Sedative/Hypnotic Agents
Therapeutic Class Review (TCR)

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FDA-APPROVED INDICATIONS

Drug	Manufacturer	Short-term Treatment of Insomnia	Treatment of Insomnia	Treatment of Non-24-hour Sleep-wake Disorder
doxepin (Silenor®)[1]	generic, Pernix		X	
estazolam[2]	generic	X		
eszopiclone (Lunesta®)[3]	generic, Sunovion		X	
flurazepam[4]	generic	X		
lemborexant (Dayvigo®)[5]	Eisai		X	
quazepam (Doral®)[6]	generic*, Galt	X		
ramelteon (Rozerem®)[7]	generic, Takeda		X	
suvorexant (Belsomra®)[8]	Merck		X	
tasimelteon capsule† (Hetlioz®)[9]	Vanda			X
tasimelteon oral suspension† (Hetlioz LQ™)[10]	Vanda			
temazepam (Restoril®)[11]	generic, Mallinckrodt	X		
triazolam (Halcion®)[12]	generic, Pfizer	X		
zaleplon[13]	generic	X		
zolpidem (Ambien®)[14]	generic, Sanofi Aventis	X		
zolpidem sublingual (Edluar®)[15]	Meda/Mylan	X		
zolpidem sublingual[16]	Par		X Middle of the night awakening	
zolpidem (Zolpimist®)[17]	Aytu	X		
zolpidem ER (Ambien® CR)[18]	generic, Sanofi Aventis		X	

ER = extended-release

* authorized generic

† Tasimelteon oral capsule (Hetlioz) and tasimelteon oral suspension (Hetlioz LQ) are indicated for the nighttime sleep disturbances in Smith-Magenis Syndrome (SMS) in patients ≥ 16 years of age and in patients 3 to 15 years of age, respectively. The oral suspension is *not* approved for non-24-hour sleep-wake disorder (N24SWD).[19]

- Eszopiclone (Lunesta), lemborexant (Dayvigo), suvorexant (Belsomra), zaleplon, zolpidem (Ambien, Ambien CR, Edluar, zolpidem sublingual, Zolpimist) and the benzodiazepines (estazolam, flurazepam, quazepam [Doral], temazepam [Restoril], and triazolam [Halcion]) are Scheduled IV controlled substances.
- Doxepin (Silenor), ramelteon (Rozerem), and tasimelteon (Hetlioz, Hetlioz LQ) are not controlled substances.

OVERVIEW

Insomnia is a symptom complex that comprises difficulties falling asleep, staying asleep, or non-refreshing sleep in combination with daytime dysfunction or distress. The symptom complex can be an independent disorder (primary insomnia) or the result of another condition (secondary insomnia).[20] Insomnia is commonly divided into 3 types based on duration. Transient insomnia lasts up to 1 week and is often referred to as adjustment sleep disorder because it is caused most often by an acute situational stress, such as a test or deadline. It is often recurrent with the same or similar stresses. The second type, short-term insomnia, by definition lasts 1 to 6 months and is usually associated with more persistent stressful situational (death or illness) or environmental (noise) factors. Finally, chronic insomnia is insomnia lasting more than 6 months, with a diagnosis established using ICSD-3 or DSM-5 criteria.[21]

