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The assessment and management of insomnia: an update

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Insomnia poses significant challenges to public health. It is a common condition associated with marked impairment in function and quality of life, psychiatric and physical morbidity, and accidents. As such, it is important that effective treatment is provided in clinical practice. To this end, this paper reviews critical aspects of the assessment of insomnia and the available treatment options. These options include both non-medication treatments, most notably cognitive behavioral therapy for insomnia, and a variety of pharmacologic therapies such as benzodiazepines, "z-drugs", melatonin receptor agonists, selective histamine H1 antagonists, orexin antagonists, antidepressants, antipsychotics, anticonvulsants, and non-selective antihistamines. A review of the available research indicates that rigorous double-blind, randomized, controlled trials are lacking for some of the most commonly administered insomnia therapies. However, there are an array of interventions which have been demonstrated to have therapeutic effects in insomnia in trials with the above features, and whose risk/benefit profiles have been well characterized. These interventions can form the basis for systematic, evidence-based treatment of insomnia in clinical practice. We review this evidence base and highlight areas where more studies are needed, with the aim of providing a resource for improving the clinical management of the many patients with insomnia.

Key words: Insomnia, cognitive behavioral therapy, pharmacotherapy, benzodiazepines, z-drugs, orexin antagonists, antihistamines, melatonin receptor agonists, antidepressants, antipsychotics, anticonvulsants

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Insomnia is defined as a complaint of difficulty falling or staying asleep which is associated with significant distress or impairment in daytime function and occurs despite an adequate opportunity for sleep[1,2]. It is a common condition, with an approximate general population point prevalence of 10%[3-6].

In the vast majority of cases, insomnia co-occurs with psychiatric or physical conditions. Although it had long been believed that, when this was the case, insomnia was a symptom of those conditions, the available evidence suggests that the relationship between such conditions and insomnia is complex and sometimes bidirectional[7-10]. In fact, insomnia is a risk factor for major depression, anxiety disorders, substance use disorders, suicidality, hypertension and diabetes[11-23]. On this basis, as well as due to the fact that insomnia is associated with impairments in quality of life and an increased risk for accidents and falls, it is recommended that treatment be targeted specifically to addressing insomnia whenever it is present, including when it occurs along with physical or psychiatric conditions[24,25].

For those who meet the diagnostic criteria for insomnia, a number of empirically supported treatments are available. These include non-medication therapies as well as medication options[25-28]. The public health impact of this condition in terms of prevalence, morbidity and consequences on health and quality of life highlights the need to effectively diagnose and treat it in clinical practice. This paper reviews the state of the art for optimally diagnosing and treating insomnia based on the available research evidence.

DIAGNOSTIC CRITERIA FOR INSOMNIA

The clinical diagnosis of insomnia is based on the complaint of trouble falling asleep, trouble staying asleep, or early morning awakening, and resultant daytime dysfunction[1,2].

This daytime dysfunction can manifest in a wide range of ways, including fatigue, malaise; impairment in attention, concentration or memory; impaired social, family, occupational or academic performance; mood disturbance, irritability, sleepiness, hyperactivity, impulsivity, aggression, reduced motivation, proneness for errors, and concerns about or dissatisfaction with sleep[2].

The sleep disturbance must occur despite adequate opportunity for sleep in a safe, dark environment. Duration is also key to the diagnosis: to meet criteria for chronic insomnia according to the third edition of the International Classification of Sleep Disorders (ICSD-3) or for persistent insomnia according to the DSM-5, symptoms must be present at least three days per week for at least three months. Short term insomnia (ICSD-3) or episodic insomnia (DSM-5) has the same criteria as chronic insomnia, but lasts for fewer than three months.

If the sleep complaints are completely explained by another physical, psychiatric or sleep disorder, the patient does not meet diagnostic criteria for insomnia. However, insomnia is not solely a symptom of other mental disorders as was once thought[29]. Even if another disorder was the trigger or is present some of the time, if insomnia is sufficiently severe to warrant independent clinical attention, it should be recognized as a separate, comorbid disorder.

Previously, both the ICSD and the DSM described various subtypes of insomnia. These included psychophysiologic insomnia, paradoxical insomnia, idiopathic insomnia, behavioral insomnia of childhood, insomnia due to a mental disorder, insomnia due to a medical disorder, and insomnia due to a drug or substance. However, the mechanism of insomnia is poorly understood, and the various subtypes are difficult to differentiate in clinical practice[30]. Therefore, the subtypes were consolidated into chronic insomnia (ICSD-3) and persistent insomnia disorder (DSM-5) in the most recent editions of the manuals.

A subtype of insomnia with objectively short sleep has been described and stands out for its probable association with increased morbidity. These individuals meet criteria for chronic insomnia and, by objective measure, sleep on average less than six hours per night. This combination of insomnia with short sleep duration has been linked to hypertension, type 2 diabetes, and worse neurocognitive function[17,31,32]. Therefore, this may ultimately become a separate category in future versions of insomnia classifications.

DEMOGRAPHICS OF INSOMNIA

Symptoms of insomnia are common, with about one in three people reporting some symptoms in the previous year[33,34]. The point prevalence of a formal diagnosis of insomnia is 6-15%, though occurrence rates vary by definition used[35].

When looking at only nighttime complaints, rates are far higher. In a large population sample in France, 57% complained of trouble falling asleep, 53% of trouble staying asleep, and 41% of non-restorative sleep, though only 19% met DSM-IV criteria of at least one complaint three times per week for one month[36].

For many, insomnia is a persistent condition, with 74% reporting symptoms for at least one year[37]. Persistence is more common in women, the elderly, and those with more severe insomnia. In a 3-year study, over half of participants did remit, but there was a 27% relapse rate[37]. Family history of insomnia is also common, occurring in 35% of individuals[38].

Women more commonly report symptoms of insomnia and daytime consequences, and are more likely to be diagnosed with insomnia than men. The male-to-female ratio is 1:1.4 for insomnia symptoms and 1:2 for insomnia diagnosis[5]. In both men and women, the prevalence of insomnia increases with age[5,39,40].

Insomnia is associated with lower income, lower education, and being divorced or widowed[5,36,41]. It is also strongly associated with physical disorders, with half of those with insomnia also reporting multiple physical problems[34,41]. People with insomnia are more likely to rate their health poorly[42,43].

Insomnia is very strongly associated with mental disorders, most commonly depression, anxiety and post-traumatic stress disorder. Across cultures, most people with major depression report insomnia[44], and those with insomnia are more likely to have depressed mood[42,43,45-47]. Insomnia is also a predictor for developing mental health problems, including depression, anxiety, bipolar disorder and suicide[45].

CLINICAL ASSESSMENT OF INSOMNIA

Chief complaint

The chief complaint for those with insomnia is typically difficulty initiating or maintaining sleep, early morning awakening or simply unrefreshing sleep. Early morning awakening is waking at least 30 minutes prior to the desired time, accounting for habitual bedtime, total sleep time, and premorbid pattern.

The specific complaint may vary over time and often includes more than one sleep concern. The duration, frequency and severity of this concern should be elucidated as well as exacerbating and relieving factors. Complaints of insomnia often arise only when probed during evaluation of another disorder, despite the impact of insomnia on multiple health issues.

Current sleep history

A good current sleep history is essential to confirm the diagnosis and determine the best treatment for a patient with insomnia. This includes sleep/wake schedule, bedtime routine, nocturnal behavior, and daytime dysfunction.

Sleep/wake schedule

A detailed account of time to bed, time to sleep, frequency of night awakenings, time to return to sleep, time waking in the morning, and time out of bed should be obtained.

What the patient does when not falling asleep is also important. For example, a patient who gets out of bed and eats ice cream or watches a favorite show when not sleeping is providing positive reinforcement for being awake, which is counterproductive. This can be a behavior to target and eliminate during treatment.

The sleep/wake schedule should be obtained for both work/school days and weekends or vacations. A large variation may signal a circadian rhythm disorder and serve as a target for intervention.

Does the patient nap during the day? If taking a nap later in the day, this may be decreasing sleep drive in the evening and can also be a target for intervention. If the patient reports a strong propensity to fall asleep during the daytime, this raises concern for another sleep disorder.

Bedtime routine

It is important to have the right conditions to ensure proper sleep. While someone with true insomnia will not be effectively treated by simply providing a dark, quiet environment, the clinician – in order to confirm the diagnosis – must ensure that poor sleep is not due to poor sleep conditions.

Detailing the bedtime routine may also highlight areas for intervention during the treatment phase. For example, mobile phone use is associated with shorter sleep duration[22].

Nocturnal behavior

What does the patient do when not sleeping at night? Are there other behaviors overnight, such as snoring or leg kicking, that may signal alternative or concomitant diagnoses?

Input from a bed partner can also be helpful. In a patient who reports being awake the entire night, a bed partner often

observes long periods of sleep, suggesting there may be some sleep state misperception.

Daytime dysfunction

Daytime dysfunction is part of the formal criteria for insomnia and must be assessed. This includes worsened quality of life, concerns about memory, fatigue, mood, and success at work or school.

The 3P model

The 3P model, a behavioral model of insomnia developed by Spielman[48], can help the clinician focus a sleep history[49]. The model highlights why insomnia occurs in certain individuals and what allows acute insomnia to become chronic insomnia.

The three Ps occur in temporal order: factors *predisposing* an individual to insomnia, factors *precipitating* an acute episode of insomnia, and factors *perpetuating* the insomnia from acute to chronic. Predisposing factors include genetic and personality traits leading to physiologic and cognitive hyperarousal[50,51]. Precipitating factors are the triggers after which the insomnia cycle begins and are typically stressful events, though they can be positive, ranging from the loss of a loved one to retirement or marriage. Perpetuating factors allow the insomnia to continue, even when the trigger is removed. These factors include behaviors and thought structures that may appear to offer short-term relief yet cause long-term harm, such as increasing time in bed and reducing daytime activity.

Past medical history

There is a large interplay between many physical or psychiatric conditions and insomnia, and typically it is thought that a bidirectional relationship exists in which the physical or psychiatric condition exacerbates insomnia and vice versa. A huge range of physical comorbidities – including pulmonary, cardiac, gastrointestinal, endocrine, neurological, musculoskeletal and genitourinary – can contribute.

It is important to ensure that the management of these comorbid conditions is optimized when treating insomnia.

Medications

Numerous medications can impact sleep, and a thorough medication list, including over-the-counter medications and substances of abuse, should be elicited.

Antidepressants such as selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs) and monoamine oxidase inhibitors (MAOIs) can cause sedation or stimulation, with individual variability. Therefore, a patient may consider moving a daily dose from morning to evening or vice versa to determine how this impacts sleep.

