Sleep Aids

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Key Points

- Insomnia relates to complaints of inadequate sleep (e.g., problems falling asleep, problems with staying asleep [sleep duration], and/or quality of sleep) and may need treatment especially if it is associated with significant patient distress and/or daytime sleepiness.
- Treatment for insomnia may require nonpharmacologic approaches as well as pharmacologic approaches.
- Medications that are FDA approved for the treatment of insomnia include benzodiazepines, "Z-drugs," and melatonin receptor agonists.
- "Z-drugs" (e.g., zaleplon, zolpidem, zopiclone, eszopiclone) may have less potential for rebound insomnia and withdrawal symptoms than benzodiazepines, but they still have a significant potential for abuse.

Introduction

Sleep is one of the most universal biological processes in existence. Depriving an organism of sleep altogether can be extremely detrimental and may even lead to death [1]. Sleep is therefore considered necessary for life, but why this is so remains unclear. Sleep is subdivided into rapid eye movement (REM) sleep, which is characterized by high-frequency electroencephalogram (EEG) recordings and muscle atonia [2], and non-REM (slow-wave) sleep, characterized by low-frequency EEG recordings and body rest [3].

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While the cholinergic and monoaminergic systems act to promote wakefulness in conjunction with the orexins, there are other neuronal groups that act to promote sleep. The primary population of sleep-promoting neurons is located in the preoptic area, specifically the ventrolateral preoptic area of the hypothalamus (VLPO). Thus, multiple mediators can be targeted in efforts to combat insomnia and/or promote sleep/sedation (e.g., acetylcholine, norepinephrine, gamma-aminobutyric acid, histamine, serotonin, adenosine dopamine, melatonin, orexin).

Insomnia is a condition of perceived inadequate sleep, with patients typically presenting with difficulty falling asleep, difficulty maintaining sleep, or poor quality sleep [4]. To manage insomnia successfully, pharmacological treatments for insomnia may be required to reduce sleep latency, increase sleep maintenance, and improve sleep quality. In addition, such treatments should enable normal wakening with no subsequent impairment of daytime function and minimal risk of dependence.

Sivertsen et al. studied insomnia symptoms and the use of health-care services and medications and concluded that insomnia symptoms represent a significant public health concern, being independently associated with substantially elevated use of health-care services, medications, and alcohol overuse [5].

Kyle and colleagues concluded from the relatively small literature that insomnia impacts on diverse areas of health-related quality of life (HRQoL), and that both pharmacological and nonpharmacological interventions can produce, to varying degrees, improvements in domains spanning physical, social, and emotional functioning [6].

Insomnia Assessment

The following questions can serve as the initial assessment regarding sleep [7]: What time do you normally go to bed at night and wake up in the morning? Do you often have trouble falling asleep at night? About how many times do you wake

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up at night? If you do wake up during the night, do you usually have trouble falling back asleep? Does your bed partner say (or are you aware) that you frequently snore, gasp for air, or stop breathing—kick, thrash about, eat, punch, or scream during sleep? Are you sleepy or tired during much of the day? Do you unintentionally doze off during the day? Do you usually take one or more naps during the day?

The ISI, developed by Morin, is a seven-item Likert-type self-rating scale designed to assess the subjective perception of the severity of insomnia [8].The scale contains items that measure the symptoms and associated features and impacts of insomnia, including difficulty falling asleep, difficulty maintaining sleep, early morning awakening, satisfaction with sleep, concerns about insomnia, and functional impacts of insomnia.

Treatment for Insomnia

The treatment for insomnia may involve pharmacologic as well as nonpharmacologic approaches.

Nonpharmacologic Approaches to Insomnia

Sleep Hygiene and Sleep Education

Sleep hygiene refers to the general rules of behavioral practices and environmental factors that are consistent with good quality sleep. When defined broadly, it includes guidelines for general health practices (e.g., diet, exercise, substance use), environmental factors (e.g., light, temperature, noise), as well as sleep-related behavioral practices (e.g., regularity of sleep schedule, pre-sleep activities, efforts to try to sleep) [9]. The International Classification of Sleep Disorders even includes the diagnostic category "inadequate sleep hygiene," which is designated for the sleep disruption associated with poor sleep hygiene practices [10]. In addition, poor sleep-related habits leading to conditioned arousal in bed are considered to be one of the major etiological factors of psychophysiological insomnia [10]. Poor sleep hygiene practices have been considered to be a contributing factor to insomnia [9].

