Insomnia

Personalized Diagnosis and Treatment Options

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KEYWORDS

• Insomnia • Sleep • Personomics • Somnomics • Cognitive behavioral therapy

KEY POINTS

- Chronic insomnia is a clinical diagnosis made through the International Classification of Sleep Disorders, third edition criteria (ICSD-3): (a) difficulty initiating or maintaining sleep, (b) inability to sleep despite having adequate opportunities for sleep, (c) experiencing negative daytime impacts due to lack of sleep, and (d) sleep difficulty not explained by other sleep/medical disorder—with symptoms occurring at least three nights per week during a period of at least 3 months.
- Cognitive behavioral therapy is the first-line treatment of chronic insomnia.
- Pharmacotherapies are the second-line treatment of insomnia and are only weakly recommended by the American Academy of Sleep Medicine (AASM) guidelines.
- Somnomics is the study of sleep and its relationship to overall patient health from the precision medicine perspective.

INTRODUCTION

The human relationship with sleep has undergone an immense evolution. Our increasing emphasis on productivity and micro-scheduling is no longer limited solely to our work but has permeated our rest. Our ability to closely monitor our sleep habits with a profusion of longitudinally trackable metrics logged on wearable technology and sleep applications has given rise to a wave of emerging "sleep athletes." Concurrently, the prevalence of insomnia continues to rise worldwide, with COVID-19 bringing an onslaught of challenges. The pandemic has augmented the society-wide mental health burden and led to a shift toward telework and virtual social immersion. The blurred line between home and workplace has upended routines and contributed to compromised sleep hygiene and practices,[1] increased insomnia,[2] and poorer sleep quality for some subgroups of sleepers.[3] Now, more than ever, we need to safeguard our sleep for better health and well-being.

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With the move toward precision medicine, there is an effort to provide personalized high value care. Although the -omics such as proteomics, metabolomics, pharmacogenomics, and so forth are more well known "tools" in the precision medicine toolbox, sleep has also been proposed to be a vital component of precision care. Coined somnomics,[4] the study of sleep, is important across all medical specialties and has been shown to affect several aspects of health. Sleep affects cognition, mood, well-being, metabolism, and immune response and can affect a variety of medical disorders. Further, it is becoming evident that the timing of medication doses may be important for individuals to promote enhanced benefits and reduced side effects, a practice called chronotherapy.[5] Somnomics thus is an area that requires more exploration to achieve high value care.

In this review, we outline the evaluation and management of insomnia while exploring the new frontiers of sleep. We hope to equip clinicians with a clear guide for gold standard management of insomnia and provide a broad overview of the variety of treatment modalities emerging on the market.

BACKGROUND

Epidemiologic studies highlight the elevated prevalence of insomnia disorder sustained over the last decade.[6] More recently in the era of a global crisis, longitudinal studies have shown a 26.7% increase in the incidence of insomnia (symptoms increased from 25.4% to 32.2%, and diagnoses increased from 16.8% to 19%),[2] a phenomenon that has been variously termed "covidsomnia" or "coronasomnia."[7] This is despite—or even possibly because of—the increases in sleep duration that were seen in the general population following COVID-19-related changes in work and social behavioral patterns.[8] Similarly, less enduring disruptions to sleep have demonstrated the consequences of the sociopolitical climate on sleeping patterns,[9] emphasizing that the profusion of the Internet of Things (IoT) can help elucidate the countless sleep disruptors in our daily lives. For example, region-specific bouts of acute insomnia were observed in large-scale smartphone sleep-tracking data sets as a consequence of critical geopolitical events (notably the 2016 U.S. Presidential election and "Brexit"[9]).

The impacts of inadequate sleep on the quality of life are manifold,[10] with some examples being increased cognitive impairment,[11] higher likelihood of mood disorders/chronic pain, elevated risk of suicide, higher rates of prescription sedative/hypnotic use,[12] increased cardiovascular morbidity and mortality, increased accidents, decreased societal productivity, and increased national economic costs.[13] These health impacts and their broad-reaching socioeconomic implications highlight the importance of identifying and addressing insomnia early in our patients.

DEFINITIONS

The International Classification of Sleep Disorders (ICSD) is the primary diagnostic resource for clinicians within sleep medicine. The ICSD-3 delineates three types of insomnia: short-term insomnia disorders, chronic insomnia disorders, and "other" insomnia disorders—which do not fulfill the criteria for the two prior categories. Nearly one in five cases of short-term insomnia develop into chronic insomnia disorders,[14] many of which can persist for years.[6]

PATHOPHYSIOLOGY

Regardless of the duration or characterization (e.g., difficulty initiating or maintaining sleep), a central aspect of insomnia is the concept of hyperarousal. Hyperarousal

may be evidenced physiologically in the central and/or peripheral nervous system. Consequently, most patients experience hyperarousal as heightened physiologic (e.g., faster heartbeat and respiration), psychological (e.g., anxiety), or cognitive (e.g., mind racing) activity. This psychophysiological overactivity can interfere with an individual's ability to adequately disengage from the environment for a sound sleep.[15]

The development of insomnia is thought to be the consequence of an individual's predisposition and exposure to a precipitating event, dubbed the "3P Model" of insomnia.[16] In such a diathesis-stress model, individuals with biopsychosocial factors, such as age, sex, and genetic predisposition, may develop insomnia in the face of stressors based on their physical and psychological reactions. The transition to a chronic issue often happens because of maladaptive behaviors and thoughts that serve to perpetuate sleep difficulties. Through repeated associations, individuals reinforce the psychological and/or physiologic hyperarousal through various mechanisms, such as classical conditioning of the bed/bedroom (unconditioned stimulus) with anxiety (conditioned response).

