Chapter 6
Sedatives and Hypnotics

William Maurice Redden

Sleep-related problems, in particular insomnia, have been problematic for ages. The prevalence of sleep disorders is high on a global level, with rates of 56% in the USA, 31% in Western Europe, and 23% in Japan [1]. Insomnia may be characterized by its duration: acute (or transient) or chronic (occurs at least three times a week and lasts for at least 1 month). Some 30% of the population will report at least occasional episodes of sleep disruption, but only 10% of the population meets the specific diagnostic criteria for an insomnia disorder. Chronic insomnia is multifactorial and highly individualized, making it a challenging condition to treat. It is associated with an often significant decrease in quality of life and can interact with comorbid conditions to worsen overall health and increase morbidity [2].

Sedatives and hypnotics are two different classes of drugs that are often used together or interchangeably. However, they each have different meanings and are meant to produce a different effect. Sedatives are drugs or chemicals that produce a relaxing and calming effect. Hypnotic compounds have the desired effects of producing sleepiness by causing one to fall asleep and maintain sleep. There are medications that can cause either state or even both, thereby leading to the blurring of the terms, with the most commonly used being sedative-hypnotics. Barbiturates and benzodiazepines are the two major categories of sedative-hypnotics. There are other types of medications that have similar mechanisms of action that are used and will be discussed in this chapter as well.

Several sleep disorders, including insomnia, are highly prevalent among patients with neurologic diagnoses, such as Parkinson's disease, epilepsy, multiple sclerosis, and Alzheimer's disease [3]. Insomnia is a common comorbidity in epilepsy that can adversely impact seizure control and has negative associations with quality of life [4]. In addition, people with insomnia have higher incidences and risks of

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G. T. Grossberg, L. J. Kinsella (eds.), *Clinical Psychopharmacology for Neurologists*, https://doi.org/10.1007/978-3-319-74604-3_6

hospitalization for stroke compared with those with a normal sleep pattern [5]. Therefore, clinicians need to recognize that assessment and treatment of insomnia in complex patients may also lead to better management of their primary conditions. This chapter will explore the current treatment options available for insomnia as well as how to choose the most appropriate agent.

Normal Sleep Cycle

There are two states of sleep: non-rapid eye movement (NREM) sleep and rapid eye movement (REM) sleep. NREM sleep is divided into four stages, each representing a continuum of relative depth. Stages 3 and 4 are referred to as slow-wave sleep (SWS), which is most commonly believed to be the restorative part of sleep. This stage is then followed by REM sleep that consists of slow alpha activity and is the stage that is associated with dreaming [6]. The transition from wakefulness to sleep occurs when going into NREM sleep then transitioning to REM sleep. After a period of REM sleep, a brief arousal or awakening may occur before entry again into NREM sleep. Over the course of the night, four to six cycles of NREM to REM sleep typically occur, with each cycle lasting about 80–110 min [7]. Sleep disorders occur when this system is dysfunctional. Benzodiazepine use, especially on a short-term basis, changes both sleep architecture and sleep quality. These changes include increased stage 2 sleep, decrease in slow-wave sleep, and prolonged REM sleep latency [8].

Definition and Classification of Insomnia

Insomnia is a subjective or patient-reported complaint of problems with sleep: either falling asleep, staying asleep, or a combination of both. The *International Classification of Sleep Disorders*, Third Edition *(ICSD-3)* diagnostic criteria for insomnia specify (1) a complaint of difficulty initiating or maintaining sleep or waking up too early. Sleep is chronically non-restorative or of poor quality, (2) poor sleep despite adequate opportunity and circumstances for sleep and (3) at least one pathophysiological abnormality causing daytime impairment such as fatigue, difficulty with attention, and daytime sleepiness. The ICSD-3 delves further in classifying chronic insomnia as a condition where the criteria for insomnia are met plus a duration of 3 months and a frequency of at least three times per week [9].

It has been suggested that about 30% of the general population complains of sleep disruption, while approximately 10% have associated symptoms of daytime functional impairments consistent with the diagnosis of insomnia [10].

Brief History of Sedatives and Hypnotics

Barbiturates

Prior to the discovery of barbiturates, several agents were used for their sedative and hypnotic properties. These included alkaloids derived from opioids, chloral hydrate, and bromides [11]. At one point, barbiturates were the gold standard for treatment of insomnia as well as for the management of seizures [12]. It was not until the mid-1950s that the Narcotics Expert Committee at the World Health Organization stated that barbiturates were habit forming and could produce a drug addiction dangerous to public health. That announcement led to recommendations that included barbiturates only being dispensed by a prescription which included the number of refills as well as a record being kept of such prescriptions [13].

