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New and emerging pharmacotherapeutic approaches for insomnia

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Abstract
Advances in understanding the neurochemistry of sleep and waking have stimulated new pharmacological directions in the treatment of insomnia. While the sedation of historic insomnia medications was discovered serendipitously, now compounds can be developed for specific molecular targets with known sleep-related actions. Numerous investigational compounds, including some entirely novel approaches, are being evaluated currently as possible insomnia treatments. In recent years the US Federal Drug Administration (FDA) has approved medications with new pharmacodynamic and pharmacokinetic properties thereby extending the options for personalized pharmacotherapy. The FDA is reviewing new applications for innovative sleep-promoting medications currently, including suvorexant and tasimelteon. Presently the FDA-approved insomnia treatment medications include benzodiazepine receptor agonists available in immediate-release, extended-release, and alternative delivery oral absorption formulations; a melatonin receptor agonist; and a histamine receptor antagonist. Clinical indications include insomnia associated with difficulty with sleep onset, sleep maintenance, and middle-of-the-night awakenings. Alternative approaches to treating insomnia have included prescription medications employed on an off-label basis for insomnia, over-the-counter sleep aids, and assorted unregulated substances marketed to enhance sleep.

Introduction

Insomnia is among the most common clinical problems encountered by health professionals. Sleep disturbances often are reported by patients in general medical settings and even more so in psychiatric practices. Many other people with persistent sleep difficulty never seek professional help. A multitude of factors may undermine sleep quality and impair the ability for an individual to achieve adequate sleep along with full alertness and a sense of well-being during waking hours. While it has been argued that insomnia is a recent affliction that has emerged from the stressors, bad habits, and chaotic schedules of modern life, the frustration of sleeplessness is well described in the literature of the classic Greek and Roman civilizations, as well as in the Bible (Mahbarg, 2013). No doubt insomnia sufferers turned to the available remedies, such as fermented beverages or opium concoctions, as today they choose from an extraordinary assortment of substances and medications with the hope of achieving deeper and longer-lasting sleep and a greater sense of alertness and vitality during their wakeful lives.

While about a third to half of the general adult population occasionally experiences insomnia symptoms, persistent difficulty with night-time insomnia accompanied by daytime impairment occurs in approximately 6–10% of adults (Ohayon, 2002). The prevalence is considerably higher in people with mental health disorders, especially with mood, anxiety, stress-related, neurocognitive, and psychotic disorders. The DSM-5 defines an insomnia disorder in terms of night-time sleep problems associated with significant daytime distress or impairment (APA, 2013). The diagnosis requires that the sleep difficulty be in the context of the person having an adequate opportunity for sleep, although the timing of the symptoms may vary for people depending on their work or school schedules and their circadian rhythm tendencies. Generally, insomnia is dissatisfaction with sleep quality or quantity associated with problems falling asleep, remaining asleep, or early morning awakenings. The sleep difficulty should occur at least three nights per week for at least three months to meet the insomnia disorder criteria. Finally, the symptoms should not be attributable to another sleep disorder, mental or physical condition, or use of a medication or substance. Common daytime symptoms include fatigue, poor concentration and memory, and irritability. Most chronic insomnia sufferers do not report excessive daytime sleepiness,

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but rather describe a craving for sleep despite an inability to nap.

The treatment plan for a patient with an insomnia disorder should evolve from a comprehensive evaluation that includes a detailed sleep history; a review of any medical, psychiatric, or other sleep disorders (e.g. obstructive sleep apnoea); a full review of systems, physical and mental status examinations, and a family history. An interview with a bed partner or household member may be especially valuable in revealing snoring and other sleep-related breathing irregularities, abnormal movements, and unusual behaviours or vocalizations. Sleep laboratory testing may be warranted when there is a suspicion of sleep disordered breathing, movement disorders, nocturnal seizures, and certain parasomnias. The insomnia evaluation should attempt to ascertain factors that may contribute to the patient's sleep disturbance. These may include co-morbid conditions, substance or medication use, circadian rhythm predispositions, psychological conditioning, and poor sleep habits.

