Neurotherapeutics (2012) 9:728–738
DOI 10.1007/s13311-012-0148-3

Insomnia Pharmacotherapy

Timothy Roehrs · Thomas Roth

Published online: 14 September 2012
© The American Society for Experimental NeuroTherapeutics, Inc. 2012

Summary The benzodiazepine receptor agonists (BzRAs) a melatonin receptor agonist and a histamine antagonist have all been approved as hypnotics. Beyond their differing mechanisms of action, they have differences in pharmacokinetics, and among the BzRAs differences in receptor subtype affinity and formulations, which provides the physician with broad options for tailoring therapy to each patient's specific needs. Consistent with their specific pharmacokinetics and formulations, these Food and Drug Administration-approved hypnotics have been shown to improve sleep with no evidence of tolerance development in long-term use. In addition, emerging data indicate these drugs also improve aspects of daytime function. Their side effects are either associated with the direct sedating effects of the drugs, doses greater than clinical doses, or a combination with alcohol or other sedating drugs. Anxiolytic BzRAs, sedating antidepressants and antipsychotics have been used off-label as hypnotics. However, in the absence of information regarding their dose range for efficacy and safety, their use as hypnotics is ill-advised.

Keywords Hypnotic efficacy · Hypnotic safety · Hypnotic pharmacology · Off-label use · Treatment considerations

Introduction

There is misperception and misinformation among patients and medical professionals regarding insomnia and appropriate pharmacotherapy for insomnia. The morbidity of insomnia and the potential for successful treatment are not fully recognized. Thus, a majority of people with insomnia have not discussed it with their physician, either because they merely did not mention it or were not asked about it. In a representative study, only 21 % of people with insomnia reported discussing their sleep problem with their physician and only 5 % received treatment [1]. But that is not to say people with insomnia do not want relief for their insomnia, because many report self-treatment. In several different population-based studies the rate of over-the-counter medication use ranged from 10 to 29 %, and the use of alcohol as a sleep aid was between 10 and 28 % [2–4]. When being treated medically, a variety of pharmacological agents are used by physicians to treat insomnia, including those agents approved by the Food and Drug Administration (FDA) for insomnia, as well as medications that have sedating side effects, but have not been systematically studied for their effectiveness and safety in insomnia.

This article will review the pharmacology, efficacy, and safety of the various agents used to treat insomnia. It should be noted that there is very limited hypnotic efficacy and safety information for some of the drugs physicians use for insomnia, and there is virtually no information for many of the various agents used in self-treatment. On the other hand, for the FDA-approved hypnotics, there is adequate efficacy and safety information, but the majority of studies have been conducted in primary insomnia. By definition, primary insomnia is not associated with any other comorbid condition, and it only represents a small proportion of all insomnia. It is estimated that 85 to 90 % of insomnia is associated with a comorbid condition [5], which includes psychiatric disorders with depression (being the most common), medical disorders (particularly those associated with pain), other sleep disorders, and circadian rhythm disorders.

The major issue is that the effective dose range of the various drugs for primary insomnia may not apply to

T. Roehrs (✉) · T. Roth
Sleep Disorders and Research Center, Henry Ford Hospital,
Detroit, MI 48202, USA
e-mail: troehrs1@hfhs.org

T. Roehrs · T. Roth
Department of Psychiatry and Behavioral Neuroscience,
School of Medicine, Wayne State University,
Detroit, MI 48202, USA

comorbid insomnia in that the dose range may be either too low or too high. Pain conditions and some psychiatric disorders may require higher doses, whereas combination of hypnotics with other sedating drugs that are being used to treat the comorbid disorder may require lower doses of the hypnotic. Unfortunately, studies of insomnia pharmacotherapy in comorbid insomnia are very few and a limited number of comorbid conditions have been studied. No studies have assessed the effective dose ranges or treatment regimens for comorbid insomnia.

Benzodiazepine Receptor Agonists

Pharmacology

The benzodiazepine receptor agonists (BzRAs) have been the drugs of choice for the treatment of insomnia since their introduction approximately 50 years ago (see Table 1). Some of these drugs have a benzodiazepine chemical structure, whereas others do not. However, they all share the characteristic that they occupy benzodiazepine alpha receptors of the gamma-aminobutyric acid $(GABA)_A$ receptor complex, hence their name of BzRAs [6]. Occupation of the receptor results in opening the chloride ion channel and facilitation of the inhibitory action of GABA, which is a widely distributed, inhibitory neurotransmitter in the central nervous system (CNS). BzRAs act allosterically, meaning that GABA must also be present on the receptor complex for BzRAs to have their inhibitory effects, which in part explains their wide therapeutic index (e.g., efficacy to safety ratio) [7]. In contrast, the barbiturates and barbiturate derivatives, which the BzRAs replaced have narrow therapeutic indices and act directly at the receptors on the GABA complex without the need for the presence of GABA. The BzRAs include drugs that have the benzodiazepine chemical structure (i.e., flurazepam, triazolam, temazepam, estazolam, and quazepam), and those that do not, but yet act at the benzodiazepine receptor (i.e., zolpidem, zaleplon, eszopiclone, zolpidem CR, and zolpidem sublingual) (see Table 1).

The BzRAs differ on 2 pharmacologic dimensions (i.e., their pharmacokinetics and their alpha receptor subtype affinity). As to pharmacokinetics, all the BzRAs are rapidly absorbed having a Tmax of 0.5 to 2 h, which accounts for their capacity to hasten sleep onset. In contrast, they differ widely in half-lives and the half-life is predictive of the likelihood of producing residual effects (see "Safety" section as follows). Among the benzodiazepine BzRAs, only triazolam has a short half-life. Temazepam and estazolam have intermediate half-lives, whereas flurazepam and quazepam have long half-lives. All of these intermediate and long-acting benzodiazepines have been shown to have residual effects (see "Safety" section as follows). Among the nonbenzodiazepine BzRAs, zolpidem and its different formulations, and zaleplon, have ultra short or short half-lives, whereas eszopiclone has an intermediate half-life.