Benzodiazepines

The first benzodiazepine, chlordiazepoxide, was identified in 1955 [14]. Since then, benzodiazepines have been the agents used most commonly to treat anxiety and sleep disorders.

There are current concerns that these agents are being abused and overprescribed. Clinicians should also be focused on the potential for physical and psychological dependence as well as withdrawal/tolerance concerns [15].

Sedative and Hypnotics in Clinical Practice

We will discuss the treatment algorithms for using hypnotics and sedatives with the following case:

> *Ms. SH is a 51-year-old female who presents to your clinic with the chief complaint of feeling tired during the day. After further questioning, it is revealed that she has not been sleeping well at night. This has been a problem since her mid-30s, but now is causing more impairment in her daily functioning. She has noticed difficulty concentrating at work which has led to her making more errors that usual. When she gets home, she is often too exhausted to help with activities around the house.*

Before prescribing medications, a thorough evaluation should be done to rule out any secondary or comorbid causes of insomnia. Therefore, the practitioner should get a detailed history of the patient's sleep problem, followed by a complete physical exam including neurological assessment. Then any pertinent diagnostic labs (such as TSH, CMP, CBC) should be done. Also if there are any abnormal findings on neurological examination (such as abnormal movements or unilateral weakness), imaging should be done as well. Hilty et al. also recommend asking specific

Table 6.1 Sleep hygiene recommendations

Maintain a regular sleep-wake cycle (go to bed at the same time each night and wake at the same time each morning)
Avoid exercise within 3 h of bedtime
Avoid caffeine after lunch
Avoid nicotine at least 2 h before bedtime
Use the bed for only sleeping and sex; do not read or watch TV in bed
If not asleep within 15–30 min, get out of bed and walk around

questions that would include as follows: (1) Do you have problems falling asleep or staying asleep? (2) Do you frequently awaken and is that associated with anything, for example, pain? (3) Do you wake up tired or refreshed despite many hours of sleep [16]?

Ms. SH denies any other signs and symptoms of mood disorder or other conditions that may impact sleep. Upon more detailed questions relative to her sleep habits, it is determined that she has trouble falling asleep and is easily awoken in the middle of the night and has trouble getting back to sleep.

Nonpharmacologic Treatment Options for Insomnia

The first treatment recommendation should be to encourage good sleep hygiene (Table 6.1), to increase daytime activity, and to search for any secondary or reversible causes such as depression, anxiety, gastroesophageal reflux, or thyroid disorders.

Cognitive Behavioral Therapy for Insomnia

Cognitive behavioral therapy for insomnia (CBT-I) is a nonpharmacological approach to treatment comprised of several strategies which include establishing a learned association between the bed and sleeping through stimulus control, restoring homeostatic regulation of sleep through sleep restriction, and altering anxious sleep-related thoughts through cognitive restructuring. It is conveyed over the course of four to eight sessions that occur weekly or every other week for 30–60 min each session. In general, CBT-I is at least as effective for treating insomnia when compared with sleep medications, and its effects may be more durable than medications [17]. The effective nature of CBT-I along with minimal side effects should make this treatment option highly attractive; however, factors such as cost, lack of available CBT practitioners, and potential problems with patient motivation and adherence may make the use of behavioral techniques difficult [18].

Ms. SH has stressed the importance to her of getting sleep and says she does not have the time to invest in therapy. She wants something that will work immediately. She has tried over-the-counter sleep products without success. There is no previous history of being on any prescribed medications for sleep. Upon further questioning she admits to drinking a glass of wine 3–4 times per week, but denies any other substance use and there is no history of abusing prescribed medications.

Medication Options

Currently, the benzodiazepines (BZD) and non-benzodiazepine receptor agonists (non-BzRA) are the main FDA-approved treatment choices for insomnia. Initially, these medications were meant for short-term or intermittent use; however, clinical experience has shown that these medications are often used for much longer periods or even chronically. The main treatment goals are (1) to improve sleep quality and quantity and (2) to improve insomnia-related daytime impairments [9].

Benzodiazepines (BDZ)

Benzodiazepines are FDA-approved for both the treatment of insomnia and anxiety (Table 6.2). At times, multiple benzodiazepines are used to treat both conditions. This can enhance the addictive potential as well as increase the tolerance for either medication [19]. There are currently five FDA-approved benzodiazepines for the treatment of insomnia (estazolam, flurazepam, quazepam, temazepam, and triazolam) [20].

