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Insomnia: assessment and treatment review

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Insomnia is a prevalent condition and a significant source of psychosocial impairments. It is associated with numerous comorbidities that affect quality of life. An adequate assessment is key to developing an efficacious treatment strategy. This paper provides a basic overview of currently available modalities for evaluation and treatment of this condition.

Insomnia, more often considered benign than not, is a widespread clinical problem best gauged by the significance of the psychosocial impairments associated with it. It must also be viewed in the context of the numerous exacerbating comorbidities that highlight its impact on quality of life. It is considered one the most common disorders in the general population. Although it may be transient in nature, it is often persistent. It is the chronicity of this condition that has warranted most attention in terms of treatment strategies.

Although the precise definition of insomnia varies in the medical community, in this discussion we will regard insomnia as daytime impairment as a result of difficulty in either the initiation or maintenance of sleep despite adequate opportunity and circumstance. Insomnia may be categorized as a primary dysfunction, as in emanating from circadian rhythm abnormalities, or a secondary one associated with and often exacerbated by another medical condition.[1] An even stronger link can be found between insomnia and psychiatric illnesses such as mood and anxiety disorders. As much as 40% of all insomnia patients may have a coexisting psychiatric condition,[2] depression being the most common.[3]

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Prevalence

Established definitions and diagnostic categories of insomnia vary between the International Classification of Sleep Disorders (ICSD-2), the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV), and the International Classification of Diseases (ICD).[4-6] Both the ICSD-2 and DSM-IV require that the duration of insomnia symptoms must persist for at least one month (Table 1), whereas the ICD requires that the symptoms occur at least three times per week. Thus, the prevalence of insomnia varies widely among reports and falls between 10% and 40%, whereas insomnia subcategories range from 5% to 10% (Table 2).[7] The key features of insomnia as listed in Table 1 include difficulty falling asleep, maintaining sleep, awakening too early, or nonrefreshing sleep, but it is the daytime impairments that hinder the quality of life of patients.

Risk factors

Many comorbid conditions, particularly chronic illness, are risk factors for insomnia, whereas other medical conditions such as gastroesophageal reflux, chronic headaches, pain conditions, and neurodegenerative disease elevate the risk of developing insomnia.[1,8-10] The onset of menses and menopause, advancing age, and depressed mood all place patients at increased risk for insomnia.

Sleep physiology

The American Academy of Sleep Medicine describes sleep in the following stages: stage Wake, stage 1, stage 2, stage 3, and rapid eye movement (REM) sleep, also known as W, N1, N2, N3, and R, respectively. Stages N1, N2, and N3 are collectively referred to as non–rapid eye movement (NREM) sleep, with stage N3 often called *slow wave sleep*. Understanding complex neurobiologic processes between systems that maintain arousal and systems that generate and sustain sleep are essential to developing treatments for insomnia and other sleep disorders.

Table 1 Definitions of insomnia

ICSD-2 general criteria for insomnia
1. A complaint of difficulty initiating sleep, difficulty maintaining sleep, or waking up to early; or sleep that is chronically unrestorative or poor in quality. In children, the sleep difficulty is often reported by the caretaker and may consist of observed bedtime resistance or inability to sleep independently.
2. The above sleep difficulty occurs despite adequate opportunity and circumstances for sleep.
3. At least one of the following forms of daytime impairment related to the nighttime sleep difficulty as reported by the patient: fatigue or malaise; attention, concentration, or memory impairment; social or vocational dysfunction or poor school performance; mood disturbance or irritability; daytime sleepiness; motivation, energy, or initiative reduction; proneness for errors or accidents at work or while driving; tension headaches or gastrointestinal symptoms in response to sleep loss; concerns or worries about sleep.