The other major pharmacological difference among the BzRAs is in their alpha receptor subtype, binding affinity [8]. For the alpha receptor of the $GABA_A$ complex, 6 subtypes have been identified [8]. All of the benzodiazepines demonstrate similar affinity to the alpha 1, 2, 3, and 5 receptor subtypes. In contrast, zolpidem and zaleplon have a higher affinity for alpha 1 than the other subtypes. Eszopiclone shows a decreased preference for the alpha 1 subtype, having a greater affinity to alpha 2 and 3. Although knock-in genetic data from animal studies suggest differential effects associated with the different alpha receptor subtypes, this has not been directly demonstrated in human studies. However, based on the animal studies, it is hypothesized that alpha 1 mediates sleep promotion and amnesic effects, whereas alpha 2 and 3 are involved in anxiolytic and

Table 1 Drugs with a FDA Indication for Insomnia

Generic name	Trade name	Dose (mg)	Mechanism of action	T max (h)	T ½ (h)
Flurazepam	Dalmane	15, 30	BzRA	0.5-1.0	47-100[a]
Triazolam	Halcion	0.125, 0.25	BzRA	2	1.5-5.5
Temazepam	Restoril	7.5, 15, 30	BzRA	1.2-1.6	3.5-18.4
Estazolam	ProSom	1, 2	BzRA	0.5-6	10-24
Quazepam	Doral	7.5, 30	BzRA	2	39-73*
Zolpidem	Ambien	5, 10	BzRA	1.6	1.4-4.5
Zaleplon	Sonata	5, 10, 20	BzRA	1.0	1.0
Eszopiclone	Lunesta	1, 2, 3	BzRA	1.0	6.0
Zolpidem CR	Ambien CR	6.25, 12.5	BzRA	1.5	2.8
Zolpidem sublingual	Intermezzo	1.75, 3.5	BzRA	0.5-0.75	1.4-3.6
Ramelteon	Rozerem	8	MtRA	0.75	1.0-2.6
Doxepin	Silenor	3, 6	H_1Ant	3.5	15.3-31[†]

BzRA=benzodiazepine receptor agonist; FDA=Food and Drug Administration; H_1Anti-histamine 1 receptor antagonist; MtRA=melatonin receptor agonist

*Half-life for active metabolites

[†]Half-life for parent drug and active metabolite

possibly antidepressant effects. In human studies, eszopiclone, which has alpha 2 and 3 affinities, has been shown to augment an antidepressant response in patients with insomnia comorbid with depression [9], as well as an anxiolytic response in patients with insomnia comorbid with generalized anxiety disorder (GAD) [10]. In contrast, identical studies performed with zolpidem CR failed to produce this augmentation [11, 12]. Recall that zolpidem has mostly an alpha 1 affinity.

Efficacy

The hypnotic efficacy of the FDA-approved BzRAs has been well-documented using objective (nocturnal polysomnography) and subjective measures of sleep induction, maintenance, and duration in clinical trials, as well as in meta-analyses of trials using various benzodiazepines and zolpidem. Thus, it can be concluded that they are effective [13–16]. Importantly, the hypnotic effects have been shown to be dose-related and the studies have been conducted in both young and elderly adults [15, 16]. Depending on their different pharmacokinetics (i.e., Tmax and T1/2) and dose, the BzRAs induce and maintain sleep. The FDA indications given to the benzodiazepine BzRAs are mostly general or all-inclusive as to insomnia subtype (i.e., "for treatment of insomnia" or "for treatment of insomnia including sleep onset, sleep maintenance, and early awakenings"). Among the nonbenzodiazepines, FDA labeling is more specific, and zaleplon, zolpidem, and zolpidem sublingual are specifically indicated for sleep induction, whereas eszopiclone and zolpidem CR are indicated for both sleep induction and sleep maintenance. A new low dose (1.75 and 3.5 mg) buffered zolpidem formulation has been recently approved for treating insomnia characterized by difficulty falling asleep after an awakening in the middle of the night [17].

With several important exceptions, the majority of efficacy studies have been short- and intermediate-term in duration (i.e., ≤6 weeks), and given a paucity of controlled long-term data, and many uncontrolled clinical observations, tolerance development has remained an area of controversy. Tolerance is defined as the loss of effects with repeated use of a stable dose, or the need to increase a dose to maintain effects for repeated use. Several recent double-blind, placebo-controlled studies using self reports have shown eszopiclone is effective for 6 to 12 months of nightly use [18, 19]. And in a recent double-blind, placebo-controlled nocturnal polysomnography study, zolpidem remained effective for 8 months of nightly use [20].

Even among the earlier shorter-term studies, in a majority of the studies the hypnotic remained effective for the study duration. A closer inspection of the data of the studies reporting tolerance development reveals that the sleep of the drug-treated group remained stable with duration of time, whereas the sleep of the placebo group improved, with the result being statistically significant group differences were lost at the end of the study, suggesting that tolerance had developed. This point is best illustrated from the data of a study of the non-BzRA hypnotic remelteon [21]. The placebo group improvement may have reflected a placebo response, or more likely a sleep hygiene effect (i.e., adherence to a regular sleep schedule, avoidance of alcohol, and so forth) required by the study restrictions of the clinical trial.

An insomnia diagnosis requires not only sleep difficulty, but also an associated daytime impairment or distress. Patient reports of quality of life, work impairment, absenteeism, daytime fatigue, and daytime sleepiness have all found impairment among people with insomnia relative to age-matched healthy controls. The fact that hypnotic efficacy should not only provide proof of improved nocturnal sleep, but also improved daytime function, is now receiving more attention in studies assessing pharmacotherapy for insomnia. A few studies have shown that the improvement in nocturnal sleep is associated with improvement in some aspects of daytime function. For example, in a 6-month study of eszopiclone, self-reports of daytime alertness, ability to function during the daytime hours, and physical well-being, showed improvement in the eszopiclone-treated group *versus* the placebo-treated group [18, 19].

Safety

Adverse reactions to BzRAs in clinical practice and clinical trials are generally mild, short in duration, and occur in a minority of patients. Many of the adverse effects of BzRAs are mediated by their desired pharmacological activity (i.e., sedation) [22]. In a study of hospital inpatients receiving hypnotics, the rate of adverse events was 1 in every 10,000 doses [23]. The major adverse effects are discussed as follows.

Residual Effects

Residual effects refer to the experience of impaired function in the morning after using a hypnotic. It is important to recognize that all BzRAs can impair many aspects of human performance while there are significant plasma concentrations. Assessments have included laboratory tests, such as digit symbol substitution, simple and complex reaction time tests, measures of daytime sleepiness (i.e., such as the Multiple Sleep Latency Test), and on-the-road automobile driving. At peak plasma concentration, assessed in the daytime or at night during an awakening, the degree of impairment relates to dose and time since ingestion [24–26]. The duration of the impairment and likelihood that it will extend to daytime, which defines residual effects, relates to the half-

life and dose of the hypnotic. Intermediate and long half-life drugs are more likely to exhibit residual effects [27, 28]. However, even short half-life drugs, taken at high doses, beyond the therapeutic dose, can produce residual effects. Such effects have been reported with 20 mg of zolpidem and 0.5 mg of triazolam, both doses being greater than the clinically recommended dose [28].