Over-the-counter allergy medications often contain stimulants such as pseudoephedrine or phenylephrine, and patients may not realize that this can contribute to insomnia. Withdrawal can also contribute, such as from alcohol, benzodiazepines or opioids. Pulmonary medications, including albuterol and theophylline, can cause insomnia as well.

While insomnia is reported as a side effect of antihypertensive medications, and beta-blockers are known to reduce melatonin levels, there is mixed evidence about the direct impact of these medications on sleep[5,52,53].

Social history

Occupation is key to the sleep history, to ensure driving safety in patients reporting daytime sleepiness. Work or school hours are also important, as variation in these hours, shift work, and frequent travel across time zones can all disturb sleep.

Use of nicotine, caffeine, alcohol and other substances should also be noted.

Physical examination

Insomnia is not associated with any specific features on physical or mental status examination. The examination can, however, provide information about alternative diagnoses and comorbid conditions. Assessments to consider include body mass index, neck circumference and airway exam for obstructive sleep apnea[54].

Differential diagnosis

Three criteria must be met for a diagnosis of insomnia: complaint of trouble falling or staying asleep, adequate opportunity for sleep, and daytime dysfunction. If a patient reports trouble sleeping for the expected 7-8 hours but does not have daytime consequences, he/she may be a short sleeper. On the other hand, if there are insufficient hours of sleep and daytime dysfunction, but the patient is able to sleep when provided opportunity, this is likely to be behaviorally induced insufficient sleep. Function during vacations and weekends can be helpful to differentiate these.

Other sleep disorders that can present with the complaint of insomnia include circadian rhythm sleep-wake disorders, restless leg syndrome, periodic leg movement disorder, and obstructive sleep apnea.

Helpful questions to distinguish circadian disorders include the time to bed and awake on weekends, holidays and vacations in contrast to work or school days and whether there is a normal duration of refreshing sleep once the patient does fall asleep. If sleeping from 3 am to 10 am provides refreshing sleep and yet the patient gets in bed at midnight and hopes to rise at 7 am, but

cannot fall asleep for several hours, a delayed sleep-wake phase disorder may be involved and the misaligned internal rhythm should be the target for treatment.

Symptoms of restless leg syndrome include an urge to move the legs at least partially relieved by moving them, typically preceded by an abnormal leg sensation, and typically occurring during times of rest at the end of the day. As the syndrome can cause trouble falling asleep, it should be ruled out or treated directly.

Obstructive sleep apnea can present with symptoms of insomnia, more commonly in women than men. Presence of snoring, frequent awakenings, witnessed apneas should be discussed and, if concern is present, polysomnography should be performed[55,56].

Insomnia assessment tools

Sleep diary

Sleep diary is a form compiled by the patient, usually for at least two consecutive weeks, in which he/she notes down the time that he/she went to bed, the time of lights out, time to sleep, time and duration of awakenings overnight, time awake in the morning, time out of bed, naps, perceived duration of sleep, and sometimes quality and depth of sleep. The use of sleep aids and alcohol is sometimes included.

This can be very useful for the diagnosis of insomnia and is core to the treatment, because it helps to characterize the specific nature of the sleep problem, delineate maladaptive behaviors and provide an indicator of treatment outcome. If a circadian rhythm disorder is being considered, a sleep diary can be very useful for making the correct diagnosis.

Actigraphy

Actigraphy is a device, typically worn on the wrist, that records movement and employs an algorithm to estimate sleep and wake periods.

It has satisfactory reliability with the "gold standard" polysomnography in good sleepers who spend little time awake and still, but not in those with sleep difficulties where significant periods of waking stillness occur[57-60]. It is often combined with a light sensor to provide an estimate of the latency from lights out to sleep onset.

Actigraphy is not required in the evaluation of insomnia, but it can be useful for a patient whose sleep log or history is not reliable or when circadian disorders are suspected.

Personal monitoring devices

Commercially available devices that purport to measure sleep, often differentiating between light and deep sleep, are increasingly available. There are little published data indicating the performance of nearly all of these consumer devices and thus the accuracy of the information regarding sleep and wake periods is unknown.

Limited data suggest that some of these monitors do not accurately reflect sleep architecture, sleep efficiency or sleep latency, and tend to overestimate sleep duration in normal sleepers with far worse accuracy in insomnia patients[61,62]. Therefore, these devices are not recommended to make clinical decisions until there are rigorous studies establishing validity and reliability. The ease of use and consumer enthusiasm, however, does suggest that these devices may play an increasing role in evaluation and treatment moving forward.

Polysomnography

Polysomnography is the gold standard to distinguish sleep from wake. It is not needed for the diagnosis of insomnia, which is based on patient self-report. This is because indices traditionally derived from polysomnographic data do not reflect the sleep problems reported by approximately 40% of insomnia patients[63].

Polysomnography can be helpful to rule out other possible explanations for poor sleep, such as sleep apnea or periodic leg movement disorder. Therefore, it may be indicated when there is concern for sleep apnea or when a patient is not responding to treatment as expected.

Questionnaires

There are multiple questionnaires that can aid in the evaluation of insomnia.

In many sleep clinics, every patient completes the Epworth Sleepiness Scale[64], given the safety concern of daytime sleepiness when driving or operating heavy machinery. The Insomnia Severity Index[65] is commonly used in research as an outcome measure. The Dysfunctional Beliefs and Attitudes about Sleep[66] can help provide additional information to guide treatment. The Pittsburgh Sleep Quality Index[67] is also commonly used to collect information about self-perceived sleep quality.

MANAGEMENT OF INSOMNIA

When a patient is diagnosed with insomnia, treatment may be initiated with one of a number of available interventions. These can be broadly categorized as non-medication treatments and pharmacological therapies. In the sections below we review these interventions, focusing on the available evidence from blinded controlled trials indicating their efficacy and adverse effects.

Non-medication treatments

There are several different non-pharmacological treatment regimens that have been tested and implemented to treat in-

somnia. Here, we review the components and evidence supporting the non-medication treatment with the best empirical background and most widespread use, i.e. cognitive behavioral therapy for insomnia (CBT-I).

Employed in a variety of formats, CBT-I has been found to be effective in reducing insomnia and improving sleep across a wide array of clinical populations[68-77]. Consequently, the American College of Physicians has recommended this intervention as the first line treatment for adults with insomnia[74].

CBT-I has been found to be as effective in the short term as pharmacological treatments, with better long-term persistence of benefit after the end of treatment[72]. Further, unlike nearly all medications, this therapy has relatively minimal side effects. Here, we provide a clinical review of the components of CBT-I followed by evidence of its efficacy, including its effectiveness among patients with comorbidities, and its use across different treatment modalities.

CBT-I is typically delivered over roughly four to seven sessions. It is unclear how many sessions confer optimal benefit, though evidence suggests that fewer than four sessions are not generally sufficient[69,78].

Educational components of CBT-I

While most patients with insomnia are likely aware of some of the behaviors that fall into the sleep hygiene category, it is important to provide them with the relevant education. This includes the importance of establishing a conducive sleep environment by keeping the bedroom dark, quiet and cool.

Patients should also be reminded not to consume sleep disturbing substances, such as caffeine, nicotine and alcohol, particularly close to bedtime. Similarly, vigorous exercise three to four hours prior to bedtime should be avoided.

Additionally, a wind down routine can be helpful in readying a patient for bed. This should include discontinuation of arousing activities, including exposure to bright light (e.g., computer screen), which can negatively affect one's circadian rhythms.

Behavioral components of CBT-I

Stimulus control

Conditioned arousal is one of the key factors implicated in the pathogenesis of insomnia. Repeated pairing of the bed/bedroom and experiences of physiologic arousal, fear, anxiety and frustration leads to the bed serving as a learned cue or conditioned stimulus for arousal, which is incompatible with sleep onset and maintenance.

In order to eliminate this conditioned response, patients are recommended to remove themselves from the bed and bedroom if not sleepy and sit somewhere quiet until the feeling of sleepiness returns. Similarly, at bedtime, the patients are recommended not to go to bed unless they feel sleepy. Use of the bed and bedroom is restricted to sleep and sex, which means that patients are recommended not to do other activities in bed, including read or watch television. Additionally, patients are recommended to wake up the same time each morning, seven days per week, and get out of bed within 10 to 15 minutes upon awakening.

Sleep restriction

Another common contributor to the development and preservation of insomnia is the tendency for patients to spend excess time in bed. On the surface, this makes reasonable sense given that the patients yearn to "catch" sleep whenever they can. Unfortunately, excess time in bed results in conditioned arousal and fragmented sleep.

In order to effectively carry out this technique, patients should provide at least one week of sleep diaries (though two weeks are preferred). The goal is to reduce a patient's time in bed to the reported total sleep time. For instance, if a patient's diary report indicated an average total sleep time of six hours but a time in bed of nine hours (bedtime 9 pm and wake time 6 am), the new sleep schedule would provide a time in bed of six hours (bedtime midnight and wake time 6 am).

Importantly, patients are recommended to not go to sleep until the new prescribed bedtime and *only* when sleepy. In choosing the sleep opportunity window, it is important to take into account the patient's chronotype.

Due to safety concerns related to sleep restriction (e.g., cognitive deficits, drowsy driving), a minimum time in bed of five hours has been used in the literature[79]. In addition, sleep restriction may exacerbate comorbidities. For instance, sleep restriction has been shown to lower seizure thresholds, increase pain sensitivity, and precipitate mania in patients with bipolar disorder[80-82].

Patients are recommended to complete sleep diaries throughout treatment. Their time in bed schedule should be reviewed in each subsequent CBT-I session, with sessions occurring every one to two weeks. The sleep diaries allow the clinician to calculate their average sleep efficiency, which is the percentage of time a patient is asleep given his/her time in bed. We recommend 85% or higher in average sleep efficiency as a metric for "good" sleep quality and a threshold to be met prior to adjusting the time in bed recommendation.

Once it is established that a patient's sleep efficiency is sufficiently high, the clinician can begin to increase the time in bed, typically by altering the prescribed bedtime by 15 min each time and tracking the patient's improvement in subjective sleep quality and daytime sleepiness.

Sleep restriction is typically the aspect of CBT-I that suffers the most from non-adherence. In the event that a patient is unable or unwilling to carry out the prescribed time in bed, sleep compression can also be used. This technique consists of slowly decreasing time in bed over time in order to meet the original prescribed time, and may be more palatable to patients, particularly those with significant anxiety about losing further sleep opportunity.

Relaxation and paradoxical intention

These behavioral techniques complement stimulus control and sleep restriction by providing the patient with tools for decreasing arousal prior to bedtime and in the event of nighttime awakenings.