DSM-IV criteria for insomnia
1. The predominant complaint is difficulty initiating or maintaining sleep for at least 1 month.
2. The sleep disturbance (or associated daytime fatigue) causes clinically significant distress or impairment in social, occupational, or other important areas of functioning.
3. The sleep disturbance does not occur exclusively during the course of narcolepsy, breath-related sleep disorder, circadian rhythm sleep disorder, or a parasomnia.
4. The disturbance does not occur exclusively during the course of another mental disorder (eg, major depressive disorder, generalized anxiety disorder, a delirium).
5. The disturbance is not caused by the direct physiologic effects of a substance (eg, drug of abuse, a medication) or a general medical condition.

ICD-10 criteria for nonorganic insomnia
A condition of unsatisfactory quantity or quality of sleep, which consists for a considerable period of time, including difficulty falling asleep, difficulty staying asleep, or early final awakening. Insomnia is a common symptom of many mental and physical disorders, and should be classified here in addition to the basic disorder only if it dominates the clinical picture.

Table 2 Insomnia diagnostic categories

ICSD-2 insomnia categories
1. Adjustment insomnia (acute insomnia)
2. Psychophysiologic insomnia
3. Paradoxical insomnia
4. Idiopathic insomnia
5. Insomnia caused by mental disorder
6. Inadequate sleep hygiene
7. Behavioral insomnia of childhood
8. Insomnia as a result of drug or substance
9. Insomnia as a result of medical condition
10. Insomnia not caused by substance or known physiologic conditions, unspecified (nonorganic insomnia NOS)
11. Physiologic (organic) insomnia, unspecified

DSM-IV-TR insomnia categories
1. Primary insomnia
2. Insomnia related to axis I or II categories

ICD-10 insomnia categories
1. Nonorganic insomnia
2. Nonorganic disorder of the sleep-wake schedule

Numerous neurotransmitters and their receptors are in play. Glutamate, acetylcholine, dopamine, serotonin, norepinephrine, histamine, and hypocretin all play roles in the ascending arousal systems in the cortex, hypothalamus, and brainstem. The actions of the inhibitory neurotransmitters γ-aminobutyric acid (GABA) and galanin are directed at the inhibition of the arousal system, whereas the metabolic product adenosine endogenously induces and maintains sleep. The timing of the multiple physiologic events associated with sleep is controlled by the secretion and action of melatonin. Additional sleep regulatory substances include interleukin-1β, tumor necrosis factor-α, prostaglandin D, and growth hormone–releasing hormone. A detailed discussion on their mechanisms is beyond the scope of this review, but it is important to understand that any medical conditions or medications affecting these neurotransmitters can play a role in a patient's sleep cycle.[11]

The normal sleep patterns of young adults and the elderly are displayed in Table 3,[11] which lists changing patterns of sleep stages with age. For example, by age 60 there is

Table 3 Normal sleep patterns in humans

	Young adults	Elderly
Wake after sleep onset	<5%	10-25%
Sleep efficiency	>90%	75-85%
Stage N1	2-5%	5-8%
Stage N2	45-50%	57-67%
Stage N3	13-23%	6-17%
Stage R	20-35%	17-20%
Stage R/NREM ratio	20:80	20:80
Time of stage R, NREM cycle	90-110 min	90-110 min
Total sleep time	7-8 hr	7 hr

reduced sleep efficiency, significant decrease in deep N3 sleep, along with fragmented slow-wave sleep without significant decline in REM. In addition, there are changes observed in the circadian rhythms of the elderly as evidenced by their going to bed too early and waking up too early compared with their younger counterparts.[12]

Insomnia has yet to be viewed under a single cognitive-behavioral model; however, it is described classically with the 3 Ps model from Spielman et al.[13] Insomnia results from the combination of: (1) Predisposing factors (tendency to worry, hyperarousal, substance abuse, genetic factors); (2) precipitating factors (new life stressors); and (3) perpetuating factors (maladaptive thinking or coping strategies such as daytime napping or alcohol consumption). Under this model, insomnia can be viewed as a maladaptive cognitive-behavioral issue that often persists chronically unless it is recognized and treated appropriately.

