

LETTER TO THE EDITOR

Navigating Melatonin Safety: Fact, Fiction, and Confounders

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ABSTRACT

As a chronobiotic with sleep-promoting properties, melatonin is frequently recommended by sleep medicine practitioners and widely available as an over-the-counter drug. Recently, two publications questioned melatonin safety profile in insomnia patients, with one of these receiving vast media coverage and noticeable resonance among the general public. This letter to the Editor critically evaluates such research, offering a broader contextualization within the existing body of literature about melatonin safety and insomnia-related health outcomes.

Dear Editor,

We read with great interest two recent publications reporting safety concerns about melatonin-associated risk of heart failure [1] and suicidal ideation development [2] in individuals with insomnia. These findings have gained significant international traction, with the related press releases being widely covered by global media outlets and scientific news platforms [1]. As a chronobiotic with sleep-promoting properties [3], melatonin is currently recommended for chronic insomnia and circadian sleep-wake rhythm disorders treatment across adult and pediatric populations [4–8]. Importantly, melatonin is widely used among the general population [9], mainly due to its over-the-counter availability and safety profile [10–12]. Within this context, we believe that further critical appraisal is warranted to examine such recent findings within the existing body of literature about melatonin safety and insomnia-related health outcomes. This broad attention provides a timely opportunity to discuss, in a proactive and constructive manner, key methodological issues whose clarification would ultimately benefit the entire field.

During the latest *American Heart Association Congress* (November 2025), Nnadi et al. presented preliminary results from a multinational, real-world, longitudinal study, suggesting long-term (> 365 days) melatonin supplementation to be associated with an

89% higher hazard of incident heart failure, a threefold increase in heart failure-related hospitalizations, and a doubling of all-cause mortality over 5 years in adult insomnia patients [1]. Notably, this study included 65,414 long-term melatonin users with insomnia and 65,414 insomnia patients, paired by means of propensity score matching and adjusted for demographics, 15 comorbidities, concomitant cardiometabolic drugs, laboratories, vitals, and healthcare utilization [1]. Furthermore, individuals prescribed with hypnotics different from melatonin were excluded from the study. Based on their work, the Authors question melatonin cardiovascular safety profile and underscore the need for further randomized trials addressing this topic [1]. While inconsistent with previously published longitudinal studies [10–15], this congress abstract had vast media coverage [1] and noticeable resonance among both the general public and individuals suffering from sleep disorders, resulting in a widespread concern about melatonin use to treat chronic insomnia.

Chronic insomnia is characterized by frequent and persistent self-reported difficulties in initiating or maintaining sleep, associated to daytime symptoms, such as fatigue, impaired cognitive performance, and sleepiness [16]. Longitudinal studies showed an increased risk of all-cause mortality and cardiovascular risk in insomnia patients with objective short sleep

duration and/or self-reported difficulties in initiating or maintaining sleep, compared to both individuals without insomnia [17, 18] and to insomnia patients without such sleep alterations [17–19]. Moreover, previous literature demonstrated that the persistence of altered sleep patterns, despite current hypnotic use, is associated with a greater likelihood of long-term treatments with hypnotics [13, 20, 21]. Altogether, these data suggest that insomnia patients undergoing long-term treatments with hypnotics suffer from more severe and persistent forms of the disease, which, in turn, contribute to increase cardiovascular risk and all-cause mortality. Within this context, no data about participants' sleep patterns nor insomnia severity were available in the abstract by Nnadi et al., leaving this relevant, and possibly causal, confounding factor unexplored when assessing the association between long-term melatonin treatment, heart failure risk, and all-cause mortality. In the absence of such data, it may be reasonable to hypothesize that insomnia patients who underwent long-term melatonin treatment suffered from significantly altered sleep patterns [13, 20], which may primarily drive the observed adverse outcomes [17–19]. Contrarily, patients diagnosed with insomnia who did not assume any hypnotic possibly showed mildly altered sleep patterns and, accordingly, favorable health-related outcomes [17–19]. Furthermore, the lack of data on melatonin dosage, timing, and formulation further complicates the interpretation of these findings. Since melatonin's effectiveness is highly sensitive to how and when it is administered [3, 7, 9], omitting these pharmacological variables makes the results difficult to validate.

