LESSONS LEARNED AT THE INTERFACE OF MEDICINE AND PSYCHIATRY

The Psychiatric Consultation Service at Massachusetts General Hospital (MGH) sees medical and surgical inpatients with comorbid psychiatric symptoms and conditions. Such consultations require the integration of medical and psychiatric knowledge. During their thrice-weekly rounds, Dr. Stern and other members of the Psychiatric Consultation Service discuss the diagnosis and management of conditions confronted. These discussions have given rise to rounds reports that will prove useful for clinicians practicing at the interface of medicine and psychiatry.

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Evaluation and Treatment of Poor Sleep

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Have you ever wondered what types of conditions can cause persistent problems with sleep? Have you been uncertain about what type of evaluation should be initiated? Have you puzzled over which interventions are best suited to your patients and to their problems? If you have, then the following case vignette (of a man with difficulty falling and staying asleep) should provide the forum for answers to these and other questions related to strategies for the workup and treatment of persistent insomnia.

CASE VIGNETTE

Mr. A, a 63-year-old man with bipolar disorder who was admitted to the hospital, was profoundly depressed and had a host of neurovegetative symptoms (including anergia, anhedonia, impaired concentration, and poor sleep [waking up several times each night and finally arising 1–2 hours earlier than usual with a pervasive feeling of dread]). Mr. A's medications included lithium carbonate 300 mg t.i.d., duloxetine 30 mg daily, and lorazepam 1 mg t.i.d. (as needed for anxiety). An inability to sleep became a focal issue for Mr. A. To treat nocturnal and early morning awakenings, zolpidem 10 mg and olanzapine 10 mg were prescribed at bedtime. These medications contributed to remission of depressed mood and improved sleep, and Mr. A was then discharged home.

Several months after discharge, Mr. A presented to his outpatient physician again complaining of difficulty with sleep. He reported that he woke up numerous times each night and did not feel rested in the morning. On physical examination, it was noted that Mr. A had gained 25 lb. Mr. A's partner reported that he had begun to snore loudly, with frequent pauses in his breathing during sleep. Polysomnography was obtained; it demonstrated 25 apneic events per hour, which indicated moderate obstructive sleep apnea. Mr. A's medication regimen was reviewed, and it was felt that lithium and olanzapine were the most likely contributors to his weight gain. Since lithium was thought to offer the greatest therapeutic advantage for treatment of his bipolar illness, olanzapine was tapered and discontinued.

How Prevalent Is the Complaint of Insomnia?

Insomnia is defined as difficulty with the initiation, maintenance, duration, or quality of sleep that results in the impairment of daytime function, despite adequate opportunity and circumstances for sleep.[1–4] The prevalence of chronic insomnia has been estimated at 10% to 15% in the general population,[2,5] though some investigators have found rates as high as 27%[6] to 33%.[7] Insomnia more frequently afflicts women, the elderly, and those with chronic medical and psychiatric disorders.[1]

Sleep disorders are classified as either primary or related to (or comorbid with) other mental disorders or medical conditions. Primary insomnia may represent a state of physiologic hyperarousal[3] and does not have a well-established etiology. Other sleep disorders may be related to another mental disorder, general medical conditions, or substance use.

What Is the Differential Diagnosis of Insomnia?

The workup of insomnia involves consideration of a variety of factors, including environment, medications, nonprescribed substances, medical conditions, or psychiatric disorders. Environmental factors (e.g., excessive heat or cold, ambient noise, psychosocial stress, daytime napping, or other situations [such as having newborn infants, sick relatives, jet lag, or changes in shift work]) often interfere with sleep and can disrupt an individual's sleep routine. Medications or other stimulatory substances also adversely affect sleep. Stimulants (e.g., amphetamines, caffeine, or β-agonists), when taken in large doses or in the evening, may disturb nocturnal sleep. Use of alcohol or other drugs (e.g., cocaine or phencyclidine) also disrupt sleep. Sedating medications (e.g., β-blockers, opiates, anticonvulsants, neuroleptics, and benzodiazepines) frequently affect the sleep-wake cycle. A host of medical conditions (e.g., paroxysmal nocturnal dyspnea) interfere with sleep by virtue of their symptoms that disturb nighttime sleep. Conditions that cause pain or other types of physical discomfort (e.g., respiratory distress, coughing, frequent urination or bowel movement, neurologic dysfunction, or movement disorders) can result in insomnia. In addition, a plethora of psychiatric disorders (e.g., affective disorders, anxiety, schizophrenia, eating disorders, alcoholism, and dementia) also alter sleep physiology and phenomenology.[8] A recent study demonstrated that complaints of insomnia were typically associated with various psychiatric conditions.[9] Mood disorders (such as unipolar major depression and bipolar depression) have been shown to be associated with rapid eye movement (REM) sleep disturbance.[10] Unipolar major depression has also been associated with a circadian rhythm that is phase advanced (i.e., it is shifted earlier than normal with respect to the sleep-wake cycle).[11] This shift could account for the relatively early onset of REM sleep and the relatively long first REM period of sleep seen in depression. In some patients with bipolar disorder, depressive episodes may be precipitated by alterations in the sleep-wake cycle.[12]