There is evidence of elevated heart rate, basal skin resistance, and core body temperature, and phasic vasoconstriction in insomniacs relative to control subjects. A small study comparing 11 insomniacs matched by body mass index and age to 13 healthy controls showed increased activation of the hypothalamic-pituitary-adrenal (HPA) axis as evidenced by significantly elevated levels of plasma cortisol ($p = .04$) and adrenocorticotropic hormone ($p = .07$) in those patients with sleep difficulties.[14] Conversely, a later study of 10 insomniacs and 10 matched healthy controls showed no significant difference between cortisol levels but did find decreased levels of melatonin in subjects with primary insomnia.[15] In addition, a study of 21 normal sleepers showed a positive correlation between the amount of REM sleep and HPA axis activation ($p < .05$).[16] Evidence supporting activation of the sympathetic system in insomnia can be found in a preliminary study of 15 insomniacs showing levels of urinary catecholamine metabolites positively correlating with the percent of stage 1 sleep ($p < .05$) and wake time after sleep onset ($p < .05$).[17] Increased basal metabolism, as measured by oxygen consumption (VO^2) at intervals over 24 hours, has also been shown to be increased in patients with insomnia compared with healthy controls. Increased heart rate with decreased variability over 36 hours is also demonstrated in insomniacs.[18] Neuroimaging studies performed with positron emission tomography demonstrate increased cerebral glucose metabolism during waking and non-REM sleep states.[19]

Along these lines, insomnia can be described as the nighttime manifestations of hyperarousal. Whatever the etiology of the underlying hyperarousal, it may remain asymptomatic until attempting to initiate sleep. Inevitably, concerns over sleep maintenance will perpetuate insomnia, leading to a vicious cycle of incorrect behaviors aimed at protecting sleep and rest (ie, daytime napping). Perpetuation of such behavior may lead to neurophysiologic changes that preserve an insomniac's state of hyperarousal.[20,21]

Evaluation

Assessment of a patient's insomnia, like all other complaints, should begin with a relevant patient history detailing sleep habits, past medical history, diagnosed psychiatric illness, medications, and social history (including employment, current sources of stress, and substance use). A patient's sleep history should detail bedtime, onset of sleep, number and duration of awakenings, wake time, and any naps. A daily sleep log or sleep diary (Fig. 1) should be used in patients who are unable to give an adequate sleep history. It is best if a sleep diary is kept for at least two weeks before beginning any intervention, and it should be continued for the duration of treatment to monitor responsiveness.[22] A sleep diary assessment yields pertinent information such as bedtime, falling asleep time, awakening time, getting out of bed time, and frequent awakenings followed by time to falling asleep again, as well as nap times. Bed partner interviews may provide enhanced insight on problems associated with other sleep disorders such as obstructive sleep apnea (OSA) or restless leg syndrome (RLS).

Waking and daytime symptoms may point toward underlying comorbid conditions such as depression or anxiety. Symptoms of fatigue, mood disturbance, and sleepiness can be adequately assessed with tools like The Epworth Sleepiness Scale,[23] and particular attention should be given to a patient's substance use because consumption and withdrawal from common substances such as caffeine, nicotine, and alcohol are known to alter sleep quality and architecture.[22]

Physical examination should focus on detecting signs consistent with other sleep disorders such as OSA or comorbid conditions such as rheumatoid arthritis, congestive heart failure, and chronic obstructive pulmonary disease. Mental status examination may be performed in patients in whom a psychiatric disorder is suspected, but is not necessary in all patients. Often patients presenting with a chief complaint of insomnia may have a completely unremarkable physical examination despite existing comorbid conditions.[22]

Laboratory testing is not usually indicated but may be useful in diagnosing comorbid conditions such as diabetes (causing nocturia) or congestive heart failure. Actinography is a noninvasive method for evaluating patients' sleep and wake cycles. It uses a watch-sized motion sensor, an actigraph, to monitor patients' movements and provides satisfactory objective data that distinguishes normal sleepers from insomniacs. However, it cannot distinguish between types of insomnia.[24,25] Polysomnography provides a biophysical profile of a patient's sleep and includes measurements of electrical brain activity, heart rhythms, eye movements, muscle activity, pulse oximetry, respiratory effort, and airflow. It is not indicated for routine screening of patients with insomnia and should only be used to diagnose or rule out other suspected sleep disorders (OSA, RLS).[26,27]