The American Academy of Sleep Medicine (AASM) has issued guidelines for the evaluation and treatment of chronic insomnia in adults (Schutte-Rodin et al., 2008). Evidence-based insomnia treatments include pharmacotherapy and psychotherapeutic approaches incorporating cognitive and behavioural modalities. The use of medications to enhance sleep should be done within the context of a broader treatment plan that addresses modifiable behaviours, routines, and substance use, optimizes the treatment of co-morbid conditions, and, when possible, integrates concomitant cognitive-behavioural therapies. Decisions regarding the selection of insomnia treatment medications may be influenced by the consideration of the patient's specific nighttime and daytime sleep-related symptoms, co-morbid conditions, age, sex, reproductive status, lifestyle routines, and work or school schedules. It is especially important to consider the potential effects of any other medications a patient may be taking that could be contributing to the sleep disturbance or might result in an adverse effect in combination with a newly prescribed insomnia medication. As a general rule, elderly individuals and people with debilitating medical conditions should be started at low doses. For all patients, medication use should be monitored over time both for efficacy outcomes and potential side effects.

It is useful to divide the broad domain of substances and medications that people take as insomnia remedies into four categories representing (1) prescription-required medications approved by regulatory agencies (e.g. the Food and Drug Administration (FDA) in the USA) for the treatment of insomnia, (2) sedating or otherwise potentially sleep-enhancing prescription-required medications employed on an off-label basis primarily for the treatment of insomnia, (3) regulatory agency-designated medications available without a prescription and regarded as over-the-counter (OTC) sleep aids, and (4) all other unregulated compounds taken for insomnia symptoms. This article will review characteristics of each of these categories with a primary focus on the FDA-approved medications, including the most recently developed compounds and formulations. Finally, there will be a discussion of the novel investigational agents that have been stimulated by emerging knowledge of the neurophysiological regulation of sleep and wakefulness.

One major safety consideration regarding the use of medications and other substances (e.g. alcohol) to treat insomnia is the associated risk of falls and fractures. Many classes of medications, including sedating drugs prescribed for insomnia, do increase the fall risk. Numerous facility-based and broader epidemiological studies specifically highlight a higher frequency of falls in individuals, especially elderly patients, prescribed hypnotic medications (Obayashi et al., 2013; van Strien et al., 2013; Vermeeren, 2004; Wu et al., 2013); while others do not find an association or emphasize the fall risk that is due to insomnia itself (Avidan et al., 2005; Brassington et al., 2000; Widera, 2013). Employing non-pharmacological treatments when possible, recommending low doses when hypnotic medications are prescribed, and educating patients and care providers about fall risks are important practices.

For many patients insomnia is a chronic condition leading to the use of benzodiazepine receptor agonists (BZRA) hypnotics on a long-term basis, including nightly, intermittent, and occasional use. (Schutte-Rodin et al., 2008) People taking hypnotic medications nightly sometimes report that the efficacy seems to wear off over time. However, habituation of efficacy was not observed in long-term (≥ 6 months), placebo-controlled clinical trials for eszopiclone and zolpidem in patients with insomnia (Krystal et al., 2003; Randall et al., 2012; Roth et al., 2005; Walsh et al., 2007). Similarly, an open-label, 6–12-month zaleplon study with elderly adults demonstrated sustained benefits (Ancoli-Israel et al., 2005).

US FDA-approved insomnia medications

The medications with formal indications by the US FDA for treating insomnia represent three general pharmacodynamic classes: (1) BZRAs, (2) melatonin receptor agonists, and (3) histamine H_1 receptor antagonists. These medications are listed in Table 1 with the available doses, approximate elimination half-lives, indications, most common side effects,

Table 1. FDA-approved medications indicated for treating insomnia (Abbott Laboratories, 2006; ECR Pharmaceuticals, 2010; King Pharmaceuticals, 2006; Meda Pharmaceuticals, 2013; Mylan Pharmaceuticals, 2010; Neuro Pharma, 2013; Purdue Pharma, 2012; Roxane Laboratories, 2012; Sanofi-Aventis, 2013a, 2013b; Somaxon Pharmaceuticals, 2010; Sunuvion Pharmaceuticals, 2012; Takeda Pharmaceuticals North America, 2010; West-Ward Pharmaceutical, 2010).