Another recent case report paper offers the opportunity to set a methodological focus on the need to distinguish between true pharmacological causality and the inherent confounding factors, in both large-scale observational datasets and single case reports. Badrfam and Zandifar described a case of a 40-year-old individual with major depressive disorder and acute insomnia developing suicidal ideation after a single, 3 mg dose of melatonin [2]. The patient never reported suicidal thoughts before and was undergoing no treatments at the time of melatonin administration. His clinical history only included a previous depressive episode at the age of 20, which resolved after a short course of antidepressants. The current depressive episode started 1 month before the described event, which led to hospitalization. The suicidal thoughts disappeared and the mood disorder improved after olanzapine was started; fluoxetine was added after the voluntary discharge of the patient, with further improvement of his mood and sleep disturbances. Based on this clinical history, the Authors hypothesize a possible causal relationship between the single melatonin dose assumed by the patient and the development of suicidal ideation, concluding that melatonin's impact on individuals with a history of mood disorder should be carefully monitored.

Despite this being the first described case of suicidal ideation development following a single melatonin dose, the limits bound to the descriptive nature of a single case should be highlighted and contextualized within the patient's clinical history and the body of literature investigating the safety of short-term melatonin treatments. In detail, the descriptive nature of this publication prevents the Authors from inferring causal relationships [2]. Moreover, several clinical factors possibly eliciting suicidal ideation should be considered when examining the patient's clinical history, including the active,

untreated major depressive disorder, the acute insomnia development, and the psychosocial stressors which contributed to depression onset [2]. Finally, published meta-analyses of randomized, placebo-controlled studies and a large-scale, observational study do not report suicidal ideation among short-term adverse events associated with melatonin use [10–12]. In partial disagreement, a single, population-based, long-term study reported higher rates of suicide and suicidal attempt in melatonin users compared to non-users [22]. Nevertheless, such discrepancy might be explained by the lack of adjustments of the performed analyses for severity of psychiatric comorbidities, which represents a major limitation of this study and possibly represents a relevant confounder [22].

This methodological challenge is not unique to melatonin research. More broadly, previous observational studies reporting positive associations between hypnotic exposure and suicide death or suicide attempts have consistently struggled to disentangle the confounding effects of treatment and underlying psychiatric diagnoses. As highlighted in a comprehensive review of hypnotics and suicidality, retrospective and prospective cohort studies are frequently unable to separate the effect of medication exposure from the severity of the condition being treated [23]. In such contexts, the apparent association may reflect baseline psychiatric vulnerability rather than a direct pharmacological effect of the hypnotic itself. Within this methodological framework, caution is warranted before attributing causal inference to isolated case reports or observational data that do not adequately address these well-recognized sources of bias.

Beyond the methodological limitations of these studies, a significant clinical concern arises: patients with chronic insomnia may become unduly alarmed by such reports and abruptly discontinue their therapy. This “alarm effect” poses a substantial risk, as it exposes the patient to the well-documented dangers of untreated, persistent sleep disturbances [17–19].

Despite pharmacovigilance being a cornerstone of modern pharmacology, we believe that warnings about drug safety—including melatonin's—should be comprehensively discussed and appropriately disseminated, emphasizing not to prematurely equate associative findings to causal inference. Such a process should primarily aim at avoiding misinformation among healthcare professionals and the general public, paving the way towards adequate drug prescription and better health outcomes for the patients. This is especially pertinent to melatonin, which is widely available as an over-the-counter medication and routinely prescribed by physicians [9], especially in the field of sleep and circadian rhythms medicine.

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Conflicts of Interest

Ugo Faraguna is President and co-founder of Sleepacta s.r.l., a University of Pisa spin-off private company, focused on sleep diagnostics.

Data Availability Statement

The authors have nothing to report.

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