Falls

Falls in the elderly are often considered a special case of psychomotor impairment associated with BzRAs, either due to elevated peak plasma concentrations or residual effects. However, data suggest that falls in the elderly is not a significant BzRA risk among insomniacs. First, falls in the elderly are not unique to BzRAs and when controlling for comorbid diseases are not independent risk factors [29, 30]. Second, in a survey of the elderly living in community dwellings, the risk of fractures was associated with sleep problems after controlling for demographic variables and concurrent medical diseases [31]; among nursing home residents, the unique risk for falls was insomnia and not BzRAs [32]. Thus, the risk of falls in the elderly associated with BzRAs is actually less than untreated insomnia. However, given an awakening during peak plasma concentration, there is a clear increase in ataxia associated with BzRAs.

Amnesia

An inability to remember information presented after drug administration, termed anterograde amnesia, is a characteristic of all BzRAs [33]. It can be due to either attention failures and or both attention and consolidation failures in the memory process. The severity of amnesia is related to plasma concentration at the time of stimulus presentation, which is determined by dose and time since drug ingestion. As to mechanisms for the amnesia, animal knock-in studies have shown that the benzodiazepine alpha 1 receptor of the $GABA_A$ complex mediates both sleep and amnesia [34]. As there are currently no BzRAs that do not bind to the alpha 1 receptor, all available BzRAs are associated with amnesia. Beyond specific BzRA receptor pharmacology, many sedating drugs with other pharmacological mechanisms also produce amnesia, which is reported to occur with sedating antidepressants, sedating antipsychotics, antihistamines, and alcohol [35]. Finally and more fundamentally, sleep itself is amnesic. People do not recall information presented during sleep, during brief awakenings from sleep, or during the sleep onset process. Words presented every minute during the sleep onset process are not remembered from the 5-minute time point on prior to electroencephalographic signs of sleep onset [36]. Furthermore, if sleep onset is delayed for 15 minutes after an awakening that is 90 minutes after triazolam, then the memory for items presented during the awakening is similar to a placebo. Memory is preserved relative to the rapid sleep onset induced by triazolam after the awakening in a nondelayed sleep onset condition [33]. Although there have been reports of "global" amnesia (i.e., a total loss of memory for events during the previous 24 h when awake and functioning after taking BzRAs), these have not been systematically verified or studied.

Rebound Insomnia

The most frequently reported discontinuation effect associated with the BzRAs is rebound insomnia, which is defined as worsened sleep for 1 or 2 nights after discontinuation relative to baseline [37]. Rebound insomnia should be distinguished from recrudescence, which is the return of insomnia to its baseline level of severity. In addition, rebound insomnia should be differentiated from a withdrawal syndrome, which is the expression of new symptoms beyond the return of the original symptom. The most important determinant of rebound insomnia is dose. Clinical doses are rarely associated with rebound, whereas doses greater than the clinical dose are more likely to produce rebound [38]. The duration of use of clinical doses is also not associated with an enhanced likelihood of rebound. Several long-term studies have now shown that 6 months of eszopiclone (3 mg) or 12 months of zolpidem (10 mg) were not associated with rebound [18, 39]. The incorrect assumption behind the clinical lore is that rebound is the expression of a withdrawal syndrome, which is not the case. In the small percentage of patients showing rebound after 12 months of a clinical dose of zolpidem (10 mg), there were no withdrawal signs and symptoms [39]. Furthermore, rebound was seen after 1 to 2 nights of a supra-clinical dose of triazolam (0.5 mg), and as well with zolpidem (15 mg), which do not produce withdrawal signs and symptoms [40]. A final determinant of rebound is the half-life of the drug, with the short- and intermediate-acting drugs more likely to produce rebound. Furthermore, rebound is unlikely to occur with long-acting drugs because of the gradual decline in plasma concentrations inherent to their pharmacokinetics. After short- and intermediate-acting drugs, rebound can be avoided by tapering the dose [37].

It has been suggested that the experience of rebound insomnia leads to continued chronic use of the hypnotic; importantly, a study directly tested this notion, and showed that the experience of rebound insomnia, induced by 1 week of nightly triazolam (dose, 0.50 mg) did not alter the subsequent likelihood of self-administering triazolam (dose, 0.25 mg) [41]. In summary, although rebound insomnia is

a reliable effect associated with "high" doses of BzRAs, its clinical significance, if any, has yet to be identified.

Abuse Liability

For a long time there has been concern that behavioral and/or physical dependence develops with chronic use of BzRAs, which leads to their abuse. There is little question that individuals with a drug abuse history will abuse BzRAs. However, the important question is whether the use of BzRAs will lead to abuse among patients without such a history. The concern is based on reports of physical and behavioral dependence with long-term daytime anxiolytic use of therapeutic doses of BzRAs [42]. An important distinction between anxiolytic and hypnotic use is duration of receptor occupancy. The anxiolytics are long-acting and thereby BzRA receptors remain occupied for a full 24-h day. With BzRA hypnotics, at least the short- and intermediate-acting ones, receptors are occupied for approximately one third (i.e., 8 h) of a day. Previously it was noted that 6 to 12 months of nightly BzRA short half-life hypnotic use did not lead to a withdrawal syndrome [18, 39]. The clinical reports of BzRA withdrawal involve supra-clinical doses and longer durations of use (18-90 months) [43]. Epidemiological studies indicate that the majority of hypnotic users report using hypnotics for 2 weeks or less and rarely escalate the dose beyond what was initially prescribed [44].

Short-term studies (1-2 weeks) directly testing the behavioral dependence liability of BzRA hypnotics suggest that they have a low behavioral dependence liability. Hypnotic self-administration by insomniacs is not associated with dose-escalation when provided an opportunity to self-administer multiple capsules nightly [45], it does not increase with rebound insomnia [36], it does not generalize to daytime use [46], and it varies as a function of the nature and severity of the patient's sleep disturbance [47]. To our knowledge, the only prospective study directly testing behavioral dependence during long-term use (i.e., 12 months) found no evidence of dose escalation in tri-monthly assessments during the 12 months of nightly use [48]. On the other hand, in both the short-term and long-term studies those insomniacs in the placebo groups did increase their placebo "dose" [45, 48]. In other words an ineffective hypnotic (i.e., placebo) is dose escalated. In 2 studies of short-acting BzRAs taken after an awakening in the middle of the night, the hypnotic was taken approximately 4 nights per week and the dose was not escalated during the 4–week study [49, 50]. Taken together, these studies suggest that hypnotics are used for a therapeutic purpose, even when used long term. Nightly use of a stable hypnotic dose does not reflect behavioral dependence.