Relaxation techniques vary, but typically include diaphragmatic breathing, the tensing and relaxing of muscle groups, and possibly visual imagery. Paradoxical intention is premised on the idea that anxiety about falling asleep is inhibiting sleep onset. Using this technique, patients are asked to stay awake as long as possible, which leads to reduced anxiety and easier sleep onset.

Cognitive components of CBT-I

Maladaptive beliefs and thoughts about sleep are typically addressed throughout treatment. It is important for a clinician to attend to sleep-related worries, as they tend to drive the inappropriate behaviors that perpetuate insomnia. Unrealistic expectations about sleep and catastrophic thinking about the consequences of sleep loss are among these worries.

One technique for countering catastrophic thoughts is by examining evidence from the patient's experience. For instance, if a patient has the belief that a poor night of sleep will leave him/her unable to be effective in his/her job, a clinician could help the patient identify instances when he/she was able to perform sufficiently despite a poor night of sleep. Additionally, providing patients with tools to reduce worry at bedtime can be helpful.

Another technique, known as a constructive worry exercise, requires patients to list in the early evening three or more problems that they believe will likely keep them up at night. For each problem, patients list the next step towards a solution. The exercise is folded and put away and, if patients awake during the night, they are to remind themselves that they have already taken the necessary step towards resolving that problem at their "problem-solving best" (i.e., not in the middle of the night).

Evidence of efficacy of CBT-I

Several meta-analytic reviews support the efficacy of CBT-I compared to active control conditions and usual care[68-70,72,78-81]. In a recent meta-analysis, van Straten et al[69] pooled data from 87 randomized controlled studies that used at least one component of CBT-I, which included 3,724 patients and 2,579 non-treated controls. The strongest effects were improvements in insomnia symptoms, as measured using the Insomnia Severity Index (Hedges' g=0.98), sleep efficiency (g=0.71), wake after sleep onset (g=0.63), sleep onset latency (g=0.57), and subjective sleep quality (g=0.40). A small effect was observed for changes in total sleep time (g=0.16).

Further, data suggest that CBT-I is effective among individuals with psychiatric and physical comorbidities[70], with some accruing evidence that it may have positive effects on comorbid outcomes[82,83]. CBT-I benefits are stronger for psychiatric than physical comorbidities[70].

CBT-I has been delivered using a number of different formats, including face-to-face individual, group and digitally delivered therapy. In addition, self-help manuals, books and videos have been developed, which allow patients to carry out treatment on their own. In general, all modalities are effective, though there is some evidence to suggest that face-to-face therapy outperforms self-help. Digitally delivered CBT-I appears to produce effects comparable to in-person therapy[84,85]; however, it is likely that in-person supervision may be required for more complicated cases[86].

Pharmacological therapies

A number of medications from several different classes have undergone randomized, double-blind, placebo-controlled trials in patients with insomnia. Those for which a statistically significant therapeutic effect compared with placebo was reported appear in Tables 1 and 2. In addition, there are a number of medications commonly used to treat insomnia that have not been demonstrated to have efficacy in at least one double-blind, randomized, placebo-controlled trial. These appear in Table 3.

In this section we review the characteristics of all of these medications (benzodiazepines, "z-drugs", melatonin receptor agonists, selective histamine H1 antagonists, orexin antagonists, antidepressants, antipsychotics, anticonvulsants, and non-selective antihistamines) and present the available evidence regarding their efficacy and safety as a basis for clinical decision making.

Benzodiazepines

Benzodiazepines are a group of compounds with a similar chemical structure. Their sleep enhancing effect is a result of positive allosteric modulation of the gamma-aminobutyric acid (GABA) type A receptor[138,139]. These agents exert this modulation by binding to a specific site on the GABA-A receptor complex (referred to as the benzodiazepine binding site), thereby changing the conformation of the receptor constituent proteins, which leads to an enhancement of the inhibition occurring when GABA binds to these receptors[140,141]. This enhancement of inhibition is associated with a broad set of dose-dependent clinical effects, including sedation, anxiety reduction, seizure inhibition and myorelaxation[139,140,142].

Of the benzodiazepine medications, triazolam, flurazepam, temazepam, quazepam and estazolam have been demonstrated to have therapeutic effects on both sleep onset and maintenance in double-blind, placebo-controlled trials in younger adults (Table 1). In older adults, triazolam and flurazepam have been found to have therapeutic effects on sleep onset and maintenance in double-blind, placebo-controlled trials, whereas temazepam has been demonstrated to have therapeutic effects on sleep maintenance only (Table 2).

Table 1 Double-blind placebo-controlled trials demonstrating efficacy in the treatment of younger adults with insomnia

Medication	Class	Efficacy for sleep onset		Efficacy for sleep maintenance		Primary adverse effects
		Dose (mg)	N	Dose (mg)	N	
Triazolam	BDZ	0.25[87]	1,507	0.5[89]	277	Dose-dependent sedation, psychomotor impairment, abuse potential
		0.25[88]	83			
		0.5[89]	277			
Flurazepam	BDZ	30[90]	60	30[91]	157	Dose-dependent sedation, psychomotor impairment, abuse potential
		30[91]	157			
Estazolam	BDZ	2[91]	148	2[91]	148	Dose-dependent sedation, psychomotor impairment, abuse potential
		1-2[92]	379	1-2[92]	379	
				0.25-2[93]	15	
Quazepam	BDZ	30[94]	57	30[94]	57	Dose-dependent sedation, psychomotor impairment, abuse potential
Temazepam	BDZ	30[95]	75	30[95]	75	Dose-dependent sedation, psychomotor impairment, abuse potential
Zolpidem	z-drug	10[96]	75	10[100]	199	Dose-dependent sedation, psychomotor impairment, abuse potential
		10[97]	203			
		10[98]	615			
		10[99]	163			
		10[100]	199			
Zolpidem (extended release)	z-drug	12.5[101]	212	12.5[101]	212	Dose-dependent sedation, psychomotor impairment, abuse potential
		12.5[102]	1,025	12.5[102]	1,025	
Zolpidem (sublingual)	z-drug			3.5[103]	295	Dose-dependent sedation, psychomotor impairment, abuse potential
Zaleplon	z-drug	10[104]	113			Dose-dependent sedation, psychomotor impairment, abuse potential
		10-20[88]	83			
		10-20[98]	615			
Zopiclone	z-drug	7.5[105]	25	7.5[105]	25	Bitter taste, dose-dependent sedation, psychomotor impairment, abuse potential
		7.5[88]	1,507	7.5[88]	1,507	
Eszopiclone	z-drug	3[106]	788	3[106]	788	Bitter taste, dose-dependent sedation, psychomotor impairment, abuse potential
		3[107]	830	3[107]	830	
		2-3[108]	308	2-3[108]	308	
Ramelteon	MT1/MT2 agonist	4-32[109]	107			
		8-32[110]	65			
		8[111]	451			
		4-16[112]	190			
		8-16[113]	405			
Doxepin	H1 antagonist	6[114]	67	1,3,6[114]	67	Sedation
				25-50[115]	47	
				6[116]	254	
				3-6[117]	221	
Suvorexant	Orexin antagonist	20-40[118]	1,211	20-40[118]	1,211	Sedation, probable abuse potential
		10-80[119]	591	10-80[119]	591	
		40[120]	380	40[120]	380	

BDZ – benzodiazepine

Table 2 Double-blind placebo-controlled trials demonstrating efficacy in the treatment of older adults with insomnia

Medication	Class	Efficacy for sleep onset		Efficacy for sleep maintenance		Adverse effects
		Dose (mg)	N	Dose (mg)	N	
Triazolam	BDZ	0.25[121]	32	0.125[125]	22	Dose-dependent sedation, psychomotor impairment, abuse potential
		0.25[122]	41	0.25[122]	41	
		0.25-0.5[123]	27	0.4-0.8[124]	25	
		0.4-0.8[124]	25			
		0.125[125]	22			
Flurazepam	BDZ	15[122]	41	30[124]	25	Dose-dependent sedation, psychomotor impairment, abuse potential
		30[124]	25			
Temazepam	BDZ			7.5-30[126]	40	Dose-dependent sedation, psychomotor impairment, abuse potential
Zolpidem	z-drug	5[127]	549			Sedation, psychomotor impairment, abuse potential
Zolpidem (extended release)	z-drug	6.5[128]	205	6.5[128]	205	Sedation, psychomotor impairment, abuse potential
Zaleplon	z-drug	5-10[129]	422			Dose-dependent sedation, psychomotor impairment, abuse potential
		10[127]	549			
Zopiclone	z-drug	5-7.5[121]	48	5-7.5[121]	48	Bitter taste, dose-dependent sedation, psychomotor impairment, abuse potential
Eszopiclone	z-drug	2[130]	231	2[130]	231	Bitter taste, dose-dependent sedation, psychomotor impairment, abuse potential
		2[131]	264	2[131]	264	
		2[132]	388	2[132]	388	
Ramelteon	MT1/MT2 agonist	8[133]	829			
		8[134]	100			
Doxepin	Selective H1 antagonist			3-6[135]	76	
				1-3[136]	240	
Suvorexant	Orexin antagonist	15[137]	520	15[137]	520	Sedation, probable abuse potential
		30[120]	319	30[120]	319	
		15-30[137]	819	15-30[137]	819	

BDZ – benzodiazepine

For many years the prevailing view of these medications, and medications used for the treatment of insomnia in general, was that they were inevitably associated with tolerance (i.e., loss of therapeutic benefit over time) and dependence (i.e., withdrawal symptoms upon discontinuation) when used nightly on a long-term basis[143]. Until relatively recently, little data were available to actually assess whether this was the case[25]. As data have become available, it has been clear that tolerance and dependence do not inevitably occur and are not characteristic of long-term nightly insomnia pharmacotherapy.

However, data on long-term treatment are only available for some medications, and the available information leaves open the possibility that dependence does occur in some individuals[25]. This limitation is particularly notable for benzodiazepines: the longest nightly treatment study of a benzodiazepine was an 8-week trial of temazepam, where dependence was not observed[126]. Studies of 2-4 weeks duration were carried out with triazolam (three trials) and flurazepam (one trial), without evidence of dependence occurring[87,121,122].

The adverse effects of benzodiazepines are dose-dependent and reflect their broad central nervous system inhibitory activity. They include sedation, psychomotor impairment, and potential for abuse by a small subset of the population[143]. The anxiolytic and myorelaxant effects can be useful in those with comorbid anxiety or pain.