Temazepam is the most common BDZ prescribed for insomnia [21]. It is absorbed more slowly and metabolized more quickly than other benzodiazepines, which leads to reduced awakenings during the night and increased sleep duration [22].

Estazolam significantly increases total sleep time and reduces time awake during sleep in a dose-dependent manner (0.25, 0.5, 1.0, and 2.0 mg) [23]. In long-term studies, estazolam 2.0 mg remained an effective hypnotic for at least 6 weeks of continuous nightly administration with no evidence of clinically significant tolerance [24]. Vogel et al. found estazolam 1 mg nightly appears to be a safe and

Table 6.2 Benzodiazepine receptor agonists

Drug (trade name)	Half-life	Dose range	Elderly
Estazolam (Prosom)	15–20 h	0.5–2 mg	1 mg
Flurazepam (Dalmane)	2.3 h (active metabolite 100 h)	15–30 mg	15 mg
Quazepam (Doral)	39–72 h	15 mg	7.5 mg
Temazepam (Restoril)	5–11 h	15–30 mg	7.5–15 mg
Triazolam (Halcion)	2–3 h	0.25–1 mg	0.125–0.5 mg

Data from Heel et al. [92], Cohn et al. [93], Pakes et al. [28], Pierce and Shu [24]

effective hypnotic for elderly patients with insomnia. Those patients had rebound insomnia the first night after discontinuation, but sleep parameters (wake time after sleep onset and total sleep time) returned to normal the following night. Also, there was no effect on daytime performance or anterograde memory [25]. Flurazepam has shown moderate improvement in sleep, in short-term use, but with higher risk of adverse effects of somnolence and hypokinesia (the following morning) when compared with estazolam [26]. Flurazepam significantly increased total sleep time while reducing the latency to stage 1 sleep, the number of awakenings in the night, and the amount of wakefulness after sleep onset as well as decreased REM sleep [27].

Triazolam is an older benzodiazepine with a short half-life, 2–3 h. In the past it has been used to treat acute or chronic insomnia, situational insomnia in hospitalized patients, and insomnia associated with other disease states [28]. Triazolam has been shown to decrease sleep latency and the number of nocturnal awakenings while increasing total sleep time in patients with insomnia [29]. In contrast, quazepam has a long half-life, 39–72 h due to two active metabolites. It is useful for inducing and maintaining sleep for acute and chronic insomnia with less incidence of rebound insomnia when discontinued [30].

Z-Drugs

With several pharmacologic treatment options available, trying to decide which agent to start can be challenging, as each may offer specific benefits versus their potential side effects (Table 6.3). Non-benzodiazepines receptor agonists (non-BzRA) offer a better safety profile, and most studies have shown them to be non-habit forming [31]. Zolpidem was the first of this class of medication to be developed and FDA-approved in 1992. The non-BzRA work at the GABA receptor site where they also have preferential subtype selectivity by binding to omega receptors [32].

The other agents in this class include zaleplon, zopiclone (not available in the United States), eszopiclone, and now the various formulations of zolpidem (immediate release vs extended release, sublingual and nasal).

Zolpidem decreases sleep latency and increases total sleep time and sleep efficiency without adversely affecting sleep architecture [33]. The optimal dose of zolpidem is 10 mg at bedtime and 5 mg for elderly patients. The hypnotic effects have been shown to be active at low doses, and there was a decrease in percent of time spent in rapid eye movement sleep at much higher doses (20 mg) [34]. While zolpidem has fewer side effects than the benzodiazepines, it may be associated with rebound insomnia, next-day residual effects, and complex sleep-related behaviors [35]. There has been growing concern relative to zolpidem causing daytime automatisms and sleep-related parasomnias. These behaviors involve confusion, amnesia, or somnambulism which has lead patients to “sleepwalk,” “sleep eat,” and even “sleep drive” [36, 37]. These events do not occur very often but clinicians should be aware of the risks.