Previous studies have shown that sleep hygiene alone is not a sufficient treatment for insomnia [11–14]. Interventions aimed to reduce physiological or cognitive arousal (e.g., relaxation training, cognitive restructuring) and stimulus control instructions to reduce conditioned arousal with bedtime cues may be indicated to generate better results.

Behaviors and habits that may impair sleep include the following [7]: frequent daytime napping, spending too much time in bed, insufficient daytime activities, late-evening exercises, insufficient bright-light exposure, excess caffeine, evening alcohol consumption, smoking in the evening, late, heavy dinner, watching television or engaging in other stimulating activities at night, anxiety and anticipation of poor sleep, clock watching, and environmental factors, such as the room being too warm, too noisy, or too bright; pets on the bed or in the bedroom; and active or noisy bed partners.

The following are helpful instructions for using stimulus control and practicing good sleep hygiene [7]: develop a sleep ritual, such as maintaining a 30-min relaxation period before bedtime or taking a hot bath 90 min before bedtime; make sure the bedroom is restful and comfortable; go to bed only if you feel sleepy; avoid heavy exercise within 2 h of bedtime; avoid sleep-fragmenting substances, such as caffeine, nicotine, and alcohol; avoid activities in the bedroom that keep you awake. Use the bedroom only for sleep and sex; do not watch television from bed or work in bed; sleep only in your bedroom; if you cannot fall asleep, leave the bedroom and return only when sleepy; maintain stable bedtimes and rising times. Arise at the same time each morning, regardless of the amount of sleep obtained that night, and avoid daytime napping. If you do nap during the day, limit it to 30 min and do not nap, if possible, after 2 p.m.

Relaxation Therapy

The goal of relaxation therapy is to guide individuals to a calm, steady state when they wish to go to sleep. The methods used include progressive muscle relaxation (tensing and then relaxing each muscle group), guided imagery, diaphragmatic breathing, meditation, and biofeedback [15].

Cognitive Behavioral Therapy

Vitiello et al. performed randomized controlled trial of cognitive behavioral therapy for insomnia (CBT-I) in patients with osteoarthritis and comorbid insomnia [16]. CBT-I subjects reported significantly improved sleep and significantly reduced pain after treatment. Control subjects reported no significant improvements. One-year follow-up found maintenance of improved sleep and reduced pain for both the CBT-I group alone and among subjects who crossed over from control to CBT-I, suggesting that improving sleep, per se, in patients with osteoarthritis may result in decreased pain [16].

Sivertsen and colleagues performed a randomized double-blind placebo-controlled trial examining short- and long-term clinical efficacies of cognitive behavioral therapy (CBT) and pharmacological treatment in older adults experiencing chronic primary insomnia [17]. Participants receiving CBT improved their sleep efficiency from 81.4 % at pretreatment to 90.1 % at 6-month follow-up compared with a decrease from 82.3 to 81.9 % in the zopiclone group, suggesting that interventions based on CBT may be superior to zopiclone treatment both in short- and long-term management of insomnia in older adults [17]. This agrees with the findings of Dolan et al. [18] and of a similar study which found

Table 9.1 Conclusions from the Agency for Healthcare Research and Quality Evidence Report/technology assessment regarding the manifestations and management of chronic insomnia [23]

Evidence exists to support that:
Chronic insomnia is associated with older age.
Benzodiazepines and nonbenzodiazepines are effective in the management of chronic insomnia. However, benzodiazepines, nonbenzodiazepines, and antidepressants pose a risk of harm.
Benzodiazepines have a greater risk of harm than nonbenzodiazepines.
Melatonin is effective in the management of chronic insomnia in subsets of the chronic insomnia population, and there is no evidence that melatonin poses a risk of harm.
Relaxation therapy and cognitive behavioral therapy are effective in the management of chronic insomnia in subsets of the chronic insomnia population.