On the other hand, there are clinical reports and safety reports of behavioral and/or physical dependence on BzRA hypnotics. For this reason, the FDA has designated BzRA hypnotics as controlled substances, giving them a schedule IV designation, which indicates these drugs have a known abuse liability. How the clinician, when prescribing hypnotics, should monitor patients for signs of potential abuse is discussed as follows.

Amnesic Parasomnia Episodes

Reports of parasomnia-like episodes with associated amnesia have appeared in the literature, which has led the FDA to issue a "black-box" warning on certain medications for insomnia. The behaviors reported have included sleep eating, sleep walking, sleep driving, and even violent behaviors [51–56]. They have been reported with zolpidem, zaleplon, triazolam, and zopiclone (a drug not available in the United States). As these case and safety reports are submitted to the FDA, the true incidence of these phenomena and the circumstances in which they occur is unclear because the rate of exposure in the population is unknown. Also, because there are no systematic, controlled data, what mediates these events is also unknown. A review of the case report literature suggests that the occurrence of parasomnia-like events is associated with high doses (i.e., doses much greater than the clinical dose), sleep deprivation, and co-ingestion of alcohol and other CNS depressant drugs [57].

Melatonin Receptor Agonist (Ramelteon)

Pharmacology

The 1 melatonin receptor agonist approved as a hypnotic is ramelteon. There is a large animal literature showing that the circadian rhythms of sleep and wake are controlled by the suprachiasmatic nucleus (SCN), which contains both MT1 and MT2 receptors. The SCN receives input from the optic nerve in regard to the presence of light, and its output to CNS sleep/wake systems is an alerting, wake-promoting signal. The MT1 receptor is thought to attenuate the alerting signal of the SCN and thereby the occupation of the MT1 receptor decreases sleep latency. The MT2 receptor is thought to have phase-shifting properties, meaning it has the potential to alter the timing of sleep and wake [58]. Remelteon, the 1 approved melatonin agonist, has a rapid onset of effect having a Tmax of 0.75 h, and it has an ultra-short half-life of 1-2.6 h (see Table 1). Remelteon does have an active metabolite with a longer duration of action.

Efficacy

Remelteon has an FDA indication for sleep onset insomnia. This indication is supported by self-report and polysomnographic studies showing that sleep onset is hastened along in a dosage range of 4 to 32 mg [59–64], although the indicated clinical dose is 8 mg. The incidence or insomnia increases in the elderly, and studies of remelteon have been conducted in elderly primary insomniacs, which show its efficacy in this population [60, 61]. Tolerance to sleep onset-inducing effects did not develop in the 6- to 12-month studies that have been conducted [63, 64]. Interestingly, unlike the BzRAs, polysomnographic measures of efficacy show a more robust effect than patient reports. Remelteon has not been shown to improve sleep maintenance, which would be predicted given its ultra-short half-life. Finally, there is some evidence that remelteon also has a phase-shifting capacity, given that it also acts at M2 receptors [65].

Safety

In the clinical trials of remelteon (8 mg), the adverse events report included somnolence, fatigue, dizziness, and nausea, all occurring at rates <5 % [59]. Given its short half-life, residual effects would not be expected and have not been observed [66, 67] and at the clinical dose, rebound insomnia has not been shown [68, 69]. In regard to the abuse liability of remelteon, a withdrawal syndrome has not been seen when it was discontinued [69], and based on behavioral assessments of abuse liability, no liability was seen [67, 70]. Consequently, remelteon is not classified as a controlled substance.

Histamine-1 Antagonist (Low-Dose Doxepin)

Pharmacology

Doxepin is a tricyclic antidepressant that is frequently used off-label as a hypnotic in antidepressant doses (25-150 mg). In this dose range, doxepin has anti-histaminic, anticholinergic, antiserotonergic, and anti-adrenergic effects [71]. In the CNS, histamine is a major alerting neurotransmitter and doxepin has its greatest affinity for the H_1 histaminic receptor, which when antagonized, it produces sedating effects. At the doses approved for insomnia (3 and 6 mg), doxepin is thought to be a relatively pure H_1 antagonist, without anticholinergic, antiserotonergic, and anti-adrenergic activity. The Tmax for doxepin is relatively long and its half-life, as well as its active metabolites, are similarly long (see Table 1).

Efficacy

The FDA indication given to low-dose doxepin is for sleep maintenance insomnia. This is consistent with the pharmacokinetics of doxepin and the limited efficacy data available. Doxepin has been shown in both adults and the elderly to maintain sleep, particularly in the last 2 h of the night, unlike the BzRAs [72, 73]. Doxepin does not produce residual effects, which given its half-life, seems counterintuitive. It is hypothesized that the normal circadian raise in histamine in the morning, recall histamine is a major alerting neurotransmitter, overriding the sedative effects of doxepin in the morning [74]. As the clinical trials have all been short- and intermediate-term (≤3 months), it is not known whether tolerance develops with long-term use.

Safety

In the clinical trials, the adverse events associated with low-dose doxepin were quite similar to those seen with a placebo [71–74]. The anti-cholinergic side effects typically seen with antidepressant doses were not seen with 3 and 6 mg. Doxepin is not a scheduled drug and is considered not to have an abuse liability. However, these considerations are based on antidepressant doses that have the additional and considerably aversive anticholinergic side effects. Low-dose doxepin with its hypothesized H_1 antagonistic activity and absence of aversive anticholinergic effects may have a mild abuse liability. H_1 antihistamines, such as diphenhydramine do have a behavioral dependence liability, albeit quite low [75]. The issue of dependence remains to be evaluated more thoroughly before definitive caution is raised regarding low-dose doxepin.

Other Off-Label Drugs Used to Treat Insomnia

Antidepressants

The most commonly used off-label drugs for the treatment of insomnia are antidepressants [76]. Trazodone, amitriptyline, and mirtazapine are the 3 most widely used antidepressants, which are used at “lower doses” for insomnia than their standard antidepressant doses [76]. Although these drugs have complex and different neural receptor-binding profiles, their commonality in having anti-histaminic and anti-serotonergic activity is thought to be responsible for their sedating effects [77, 78].