Table 6.3 Non-benzodiazepine receptor agonists and other sedatives

Drug (trade name	Mechanism of action	Dose range	Special considerations
Eszopiclone (Lunesta)	Non-BzRA	2–3 mg	Unpleasant taste
Zaleplon (Sonata)	Non-BzRA	5–10 mg	Low risk of withdrawal symptoms and rebound insomnia
Zolpidem (Ambien)	Non-BzRA	5–10 mg	Comes in several forms including nasal spray, concern for sleep-related behaviors
		6.25–12.5 mg (CR)	
Ramelteon (Rozerem)	MT_1 and MT_2 agonist	8 mg	Short half-life, no abuse potential
Trazodone	$5HT_2$, alpha$_1$, H_1 antagonist	25–200 mg	Risk of orthostasis, dizziness, priapism
Mirtazapine (Remeron)	$5HT_{2-3}$, alpha$_{1-2}$, H_1, M_1, NE antagonist	7.5–30 mg	Risk of increased weight and appetite
Doxepin (Silenor)	H_1, $5HT_2$, alpha$_1$, M_1 antagonist	3–6 mg (capsules)	Risk of orthostatic hypotension, dry mouth, delirium
		10–100 mg (tablets)	
Suvorexant (Belsomra)	Orexin$_{1-2}$ antagonist	5–20 mg	Low risk of withdrawal symptoms and rebound insomnia, chance of abnormal dreams
Quetiapine (Seroquel)	$5HT_{1-2}$, D_{1-2}, alpha$_{1-2}$, H_1 antagonist	50–200 mg	Indicated for schizophrenia and bipolar disorder, increased risk of weight gain, dry mouth, EPS
Gabapentin (Neurontin)	Interacts at the GABA transporter, decreases glutamate	100–900 mg	Anticonvulsant, not effective as mood stabilizer, recent reports of abuse risk

Data from FDA prescribing information; Asnis et al. [69], Stahl [94]
MT melatonin receptor, *5HT* serotonin, *H* histamine, *M* muscarinic receptor, *NE* norepinephrine

Zopiclone is a non-BzRA that has been recognized as an effective and well-tolerated hypnotic agent. It has a relatively low risk of causing residual clinical effects (such as difficulty in waking or reduced morning alertness) as well as a decreased incidence of rebound insomnia [38].

Eszopiclone is the stereoisomer of zopiclone which is effective at reducing sleep onset time as well as improving overall sleep maintenance [39]. Within this same study, it was discovered there was little indication that eszopiclone was associated with withdrawal effects or rebound insomnia. There is also evidence that eszopiclone is beneficial in long-term use for chronic insomnia with enhanced quality of life, reduced work limitations, and reduced global insomnia severity [40]. The most commonly reported adverse effects include bitter taste, dizziness, and dry mouth, with low risk for tolerance [41]. If both options are available, eszopiclone is as efficacious as zopiclone in the treatment of insomnia, increasing total sleep time as well as sleep efficiency as evidenced by polysomnography [42].

Zaleplon has been shown to be efficacious in promoting sleep initiation, but less so in promoting sleep maintenance. Elie et al. demonstrated that zaleplon is an effective treatment option for patients with difficulty falling asleep by reducing sleep latency. They also validated the favorable safety profile of zaleplon as shown by the absence of rebound insomnia and withdrawal symptoms after treatment was stopped. Interestingly, they have also shown that zolpidem was associated with higher incidence of withdrawal symptoms and rebound insomnia than with placebo. These withdrawal symptoms consisted of depressed mood, muscle pain, a peculiar taste, loss of memory, and olfactory discrimination [43]. Zaleplon has a rapid onset of action and undergoes rapid elimination, which may explain its more favorable safety profile [44].

This class of medication has been shown to be effective up to 12 months with evidence in improvement in daytime functioning and with little risk of rebound insomnia after discontinuation [45–47]. Overall, prolonged use of non-BzRA has been shown to be well tolerated without evidence of tolerance [45].

Orexin Antagonist

Orexin neuropeptides are secreted from the lateral hypothalamus and are critical for maintaining normal wakefulness. When they are malfunctioning or destroyed, they can cause narcolepsy as they play a vital role in keeping people awake [48].

Suvorexant is the first dual receptor orexin antagonist that was FDA-approved in 2014. Dual orexin receptor antagonists block the activity of orexin 1 and 2 receptors to both reduce the threshold to the transition of sleep and attenuate orexin-mediated arousal [49]. Initially, the pharmaceutical company which developed suvorexant requested approval of doses between 20 and 40 mg. But after much debate and discussion, it was determined that this drug provides maximum benefit with low risk of tolerance/dependence at doses less than 20 mg per night [50].