Obstructive sleep apnea (OSA), a common cause of poor quality sleep, is one type of apnea syndrome (in contrast to central apnea syndromes). It is characterized by sleep-disordered breathing caused by upper airway obstruction that leads to apneic episodes, hypoxia, and sleep arousal.[13] It has been estimated that 2% to 4% of middle-aged men and 1% to 2% of middle-aged woman suffer from OSA.[14] However, the majority of individuals remain unidentified; a community survey in the United States found that 82% of men and 92% of women with moderate to severe OSA went undiagnosed.[15] Diagnosis of OSA is associated with obesity, with male gender, and with advancing age (peaking in the fifth and sixth decades and then declining).[14] The cardinal symptom of OSA is excessive daytime sleepiness that appears to be related to recurrent sleep arousals associated with apneic events.[16] Other associated symptoms include snoring,unrefreshing sleep, nocturnal choking, witnessed apneas, nocturia, morning headaches, reduced libido, and enuresis.[13] Diagnosis is confirmed by assessment of sleep, typically via polysomnography (with a mean of 5–15 apneic events per hour representing mild dysfunction, 15–30 events per hour representing moderate dysfunction, and more than 30 events per hour representing severe dysfunction).[17] Treatment of OSA consists of weight loss, including discontinuation of weight-increasing medications, positional therapy, continuous positive airway pressure, or surgery for clearly identifiable causes of upper airway obstruction.[16]

Primary sleep disorders include dyssomnias (e.g., primary insomnia, hypersomnia, narcolepsy, periodic limb movements during sleep, breathing-related sleep disorder, and circadian rhythm sleep disorder) and parasomnias (e.g., night terrors, enuresis, or sleepwalking). If insomnia does not respond to the treatment of potential mental, medical, or substance-related causes, a workup for primary insomnia may be indicated. Workup and treatment for primary insomnia generally warrant consultation by a clinician who specializes in sleep disorders.[4]

How Can One Evaluate Insomnia?

The most important aspect of an evaluation for insomnia is a complete and accurate history. A comprehensive history starts with a description of insomnia. Questions to ask include: When did the insomnia begin? How often does it affect you? When do you go to bed? How long does it take to fall asleep? How many times do you wake up during the night? Do you get out of bed when you wake up? Are you able to return to sleep? How long do you stay awake? and When you wake up in the morning, do you feel well rested? In addition, it is important to inquire about any physical or psychological symptoms that interfere with sleep. A complete medical history (including current symptoms and the use of medications [including over-the-counter, traditional, or herbal agents], illicit drugs, or alcohol) should be assessed as well. Psychological symptoms that should be assessed include worrisome thoughts, ruminations, fears, anxiety, depression, mania, hallucinations, paranoia, or other delusions. It is also important to inquire about snoring, any difficulty with breathing, unusual or abnormal body movements, and nightmares. Not uncommonly, it is difficult for an individual to assess aspects of his or her own sleep. In these instances (especially for evaluation of snoring, abnormal breathing, or abnormal movements), the report of a bed partner can provide critical information.[3]

In addition to gathering the history, it is useful diagnostically to obtain a daily sleep diary (which may be kept at the patient's bedside). Upon awakening, the patient is instructed to record the time to bed, latency of sleep onset (i.e., the time between going to bed and falling asleep), the number and duration of awakenings during the night, the time of the final awakening, the time out of bed, the quality of a night's sleep, and the degree to which one feels rested upon wakening. In addition, use of any pharmacologic or nonpharmacologic interventions or the occurrence of naps the previous day should be recorded.[18]

