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COMMENTARY

The clinical problem of the lethality of insomnia: a new empirical exploration from a clinical trial

Commentary on Rumble ME, McCall WV, Dickson DA, Krystal AD, Rosenquist PB, Benca RM. An exploratory analysis of the association of circadian rhythm dysregulation and insomnia with suicidal ideation over the course of treatment in individuals with depression, insomnia and suicidal ideation. *J Clin Sleep Med*. 2020;16(8):1311–1319. doi:10.5664/jcsm.8508

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The risks of suicides and near suicides in patients with severe insomnia have long been obvious to practicing clinicians. While true, to demonstrate it generalizably might serve to convince implacable skeptics or to influence public policy toward more suicide mitigation. And there is always the need to understand how clinical practice may be improved, which quantitative study methods may aid. Some ecological studies[1] have been done in this area.

Insomnia has been established epidemiologically as a plausible risk factor for initiating major depression.[2,3] Now it is probably true that nonverbal animals do not commit suicide, even if depressed. In this issue of the *Journal of Clinical Sleep Medicine*, Rumble and colleagues[4] review study indicating that chronic insomnia in humans leads to higher rates of verbally acknowledged suicidal ideation. In their own prior work, Rumble and colleagues[5] conducted a randomized clinical trial focused on specifically testing whether an insomnia intervention might reduce suicidal ideation in depressed patients. They tested whether bedtime use of zolpidem would reduce suicidal ideations. Their findings indicated that use of zolpidem might indeed reduce suicidal ideations in patients at risk of major depression worsening. With the use of zolpidem, the authors were utilizing a medication broadly distained by many prescribers, although other treatments[6,7] for insomnia likely have similar benefits. The provocative implication of using zolpidem, though, is that proscribing even stigmatized sleep medications may be countertherapeutic in those patients at higher risk of suicide, with greater psychological impairment and presumably subject to greater medical stigma.[8] Even FDA guidance about sleep medications may contribute to undertreatment in severe insomnia, as it has listed some benzodiazepines as causative of suicide ideation, when there is reason to suspect that this may be at least a partial misattribution or overattribution.[9]

Here as a secondary aim, however, the authors used their highly selected sample of patients with depression and insomnia to explore possible relationships to variables that would be related to other sleep-related sleep, circadian, and seasonal measures. For assessing symptoms, they used self-reporting measures for depression, insomnia, and suicidality, but also for seasonality and morning-eveningness. They used actigraphy to obtain objective proxy measures for sleep parameters and general circadian-period activity rates. This conjoint measurement regimen is an advance in study methodology. Additionally, the authors used statistical methods to try to quantify what potential causal factors might be present, coadjusting for other factors that may also influence the outcome of suicidal ideation. This overall collection of measures might have some chance of being utilized in usual clinical practices.

The authors put forth that suicidal ideation is an urgent public health concern in relation to actual suicides, as the suicide rate has increased some recently. As a clinician, one naturally agrees that suicide prevention should be considered an important public health goal; however, compared with other latent causes of avoidable early death, suicide does not rank highly. Because insomnia and depression are conditions with higher prevalence, it was more plausible that one could find supportable findings about the mutual interdependency of insomnia and depression, with implications for public policy. However, to quantify the risk of actual suicide for targeted public policy initiatives will require more exacting methods. One will need a large enough representative sample to afford stable statistical estimates of this comparatively rare event of completed suicide. Epidemiologically, the suicide rate is something on the order of 12–30 suicides per 100,000 population, depending on subpopulations.

The population prevalence of suicidal ideation of some kind has been reported as 3.5% in employed adults,[10] but is likely higher in the ill and the unemployed. The disparity between 3,500 per 100,000 with suicidal ideas, but even with a liberal 30 per 100,000 completed suicides, means that to quantify the hazard estimate of completed suicide over relevant amounts of time, one must be able to use large, longitudinal samples to quantify the population-attributable risk of completed suicide. This quantification, here specifically about the insomnia effects, would need to be estimated while also accurately adjusting for other longitudinal or precipitating causes besides mere suicidal ideation that would also expectably be predictive of suicide.

These confounds can be by indication (ie, "what was the person's reason[11] for killing himself?") or by factor (eg, was it the hopelessness level about one's disability, the level of anxiety, or a neurobiological cause?). Such analysis can only be done with statistical modeling approaches to estimate effect sizes pertinent to deciding among targeted public health interventions. Epidemiologically it will be difficult to show insomnia as a broadly and generalizably specific cause of completed suicide, when insomnia has a prevalence of perhaps 30% in primary care clinics and depression has a 1-year prevalence of perhaps 12%, each with a female predominance of 2:1[12], with both depression and insomnia being treated variously.