Suvorexant is indicated for the treatment of insomnia characterized by difficulties with sleep onset and poor sleep maintenance. The recommended dose is 10 mg at bedtime which can provide up to 7 h of sleep. The maximum recommended dose is 20 mg per 24 h [51]. Suvorexant is generally safe and well tolerated for chronic use (longer than 3 months [52]).

Melatonin

Melatonin (5-methoxy-N-acetyltryptamine) is endogenously synthesized, secreted by the pineal gland and plays a key role in maintaining regular circadian rhythms [53]. In most studies exogenous melatonin reduced sleep onset latency to a greater extent in people with delayed sleep phase syndrome than in people with insomnia. Otherwise, melatonin was not effective in treating most primary sleep disorders with short-term use (4 weeks or less) [54].

Ramelteon is a melatonin receptor agonist that has high affinity for MT1 and MT2 receptors [55]. At doses of 4–32 mg, ramelteon had statistically significant reductions in latency to persistent sleep (LPS) and increases total sleep time (TST). Also, at these same doses, there were no next-day residual effects, as compared with placebo. The most commonly reported adverse events were headache, somnolence, and sore throat [56]. The FDA-recommended dose of ramelteon is 8 mg nightly. One concerning side effect to be mindful of is that ramelteon can affect road-tracking performance (the number of subjects who slid off the track), visual attention and/or psychomotor speed, subjective sleepiness, and equilibrium function with acute treatment [57].

Sedating Antidepressants

We have been using sedating antidepressants such as trazodone, amitriptyline, and doxepin to treat insomnia. However, there have been little if any double-blind, placebo-controlled studies to validate their use. Buscemi et al. conducted a meta-analysis on drugs used for the treatment of chronic insomnia. The analysis suggested that sedating antidepressants, particularly doxepin and trazadone, may have a role in the management of chronic insomnia [54].

Some reasons that clinicians prescribe antidepressants off-label for insomnia include (1) the benefit of using a single medication with sedating properties to manage both a psychiatric or medical disorder and concurrent insomnia, (2) using a medication with sedating properties to offset sleep difficulties caused by another medication, and (3) avoiding the use of hypnotics due to concerns about dependency and side effects [58].

Trazodone at doses of 25–50 mg has been shown to have modest effects on insomnia [59]. In a double-blind, placebo-controlled study using trazodone 50 mg prior to bedtime, Roth et al. demonstrated that compared to placebo, trazodone was associated with fewer nighttime awakenings, decreased minutes of stage 1 sleep, and fewer self-reports of difficulty sleeping. However high doses of trazodone (200–300 mg) may cause some concerning side effects including significant impairments of short-term memory, difficulty with verbal learning, and some trouble with equilibrium and orthostasis, in both the adult and geriatric populations [60].

Doxepin is a tricyclic antidepressant that at low doses selectively antagonizes histaminic receptors, which is believed to cause its sedative effects. In the first placebo-controlled, double-blind, polysomnographic study, low-dose doxepin (25–50 mg) was shown to improve sleep efficiency and increase total sleep over 4 weeks. There was an increase in stage 2 sleep without significantly affecting total REM sleep. Withdrawal and rebound symptoms were seen when doxepin was stopped abruptly. Therefore, it is recommended to slowly taper off this medication. In addition, some severe side effects of leukopenia, thrombocytopenia, and elevated liver enzymes were observed [61]. In three large, well-designed phase III trials in adult or elderly patients with chronic primary insomnia, oral, low-dose doxepin 3 or 6 mg

capsules once daily improved wake time after sleep onset, total sleep time, and sleep efficiency to a significantly greater extent than placebo [62]. This led to the FDA approval of doxepin as Silenor. Being a tricyclic, anticholinergicity, cardiotoxicity, and overdose potential need to be kept in mind.

Mirtazapine is tetracyclic antidepressant that blocks the noradrenergic alpha2-auto- and heteroreceptors responsible for controlling noradrenaline and serotonin release. It also has a low affinity for serotonin (5-HT)1A receptors but potently blocks 5-HT2 and 5-HT3 receptors. The blockade of 5-HT2 and 5-HT3 receptors along with histamine-1 receptors prevents development of the side effects associated with nonselective 5-HT activation and may contribute to its calming and sleep-improving effects [63]. In patients without primary sleep disorders, mirtazapine has been shown to increase sleep efficiency by increasing slow-wave sleep time while decreasing stage 1 sleep time. In addition, there was no significant effect on rapid eye movement sleep variables [64]. Mirtazapine may also be effective in treating insomnia in patients who are also depressed. This medication improves sleep disturbance as well as counteracts the key biological symptoms of depression due to its unique pattern of neurotransmitter modulation [65]. In depressed patients, the acute effects of mirtazapine on improvement of sleep efficiency are evident, and these effects may persist with chronic use as well [66].