TWO WEEK SLEEP DIARY

INSTRUCTIONS:
1. Write the date, day of the week, and type of day: Work, School, Day Off, or Vacation.
2. Put the letter "C" in the box when you have coffee, cola or tea. Put "M" when you take any medicine. Put "A" when you drink alcohol. Put "E" when you exercise.
3. Put a line (I) to show when you go to bed. Shade in the box that shows when you think you fell asleep.
4. Shade in all the boxes that show when you are asleep at night or when you take a nap during the day.
5. Leave boxes unshaded to show when you wake up at night and when you are awake during the day.

SAMPLE ENTRY BELOW: On a Monday when I worked, I jogged on my lunch break at 1 PM, had a glass of wine with dinner at 6 PM, fell asleep watching TV from 7 to 8 PM, went to bed at 10:30 PM, fell asleep around Midnight, woke up and couldn't got back to sleep at about 4 AM, went back to sleep from 5 to 7 AM, and had coffee and medicine at 7:00 in the morning.

Today's Date	Day of the week	Type of Day Work, School, Off, Vacation	Noon	1PM	2	3	4	5	6PM	7	8	9	10	11PM	Midnight	1AM	2	3	4	5	6AM	7	8	9	10	11AM
sample	Mon.	Work		E					A				I									C M				
																							week 1			
																									week 2	

Figure 1 Sleep Diary.

Management

Treatment of insomnia must stagger priorities and focus on some of the underlying causes and comorbid conditions. For example, treatment with opioids for pain may enhance sleep because of opioids' sedative effect, but in patients with cardiopulmonary dysfunction, they may have a dangerous respiratory suppressive effect. On the other hand, treatment with gabapentin may help enhance sleep and could be used safely in many such patients with cardiopulmonary dysfunction. A cursory survey of usage trends of sedative-hypnotics over the last few years indicates that nonbenzodiazepines (non-BZDs) are becoming increasingly favored over BZDs because there is less concern about safety in long-term use and addiction.

It is imperative to understand the presleep circumstances as well as any other underlying socioeconomic factors, such as rapidly changing work schedules or shift work, before considering appropriate treatment. Furthermore, habitual conditioning, such as restricting caffeine intake, as the mainstay of a nonpharmaceutical approach, is highly recommended. Discussion of treatment goals between patient and physician is necessary to tailor a specific plan to address these issues. The results of any such treatment should be measured with both subjective (questionnaires) and objective data (sleep logs).

Nonpharmacologic approache

The nonpharmacologic approach allows improvement in overall sleep hygiene or presleep patterns. One such approach could involve sleep restriction by cutting time in bed to actual hours of sleep and avoiding daytime naps to increase sleep efficiency (time asleep/total time in bed).[28] Furthermore, stimulus control helps to both improve sleep latency and reduce sleep anxiety. Examples of this include going to bed only when sleepy, using the bed only for sleep (ie, not watching television), and moving or changing rooms if unable to fall asleep. Relaxation training and avoidance of coffee, alcohol, chocolate, and even bedroom clocks would help as well. It is also important to maintain a the same awakening time each morning.[29]

All patients should be counseled on the basics of sleep hygiene and stimulus control. Should additional interven-

tion be necessary, more formal cognitive behavioral therapy for insomnia (CBT-I) should be considered. CBT-I is a combination of treatments combining sleep hygiene and stimulus control strategies with relaxation, sleep restriction, and cognitive therapy over several weeks.

