Reconsidering Insomnia as a Disorder Rather Than Just a Symptom in Psychiatric Practice

Ruth M. Benca, MD, PhD, and Daniel J. Buysse, MD

This Academic Highlights summarizes a presentation given by **Ruth M. Benca, MD, PhD,** and **Daniel J. Buysse, MD,** both of whom are experts in insomnia. Together they discussed the need to reconsider insomnia as a comorbid condition rather than as a symptom of psychiatric disorders, as well as the diagnostic and treatment implications of this paradigm shift when managing patients with psychiatric disorders.

INSOMNIA AND PSYCHIATRIC DISORDERS: HOW ARE THEY CONNECTED?

Insomnia is an important consideration when evaluating patients with psychiatric disorders, because many of the symptoms of insomnia and psychiatric disorders overlap (Figure 1).[1,2] Several of the most common psychiatric disorders include symptoms of irritability, depression, inattention, cognitive impairment, and fatigue.[1] These symptoms are also associated with a number of sleep disorders.[1,2] Furthermore, insomnia and mental illness are frequently comorbid, and some symptoms may be difficult to attribute to either insomnia or the mental health disorder alone.[1,3] Roth and colleagues[3] analyzed data from the National Comorbidity Survey Replication (NCS-R) and found that sleep problems were significantly associated with *DSM-IV*[4] anxiety, mood, impulse-control, and substance disorders (odds ratio for association of any insomnia symptom with any psychiatric disorder = 4.1), and the likelihood of having sleep problems increased with the number of *DSM-IV* diagnoses.[3] Study participants also reported substantial role impairment that persisted after controlling for comorbid mental disorders, thus indicating that at least some of these patients' impairment was due exclusively to the effect of their sleep problems.[3]

ASSESSMENT OF INSOMNIA IN PATIENTS WITH PSYCHIATRIC DISORDERS

The current diagnostic criteria for insomnia according to the *Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition (*DSM-5*),[1] state that an individual should be diagnosed with insomnia if he or she experiences dissatisfaction with quantity or quality of sleep associated with difficulty initiating or maintaining sleep or with early morning awakening with the inability to return to sleep. This sleep difficulty must occur

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This Academic Highlights section of *The Journal of Clinical Psychiatry* presents the highlights of the planning teleconference series "Reconsidering Insomnia as a Disorder Rather Than Just a Symptom in Psychiatric Practice," which was held in August and September 2017. This report was prepared and independently developed by the CME Institute of Physicians Postgraduate Press, Inc., and was supported by an educational grant from Merck & Co., Inc.

CME Objective

After studying this article, you should be able to:

- Consider whether patients with psychiatric disorders and sleep symptoms have a comorbid insomnia disorder
- Tailor insomnia treatment for patients with psychiatric disorders by considering cognitive-behavioral therapy as well as drug mechanisms of action in relation to specific symptoms

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The teleconference was chaired by **Ruth M. Benca, MD, PhD,** Department of Psychiatry and Human Behavior, University of California, Irvine. The faculty was **Daniel J. Buysse, MD,** from the Department of Psychiatry, University of Pittsburgh School of Medicine, Pennsylvania.

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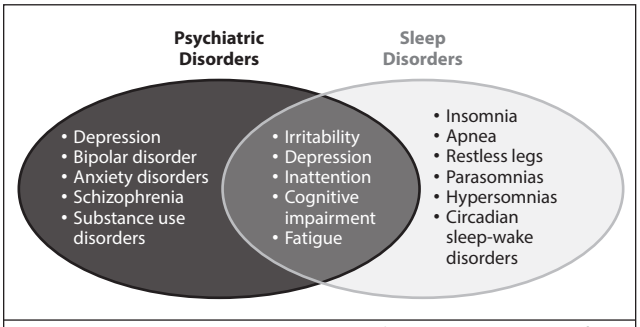
The opinions expressed herein are those of the faculty and do not necessarily reflect the opinions of the CME provider and publisher or the commercial supporter.