Esmirtazapine (Org 50081), which was in development for the treatment of insomnia, is the maleic acid salt of the S(+) enantiomer of mirtazapine. As esmirtazapine has a shorter half-life (10 h) than racemic mirtazapine, it is anticipated that esmirtazapine will have a smaller risk for residual sedative effects the next day. In a 6-week, double-blind, randomized, polysomnography (PSG) study, esmirtazapine was associated with consistent and sustained improvements in sleep in adults with primary insomnia. Overall, it was well tolerated, and there was minimal residual daytime effect [67]. However, its clinical development was stopped in 2010 for strategic reasons [68].

Other medications have been tried off-label due to their sedating properties. The primary agents include quetiapine and gabapentin. Thus far, there has been limited evidence for their efficacy in treating insomnia. However, it may be beneficial to use such medications off-label for insomnia when patients also have a comorbid medical condition for which the drug is FDA-approved, e.g., neuropathy with gabapentin [69]. Obviously, one needs to consider the risks of using sedating antipsychotics for insomnia, which include increased mortality in geriatric patients with dementia.

Major Side Effects and Concerns

Rebound Insomnia

When sedatives or hypnotics, especially those with short-half lives, are abruptly discontinued, some patients may experience insomnia worse than it was prior to treatment. This usually lasts one to two nights. To avoid this, it is recommended to taper down the medication dosage over a few nights.

Residual Effects

Another concern associated with the use of hypnotics is residual effects such as daytime sleepiness and impairment of psychomotor and cognitive functioning the morning following taking the medication.

It seems that compounds with longer half-lives greatly increase these risks, but those with shorter half-lives have also been associated [70].

Memory Loss

Morning sedation and difficulties with memory have always been concerns associated with benzodiazepines. They may be failure of memory consolidation rather than failure of retrieval, and those with shorter sleep latency may have better memory consolidation than those who stayed up more during the night [71].

Falls

Hypnotics and sedatives may significantly contribute to falls, since these drugs affect balance and can produce body sway even after a single dose. This effect is dose-dependent and made worse by addition of other psychoactive drugs or alcohol [72].

Chronic Use Issues and Concerns

Sedatives and hypnotics have the potential for misuse and abuse due to the euphoric feelings they can cause. Occasionally, patients may intentionally exaggerate their symptoms to get these medications. Presentations of intentional malingering may include resisting access to outside medical records; nonadherence with diagnostic or treatment recommendations; reemergence, or a worsening of symptoms when medication dose is due to be reduced; and when evidence from medical testing disputes information provided by the patient [73].

Treatment of Alcohol- and Substance-Dependent Patients

There are high prevalence rates (36–91%) of insomnia in alcohol-dependent patients [74]. Alcohol withdrawal-related insomnia is common among this patient population and is related to a lifetime co-occurring diagnosis of insomnia. There is a 50%

prevalence rate among individuals who meet lifetime criteria for both alcohol dependence and alcohol withdrawal insomnia [75].

When addressing treatment options in this complex patient population, one should make sure to (1) emphasize that abstinence is necessary and is reasonable, (2) target other modifiable causes including poor sleep hygiene, (3) include behavioral therapy as an appropriate treatment option, and (4) when selecting medications, try at all cost to avoid benzodiazepine receptor antagonists due to their addictive properties in this addiction-prone population [76].

Trazodone is an antidepressant that is often used off-label for treating insomnia. However, in patients with alcohol dependency, it has been shown that despite short-term benefits in sleep quality, trazodone may impede improvements in alcohol consumption and lead to increased drinking when stopped [77].

Use in the Elderly

As we age, our sleep cycle patterns change. It usually takes one longer to fall asleep and we also see more frequent awakenings during the night. Older adults often display a different circadian pattern, usually going to bed earlier and waking up earlier than their younger counterparts. Sleep architecture changes include spending an increased proportion of time in stages 1 and 2 sleep and a decreased proportion of time in stage 3 sleep and REM sleep (the deeper stages) [78].

Sleep disturbances, particularly among older persons, often may be secondary to coexisting diseases and are associated with an increasing number of respiratory symptoms and physical disabilities [79].