Often accompanying the physiologic sleep associations are cognitive distortions and behavioral adaptations that further reinforce the sleep dysfunctions. For example, many individuals will spend excessive amounts of time worrying about and trying to sleep, often contributing to their insomnia through dilation of the sleep period and "nesting" behaviors that prevent them from straying too far from the bed/bedroom for fear of missing out on the opportunity for sleep.[14] Other cognitive reactions may result in patients developing a "performance anxiety" in response to the approaching sleep period, whereas others have just resigned themselves to the belief that they simply "cannot sleep."[17]

Underpinning the perpetuation of insomnia, as well as the theory behind its treatment, is a disruption of the core physiology of sleep. The two-process model of sleep regulation (**Fig. 1**) explains sleep as a product of the interaction of two components: Process C, a circadian process that is a ~24-h oscillating wakefulness signal, which interacts with and guides Process S, a homeostatic process of sleep debt that gradually accumulates over the course of wake and dissipates over a period of sleep.[18] Factors reducing sleep homeostasis, and thereby, sleep drive, include the caffeine used to combat exhaustion, excessive sleeping (e.g., napping, sleeping longer than the body needs) to make up for perceived sleep inadequacy, and inactivity (e.g., nesting in bed, a generally sedentary lifestyle). Disrupted exposure to typical clock-setting

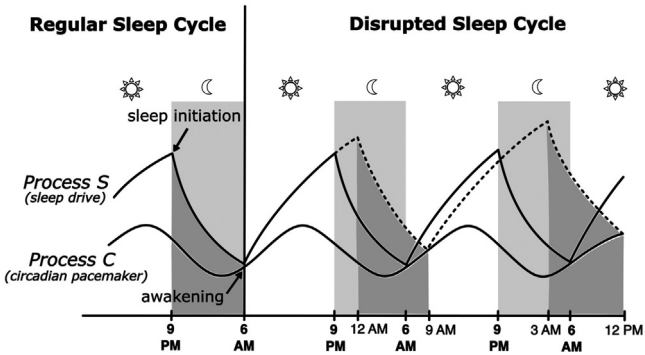

Fig. 1. A representation of the interaction between Process S and Process C and the consequences of delays in sleep onset. The point at which the homeostatic sleep drive (Process S) diminishes to the level where the alerting circadian signal (Process C) is elevated enough to promote awakening takes longer following prolonged wakefulness.

zeitgebers ("time givers"/sleep cues) can cause circadian misalignment with the intended sleep period. From misplaced light exposure at night (instead of at the desired wake time) to mistiming of dietary intake, environmental temperature fluctuations, and even late-night socialization (e.g., the endless stream of social media), the cues necessary for our body to entrain our biological rhythms to our sleep–wake schedule often become desynchronized as individuals with insomnia attempt to orchestrate their lives around their sleep dysfunction.

CLINICAL EVALUATION

Chronic insomnia is primarily a clinical diagnosis. According to the ICSD-3, an insomnia diagnosis necessitates meeting the following criteria:

1. Difficulty with sleep initiation or maintenance.
2. Persisting sleep difficulties despite adequate opportunity for sleep.
3. Negative daytime impacts attributable to lack of sleep, such as fatigue, lack of energy, diminished concentration, emotional lability, and accidents while driving.
4. No other more likely diagnosis.

Chronic insomnia presents as at least 3 months of sleep disturbance and daytime dysfunction at least 3 nights/week, whereas short-term insomnia does not have to last 3 months.[19]

Because insomnia can be either a symptom or a disorder, a thorough sleep history is the first and most important step in evaluating insomnia. The two-process model of sleep regulation and Spielman's 3P behavioral model of insomnia can help inform the history. During the initial visit, one can capture the patient's presleep conditions, difficulty in initiating or maintaining sleep, sleep–wake patterns, sleep-related symptoms, and impact on daytime function. In addition, a sleep environmental scan should be done to search for disruptive factors in the patient's sleep environment from pets and co-sleepers to ambient noises and light pollution. Such questioning can also reveal maladaptive behavior patterns. Moreover, making a distinction between what times in the sleep period are disrupted by insomnia can also be important, as they can have different therapeutic approaches (**Table 1**). Finally, at the initial visit, it will also be important to evaluate for other sleep disorders (e.g., sleep apnea, restless leg syndrome), comorbities, or medications that could be causing the symptom of insomnia.

Questionnaires that can be used as aids in this initial stage include the Pittsburgh Sleep Quality Index, Epworth Sleepiness Scale, and Insomnia Severity Index. These measures provide a validated means of quantifying the severity of a patient's sleep disturbance and daytime impairments at baseline and monitoring the patient's progress during treatment. If additional information is needed, asking the patient to maintain a daily sleep diary can provide a more accurate, real-time account of the patient's sleep. Patients may also be utilizing sleep tracking devices (eg, Sleep Sensing on Nest Hub), which can provide meaningful insights into their sleep patterns and progress. Although commercial sleep trackers provide the benefit of a consistent measure of longitudinal sleep trends within an individual, it must be recognized that these devices often measure and report on metrics that do not yet have a clear, validated role in the clinical management of sleep disorders. In addition, the accuracy of absolute sleep metrics is often poor compared with polysomnography, particularly in clinical populations in which the devices have not been adequately validated.[20,21] Toward this end, consumer wearable companies are attempting to provide transparency regarding their devices and metrics to assist clinicians in using and interpreting patient-generated data (e.g., Fitbit Health Solutions: https://healthsolutions.fitbit.com/providers/).