Figure 1. Overlap of Symptoms Between Psychiatric and Sleep Disorders[a]



[a]Based on American Psychiatric Association[1] and Palmer and Alfano[2]

at least 3 nights per week for at least 3 months, despite adequate opportunity for sleep, and the individual must experience clinically significant distress or impairment as a result. The patient's symptoms cannot be attributable to the direct physiologic effects of a substance or be better explained by another sleep-wake disorder.

An important change in the *DSM-5* is that rather than conceiving of insomnia as primary or secondary as previous criteria specified,[5] an insomnia diagnosis now simply includes a specifier to indicate the presence of a comorbidity, including medical, mental, or other sleep disorders.[1] As a result of this shift, insomnia is now considered a comorbid disorder that should be a separate focus of treatment, because in patients who have both a psychiatric disorder and insomnia, the insomnia may not necessarily improve as a result of treatment for the psychiatric disorder.

Another important implication of the shift in *DSM-5* is that it removes any assignment of causality. A mental disorder can contribute to insomnia or vice versa. The key point is that insomnia and psychiatric disorders are strongly related and should be considered risk factors for each other.[3] For example, Furihata and colleagues[6] assessed more than 6,000 older women and found that the greater the number of sleep dimensions reported as poor, the greater the likelihood of experiencing depression, both cross-sectionally and longitudinally.

In addition to using the *DSM-5* criteria to diagnose insomnia, the clinical assessment of patients with insomnia and psychiatric disorders should consist of a thorough clinical history including the following information:

- the patient's sleep-related behaviors and use of substances that might affect sleep;
- the times at which the patient goes to bed, actually attempts to go to sleep, wakes up, and gets out of bed;
- the quantity of sleep the patient obtains;
- variations in the patient's sleep schedule due to weekends or time off;
- any daytime symptoms, including fatigue, mood symptoms, and cognitive or functional impairments, as well as napping behaviors;
- social, economic, or occupational stressors that may be creating anxiety that contributes to sleep difficulties;
- the duration and chronology of the patient's sleep difficulties, as well as response to any previous treatment trials; and
- assessment for other sleep symptoms and disorders, including sleep apnea, restless legs syndrome, parasomnias, and circadian rhythm disorders.[7]

It is important to emphasize that the patient evaluation should be based on a 24-hour history and the focus should be on daytime functioning as well as the amount of sleep obtained during the night.

TREATING INSOMNIA IN PATIENTS WITH PSYCHIATRIC DISORDERS

The treatment of insomnia in patients with psychiatric disorders can include both pharmacologic and behavioral interventions. Although individuals with insomnia tend to rely heavily on sleep medications, current practice guidelines[8] recommend that all adults with chronic insomnia disorder receive cognitive-behavioral therapy for insomnia (CBT-I) as their initial treatment. If CBT-I alone is unsuccessful, a shared decision-making approach should be implemented to determine if pharmacotherapy should be added.

Behavioral Treatments

Numerous behavioral techniques have been explored for the treatment of insomnia, including CBT-I, sleep hygiene education, stimulus control, sleep restriction, and relaxation training, among others,[9] but a shortage of trained providers

exists,[10] and the demand for these services, therefore, greatly exceeds the supply.

To understand behavioral treatments, it is helpful to consider them in relation to how the brain controls sleep and wakefulness—through the homeostatic sleep drive that builds up with time awake and the endogenous circadian rhythm; the different mechanisms can be conceived of as an hourglass, a clock, and an alarm.[11] The hourglass monitors the body's duration of wakefulness, the clock regulates sleep and wake times over a 24-hour day, and the alarm influences momentary levels of arousal. Different types of behavioral treatments can be understood in terms of which part of the process they target.

Dr Buysse and his colleagues at the University of Pittsburgh School of Medicine developed a simplified version of CBT-I called Brief Behavioral Treatment for Insomnia (BBTI), which consists of 4 behavioral recommendations that can easily be implemented in primary or psychiatric practice.[12] The components of BBTI are designed to address the body's hourglass, clock, and alarm mechanisms, and include the following instructions:

1. Reduce time in bed
2. Wake up at the same time every day, regardless of sleep duration
3. Do not go to bed until sleepy
4. Do not stay in bed unless asleep