temazepam equal to CBT in the short term but inferior to CBT in the long term [19]. Three meta-analyses [12, 14, 20] have concluded that 70–80 % of middle-aged adults with insomnia benefit from interventions based on CBT. Irwin et al. performed a meta-analysis and concluded that behavioral interventions were more effective in middle-aged adults versus older adults in improving both total sleep time and sleep efficiency [20]. Morin et al. conducted a prospective, randomized controlled trial involving 2-stage therapy for 160 adults with persistent insomnia [21]. Participants received CBT alone or CBT plus 10 mg/day (taken at bedtime) of zolpidem for an initial 6-week acute therapy, followed by extended 6-month therapy. The best long-term outcome was obtained with patients treated with combined therapy initially, followed by CBT alone, as evidenced by higher remission rates at the 6-month follow-up compared with patients who continued to take zolpidem during extended therapy [21].

Acupuncture

Cao and colleagues performed a systematic review of randomized controlled trials (RCTs) of acupuncture for treatment of insomnia [22]. They found that acupuncture appears to be effective in treatment of insomnia; however, further large, rigorous designed trials are warranted [22].

Pharmacologic Approaches to Insomnia

In 2005, the Agency for Healthcare Research and Quality released its Evidence Report/Technology Assessment (see Table 9.1) [23]. Several nutritional or herbal products are sold for the treatment of insomnia (e.g., valerian root, melatonin, hops, chamomile, St. John's wort). Only valerian and melatonin have demonstrated some benefit in promoting sleep. Melatonin, however, can cause sleep disruption, daytime fatigue, headaches, and dizziness at higher doses, while valerian root can cause residual daytime sedation and, in rare instances, hepatotoxicity [24].

Common drug classes used to treat insomnia, but not FDA approved for that use, include antihistamines (e.g., diphenhydramine), antidepressants (e.g., amitriptyline, doxepin, trazodone), atypical antipsychotics (quetiapine), and sedatives (e.g., chloral hydrate). These drug classes are used due to their sedative properties.

FDA-Approved Pharmacologic Therapies for Management of Insomnia

The FDA-approved therapies for the management of insomnia are classified as sedative-hypnotic agents. These sedative hypnotics can be categorized into three groups: benzodiazepines, nonbenzodiazepine selective GABA agonists, and melatonin receptor agonists (see Table 9.2).

Benzodiazepines

The first benzodiazepine, chlordiazepoxide (discovered serendipitously by Leo Sternbach in 1955), is a fusion of a benzene ring and a diazepine ring. Benzodiazepines such as chlordiazepoxide (Librium) and diazepam (Valium) were first developed as sedatives in the 1960s and rapidly gained popularity essentially replacing barbiturates as the sedatives of choice for "sleeping pills" [25]. Benzodiazepines could be acting on receptors directly within the VLPO to promote sleep, or they could be acting more globally to facilitate inhibitory GABA transmission [26]. The α1 subunit of the GABAA receptor is especially important for benzodiazepine-induced sedation. Mice with mutations in the α1 subunit are insensitive to the sedative effects of the traditional benzodiazepine diazepam but maintain sensitivity to its anxiolytic, myorelaxant, and motor-impairing functions, indicating that the sedating effects of benzodiazepines are primarily mediated by actions on the α1 subunit [27].

Nonbenzodiazepine Selective GABA Agonists

The $GABA_A$ receptor is a pentameric molecule composed of a combination of one or more specific subunit types. Although 19 different subunits are known to exist, the majority of $GABA_A$ receptors in the central nervous system consist of $\alpha_{(1-6)}$, $\beta_{(1-3)}$, and $\gamma_{(1-3)}$ subunits [28]. The interaction of benzodiazepines with multiple $GABA_A$ receptor subunits containing $\alpha_{(1-3,5)}$ is thought to elicit the variety of effects seen with these agents such as anxiolysis, amnesia, muscle relaxation, sedation, and anticonvulsant activity [28]. The theoretical advantage of having a selective α_1 subunit agonist of the GABA receptor is that sedating effects are achieved while avoiding other effects thought to be mediated by the other α subunits to which benzodiazepines bind.