Among the available options, these agents are relatively effective at treating sleep onset problems and, as a result, may be needed in some individuals with this type of sleep problem. The

Table 3 Medications used to treat insomnia not demonstrated to have efficacy in at least one double-blind placebo-controlled trial in insomnia patients

Medication	FDA approved indication	Primary known side effects
Trazodone	Major depressive disorder	Sedation, dizziness, headache, dry mouth, blurred vision, orthostatic hypotension, priapism
Mirtazapine	Major depressive disorder	Sedation, dry mouth, increased appetite/weight gain, constipation
Amitriptyline	Major depressive disorder	Sedation, dizziness, weight gain, dry mouth, blurred vision, constipation, urinary retention
Gabapentin	Partial seizures, pain	Sedation, dizziness, ataxia, diplopia
Pregabalin	Fibromyalgia, pain, partial seizures	Sedation, dizziness, dry mouth, cognitive impairment, increased appetite, discontinuation effects
Quetiapine	Schizophrenia, mania, major depressive disorder	Sedation, orthostatic hypotension, dry mouth, tachycardia, increased appetite/weight gain
Olanzapine	Schizophrenia, mania	Sedation, agitation, dizziness, constipation, orthostatic hypotension, akathisia, weight gain, increased incidence of cerebrovascular events in dementia patients
Diphenhydramine	Over-the-counter antihistamine	Sedation, dizziness, dry mouth, blurred vision, constipation, urinary retention
Doxylamine	Over-the-counter antihistamine	Sedation, dizziness, dry mouth, blurred vision, constipation, urinary retention
Melatonin	Over-the-counter hormone	Headache, sedation

FDA – US Food and Drug Administration

only relative contraindication to their use is a history of polysubstance abuse or a specific predisposition to benzodiazepine abuse.

"Z-drugs"

These agents are an unrelated group of compounds which act by the same mechanism as benzodiazepines, but do not share the benzodiazepine chemical structure[138-142]. There is some evidence that they may differ somewhat from benzodiazepines in that their action is relatively restricted to subsets of GABA-A receptors. As a result, they may have less broad clinical effects[25,138-142].

Double-blind, placebo-controlled trials demonstrate the efficacy of zaleplon for sleep onset, and of zolpidem extended-release, zopiclone and eszopiclone (the S isomer of zopiclone) for sleep onset and maintenance in both younger and older adults. Zolpidem has a documented efficacy for sleep onset and maintenance problems in younger adults, but for sleep onset problems only in older adults (Tables 1 and 2).

More data on long-term treatment are available for "z-drugs" than for benzodiazepines. The sustained efficacy of eszopiclone and zolpidem has been demonstrated in studies of nightly dosing up to one year in duration without any evidence of dependence occurring, nor was dependence found in a 6-month study of non-nightly treatment with extended-release zolpidem[101,106,107].

The potential adverse effects of the "z-drugs" are the same as the benzodiazepines. Because of the relatively narrower effects of some of these agents, they may not be as helpful as benzodiazepines in addressing concomitant anxiety or pain. This appears to be the case for zolpidem. However, eszopiclone and zolpidem extended-release have been found to have therapeutic effects on pain, anxiety and depression concomitant with insomnia[144-151].

Like benzodiazepines, these agents are relatively more effective than other options in treating problems with sleep maintenance, and may be problematic in those predisposed towards substance abuse.

Melatonin receptor agonists

There are two melatonin receptor agonists used in the treatment of insomnia: melatonin and ramelteon.

Melatonin is a hormone that is taken by many individuals with insomnia. Normally, it is released by the pineal gland during the dark period of the day. It binds predominantly to the MT1 and MT2 receptors, though the mechanism by which this might enhance sleep is not well understood[152].

No clear dose-response relationship has been established for the use of melatonin for treating insomnia, and there is some evidence that sleep enhancement may depend on the time of day and may not occur until 3-4 hours after administration[153-155].

A substantial number of studies have evaluated the effects of a variety of dosages, administration times, and both immediate and prolonged release formulations of melatonin in individuals with sleep problems[156,157]. The available evidence suggests that this agent has a clear therapeutic effect in individuals with delayed sleep-phase syndrome, that it has an excellent safety profile, and that there may be a modest therapeutic effect on sleep onset latency in individuals with insomnia (although it remains unclear whether this effect is of clinical significance). Some preliminary evidence supports the use of melatonin to treat sleep problems in children with neurodevelopmental disorders, in whom this agent has been established to have an excellent safety profile[158-163].

The most common adverse effect of melatonin is headache, and slowing of reaction time and sedation can occur during the day. Melatonin is without abuse potential, so it could be admin-

istered to abuse-prone individuals with insomnia. Because it is a hormone that regulates reproductive function, when taken in higher dosages it can in theory impair fertility. Therefore, it has been recommended that it not be taken in those attempting to conceive[164-167].

Like melatonin, ramelteon is an agonist at MT1 and MT2 receptors. However, it is a substantially more potent agonist at these receptors than melatonin. Double-blind, placebo-controlled trials demonstrate the efficacy of ramelteon for sleep onset insomnia in both younger and older adults (Tables 1 and 2). Efficacy has been more consistently found with polysomnographic measures than self-report measures of sleep onset. Nightly treatment for six months was evaluated and no evidence of dependence phenomena was reported[111].

Ramelteon has a relatively benign profile of adverse effects, among which the most commonly reported are headache, sedation, fatigue and nausea. It does not have significant abuse potential and could be used for abuse-prone individuals with sleep onset problems, though no studies have evaluated its therapeutic effects in this population. Due to its good safety profile, it may be considered for use in individuals with difficulty in sleep onset only.

Selective H1 antagonists

The only highly selective histamine H1 receptor antagonist that has been systematically studied is doxepin in the 3-6 mg dosage range[25].

Doxepin, originally developed as an antidepressant in dosages of 75-150 mg/day, has H1 antagonism as its most potent pharmacological effect[168]. As a result, as the dosage is decreased, this agent becomes an increasingly specific H1 antagonist[168].

Double-blind, placebo-controlled trials carried out in both younger and older adults, using both self-report and polysomnographic endpoints, demonstrate the sleep maintenance efficacy of this medication in the 3-6 mg range (Tables 1 and 2). It is notable that the therapeutic effects appear to be largest towards the end of the night, without increasing morning impairment. As such, this agent appears to be uniquely well suited for use in individuals waking up towards the end of the night and having difficulty returning to sleep. Studies of up to 3-month duration of nightly treatment have been carried out without dependence occurring[136].

The most common adverse effect reported in younger adults is daytime sedation. However, in older adults there were no adverse effects reported more frequently with doxepin 3 mg compared to placebo. As such, older adults with early morning awakening would be a particularly appropriate group to treat with this medication. Also, given its potent H1 antagonism, doxepin could also be considered for use in people with insomnia occurring with allergy symptoms. As this agent is without abuse potential, it could also be used in patients with sleep maintenance problems who are prone to abuse, although no data exist on its use in this population.

Orexin receptor antagonists

The name "orexins" was given to two peptides that were relatively recently discovered to arise from the neurons of the lateral hypothalamus and to promote wakefulness/arousal[118-120]. Agents which are orexin receptor antagonists are sleep promoting, owing to their ability to block the arousal mediated by the orexins.

Suvorexant is an agent which blocks both types of orexin receptors (orexin A and B) and has been demonstrated in double-blind placebo-controlled trials to have therapeutic effects on sleep onset and maintenance (including in the last third of the night) in both younger and older insomnia patients, at dosages from 10 to 40 mg (Tables 1 and 2). This includes a placebo-controlled trial of nightly treatment for a year, which demonstrated sustained therapeutic effects and no significant rebound insomnia on discontinuation[120].

The adverse effect of suvorexant that is of most importance is daytime sedation. Available studies suggest that this agent is associated with some abuse potential that is roughly comparable to that of zolpidem, so that it is probably best avoided in people predisposed to abuse.

Suvorexant is the only agent with therapeutic effects in the last third of the night without substantially increasing morning sedation that also has a robust therapeutic effect on sleep onset. As such, it could be considered for use in those patients with both sleep onset difficulties and early morning awakening.

Antidepressants

There are several medications originally developed for the treatment of major depressive disorder that are commonly used for treating insomnia. These agents may produce sleep enhancing effects by blocking the receptors for neurotransmitters that are wake enhancing, such as norepinephrine, histamine, acetylcholine and serotonin[25].

The antidepressants most commonly used to treat insomnia are trazodone 50-150 mg, doxepin 10-75 mg, mirtazapine 15 mg, and amitriptyline 10-100 mg[25]. Of these agents, only doxepin 25-50 mg has been demonstrated to have therapeutic effects in insomnia patients in at least one placebo-controlled, double-blind, randomized trial, and this study was small (N=47) (Table 1).

Although trazodone is widely prescribed in the treatment of insomnia, it has not been found to have therapeutic effects in insomnia patients in any randomized, double-blind, placebo-controlled trial. It was evaluated in one such trial in younger adults, but significant effects compared with placebo were not found[97]. This should not be interpreted as definitive evidence that it lacks therapeutic effects in insomnia. In fact, that study evaluated only one dose of trazodone (50 mg), whereas clinically a range of doses from 50 to 150 mg is prescribed[25].

There are data available on the efficacy and side effects of the S isomer of mirtazapine, which is not currently available for prescription. S-mirtazapine, like doxepin, is a selective H1

antagonist and has been evaluated in a dosing range far below the antidepressant dosage, at which it is expected to have only H1 antagonist effects of clinical significance[169-171]. Placebo-controlled, randomized, double-blind trials carried out with this agent suggest that, like doxepin, it has robust effects on sleep maintenance, with less pronounced therapeutic effects on sleep onset[169-171].

The adverse effects of the antidepressants used to treat insomnia vary. All of them can cause daytime sedation, and most may cause orthostatic hypotension. The tricyclic antidepressants doxepin (25-50 mg) and amitriptyline can cause dry mouth, constipation, blurred vision, urinary retention, cognitive impairment, arrhythmias, and increased appetite/weight gain[25]. Mirtazapine's most important adverse effects tend to be sedation and increased appetite/weight gain. Trazodone's most important adverse effects include sedation and orthostatic hypotension; it may also induce priapism[25].

As none of these agents has significant abuse potential, they can be considered in people with a predisposition to substance abuse. They can also be considered for use in patients who fail usual therapy or have concomitant conditions such as mood, anxiety or pain difficulties, owing to their broad pharmacological effects[25]. Doxepin and amitriptyline should be used with caution in individuals prone to cognitive impairment, urinary obstruction or glaucoma. The use of all these agents is problematic in patients with bipolar depression, because of the risk of precipitating mania[172].