This analytic problem of isolating suicidal ideation as a specific cause of suicide is analogous to trying to derive general predictions about the specific timing and location of tornados, also rare events, from, say temperature gradients within a weather system: one can expect some background, quantitatively lawful general predictions about the temperature gradients contributing to the causation of tornados amid a plenitude of other temporal variations, but it will only be quantitatively supportable if one takes into account the other possible accurately well-measured confounding causes or causal modifiers. Absent such modeling perfections, implacable skeptics can criticize modeling defects.

While their public policy appeals may be overdrawn, these authors have advanced the research methods used to deconfound causal relationships in relation to suicidal ideations. They worked with their small, but well-characterized sample, albeit with very limited external validity: as noted in the report's Table 1, the sample was comprised of notably ill individuals, approximately 1/3 of whom had prior suicidal attempts! The study exclusion criteria essentially excluded currently extreme cases of depression or insomnia for study safety reasons and excluded a variety of conditions that one normally encounters in psychiatric practice. (In our threatened tornado analogy here, this would be akin to limiting one's sample to studying only violent—but not too violent—"ideational" storms linked to the possible development of "suicidal" tornados, and pretermit considerations about exact measurement for long-term latent influences, such as the high-risk contexts for the events.) The study's sampling constraints did provide the mandatory experimental controls that made possible the groundbreaking REST-IT trial[5] from which this study data are drawn. So these constraints limit the generalizability of the study's scope of direct clinical application, but, interestingly, not of the study's conceptual scope.

The study was faced with some unavoidable limitations in its measures and empirical background, however. A longstanding problem facing research and clinical practice is how reliably and validly to distinguish insomnia as a clinical complaint that would include self-perceived daytime impairments[13], versus sleep dissatisfaction as such[14], versus lowered sleep time as such, versus presumed-normal sleep time, versus excessive sleep time felt as poor quality sleep. A second problem is to be able easily and reliably to determine the patients' individual circadian phase positions. The nearest cost-effective, easily deployable approximate measure for the objective aspects of these first 2 problems so far has been actigraphy, which the authors used in this study, having justly noted its general measurement limitations. Indeed, in a recent American Academy of Sleep Medicine meta-analytic review of actigraphy[15], there were cautions raised that actigraphy may provide distinctly different information compared with sleep logs and polysomnography in particular metrics even within clinical trials. Consequently, to avoid actual metaphysical debates about the kinds of collected temporal data, more cost-effective, consistently reliable, and valid measures for these biological variables with patients with insomnia remain to be invented for more general use than could be used in this study. The authors here have helpfully pioneered ways to analyze relevant comeasured variables statistically in the service of looking for risk factors in a clinical sample.

But as their ventures, and those of others,[16] into using seasonality measures also reminds us, a third problem is that there is little research[17] on what the autochthonous seasonal sleep neurophysiology for humans happens to be. Contemporary sleeping patterns probably are not natural patterns for the human species. We do not know comparatively what the latent side effects are, perhaps insomnia,[18] of postindustrial work, sleep, and light-exposure patterns, insofar as such patterns likely varied more seasonally in the not-too-distant past[19] than they do now. Tom Wehr over 30 years ago made the point that living in our prpetual hyper-summer conditions may affect our emotional functioning.

The authors note that they did not measure psychosocial stressors as possibly influential variables on suicidal ideation, and one would have preferred them to have some measures for anxiety or ruminations, as they are often associated with insomnia too. Unhappily, measures for depression, anxiety, and insomnia are often correlated more than 0.5 due to common semantic variance and/or general distress variance. And then it is not established that the subjunctive domains of depression, insomnia, and suicidality are psychometrically independent of each other. Nonetheless, even though it is a secondary analysis of a data set that was sampled for other primary aims, it is unlikely that early polyvariable investigations like this can first emerge otherwise. This study is well worth reviewing for both its conceptual structure and its exploratory findings about insomnia and other possible determinants of suicidal ideations and their severity. Future epidemiological and clinical studies will benefit from review of the authors' exploration here, in the service of advancing clinical care. Suicide related to insomnia is not an ignorable clinical topic.

CITATION

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DISCLOSURE STATEMENT

The author reports no conflicts of interest.