In contrast to benzodiazepines, the nonbenzodiazepine sedative hypnotics (i.e., zolpidem, eszopiclone, zopiclone, zaleplon) are more selective for the $GABA_A$ receptors with

Table 9.2 Food and Drug Administration–approved drugs for insomnia

Drugs	Adult dose (mg)	Half-life (h)	Onset (min)	Peak effect (h)
BzRAs				
Estazolam (*ProSom™*)	(1, 2) 0.5–2	10–24	15–60	0.5–1.6
Flurazepam (*Dalmane™*)	(15, 30) 15–30	47–100	15–20	3–6
Quazepam (*Doral™*)	(15) 7.5–15 (max. 30)	P: 25–41 AM: 40–114 (2-oxoquazepam-[2 h] *N*-desalkyl-2-oxoquazepam [40–114 h])	15–60	15–3
Temazepam (*Restoril™*)	(17.5, 15, 22.5, 30) 7.5–30	6–16	15–60	1.5–3
Triazolam (*Halcion™*)	(0.125, 0.25) 0.125–0.25 (max. 0.5)	1.5–5.5	15–30	1.7–5
Non–BzRAs				
Eszopiclone (*Lunesta™*)	(1, 2, 3) 1–2 (max. 3)	6 (9 in elderly)	30	1
Zaleplon (*Sonata™, Starnoc™*)	(5, 10) 5–10 (max. 20)	1	Rapid	1
Zopiclone (*Imovane™*)	(5, 7.5) 5–15	~5–6 (5–10 in elderly)	30	1–2
Zolpidem tartrate IR (*Ambien™*)	(5, 10) 5–20	~2.5	15–30	1–3
Zolpidem tartarate ER (*Ambien CR™*)	(6.25, 12.5) 6.25–12.5	~3	30	1.5–4
Melatonin receptor agonist				
Ramelton (*Rozerem™*)	(8) 8½ h before bedtime	P: 0.5–2.6 AM: 2–5 (M-II)	30	0.5–1.5

Abbreviations: *P* parent drug, *AM* active metabolite, *BzRAs* benzodiazepines, *Non-BzRAs* nonbenzodiazepines, *IR* immediate release, *ER* extended release, *CR* controlled release, *( )* dosage forms

the α_1-receptor subunit [29]. Indiplon is a novel pyrazolopyrimidine, nonbenzodiazepine γ-aminobutyric acid (GABA) agonist with a high affinity and selectivity for the α1 subunit associated with sedation for the treatment of insomnia [29]. Petroski and colleagues [30] showed indiplon to be at least nine times more selective for α_1 as compared to α_2, α_3, and α_5 subunits [30]; a greater degree of selectivity for α_1, over the α_2 and α_3 subunits, was greater for indiplon as compared to zolpidem, zopiclone, and zaleplon.

"Z-DRUGS"

Initial nonbenzodiazepine selective GABA agonists are often referred to as the "Z-drugs" because they include zolpidem (Ambien), zaleplon (Sonata), zopiclone (Imovane), and eszopiclone (Lunesta). Zaleplon and zolpidem have much higher efficacy at benzodiazepine receptors containing the α1 subunit compared with other types of α subunits, whereas traditional benzodiazepines (e.g., triazolam) lack this specificity [31].

Zaleplon

It appears that zaleplon binds preferentially to alpha 1-containing GABAA receptors [32] and may be considered alpha 1-selective, and so zaleplon's effects are likely mediated via the alpha 1 receptor and are predominantly sedative in nature [30]. Zaleplon has a short T_{max} and the shortest $t_{½}$ of the current Z-drugs (see Table 9.2), explaining its fast onset and the fastest offset of action. Zolpidem IR has a longer $t_{½}$ than zaleplon, resulting in a longer duration of action. Zolpidem CR consists of a two-layer tablet: The outer layer dissolves quickly, while the second layer dissolves slowly to maintain plasma zolpidem concentrations above those seen for the IR formulation, particularly at 3–6 h post-dose [33].