The major problem with using these drugs as hypnotics is that there is limited information regarding the dose range along which they improve sleep and their safety at those doses. A review of the literature indicates that there are no studies in primary insomnia with amitryptoline or mirtazepne, and there

are only 2 studies with trazodone [79, 80]. Trazodone (150 mg) failed to reduce sleep latency or increase total sleep time, although it did decrease wake after sleep onset for the 3-week study [79]. In contrast, trazodone at a threefold lower dose (50 mg) reduced sleep latency and increased total sleep time, but the effect on total sleep time was present for only 1 week [80]. The inconsistency in dose effects on total sleep time and the apparent tolerance development raise concerns regarding the dose-related effects of trazodone as a hypnotic. The issue of a proper hypnotic dose is also illustrated with doxepin. Before doxepin was developed as a hypnotic, the doses recommended for use as a hypnotic were "low" (i.e., 25 to 50 mg). As previously described, the approved hypnotic doses (i.e., 3 and 6 mg) ended up being 4 to 8 times lower.

A second matter of concern in using antidepressants as hypnotics is their safety at "low" doses. The information regarding the safety of antidepressants comes from their use at antidepressant doses. At such doses, a variety of serious side effects ranging from suicidality, residual effects, anticholinergic effects (i.e., dry mouth, urinary retention, and hallucinations) to orthostatic hypotension, priapism, cardiac arrhythmias, and conduction abnormalities have been reported [81–83]. Whether "low doses" would carry the same risk profile is unknown. Given that there is no clear understanding in regard to the dose range for the hypnotic efficacy and safety of these drugs, it is recommended they not be used as hypnotics [5].

Atypical Antipsychotics

The atypical antipsychotics quetiapine and olanzepine are also frequently used for the treatment of insomnia in non-psychiatric patients. As with the antidepressants, these drugs affect multiple transmitter systems, but their sleep promoting effects are thought to be mediated by their antihistaminic activity. The concern for the use of these drugs, as with the other off-label drugs, is that there is limited information regarding efficacious and safe doses. There have been 3 open-label studies in primary or comorbid insomnia, suggesting improvement in self-reported sleep [84–86]. However, their safety is unknown. Although the risks of dopamine-associated movement disorders characteristic of typical antipsychotics are reduced with these atypical antipsychotics, a metabolic disorder is a known risk [87]. Again, given the limited information regarding the dose range for the efficacy and safety of these drugs, it is recommended they not be used as hypnotics [5].

Off-Label BzRAs

Anxiolytic BzRAs are also often used as hypnotics with clonazepam, alprazolam, and lorazepam, the most commonly used off-label BzRAs. Although these drugs share the same mechanism of action with the hypnotic BzRAs, their hypnotic doses are not known, and given the pharmacokinetics of those that are long-acting (i.e., clonazepam and lorazepam), they are likely to produce residual effects. What may have been the reason to prescribe these drugs as hypnotics is that there are no limitations in regard to the duration of use. With the exception of hypnotics approved after 2005, the BzRA FDA indications all limited their use at 2 to 4 weeks. In an assessment of hypnotic prescribing practices in a large Michigan health maintenance organization, compared to zolpidem, the anxiolytic BzRAs were prescribed for longer durations and with more refills [88]. The recently approved hypnotics (i.e., escopiclone, zolpidem CR, zolpidem sublingual, rozerem, and low-dose doxepin) all have no duration limitations. As previously noted, there is no suggestion of tolerance development with long-term nightly use of the BzRA hypnotics. There is no advantage to using BzRAs off-label as hypnotics.

Treatment Considerations

Duration of Treatment

There has always been a clear agreement that the FDA-approved hypnotics are the appropriate pharmacological treatment for transient and short-term insomnia. However, a 2005 National Institutes of Health consensus conference led to a paradigm shift in understanding chronic insomnia and its treatment [5]. The conference concluded that approximately 10 % of the general population experiences chronic and persistent insomnia, and there is clear morbidity associated with chronic insomnia; for a small percentage of chronic insomniacs, their insomnia is a primary condition without precipitating psychiatric or medical disorders, and for the majority of chronic insomniacs, their insomnia coexists with other psychiatric and medical disorders with the degree of sleep disturbance contributing to the patient's overall clinical status.

The importance of identifying and treating chronic insomnia is evident in that it is a major risk factor for mood disorders [89], and there is evidence that improved sleep is associated with a more rapid antidepressant response [90] and a reduced suicide risk [91]. In addition, there is some evidence that treating insomnia comorbid with various medical disorders improves the status of the medical condition [92]. Finally, when insomnia is comorbid, treating the comorbid condition alone will sometimes not lead to remission or improvement in the insomnia [93].

As the previously described presentation indicates, the efficacy and safety profile of hypnotics is favorable and there is emerging placebo-controlled evidence that hypnotics remain effective with chronic use. However, this

requires that physicians carefully discuss with their patients the chronic nature of their insomnia and the benefits and risks associated with chronic treatment. The treatment plan should also include instructions as to the timing of drug administration, nightly *versus* as needed use, and the various precautions as discussed in more detail as follows.

Specific Nature of Insomnia and Patient Characteristics

The diagnostic criteria for insomnia include complaints of initiating sleep, maintaining sleep, early morning awakening, or nonrestorative sleep. Patients may present with single or multiple sleep complaints and the nature of the complaints may vary with various patient characteristics. As examples, specific sleep onset problems are often seen in younger insomniacs, whereas sleep maintenance problems are more characteristic of insomnia in middle age or elderly patients. Sleep maintenance difficulty is often associated with sleep-related breathing disturbances or periodic leg movements, or it can be comorbid with chronic pain disorders. Early morning awakening is a complaint often associated with primary depression, as well as phase advance syndromes in the elderly.

The specificity or nonspecificity of the patient's sleep complaint can guide the physician in choosing the hypnotic. Some of the hypnotics have indications for sleep onset, some for sleep maintenance, some for both and more recently for falling back to sleep after an awakening (see Table 1). Once a specific hypnotic is chosen, consideration of the appropriate dose must be made. The lowest clinically indicated dose is chosen in light of the patient's age, comorbid medical conditions, and medications. Dose adjustments in the first week of treatment should be made by the physician in consultation with the patient. Generally, the patient should not be allowed to self-initiate dose adjustments.

A final and important consideration is the patient's previous history of response or nonresponse to hypnotics. If the patient has failed to respond to an appropriately chosen hypnotic and dose, further diagnostic assessment may be indicated. For example, insomnia is known to be associated with depression and anxiety disorders. In addition, the patient and clinician together may consider a cognitive behavioral insomnia treatment trial.