Generic (brand) name	Doses (mg)	Half-life (h)	Indications	Most common side effects	DEA class	FDA pregnancy category
Benzodiazepine immediate release						
Flurazepam (Dalmane)	15, 30	48–120	'treatment of insomnia characterized by difficulty in falling asleep, frequent nocturnal awakenings, and/or early morning awakening'	Dizziness, drowsiness, lightheadedness, staggering, loss of coordination, falling	IV	X
Temazepam (Restoril)	7.5, 15, 22.5, 30	8–20	'short-term treatment of insomnia'	Drowsiness, dizziness, lightheadedness, difficulty with coordination	IV	X
Triazolam (Halcion)	0.125, 0.25	2–4	'short-term treatment of insomnia'	Drowsiness, headache, dizziness, lightheadedness, 'pins and needles' feelings on your skin, difficulty with coordination	IV	X
Quazepam (Doral)	7.5, 15	48–120	'treatment of insomnia characterized by difficulty in falling asleep, frequent nocturnal awakenings, and/or early morning awakenings'	Drowsiness, headache	IV	X
Estazolam (ProSom)	1, 2	8–24	'short-term management of insomnia characterized by difficulty in falling asleep, frequent nocturnal awakenings, and/or early morning awakenings … administered at bedtime improved sleep induction and sleep maintenance'	Somnolence, hypokinesia, dizziness, abnormal coordination	IV	X
Non-benzodiazepine immediate release						
Zolpidem (Ambien)	5, 10	1.5–2.4	'short-term treatment of insomnia characterized by difficulties with sleep initiation'	Drowsiness, dizziness, diarrhoea, drugged feelings	IV	C
Zaleplon (Sonata)	5, 10	1	'short-term treatment of insomnia … shown to decrease the time to sleep onset'	Drowsiness, lightheadedness, dizziness, 'pins and needles' feeling on your skin, difficulty with coordination	IV	C
Eszopiclone (Lunesta)	1, 2, 3	5–7	'treatment of insomnia … administered at bedtime decreased sleep latency and improved sleep maintenance'	Unpleasant taste in mouth, dry mouth , drowsiness, dizziness, headache, symptoms of the common cold	IV	C
Non-benzodiazepine extended release						
Zolpidem extended release (Ambien controlled release)	6.25, 12.5	2.8–2.9	'treatment of insomnia characterized by difficulties with sleep onset and/or sleep maintenance (as measured by wake time after sleep onset)'	Headache, sleepiness, dizziness	IV	C
Non-benzodiazepine alternative delivery						
Zolpidem oral spray (ZolpiMist)	5, 10	~2.5	'short-term treatment of insomnia characterized by difficulties with sleep initiation'	Drowsiness, dizziness, diarrhoea, drugged feelings	IV	C
Zolpidem sublingual (Edluar)	5, 10	~2.5	'short-term treatment of insomnia characterized by difficulties with sleep initiation'	Drowsiness, dizziness, diarrhoea, drugged feelings	IV	C
Zolpidem sublingual (Intermezzo)	1.75, 3.5	~2.5	'for use as needed for the treatment of insomnia when a middle-of-the-night awakening is followed by difficulty returning to sleep. Not indicated … when the patient has fewer than 4 hours of bedtime remaining before the planned time of waking'	Headache, nausea, fatigue	IV	C

(*Continued*)

Table 1. (*Continued*)

Generic (brand) name	Doses (mg)	Half-life (h)	Indications	Most common side effects	DEA class	FDA pregnancy category
Selective melatonin receptor agonist						
Ramelteon (Rozerem)	8	1–2.6	'treatment of insomnia characterized by difficulty with sleep onset'	Drowsiness, tiredness, dizziness	None	C
Selective histamine H_1 receptor antagonist						
Doxepin (Silenor)	3, 6	15.3	'treatment of insomnia characterized by difficulties with sleep maintenance'	Somnolence/sedation, nausea, upper respiratory tract infection	None	C

Drug Enforcement Agency (DEA) schedule, and FDA pregnancy category. There are numerous BZRAs, but currently only one melatonin agonist and one histamine antagonist. All have demonstrated efficacy with randomized, controlled clinical trials for one or more insomnia symptoms, and the safety profile for each is well characterized. The medication indications for some are broadly described for the treatment of insomnia, while others specifically note indications for insomnia characterized by difficulty with sleep onset, sleep maintenance, or middle-of-the-night awakenings with difficulty returning to sleep. While each medication has unique safety considerations, the FDA in 2007 issued broad warnings for all insomnia medications regarding two issues (US FDA, 2013a). The first is the potential for rare severe anaphylactic or anaphylactoid reactions with the advice that patients exhibiting these symptoms not be rechallenged with the same medications. The other concerns the possibility of abnormal thinking or behavioural changes that may manifest as complex behaviours with amnesia, such as driving, preparing and eating food, having telephone conversations, or pursuing sexual activities when not fully awake. The warning advises the discontinuation of the medication if these confused behaviours occur. Selected insomnia medications also include warnings about possible next-morning drowsiness and impairment.