Treatment for insomnia should first consist of identification and treatment and/or control of secondary causes. Whenever possible, non-pharmacological measures should be used to treat insomnia. When such measures fail to address the condition, use of pharmacologic hypnotics may be necessary. [22] The American Academy of Sleep Medicine (AASM) guidelines recommend psychological and behavioral strategies, which are effective in both primary and secondary insomnia, as are pharmacological interventions.[23,24] The guidelines recommend that initial behavioral interventions should include stimulus control therapy or relaxation therapy, or a combination of therapies referred to as cognitive behavioral therapy for insomnia (CBT-I). Cognitive behavioral therapy for insomnia includes traditional cognitive behavioral therapy (CBT), stimulus control, sleep hygiene education, sleep restriction therapy, and relaxation therapy. Paradoxical intention and biofeedback therapy may also be effective. Behavioral therapy should always include good sleep hygiene in combination with other therapies. Additionally, the AASM guideline recommends that pharmacotherapy should be used to treat patients who failed to respond to CBT (Grade: weak recommendation, low-quality evidence). The AASM recommends zaleplon, triazolam, and ramelteon versus no treatment for sleep onset insomnia (weak recommendations), suvorexant and doxepin over no treatment for sleep maintenance insomnia (weak recommendations), and eszopiclone, zolpidem, and temazepam for both sleep onset and sleep maintenance insomnia. The AASM guidelines recommend against the use of trazodone or tiagabine for sleep onset or sleep maintenance insomnia in adults (Grade: weak recommendation, low-quality evidence). The AASM recommends against the use of over-the-counter (OTC) medications or supplements (e.g., diphenhydramine, tryptophan, melatonin) or herbal products (e.g., valerian) as a treatment for sleep onset and sleep maintenance for chronic insomnia (Grade: weak recommendation, low-quality evidence). Choice of agent should be based on symptom pattern, treatment goals, past treatment response, patient preference, cost, availability of other treatments options, comorbid conditions, contraindications, potential interaction with concurrent medication, and side effects.

The American College of Physicians (ACP) released 2016 clinical practice guidelines on the management of chronic insomnia disorder in adults.[25] Recommendations include CBT-I as the initial treatment for chronic insomnia disorder (Grade: strong recommendation, moderate-quality evidence). Clinicians should use a shared decision-making approach with the patient with a discussion of benefits, harms, and costs of short-term use of medications when deciding whether to add pharmacological therapy in adults with chronic insomnia in whom CBT-I alone was not successful (Grade: weak recommendation, low-quality evidence). The ACP guidelines state that the FDA has approved medications for short-term use (4 to 5 weeks), and patients should not continue taking them for

extended periods of time. Patients should be further evaluated if insomnia does not remit within 7 to 10 days of treatment.

In September 2019, the US Department of Veterans Affairs (VA) and US Department of Defense (DoD) Evidence-Based Practice Work Group published clinical practice guidelines for the management of chronic insomnia disorder and obstructive sleep apnea (OSA).[26] The guideline is designed to be used by healthcare professionals to assist in the evaluation, treatment, and management of VA and DoD patients with either of these sleep disorders. Recommendations for chronic insomnia are summarized. For the treatment of chronic insomnia disorder, the guidelines recommend CBT-I. Behavioral components of CBT-I include sleep restriction therapy, stimulus modification, relaxation techniques, and education on sleep hygiene. Cognitive components focus on changing maladaptive thoughts regarding sleep. The work group suggests CBT-I as first-line therapy for the treatment of chronic insomnia disorder over pharmacotherapy. Additionally, the guidelines suggest against the use of sleep hygiene education alone for chronic insomnia disorder. The guidelines state that nonpharmacological interventions for the treatment of insomnia are more effective than pharmacotherapy; however, the work group recognizes that some patients will require short-term pharmacotherapy. For patients in whom a short course of pharmacotherapy is appropriate, low-dose doxepin (3 mg or 6 mg) or a nonbenzodiazepine benzodiazepine receptor agonist (BZRA) (e.g., zolpidem, zaleplon, eszopiclone) is suggested. If a nonbenzodiazepine BZRA is utilized, the lowest effective dose should be used for the shortest duration, and patients should be counseled regarding risks of these medications. Evidence is currently inadequate to recommend for or against use of either ramelteon or suvorexant for chronic insomnia disorder. Benzodiazepines, trazodone, and antipsychotics are suggested against for the treatment of chronic insomnia disorder. In addition, the work group suggests against the use of the following OTC or herbal agents for the treatment of chronic insomnia disorder: diphenhydramine, melatonin, valerian, chamomile, and kava.

