

Resistant Insomnia: A Combination of Cognitive-Behavioral Psychotherapy and Transcranial Stimulation

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INTRODUCTION

I'd like to begin this article by recalling the story of one of my patients, whose insomnia began over 10 years ago. It began after discontinuing a course of sedatives prescribed by a gastroenterologist for irritable bowel syndrome. During this time, the patient was hospitalized at the National Center for Mental Health, but psychiatrists were unable to find the right medication, as she complained of not sleeping, not feeling sleepy, unable to fall asleep, tossing and turning all night, and not feeling deep sleep. At the hospital, they tried literally every medication, but the patient still reported that the quality of her sleep was terrible and unsatisfactory. She herself noted that "the peculiarity of her case is that without medication, or with inappropriate, weak ones, she cannot fall asleep at all, never, not during the day or at night. Not after a day, not after two". This became clear, of course, even before she started taking the medications, because once the patient started taking them, she never stopped; they were simply changed and the dosage increased. She visited psychologists and psychotherapists multiple times and found the sleep restriction technique completely ineffective. When practicing it, the patient remarked that she was "dying from lack of sleep, and it wasn't helping her sleep at all. Even with medication, her sleep was very poor, not to mention exercises". The patient complained extensively about her sleep: "I have all sorts of insomnia. It ranges from severely interrupted sleep, to extremely shallow sleep, to a complete inability to fall asleep—I experience all of these". Neither neurological nor psychiatric assessments revealed any abnormalities. The patient noted that she knew all the psychological relaxation techniques, and they weren't helping her. In fact, she didn't report any tension or anxiety before bed. She noted, "I lie there, calmly, relaxed, and motionless, but with a complete inability to fall asleep. Or I fall asleep from my mountain of medications but quickly wake up. Consequently, I'm barely alive due to the severe lack of daytime sleep". The patient noted that her psychiatrist's latest regimen, which had been giving her very

intermittent and painful, but still manageable, sleep, consisted of "diazepam, azaleptin, imovane, high-dose melatonin, and atarax". Over the past month, she began trying to taper off the diazepam. Very slowly and carefully, of course, and her sleep deteriorated significantly again; in fact, she said it disappeared completely. The patient noted that the medications had seriously disrupted her brain chemistry. And that "this lack of neurotransmitters or receptor sensitivity to them is now irreversible".

The patient was rightly worried about her condition and shared her concerns [1]:

- "I take four medications (diazepam, azaleptin, imovane, melatonin). For other people with insomnia, any one of them is enough to sleep. For me, even all of this is not enough. My sleep is short, very intermittent, and sometimes very shallow. And this is with so many sleeping pills".
- "Periodically during the day, I am overcome by extreme drowsiness. So intense that it seems I'm just going to fall over and pass out. Before my insomnia, I could fall asleep in a second in this state. Now, of course, I can fall (lie down), but my brain doesn't switch off at all, even in a light nap. I lie with my eyes closed, but fully conscious, for an hour or two. I still don't have the strength to get up, but I don't sleep at all".
- "Could it be that my independent ability has completely atrophied? "Sleep. Are these irreversible changes in brain biochemistry?"
- "I sleep in short bursts and get up when I realize I can't get any more sleep. And even then, not always. For example, in the last few days, I haven't slept after 5 AM. But I lie there painfully, "relaxing", for several more hours. And before 5 AM, I wake up every hour (having fallen asleep after midnight). But this is not at all how I would like".
- "If only I could actually sleep with medication. Fall asleep and wake up a certain number of hours later. But no, either the medications don't work at all, or they give me very short and intermittent sleep. And consequently, I



can barely function during the day, I'm barely alert—my head is dull and shaky".

- "Psychiatrists are suggesting increasing the medication dosage, but I'm skeptical".