Table 1
Insomnia issues can affect sleep onset latency, wake after sleep onset, and early morning awakening, each characterized by different criteria and therapeutic approaches

	Sleep Onset Latency Insomnia	Wake After Sleep Onset Insomnia	Early Morning Awakening Insomnia
Definition	Sleep onset latency exceeding 30 min 3 days/wk or more during the last month	Wakefulness exceeding 30 min between periods of sleep 3 days per week or more during the last month	Early morning awakening exceeding 30 min 3 day/wk or more during the last month
Common differential considerations	Medications, anxiety and affective disorders, restless legs syndrome, sleep starts (hypnic jerks), hypnagogic foot tremor, alternating leg muscle activation, sleep-related leg cramps, exploding head syndrome, delayed sleep–wake phase disorder, environmental sleep disturbance	Medications, anxiety and affective disorders, sleep apnea, periodic limb movement disorder, nightmare disorder, narcolepsy, sleep-related leg cramps, environmental sleep disturbance	Medications, anxiety and affective disorders, advanced sleep–wake phase disorder, natural short sleep, nightmare disorder, environmental sleep disturbance
Therapeutic strategies	Limit time in bed before sleep intent Establish pre-bedtime routines that facilitate preparation for sleep (eg, dimming lights, cooling the environment, tech curfew) Techniques to help quiet the mind (eg, meditation) and calm the body (eg, box breathing) Homeostatic-circadian alignment Pharmacologic adjunctive therapy with fast onset and relatively short half-life	Stimulus control (eg, leave the sleep space until sleepy) Techniques to help quiet the mind (eg, meditation) and calm the body (eg, box breathing) Homeostatic-circadian alignment Sleep environment optimization (eg, noise, light, temperature optimization) Pharmacologic adjunctive therapy with either a medium half-life agent at bedtime or a rapid onset, short half-life preparation	Stimulus control (eg, get up and start the morning routine) Homeostatic-circadian alignment Sleep environment optimization (eg, noise, light, temperature optimization)

At the end of the visit, clinicians can decide whether more in-depth testing is warranted to investigate or validate the experience using in-lab or home polysomnography, actigraphy, or the like. Devices such as the Sleep Profiler can be used for in-home patient-applied polysomnography.[22] However, such diagnostics are often used to

elucidate the presence of other primary sleep disorders, such as obstructive sleep apnea, that may be contributory to or causative of insomnia.

MANAGEMENT OF INSOMNIA

Cognitive Behavioral Therapy

As outlined in the Choosing Wisely recommendations,[23] the first-line treatment of chronic insomnia is cognitive behavioral therapy for insomnia (CBT-I). There are various components of CBT-I that can be explored with a patient (**Table 2**). In contrast, only providing patients with general tips on “sleep hygiene” is typically discouraged due to the lack of proven efficacy.[24]

Cognitive interventions involve changing misconceptions that a patient has regarding sleep. These can include negative thoughts around bedtime, such as the fear of not being able to go to sleep, believing that one needs to get more sleep than is necessary or appropriate, or believing that one needs a medication aid to go to sleep. In this vein, education surrounding sleep mechanisms and interactions with daily behaviors is often coupled with an exploration of beliefs that patients have regarding their sleep and impediments thereof. Efforts are made to guide patients to better understand their relationship with sleep, empower them with a sense of control over their ability to get the sleep that they need, and help them set realistic expectations for their sleep and waking function.

Behavioral therapy aims to strengthen the association between the bedroom and sleep with components such as stimulus control and sleep compression. Stimulus control leverages classical conditioning to reestablish the bed and sleep environment as cues to sleep rather than as places where waking activities occur. Establishing a consistent morning rise time and remaining in bed only when sleepy or sleeping leads to the reinforcement of the association between the bedroom and sleep. Sleep compression is another tool that limits "sleep opportunity" to increase sleep efficiency—the proportion of the time in bed spent sleeping—to above 85%.

Although there is efficacy of any individual component of the therapeutic approach to reframing misconceptions or adjusting sleep/wake habits to coordinate sleep drives, the American Academy of Sleep Medicine (AASM)’s 2021 guidelines for the behavioral and psychological treatments for chronic insomnia disorder in adults highlight that a multicomponent therapy integrating cognitive and behavioral aspects has the greatest supporting evidence for most insomnia subtypes in various patient populations.[24] Unfortunately, traditional CBT-I is limited in accessibility due to a dearth of qualified behavioral sleep medicine specialists.[25] Consequently, equivalently effective digital CTB-I (dCTB-I) offerings have developed quickly as a means of increasing accessibility and cost-efficacy.[26,27] Although the efficacy of CBT-I in numerous groups has been established, it has been cited that up to 40% of patients do not achieve remission due to heterogeneity within insomnia.[28] As such, groups have sought to use various means—from objective sleep pattern quantification[29] to affective and personality trait characterization[30]—to derive insomnia phenotypes that can provide pathophysiologic insights and identify optimal therapeutic approaches. Interestingly, in one study that identified five stable subtypes of insomnia, therapeutic responses to CBT-I and pharmacotherapies differed between subtypes,[30] suggesting that the potential for a more personalized, data-driven approach to insomnia treatment is on the horizon.

Pharmacotherapy

If CBT-I fails in insomnia remission, pharmacotherapy can be prescribed (**Table 3**). However, it should be noted that every class of agent currently used in the treatment

Table 2
Summary of cognitive behavioral therapy components and targets

Approaches[a]	AASM Strength of Recommendation[b]	What Is This Intervention Trying to Do?	What Does It Involve?	Timeline
CBT-I (multicomponent)	Strong	Address cognitive misperceptions and maladaptive behaviors that are perpetuating sleep difficulties	Cognitive behavioral therapy involving stimulus control and sleep restriction, and mindfulness training involving relaxation promotion	6–10 1-h sessions over a 6–20 wk period
Brief therapy for insomnia (multicomponent)	Conditional recommendation for use	Address cognitive misperceptions and maladaptive behaviors that are perpetuating sleep difficulties	Abbreviated version of CBT-I	4 sessions over 4 wk
Stimulus control therapy (single component)	Conditional recommendation for use	Weaken association between bed/bedroom and wakefulness	Instruct patient to (a) maintain a regular wake time, (b) limit time in bed to only when sleepy, (c) get out of bed if they are unable to sleep, (d) use bedroom for sleep and sex only, and (e) reduce napping in the daytime	Variable
Sleep restriction therapy (single component)	Conditional recommendation for use	Increase sleep drive (pressure for sleep) and sleep efficiency by compressing sleep	Restrict time in bed to patient's average sleep duration (not <5 h), subsequently adjusting time based on sleep efficiency; time in bed is increased by 15–30 min when sleep efficiency is 80%–85% and is decreased by 15–30 min when sleep efficiency is <80%	Variable, but generally weeks (periodic adjustments)
Relaxation therapy (single component)	Conditional recommendation for use	Promote muscle relaxation while reducing cognitive arousal	Exercises to reduce tension such as abdominal breathing, progressive muscle relaxation, and autogenic training; reduced cognitive arousal through guided imagery training and meditation	Variable