The incidence of insomnia in children ranges from 1% to 6%; in children with neurodevelopmental or psychiatric comorbidities, the incidence is as high as 50% to 75%.[27,28,29] Insomnia in children may result in irritability, restlessness, lack of concentration, suicide risk, and poor memory.[30] The AASM's task force on Pharmacotherapy in Pediatric Sleep Medicine published guidelines in 2005 that do not recommend any one hypnotic over another for use in children.[31] Rather, the consensus statement urges caution when using any of these drugs for the pediatric patient and calls for additional research to be completed.

Guidelines from the 2006 National Sleep Foundation state that there is a need for pharmacologic management of pediatric insomnia.[32] Acknowledging that there is an absence of pharmaceuticals indicated for hypnotic use in the pediatric population, this organization stated that there is a need for trials to confirm the safety and efficacy of such agents in these patients.

Non-24-hour sleep-wake disorder (N24SWD or non-24) is a chronic circadian rhythm disorder that causes problems with the timing of sleep and sleep patterns.[33] It occurs in approximately 55% to 70% of people who are completely blind, but can also be experienced in sighted people; prevalence among people with sight is unknown. The National Organization for Rare Disorders (NORD) states that the condition is characterized by the failure of a person's biological clock to synchronize to a 24-hour day light-dark cycle. In people who are completely blind (e.g., have no perception of light), this is due to their eyes inability to register light signals. In sighted people N24SWD may be due to a number of factors, such as altered sensitivity of light on circadian rhythm; self-selected changes in light exposure late in the day; and hormonal factors. Those with the disorder may have difficulty falling or staying

asleep, and may wake up feeling as if they need more rest. People with N24SWD may find their sleep patterns reversed (e.g., needing to sleep during the day and to be awake at night). N24SWD onset most often occurs in late teens or early twenties but can occur at any age and appears to be a life-long effect.

In 2015, the AASM updated their guidelines for the treatment of intrinsic circadian rhythm sleep-wake disorders, which includes N24SWD.[34] They endorse strategically-timed melatonin or light therapy for select patients with Circadian Rhythm Sleep-Wake Disorders (CRSWD), including N24SWD. The AASM Task Force also strongly recommends avoiding the use of sleep-promoting medications to treat elderly patients with dementia and Irregular Sleep-Wake Rhythm Disorder (ISWRD). Tasimelteon (Hetlioz), FDA approved in October 2014 to treat N24SWD, was not addressed in the guidelines.

Smith-Magenis syndrome (SMS) is a genetic disorder of deletion (90%) or mutation (10%) in chromosome 17 in a section that includes the retinoic acid-induced 1 (*RAI1*) gene.[35] All cases in literature are due to a spontaneous genetic change. SMS affects an estimated 1 in 15,000 to 25,000 individuals in the United States (US). The primary characteristics of this condition include mild to moderate cognitive disability, speech and motor delays, distinctive facial features, skeletal malformations, sleep disturbances, and behavioral problems. Patients may also exhibit reduced sensitivity to pain, visual and hearing abnormalities, and a hoarse voice. Other neurologic and organ dysfunction may also be present. Pharmacologic treatments are used to treat various aspects of the disorder. These include medications for sleep disorder, including tasimelteon (approved December 2020) and melatonin, as well as agents for attention deficit or hyperactivity disorder and seizures.

This review will focus on agents indicated for sleep disorders and contemporary treatment in adults.

PHARMACOLOGY

Benzodiazepines are believed to potentiate gamma aminobutyric acid (GABA) neuronal inhibition. The sedative and anticonvulsant actions of these drugs involve GABA receptors located in the limbic, neocortical, and mesencephalic reticular systems. At least 2 benzodiazepine receptor subtypes have been identified in the brain, BZ-1 and BZ-2. BZ-1 is thought to be associated with sleep mechanisms while BZ-2 is thought to be associated with memory, motor, sensory, and cognitive functions. Benzodiazepines generally decrease the time to onset of persistent sleep (sleep onset latency, SOL) and reduce the number of awakenings.[36] Benzodiazepines in this class review include estazolam, flurazepam, quazepam, temazepam, and triazolam.