Zolpidem

Zolpidem was the first subtype-selective GABAA receptor agonist and has the highest affinity at the alpha 1 subtype of all the nonbenzodiazepine GABAA receptor modulators. Zolpidem will activate alpha 2 and alpha 3 receptors, though at considerably higher concentrations than those that activate the alpha 1 subtype.

Zopiclone

Zopiclone shows relatively high binding affinity for the alpha 1 over the alpha 3 receptor subtype [34], and zopiclone also

binds to the alpha 5 receptor with high affinity [35]. Sivertsen et al. examined polysomnographic parameters and sleep apnea and periodic limb movement disorder (PLMD) in chronic users of zopiclone compared with aged-matched drug-free patients with insomnia versus "good sleepers" [36]. Forty-one percent of the patients treated pharmacologically for insomnia also had sleep apnea. There were no differences between the zopiclone and insomnia group on any of the polysomnography parameters, and a similar pattern was found for data based on sleep diaries [36]. This study suggests that the sleep of chronic users of zopiclone is no better than that of drug-free patients with insomnia [36].

Zopiclone is a racemic mixture of (S)- and (R)-isomers, with stereoselective PK profiles [37, 38] and clinical outcomes [39]. Racemic zopiclone has the longest T_{max} of the Z-drugs, and plasma concentrations of the more active enantiomer, (S)-zopiclone, remain below the sleep-inducing threshold (of 10 ng/ml) for more than half an hour after administration [40]. Racemic zopiclone has a longer $t_{½}$ than either zaleplon or zolpidem, suggesting a longer duration of action. However, this means that (S)-zopiclone plasma concentrations may not fall below the sleep-inducing threshold until more than 9 h after racemic zopiclone dosing. An additional consideration is the duration of effects of zopiclone's active metabolite, (S)-desmethylzopiclone (SDMZ), and the less active enantiomer, (R)-zopiclone. Measurable plasma concentrations of both SDMZ and (R)-zopiclone are present 8 h after zopiclone dosing and could contribute to unwanted next-day residual effects [41].

Eszopiclone

Eszopiclone is the pure (S)-enantiomer of racemic zopiclone [42] and was licensed in the USA in December 2004. Although eszopiclone is the isolated (S)-enantiomer of zopiclone, this study revealed notable differences in the pharmacodynamic effects of eszopiclone compared with racemic (R,S)-zopiclone. The pattern of eszopiclone binding at alpha 1, alpha 2, alpha 3, and alpha 5 subtypes is similar (although not identical) to that of zopiclone, but the binding affinities of eszopiclone are all higher than those seen with zopiclone. Eszopiclone's potency is greatest at alpha 5 receptors, followed by alpha 2 and alpha 3 receptors, but it is still a very potent drug at the alpha 1 receptor subtype with an EC50 of the same order of magnitude as zaleplon and zopiclone. Eszopiclone is particularly efficacious at alpha 2 and 3 receptors, with the highest efficacy of the nonbenzodiazepine GABAA modulators when examined in the same study [35].

Melatonin Receptor Agonists (MRAs)