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Table 2 (*continued*)

Approaches[a]	AASM Strength of Recommendation[b]	What Is This Intervention Trying to Do?	What Does It Involve?	Timeline
Sleep hygiene (single component)	Conditional recommendation against use	Modify lifestyle and environmental factors to improve sleep conditions	General recommendations about sleep hygiene regarding diet, exercise, substance use, and environmental factors (light, noise, temperature)	Variable
Cognitive therapy (single component)	No recommendation	Address potentially harmful beliefs about sleep that may cause increased anxiety and interfere with sleep	Structured psychoeducation, Socratic questioning, thought records, behavioral experiments	Weeks
Biofeedback (single component)	No recommendation	Train physiologic relaxation	Biofeedback device links reduced patient muscle tone (frontalis electromyography) with patient control of auditory tone to train muscle relaxation	4–6 sessions, 30–60 min
Paradoxic intention (single component)	No recommendation	Reduce sleep anxiety by confronting fear	Patient instructed to remain awake as long as possible after staying in bed	Variable
Intensive sleep retraining (single component)	No recommendation	Enhance sleep drive	After 5-h time period in bed, patient undergoes 24-h time period in which they are given opportunities to fall asleep every 30 min; if successful sleep attained, patient is woken up 3 min later, informed of success, and is instructed to remain awake until subsequent 30 min trial	Multiple periods of attempted sleep over a 24-h time period
Mindfulness therapies (multicomponent or single component)	No recommendation	Enhance awareness of one's thoughts and emotions surrounding sleep	Structured exercises to emphasize self-awareness and acceptance conducted either at home or in a group setting	Variable

[a] Multimodal refers to the named therapy offered in conjunction with other CBT components. Single-component therapy is referring to solely the intervention indicated above.
[b] The AASM clinical guidelines provide the recommendation strength for each intervention using the GRADE framework.

of insomnia has been given only a "WEAK" recommendation in the AASM's most recent guidelines.[31] Nonetheless, pharmacotherapies are being prescribed as sleep aids more frequently over the last several decades.[32,33] Commonly used medications with regulatory approval for insomnia include benzodiazepine receptor agonists (BZRAs), nonbenzodiazepine BZRAs ("Z-drugs"), histamine receptor antagonists (e.g., low-dose doxepin), and melatonin receptor agonists (e.g., ramelteon). The first two classes of medications—BZRAs and Z-drugs—both work through activation of the inhibitory γ-aminobutyric acid type A ($GABA_A$) receptor, which results in a global depression of brain function. This rather shotgun approach could be more likened to light anesthesia than physiologic sleep, based on the electroencephalographic changes noted with these agents.[34] It is important to note that benzodiazepines carry a risk of misuse, dependence, tolerance, and withdrawal reactions. Similar risk profiles are seen among the Z-drugs (e.g., zolpidem, eszopiclone, zaleplon), in addition to a risk of parasomnias,such as sleep walking, that prompted the United States Food and Drug Administration (FDA) to issue a black box warning to the entire class of medications.

Antidepressants are also commonly used off-label to treat chronic insomnia; typically trazodone and mirtazapine are used since they have highly selective antihistamine activity at low doses.[35] There is one antidepressant that is FDA-approved for the treatment of insomnia: the low-dose tricyclic antidepressant doxepin that is predominantly antihistaminergic at doses from 3 to 6 mg, and has antiadrenergic, antiserotonergic, and anticholinergic activity typically seen at doses above 75 mg. Toward this end, due to the relative lack of data or regulatory approvals for most antidepressants, such therapies should be reserved for management of a primary psychiatric disorder when comorbid insomnia can be addressed with a single agent.

In 2014, the FDA approved the first dual orexin receptor antagonist for the treatment of insomnia, with subsequent agents (suvorexant, lemborexant) that gained clinical approval demonstrating similar efficacy.[31,36] These agents work to temporarily suppress the activity of the hypocretin system, essentially inducing a state of narcolepsy for the night. Although this is a step toward precision sleep medicine, facilitated by advancements in our understanding of the sleep–wake neurocircuitry, it should be noted that hypocretin is more of a sleep–wake state stabilizer rather than a wake promoting neurotransmitter, per se. As such, individuals with narcolepsy often have sleep instability and disorganized sleep macroarchitecture during the night.[37]

Given that the choice of therapies used in the treatment of insomnia is most strongly predicted by historical prescribing practices (i.e., familiarity),[33] the initiation of more appropriate pharmacotherapies will permeate clinical practice at a relatively glacial pace. However, pharmacogenetics may offer a more patient-centric approach to medication selection that could help tailor treatments to patients while promoting awareness of modern agents that provide a better balance of benefits and risks.[38] Using next-generation sequencing to identify genetic polymorphisms in patients can inform responsiveness and side-effect risks from the array of potential sleep medications, helping clinicians choose an optimal pharmacotherapeutic agent that suits the unique needs of the patient before them.[39]

Complementary Treatments

An important part of precision medicine is personomics[40] which involves respecting the unique belief systems that each patient brings into the clinic. Respecting patients' core beliefs involves focused listening during medical history acquisition and being open to including patient suggestions in an integrated care plan to promote clinician–patient trust, safeguard autonomy, and encourage hope in their clinical