Antipsychotics

Antipsychotics are a group of medications developed for treatment of psychotic conditions that are sometimes used in clinical practice to treat insomnia, generally at a dosage lower than that typically used to treat individuals with psychosis[25]. These agents may have therapeutic effects in insomnia due to their broad antagonism of wake promoting neurotransmitter receptors, such as dopamine, histamine, serotonin, cholinergic and adrenergic receptors.

The antipsychotic medications that are most commonly used to treat insomnia in clinical practice are quetiapine 25-250 mg and olanzapine 2.5-20 mg. There are no rigorous double-blind, randomized, placebo-controlled trials demonstrating the efficacy of any antipsychotic medication for the treatment of insomnia.

A few small studies of quetiapine have been carried out. This agent was reported to improve wake time after sleep onset as compared to placebo in a trial of 20 patients with alcohol use disorder in recovery and sleep disturbance[173]. A double-blind, randomized, placebo-controlled trial of quetiapine 25 mg was also carried out in 13 patients with primary insomnia and demonstrated an advantage for quetiapine on sleep latency and total sleep time, although neither reached statistical significance[174].

The primary side effects of these agents include sedation, orthostatic hypotension, dry mouth, tachycardia, increased appetite/weight gain, agitation, dizziness, constipation and akathisia. More concerning, though far less common, is the risk of tardive dyskinesia. The increased risk of cerebrovascular events in patients with dementia should also be taken into account.

As these agents are without abuse potential, they can be considered for use in people who are abuse-prone. They are best suited, however, for insomnia occurring in patients with psychosis or bipolar disorder.

These agents should be used with caution in those with dementia, hypotension or at risk for myocardial infarction, closed-angle glaucoma, constipation or urinary retention.

Non-selective antihistamines

Non-selective antihistamines that are often used to treat insomnia include diphenhydramine and doxylamine, which are ingredients in many over-the-counter insomnia therapies. Both of these agents have, in addition to H1 antagonism, clinically relevant M1 muscarinic cholinergic antagonism.

There are highly limited data establishing the insomnia efficacy of these drugs. A therapeutic effect of diphenhydramine 50 mg on self-reported number of awakenings, but not sleep quality, total sleep time or sleep onset latency, was reported in a placebo-controlled cross-over study in 20 older primary insomnia patients[175]. Diphenhydramine 25 mg was also evaluated in a parallel-group study along with a combination of valerian and hops in 184 insomnia patients, and found to have a significant effect vs. placebo on self-reported sleep efficiency, but not self-reported or polysomnographic sleep onset latency, total sleep time, or polysomnographic sleep efficiency[176].

The most important adverse effects of these medications are sedation, dizziness, psychomotor impairment, cognitive impairment, dry mouth, blurred vision, constipation, urinary retention and weight gain. Less common side effects of diphenhydramine include agitation and insomnia, whereas doxylamine has been linked in case reports to coma and rhabdomyolysis[177].

As these agents do not have significant abuse potential, they can, in theory, be considered for use in substance abuse-prone insomnia patients. They are best suited for use in those with insomnia occurring in the setting of allergy symptoms or upper respiratory infections. They are best avoided in those with closed-angle glaucoma, decreased gastrointestinal motility, urinary retention, asthma and chronic obstructive pulmonary disease.

Anticonvulsants

Some agents originally developed for treatment of seizures are at times used in the management of insomnia. They include gabapentin and pregabalin, whose potential therapeutic effects in insomnia are ascribed to a decreased release of glutamate and norepinephrine through binding to the alpha-2-delta subunit of N-type voltage-gated calcium channels[178,179].

There are no double-blind, randomized, placebo-controlled trials evaluating the efficacy of these agents in insomnia pa-

tients. Two double-blind, randomized, placebo-controlled trials were carried out evaluating the effects of gabapentin 250-500 mg on sleep disturbance created by putting people to bed five hours earlier than usual (five-hour phase advance model). They reported that this agent significantly improved both self-reported and polysomnographic wake time after sleep onset and total sleep time compared with placebo, but not sleep onset latency[180,181].

Therapeutic effects of gabapentin and pregabalin on sleep disturbance have also been reported in studies of patients with pain, restless legs syndrome, generalized anxiety disorder, and epilepsy[182-185].

The most important side effects of gabapentin are sedation, dizziness, ataxia and diplopia, whereas the most important adverse effects of pregabalin include sedation, dizziness, dry mouth, cognitive impairment and appetite increase. Pregabalin appears to have some abuse potential, whereas this is not the case for gabapentin[186].

These agents could be considered for use in insomnia occurring in patients with pain, partial seizures or restless legs syndrome. There is some evidence supporting the use of pregabalin to treat insomnia occurring in those with alcohol use disorder[187,188]. Both of these medications should be avoided in patients with impaired renal function.

UNMET NEEDS

Insomnia is a common and often debilitating disorder that is associated with significant adverse consequences for physical health and well-being. Fortunately, there are behavioral and pharmacological treatments available for treating this condition. In this paper we reviewed the evidence base for those treatments in order to provide a resource for practitioners, with the hope that this would improve the clinical management of insomnia. However, our review also illustrates that there are a number of important gaps in the research carried out to date.

We lack information on the specific effects of the various components of CBT-I which might allow greater treatment efficiency and tailoring. While meta-analyses demonstrate the value of CBT-I, they also note significant heterogeneity. Variability in CBT-I components across trials makes it difficult to determine which aspects are most responsible for the observed benefits. As such, there is a need for studies aimed at providing this information.

There are also a number of key gaps related to pharmacotherapy. The most glaring one is that we lack any double-blind, placebo-controlled, randomized trial demonstrating the efficacy of any pharmacological treatment for insomnia in children or adolescents. There is clearly an urgent need to carry out these studies in order to guide effective clinical practice in younger individuals with insomnia.

Another gap in insomnia pharmacotherapy research is that we lack rigorous double-blind, placebo-controlled trials of a number of agents commonly used to treat this condition in clinical practice. This includes agents such as trazodone, quetiapine and gabapentin. It would be of great value to those clinicians who tend to prescribe these medications if they had data delineating their risks and benefits to help guide their clinical decision making.

We also lack studies of the pharmacological treatment of insomnia in the setting of several key conditions where this treatment is very often needed, such as dementia, mild cognitive impairment and substance use disorders.

A final critical gap in our knowledge base reflected in our review is that we lack research to help guide personalization of therapy. The vast majority of studies carried out evaluate a single therapy vs. a placebo or another control intervention. More trials are needed comparing effective treatments and aimed at optimally matching treatments to specific patient types, so that we can move to greater personalization in clinical practice.

REFERENCES

1. American Psychiatric Association. Diagnostic and statistical manual of mental disorders, 5th ed. Arlington: American Psychiatric Association, 2013.
2. American Academy of Sleep Medicine. International classification of sleep disorders, 3rd ed. Darien: American Academy of Sleep Medicine, 2014.
3. Ohayon MM, Reynolds CF. Epidemiological and clinical relevance of insomnia diagnosis algorithms according to the DSM-IV and the International Classification of Sleep Disorders (ICSD). Sleep Med 2009;10:952-60.
4. Roth T, Coulouvrat C, Hajak G et al. Prevalence and perceived health associated with insomnia based on DSM-IV-TR; International Statistical Classification of Diseases and Related Health Problems, tenth revision; and Research Diagnostic Criteria/International Classification of Sleep Disorders. Biol Psychiatry 2011;69:592-600.
5. Ohayon MM. Epidemiology of insomnia: what we know and what we still need to learn. Sleep Med Rev 2002;6:97-111.
6. Morin CM, LeBlanc M, Bélanger L et al. Prevalence of insomnia and its treatment in Canada. Can J Psychiatry 2011;56:540-8.
7. Pearson NJ, Johnson LL, Nahin RL. Insomnia, trouble sleeping, and complementary and alternative medicine: analysis of the 2002 National Health Interview Survey data. Arch Intern Med 2006;166:1775-82.
8. Roth T, Jaeger S, Jin R et al. Sleep problems, comorbid mental disorders, and role functioning in the National Comorbidity Survey Replication. Biol Psychiatry 2006;60:1364-71.
9. Sarsour K, Morin CM, Foley K et al. Association of insomnia severity and comorbid medical and psychiatric disorders in a health plan-based sample: insomnia severity and comorbidities. Sleep Med 2010;11:69-74.
10. Budhiraja R, Roth T, Hudgel DW et al. Prevalence and polysomnographic correlates of insomnia comorbid with medical disorders. Sleep 2011;34:859-67.
11. Baglioni C, Battagliese G, Feige B et al. Insomnia as a predictor of depression: a meta-analytic evaluation of longitudinal epidemiological studies. J Affect Disord 2011;135:10-9.
12. Breslau N, Roth T, Rosenthal L et al. Sleep disturbance and psychiatric disorders: a longitudinal epidemiological study of young adults. Biol Psychiatry 1996;39:411-8.
13. Drake CL, Pillai V, Roth T. Stress and sleep reactivity: a prospective investigation of the stress diathesis model of insomnia. Sleep 2014;37:1295-304.
14. Johnson EO, Chilcoat HD, Breslau N. Trouble sleeping and anxiety/depression in childhood. Psychiatry Res 2000;94:93-102.
15. Johnson EO, Roth T, Breslau N. The association of insomnia with anxiety disorders and depression: exploration of the direction of risk. J Psychiatr Res 2006;40:700-8.
16. Pigeon WR, Pinquart M, Conner K. Meta-analysis of sleep disturbance and suicidal thoughts and behaviors. J Clin Psychiatry 2012;73:e1160-7.
17. Vgontzas AN, Liao D, Bixler EO et al. Insomnia with objective short sleep duration is associated with a high risk for hypertension. Sleep 2009;32:491-7.