In this study,[12] the participants who received BBTI showed significantly greater improvement in multiple sleep domains compared with the control group ($P < .001$). Thus, BBTI is an effective and practical intervention that is easy to administer. Patients who do not have access to other forms of behavioral treatment may benefit from web-based CBT-I programs that are available and have been found to be effective.[13]

Pharmacologic Treatments

The use of prescription agents to treat insomnia has increased considerably in recent years.[14] This includes both US Food and Drug Administration (FDA)–approved and off-label prescribing. In addition, many individuals rely on over-the-counter treatments or substances such as alcohol to manage their insomnia.[15] Polypharmacy is common[14] and may increase the risk of drug-drug interactions in patients who are already taking pharmacotherapies for psychiatric disorders. Practice guidelines[16,17] from the American Academy of Sleep Medicine (AASM) recommend that treatments be selected based on characteristics of the patient's insomnia, comorbidities, and patient preference.

Over-the-counter agents. Many individuals with insomnia do not consult their health care providers about their sleep difficulties and rely instead on over-the-counter medications.[15] These medications include antihistamines, melatonin, and valerian; however, there are few studies assessing their use in insomnia, and the data that are available suggest that they have not been found to be particularly effective for insomnia.[17,18]

Clinical Points

- Assess patients with psychiatric disorders and sleep difficulties for a comorbid insomnia disorder
- Attempt initial behavioral therapy for all patients with comorbid psychiatric disorders and insomnia
- For patients whose insomnia does not fully remit following behavioral treatment, consider adding a pharmacologic treatment
- Select pharmacotherapy for insomnia based on the nature of the patient's insomnia, individual patient characteristics and preferences, and the presence of any comorbidities

The over-the-counter antihistamines diphenhydramine and doxylamine are commonly taken for insomnia. Available evidence from clinical trials is poor, and common side effects include drowsiness and grogginess.[17] This hangover effect can persist for up to 12 hours after administration of the agent.[19] Another problem is that people tend to use these agents routinely for insomnia, but tolerance to the sedative effects of antihistamines such as diphenhydramine has been found to develop quite quickly, in some cases after just 3 days.[20]

Melatonin is available as an over-the-counter supplement in a variety of dosages, and the dose used in clinical trials has varied considerably.[18] Regardless of the dose used, however, studies have found that melatonin use is associated with only small and not clinically significant improvements in sleep latency, total sleep time, and sleep efficiency.[17] However, melatonin may be helpful in patients whose insomnia complaints relate to problems with circadian rhythm entrainment.

FDA-approved agents. A variety of medications have been approved for the treatment of insomnia (Table 1).[17,18,21] Although practice guidelines can assist in the selection of insomnia treatments, special consideration should be given for patients with comorbid psychiatric disorders.[17,18]

The benzodiazepines that are FDA-approved for the treatment of insomnia include temazepam, triazolam, flurazepam, estazolam, and quazepam, but current practice guidelines[17] recommend only temazepam and triazolam. The other 3 approved benzodiazepines have inadequate data as well as longer half-lives that increase the risk of a next-day hangover effect and can lead to the agent building up in the patient's system with chronic use. Benzodiazepines increase sleep by binding to GABA-A receptors, but because these receptors are found throughout the brain, benzodiazepines have additional effects. Some of these, such as anxiolytic and myorelaxant effects, may be beneficial to patients, but others, such as cognitive and motor impairment, are considered adverse effects. Furthermore, because of their effect on reward circuits, benzodiazepines have the potential for abuse.[18] Temazepam is recommended for sleep onset and sleep maintenance insomnia; triazolam is recommended for sleep onset insomnia.[17]

Benzodiazepine receptor agonists (BZRAs) are the most commonly used prescription agents for the treatment of

Table 1. Overview of Drugs Indicated for Insomnia[a]