The assessment of sleep hygiene is also useful. Sleep hygiene refers to the behavioral habits and management of environmental factors in which one sleeps. Aspects of sleep hygiene worthy of inquiry include one's sleep environment (e.g., a quiet, dark area), the occurrence of daytime naps, the amount of physical activity engaged in as bedtime approaches, the use of stimulating medications in the evening, the existence of a routine prior to sleep, work-shift changes, or travel that results in jet lag or the crossing of time zones. If possible, one's sleeping area should be quiet and darkened, without distractions; it should be used solely for sleeping.[19]

A polysomnogram (a sleep study involving an electroencephalogram, an electroculogram, an electromyogram, oxygen saturation monitoring, respiratory parameters, and an electrocardiogram performed in a sleep laboratory) is not routinely used for the evaluation of insomnia, in part because the results of the polysomnogram do not correlate well with self-reports of insomnia.[20] A polysomnogram is indicated if the diagnosis is uncertain, if usual treatments for insomnia are ineffective, or if one suspects a diagnosis of sleep apnea or abnormal periodic limb movements during sleep.

What Pharmacologic Treatments Are Available for Insomnia and How Safe and Efficacious Are They?

A wide variety of pharmacologic agents are available for the treatment of insomnia. Some of the following recommendations are U.S. Food and Drug Administration–approved agents for insomnia, while others reflect the clinical experience of practitioners and patients. Treatment decisions should take into account severity of insomnia, the pattern of insomnia, the etiology of insomnia, associated symptomatology, and comorbid medical and psychiatric conditions.

For mild cases, over-the-counter treatments, such as antihistamines (e.g., diphenhydramine), may be considered for short-term use.[8] In general, they are not FDA-approved for the treatment of insomnia, though their use is supported by a large body of patient and clinician experience. Examples of over-the-counter treatments containing antihistamines include Tylenol PM and Nyquil.

Melatonin, a sleep-regulating hormone, is available without prescription as a neutraceutical agent; though thought by some to improve difficulties with sleep initiation, meta-analyses of published studies have not proven its efficacy.[21]

Agents available by prescription include more potent antihistaminic agents (hydroxyzine and promethazine), benzodiazepines (lorazepam), benzodiazepine receptor-agonists (zolpidem and zaleplon), anticonvulsant agents (gabapentin), β-blockers (propranolol), α-agonists (clonidine), melatonin receptor-agonists (ramelteon), and other sedating psychotropics (trazodone, mirtazapine, doxepin, or quetiapine). Of these agents, only the benzodiazepine receptor-agonists and some benzodiazepines (triazolam, temazepam, and flurazepam) are FDA-approved for insomnia.[3] Off-label use of other agents for insomnia, including other benzodiazepines, is common and effective.

Benzodiazepines are a popular class of medications used for the treatment of moderate to severe insomnia. A number of benzodiazepines are available; they vary with regard to their pharmacodynamic properties.[22] Agents with a relatively long duration of action include clonazepam, diazepam, and chlordiazepoxide. Those with an intermediate duration of action include alprazolam, temazepam, and lorazepam, while short-lasting agents include triazolam. Long-lasting agents are often used when there is difficulty with maintenance of sleep throughout the night, while agents with a shorter duration of action are used when sleep initiation is a primary complaint. Selection of a benzodiazepine, given its pharmacologic activity and pharmacodynamics, should be individually tailored to a specific sleep disturbance (and those agents with a more rapid onset of action can be effective even when taken just before bedtime). Benzodiazepines improve insomnia by decreasing sleep latency and by decreasing nocturnal awakenings[19]; clonazepam has also proven effective for insomnia related to restless legs syndrome, periodic limb movement disorder,[23] and sleep bruxism.[24] All benzodiazepines act on the benzodiazepine γ-aminobutyric acid (GABA) receptor-complex and may lead to physiologic and psychological dependence. Physical dependence can be clinically significant; in a study of long-term usage, 43% of individuals taking diazepam for 8 months or longer developed withdrawal symptoms when the medication was tapered rapidly or discontinued.[25] Careful consideration should be given to administration of these agents to patients with substance abuse problems; they are not intended for long-term use in the general population.

Barbiturates (such as phenobarbital and pentobarbital) also work as GABA-agonists and are associated with an even higher risk of dependence.[26] Barbiturates also have a high potential for overdose and suicide; they should only be considered if all other treatment options have been exhausted.