Nightly *versus* Non-Nightly Treatment

Typically hypnotics have been prescribed to be taken nightly before sleep. Non-nightly treatment regimens (i.e., every third night or as needed) have been studied in several controlled trials. Non-nightly zolpidem was effective on the nights it was taken and on the off nights rebound insomnia was not experienced [94]. Non-nightly treatment regimens have been suggested due to concerns in regard to tolerance development and the development of physical/behavioral dependence. As previously noted, tolerance does not readily develop, physical dependence is not observed, and a non-nightly treatment regimen did not alter the likelihood of behavioral dependence in a short-term study [95]. There is no clear advantage to non-nightly treatment regimens, at least in regard to the risks of tolerance or abuse. Patients are generally conservative in their use of hypnotics; in an as needed treatment regimen condition, patients took hypnotics 3 to 5 nights a week [88]. The nightly *versus* non-nightly choice can be made based on the patient's preference and comfort.

Middle of the Night

The principle complaint of some insomniacs is difficulty returning to sleep after a major awakening in the middle of the night. Most recently a hypnotic has been approved by the FDA for use in the middle of the night (see Table 1). Studies show that this drug with a short half-life and a novel formulation will hasten the return to sleep after an awakening in the middle of the night [17]. Of course, to avoid residual effects the next morning, the caution is made that the patient is able to remain in bed for an additional 4 to 5 h.

Abuse Liability Signs

As previously discussed, there is an abuse liability associated with the BzRA hypnotics. The 2 FDA-approved non-BzRAs that not scheduled have limitations in regard to their indications, 1 being only for sleep onset and the other 1 only for sleep maintenance insomnia (see Table 1). Therefore, a BzRA may be the preferred drug. In assessing clinical reports of physical/behavioral dependence on BzRAs, 2 important signs were identified [43]. In many cases within the first week of treatment the dose was escalated much beyond the indicated clinical hypnotic dose. This pattern suggests that other effects of drug, beyond its sleep-inducing effects, were being sought. Hence, the earlier guidance to closely monitor the patient during the first week of use and not allow patient-initiated dose adjustments. The second sign was that the drug was used during the daytime with multiple daytime doses being taken, again suggesting non-hypnotic drug effects that were being sought.

Precautions and Contraindications

The important contraindications for hypnotic pharmacotherapy include advanced hepatic disease and pregnancy, and the precautions include concomitant illnesses, such as sleep apnea syndrome and concomitant-sedating medications. A special consideration is taken with patients who have histories of drug or alcohol abuse with difficulty sleeping,

particularly sleep maintenance, which is a chief complaint among abstinent alcohol and drug abuse patients; these disturbances can continue for a year or more. The non-BzRA, low-dose doxepin, may be an option, although as previously noted, it may have a dependence potential. If the physician considers the use of a BzRA hypnotic in an outpatient setting, the patient must be monitored closely beyond the initial week of use. Within the alcohol and drug abuse treatment, community stress-induced relapse is a well-recognized phenomenon that can occur after months of successful abstinence. In such cases, the experience of new life stresses can induce a relapse to drug and alcohol abuse.

Investigational and Emerging Pharmacotherapies

Most of the approved hypnotics previously discussed act by enhancing or signaling the neurobiological mechanisms that control sleep. New emerging pharmacotherapies have begun to focus on antagonizing known wake neurobiological mechanisms, including histamine, serotonin, and orexin. The recently approved hypnotic, low-dose doxepin, at the approved low doses is primarily a histamine antagonist, as previously noted. A new study of an orexin antagonist reported a dose-related increase in the total sleep time of men with insomnia [96]. Earlier studies explored the hypnotic potential of antagonizing serotonin receptor subtypes. For example, a 5-HT2 antagonist was shown to increase slow wave sleep, but did not increase sleep time [97].

Required Author Forms Disclosure forms provided by the authors are available with the online version of this article.

References

1. Gallup. Sleep in America. Princeton: Gallup, 1995:1–78.
2. Johnson EO, Roehrs T, Roth T, et al. Epidemiology of alcohol and medication as aids to sleep in early adulthood. Sleep 1998;21:178–186.
3. Roehrs T, Hollebeek E, Drake C, et al. Substance use for insomnia in Metropolitan Detroit. J Psychosom Res 2003;53:571–576.
4. Roehrs T, Roth T. Sleep, sleepiness, sleep disorders and alcohol use and abuse. Sleep Med Rev 2001;5:287–297.
5. 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;28:1049–1057.
6. Mohler H, Fritschy JM, Rudolph U. A new benzodiazepine pharmacology. J Pharmacol Exp Ther 2002;300:2–8.
7. Mendelson WB, Thompson C, Franko T. Adverse reactions to sedative hypnotics: three years' experience. Sleep 1996;19:702–706.
8. Nutt D. GABA-A receptors: subtypes, regional distribution, and function. J Clin Sleep Med 2006;2:S7–S11.
9. Fava M, Schaefer K, Huang H, Wilson A, et al. A post hoc analysis of the effect of nightly administration of eszopiclone and a selective serotonin reuptake inhibitor in patients with insomnia and anxious depression. J Clin Psychiat 2011;72:473–479.
10. Pollack M, Kinrys G, Krystal A, et al. Eszopiclone co-administered with escitalopram in patients with insomnia and comorbid generalized anxiety disorder. Arch Gen Psychiat 2009;65:551–562.
11. 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 Psychiat 2011;72:914–928.
12. Fava M, Asnis GM, Shrivastava R, Lydiard B, et al. Zolpidem extended-release improves sleep and next-day symptoms in comorbid insomnia and generalized anxiety disorder. J Clin Psychopharm 2009;29:222–230.
13. Nowell PD, Mazumdar S, Buysse DJ, et al. Benzodiazepines and zolpidem for chronic insomnia: a meta-analysis of treatment efficacy. JAMA 1997;278:2170–2177.
14. Holbrook AM, Crowther R, Lotter A, et al. Meta-anlysis of benzodiazepine use in the treatment of insomnia. Can Med Assoc J 2000;162:225–233.
15. Merlotti L, Roehrs T, Koshorek G, Zorick F, Lamphere J, Roth T. The dose effects of zolpidem on the sleep of healthy normals. J of Clin Psychopharm 1989;9:9–14.
16. Lamphere JK, Roehrs TA, Zorick FJ, Koshorek G, Roth T. The dose effects of zopiclone. Hum Psychopharm 1989;4:41–46.
17. Roth T, Hull SG, Lankford DA, et al. Low-dose sublingual zolpidem tartrate is associated with dose-related improvement in sleep onset and duration in insomnia characterized by middle-of-the-night [MOTN] awakenings. Sleep 2008;31:277–1284.
18. Krystal AD, Walsh JK, Laska E, et al. Sustained efficacy of eszopiclone over 6 months of nightly treatment: results of a randomized, doubled blinded, placebo controlled study in adults with chronic insomnia. Sleep 2003;26:793–799.
19. Walsh JK., Krystal AD, Amato DA, et al. Nightly treatment of primary insomnia with eszopiclone for six months: effects on sleep, quality of life, and work limitations. Sleep 2007;30:959–968.
20. Randall S, Roehrs T, Roth T. Efficacy of eight months of nightly zolpidem: a prospective placebo controlled study. Sleep (in press).
21. Karin A, Tolbert D, Cao C. Disposition kinetics and tolerance of escalating single doses of remelteon, a high-affinity MT_1 and MT_2 melatonin receptor agonist indicated for treatment of insomnia. J Clin Pharmacol 2006;46:140–148.
22. Roth T, Roehrs T. Issues in the use of benzodiazepine therapy. J Clin Psychiatry 1992;53:S14–S18.
23. Mendelson WB, Thompson C, Franko T. Adverse reactions to sedative/hypnotics: three years' experience. Sleep 1996;9:702–706.
24. Rush CR, Griffiths RR. Zolpidem, triazolam and temazepam: behavioral and subject-rated effects in normal volunteers. J Clin Psychopharmacol 1996;6:46–57.
25. Roehrs T, Merlotti L, Zorick F, et al. Sedative, memory and performance effects of hypnotics. Psychpharmacology [Berl] 1994;16:30–34.
26. Danjou P, Fruncillo PR, Worthington P, et al. A comparison of the residual effects of zaleplon and zolpidem following administration 5 to 2 h before awakening. Br J Clin Pharmacol 1999;48:367–374.
27. Carskadon MA, Seidel WF, Greenblatt DJ, et al. Daytime carry-over of triazolam and flurazepam in elderly insomniacs. Sleep 1982;5:362–371.
28. Riedel BW, Lichstein KL. Insomnia and daytime functioning. Sleep Med Rev 2000;4:277–298.
29. Kelly KD, Pickett W, Yiannakaoulias N, et al. Medication use and falls in community-dwelling older persons. Age Ageing 2003;32:503–509.