18. Fernandez-Mendoza J, Vgontzas AN, Liao D et al. Insomnia with objective short sleep duration and incident hypertension: the Penn State Cohort. Hypertension 2012;60:929-35.
19. Parthasarathy S, Vasquez MM, Halonen M et al. Persistent insomnia is associated with mortality risk. Am J Med 2015;128:268-75.
20. Kessler RC, Berglund PA, Coulouvrat C et al. Insomnia, comorbidity, and risk of injury among insured Americans: results from the America Insomnia Survey. Sleep 2012;35:825-34.
21. Koski K, Luukinen H, Laippala P et al. Risk factors for major injurious falls among the home dwelling elderly by functional abilities. A prospective population-based study. Gerontology 1998;44:232-8.
22. Avidan AY, Fries BE, James ML et al. Insomnia and hypnotic use, recorded in the minimum data set, as predictors of falls and hip fractures in Michigan nursing homes. J Am Geriatr Soc 2005;53:955-62.
23. Stone KL, Blackwell TL, Ancoli-Israel S et al. Sleep disturbances and risk of falls in older community-dwelling men: the outcomes of Sleep Disorders in Older Men (MrOS Sleep) Study. J Am Geriatr Soc 2014;62:299-305.
24. National Institutes of Health. National Institutes of Health state of the science conference statement on manifestations and management of chronic insomnia in adults, June 13-15, 2005. Sleep 2005;28:1049-57.
25. Krystal AD. A compendium of placebo-controlled trials of the risks/benefits of pharmacological treatments for insomnia: the empirical basis for U.S. clinical practice. Sleep Med Rev 2009;13:265-74.
26. 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;13:307-49.
27. Miller CB, Espie CA, Epstein DR et al. The evidence base of sleep restriction therapy for treating insomnia disorder. Sleep Med Rev 2014;18:415-24.
28. Morin CM, Bootzin RR, Buysse DJ et al. Psychological and behavioral treatment of insomnia: update of the recent evidence. Sleep 2006;29:1398-414.
29. Matteson-Rusby SE, Pigeon WR, Gehrman P et al. Why treat insomnia? Prim Care Companion J Clin Psychiatry 2010;12:PCC.08r00743.
30. Edinger JD, Wyatt JK, Stepanski EJ et al. Testing the reliability and validity of DSM-IV-TR and ICSD-2 insomnia diagnoses. Arch Gen Psychiatry 2011;68:992-1002.
31. Vgontzas AN, Liao D, Pejovic S et al. Insomnia with objective short sleep duration is associated with type 2 diabetes: a population-based study. Diabetes Care 2009;32:1980-5.
32. Fernandez-Mendoza J, Calhoun S, Bixler EO et al. Insomnia with objective short sleep duration is associated with deficits in neuropsychological performance: a general population study. Sleep 2010;33:459-65.
33. Johnson EO. Epidemiology of insomnia: from adolescence to old age. Sleep Med Clin 2006;1:305-17.
34. Mellinger GD, Balter MB, Uhlenhuth EH. Insomnia and its treatment. Prevalence and correlates. Arch Gen Psychiatry 1985;42:225-32.
35. Roth T. Insomnia: definition, prevalence, etiology, and consequences. J Clin Sleep Med 2007;3(Suppl.5):S7-10.
36. Leger D, Guilleminault C, Dreyfus JP et al. Prevalence of insomnia in a survey of 12,778 adults in France. J Sleep Res 2000;9:35-42.
37. Morin CM, Bélanger L, LeBlanc M et al. The natural history of insomnia: a population-based 3-year longitudinal study. Arch Intern Med 2009;169:447-53.
38. Beaulieu-Bonneau S, LeBlanc M, Mérette C et al. Family history of insomnia in a population-based sample. Sleep 2007;30:1739-45.
39. Kim K, Uchiyama M, Okawa M et al. An epidemiological study of insomnia among the Japanese general population. Sleep 2000;23:41-7.
40. Ohayon M. Epidemiological study on insomnia in the general population. Sleep 1996;19(Suppl. 3):S7-15.
41. Bixler EO, Kales A, Soldatos CR et al. Prevalence of sleep disorders in the Los Angeles metropolitan area. Am J Psychiatry 1979;136:1257-62.
42. Maggi S, Langlois JA, Minicuci N et al. Sleep complaints in community-dwelling older persons: prevalence, associated factors, and reported causes. J Am Geriatr Soc 1998;46:161-8.
43. Foley DJ, Monjan AA, Brown SL et al. Sleep complaints among elderly persons: an epidemiologic study of three communities. Sleep 1995;18:425-32.
44. Weissman MM, Bland RC, Canino GJ et al. Cross-national epidemiology of major depression and bipolar disorder. JAMA 1996;276:293-9.
45. Ford DE, Kamerow DB. Epidemiologic study of sleep disturbances and psychiatric disorders. An opportunity for prevention? JAMA 1989;262:1479-84.
46. Henderson S, Jorm AF, Scott LR et al. Insomnia in the elderly: its prevalence and correlates in the general population. Med J Aust 1995;162:22-4.
47. Tamura H, Nishida T, Tsuji A et al. Association between excessive use of mobile phone and insomnia and depression among Japanese adolescents. Int J Environ Res Publ Health 2017;14:701.
48. Spielman AJ, Caruso LS, Glovinsky PB. A behavioral-perspective on insomnia treatment. Psychiatr Clin North Am 1987;10:541-53.
49. Brainard GC, Hanifin JP, Greeson JM et al. Action spectrum for melatonin regulation in humans: evidence for a novel circadian photoreceptor. J Neurosci 2001;21:6405-12.
50. Yang C-M, Spielman AJ, Glovinsky P. Nonpharmacologic strategies in the management of insomnia. Psychiatr Clin North Am 2006;29:895-919.
51. Ebben MR, Spielman AJ. Non-pharmacological treatments for insomnia. J Behav Med 2009;32:244-54.
52. Gislason T, Almqvist M. Somatic diseases and sleep complaints. An epidemiological study of 3,201 Swedish men. Acta Med Scand 1987;221:475-81.
53. Stoschitzky K, Sakotnik A, Lercher P et al. Influence of beta-blockers on melatonin release. Eur J Clin Pharmacol 1999;55:111-5.
54. Schutte-Rodin S, Broch L, Buysse D et al. Clinical guideline for the evaluation and management of chronic insomnia in adults. J Clin Sleep Med 2008;4:487-504.
55. Theorell-Haglow J, Miller CB, Bartlett DJ et al. Gender differences in obstructive sleep apnoea, insomnia and restless legs syndrome in adults - What do we know? A clinical update. Sleep Med Rev 2018;38:28-38.
56. Valipour A, Lothaller H, Rauscher H et al. Gender-related differences in symptoms of patients with suspected breathing disorders in sleep: a clinical population study using the sleep disorders questionnaire. Sleep 2007;30:312-9.
57. Morgenthaler T, Alessi C, Friedman L et al. Practice parameters for the use of actigraphy in the assessment of sleep and sleep disorders: an update for 2007. Sleep 2007;30:519-29.
58. Hyde M, O'Driscoll DM, Binette S et al. Validation of actigraphy for determining sleep and wake in children with sleep disordered breathing. J Sleep Res 2007;16:213-6.
59. Hedner J, Pillar G, Pittman SD et al. A novel adaptive wrist actigraphy algorithm for sleep-wake assessment in sleep apnea patients. Sleep 2004;27:1560-6.
60. Martin JL, Hakim AD. Wrist actigraphy. Chest 2011;139:1514-27.
61. Gruwez A, Libert W, Ameye L et al. Reliability of commercially available sleep and activity trackers with manual switch-to-sleep mode activation in free-living healthy individuals. Int J Med Inform 2017;102:87-92.
62. Ko PR, Kientz JA, Choe EK et al. Consumer sleep technologies: a review of the landscape. J Clin Sleep Med 2015;11:1455-61.
63. Krystal AD, Edinger JD, Wohlgemuth WK et al. NREM sleep EEG frequency spectral correlates of sleep complaints in primary insomnia subtypes. Sleep 2002;25:630-40.
64. Johns MW. A new method for measuring daytime sleepiness: the Epworth Sleepiness Scale. Sleep 1991;14:540-5.
65. Morin CM, Belleville G, Bélanger L et al. The Insomnia Severity Index: psychometric indicators to detect insomnia cases and evaluate treatment response. Sleep 2011;34:601-8.
66. Morin CM, Vallières A, Ivers H. Dysfunctional beliefs and attitudes about sleep (DBAS): validation of a brief version (DBAS-16). Sleep 2007;30:1547-54.
67. Buysse DJ, Reynolds CF 3rd, Monk TH et al. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. Psychiatr Res 1989;28:193-213.
68. Koffel EA, Koffel JB, Gehrman PR. A meta-analysis of group cognitive behavioral therapy for insomnia. Sleep Med Rev 2015;19:6-16.
69. van Straten A, van der Zweerde T, Kleiboer A et al. Cognitive and behavioral therapies in the treatment of insomnia: a meta-analysis. Sleep Med Rev 2018;38:3-16.
70. Wu JQ, Appleman ER, Salazar RD et al. Cognitive behavioral therapy for insomnia comorbid with psychiatric and medical conditions: a meta-analysis. JAMA Intern Med 2015;175:1461-72.
71. Irwin MR, Cole JC, Nicassio PM. Comparative meta-analysis of behavioral interventions for insomnia and their efficacy in middle-aged adults and in older adults 55+ years of age. Health Psychol 2006;25:3-14.
72. Smith MT, Perlis ML, Park A et al. Comparative meta-analysis of pharmacotherapy and behavior therapy for persistent insomnia. Am J Psychiatry 2002;159:5-11.

