

COMMENTARY

## Do prescription hypnotic medications increase or decrease suicidality?

Commentary on Tubbs AS, Fernandez F-X, Ghani SB, et al. Prescription medications for insomnia are associated with suicidal thoughts and behaviors in two nationally representative samples. *J Clin Sleep Med*. 2021;17(5):1025–1030.

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Mehmet Y. Ağargün, MD<sup>1</sup>; Sema Ateş, MD<sup>2</sup>

<sup>1</sup>Department of Psychiatry and Sleep, Dream, and Hypnosis Research Center, Istanbul Medipol University Medical School, Istanbul, Turkey; <sup>2</sup>Department of Psychiatry, Istanbul Medipol University Medical School, Istanbul, Turkey

There has been a growing interest in the association of sleep disturbances with suicidality for 4 decades. Epidemiological and clinical research show that insomnia, hypersomnia, and nightmares are independent risk factors for suicidal behavior. Fawcett et al,<sup>1</sup> in a clinical study, suggested that insomnia was one of the “modifiable risks” for suicide. Seven years later, Ağargün, Kara, et al<sup>2</sup> showed that not only insomnia but also hypersomnia was associated with suicidal behavior in patients with major depression. With regard to the relationship between dreams and suicide, Ağargün, Cilli, et al<sup>3</sup> examined the association between repetitive and frightening dreams and suicidal tendency in patients with major depression. The patients with frequent nightmares, particularly women, had higher suicidality scores and were more likely to be classified as more suicidal than the other patients. A prospective follow-up study also reported that the frequency of nightmares is directly related to the risk of suicide in the general population.<sup>4</sup> Interestingly, only nightmares were associated with suicidal ideation, after controlling for depressive symptoms.

There are several consecutive studies examining the association between suicidality and sleep disturbances in the general population. However, only a few electroencephalographic sleep studies have examined the relationship between sleep and suicidal behavior rather than epidemiological and clinical studies. Sabo et al<sup>5</sup> compared the sleep of patients with major depressive disorder with and without a history of suicidal behavior using electroencephalography and found that those who attempted suicide had longer sleep latency, lower sleep efficiency, and fewer late-night delta wave counts than normal control patients. In another study, Ağargün and Cartwright<sup>6</sup> found a significant negative correlation between suicidality scores and rapid eye movement (REM) sleep latency and a positive correlation between suicidality and REM sleep percentage. Patients who were suicidal had a significantly shorter mean REM sleep latency and a higher mean REM sleep percentage than patients who were nonsuicidal. According to the relevant literature, we can conclude that sleep disturbances including nightmares predict suicide risk.<sup>7</sup>

Regarding suicide and sleep, the authors have seen a new trend over the past 10 years: a relationship between sleep medications and suicidal tendency. This is a relatively novel area in which there are a number of contradictions. Among sleep medications for insomnia, nonbenzodiazepine sedative hypnotics (“Z-drugs”) are the most common prescriptions. The critical question is whether these drugs (zolpidem, eszopiclone, and zaleplon) are related to suicide risk. Insomnia is a strong predictor for suicidal behavior in both clinical and community samples. However, prescriptions of sedative hypnotics are expected to be effective for treating insomnia and preventing suicide risk. These circumstances are highly challenging. A recent review<sup>8</sup> suggests that hypnotic medications are associated with suicidal ideation. This commentary also indicates 2 possible and controversial effects: an increase in suicidality because of central nervous system impairments from a given hypnotic medication, and a decrease in suicidality because of improving insomnia. Thus, researchers should clarify this contradiction.

In this issue of the *Journal of Clinical Sleep Medicine*, Tubbs and colleagues<sup>9</sup> directly address the real question regarding the associations between multiple prescription insomnia medications and suicidal thoughts and behaviors using data from 2 nationally representative survey samples. Their hypothesis was that all prescription sleep aids investigated would be associated with suicidal thoughts and behaviors and that the magnitude of these associations would be similar across medications.

They showed that individuals who were prescribed Z-drugs, trazodone, or sedative benzodiazepines were more likely to report suicidal thoughts and behaviors than those who were not. Moreover, these associations were significant after accounting for sociodemographic factors and mental health confounders. However, there are several limitations in this study. First, their data were cross-sectional and did not include follow-up measures. Second, specific sleep disorders, such as sleep apnea, nightmares, or other parasomnias, were not considered. Third, insomnia was not classified as

initial, maintenance, or terminal. This classification is an important clinical predictor for suicidal behavior. In a previous study examining the relationship between nightmares and suicide attempts comparing patients with and without melancholic features, middle and terminal insomnia were found to be related to suicide attempts in patients who were depressed with melancholic features than in those without melancholic features.<sup>10</sup> Finally, the major weakness of Tubbs et al<sup>9</sup> is that participants were not evaluated in terms of psychiatric diagnosis, particularly mood and anxiety disorders.

What about future research concerning this area? Where do we go from here? First, we should determine the underlying mechanism of the relationship between insomnia and suicidal behavior. Although a few scenarios are reinforced by published case reports and the U.S. Food & Drug Administration adverse event reports, this mechanism seems to be related to disinhibition or increased impulsivity during the time of peak drug effect for sedative hypnotics.<sup>8</sup> The effects of sedative-hypnotic drugs on cognitive and executive functions may be responsible for suicidal tendency. These drugs can also cause non-REM sleep parasomnias and sleep-related violence. The U.S. Food & Drug Administration recently added a black box warning to the prescription information and patient medication guides for Z-drugs because rare but serious injuries and death have occurred as a result of sleep behaviors, including sleepwalking and sleep driving.<sup>11</sup>

Clinicians should be careful when they use these agents. They should predict suicide risk before prescribing these drugs. The presence of depressive disorder, melancholic features, and other risk factors for suicide, such as psychotic features, agitation, history of suicide attempts, positive family history for suicide, and alcohol and substance abuse are among the factors to be considered. Cognitive status and executive functions should be assessed particularly in suspected at-risk individuals. Age is another risk factor for usage of these drugs. Insomnia is relatively common in older adults and is associated with cognitive impairment, so these medications need to be avoided in this population. Thus, these drugs should be prescribed at the lowest effective dose, if needed. Patients should be warned in terms of avoiding alcohol and drug interactions. Finally, achieving a balance between these 2 complicated issues and resolving this dilemma is an art. The authors recommend introducing a guideline for clinicians that describes steps to take when prescribing sedative hypnotics.

## CITATION

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Address correspondence to: Mehmet Y. Ağargün, MD, Department of Psychiatry, Istanbul Medipol University Medical School, Kavacik Ekinciler Street, Beykoz, Istanbul, Turkey; Email: myagargun@medipol.edu.tr

## DISCLOSURE STATEMENT

All authors have seen and approved the manuscript. The authors report no conflicts of interest.