Although structurally different from the benzodiazepines and from one another, the cyclopyrrolone hypnotics (Z-drugs), eszopiclone (Lunesta), zaleplon, and zolpidem (Ambien, Ambien CR, Edluar, Zolpimist, zolpidem sublingual), are all active at the GABA-BZ receptor complex.[37] Unlike the benzodiazepines, these agents bind selectively to the BZ-1 receptor.

Ramelteon (Rozerem) is a highly selective and potent agonist of the MT1 and MT2 melatonin receptors, which are believed to be involved in the regulation of the circadian rhythm.[38] Tasimelteon (Hetlioz, Hetlioz LQ) is also an agonist at the MT1 and MT2 receptors, with greater affinity for the MT2 receptor.[39] The MT1 receptor is believed to regulate sleepiness, whereas the MT2 receptor is thought to help the body shift between day and night. Ramelteon has been reported to have greater affinity, selectivity, and potency than melatonin for the MT1 receptor, resulting in a better ability to induce sleep onset. Ramelteon has shown no affinity for the GABA-receptor complex, which is the primary target area for most of the other agents in this class.[40]

Doxepin (Silenor) is a formulation of the sedative tricyclic antidepressant that is approved for treatment of insomnia, in particular in patients with sleep maintenance problems. Doxepin binds with a high affinity to H_1 histamine receptors where it functions as an antagonist and may result in its sedative effect.[41]

Lemborexant (Dayvigo) and suvorexant (Belsomra) are orexin receptor antagonists. The orexin neuropeptide signaling system is a central promoter of wakefulness. Blocking the orexin receptor suppresses wakefulness.[42,43]

PHARMACOKINETICS[44,45,46,47,48,49,50,51,52,53,54,55,56,57,58,59,60,61]

Drug	Onset of Action (minutes)	Duration of Action (hours)	Half-Life of Parent Compound (hours)	Active Metabolite(s) (Half-Life)	Metabolism
doxepin (Silenor)	n/a	3 (delayed in presence of high fat meal)	15.3	N-desmethyldoxepin	oxidation and demethylation
estazolam[62]	15-120	6-8	14.4-15	None	CYP 3A4
eszopiclone (Lunesta)[63]	≤ 30	6-8	6	(S)-zopiclone-N-oxide (S)-N-desmethylzopiclone	CYP 3A4 CYP 2E1
flurazepam	30-60	7-10	2.3	N_1-desalkylflurazepam (47-100 hrs; up to 160 hrs in elderly) N_1-hydroxyethylflurazepam (2-4 hrs)	oxidation
lemborexant (Dayvigo)	60-180 (delayed by 2 hrs in presence of high-fat meal)	nr	17-19	M10	CYP3A4 (major) CYP3A5 (minor)
quazepam (Doral)	20-60	7-10	39	2-oxoquazepam (39 hrs) N-desalkyl-2-oxoquazepam (73 hrs)	hepatic
ramelteon (Rozerem)	≤ 30	nr	1-2.6	MII (2-5 hrs)	oxidation CYP 1A2
suvorexant (Belsomra)	30 mins to 6 hrs (delayed by 1.5 hrs in presence of food)	nr	12	None	CYP3A (major) CYP2C19 (minor)
tasimelteon (Hetlioz, Hetlioz LQ)	n/a	nr	1.3±0.4	None	oxidation and oxidative dealkylation
temazepam (Restoril)	15-120	6-8	3.5-18.4	None	conjugation

hrs = hours

Pharmacokinetics (continued)