73. Seyffert M, Lagisetty P, Landgraf J et al. Internet-delivered cognitive behavioral therapy to treat insomnia: a systematic review and meta-analysis. PLoS One 2016;11:e0149139.
74. Qaseem A, Kansagara D, Forciea MA et al. Management of chronic insomnia disorder in adults: a clinical practice guideline from the American College of Physicians. Ann Intern Med 2016;165:125-33.
75. Manber R, Carney C. Treatment plans and interventions for insomnia: a case formulation approach. New York: Guilford, 2015.
76. Edinger J, Carney C. Overcoming insomnia: a cognitive-behavioral therapy approach. Oxford: Oxford University Press, 2015.
77. Edinger JD, Wohlgemuth WK, Radtke RA et al. Cognitive behavioral therapy for treatment of chronic primary insomnia: a randomized controlled trial. JAMA 2001;285:1856-64.
78. Haack M, Scott-Sutherland J, Santangelo G et al. Pain sensitivity and modulation in primary insomnia. Eur J Pain 2012;16:522-33.
79. Colombo C, Benedetti F, Barbini B et al. Rate of switch from depression into mania after therapeutic sleep deprivation in bipolar depression. Psychiatry Res 1999;86:267-70.
80. Trauer JM, Qian MY, Doyle JS et al. Cognitive behavioral therapy for chronic insomnia: a systematic review and meta-analysis. Ann Intern Med 163; 191-204.
81. Geiger-Brown JM, Rogers VE, Liu W et al. Cognitive behavioral therapy in persons with comorbid insomnia: a meta-analysis. Sleep Med Rev 2015;23:54-67.
82. Ho FY, Chan CS, Tang KN. Cognitive-behavioral therapy for sleep disturbances in treating posttraumatic stress disorder symptoms: a meta-analysis of randomized controlled trials. Clin Psychol Rev 2016;43:90-102.
83. Belleville G, Cousineau H, Levrier K et al. Meta-analytic review of the impact of cognitive-behavior therapy for insomnia on concomitant anxiety. Clin Psychol Rev 2011;31:638-52.
84. Ye YY, Zhang YF, Chen J et al. Internet-based cognitive behavioral therapy for insomnia (ICBT-I) improves comorbid anxiety and depression – a meta-analysis of randomized controlled trials. PLoS One 2015;10:e0142258.
85. Espie CA, Emsley R, Kyle SD et al. Effect of digital cognitive behavioral therapy for insomnia on health, psychological well-being and sleep-related quality of life: a randomized clinical trial. JAMA Psychiatry 2019;76:21-30.
86. Krystal AD, Prather AA. Should internet cognitive behavioral therapy for insomnia be the primary treatment option for insomnia?: Toward getting more SHUTi. JAMA Psychiatry 2017;74:15-6.
87. Hajak G, Clarenbach P, Fischer W et al. Zopiclone improves sleep quality and daytime well-being in insomniac patients: comparison with triazolam, flunitrazepam and placebo. Int Clin Psychopharmacol 1994;9:251-61.
88. Drake CL, Roehrs TA, Mangano RM et al. Dose-response effects of zaleplon as compared with triazolam (0.25 mg) and placebo in chronic primary insomnia. Hum Psychopharmacol 2000;15:595-604.
89. Fabre LF Jr, Brachfeld J, Meyer LR et al. Multi-clinic double-blind comparison of triazolam (Halcion) and placebo administered for 14 consecutive nights in outpatients with insomnia. J Clin Psychiatry 1978;39:679-82.
90. Nair NP, Schwartz G, Dimitri R et al. A dose-range finding study of zopiclone in insomniac patients. Int Clin Psychopharmacol 1990;5(Suppl. 2): 1-10.
91. Scharf MB, Roth PB, Dominguez RA et al. Estazolam and flurazepam: a multicenter, placebo-controlled comparative study in outpatients with insomnia. J Clin Pharmacol 1990;30:461-7.
92. Walsh JK, Targum SD, Pegram V. A multi-center clinical investigation of estazolam: short-term efficacy. Curr Ther Res 1984;36:866-74.
93. Roehrs T, Zorick F, Lord N et al. Dose-related effects of estazolam on sleep of patients with insomnia. J Clin Psychopharmacol 1983;3:152-6.
94. Aden GC, Thatcher C. Quazepam in the short-term treatment of insomnia in outpatients. J Clin Psychiatry 1983;44:454-6.
95. Fillingim JM. Double-blind evaluation of the efficacy and safety of temazepam in outpatients with insomnia. Br J Clin Pharmacol 1979;8:73S-7.
96. Scharf MB, Roth T, Vogel GW et al. A multicenter, placebo-controlled study evaluating zolpidem in the treatment of chronic insomnia. J Clin Psychiatry 1994;55:192-9.
97. Walsh JK, Erman M, Erwin CW et al. Subjective hypnotic efficacy of trazodone and zolpidem in DSM-III-R primary insomnia. Hum Psychopharmacol 1998;13:191-8.
98. Elie R, Ruther E, Farr I et al. Sleep latency is shortened during 4 weeks of treatment with zaleplon, a novel nonbenzodiazepine hypnotic. Zaleplon Clinical Study Group. J Clin Psychiatry 1999;60:536-44.
99. Walsh JK, Roth T, Randazzo A et al. Eight weeks of non-nightly use of zolpidem for primary insomnia. Sleep 2000;23:1087-96.
100. Perlis ML, McCall WV, Krystal AD et al. Long-term, non-nightly administration of zolpidem in the treatment of patients with primary insomnia. J Clin Psychiatry 2004;65:1128-37.
101. Roth T, Soubrane C, Titeux L et al. Zoladult Study Group. Efficacy and safety of zolpidem-MR: a double-blind, placebo-controlled study in adults with primary insomnia. Sleep Med 2006;7:397-406.
102. Krystal AD, Erman M, Zammit GK et al. Long-term efficacy and safety of zolpidem extended-release 12.5 mg, administered 3 to 7 nights per week for 24 weeks, in patients with chronic primary insomnia: a 6-month, randomized, double-blind, placebo-controlled, parallel-group, multicenter study. Sleep 2008;31:79-90.
103. Roth T, Krystal A, Steinberg FJ et al. Novel sublingual low-dose zolpidem tablet reduces latency to sleep onset following spontaneous middle-of-the-night awakening in insomnia in a randomized, double-blind, placebo-controlled, outpatient study. Sleep 2013;36:189-96.
104. Walsh JK, Vogel GW, Scharf M et al. A five week, polysomnographic assessment of zaleplon 10 mg for the treatment of primary insomnia. Sleep Med 2000;1:41-9.
105. Ngen CC, Hassan R. A double-blind placebo-controlled trial of zopiclone 7.5 mg and temazepam 20 mg in insomnia. Int Clin Psychopharmacol 1990;5:165-71.
106. Krystal AD, Walsh JK, Laska E et al. Sustained efficacy of eszopiclone over six months of nightly treatment: results of a randomized, double-blind, placebo controlled study in adults with chronic insomnia. Sleep 2003;26:793-9.
107. Walsh JK, Krystal AD, Amata DA et al. Nightly treatment of primary insomnia with eszopiclone for six months: effect on sleep, quality of life, and work limitations. Sleep 2007;30:959-68.
108. Zammit GK, McNabb LJ, Caron J et al. Efficacy and safety of eszopiclone across 6-weeks of treatment for primary insomnia. Curr Med Res Opin 2004; 20:1979-91.
109. Erman M, Seiden D, Zammit G et al. An efficacy, safety, and dose-response study of ramelteon in patients with chronic primary insomnia. Sleep Med 2006;7:17-24.
110. Kohsaka M, Kanemura T, Taniguchi M et al. Efficacy and tolerability of ramelteon in a double-blind, placebo-controlled, crossover study in Japanese patients with chronic primary insomnia. Expert Rev Neurother 2011;11:1389-97.
111. Mayer G, Wang-Weigand S, Roth-Schechter B et al. Efficacy and safety of 6-month nightly ramelteon administration in adults with chronic primary insomnia. Sleep 2009;32:351-60.
112. Uchiyama M, Hamamura M, Kuwano T et al. Long-term safety and efficacy of ramelteon in Japanese patients with chronic insomnia. Sleep Med 2011; 12:127-33.
113. Zammit G, Erman M, Wang-Weigand S et al. Evaluation of the efficacy and safety of ramelteon in subjects with chronic insomnia. J Clin Sleep Med 2007;3:495-504.
114. Roth T, Rogowski R, Hull S et al. Efficacy and safety of doxepin 1 mg, 3 mg, and 6 mg in adults with primary insomnia. Sleep 2007;30:1555-61.
115. Hajak G, Rodenbeck A, Voderholzer U et al. Doxepin in the treatment of primary insomnia: a placebo-controlled, double blind, polysomnographic study. J Clin Psychiatry 2001;62:453-63.
116. Lankford A, Rogowski R, Essink B et al. Efficacy and safety of doxepin 6 mg in a four-week outpatient trial of elderly adults with chronic primary insomnia. Sleep Med 2012;13:133-8.
117. Krystal AD, Lankford A, Durrence HH et al. Efficacy and safety of doxepin 3 and 6 mg in a 35-day sleep laboratory trial in adults with chronic primary insomnia. Sleep 2011;34:1433-42.
118. Herring WJ, Connor KM, Ivgy-May N et al. Suvorexant in patients with insomnia: results from two 3-month randomized controlled clinical trials. Biol Psychiatry 2016;79:136-48.
119. Herring WJ, Snyder E, Budd K et al. Orexin receptor antagonism for treatment of insomnia: a randomized clinical trial of suvorexant. Neurology 2012;79:2265-74.
120. Michelson D, Snyder E, Paradis E et al. Safety and efficacy of suvorexant during 1-year treatment of insomnia with subsequent abrupt treatment discontinuation: a phase 3 randomised, double-blind, placebo-controlled trial. Lancet Neurol 2014;13:461-71.
121. Elie R, Frenay M, Le Morvan P et al. Efficacy and safety of zopiclone and triazolam in the treatment of geriatric insomniacs. Int Clin Psychopharmacol 1990;5(Suppl. 2):39-46.
122. Reeves RL. Comparison of triazolam, flurazepam, and placebo as hypnotics in geriatric patients with insomnia. J Clin Pharmacol 1977;17:319-23.