Benzodiazepine receptor agonist hypnotics

BZRA hypnotics have been the primary medications prescribed for insomnia since the 1970s when the first medications in this class were a welcome replacement for the more problematic barbiturate and related compounds with serious safety concerns. Currently the BZRAs comprise two classes: (1) benzodiazepines with the characteristic benzene ring linked with a seven-member diazepine ring and (2) compounds, for convenience termed non-benzodiazepines, having unique structures but sharing fundamental pharmacodynamic features with the benzodiazepines. All of the BZRA hypnotics are relatively rapidly absorbed, so may be beneficial for sleep onset. They vary considerably in their pharmacokinetic properties and therefore in the duration of action that influences both desired night-time sedating effects and undesired next-day residual effects that may result in a 'hangover' feeling or impairment in driving or other activities.

The BZRA hypnotics are all positive allosteric modulators of gamma-aminobutyric acid (GABA) responses at the $GABA_A$ receptor complex. The $GABA_A$ receptor complex is a five-subunit transmembrane structure with a central chloride channel (Bateson, 2006). The receptor most typically constitutes two α, two β, and one γ subunit. GABA attaches to an α-β

interface site thereby allowing the chloride ions to enter the neuron. The increased intracellular chloride ion concentration results in an inhibitory effect due to the decreased charge across the membrane and subsequent decreased likelihood of an action potential. When a BZRA attaches to a benzodiazepine recognition site at the α-γ interface, more chloride ions are able to enter the cell thereby enhancing the inhibitory effect. All of the BZRA hypnotics are in the DEA schedule IV category due to having relatively low risks of abuse potential.

The benzodiazepine BZRAs became available in the US between 1970 and 1990. The currently available medications in this group are flurazepam, quazepam, temazepam, and triazolam. The production of estazolam recently was discontinued. With the exception of triazolam, these hypnotics are relatively long acting with elimination half-lives up to several days in some cases. Headaches, dizziness, nausea, and fatigue are the more commonly reported side effects noted in a meta-analysis by Buscemi et al. (2007).

Non-benzodiazepine BZRA hypnotics were introduced from the early 1990s. The three key compounds available in the USA are eszopiclone, zaleplon, and zolpidem. While eszopiclone and zaleplon are still only produced in immediate-release formulations, zolpidem is available now in the original immediate-release form along with an extended-release version, an oral spray, and two different orally dissolvable formulations. Generally these non-benzodiazepine hypnotics have a safety advantage in shorter durations of action with approximate elimination half-lives ranging from about 1–6 h in adults. It has been speculated also that these non-benzodiazepines have greater specificity for selected α subunit subtypes (α_1 and α_3) that confer improved safety profiles compared with benzodiazepine hypnotics (Rudolph & Mohler, 2006). The above-noted hypnotic meta-analysis found headaches, dizziness, nausea, and somnolence to be the more common side effects encountered with the non-benzodiazepines (Buscemi et al., 2007).

The alternative delivery zolpidem formulations designed for oral absorption represent the latest innovations with BZRA hypnotics, although investigations continue with other unique BZRA hypnotic delivery systems. Proposed benefits of the liquid spray and the two types of orally dissolvable zolpidem preparations are more rapid absorption, avoidance of the hepatic first-pass effect, and the absence of the requirement to swallow a pill. However, pharmacokinetic studies have demonstrated that the peak blood levels of these medications were delayed following a high fat meal, suggesting that a substantial portion of the zolpidem was still absorbed through the gastrointestinal tract. The bedtime-dosed dissolvable zolpidem and the liquid spray have the same available doses, warnings, clinical dosing guidelines, and indication (short-term treatment of insomnia characterized by sleep-onset difficulty) as the original immediate-release zolpidem pill since they were approved through an FDA pathway that encourages the development of new formulations based on previously approved medications. The bedtime dissolvable zolpidem is manufactured in 5 mg and 10 mg pills, while the oral spray is dosed as 5 mg for each device actuation. The FDA required bioequivalence and safety studies, but clinical efficacy trials for these new formulations were not necessary. The new middle-of-the-night dissolvable 1.75 mg and 3.5 mg zolpidem formulations did require comprehensive safety and efficacy studies since this represented a new indication and new doses. The formal indication for this lower dose product is for the treatment of insomnia when a middle-of-the-night awakening is followed by difficulty returning to sleep. The label further specifies that the individual should have at least 4 h of bedtime remaining before the planned time of awakening. The prescribing guideline additionally recommends the 3.5 mg dose for men and the 1.75 mg dose for women, as well as for geriatric patients, people with hepatic impairment, and when it is co-administered with central nervous system (CNS) depressants.