What does treatment-resistant insomnia mean? There is no standardized definition of treatment-resistant insomnia. In medical literature, it is also known as resistant insomnia, residual insomnia, or persistent insomnia. Despite the lack of a clear universal definition, the term "treatment-resistant" insomnia is often used to describe insomnia that fails to show significant improvement after treatment with two or more first-line medications. This treatment-resistant insomnia is associated with multiple physiological, psychological, and environmental factors, making it difficult to achieve sustained and effective symptom control with a single therapeutic approach. Consequently, there is a pressing need for safe and effective comprehensive treatment programs for insomnia. Transcranial direct current stimulation (tDCS) is a non-invasive cranial electrical stimulation consisting of low-intensity direct electrical current delivered to the scalp to modulate brain activity. Weak direct currents can penetrate the cranium, modulating the amplitude and orientation of the intracranial electric field, thereby inducing excitatory changes in the cerebral cortex. Anodal stimulation causes depolarization of neurons, increasing cortical excitability, while cathodal stimulation causes hyperpolarization of neurons, reducing cortical excitability. Data from numerous studies show that patients with resistant insomnia receiving TMS therapy demonstrate improved subjective sleep quality, as measured by a reduction in the Pittsburgh Sleep Quality Index (PSQI) scores [1]. A 12-week study demonstrated significant improvement in patients' sleep quality. In addition to symptom relief, a mechanistic study combining TMS with electroencephalography (EEG) showed that slow-wave stimulation synchronizes brain waves to the slow-wave frequency during sleep in patients with insomnia, potentially promoting long-term sleep stabilization. TMS has a long-lasting therapeutic effect of "addressing the root cause" through long-lasting neuromodulation, but it acts slowly. The effect of a combination of TMS, pharmacotherapy, and cognitive behavioral therapy on treatment-resistant insomnia remains unclear. In particular, whether this combination is more effective than monotherapy or medication alone requires further study. Evidence that CBT is an ideal first-line treatment for insomnia, While convincing and substantial research is lacking on treatment-resistant insomnia, the clinical case described above demonstrates that the patient harbors a number of distorted, dysfunctional, and persistent beliefs about sleep itself, including that "something is broken in the brain" and "I can't fall asleep without strong medication". Sleep hygiene education was once considered a key intervention for insomnia. Research shows that in patients with treatment-resistant insomnia aged 18 to 65, four weeks of brief behavioral treatment for insomnia (BBTI) can effectively improve sleep quality and daytime functioning [2].

The therapeutic effect of BBTI is significantly greater than that of sleep hygiene and relaxation training alone. Buysse et al. conducted a 4-week BBTI course in elderly patients with treatment-resistant insomnia, and the results showed that BBTI, like CBTI, can also effectively improve sleep quality. Scores on the ISI and PSQI scales were significantly reduced, indicating an improvement in overall sleep quality. Analysis of the sleep diary shows that improvements in SL, SE, WASO, and sleep quality were greater. Insomnia is considered a 24-hour disorder, as patients' daytime functions are as important as their nighttime sleep complaints. The ESS score, which reflects daytime sleepiness, improves with this CBT protocol. These results

suggest that in patients with insomnia who have had a poor response to hypnotic medications, 4 weeks of BBTI therapy may be more effective than sleep hygiene training. Furthermore, the effect of BBTI may be independent of the pharmacotherapeutic effect, as patients make greater progress during behavioral treatment and are less likely to adhere to medication. This protocol also reduces the time spent awake in bed (TIB). Patients with resistant insomnia have inaccurate cognitive beliefs about sleep and its impact on daytime activities, which ultimately leads to increased arousal and persistent insomnia. Traditional CBT typically involves cognitive restructuring aimed at correcting patients' cognitive misconceptions. Unlike traditional methods, BBTI focuses more on behavioral changes in patients. Even the simplest form of behavioral therapy can, to some extent, improve patients' cognitive beliefs, although this is disputed by the actual results [3].

I hypothesize that the combination of TMS and CBT may have an additive effect: the former provides a sustained neuroplastic effect, while CBT provides immediate symptom relief. Although combination therapy is theoretically attractive, it lacks robust evidence from well-designed, randomized, controlled trials. The DLPFC plays a central role in the cognitive-emotional regulation of sleep and interacts with subcortical structures such as the hypothalamus and thalamus. Dysfunctional prefrontal-limbic connectivity has been linked to increased excitability and sleep onset difficulties. Anodal stimulation of the left DLPFC with TMS is expected to increase cortical excitability, normalize aberrant neural activity, and modulate descending inhibitory control over arousal systems. Concomitant CBT and appropriately selected pharmacotherapy that enhances GABAergic neurotransmission may promote synchronization of sleep-related oscillations, particularly in the slow-wave frequency range, thereby enhancing restorative sleep. Functional MRI metrics such as fALFF, ReHo, and seed-based functional connectivity will provide insight into whether this combination therapy induces neuroplastic remodeling in prefrontal and thalamocortical networks, potentially leading to a more stable and efficient sleep architecture. Such mechanistic understanding is crucial for future personalized treatment (e.g., selecting treatment regimens for patients with specific neurofunctional phenotypes) and the development of new therapeutic targets. If proven effective, this combination therapy could transform existing treatment algorithms for treatment-resistant insomnia by implementing a personalized, mechanism-based approach. For example, the immediate pharmacological effects of zolpidem may alleviate acute symptoms and improve treatment adherence, while the neuromodulatory effects of TMS and CBT may provide long-term stabilization of neural circuits [4].

This dual mechanism may prevent relapse and reduce dependence on sedative-hypnotics. From a translational perspective, elucidating the neural correlates of treatment response may help identify imaging biomarkers predicting therapeutic efficacy, thereby supporting precision sleep medicine. In conclusion, if a patient has resistant insomnia, more detailed psychological testing should be performed, sleep apnea should be ruled out, and a combination treatment using cognitive behavioral therapy, transcranial magnetic stimulation, and personalized psychopharmacotherapy should be used.

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