Drug	Onset of Action (minutes)	Duration of Action (hours)	Half-Life of Parent Compound (hours)	Active Metabolite(s) (Half-Life)	Metabolism
triazolam (Halcion)	15-30	1.7-3	1.5-5.5	None	oxidation CYP 3A4
zaleplon[64]	10-30	4	1	None	aldehyde oxidase CYP 3A4
zolpidem (Ambien) zolpidem ER (Ambien CR)	<30-96 (delayed in presence of food)	8	2.5-2.6 2.8	None	CYP 3A4
zolpidem sublingual (Edluar)	delayed in presence of food	8	2.65-2.85	None	CYP 3A4
zolpidem sublingual[65]	35 (delayed in presence of food)	4	2.5	None	CYP 3A4

hrs = hours

Tasimelteon (Hetlioz) effects may not occur for weeks or months due to of individual differences in circadian rhythms.

Zolpidem ER (Ambien CR) is a coated 2-layer tablet with 1 layer that releases the drug content immediately and another layer that slowly releases additional drug beyond 3 hours after administration. Compared to the immediate-release formulation (Ambien), the peak concentration of zolpidem ER is reached at a later time (2.4 versus 2 hours; $p<0.004$) and is approximately 13% lower.[66]

Zolpidem (Zolpimist) is bioequivalent to zolpidem (Ambien) tablets.

The difference in flurazepam and zolpidem (Ambien, Ambien CR, Edluar, zolpidem sublingual, and Zolpimist) dosing between men and women is due to the lower rate of clearance by women compared to men.

CONTRAINDICATIONS/WARNINGS[67,68,69,70,71,72,73,74,75,76,77,78,79,80,81,82,83]

Eszopiclone (Lunesta), zaleplon, and zolpidem (Ambien, Ambien CR, Edluar, zolpidem sublingual, and Zolpimist) carry a boxed warning for complex sleep behaviors while using the medications.[84] These behaviors, such as sleep-walking, sleep-driving, and other activities while not fully awake, may result in serious injury and death. If a complex sleep behavior occurs, the medication should be discontinued. Post-marketing reports have shown that complex sleep behaviors may occur when these medications are used as prescribed or when combined with alcohol or other central nervous system (CNS) depressants.

All agents in this class, except doxepin (Silenor), lemborexant (Dayvigo), suvorexant (Belsomra), and tasimelteon (Hetlioz, Hetlioz LQ), have a warning regarding their potential for anaphylaxis and angioedema that can occur as early as the first dose.

These drugs, with the exception of zolpidem SL, should be administered immediately before going to bed or once the patient experiences difficulty falling asleep. Zolpidem SL should be utilized for middle of the night awakenings when the patient has more than 4 hours before planned waking time.

All of these agents may result in short-term memory impairment, hallucinations, impaired coordination, dizziness, and light-headedness. The FDA-approved hypnotics, including non-benzodiazepine sedative hypnotics, hypnotics, and doxepin, carry a warning regarding complex sleep-related behaviors such as sleep-driving, making phone calls, sexual activity, and preparing and eating food while asleep; often patients have no memory of these events. These behaviors are more likely to occur when the sedative-hypnotic is taken concurrently with alcohol or other CNS depressants.

All drugs in this class should be used at the lowest effective dose. In January 2013, the FDA announced lower dosing recommendations for zolpidem due to new data showing that blood levels in some patients may be high enough the morning after use to impair activities that require alertness, including driving.[85] Women appear to be more susceptible to this risk as they eliminate zolpidem more slowly compared to men. The FDA lowered the recommended dose of zolpidem for women from 10 mg to 5 mg for immediate-release products (Ambien, Edluar, and Zolpimist) and from 12.5 mg to 6.25 mg for extended-release products (Ambien CR). Prescribers should consider lower zolpidem doses for men, but it is not required. At the time of zolpidem sublingual's approval, the label recommended a lower dosage for women than for men.