Difficulty maintaining sleep is the most common sleep problem among people with insomnia. While some insomnia patients also have difficulty falling asleep, many only suffer with frequent middle-of-the-night awakenings (Roth et al., 2013a). As noted above, only recently was a hypnotic medication (sublingual low-dose zolpidem) approved by the FDA for insomnia characterized by middle-of-the-night awakenings (Roth et al., 2013b). The short elimination half-life of zaleplon, which is indicated for bedtime use, has led some prescribers to suggest off-label use during middle-of-the-night awakenings, as long as the individual had at least 4 h available to remain in bed before the planned awakening. A study of sleep maintenance insomnia patients given zaleplon 10 mg at experimental awakenings showed that it shortened sleep latency and lengthened the duration of sleep following the awakening, and was not associated with residual sedation 4 h later (Zammit et al., 2006).

The recognition that women tend to metabolize zolpidem more slowly than men led to concern about potential next-morning residual sleepiness and impairment following bedtime dosing. Accordingly, in 2013 the FDA issued a Drug Safety Communication recommending lower available doses (5 mg immediate release and 6.25 mg extended release) for women. It was suggested that men could also be started at these lower doses since they might be sufficient and would reduce the risk of adverse effects (US FDA, 2013b).

For many patients insomnia is a chronic condition and they may take BZRA hypnotics on a long-term basis, including nightly, intermittent, and occasional use. (Schutte-Rodin et al., 2008) People taking hypnotic medications nightly sometimes report that the efficacy seems to wear off over time. However, habituation of efficacy was not observed in the long-term clinical trials for the BZRA hypnotics approved for use without any implied limitation on the duration of use. New safety problems associated with long-term use were also not observed.

Another safety issue related to sleep aids is whether their use could be associated with an increase in mortality. Epidemiological studies have investigated the degree to which insomnia or treatment with hypnotics may contribute to mortality (Buysse & Ganguli, 2002). While several large-scale studies have documented increased mortality with hypnotic use, others have not found any significant relationship (Jaussent et al., 2013; Kripke et al., 2002, 2012). As with the question of fall risk, the best approach is a combination of providing patient and caregiver education, limiting unnecessary medication exposure, maintaining close follow up, and making sure that the management of co-morbid conditions is optimized.

Selective melatonin receptor agonist

Ramelteon is the sole melatonin-related medication approved for the treatment of insomnia in the USA at present. The formal indication is for insomnia characterized by difficulty with sleep onset (Takeda Pharmaceuticals North America, 2010). The prescribing guidelines do not suggest a limitation of the duration of use. Ramelteon is an agonist of the MT_1 and MT_2 melatonin receptor subtypes that are found in high concentrations in the suprachiasmatic nucleus, the master timekeeper of the circadian system (Kato et al., 2005). Normally, the homeostatic drive determines one's sleep requirement while the circadian system optimizes the ability to sleep at night-time through entrainment with the day–night photoperiod. Circadian-driven arousal peaks in the evening and declines as bedtime approaches while endogenous melatonin is produced and released from the pineal gland. Agonist activity at the MT_1 receptor decreases the circadian arousal thus facilitating sleep onset. Melatonin action at the MT_2 receptor reinforces the rhythmicity of the circadian cycle. Accordingly, an evening exogenous melatonin agonist dose should aid sleep onset and help stabilize an individual's circadian rhythm.

Ramelteon is available in a single 8 mg dose which is suggested for adults and elderly patients. The prescribing guideline advises use about 30 min prior to bedtime with the caution not to drive or perform other critical tasks following ingestion of the medication. Studies have demonstrated the safety of ramelteon in patients with mild to moderate hepatic impairment or chronic obstructive pulmonary disease, and with any severity of obstructive sleep apnoea (Kryger et al., 2007a, 2007b, 2008) The potential for drug–drug interactions is low; however, since fluvoxamine markedly inhibits CYP1A2, a major ramelteon metabolic pathway, these two medications should not be combined. Due to the lack of abuse potential, ramelteon is considered a non-scheduled medication. It is classed as FDA pregnancy category C. The more common side effects include drowsiness, tiredness, and dizziness.