The patients successfully treated with CBT-I are likely to report improvement in both day- and nighttime symptoms. A study of 9 patients with psycho-physiological insomnia showed significant differences in subjective measurements of insomnia as well as increased duration of stage 2, slow-wave, and REM sleep after only one week of treatment.[30] Even in patients with comorbid conditions such as chronic pain or chronic obstructive pulmonary disease, CBT-I has been shown to improve self-reported sleep parameters in numerous clinical trials.[31-34] CBT-I has the advantage of being free of side effects; however, cost, inconvenience, and availability may limit its effectiveness.[35] Benefits of CBT-I extend beyond the active treatment period[36] and may help patients cope with future life stressors.[37,38]

Pharmacologic approaches

Patients treated successfully with pharmacologic therapy are likely to report improved daytime symptoms. However, side effects, dependency, and addiction are risks that need to be considered when initiating drug therapy. Factors such as age, pregnancy risk, alcohol consumption, previous drug addiction, and renal, hepatic, or pulmonary diseases all need to be considered before sleep aids are prescribed. An ideal sleep aid is an over-the-counter hypnotic that has rapid onset of action, has concentrations effective throughout sleep, and is eliminated before waking.[39,40]

Non-BZDs such as zolpidem, zaleplon, and eszopiclone are type 1 GABA-A receptor agonists. Non-BZDs result in minimal changes in sleep architecture and only mild suppression of REM is noted.[41] They are considered safer with minimal next-day sedative effects but have little benefit for sleep maintenance because most have short half-lives and are best prescribed for sleep-onset insomnia.

Side effects such as nightmares, amnesia, and parasomnia are associated with zolpidem,[42] whereas anxiety, menstrual pain, and paresthesia are reported with zaleplon.[43] Both are approved for sleep latency insomnia; however, because of their very short half-lives, some experts prescribe these medications in an off-label fashion to help a patient resume sleep in the event of sleep interruption. Controlled-release forms of zolpidem are available to address the sleep onset latency and sleep maintenance difficulty.[44,45] Eszopiclone has the longest half-life of the current non-BZDs, and may be more appropriate for patients with sleep maintenance insomnia.[46,47] When used at low doses for short durations, non-BZDs have no significant rebound insomnia and numerous clinical trials have shown them to be safe and effective for six months.[48,49]

Ramelteon, a melatonin receptor agonist, interacts with both melatonin-1 and melatonin-2 receptors to promote sleep. It binds with much greater affinity to these receptors than naturally occurring or supplemental melatonin.[50] A one-year, open-label study of ramelteon showed significant improvement in subjective sleep latency and total sleep time, without noteworthy changes in vital signs, physical examinations, laboratory values, or electrocardiogram readings. It is the treatment of choice for insomnia in the context of substance dependence and is one of the only Food and Drug Administration–approved sedative-hypnotic medications that is not a scheduled substance.[51]

Benzodiazepines including triazolam, estazolam, alprazolam, lorazepam, flurazepam, diazepam, and temazepam have been used frequently for sleep induction. Although useful, they have side effects including confusion, hallucinations, and next-day sedation. Disruption of sleep architecture and risk of medication dependency has reduced their effectiveness for long-term use. Tolerance to the sedating effects of BZDs develops quickly after only a few days of consistent use. BZDs suppress slow-wave sleep (SWS) and to a lesser extent REM sleep, while prolonging REM latency. Of note, stage 2 sleep latency is shortened while total sleep time (TST) is increased.[52] Acute withdrawal from BZDs is associated with decreased TST as well as REM and SWS rebound. Long-acting BZDs should be avoided in older patients because of the risk of adverse effects.[36] The speed of onset is a key factor in the abuse potential of BZDs,[53] because higher rates of abuse are noted in rapid-action-onset BZDs such as diazepam. Development of extended release formulas may reduce the abuse potential of BZDs.[54]