Table 3
Summary of pharmacologic interventions for chronic insomnia

Classes	Medications	AASM Target Recommendation	AASM Strength of Recommendation[a] (Quality of Evidence)	Overdose Side Effects	Withdrawal Side Effects
Dual orexin (hypocretin) receptor antagonists	Suvorexant, Lemborexant, Daridorexant	Sleep maintenance	Weak (low)	Headache, dry mouth, dizziness, dry mouth, abnormal dreams, daytime sleepiness	Typically no withdrawal syndrome
Benzodiazepine receptor agonists	Eszopiclone	Sleep onset and sleep maintenance	Weak (very low)	Headache, dry mouth, nausea, dizziness, tolerance, dependence, bitter/metallic taste Black box: non-rapid eye movement (NREM) parasomnias	Insomnia, irritability, anxiety, tremor, sweating, palpitations, headache, muscular pain and stiffness, perceptual changes
	Zaleplon	Sleep onset	Weak (low)	Drowsiness, dizziness, decreased alertness and concentration, tolerance, dependence Black box: NREM parasomnias	Insomnia, irritability, anxiety, tremor, sweating, palpitations, headache, muscular pain and stiffness, perceptual changes
	Zolpidem	Sleep onset and sleep Maintenance	Weak (very low)	Headache, nausea, diarrhea, daytime sleepiness, tolerance, dependence, Black box:NREM parasomnias	Insomnia, irritability, anxiety, tremor, sweating, palpitations, headache, muscular pain and stiffness, perceptual changes

Benzodiazepines	Triazolam	Sleep onset	Weak (high)	Dizziness, lightheadedness, coordination difficulties, confusion, headache, tolerance, dependence, respiratory depression	Insomnia, irritability, anxiety, tremor, sweating, palpitations, headache, muscular pain and stiffness, seizure, perceptual changes
	Temazepam	Sleep onset and sleep maintenance	Weak (moderate)	Drowsiness, headache, dizziness, nausea, tiredness, tolerance, dependence, respiratory depression	Insomnia, irritability, anxiety, tremor, sweating, palpitations, headache, muscular pain and stiffness, seizures, perceptual changes
Melatonin receptor agonists	Ramelteon	Sleep onset	Weak (very low)	Dizziness, drowsiness, nausea	Typically no withdrawal syndrome
Heterocyclics	Doxepin	Sleep maintenance	Weak (low)	Drowsiness, dry mouth, constipation, nausea, blurry vision, orthostatic hypotension	Typically minimal: agitation, anxiety, insomnia, dizziness, confusion, headache, irritability, nervousness, depressed mood
	Trazodone	Not recommended	Weak (moderate)	Dry mouth, nausea, headache	Typically minimal: agitation, anxiety, insomnia, dizziness, confusion, headache, irritability, nervousness, depressed mood
Anticonvulsants	Tiagabine	Not recommended	Weak (very low)	Dizziness, memory impairment, headache, diarrhea, asthenia, respiratory depression	Insomnia, irritability, anxiety, tremor, sweating, palpitations, headache, muscular pain and stiffness, seizures, perceptual changes

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Table 3 (*continued*)

Classes	Medications	AASM Target Recommendation	AASM Strength of Recommendation[a] (Quality of Evidence)	Overdose Side Effects	Withdrawal Side Effects
OTC preparations	Diphenhydramine	Not recommended	Weak (low)	Dry mouth, urinary retention, pupil dilation, constipation, delirium	Tachycardia, sweating, hypersalivation, mydriasis, hypomimia and hypophonia, dysarthria, eye-movement abnormalities
	Melatonin	Not recommended	Weak (very low)	Headache, dizziness, nausea, drowsiness	Typically no withdrawal syndrome
	L-tryptophan	Not recommended	Weak (high)	Drowsiness, vomiting, diarrhea, headache, blurry vision	Typically no withdrawal syndrome
	Valerian	Not recommended	Weak (low)	Headache, dizziness	Possibly associated with elevated heart rate, unstable blood pressure, tremors, and confusion

[a] The AASM clinical guidelines provide the recommendation strength for each intervention using the GRADE framework.

journey (Table 4). Although around 4.5% of patients experiencing insomnia used complementary medicine outside of standard medical care, physicians do not receive sufficient training regarding these treatment modalities.[41]

Many interventions focus on promoting mindfulness within users, a practice that has demonstrated meaningful improvements in measures of insomnia.[42] There has been an explosion of digital offerings such as Headspace and Calm that offer direct-to-consumer options for mindfulness practices and other techniques for winding down for sleep. Somryst, the first and only prescription dCBT-I therapeutic for chronic insomnia, has created lasting improvements in insomnia symptoms. Patients can also explore yoga nidra, massage, acupuncture, meditation, and various forms of sensory stimulation (e.g., tactile, auditory, thermal) to promote relaxation.

Patients often turn to natural supplements to aid in their sleep journey. Some commonly used natural sleep aids include valerian root, lavender, chamomile, passionflower, cannabidiol, and magnesium, most of which have a weak or nonexistent evidence base to support their use.[43] One of the most commonly used over-the-counter sleep aids is melatonin. Although melatonin is better used in physiologic 300 to 500 μg doses for circadian rhythm timing, most individuals typically use 1 to 5 mg due to the slight hypnotic effects. Meta-analyses suggest modest benefits in objective[44,45] and subjective[45] sleep measures; however patients should still be

Table 4
Summary of complementary sleep therapeutics with varying approaches to address sleep difficulties

Approaches	Description	Examples
Digital therapeutics	Prescription digital therapeutics Nonprescription digital therapeutics	Somryst (digital CBT program) Digital CBT programs: SleepHub, Sleepio Meditation apps: Aura, Calm, Headspace
Auditory	Neutral or calming noises	White noise, pink noise, binaural beats, autonomous sensory meridian response
Thermoregulation	Products to maintain comfortable internal temperature or trigger circadian mechanisms	Cooling therapy (eg, Chillow, Chili Cool Mesh Mattress Pad)
Tactile	Intimacy-mimicking compression devices Sensory-stimulating devices or techniques	Sleep Pod, weighted blankets Apollo (vibration therapy), Acupuncture
Visual	Visual cues of sleep-/wake-promoting mechanisms	Light therapy, red light usage
Olfactory	Aromatherapy promoting calming or relaxing effects	Essential oils (lavender, peppermint, chamomile, and so forth)
Relaxation training	Techniques to quiet the mind and calm the body (through parasympathetic tone)	Meditation, yoga Nidra, hypnotherapy, biofeedback, progressive muscle relaxation, guided imagery
Natural Sleep Aids	Various agents with sedating/hypnotic effects	Valerian root, lavender, chamomile, passionflower, cannabidiol, and magnesium

cautious with using supplements since melatonin is unregulated in the United States and studies have demonstrated wide discrepancies between labels and contents (sometimes with no melatonin in the product at all).[46] Although the listed sleep aids often do not produce adverse effects, many of these over-the-counter (OTC) products are unregulated and, like melatonin in the United States, may not contain the ingredient amounts specified.