Melatonin is an endogenous neuromodulator synthesized by the pineal gland, and its secretion is regulated by the suprachiasmatic nucleus (SCN), the circadian pacemaker of the brain [43]. The SCN receives light signals from the retina, which are transmitted to the dorsal medial hypothalamus (DMH), which acts as a relay center for signals to regions involved in sleep and wake maintenance [e.g., VLPO, locus coeruleus (LC)]. Melatonin acts largely through MT1 receptors in the SCN to suppress firing of SCN neurons, thereby disinhibiting the sleep-promoting neurons in the VLPO [43]. Secretion of melatonin is low during the day and high at night, and the onset of melatonin secretion coincides with the onset of nightly sleepiness. Exogenous melatonin crosses the blood–brain barrier, and various over-the-counter melatonin preparations are used to treat insomnia, jet lag, shift-work-related sleepiness, and delayed phase syndrome, with various degrees of effectiveness [44]. Melatonin, ramelteon (Rozerem), and agomelatine (Valdoxan) are all agonists for melatonin 1 (MT1) and melatonin 2 (MT2) receptors [43]. Ramelteon has an affinity for both receptors that is 3–16 times greater than melatonin, and it has a longer half-life. Agomelatine also has a high affinity for melatonin receptors, in addition to acting as an antagonist at serotonin 5-HT2C receptors to decrease anxiety as well as promote sleep. Both MT1 and MT2 play a role in sleep induction; MT1 activation suppresses firing of SCN neurons, and MT2 receptors are involved in entraining circadian rhythms.

The administration of melatonin (MEL) during the daytime, i.e., out of the phase of its endogenous secretion, can facilitate sleep [45]; however, if the treatment goal is to maintain daytime sleep for ~8 h, then fast-release oral MEL with its short elimination half-life (~40 min) may be more appropriate [46]. Aeschbach et al. show in healthy subjects that transdermal delivery of MEL during the daytime can elevate plasma MEL and reduce waking after sleep onset, by promoting sleep in the latter part of an 8-h sleep opportunity [46].

Antihistamines

Antihistaminergics exert their sedative effects by antagonizing the H1 receptors in the brain. The H1 antagonist cyproheptadine (Periactin) is effective at increasing slow-wave sleep and REM sleep in rats [47], whereas the H1 antagonists diphenhydramine (Benadryl) and chlorpheniramine (Chlor-Trimeton) decrease sleep latency but have no effect on amount of sleep. In humans, diphenhydramine initially increases subjective sleepiness and reduces latency to sleep compared with placebo, but after 4 days of administration, this effect is abolished, indicating tolerance to its effects [48].

Antidepressants/Atypical Antipsychotics

The effects of antidepressants on sleep are diverse, even within a class of medications. Sedation and drowsiness are common side effects of the TCAs (e.g., desipramine (Norpramin), imipramine (Tofranil), and amitriptyline (Elavil)). Amitriptyline increases drowsiness and shortens

sleep latency compared with placebo, whereas imipramine actually increases sleep latency and decreases total sleep time. MAOIs and SSRIs (e.g., fluoxetine (Prozac), sertraline (Zoloft), and citalopram (Celexa)) can cause insomnia and decreased sleep efficiency. The TCAs which seem to be utilized most commonly to help combat insomnia include amitriptyline and doxepin. Notably, all these classes of antidepressants suppress REM sleep to some degree and have significant anticholinergic effects while doxepin has significant antihistaminergic effects. Cyclobenzaprine (an agent traditionally viewed as a muscle relaxant but structurally very similar to amitriptyline) has been used to help combat insomnia by some clinicians.

Trazodone (Desyrel) is an antidepressant that is also commonly prescribed for insomnia [49]. Trazodone acts as both a weak serotonin (5-HT) reuptake inhibitor and as an antagonist at 5-HT_{2A} and 5-HT_{2C}, α_1-adrenergic, and histamine H_1 receptors [50]. Trazodone has been shown to suppress REM sleep; however, its effects on sleep latency, sleep duration, and number of wakenings are controversial.

Schwartz et al. attempted to compare the effectiveness and tolerability of two hypnotic agents, trazodone (Desyrel) (50–100 mg) and zaleplon (Sonata) (10–20 mg), on psychiatric inpatients with insomnia. Schwartz and colleagues suggested that in their pilot study, it appeared that trazodone may be a better agent to promote longer, deeper subjective quality sleep for psychiatric inpatients with insomnia in terms of effectiveness. However, tolerability was much better with zaleplon as daytime residual side effects were less [51]. Meta-chlorophenylpiperazine (mCPP) is a synthetic drug that was identified for the first time in 2004 in Sweden as an illicit recreational drug and is also a metabolite of trazodone [52]. mCPP has stimulant and hallucinogenic effects similar to those of 3,4-methylenedioxymethamphetamine (MDMA) and has the potential to lead to the development of serotonergic syndrome when interacting with certain agents [53].