All sedative/hypnotics should be administered with caution to patients exhibiting signs and symptoms of depression. Suicidal tendencies may be present in such patients, and protective measures may be required. Intentional overdose is more common in this group of patients; therefore, the smallest amount of drug that is feasible should be prescribed for the patient at any one time. Special attention should be given to doxepin (Silenor) because the active ingredient is a tricyclic antidepressant. Administration of antidepressants in children, adolescents, and young adults with major depressive disorder (MDD) and other psychiatric disorders could also increase suicidal thoughts and actions.

All drugs in this class should be used only after careful assessment of the cause of sleep disturbances, behavioral changes, amnesia, withdrawal symptoms, and emergence or worsening of psychiatric or physical disorders. Patients whose insomnia fails to remit after 7 to 10 days of treatment with a sedative-hypnotic may have a primary psychiatric or medical illness that should be evaluated.

The benzodiazepines carry boxed warnings for the risk of abuse, misuse, addiction, dependence, and withdrawal. A gradual taper to discontinue or reduce the dose is required to prevent acute withdrawal symptoms which could be fatal.

In 2016, the FDA informed healthcare professionals that concurrent use of opioids and benzodiazepines or other CNS depressants has resulted in serious adverse reactions such as profound sedation, respiratory depression, coma, and death.[86] Providers should limit prescribing of opioids with benzodiazepines (e.g., estazolam, flurazepam, quazepam, temazepam, triazolam) to patients without alternative treatment options. If used together, dosages and duration of therapy should be minimized and patients should be monitored for signs and symptoms of respiratory depression and sedation. Boxed warnings were added to the labeling of all prescription opioids, including those indicated for pain and for cough, and benzodiazepines. In 2017, the safety warning was updated to urge prescribers to consider the risks and benefits for the use of opioid addiction medications such as buprenorphine and methadone in combination with benzodiazepines. Careful medication management is recommended over withholding opioid addiction medications for patients using benzodiazepines.[87]

All sedative hypnotics can cause drowsiness and a decreased level of consciousness, which may lead to falls and, consequently, to severe injuries such as hip fractures and intracranial hemorrhage. Daytime functions, such as driving or activities requiring complete mental alertness, may be impaired when flurazepam is used as prescribed. These risks are especially concerning in the elderly. In addition, a meta-analysis of sleep medications in older adults reviewed the risk for hip fracture during short-term and long-term use of benzodiazepines and non-benzodiazepines.[88] The short-term use (≤ 14 days) was associated with the highest risk (RR, 2.4; [95% confidence interval, 1.88 to 3.05]; and RR, 2.39 [95% confidence interval, 1.74 to 3.29]). In the absence of direct clinical trials comparing agents in this class and the increased risk of falls and hip fractures, benzodiazepines and non-benzodiazepines should be prescribed with equal caution for short-term use in older adults.

Lemborexant and suvorexant are contraindicated in patients with narcolepsy.

Benzodiazepines, including estazolam, flurazepam, quazepam, temazepam, and triazolam, are contraindicated in patients with suspected or established sleep apnea. Doxepin, suvorexant, or tasimelteon have not been studied in subjects with severe sleep apnea or severe chronic obstructive pulmonary disease (COPD), and they are not recommended for use in these populations. Single doses of ramelteon did not result in respiratory depression in patients with mild to severe COPD or in patients with mild to moderate sleep apnea; there is no data available on the effect of multiple doses in patients with either condition. Ramelteon has not been studied in patients with severe obstructive sleep apnea; therefore, it is not recommended in this patient population. Similarly, lemborexant has not been studied in patients with moderate to severe OSA or in patients with COPD, and therefore the potential impact of lemborexant on respiration should be considered if given to those with impaired respiratory function.

Patients with compromised respiratory function should be cautioned prior to the use of zolpidem (Ambien, Ambien CR, Edluar, zolpidem sublingual, Zolpimist) since respiratory depression can occur.