Alternatives to benzodiazepines and barbiturates include benzodiazepine receptor-agonists (zolpidem and zaleplon), which act on the $GABA_A$ α_1 subtype receptor and typically demonstrate lower dependency potential. Zolpidem, an imidazopyridine, has a half-life of 3 hours, while zaleplon (a pyrazolopyrimidine) has a half-life of 1 hour; it is best used only for difficulties with sleep initiation. Zolpidem, in particular, is efficacious for insomnia, and it does not appear to have detrimental effects on sleep architecture.[27,28]

Agents recently approved by the FDA for use in the treatment of insomnia include eszopiclone and ramelteon. Eszopiclone is another agent in the family of $GABA_A$ α_1 subtype receptor-agonists, with a half-life of 5 to 7 hours.[29] Ramelteon, a melatonin M_1 and M_2 receptor-agonist has demonstrated efficacy for insomnia (particularly initial insomnia) with little to no potential for abuse or dependence.[30]

For patients with more persistent sleep problems, agents such as trazodone (an agent originally FDA-approved as an antidepressant that is effective for sleep induction) or chloral hydrate may be considered. Fortunately, dependency on trazodone is not an issue with its long-term use; individuals rarely abuse this agent. Unfortunately, a rare side effect of trazodone is priapism that may require surgical decompression.[31] Chloral hydrate is another option for significant sleep difficulty that is refractory to other hypnotics.[26] Tolerance is known to develop to this agent; therefore, it is not recommended for more than 2 weeks of use.

Other nonbenzodiazepine sleep aides include β-blockers (propranolol) and the α-agonist, clonidine. While these are not first-line agents (and are not FDA-approved for insomnia), clinical experience suggests that they may have a soporific effect for some patients; nighttime administration may facilitate sleep. Clinical situations that would warrant consideration of these agents include situations in which hypertension, anxiety, or psychomotor agitation accompany insomnia.

For patients with insomnia and comorbid psychiatric conditions, a number of psychotropic agents may be considered. In general, a useful strategy is to prescribe medications that are indicated for the primary psychiatric diagnosis that also have a sedating effect. For instance, to treat insomnia associated with unipolar major depression, one could consider the use of a sedating antidepressant.[32] Such agents include tricyclic antidepressants (TCAs) (tertiary amine TCAs, such as doxepin or amitriptyline, have potent anticholinergic side effects and predispose patients to cardiac arrhythmias, which limit their use) or antidepressants with novel mechanisms of action (mirtazapine). Mirtazapine, an effective antidepressant, is also a potent sleep aide.[33] Though there are no firm empirical data, certain selective serotonin reuptake inhibitors (SSRIs) (paroxetine or fluvoxamine) may be dosed at night to facilitate sleep.

For patients with psychotic symptoms, manic or mixed states, or refractory anxiety, both atypical and typical neuroleptic agents may be administered at bedtime and anecdotally have improved comorbid sleep disturbances. Atypical antipsychotics (quetiapine, olanzapine, risperidone, and clozapine) may be prescribed at bedtime and tend to improve both sleep and psychotic symptoms. Sedating typical neuroleptics (chlorpromazine or thioridazine) are low-potency agents that have significant sedative and anticholinergic properties. Although the risk of extrapyramidal symptomatology (akathisia, dystonia, and tardive dyskinesia) is lower than with use of high-potency agents, long-term use of these agents is associated with an increased risk of adverse effects (tardive dyskinesia).

For patients with bipolar disorder who present in manic or mixed states, in addition to atypical and typical neuroleptics, sedating anticonvulsants have been used clinically to treat insomnia. Of these agents (valproic acid, carbamazepine, gabapentin, and topiramate), only valproic acid and carbamazepine are efficacious as mood-stabilizing agents, though they all may be effective in the treatment of insomnia. Lithium, an effective nonanticonvulsant mood-stabilizing agent, may have beneficial effects on sleep by treating the primary manic or mixed state. While there are few data for the efficacy of these agents for insomnia, in clinical practice, they are often administered at night to optimize their sedating effects. Atypical antipsychotics (olanzapine or clozapine), mood-stabilizing medications (such as lithium, valproic acid, and carbamazepine), and antidepressants (such as mirtazapine or TCAs) may exacerbate OSA by increasing weight gain; this appears to have happened in the case of Mr. A. Medications that cause oversedation in a patient with OSA may also exacerbate sleep problems and induce daytime sleepiness. In the context of OSA, any sedative agent can precipitate an excessively drowsy state that could inhibit sleep arousals that are critical to the resumption of breathing. Given their efficacy in inducing sleep, and their relative wide use, benzodiazepines are often implicated in the exacerbation of underlying OSA.

What Behavioral Approaches to Insomnia Are Available and Who Can Apply Them?