Cankurtaran and colleagues compared the effectiveness of mirtazapine and imipramine on multiple distressing symptoms (e.g., pain, nausea) and other symptoms, e.g., sleep disturbances and also depressive and anxiety symptoms [54]. For initial, middle, and late insomnia, only the mirtazapine group showed improvements, suggesting that mirtazapine is effective for helping to resolve insomnia [54].

If antidepressants are used to address insomnia, sedating ones should be preferred over activating agents such as serotonin reuptake inhibitors. In general, drugs lacking strong cholinergic activity should be preferred over agents with strong cholinergic activity (e.g., amitriptyline). Drugs blocking serotonin 5-HT2A or 5-HT2C receptors should be preferred over those whose sedative property is caused largely by histamine receptor blockade (e.g., doxepin). However, sometimes these "nonpreferred" agents (which tend to be very sedating) appear to address insomnia the best. The dose should be as low as possible (e.g., as an initial dose: doxepin 25 mg, mirtazapine 15 mg, trazodone 50 mg, trimipramine 25 mg) [55]. Regarding the lack of substantial data allowing for evidence-based recommendations, we are facing a clear need for well-designed, long-term, comparative studies to further define the role of antidepressants versus other agents in the management of insomnia. Atypical antipsychotic agents which have been utilized (largely because of their sedative effects) in patients that also have chronic insomnia with relatively little data include olanzapine, quetiapine, and clozapine [56].

Alpha 2-Delta Ligands

The use of gabapentin has been evaluated for sleep on healthy persons, patients with seizure, or alcoholic patients [57–60]. All of these studies, though not on persons with primary insomnia, showed generally beneficial effects of sleep and increased slow-wave sleep. Lo and colleagues studied 18 patients with primary insomnia who received gabapentin treatment for at least 4 weeks [61]. All patients received polysomnography, a biochemical blood test, and neuropsychological tests before and after the treatment period. They found that gabapentin enhances slow-wave sleep in patients with primary insomnia [61]. It also improves sleep quality by elevating sleep efficiency and decreasing spontaneous arousal. The results suggest that gabapentin may be beneficial in the treatment of primary insomnia [61]. Hindmarch and colleagues assessed the effects of pregabalin compared with alprazolam and placebo on aspects of sleep in healthy volunteers using a randomized, double-blind, placebo- and active-controlled, 3-way crossover study design [62]. Although there were no differences between the active treatments, both pregabalin and alprazolam reduced rapid eye movement sleep as a proportion of the total sleep period compared with placebo. Pregabalin also significantly reduced the number of awakenings of more than 1 min in duration [62]. Leeds Sleep Evaluation Questionnaire ratings of the ease of getting to sleep and the perceived quality of sleep were significantly improved following both active treatments, and ratings of behavior following awakening were significantly impaired by both drug treatments [62].

Sympatholytics

Sedation and fatigue are among the most common side effects in patients taking βAR antagonists, α1AR antagonists, and clonidine, an agonist for α2AR inhibitor autoreceptors that attenuates NE release. Interestingly, prazosin is used to alleviate nightmares in posttraumatic stress disorder patients [63], potentially by acting as a dual anxiolytic and sedative. Twenty-two veterans with posttraumatic stress disorder (PTSD) were assessed for trauma-related nightmares and nonnightmare distressed awakenings (NNDA) before and after treatment with the alpha-1 adrenoreceptor antagonist prazosin at an average bedtime dose of 9.6 mg/day. Ratings combining frequency and intensity dimensions of trauma-related nightmares decreased from 3.6 to 2.2, NNDA