Long-term benzodiazepine use includes the risks of developing tolerance or dependence, rebound insomnia, residual daytime sedation, cognitive impairment, and motor incoordination/fall risk, which are magnified in the elderly. Therefore, it is recommended that benzodiazepines be used for short-term (usually <35 days) management of insomnia in the elderly [10].

However, recent studies have shown that elderly patients with persistent/chronic insomnia are also at greater risk for the development of new-onset depression [80]. In addition, the risk of falls and fractures is higher in the elderly when prescribed zolpidem, being almost twice as high as in those patients who are prescribed benzodiazepines [81, 82].

General Prescribing Recommendations

There are several factors that should be assessed before deciding which medication to prescribe for insomnia. Comorbid conditions can guide clinicians on what medications are appropriate or not. For example, in patients with severe pulmonary disease, CNS-sedating medications should be avoided if possible [69]. Or in patients

with coexisting anxiety and insomnia who may already be on a benzodiazepine, adding a melatonin receptor agonist or an orexin antagonist might be beneficial.

When prescribing medications which may be misused or abused, trying to obtain records from previous providers and information from significant others is useful. Also, obtaining a detailed substance abuse history including sharing medications with a friend or family member or of legal issues stemming from drug use is vital [73].

Middle-age persons may be more susceptible to the effects of alcohol and sedative-hypnotic drug interactions by engaging in risky drinking behaviors (i.e., binge drinking) when compared to the older patient population. Despite the lower overall prevalence, older persons may be particularly susceptible to additive CNS-depressant effects due to physiologic changes in drug and alcohol metabolism. Therefore, clinicians should carefully consider patients' level and pattern of alcohol consumption before prescribing sedatives and/or hypnotics [83].

Drugs with shorter time to peak blood concentration (tmax) will probably have a more rapid onset of action and aid sleep onset, whereas those with longer half-lives (t1/2) can provide better sleep maintenance but have the potential for daytime hangover. Therefore, medication treatment should be focused on patient's symptom pattern and treatment goals (acute vs chronic). Starting with a short- to intermediate-acting BZA or non-BzRA followed by ramelteon is advised. If the initial agents are not successful, then try another medication in the same class. If that proves unsuccessful, then switch classes of medications. Clinicians should consider using sedating mediations such as antidepressants, antipsychotics, or anticonvulsants when treating comorbid conditions for which these drugs are appropriate [84] (Fig. 6.1). It is also recommended that all patients with insomnia be offered the option of CBT-I as an initial treatment [85].

After a, thorough discussion of benefits, risk and the option of short-term use versus *long-term use, it was decided to start Ms. SH on a non-BzRA. It was agreed that this would be for short-term use during which period she would also practice healthy sleep habits. She was advised to avoid alcohol and other sedating medications with her non-BzRA.*

Considerations of Use in Comorbid Neurological Conditions

In patients with Parkinson's disease, non-motor symptoms, including fatigue, depressed mood, and autonomic instability, are most closely and independently associated with reported insomnia [86]. Disrupted sleep, early morning awakenings, and non-restorative sleep are the most common insomnia symptoms in Parkinson's patients [87]. Therefore, at times, patients may be on two or more psychoactive mediations that may cause sedation. For example, a patient may be on levodopa/carbidopa therapy and/or an anticholinergic drug, but still complain of difficulty sleeping. In this instance using a short-acting BZA or non-BzRA could be beneficial and improve quality of life for the patient. As with the use of any controlled substance, the ongoing screening for aberrant behavior, monitoring of treatment compliance, documentation of medical necessity, and the adjustment of treatment to clinical changes are essential [88].