Behavioral approaches for the treatment of insomnia generally fall into 2 categories (efforts to improve sleep hygiene and specific nonpharmacologic treatments for improvement of sleep). All patients with a sleep disturbance should be encouraged to optimize the conditions that pertain to sleep. Establishing a consistent sleep process (i.e., with a regular bedtime and awakening time) is important. A relaxing bedtime routine, perhaps including a light snack containing tryptophan (because tryptophan

in doses of 1 g or more has improved sleep[34]) will prepare an individual for sleep. Patients with insomnia should be advised not to sleep too much (i.e., they should sleep only until they feel refreshed). Daytime naps should be avoided. Exposure to sunlight and exercise during the day should also help with nighttime sleep. Use of stimulants, alcohol, or nicotine should be avoided, particularly in the evening.[8]

Several psychotherapeutic techniques may also improve sleep. As insomnia becomes a long-term issue for an individual, being anxious about not being able to fall asleep and having negative associations with the sleep environment compound the problem.[26] Cognitive-behavioral therapy for insomnia utilizes techniques (such as stimulus-control therapy) to eliminate maladaptive responses to the sleep environment (e.g., engaging in other activities, such as reading or watching television in the bedroom). Sleep-restriction therapy creates a condition of relative sleep deprivation by limiting time in bed (to increase the amount and quality of sleep). Relaxation training employs techniques (such as progressive muscle relaxation, biofeedback, imagery training, and meditation) that promote a relaxed state prior to sleep.[3] Cognitive-behavioral therapy for insomnia is provided by clinicians who have special training and credentialing. A related technique, hypnosis, has also been used successfully to promote sleep.

Should Hypnotics Be Prescribed for Persistent Problems With Insomnia?

Long-term use of hypnotic agents may result in physical and psychological dependence. Some agents (such as barbiturates and benzodiazepines) are associated with a high risk of dependence, while others (trazodone and ramelteon) have a low risk of dependence. However, even in the face of physical dependence, these agents can be used effectively and safely. Benzodiazepines are effective for many sleep disorders and should be considered as the first-line treatment in many cases. Prescribed appropriately, the risk of a withdrawal syndrome, rebound insomnia, or dose escalation can be minimized. Abuse potential is also related to dependency issues.[35] There is always a possibility that an individual may abuse medications for sleep. For each patient, a risk/benefit analysis helps to make an informed choice about medication selection. For instance, in a patient with a history of substance abuse or dependence, it may be wise to prescribe a medication with a lower risk of dependency (such as trazodone, ramelteon, or an atypical antipsychotic, such as quetiapine). Risk of dependency can also be decreased by use of a benzodiazepine with a slower onset of action (such as oxazepam) and avoidance of agents with a longer half-life and a more rapid onset of action (such as diazepam).[35] The benzodiazepine receptor-agonists (zolpidem and zaleplon) have relatively less abuse potential than their benzodiazepine counterparts.

How Easy Is It to Taper and to Discontinue Sedative Hypnotics That Have Been Prescribed for Extended Periods?

It is imperative that sleep agents be titrated for use and tapered for discontinuation. Benzodiazepines, barbiturates, and other agents that predispose to dependency must be slowly tapered to avoid withdrawal reactions or rebound syndromes. Benzodiazepines, barbiturates, and other GABA-agonists are associated with a severe and potentially life-threatening withdrawal syndrome.[35] Long-term use of these agents, with escalating dose schedules, greatly increases the risk of withdrawal symptoms upon sudden discontinuation. Other agents, even if they are not commonly associated with physical dependency, may also be associated with withdrawal symptoms or rebound insomnia when their doses are tapered too quickly. Rebound insomnia is the phenomenon in which a sleep disturbance worsens (for a short period of time) when sleep medications are discontinued. When medications are properly administered, withdrawal reactions and rebound insomnia are infrequent.[36] Still, dependency, abuse, and addiction can occur with benzodiazepines and barbiturates, and it is important to consider this risk when prescribing them.

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–This article outlines the classifications of insomnia based on symptomatology, duration, and etiology. It also reviews diagnostic tools that may aid in distinguishing symptom types.

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–This chapter presents basic research pertaining to biological rhythms, the sleep cycle, and mood disorders and provides theories to understand the relationship between these factors.

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–The authors define insomnia and then provide a useful clinical approach to evaluating and diagnosing the condition. They suggest various treatment interventions, focusing on benzodiazepine receptor-agonists, older hypnotics (such as chloral hydrate), antidepressants, melatonin, and antihistamines.