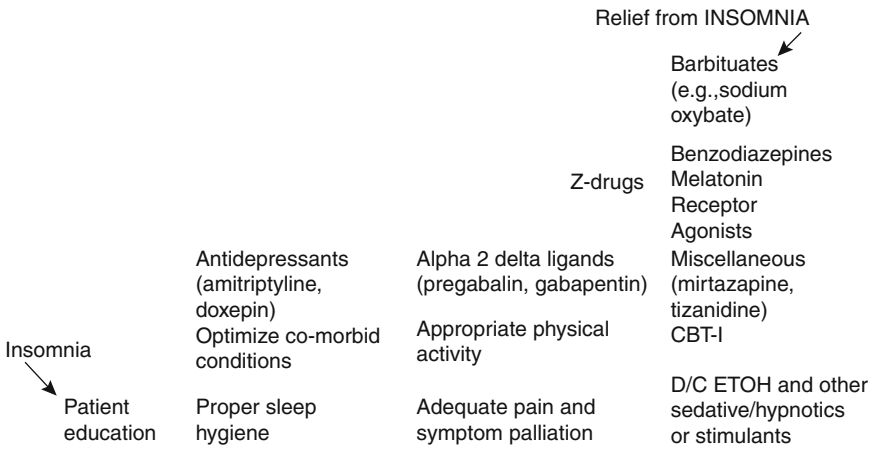

Fig. 9.1 Insomnia relief ladder

from 5.2 to 2.1, and sleep difficulty from 7.2 to 4.1 per week [64]. Tizanidine (an alpha 2 agonist traditionally viewed as a muscle relaxant/antispasticity agent) has been used by some clinicians to help combat insomnia.

Barbiturates

Gamma-hydroxybutyrate (GHB) is not a barbiturate; it is a euphoric, prosocial, and sleep-inducing drug that binds with high affinity to its own GHB receptor site and also more weakly to GABA (B) receptors [65]. GHB is only available from one pharmacy and has been used for patients with severe intractable sleep disturbances who also have fibromyalgia.

In addition to its established efficacy for the treatment of cataplexy and EDS, nightly sodium oxybate administration significantly reduces measures of sleep disruption and significantly increases slow-wave sleep in patients with narcolepsy [66].

Potential Future Sleep Aids

Accumulating evidence supports a role for 5-HT2A antagonism in the treatment of sleep maintenance insomnias [67]. Indeed, several selective 5-HT2A inverse agonists have entered clinical development for the treatment of insomnia; these include eplivanserin, volinanserin, pruvanserin, and nelotanserin [68].

In healthy human volunteers, nelotanserin was rapidly absorbed after oral administration and achieved maximum concentrations 1 h later. All doses (up to 40 mg) of nelotanserin significantly improved measures of sleep consolidation, including decreases in the number of stage shifts, number of awakenings after sleep onset, microarousal index, and number of sleep bouts, concomitant with increases in sleep bout duration [69].

EVT 201 is considered a partial $GABA_A$ receptor agonist because it produces a lower maximal potentiation of $GABA_A$ receptors than a full agonist [70]. It has an elimination half-life of 3–4 h and an active metabolite with similar affinity and elimination characteristics but lower intrinsic activity [71]. Compared to placebo, EVT 201 1.5 and 2.5 mg increased total sleep time (TST), reduced wake after sleep onset, and reduced latency to persistent sleep [72].

Orexin Receptor Modulators

Almorexant (ACT-078573) is an orally active dual orexin receptor antagonist that is being developed for the treatment of primary insomnia [73]. Hoever and colleagues enrolled 70 healthy male subjects in a double-blind, placebo- and active-controlled study [74]. Population pharmacokinetic/pharmacodynamic modeling suggested that doses of ~500 mg almorexant and 10 mg zolpidem are equivalent with respect to subjectively assessed alertness [74].

Conclusion

The approach to insomnia/sleep disturbances is challenging and like the approach to patients with pain involves a multidimensional assessment with a history and physical examination as well as perhaps with other testing to develop a working diagnosis. Treatment approaches should begin with nonpharmacologic approaches and if necessary also involve pharmacologic approaches. An interdisciplinary team and sleep medicine specialist should be involved in complex and poorly responsive cases. A step-ladder approach may be helpful to health-care providers unfamiliar with sleep disturbance issues (Fig. 9.1) [75].

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