Mood Disorders %</i>	92.6	93.3	91.7
<i>Suicide %</i>	38.9	40.0	37.5
<i>Alcohol Dependence %</i>	33.3	36.7	29.2
<i>Psychiatric Hospitalizations %</i>	70.4	56.7	87.5
<i>History of Alcohol Dependence %</i>	35.2	23.3	50.0
<i>Age of Onset</i>	20.0 (11.1)	22.3 (12.9)	17.1 (7.9)
<i>Length of Illness (Years)</i>	26.0 (12.1)	25.1 (13.3)	27.2 (10.7)
<i>Comorbid Diagnosis %</i>			
<i>Generalized Anxiety Disorder</i>	19.6	18.5	20.8
<i>Obsessive Compulsive Disorder</i>	3.9	0.0	8.3
<i>Post-Traumatic Stress Disorder</i>	2.0	0.0	4.2
<i>Specific Phobia</i>	11.8	0.0	25.0

Note: Sample characteristics are displayed for the full sample, as well as by diagnostic subgroup. Unless represented by percentage, group means (M) and standard deviation (SD) are reported for the full sample (Full), bipolar (BD), and major depressive disorder (MDD) groups.

Table 2

Descriptive Statistics

Variable	Full (N = 54) M (SD)	MDD (n = 30) M (SD)	BD (n = 24) M (SD)
<i>Sleep Parameters</i>			
<i>SE %</i>	87.39 (11.91)	87.88 (11.61)	86.79 (12.62)
<i>WASO (m)</i>	50.4 (52.3)	47.6 (52.0)	54.0 (54.1)
<i>TST (h)</i>	6.07 (1.14)	6.03 (1.37)	6.09 (0.96)
<i>REM %</i>	21.11 (8.39)	22.53 (8.05)	19.35 (8.84)
<i>REM Latency</i>	66.8 (56.5)	49.0 (28.9)	89.0 (74.4)
<i>NREM Stage 1 (m)</i>	32.0 (21.8)	34.05 (21.29)	29.4 (22.7)
<i>NREM Stage 2 (m)</i>	227.0 (56.4)	226.2 (48.9)	227.9 (66.8)
<i>NREM Stage 3 (m)</i>	14.3 (14.9)	12.7 (14.8)	16.4 (15.4)
<i>NREM Stage 4 (m)</i>	2.8 (8.9)	0.6 (1.4)	5.5 (13.1)
<i>Sleep Onset (Clock Time)</i>	11:40 PM (44m)	11:09 PM (31m)	11:44 PM (56m)
<i>MDD Symptoms</i>			
<i>HAM-D Total (0-53)</i>	21.33 (4.54)	20.50 (4.70)	22.38 (4.18)
<i>HAM-DA Total (0-43)</i>	17.37 (3.36)	16.87 (3.36)	18.00 (1.07)
<i>Suicide Symptoms</i>			
<i>HAM-D Item-3 (0-4)</i>	1.02 (1.04)	0.97 (1.07)	1.08 (1.02)

Abbreviations: Descriptive statistics are displayed for the full sample, as well as by diagnostic subgroup. Sleep efficiency (SE), total sleep time (TST), wake after sleep onset (WASO), rapid eye movement (REM), non-rapid eye movement (NREM), Hamilton Depression Rating Scale-17 (HAM-D), and Adjusted Hamilton Depression Rating Scale-17 (HAM-DA; total HAM-D total score, adjusted for removal of overlapping sleep and suicidal symptom items). Group means (M) and standard deviations (SD) are reported for the full sample (Full), major depressive disorder (MDD) and bipolar disorder (BD) groups. For clock time variables, minutes (m) and hours (h) are reported.