Drug	Drug Class	Elimination Half-Life, h	AASM Recommendations: Sleep Onset	AASM Recommendations: Sleep Maintenance	Important Considerations in Psychiatric Populations
Flurazepam[b] Temazepam Triazolam Estazolam[b] Quazepam[b]	Benzodiazepine Benzodiazepine Benzodiazepine Benzodiazepine Benzodiazepine	24–100 8–15 1.5–5.5 10–24 25–41	 ✓ ✓ 	 ✓ 	• May cause somnolence or next-day hangover effect • Some patients may develop dependence or tolerance, or rebound insomnia may occur with abrupt discontinuation • Increased depressant effects can occur when taken with other CNS depressants • May be habit forming and should be avoided in patients with or at risk for substance use
Zolpidem Zaleplon Eszopiclone	Benzodiazepine receptor agonist Benzodiazepine receptor agonist Benzodiazepine receptor agonist	About 2.5 About 1 About 6	✓ ✓ ✓	✓ ✓	• Some patients may develop dependence or tolerance, or rebound insomnia may occur with abrupt discontinuation • May be habit forming and should be avoided in patients with or at risk for substance use • In rare cases, complex sleep-related behaviors may occur
Ramelteon	Melatonin receptor agonist	1–3	✓		• Common side effects include sedation, dizziness, fatigue, and headache • Does not carry a risk of dependence and is, therefore, a good treatment option for patients at risk for substance abuse • Metabolized by CYP1A2; thus, CYP1A2 inhibitors such as fluvoxamine may increase plasma levels
Doxepin	Tricyclic antidepressant	8–24		✓	• Side effects may include weight gain, sedation, anticholinergic effects, or cardiotoxicity • Slight chance of inducing mania; therefore, should be used with caution in patients with bipolar disorder
Suvorexant	Orexin receptor antagonist	About 12		✓	• Side effects may include sedation, headache, abnormal dreams, sleep paralysis, or hypnagogic/hypnopompic hallucinations • No evidence of dependence or withdrawal • Should be avoided in combination with strong CYP3A4 inhibitors

[a]Data from Sateia et al,[17] Stahl,[21] and Minkel and Krystal.[18]
[b]No recommendations made due to inadequate data.
Abbreviations: AASM = American Academy of Sleep Medicine, CNS = central nervous system, CYP = cytochrome P450.

insomnia.[17] Agents in this class that are FDA-approved for the treatment of insomnia include zolpidem (both immediate- and extended-release formulations), zaleplon, and eszopiclone. Like benzodiazepines, these agents bind to GABA-A receptors, but they do so more selectively, and they have shorter half-lives, which makes them effective for insomnia with fewer next-day effects.[18] Eszopiclone and the extended-release formulation of zolpidem have longer durations of action and are effective for sleep maintenance as well as sleep onset insomnia. BZRAs do have a risk for abuse, and next-day sedation may occur with the longer-acting agents.[18] Other adverse effects associated with BZRAs include tolerance and rebound insomnia following abrupt discontinuation. These agents have also been associated with complex sleep-related behaviors, or parasomnias, such as sleep eating, sleep walking, and sleep driving.[22,23] Although these types of sleep-related behaviors are infrequent, they are potentially serious, and patients with comorbid psychiatric disorders may be at an increased risk of experiencing these adverse events.[22,23]

The melatonin receptor agonist ramelteon has a short half-life, from 1 to 3 hours, which makes it an appropriate treatment for sleep onset insomnia but with little effect on sleep maintenance.[18] Ramelteon has a favorable side effect profile with no evidence of abuse or dependence potential.[17,18]

Suvorexant is thought to alleviate insomnia by binding to the orexin receptor types 1 and 2, which are located in the regions of the brain that promote arousal and vigilance.[24] Suvorexant has been found to decrease sleep latency and wake after sleep onset, increasing total sleep time.[25] No withdrawal effects have been observed following discontinuation from this treatment, but it carries a risk for side effects similar to other hypnotic agents, such as complex sleep-related behaviors and sleepiness during the day.[25] Additional side effects, although rare, can include temporary sleep paralysis upon falling asleep or waking up or temporary weakness in the legs. Patients who have narcolepsy should not take suvorexant.