Selective histamine H_1 receptor antagonist

Histamine is a wake-promoting neurotransmitter that in the CNS is produced in the tuberomammillary bodies of the hypothalamus. Histamine H_1 receptor antagonists in the CNS have sedating properties. While many prescription and OTC medications include antihistaminic activity among their pharmacodynamic actions, doxepin has especially high selectivity for the H_1 receptor such that at very low doses sedation is the primary action (Krystal et al., 2013). Doxepin is a tricyclic antidepressant that was approved originally for the treatment of depression in 1969 at doses up to 300 mg. In 2010 the FDA approved 3 mg and 6 mg doses for the treatment of insomnia characterized by difficulty with sleep maintenance. There is no limitation on the duration of use in the prescribing guidelines. The clinical trials demonstrated that doxepin did not necessarily help with sleep onset, but was particularly effective in improving sleep during the latter part of the night (Lankford et al., 2007, 2008; Roth et al., 2007). It has been suggested that doxepin is most sedating at low doses. At higher doses potential stimulating effects from the activation of other receptors may compete with the H_1 sedating effect. Further, it is argued that doxepin's efficacy is due to the circadian pattern of histamine being relatively active during the night when other wake-promoting neurotransmitters are more quiescent (Krystal et al., 2013).

Low-dose doxepin approved for insomnia is recommended for bedtime doses at 6 mg for adults and at 3 mg for elderly patients (Somaxon Pharmaceuticals, 2010). It is also regarded as non-scheduled due to the absence of an abuse potential. It is FDA pregnancy category C. The more common side effects include somnolence/sedation, nausea, and upper respiratory tract infection. Contraindications include the presence of untreated narrow angle glaucoma, severe urinary retention, and co-administration with monoamine oxidase inhibitors.

Off-label insomnia medications

A substantial portion of medications prescribed for the treatment of insomnia are compounds with sedating or other sleep-promoting properties that are not specifically indicated for insomnia (Krystal, 2010). While the pharmacological properties of these medications have been well described generally, rarely have their efficacy and safety been established in relation to sleep parameters in controlled clinical trials with insomnia patients not having psychiatric co-morbidity. The risk–benefit ratio for a medication prescribed for depression or psychosis may be very different for insomnia populations, especially when these medications are chosen as first-line therapies. This off-label insomnia treatment has been mostly with antidepressants, but sometimes has included antipsychotics and other psychotropic agents. Historically, trazodone, amitriptyline, doxepin, and mirtazapine have been the more common antidepressants prescribed for insomnia. Quetiapine is the antipsychotic most commonly prescribed for the treatment of insomnia. Varying degrees of postsynaptic serotonergic, adrenergic, cholinergic, and histaminergic receptor antagonism accounts for the sedation associated with most of these compounds. A common problem with this off-label use for insomnia is excessive sedation due to the relatively long half-lives of many of these psychotropics. The AASM insomnia management guidelines suggest that these medications may be most appropriate when FDA-indicated drugs have been ineffective and when patients have co-morbid psychiatric conditions for which alternative medications have been approved (Schutte-Rodin et al., 2008). One major treatment challenge has been with pharmacological approaches to insomnia in children, especially since there are no FDA-approved insomnia medications for this population. The off-label use of clonidine is employed sometimes for children, although this is not an evidence-based practice. Most published support for the use of clonidine in children is in populations diagnosed with attention deficit hyperactivity disorder (Barrett et al., 2013).

Prazosin warrants special attention due to the research in military and civilian populations supporting its use in effectively treating insomnia symptoms and nightmares in post-traumatic stress disorder (PTSD) patients (Raskind et al., 2007, 2013; Taylor et al., 2008). Prazosin is an α_1 adrenergic receptor antagonist that is FDA-approved as an antihypertensive. The AASM best practices guidelines for treating nightmares, based primarily on studies with PTSD patients, lists prazosin as the only medication with the highest level of evidence-based support (Aurora et al., 2010).

Trazodone also deserves extra attention here since a large proportion of prescriptions for this medication appear to be exclusively for insomnia symptoms, especially when recommended at low to moderate doses (Walsh, 2004). Trazodone has multiple pharmacodynamic actions, including 5-HT_{1A}, 5-HT_{1C}, 5-HT_2, histamine H_1, and α_1 adrenergic receptor antagonism, in addition to limited presynaptic serotonin reuptake inhibition (Krystal, 2010). Next-morning grogginess and orthostatic hypotension are not uncommon. Male patients should be warned about the potential for priapism, a rare, serious but adverse event that may occur with trazodone. Serotonin syndrome rarely may occur with trazodone; however, the risk is increased when combined with other serotonergic agents.