Antidepressants are commonly prescribed for the psychiatric comorbidities of insomnia. Tricyclic antidepressants (TCAs) such as amitryptiline and nortryptiline are generally effective at sleep induction and maintenance. They are known to cause next-day sedation, suppress REM sleep, and have anticholinergic side effects.[55-57] An exception to TCAs is low-dose doxepin, which has fewer residual symptoms and no significant anticholinergic effects, and has been shown to improve sleep onset latency and maintenance.[58-60] Selective serotonin reuptake inhibitors (SSRIs) generally disrupt sleep continuity, decrease TST, suppress REM, and increase N1 sleep.[61] The serotonin modulator trazodone is sedative through histamine-1 and 5-HT2 receptor antagonism. Clinical studies of trazodone have shown improvement in sleep parameters after one week, but no significant difference from placebo after two weeks.[62] In addition, trazodone should be avoided in patients with OSA or those at risk for it; a double-blind, randomized study of 9 OSA patients showed a dose of trazodone 100 mg increased the effort-related arousal threshold in response to hypercapnia (allowing patients to remain asleep at higher carbon dioxide levels).[63] Mirtazapine is a tetracyclic antidepressant sometimes used as a hypnotic. Clinical studies regarding mirtazapine and insomnia have focused mainly on patients with major depression[64] and cancer.[65] Although mirtazapine is a generally well-tolerated antidepressant, evidence supporting

the safety and efficacy of mirtazapine for the treatment of insomnia is limited.

Many over-the-counter and unregulated substances marketed specifically for the treatment of insomnia are available to patients. Up to 10% of young adults use over-the-counter medications or alcohol to improve sleep.[41] Diphenhydramine, often combined with a pain reliever, is one of the most common and widely used medications to self-treat. However, tolerance to diphenhydramine's sedating effects builds quickly and may cause delirium in elderly patients. It is known to decrease REM sleep and can induce paradoxical insomnia in patients.[66-68]

Melatonin, although generally harmless, is not terribly effective in the treatment of insomnia, though it has been shown to assist in regulating circadian rhythms or disturbances related to jet lag or shift work.[69,70] Valerian root is shown to be safe and sedating but larger, randomized, clinical trials are needed to prove its worth in treating insomnia.[71,72] Kava extracts were once marketed as herbal panaceas, effective for treatment of many ailments including insomnia, but studies showing the risks of hepatotoxicity have led to its being banned in many countries.[73-75]

Alcohol, a central nervous system suppressant and GABA-gated channels agonist, actually reduces sleep-onset latency, increases wakefulness after sleep onset, and suppresses REM sleep.[41]

A general treatment approach

Although the mainstay of insomnia treatment remains pharmacologic, it should be noted that nonpharmacologic approaches provide safe adjunctive therapy. Combining CBT-I with drug therapy has the greatest chance of improving measures of insomnia long term. There may be greater risk of remission in patients who initially receive drug or combination therapy instead of CBT-I alone. With regards to pharmacy, a general approach would be to start with a non-BZD such as zolpidem to reduce sleep onset latency. These are considered safer even in long-term use. A low dose in elderly patients may be a better start because there are side effects such as amnesia or delirium. However, because of its longer half-life, eszopiclone may be useful in patients who continue to wake during the night and cannot fall back asleep. Some sleep experts recommend (off-label) use of non-BZDs with short half-lives as the first dose of the night and then repeat an additional second dose in a patient who would awaken during the night.

Alternatively, a medication like ramelteon may be useful before bedtime to induce and maintain sleep and is also considered safe for long-term use. Furthermore, low-dose TCAs such as a new formulation of a lower-dose doxepin (6 mg) marketed as Silenor (Somaxon Pharmaceuticals, San Diego, CA) is also available. This class of medications has long been used off-label to treat conditions such as chronic daily headaches, and in this setting, low-dose doxepin, amitryptiline, or nortryptiline may help address insomnia as well so long as precautions are given regarding possible next-day sedation. Underlying depression and anxiety disorders warrant extensive treatment with or without use of sleep-inducing medications.

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September/October 2012 Answers

1. c, 2. a, 3. a, 4. a, 5. d, 6. d, 7. a, 8. b, 9. c, 10. b