30. Ensrud KE, Blackwell T, Mangione CM, et al. Central nervous system active medications and risk for fractures in older women. Arch Intern Med 2003;163:949–957.
31. Brassington GS, King AC, Bliwise DL. Sleep problems as a risk factor for falls in a sample of community-dwelling adults aged 64-99 years. J Am Ger Soc 2000;48:1234–1240.
32. Avidan AY, Fries BE, James ML, Szafara KL, Wright GT, Chervin RD. Insomnia and hypnotic use recorded in the minimum data set as predictors of fall and hip fractures in Michigan nursing homes. J Am Ger Soc 2005;53:955–962.
33. Roehrs T, Zorick F, Sicklesteel J, et al. Effects of hypnotics on memory. J Clin Psychopharmacol 1983;3:310–313.
34. Green JF, McElholm A, King DJ. A comparison of the sedative and amnestic effects of chlorpromazine and lorazepam. Psychopharmacology [Berl] 1996;128:67–73.
35. Mohler H, Crestani F, Rudolph U. GABA-A receptor subtypes: a new pharmacology. Curr Opin Pharmacol 2001;1:22–25.
36. Guillmineau C, Dement WC. Amnesia and disorders of excessive sleepiness. In: Drucker-Colin RR, McGaugh JL, eds. Neurobiology of sleep and memory. London: Academic Press, 1977.
37. Roehrs TA, Vogel G, Roth T. Rebound insomnia: Its determinants and significance. Am J Med 1990;88:43S–46S.
38. Roehrs T, Zorick F, Wittig R, et al. Dose determinants of rebound insomnia. Brit J Clin Pharmacology 1986;22:143–147.
39. Roehrs TA, Randall S, Harris E, et al. Twelve months of nightly zolpidem does not lead to rebound insomnia or withdrawal symptoms: a prospective placebo-controlled study. J Psychopharm 2012;26:1088–1095.
40. Merlotti L, Roehrs T, Zorick F, et al. Rebound insomnia: duration of use and individual differences. J Clin Psychopharm 1991;11:368–373.
41. Roehrs T, Merlotti L, Zorick F, et al. Rebound insomnia and hypnotic self administration. Psychopharmacology 1992;107:480–484.
42. Woods JH, Winger G. Current benzodiazepine issues. Psychopharmacology 1995;118:103–107.
43. Kan CC, Hilldebrink SR, Breteier MHM. Determination of the main risk factors for benzodiazepine dependence using a multidimensional approach. Compr Psychiatry 2004;45:88–94.
44. Mellinger GD, Balter MB, Uhlenhuth EH. Insomnia and its treatment. Arch Gen Psychiatry 1985;42:225–232.
45. Roehrs T, Pedrosi B, Rosenthal L, et al. Hypnotic self administration and dose escalation. Psychopharmacology [Berl] 1996;127:150–154.
46. Roehrs T, Bonahoom A, Pedrosi B, et al. Nighttime versus daytime hypnotic self-administration. Psychopharmacology 2002;161:137–142.
47. Roehrs T, Bonahoom A, Pedrosi B, et al. Disturbed sleep predicts hypnotic self administration. Sleep Med 2002;3:61–66.
48. Roehrs TA, Randall S, Harris E, et al. Twelve months of nightly zolpidem does not lead to dose escalation: a prospective placebo-controlled study. Sleep 2011;34:201–212.
49. Roth T, Singh NN, Steinbert FJ, Rosenberg R, Krystal A. Absence of tolerance, dependence potential, and rebound during PRN treatment of middle-of-the-night awakening with zolpidem tartrate sublingual tablet 3.5 MG. Sleep Med 2011;12(suppl 1):S58.
50. Roth T, Zammit GK, Scharf MB, Farber R. Efficacy and safety of as-needed, post bedtime dosing with Indiplon in insomnia patients with chronic difficulty maintaining sleep. Sleep 2007;30:1731–1738.
51. Lisko B, Pikalov A. Zaleplon overdose associated with sleepwalking and complex behavior. J Am Acad Child Adolesc Psychiatry 2004;43:927–928.
52. Menkes DB. Triazolam-induced nocturnal bingeing with amnesia. Aust N Z J Psychaitry 1992;26:320–321.
53. Morgenthaler TI, Silber MH. Amnestic sleep-related eating disorder associated with zolpidem. Sleep Med 2002;3:323–327.
54. Yang W, Dollear M, Muthukrishnan SR. One rare side effect of zolpidem – sleepwalking: a case report. Arch Phys Med Rehabil 2005;86:1265–1266.
55. Lange CL. Medication-associated somnambulism. J Am Acad Child Adoles Psychiatry 2005;44:211–212.
56. Lauerma H. Nocturnal wandering caused by restless legs and short-acting benzodiazepines. Acta Psychiatr Scand 1991;83:492–493.
57. Roehrs TA, Roth T. Safety of insomnia pharmacotherapy. Sleep Med Clinics 2006;1:399–407.
58. Kato K, Hirai K, Nichiyama K, et al. Neurochemical properties of ramelteon [TAK-375], a selective MT_1 and MT_2 receptor agonist. Neuropharmacology 2005;48:301–310.
59. Erman M, Seiden D, Zammit G, et al. An efficacy, safety, and dose-response study of remelteon in patients with chronic primary insomnia. Sleep Med 2006;7:17–24.
60. Roth T, Seiden D, Saimati S, et al. Effects of ramelteon on patient-reported sleep latency in older adults with chronic insomnia. Sleep Med 2006;7:312–318.
61. 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;23:1005–1014.
62. 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.
63. 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;32:351–360.
64. DeMicco M, Wang-Weigand S, Zhang J. Long-term therapeutic effects of ramelteon treatment in adults with chronic insomnia: a 1 year study. Sleep 2006;29(suppl):A234.
65. Richardson GS, Zee PC, Wang-Weigand S, et al. Circadian phase-shifting effects of repeated ramelteon administration in healthy adults. J Clin Sleep Med 2008;4:456–461.
66. Roth T, Stubbs C, Walsh J. Ramelteon [TAK-375], a selective MT1/MT2 receptor agonist, reduces latency to persistent sleep in a model of transient insomnia related to a novel sleep environment. Sleep 2005;28:303–307.
67. Griffiths R, Suess P, Johnson M. Ramelteon and triazolam in humans: behavioral effects and abuse potential. Sleep 2005;28:A44.
68. 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;7:312–318.
69. Zammit G, Roth T, Erman M, et al. Double-blind, placebo-controlled polysomnography and outpatient trial to evaluate the efficacy and safety of ramelteon in adult patients with chronic insomnia. Sleep 2005;28(suppl):A228–A229.
70. Johnson MW, Suess PE, Griffiths RR. Ramelteon: a novel hypnotic lacking abuse liability and sedative adverse effects. Arch Gen Psychiatry 2006;63:1149–1157.
71. 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;62:453–463.
72. 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;30:1555–1561.
73. 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 cross-over study. J Clin Psychiatry 2008;69:1557–1564.
74. Owen RT. Selective histamine H[1] antagonism: a novel approach to insomnia using low-dose doxepin. Drugs Today 2009;45:261–267.
75. Wolf B, Guarino JJ, Preston KL, Griffiths RR. Abuse liability of diphenhydramine in sedative abuser. NIDA Res Monogr 1989;95:486–487.
76. Walsh JK. Drugs used to treat insomnia in 2002: regulatory-based rather than evidence-based medicine. Sleep 2004;27:1441–1442.
77. Jenck F, Moreau JL, Mutel V, et al. Evidence for a role of 5-HT1C receptors in the antiserotonergic properties of some antidepressant drugs. Eur J Pharmacol 1993;231:223–229.