DISCUSSION

The high and increasing prevalence of insomnia disorders and insomnia symptoms in the general population highlights that the scale of sleep issues in the United States and globally is exceeding the capacity of sleep specialists. Often, individuals turn to their primary care provider or take matters into their own hands. Unfortunately, in such circumstances, many of the best practices in the diagnosis and management of insomnia are often not followed due to a lack of experience or expertise in the management of this common sleep disorder. Nonetheless, front-line clinicians are especially well-poised to make impactful advances in preventing, identifying, and treating insomnia due to their thorough understanding of the various biopsychosocial factors that can promote their patients' sleep health or, when neglected, can result in sleep disorders.. Toward this end, we sought to improve awareness of the state of the field in relation to insomnia to familiarize front-line clinicians, from neurologists to other specialists who may serve as the primary care provider, with the multifaceted nature of the condition and its therapeutic strategies.

First, it is important to understand how insomnia develops and manifests in our current society. Some contend that industrialization transformed our environments and behaviors in ways that are insomniogenic.[47] Prolonged exposure to artificial light and other psychophysiological cues (e.g., social engagement, dietary intake), decreased waking activity levels, [mis]use of readily available psychoactive stimulants (e.g., caffeine) and depressants (e.g., alcohol), and an overemphasis on structured/scheduled efficiency imposed on our sleep schedule are just a few of the potential cognitive and behavioral contributors that have resulted in high rates of sleep dissatisfaction and disordered sleep. Relying on the 3P conceptual framework, we can also see how extrinsic factors may serve to precipitate sleep disruptions that can snowball into long-term sleep issues. However, it is also important to recognize that the breakdown of our usual social rhythms—from the lack of demarcation between professional and social lives to reductions in activity levels—likely compounded the problem.

Given the regular evolution of our society and the challenges it faces, broad prevention of sleep disruption in the face of the next societal stressor is all but impossible. However, individuals and their care partners will need assistance in navigating the complex network of sleep-related factors to prevent acute sleep disruptions from turning into chronic sleep disorders. This often begins with simply discussing sleep health as part of a patient's routine care. The validated RU-SATED paradigm provides a simple mnemonic to aid providers in assessing the many dimensions of sleep health: Routine regularity, Satistfaction, Alertness, Timing (of the sleep period), Efficiency, and Duration.[48] Once issues with sleep have been identified, refining the understanding of an individual's sleep pathology can be accomplished through the involvement of specialized consultations, further diagnostics, and even the incorporation of some of the cutting-edge tools discussed above to create a multifaceted clinical picture of each patient. From discerned patterns in consumer wearable actigraphic data that identify an individual's daily circadian phase,[49] to data-driven sleep phenotypes that predict outcomes[50] as well as response to therapies,[51] to personalized

pharmacogenomic profiles that help clinicians choose the optimal treatment regimen by means of identifying the medication with maximal benefit, low side effect profile, and least amount of drug–drug interactions, sleep is at the forefront of integrating various data streams to tailor clinical management to each patient's unique needs.

Despite the promise that the IoT and analytical advances offer to patients and providers alike, we must be careful not to exacerbate the situation through the tools that we use to solve the problem. From the pathology of "orthosomnic" consumers obsessing over impractical sleep goals,[52] which may not be appropriate for them, to a deterministic sense of being "hard wired" for a certain sleep pathology or therapeutic response, the risk of patients getting the wrong message and being led astray by contextless data is high. Particularly as cheap sleep tracking technologies and direct-to-consumer offerings are becoming more ubiquitous, clinicians must become more familiar with the evidence underpinning them to competently assess their limitations and be comfortable interpreting their data in the context of the patient sitting before them.

Beyond the feed-forward model of optimizing insomnia management through precision medicine approaches, we must also consider each patient's unique needs and values. Meeting patients where they are takes a discernment of the biopsychosocial factors that are likely contributing to the perpetuation of their insomnia. Exploring a patient's circumstances through the lens of "personomics" not only provides insights into the misconceptions and maladaptive habits that may be the focus of CBTs, but also serves to offer insight and agency to our patients as part of shared decision-making that helps map out the therapeutic journey together. Without "peeking into the bedroom" to get a glimpse of the sleeping and waking lives of our patients, we cannot truly begin to understand what obstacles are preventing them from sleeping soundly.

SUMMARY

Fundamentally, sleep medicine has always been a forward-looking specialty that embraces big data: distilling hours of physiologic signals into a concerted understanding of someone's night, tracking behavioral patterns of sleep and wake over weeks to discern circadian phase, monitoring therapy adherence from breath to breath in positive airway pressure (PAP) device data downloads. However, simply gathering data will not result in the desired outcomes; engaging patients to provide context to the data and customization to the care is essential to the health care relationship. This therapeutic journey begins by simply asking.

CLINICS CARE POINTS

- Insomnia symptoms and insomnia disorder are highly prevalent in the general population.
- Numerous biopsychosocial factors influence the likelihood of acute onset of insomnia symptoms, including societal stressors such as the COVID-19 pandemic.
- Chronic insomnia is a clinical diagnosis where the following criteria have to be fulfilled: (a) difficulty with sleep initiation/maintenance, (b) inability to sleep despite adequate opportunities for sleep, (c) negative daytime impacts due to lack of sleep, and (d) sleep difficulty is not explained by other sleep/medical disorder. Chronic insomnia involves at least 3 months of sleep disturbances and daytime dysfunction for at least 3 nights/week.