Over-the-counter sleep aids

OTC medications are regulated in the USA by the FDA but are available without a prescription, although sometimes only at selected low doses. All of the OTC sleep aids are antihistamine compounds. Most of these products contain diphenhydramine, although some have doxylamine as the active ingredient (Krystal et al., 2013). These compounds are marketed in a great many OTC products – either independently or in combination with an analgesic (e.g. acetaminophen) and are then often labelled as a bedtime formulation. OTC diphenhydramine doses are as high as 50 mg, and for doxylamine are up to 25 mg. Generally these medications are rapidly absorbed so may benefit sleep onset. They have relatively long elimination half-lives that may help with sleep maintenance, but may also be associated with next morning residual sedation. Tolerance to the sedating effects may occur with continued use (Richardson et al., 2002). These OTC products are not intended as ongoing treatments for an insomnia disorder, but rather for occasional use for sleeplessness.

While sedation is promoted by the CNS histamine H_1 receptor antagonism, the OTC sleep aids additionally incorporate anticholinergic action due to antagonist activity at the muscarinic receptor (Krystal et al., 2013). Accordingly, the use of these sleep aids may be associated with anticholinergic effects, including dry mouth, blurred vision, constipation, urinary retention, confusion, and delirium. Elderly patients and people concomitantly taking other medications with anticholinergic properties are at the greatest risk for these side effects.

Unregulated sleep-promoting compounds

This rather broad category of unregulated compounds includes a huge array of products marketed to aid the ability to sleep better. Often they are

described as natural, drug-free, or homeopathic. They may be considered complementary or alternative approaches to treating insomnia. Most typically they contain plant preparations or extracts, but there may be synthesized compounds, vitamins, and minerals (e.g. magnesium) among the ingredients. Valerian and melatonin are highly represented among these products, but other common ingredients include hops, chamomile, passion flower, skullcap, lavender, L-tryptophan, glycine, and kava-kava. Generally, there is limited evidence to support the claims of improved sleep, but the substances are mostly regarded as safe. One possible safety exception is kava-kava, which some countries have banned for use, and in the USA the FDA has issued a warning regarding reports of hepatic failure (US FDA Center for Food Safety and Applied Nutrition, 2007). Melatonin is unique in this category since it is a hormone known to have circadian rhythm and sleep-wake cycle regulatory properties, and has demonstrated efficacy evidence, especially with circadian rhythm sleep disorders.

Alcohol deserves special attention, since many people use it as a sleep aid, though rarely successfully. While the sedating effects of alcohol may promote sleep onset, the net effect generally is deterioration in sleep quality. Many studies have documented that late evening alcohol consumption leads to the suppression of REM sleep and increased slow wave sleep during the first half of the night followed by a rebound increase in REM and greater sleep disruption during the second half. People typically rapidly become tolerant to any initial beneficial effects. Alcohol has also been shown to exacerbate other sleep disorders, such as obstructive sleep apnoea and various parasomnias (Roehrs & Roth, 2001).

Investigational compounds

The search continues for new pharmacological approaches for treating insomnia due to the high prevalence of this clinical problem, variations in patient sleep disturbance patterns, scientific advances in understanding the regulation of sleep and waking, limitations or dissatisfaction with current insomnia medication options, and potential pharmaceutical profits that could reach blockbuster status. Compounds tested in clinical trials have included variations on well-established treatment approaches but newly developed with modifications in the pharmacodynamic actions or pharmacokinetic properties, such as the route of administration or formulations for extended release. Pharmaceutical companies have also performed insomnia clinical trials with some currently available medications approved for other disorders with the hope that the formal indications could be extended to include the treatment of insomnia. Finally, extensive basic science and clinical research have investigated several entirely novel pharmacodynamic strategies to promote improved sleep for insomnia patients. Numerous compounds have been studied and abandoned, sometimes after progressing as far as phase III clinical trials, due to assorted efficacy, safety, financial, or regulatory difficulties. However, others remain in different stages of active development with at least two that could be approved by the FDA by the time of this publication. These medications, tasimelteon and suvorexant, are discussed below. Other investigational insomnia treatments have included an inhaled zaleplon (Avram et al., 2013), controlled-release zaleplon, partial agonist GABA positive allosteric modulators, $\alpha 2\delta$ ligands, 5-HT_{2a} antagonists, propofol (Xu et al., 2011), and histamine H_3 autoreceptor agonists.