78. Richelson E. The pharmacology of antidepressants at the synapse: focus on newer compounds. J Clin Psychiatry 1994;55(suppl A):34–39
79. Montgomery I, Oswald I, Morgan K, et al. Trazodone enhances sleep in subjective quality but not in objective duration. Br J Clin Pharmacol 1983;16:139–144.
80. Walsh JK, Erman M, Erwin CW, et al. Subjective hypnotic efficacy of trazodone and zolpidem in DSM-III-R primary insomnia. Hum Psychopharmacol 1998:13:191–198.
81. Golden RN, Dawkins K, Nicholas L. Trazadone and nefazodone. In: Schatzberg A, Nemeroff C, eds. The American Psychiatric Textbook Of Psychopharmacology. Washington, DC: American Psychiatric Textbook, Inc., 2004:315–325.
82. Levenson JL. Prolonged QT interval after trazodone overdose. Am J Psychiatry 1999;156:969–970.
83. Haria M, Fitton A, McTavish D. Trazodone. A review of its pharmacology, therapeutic use in depression and therapeutic potential in other disorders. Drugs Aging 1994;4:331–355.
84. Wiegard M, Landry T, Bruckner T, et al. Quetiapine in primary insomnia: a pilot study. Psychopharmacology 2008;196:337–338.
85. Juni C, Chana P, Tapia J, et al. Quetiapine for insomnia in Parkinson Disease: results from an open-label trial. Clin Neuropharmacol 2005;28:185–187.
86. Estivill E, de la Fuente V, Segarra F, et al. The use of olanzapine in sleep disorders. An open trial with nine patients. Rev Neurol 2004;38:829–831.
87. Cates ME, Jackson CW, Feldman JM, et al. Metabolic consequences of using low-dose quetiapine for insomnia in psychiatric patients. Community Ment Health J 2009;45:251–254.
88. Roehrs T, Roth T. “Hypnotic” prescription patterns in a large managed-care population: Sleep Med 2004;5:463–466.
89. Breslau N, Roth T, Rosenthal L, et al. Sleep disturbance and psychiatric disorders: a longitudinal epidemiological study of young adults. Biol Psychiatry 1996;39:411–418.
90. Perlis ML, Giles DE, Buysse DJ, et al. Self-reported sleep disturbance as a prodromal symptom in recurrent depression. J Affect Disord 1997;42:209–212.
91. Hall RC, Platt DE. Suicide risk assessment: a review of risk factors for suicide in 100 patients who made severe suicide attempts. Evaluation of suicide risk in a time of managed care. Psychosomatics 1999;40:18–27.
92. Roehrs TA. Does effective management of sleep disorders improve pain symptoms? Drugs 2009;69:S5–S11.
93. Stark P, Hardison CD. A review of multicenter controlled studies of fluoxetine vs. imipramine and placebo in outpatients with major depressive disorder. J Clin Psychiatry 1985;46:53–58.
94. Walsh JK, Roth T, Randazzo AC, et al. Eight weeks of non-nightly use of zolpidem for primary insomnia. Sleep 2000;23:1087–1096.
95. Roehrs T, Bonahoom A, Pedrosi B, Rosenthal L, Roth T. Treatment regimen and hypnotic self-administration. Psychopharmacology 2001;155:11–17.
96. Bettica P, Squassante L, Zamuner S, Nucci G, Danker-Hopfe H, Ratti E. The orexin antagonist SB-649868 promotes and maintains sleep in men with primary insomnia. Sleep 2012;35:1097–1104.
97. Landolt HHP, Meier V, Burgess HJ, et al. Serotonin-2 receptors and human sleep: effect of a selective antagonist on EEG power spectra. Neuropsychopharmacology 1999;21:455–466.