Eszopiclone (Lunesta), lemborexant (Dayvigo), suvorexant (Belsomra), zaleplon, zolpidem (Ambien, Ambien CR, Edluar, zolpidem sublingual, Zolpimist) and benzodiazepines (estazolam, flurazepam, quazepam [Doral], temazepam [Restoril], and triazolam [Halcion]) are Scheduled IV controlled substances. Patients with a history of addiction to, or abuse of, drugs or alcohol are at increased risk for misuse, abuse, and addiction with these agents; patients should be monitored carefully when taking these agents. Furthermore, to lower the likelihood for withdrawal reactions, a gradual taper should be used to discontinue benzodiazepines, such as quazepam. Doxepin (Silenor), ramelteon (Rozerem), and tasimelteon (Hetlioz, Hetlioz LQ) are not controlled substances and are not associated with abuse or physical dependence.

Patients with untreated narrow angle glaucoma or severe urinary retention should not use doxepin (Silenor).

Sleep paralysis, an inability to move or speak for up to several minutes during sleep-wake transitions, hypnagogic/hypnopompic hallucinations, and cataplexy-like symptoms can occur with lemborexant and suvorexant.

DRUG INTERACTIONS[89,90,91,92,93,94,95,96,97,98,99,100,101,102,103,104,105]

Drugs in this class should be used with caution in patients receiving other CNS depressants as the effects may be additive, resulting in decreased alertness and impaired psychomotor performance.

Increased CNS depressant effects of the benzodiazepines that are metabolized by oxidation have been reported when co-administered with isoniazid, oral contraceptives, cimetidine, and disulfiram.

Estazolam, eszopiclone (Lunesta), ramelteon (Rozerem) and its active M-II metabolite, tasimelteon (Hetlioz, Hetlioz LQ), triazolam, zaleplon, and zolpidem (Ambien, Ambien CR, Edluar, zolpidem sublingual, Zolpimist) are substrates for the CYP450 3A4 enzyme. As such, inducers of CYP450 3A4 (e.g., rifampin) increase the clearance and reduce the bioavailability of these agents by approximately 80%. Inhibitors of CYP450 3A4 (e.g., cimetidine, clarithromycin, ketoconazole) increase the bioavailability of these drugs by up to 84%.

Doxepin (Silenor) is primarily metabolized by CYP2C19 and CYP2D6 hepatic cytochrome P450 isozymes. Inhibitors of these isozymes may increase the exposure of doxepin in patients. Concomitant administration of doxepin with CNS depressants, including alcohol, and sedative antihistamines has shown increased sedative effects. Severe hypoglycemia has been reported with the simultaneous use of tolazamide. Using doxepin and cimetidine together has caused an increased exposure to doxepin. Patients should not use monoamine oxidase inhibitor (MAOI) medications within 14 days of doxepin.

Concurrent use of moderate CYP3A (e.g., fluconazole, verapamil) or strong CYP3A inhibitors (e.g., itraconazole, clarithromycin) may increase exposure and the maximum concentration of lemborexant (Dayvigo) potentiating adverse reactions and should be avoided. The maximum recommended dose of lemborexant (Dayvigo) is 5 mg per night when used in patients receiving weak CYP3A inhibitors (e.g., chlorzoxazone, ranitidine). Lemborexant efficacy is reduced when co-administered with a moderate CYP3A inducer (e.g., bosentan, efavirenz, etravirine, modafinil) or strong CYP3A inducer (e.g., rifampin, carbamazepine, St. John's wort). As a result, avoid concurrent use with strong or moderate CYP3A inducers. Lemborexant can decrease the exposure of CYP2B6 substrates (e.g., bupropion, methadone) which can lead to decreased efficacy; as a result, if concurrent use is required, monitor for clinical response of the CYP2B6 substrate as a dose increase of the CYP2B6 substrate may be necessary.