Soon after the wake-promoting orexin (also called hypocretin) system was discovered in the late 1990s it was speculated that a pharmacological approach that reduces orexin activity might represent an effective strategy to address both night-time and daytime symptoms of insomnia (Brisbare-Roch et al., 2007; de Lecea et al., 1998; Sakurai et al., 1998). Compounds with antagonist activity at one or both of the orexin receptors have been investigated (Hoever et al., 2012). Recent studies have suggested that OX_2 antagonist activity may be adequate for sleep promotion (Betschart et al., 2013). The most extensive clinical trials have been done with dual orexin receptor antagonists (DORAs), including almorexant, which is no longer in development, and suvorexant, which remains in active development by Merck. Clinical trials have demonstrated benefits in sleep onset and maintenance along with a favourable safety profile (Herring et al., 2012). Generally suvorexant has been well tolerated, although there has been a question of next morning residual sleepiness at the higher tested doses. Recommended therapeutic doses are yet to be established. At present the FDA review of this compound continues. The use of an orexin antagonist to treat insomnia would be a rather novel approach with highly targeted pharmacodynamic action.

Tasimelteon is a melatonin receptor agonist active at the MT_1 and MT_2 receptors of the suprachiasmatic nucleus, which is the master circadian system timekeeper (Saper, 2013). Accordingly it should have the potential to enhance sleep onset and stabilize the timing of the circadian rhythm that strongly influences sleep and waking. In selected populations a melatonin agonist may improve total sleep time. While tasimelteon should represent an effective insomnia treatment for selected patients, it is being developed by Vanda Pharmaceuticals specifically for an indication to treat the free-running

non-24-h type of circadian rhythm sleep disorder in totally blind individuals. People who are totally blind typically are unable to benefit from the entraining effects of the photoperiod and therefore gradually may shift in and out of synchronization with the typical 24-h day resulting in periods of time characterized by night-time insomnia and daytime sleepiness (Sack & Lewy, 2001). Vanda has obtained an orphan drug status for tasimelteon in this unique population. Clinical trials have demonstrated improvements in night-time sleep in totally blind patients with episodic insomnia. The compound has been favourably reviewed for efficacy and safety by an FDA advisory committee and is poised for FDA approval in the near future.

International perspective

This article has focused on the current pharmacological treatment of insomnia in the USA. While the pharmacological properties of medications do not recognize political boundaries, regulatory requirements and pharmaceutical business practices certainly do. Although there is considerable overlap, certain compounds and formulations are available only in selected countries, where they may or may not be regulated. For example, melatonin is entirely unregulated and is widely available in the USA, while in the European Union it is available only by prescription with an indication for the treatment of insomnia in individuals at least 55 years of age. The specific lists of available benzodiazepine and non-benzodiazepine hypnotics vary considerably among countries. Zolpidem is widely available internationally, but not the newer alternative delivery formulations. Zopiclone is approved in numerous countries, but only the S-enantiomer, eszopiclone, is available in the USA. The availability of insomnia medications depends upon pharmaceutical companies compiling extensive (and expensive) basic science and clinical evidence to present to regulatory agencies that will analyse the efficacy and safety data for the intended use in specified populations. The company business decisions are influenced by the required research costs, anticipated market competition, potential marketing strategies, and patent protection. The pharmacological treatment of insomnia seems to remain potentially profitable due to it being such widespread clinical problem and the safety concerns and efficacy limitations of the current medications for some patients.

Conclusions

Evidence-based insomnia disorder management guidelines support treatment with psychotherapeutic/behavioural strategies (e.g. cognitive behavioural therapy for insomnia) and the use of selected medications, most typically those approved by the FDA for this indication. In recent years there have been significant advances in the pharmacodynamic and pharmacokinetic scope of available medications for insomnia such that treatment strategies now can be more personalized. Medication selection decision-making can incorporate patient insomnia patterns, demographic factors, co-morbid conditions, and concomitant medications. While the FDA-approved insomnia medications have been evaluated for efficacy and safety in the treatment of insomnia patients, the efficacy and safety of medications prescribed on an off-label basis, OTC sleep aids, and unregulated substances marketed to enhance sleep are much less well established. Research continues in the effort to develop new formulations and novel approaches to address still unmet needs in the pharmacological treatment of this very common clinical condition. Additional approved medications for insomnia and related conditions are anticipated in the near future.

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