



Treatment-Resistant Insomnia: A Common Undefined Condition

Insomnia is a highly prevalent sleep disorder associated with a significant public health burden. Approximately a third of the general population experiences insomnia, and about 10%-15% of adults are labeled as having chronic insomnia.¹ Despite the decline in the use of sedative hypnotic drugs between 2015 and 2019, the emergence of COVID-19 in late 2019 has in all likelihood aggravated sleeping difficulties and accelerated the rate of new cases of insomnia, as evidenced by a 14.8% increase in sleep medication prescriptions since the onset of the pandemic, according to new data from Express Scripts.²

There is little doubt that insomnia has deleterious impact on overall quality of life. The presence of insomnia has been linked to cognitive and functional impairments, decrements in social and emotional well-being, and serious health conditions.¹ Epidemiologic evidence from the past 2 decades has demonstrated a significant correlation between insomnia and incident cardiovascular morbidity and mortality, including hypertension, coronary heart disease, and heart failure.^{1,3} Similarly, the negative effect of insomnia on mental health is evidenced by its association with the increased risk of anxiety, depression, weight gain, and alcoholism.⁴ As a result, the economic burden due to reduced productivity, higher rate of absenteeism, and increased work-related accidents is estimated in billions of dollars annually.¹

Although existing guidelines and recommendations target the management of insomnia per se, the existing body of literature does not often distinguish between treatment-naïve and treatment-resistant insomnia. Outcome assessments of randomized clinical trials involving cognitive behavioral therapy (CBT), pharmacological agents, or both, demonstrate a clinically meaningful response rate between 50% and 75%; however, these studies rarely extend beyond 12 months.⁵ At least a quarter of these patients experience a relapse within the first

year, more so in those who were on sedatives and hypnotics than those who received psychobehavioral treatment.⁶ Further, most of the clinical trials exclude patients with severe comorbid conditions or who have failed prior therapy.⁵

In clinical practice, insomnia is defined as difficulty falling asleep, difficulty in maintaining sleep, or lacking restorative sleep associated with subjective daytime sleepiness, fatigue, difficulties in cognitive functions, or mood disturbances despite an adequate opportunity for sleep. These symptoms must be present for at least 3 days per week for at least 3 months to establish the diagnosis of chronic insomnia.⁷ Prior to the publication of the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), insomnia was categorized as either a primary sleep disorder or secondary to other ailments (referred to also as comorbid insomnia), including medical and psychiatric disorders, and insomnia due to medication or drug use.⁸ This distinction was based on the premise that insomnia will resolve with appropriate treatment of the comorbid condition. However, results of clinical studies addressing comorbid insomnia showed that nearly 71% of individuals with insomnia at baseline continue to report insomnia, and more than 50% still have insomnia up to 2 years later.⁹ With the introduction of the DSM-5, the distinction between primary and secondary insomnia has been effaced. Instead, the multiaxial system that dominated the DSM-4 gave way to a unitary diagnosis of insomnia disorder with concurrent specification of clinically comorbid conditions.

Currently, there is no standardized definition for treatment-resistant insomnia. Neither the American Academy of Sleep Medicine¹⁰ or the European guideline for the diagnosis and treatment of insomnia¹¹ offers a distinct definition for those who exhibit persistent symptoms despite adequate therapy. Clinical studies have referred to these patients as having treatment-resistant insomnia, refractory insomnia, residual insomnia, or persistent insomnia.^{9,12,13} These terms are often used interchangeably. While persistent residual insomnia is applied to treatment-resistant insomnia following insomnia-targeted therapy, the term is also used to refer to persistent symptoms of difficulty initiating or maintaining sleep after management of the underlying comorbid conditions irrespective of whether treatment of insomnia per se has been provided. The

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complexity of defining “treatment-resistant” insomnia is further compounded by the fact that there are two approved modalities for managing insomnia. Although both CBT and pharmacotherapy are efficacious, at least in the short-term, the lack of response to one modality may not necessarily represent a case of treatment-resistant insomnia. Accordingly, what criteria would have to be met for insomnia treatment to be defined as resistant, and should both modalities be administered, whether consecutively or concomitantly, before the term is applied? To add another dimension to this construct, the criteria to define patients who failed insomnia pharmacotherapy have included a minimum of used prescribed hypnotics between 3 to 6 months, yet there is no time limit defined for those who received CBT. Should the definition take into consideration the duration of therapy, the number of interventions provided, or both?

There are currently several self-reported questionnaires available for assessing insomnia symptoms and severity, with built-in constructs designed to decipher the etiology of insomnia. Selecting the appropriate instrument is paramount for determining treatment resistance when comparing therapeutic regimens. With more than 31 instruments identified, the psychometrics testing for several of the available sleep instruments remains incomplete, particularly regarding responsiveness and interpretability.¹⁴ Considering that the instruments upon which the lack of response to insomnia treatment is based on are not always insomnia-specific assessment tools, comparison of different therapeutic regimens is needed.

The long-term prognosis of treatment-resistant insomnia is not well documented; however, persistent, residual, or treatment-resistant insomnia has been associated with poor quality of life and depressive relapse. Unless a precise nomenclature is established, progress toward a precision medicine in insomnia will remain limited in scope.

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