The tricyclic antidepressant doxepin is also an FDA-approved treatment for insomnia, albeit at a much lower dose than used for depression. Although doxepin is an antidepressant at doses of 75 to 150 mg/d, as an insomnia treatment, a dose of only 3 to 6 mg/d is used[18]; at this low dose, doxepin acts primarily as a selective antagonist of H_1 histamine receptors in the brain. Doxepin is effective for the treatment of sleep maintenance insomnia and at the low hypnotic dose has not been found to be associated with any serious adverse events or residual next-day effects.[17,18]

Off-label agents. The prescription medications most commonly used off-label to treat insomnia are sedating antidepressants, anticonvulsants, and second-generation antipsychotics. Antidepressants are a particularly popular

treatment option in patients with psychiatric disorders and insomnia, because clinicians hope to treat both conditions with one agent. In fact, trazodone is one of the most frequently prescribed insomnia treatments,[18] although unfortunately the hypnotic dose is well below that recommended for depression. As a result, trazodone is frequently an add-on therapy to other antidepressant medications. Sedating antidepressants, such as mirtazapine, tricyclics, and trazodone, are thought to combat insomnia through antagonism of wake-promoting systems such as serotonin, norepinephrine, acetylcholine, and histamine.[18] However, no evidence is available to support the effectiveness of antidepressants for insomnia, and they can potentially cause numerous side effects, including sedation, weight gain, anticholinergic symptoms, and cardiotoxicity.[17,18] In addition, certain antidepressants, such as bupropion and desvenlafaxine,[26] are known to have activating properties and should be avoided if possible in patients with sleep difficulties.

Anticonvulsants that are sometimes used to treat insomnia include gabapentin, pregabalin, and tiagabine. The first two are thought to decrease insomnia by decreasing the activity of wake-promoting glutamate and norepinephrine systems, whereas tiagabine promotes sleep by inhibiting the reuptake of GABA.[18] Gabapentin and pregabalin have been found to enhance slow-wave sleep and to reduce sleep disturbance in patients with pain-related disorders.[27] Furthermore, these agents have a low potential for abuse, although they can be associated with next-day sedation and cognitive impairment. Although they may be helpful for sleep in patients with chronic pain syndromes,[28] there are few data on their efficacy for insomnia.[18]

Second-generation antipsychotics that are frequently used for insomnia are quetiapine, olanzapine, and risperidone. These agents promote sleep through antagonism of dopamine, histamine, serotonin, acetylcholine, and norepinephrine.[18] Second-generation antipsychotics may be appealing treatment options for insomnia in patients with psychiatric disorders because of their low potential for abuse and their ability to treat anxiety, psychosis, and mood disorders. However, clinicians need to keep in mind the well-known side effects of second-generation antipsychotics, such as weight gain, risk of movement abnormalities, and metabolic syndrome.

Case Practice Question

Discussion of best response can be found at the end of the activity.

Case 1. Sue is a 57-year-old married woman who is an artist with 2 adult children. She has a history of depression, with several previous episodes that lasted for weeks to months at a time, but she has generally functioned well with pharmacotherapy and supportive psychotherapy. She is physically healthy and has no history of substance use.

Sue presents with insomnia symptoms that have been increasing over the past month and depressive symptoms that have been increasing over the past 2 weeks. Her sleep started to worsen as she began to feel the stress from preparing for her son's wedding. She initially had difficulty falling asleep, sometimes taking as long as 90 minutes, and then she began awakening frequently during the night. To compensate, she tried going to bed earlier. She now goes to bed around 10:00 PM and stays in bed until 7:00 AM, and later on weekends, but still reports only 6 to 7 hours of total sleep. Her depressive symptoms have worsened along with her sleep difficulties. She reports reduced daytime energy, difficulty concentrating, and apathy. Her depressive episodes often follow a seasonal pattern, getting worse during winter months. In the past, her episodes of depression have been accompanied by insomnia, but she has also experienced insomnia in the absence of depressive symptoms but during stressful periods. Sue is currently taking 300 mg/d of extended release bupropion for depression and 25 to 50 mg/d of diphenhydramine at bedtime as needed, with variable success.

What is the *best* option for addressing Sue's insomnia?

a. Prescribe a short-term BZRA to help her get through this stressful period and then see if symptoms remit
b. Switch Sue from bupropion to a less activating antidepressant
c. Begin behavioral treatments such as reducing time in bed and maintaining a regular sleep-wake schedule
d. a and c
e. b and c

Case Practice Question

Discussion of best response can be found at the end of the activity.