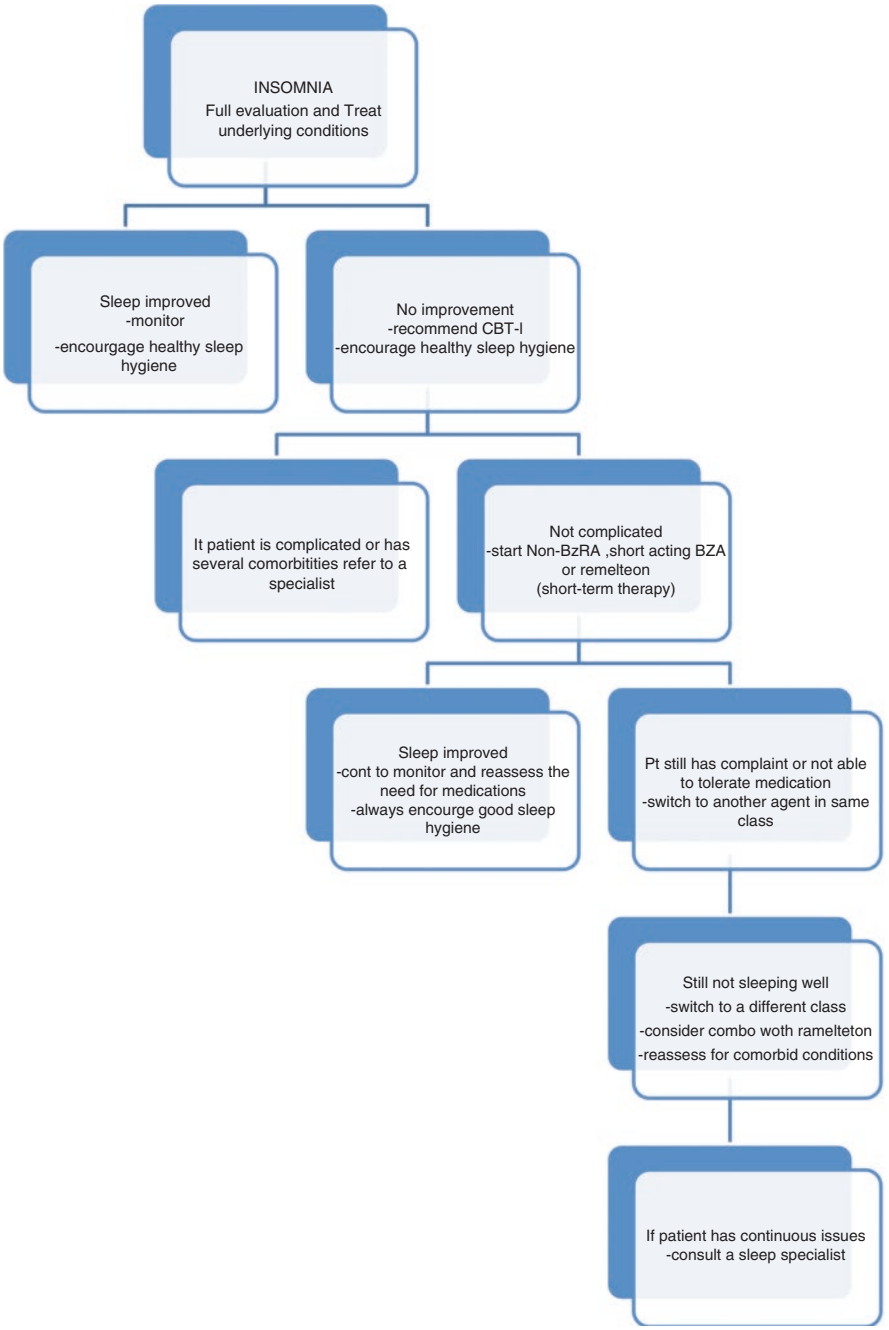

Fig. 6.1 Treatment algorithm for insomnia

Scales

Ford Insomnia in Response to Stress Test

FIRST (Ford Insomnia in Response to Stress Test) is a self-reported measure that may help at predicting initial onset insomnia in individuals without history of insomnia or depression. It consists of questions such as: (1) "In the past year, have you experienced difficulty falling asleep and/or staying asleep?" (2) On average, how long does it take you to fall back asleep after waking up (during the past month)?" and (3) "To what extent do you consider your sleep problem to interfere with your daily functioning (e.g. daytime fatigue, ability to function at work/daily chores, concentration, memory, mood, etc.)?" [89].

The Pittsburgh Sleep Quality Index (PSQI) is a self-rated questionnaire which assesses sleep quality and disturbances over a 1-month time interval. There are 19 individual items that measure 7 components of sleep: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction. The higher the score indicates greater sleep dysfunction [90].

Conclusion

Pharmacologic treatment of sleeplessness continues to increase with the formal diagnosis of insomnia, suggesting that life problems are being treated with medication solutions, without benefit of formal complaint or diagnosis [91]. This can lead to patients being on multiple hypnotics and or sedatives. We as clinicians, with the aid of self-assessment tools, should be able to screen more efficiently for patients with insomnia. With more accurate delineation of symptoms, we will be able to tailor better treatment options for patients. Good sleep hygiene and the possibility of CBT-I treatment should always be recommended.

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