- Spielman's "3P Model" of chronic insomnia can be useful during history taking by allowing the physician to explore (a) predisposing factors, (b) precipitating events, and(c) perpetuating factors for insomnia.
- Assessing sleep health should be done at every clinical visit (as with other vital signs), leveraging simple frameworks that account for its multifaceted nature (e.g., RU-SATED).
- The first-line treatment of insomnia is cognitive behavioral therapy for insomnia (CBT-I); pharmacotherapies should be avoided until a patient has had the opportunity to go through a CBT-I program.
- The second-line treatment of chronic insomnia involves pharmacotherapies, though it is important to note that every class is only weakly recommended by AASM's most recent guidelines.
- The practice of "somnomics" involves the study of sleep and its relationship on overall health and is part of the precision medicine toolbox.

DISCLOSURE

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REFERENCES

1. Cellini N, Canale N, Mioni G, et al. Changes in sleep pattern, sense of time and digital media use during COVID-19 lockdown in Italy. J Sleep Res 2020;29(4). https://doi.org/10.1111/JSR.13074.
2. Morin CM, Vézina-Im LA, Ivers H, et al. Prevalent, incident, and persistent insomnia in a population-based cohort tested before (2018) and during the first-wave of COVID-19 pandemic (2020). Sleep 2022;45(1). https://doi.org/10.1093/SLEEP/ZSAB258.
3. Kocevska D, Blanken TF, van Someren EJW, et al. Sleep quality during the COVID-19 pandemic: not one size fits all. Sleep Med 2020;76:86.
4. Somnomics: the intersection of sleep medicine and personalized care | Neurodiem. Available at: https://www.neurodiem.com/news/somnomics-the-intersection-of-sleep-medicine-and-personalized-care-BdXnXJdkFGvS94S4ama7Y. Accessed May 10, 2022.
5. Smolensky MH, Hermida RC, Geng YJ. Chronotherapy of cardiac and vascular disease: timing medications to circadian rhythms to optimize treatment effects and outcomes. Curr Opin Pharmacol 2021;57:41–8.
6. Morin CM, Jarrin DC, Ivers H, et al. Incidence, Persistence, and Remission Rates of Insomnia Over 5 Years. JAMA Netw Open 2020;3(11):e2018782.
7. Coronasomnia: Definition, Symptoms, and Solutions | Sleep Foundation. Available at: https://www.sleepfoundation.org/covid-19-and-sleep/coronasomnia. Accessed May 10, 2022.
8. Robbins R, Affouf M, Weaver MD, et al. Estimated Sleep Duration Before and During the COVID-19 Pandemic in Major Metropolitan Areas on Different Continents:

Observational Study of Smartphone App Data. J Med Internet Res 2021;23(2). https://doi.org/10.2196/20546.
9. Anýž J, Bakštein E, Dudysová D, et al. No wink of sleep: Population sleep characteristics in response to the brexit poll and the 2016 U.S. presidential election. Soc Sci Med 2019;222:112–21.
10. Olfson M, Wall M, Liu SM, et al. Insomnia and Impaired Quality of Life in the United States. J Clin Psychiatry 2018;79(5). https://doi.org/10.4088/JCP.17M12020.
11. Fernandez-Mendoza J, He F, Puzino K, et al. Insomnia with objective short sleep duration is associated with cognitive impairment: a first look at cardiometabolic contributors to brain health. Sleep 2021;44(1). https://doi.org/10.1093/SLEEP/ZSAA150.
12. Bertisch SM, Herzig SJ, Winkelman JW, et al. National use of prescription medications for insomnia: NHANES 1999-2010. Sleep 2014;37(2):343–9.
13. Streatfeild J, Smith J, Mansfield D, et al. The social and economic cost of sleep disorders. Sleep 2021;44(11). https://doi.org/10.1093/SLEEP/ZSAB132.
14. Perlis ML, Vargas I, Ellis JG, et al. The Natural History of Insomnia: the incidence of acute insomnia and subsequent progression to chronic insomnia or recovery in good sleeper subjects. Sleep 2020;43(6):1–8.
15. Levenson JC, Kay DB, Buysse DJ. The Pathophysiology of Insomnia. Chest 2015;147(4):1179.
16. Spielman AJ, Caruso LS, Glovinsky PB. A Behavioral Perspective on Insomnia Treatment. Psychiatr Clin North Am 1987;10(4):541–53.
17. Yang CM, Hung CY, Lee HC. Stress-Related Sleep Vulnerability and Maladaptive Sleep Beliefs Predict Insomnia at Long-Term Follow-Up. J Clin Sleep Med 2014;10(9):997.
18. Borbély AA, Daan S, Wirz-Justice A, et al. The two-process model of sleep regulation: a reappraisal. J Sleep Res 2016;25(2):131–43.
19. Medicine AA of S. International Classification of Sleep Disorders. 3rd ed. Darien, IL: American Academy of Sleep Medicine, 2014. Available at: https://learn.aasm.org/Listing/a1341000002XmRvAAKIt's.
20. Haghayegh S, Khoshnevis S, Smolensky MH, et al. Accuracy of Wristband Fitbit Models in Assessing Sleep: Systematic Review and Meta-Analysis. J Med Internet Res 2019;21(11). https://doi.org/10.2196/16273.
21. Chinoy ED, Cuellar JA, Huwa KE, et al. Performance of seven consumer sleep-tracking devices compared with polysomnography. Sleep 2021;44(5):1–16.
22. Finan PH, Richards JM, Gamaldo CE, et al. Validation of a Wireless, Self-Application, Ambulatory Electroencephalographic Sleep Monitoring Device in Healthy Volunteers. J Clin Sleep Med 2016;12(11):1443.
23. American Academy of Sleep Medicine. Five Things Physicians and Patients Should Question. 2021. Available at: www.aasm.org. Accessed May 10, 2022.
24. Edinger JD, Arnedt JT, Bertisch SM, et al. Behavioral and psychological treatments for chronic insomnia disorder in adults: an American Academy of Sleep Medicine clinical practice guideline. J Clin Sleep Med 2021;17(2):255–62.
25. Thomas A, Grandner M, Nowakowski S, et al. Where are the Behavioral Sleep Medicine Providers and Where are They Needed? A Geographic Assessment. Behav Sleep Med 2016;14(6):687.
26. Darden M, Espie CA, Carl JR, et al. Cost-effectiveness of digital cognitive behavioral therapy (Sleepio) for insomnia: a Markov simulation model in the United States. Sleep 2021;44(4). https://doi.org/10.1093/SLEEP/ZSAA223.