Table 3

Inter-Item Correlation Matrix

No.	Variable	1	2	3	4	5	6	7	8	9	10	11
1	<i>SE</i>	NA	-	-	-	-	-	-	-	-	-	-
2	<i>WASO (m)</i>	-.97 ^b	NA	-	-	-	-	-	-	-	-	-
3	<i>TST (h)</i>	.60 ^b	-.51 ^b	NA	-	-	-	-	-	-	-	-
4	<i>REM %</i>	.51 ^b	-.49 ^b	.39 ^b	NA	-	-	-	-	-	-	-
5	<i>REM Latency</i>	-.06	.02	-.09	-.43 ^b	NA	-	-	-	-	-	-
6	<i>NREM Stage 1 (m)</i>	-.49 ^b	.48 ^b	-.06	-.14	-.23	NA	-	-	-	-	-
7	<i>NREM Stage 2 (m)</i>	.36 ^b	-.31 ^a	.65 ^b	-.09	.25	-.24	NA	-	-	-	-
8	<i>NREM Stage 3 (m)</i>	.28 ^a	-.26	.24	.07	.22	-.24	-.02	NA	-	-	-
9	<i>NREM Stage 4 (m)</i>	.25	-.22	.21	.16	-.08	-.15	-.17	.58 ^b	NA	-	-
10	<i>HAM-D Total</i>	-.18	.17	-.20	-.21	.31 ^a	-.02	-.08	.23	-.09	NA	-
11	<i>HAM-D-A Total</i>	-.13	.12	-.16	-.16	.29 ^a	-.04	-.08	.23	-.01	.98 ^b	NA
12	<i>HAM-D Item-3</i>	-.27	.27 ^a	-.17	-.09	.21	.03	-.06	.10	-.31 ^a	.56 ^b	.39 ^b

Abbreviations: Sleep efficiency (SE), total sleep time (TST), wake after sleep onset (WASO), rapid eye movement (REM), non-rapid eye movement (NREM), minutes (m), hours (h), Hamilton Depression Rating Scale (HAM-D) Total, Hamilton Depression Rating Scale-Adjusted (HAM-DA; total HAM-D total score, adjusted for removal of overlapping sleep and suicidal symptom items).

^a significance at the 0.05 level (two-tailed)

^b significance at the 0.01 level (two-tailed)

Table 4

Model Statistics for Full Sample

Variable	Mean (SD)		Model 1: Group		Model 2: Group		Model 3: Group		Model 3: Group × Diagnosis	
	SI (n = 31)	Non-SI (n = 23)	F _(1,52)	p	F _(1,51)	p	F _(1,49)	p	F _(1,49)	p
<i>SE</i>	85.21 (12.95)	90.33 (9.57)	2.55	.12	4.35	.04 ^a	5.13	.03 ^a	2.36	.13
<i>WASO (m)</i>	59.23 (54.59)	38.61 (46.41)	2.13	.15	3.53	.07	4.41	.04 ^a	3.12	.08
<i>Total Sleep Time (h)</i>	5.96 (1.08)	6.20 (1.20)	0.58	.45	0.63	.43	0.52	.47	0.52	.47
<i>REM %</i>	21.02 (7.77)	21.24 (9.16)	0.01	.93	0.00	.97	0.00	.95	0.36	.55
<i>REM Latency</i>	73.44 (57.12)	57.78 (54.47)	1.03	.32	0.16	.69	0.12	.73	0.07	.79
<i>NREM Stage 1 (m)</i>	32.31 (21.37)	31.54 (22.31)	0.02	.90	0.29	.59	0.94	.34	7.97	.007 ^b
<i>NREM Stage 2 (m)</i>	225.32 (56.94)	229.20 (55.55)	0.06	.80	0.22	.64	0.18	.67	0.06	.81
<i>NREM Stage 3 (m)</i>	13.58 (13.17)	15.37 (16.94)	0.19	.66	0.68	.41	1.05	.31	1.73	.19
<i>NREM Stage 4 (m)</i>	0.32 (1.31)	6.09 (12.90)	6.15	.02 ^a	4.87	.03 ^a	8.86	.005 ^b	9.01	.004 ^b

Data are presented as the unadjusted means (SD). Model 1 represents ANOVA results, Model 2 represents ANCOVA results with severity of depression as a covariate, and Model 3 represents ANCOVA results with diagnosis added as a factor. Groupings refer to participants endorsing current suicidal ideation (SI) compared to those without current suicidal ideation (Non-SI) symptoms, as endorsed by Hamilton Depression Rating Scale Item 3 (HAM-D3).

Abbreviations: Sleep efficiency (SE), total sleep time (TST), wake after sleep onset (WASO), rapid eye movement (REM), non-rapid eye movement (NREM), hours (h), minutes (m).

^a significance at the 0.05 level (2-tailed)

^b significance at the 0.01 level (2-tailed)