Case 2. Summer is a 24-year-old white woman who worked as a sales clerk and had her own apartment, but she recently lost her job, got evicted, and is now staying with friends. Summer has a history of posttraumatic stress disorder (PTSD) stemming from being repeatedly sexually abused by her mother's boyfriend when she was a teenager. He would come into her room after her mother had gone to bed. She had never been a good sleeper, and once the abuse started, she developed fears of going to bed, difficulty falling asleep and staying asleep, and nightmares. During adolescence, she began experiencing depression and was hospitalized twice for suicide attempts. She was treated with a selective serotonin reuptake inhibitor (SSRI), which improved her mood but not her insomnia or nightmares, so she discontinued treatment. She began to use marijuana and abuse alcohol as a teenager to help manage her PTSD symptoms. More recently, she was prescribed 1 mg of alprazolam, 4 times a day, which she said helped, yet her previous psychiatrist abruptly discontinued this for unknown reasons.

Summer presents to the clinic to establish care with a new clinician. Her mood has worsened since losing her job and she fears becoming suicidal. Her insomnia symptoms have also worsened and her nightmares have increased. She sleeps with a light on at all times. She says her current sleep pattern is to try to go to bed around 10:00 PM, but she lies in bed feeling anxious and fearful. Then, she gets up, smokes marijuana and has a couple drinks of liquor, and usually falls asleep for a couple hours before she is awakened by a nightmare and has difficulty getting back to sleep. She wakes up between 5:00 AM and 6:00 AM and tries to go back to sleep, usually unsuccessfully, and gets out of bed around 7:00 AM, having only gotten about 5 hours of sleep total.

Which of the following should *NOT* be a component of Summer's treatment plan?

a. Because of her positive experience with alprazolam, prescribe a benzodiazepine to be taken before bed
b. Begin treatment with an SSRI to alleviate the symptoms of PTSD, which should be beneficial for her insomnia and nightmares
c. Recommend behavioral treatments, including improving sleep hygiene, reducing time in bed, and maintaining low light during sleep time
d. Initiate substance abuse treatment to address her marijuana use and binge drinking because alcohol is known to contribute to poor sleep maintenance

Discussion of Case Practice Questions

Case 1.

Preferred response: e. Both b and c

Sue is currently experiencing a major depressive episode with significant insomnia symptoms, despite current treatment with bupropion. Because the bupropion is not effectively treating her depression and may be exacerbating her insomnia,[26] a reasonable option would be to switch her to an antidepressant less associated with sleep disturbance. She should also be advised to spend less time in bed in order to enhance her homeostatic sleep drive, and to avoid oversleeping on weekends.

Case 2.

Preferred response: a. Because of her positive experience with alprazolam, prescribe a benzodiazepine or BZRA to be taken before bed

Since Summer has been binge drinking and using marijuana, she should *not* be prescribed a sleep aid with a potential for abuse such as a benzodiazepine or BZRA. Her treatment should include assessment and treatment of depression and substance use and behavioral therapy promoting more effective sleep routines.

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POSTTEST

To obtain credit, go to PSYCHIATRIST.COM (Keyword: February) to take this Posttest and complete the Evaluation.

1. **Mr G is a 45-year-old man with a history of posttraumatic stress disorder. Over the past 2 months, he has been waking up at 3:00 in the morning 2 days per week. Upon awakening, he cannot go back to sleep. His sleep problems are beginning to affect his job performance, as he is exhausted throughout the day. To cope with the stress of possibly losing his job, he has started drinking a pint of whiskey every night before going to bed. Based on the symptoms presented, does Mr G meet the diagnostic criteria for insomnia?**

   a. Yes

   b. No

2. **Ms C is a 33-year-old woman with 2 young children who works full-time. By the time she goes to bed, she is exhausted but not sleepy, and it takes her hours to fall asleep. She was diagnosed with major depressive disorder at age 20 years and was prescribed an SSRI. Her mood remained stable until her sleep difficulties began 5 months ago. Now, she is feeling depressed and reports that by the time she falls asleep, she is only able to get about 6 hours of total sleep per night. What is the *best* pharmacologic option to treat Ms C's insomnia?**

   a. A tricyclic antidepressant

   b. An anticonvulsant

   c. Melatonin

   d. A benzodiazepine receptor agonist