123. Piccione P, Zorick F, Lutz T et al. The efficacy of triazolam and chloral hydrate in geriatric insomniacs. J Int Med Res 1980;8:361-7.
124. Sunshine A. Comparison of the hypnotic activity of triazolam, flurazepam hydrochloride, and placebo. Clin Pharmacol Ther 1975;17:573-7.
125. Roehrs T, Zorick F, Wittig R et al. Efficacy of a reduced triazolam dose in elderly insomniacs. Neurobiol Aging 1985;6:293-6.
126. Morin CM, Colecchi C, Stone J et al. Behavioral and pharmacological therapies for late-life insomnia: a randomized controlled trial. JAMA 1999;281: 991-9.
127. Ancoli-Israel S, Walsh JK, Mangano RM et al. Zaleplon, a novel nonbenzodiazepine hypnotic, effectively treats insomnia in elderly patients without causing rebound effects. Prim Care Companion J Clin Psychiatry 1999;1:114-20.
128. Walsh JK, Soubrane C, Roth T. Efficacy and safety of zolpidem extended release in elderly primary insomnia patients. Am J Geriatr Psychiatry 2008;16:44-57.
129. Hedner J, Yaeche R, Emilien G et al. Zaleplon shortens subjective sleep latency and improves subjective sleep quality in elderly patients with insomnia. The Zaleplon Clinical Investigator Study Group. Int J Geriatr Psychiatry 2000;15:704-12.
130. Scharf M, Erman M, Rosenberg R et al. A 2-week efficacy and safety study of eszopiclone in elderly patients with primary insomnia. Sleep 2005;28: 720-7.
131. McCall WV, Erman M, Krystal AD et al. A polysomnography study of eszopiclone in elderly patients with insomnia. Curr Med Res Opin 2006;22:1633-42.
132. Ancoli-Israel S, Krystal AD, McCall WV et al. A 12-week, randomized, double-blind, placebo-controlled study evaluating the effect of eszopiclone 2 mg on sleep/wake function in older adults with primary and comorbid insomnia. Sleep 2010;33:225-34.
133. Roth T, Seiden D, Wang-Weigand S et al. A 2-night, 3-period, crossover study of ramelteon's efficacy and safety in older adults with chronic insomnia. Curr Med Res Opin 2007;23:1005-14.
134. Roth T, Seiden D, Sainati S et al. Effects of ramelteon on patient-reported sleep latency in older adults with chronic insomnia. Sleep Med 2006;7:312-8.
135. Scharf M, Rogowski R, Hull S et al. Efficacy and safety of doxepin 1 mg, 3 mg, and 6 mg in elderly patients with primary insomnia: a randomized, double-blind, placebo-controlled crossover study. J Clin Psychiatry 2008; 69:1557-64.
136. Krystal AD, Durrence HH, Scharf M et al. Efficacy and safety of doxepin 1 mg and 3 mg in a 12-week sleep laboratory and outpatient trial of elderly subjects with chronic primary insomnia. Sleep 2010;33:1553-61.
137. Herring WJ, Connor KM, Snyder E et al. Suvorexant in elderly patients with insomnia: pooled analyses of data from phase III randomized controlled clinical trials. Am J Geriatr Psychiatry 2017;25:791-802.
138. Downing SS, Lee YT, Farb DH et al. Benzodiazepine modulation of partial agonist efficacy and spontaneously active GABA receptors supports an allosteric model of modulation. Br J Pharmacol 2005;145:894-906.
139. Katzung BG, Masters SB, Trevor AJ. Basic and clinical pharmacology. New York: McGraw-Hill Medical, 2009.
140. Sieghart W, Sperk G. Subunit composition, distribution and function of GABA(A) receptor subtypes, Curr Top Med Chem 2002;2:795-816.
141. Krogsgaard-Larsen P, Frolund B, Liljefors T. Specific GABA(A) agonists and partial agonists. Chem Rec 2002;2:419-30.
142. Morin CM, Drake CL, Harvey AG et al. Insomnia disorder. Nat Rev Dis Primers 2015;1:15026
143. National Institutes of Health. Consensus conference. Drugs and insomnia. The use of medications to promote sleep. JAMA 1984;251:2410-4.
144. Krystal AD, McCall WV, Fava M et al. Eszopiclone treatment for insomnia: effect size comparisons in patients with primary insomnia and insomnia with medical and psychiatric comorbidity. Prim Care Companion CNS Disord 2012;14(4).
145. Pollack MH, Hoge EA, Worthington JJ et al. Eszopiclone for the treatment of posttraumatic stress disorder and associated insomnia: a randomized, double-blind, placebo-controlled trial. J Clin Psychiatry 2011;72:892-7.
146. Pollack M, Kinrys G, Krystal A et al. Eszopiclone coadministered with escitalopram in patients with insomnia and comorbid generalized anxiety disorder. Arch Gen Psychiatry 2008;65:551-62.
147. Goforth HW, Preud'homme XA, Krystal AD. A randomized, double-blind, placebo-controlled trial of eszopiclone for the treatment of insomnia in patients with chronic low back pain. Sleep 2014;37:1053-60.
148. Krystal A, Fava M, Rubens R et al. Evaluation of eszopiclone discontinuation after cotherapy with fluoxetine for insomnia with coexisting depression. J Clin Sleep Med 2007;3:48-55.
149. Fava M, McCall WV, Krystal A et al. Eszopiclone co-administered with fluoxetine in patients with insomnia coexisting with major depressive disorder. Biol Psychiatry 2006;59:1052-60.
150. Fava M, Asnis GM, Shrivastava RK et al. Improved insomnia symptoms and sleep-related next-day functioning in patients with comorbid major depressive disorder and insomnia following concomitant zolpidem extended-release 12.5 mg and escitalopram treatment: a randomized controlled trial. J Clin Psychiatry 2011;72:914-28.
151. Fava M, Asnis GM, Shrivastava R et al. Zolpidem extended-release improves sleep and next-day symptoms in comorbid insomnia and generalized anxiety disorder. J Clin Psychopharmacol 2009;29:222-30.
152. Ng KY, Leong MK, Liang H et al. Melatonin receptors: distribution in mammalian brain and their respective putative functions. Brain Struct Funct 2017;222:2921-39.
153. Krystal A. The possibility of preventing functional impairment due to sleep loss by pharmacologically enhancing sleep. Sleep 2005;28:16-7.
154. Slotten H, Krekling S. Does melatonin have an effect on cognitive performance. Psychoneuroendocrinology 1996;21:673-80.
155. Hughes R, Badia P. Sleep-promoting and hypothermic effects of daytime melatonin administration in humans. Sleep 1997;20:124-31.
156. Ferracioli-Oda E, Qawasmi A, Bloch MH. Meta-analysis: melatonin for the treatment of primary sleep disorders. PLoS One 2013;8:e63773.
157. Buscemi N, Vandermeer B, Hooton N et al. The efficacy and safety of exogenous melatonin for primary sleep disorders. A meta-analysis. J Gen Intern Med 2005;20:1151-8.
158. Smits M, Nagtegaal EE, van der Heijden J et al. Melatonin for chronic sleep onset insomnia in children: a randomized placebo-controlled trial. J Child Neurol 2001;16:86-92.
159. Zhdanova I, Wurtman RJ, Morabito C et al. Effects of low oral doses of melatonin, given 2-4 hours before habitual bedtime, on sleep in normal young humans. Sleep 1996;19:423-31.
160. Zhdanova I, Wurtman RJ, Wagstaff J. Effects of a low dose of melatonin on sleep in children with Angelman syndrome. J Pediatr Endocrinol 1999;12:57-67.
161. Van der Heijden K, Smits MG, Van Someren EJ et al. Effect of melatonin on sleep, behavior, and cognition in ADHD and chronic sleep-onset insomnia. J Am Acad Child Adolesc Psychiatry 2007;46:233-41.
162. Wasdell M, Jan JE, Bomben MM et al. A randomized, placebo-controlled trial of controlled release melatonin treatment of delayed sleep phase syndrome and impaired sleep maintenance in children with neurodevelopmental disabilities. J Pineal Res 2008;44:57-64.
163. Braam W, Didden R, Smits M et al. Melatonin treatment in individuals with intellectual disability and chronic insomnia: a randomized placebo-controlled study. J Intellect Disabil Res 2008;52:256-64.
164. Lerchl A. Melatonin administration alters semen quality in normal men. J Androl 2004;25:185-6.
165. Ianas O, Manda D, Câmpean D et al. Effects of melatonin and its relation to the hypothalamic-hypophyseal-gonadal axis. Adv Exp Med Biol 1999; 460:321-8.
166. Partonen T. Melatonin-dependent infertility. Med Hypotheses 1999;52:269-70.
167. Pang SF, Li L, Ayre EA et al. Neuroendocrinology of melatonin in reproduction: recent developments. J Chem Neuroanat 1998;14:157-66.
168. Krystal AD, Richelson E, Roth T. Review of the histamine system and the clinical effects of H1 antagonists: basis for a new model for understanding the effects of insomnia medications. Sleep Med Rev 2013;17:263-72.
169. Ruwe F, IJzerman-Boon P, Roth T et al. A phase 2 randomized dose-finding study with esmirtazapine in patients with primary insomnia. J Clin Psychopharmacol 2016;36:457-64.
170. Ivgy-May N, Ruwe F, Krystal A et al. Esmirtazapine in non-elderly adult patients with primary insomnia: efficacy and safety from a randomized, 6-week sleep laboratory trial. Sleep Med 2015;16:838-44.
171. Ivgy-May N, Roth T, Ruwe F et al. Esmirtazapine in non-elderly adult patients with primary insomnia: efficacy and safety from a 2-week randomized outpatient trial. Sleep Med 2015;16:831-7.
172. Suppes T, Kelly DI, Perla JM et al. Challenges in the management of bipolar depression. J Clin Psychiatry 2005;66(Suppl. 5):11-6.
173. Chakravorty S, Hanlon AL, Kuna ST et al. The effects of quetiapine on sleep in recovering alcohol-dependent subjects: a pilot study. J Clin Psychopharmacol 2014;34:350-4.
174. Tassniyom K, Paholpak S, Tassniyom S et al. Quetiapine for primary insomnia: a double blind, randomized controlled trial. J Med Assoc Thai 2010;93:729-34.

175. Glass JR, Sproule BA, Herrmann N et al. Effects of 2-week treatment with temazepam and diphenhydramine in elderly insomniacs: a randomized, placebo-controlled trial. J Clin Psychopharmacol 2008;28:182-8.
176. Morin CM, Koetter U, Bastien C et al. Valerian-hops combination and diphenhydramine for treating insomnia: a randomized placebo-controlled clinical trial. Sleep 2005;28:1465-71.
177. Koppel C, Tenczer J, Ibe K. Poisoning with over-the-counter doxylamine preparations: an evaluation of 109 cases. Hum Toxicol 1987;6:355-9.
178. Rose M, Kam CA. Gabapentin: pharmacology and its use in pain management. Anaesthesia 2002;57:451-62.
179. Gajraj N. Pregabalin: its pharmacology and use in pain management. Anesth Analg 2007;105:1805-15.
180. Furey SA, Hull SG, Leibowitz MT et al. A randomized, double-blind, placebo-controlled, multicenter, 28-day, polysomnographic study of gabapentin in transient insomnia induced by sleep phase advance. J Clin Sleep Med 2014;10:1101-9.
181. Rosenberg RP, Hull SG, Lankford DA et al. A randomized, double-blind, single-dose, placebo-controlled, multicenter, polysomnographic study of gabapentin in transient insomnia induced by sleep phase advance. J Clin Sleep Med 2014;10:1093-100.
182. Gilron I. Gabapentin and pregabalin for chronic neuropathic and early postsurgical pain: current evidence and future directions. Curr Opin Anaesthesiol 2007;20:456-72.
183. de Haas S, Otte A, de Weerd A et al. Exploratory polysomnographic evaluation of pregabalin on sleep disturbance in patients with epilepsy. J Clin Sleep Med 2007;3:473-8.
184. Garcia-Borreguero D, Larrosa O, de la Llave Y et al. Treatment of restless legs syndrome with gabapentin: a double-blind, cross-over study. Neurology 2002;59:1573-9.
185. Holsboer-Trachsler E, Prieto R. Effects of pregabalin on sleep in generalized anxiety disorder. Int J Neuropsychopharmacol 2013;16:925-36.
186. Guay D. Pregabalin in neuropathic pain: a more "pharmaceutically elegant" gabapentin? Am J Geriatr Pharmacother 2005;3:274-87.
187. Brower K, Myra Kim H, Strobbe S et al. A randomized double-blind pilot trial of gabapentin versus placebo to treat alcohol dependence and comorbid insomnia. Alcohol Clin Exp Res 2008;32:1429-38.
188. Voris J, Smith NL, Rao SM et al. Gabapentin for the treatment of ethanol withdrawal. Subst Abus 2003;24:129-32.

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