27. Henry AL, Miller CB, Emsley R, et al. Insomnia as a mediating therapeutic target for depressive symptoms: A sub-analysis of participant data from two large randomized controlled trials of a digital sleep intervention. J Sleep Res 2021;30(1): e13140.
28. Galbiati A, Sforza M, Fasiello E, et al. Impact Of Phenotypic Heterogeneity Of Insomnia On The Patients' Response To Cognitive-Behavioral Therapy For Insomnia: Current Perspectives. Nat Sci Sleep 2019;11:367.
29. Foldager J, Peppard PE, Hagen EW, et al. Genetic risk for subjective reports of insomnia associates only weakly with polygraphic measures of insomnia in 2,770 adults. J Clin Sleep Med 2022;18(1):21–9.
30. Blanken TF, Benjamins JS, Borsboom D, et al. Insomnia disorder subtypes derived from life history and traits of affect and personality. Lancet Psychiatry 2019;6(2):151–63.
31. Sateia MJ, Buysse DJ, Krystal AD, et al. Clinical Practice Guideline for the Pharmacologic Treatment of Chronic Insomnia in Adults: An American Academy of Sleep Medicine Clinical Practice Guideline. J Clin Sleep Med 2017;13(2):307–49.
32. America's State of Mind Report | Express Scripts. Available at: https://www.express-scripts.com/corporate/americas-state-of-mind-report. Accessed May 10, 2022.
33. Beam AL, Kartoun U, Pai JK, et al. Predictive Modeling of Physician-Patient Dynamics That Influence Sleep Medication Prescriptions and Clinical Decision-Making. Sci Rep 2017;7(1):1–7.
34. Jang DJ, Lim DK, Kim JK. Polysomnography Analysis of Electroencephalography in Patients Expending Benzodiazepine Drugs. Korean J Clin Lab Sci 2021;53(4): 333–41.
35. Stahl SM. Selective histamine H1 antagonism: novel hypnotic and pharmacologic actions challenge classical notions of antihistamines. CNS Spectr 2008;13(12): 1027–38.
36. Rosenberg R, Citrome L, Drake CL. Advances in the Treatment of Chronic Insomnia: A Narrative Review of New Nonpharmacologic and Pharmacologic Therapies. Neuropsychiatr Dis Treat 2021;17:2549.
37. Roth T, Dauvilliers Y, Mignot E, et al. Disrupted Nighttime Sleep in Narcolepsy. J Clin Sleep Med 2013;9(9):955.
38. Landolt HP, Holst SC, Valomon A. Clinical and Experimental Human Sleep-Wake Pharmacogenetics. Handb Exp Pharmacol 2019;253:207–41.
39. Krystal AD, Prather AA. Sleep Pharmacogenetics: The Promise of Precision Medicine. Sleep Med Clin 2019;14(3):317–31.
40. Ziegelstein RC. Personomics *JAMA Intern Med* 2015;175(6):888–9.
41. Ng JY, Parakh ND. A systematic review and quality assessment of complementary and alternative medicine recommendations in insomnia clinical practice guidelines. BMC Complement Med Therapies 2021;21(1). https://doi.org/10.1186/S12906-021-03223-3.
42. Gong H, Ni CX, Liu YZ, et al. Mindfulness meditation for insomnia: A meta-analysis of randomized controlled trials. J Psychosom Res 2016;89:1–6.
43. Kim J, Lee SL, Kang I, et al. Natural Products from Single Plants as Sleep Aids: A Systematic Review. J Med Food 2018;21(5):433–44.
44. Li T, Jiang S, Han M, et al. Exogenous melatonin as a treatment for secondary sleep disorders: A systematic review and meta-analysis. Front Neuroendocrinol 2019;52:22–8.

45. Fatemeh G, Sajjad M, Niloufar R, et al. Effect of melatonin supplementation on sleep quality: a systematic review and meta-analysis of randomized controlled trials. J Neurol 2022;269(1):205–16.
46. Erland LAE, Saxena PK. Melatonin Natural Health Products and Supplements: Presence of Serotonin and Significant Variability of Melatonin Content. J Clin Sleep Med 2017;13(2):275–81.
47. Ekirch AR. Sleep we have lost: Pre-industrial slumber in the British Isles. Am Hist Rev 2001;106(2):343–85.
48. Buysse DJ. Sleep Health: Can We Define It? Does It Matter? Sleep 2014;37(1):9.
49. Cheng P, Walch O, Huang Y, et al. Predicting circadian misalignment with wearable technology: validation of wrist-worn actigraphy and photometry in night shift workers. Sleep 2021;44(2):1–8.
50. Wallace ML, Lee S, Stone KL, et al. Actigraphy-derived sleep health profiles and mortality in older men and women. Sleep 2022;45(4). https://doi.org/10.1093/SLEEP/ZSAC015.
51. Benjamins JS, Migliorati F, Dekker K, et al. Insomnia heterogeneity: Characteristics to consider for data-driven multivariate subtyping. Sleep Med Rev 2017;36:71–81.
52. Baron KG, Abbott S, Jao N, et al. Orthosomnia: Are Some Patients Taking the Quantified Self Too Far? J Clin Sleep Med 2017;13(2):351.