Ramelteon (Rozerem) is contraindicated for concomitant use with fluvoxamine, a strong CYP1A2 inhibitor. It should be used with caution in patients taking less strong CYP1A2 inhibitors. Administration of ramelteon with fluconazole increases the bioavailability of ramelteon and the M-II metabolite by approximately 150%. Similarly, the use of tasimelteon (Hetlioz, Hetlioz LQ) with fluvoxamine or other strong CYP1A2 inhibitors should be avoided due to the potential for a substantial increase in tasimelteon exposure and increased risk for adverse effects.

Suvorexant (Belsomra) is not recommended with strong inhibitors of CYP450 3A (e.g., ketoconazole, itraconazole, posaconazole, clarithromycin, nefazodone, ritonavir, saquinavir, nelfinavir, indinavir, boceprevir, telaprevir, telithromycin, and conivaptan). Furthermore, the recommended dose in patients receiving moderate CYP3A inhibitors (amprenavir, aprepitant, atazanavir, ciprofloxacin, diltiazem, erythromycin, fluconazole, fosamprenavir, grapefruit juice, imatinib, verapamil) is 5 mg; the dosage may be increased to 10 mg, if needed for efficacy. However, the dose usually should not exceed 10 mg in patients concurrently taking moderate CYP3A inhibitors. CYP3A inducers (e.g., rifampin, carbamazepine, and phenytoin) can substantially decrease suvorexant exposure thereby minimizing the efficacy.

Concurrent administration of triazolam with efavirenz, delavirdine, azole antifungals, nefazodone, protease inhibitors, and any drug that significantly impairs the CYP3A mediated oxidative metabolism are contraindicated. Caution is recommended when administering triazolam with grapefruit juice,

fluvoxamine, diltiazem, verapamil, amiodarone, nicardipine, nifedipine, cimetidine, and ranitidine because these agents can increase plasma concentration of triazolam.

The efficacy of tasimelteon (Hetlioz, Hetlioz LQ) may be reduced in patients on concomitant beta adrenergic receptor antagonists (e.g., acebutolol, metoprolol).

The concurrent use of a CYP3A4 inducer (e.g., St. John's wort, rifampin) with zolpidem (Ambien, Ambien CR, Edluar, zolpidem sublingual, Zolpimist) is not recommended as it may reduce the blood levels of zolpidem.

ADVERSE EFFECTS[106,107,108,109,110,111,112,113,114,115,116,117,118,119,120,121,122,123]

Drug	Headache	Myalgia	Amnesia	Dizziness	Daytime Drowsiness/ Somnolence
doxepin (Silenor)	nr	<2	nr	reported	6-9
estazolam	16 (27)	≤ 1	≤ 1	7 (3)	3 (2)
eszopiclone (Lunesta)	16-20 (13)	nr	nr	5-7 (4)	8-10 (3)
flurazepam	reported	nr	reported	reported	reported
lemborexant (Dayvigo)	4.5-5.9 (3.4)	nr	nr	nr	6.9-9.6 (1.3)
quazepam (Doral)	4.5 (2.2)	nr	reported	1.5 (< 1)	12 (3.3)
ramelteon (Rozerem)	< 1	nr	nr	4 (3)	3 (2)
suvorexant (Belsomra)	7 (6)	nr	reported	3 (2)	7 (3)
tasimelteon (Hetlioz, Hetlioz LQ)	17 (7)	nr	nr	nr	nr
temazepam (Restoril)	8.5 (9.1)	nr	< 0.5	4.5 (3.3)	2.5 (1.1)
triazolam (Halcion)	9.7 (8.4)	nr	reported	7.8 (3.1)	nr
zaleplon	30-42 (35)	7 (4)	2-4 (1)	7-9 (7)	nr
zolpidem (Ambien, Edluar, Zolpimist)	7 (6)	> 1	1 (0)	5 (1)	8 (6)
zolpidem sublingual	3 (1)	nr	nr	nr	nr
zolpidem ER (Ambien CR)	14-19 (11-16)	< 1-4 (0)	1-3 (0)	8-12 (3-5)	6-15 (2-5)

Adverse effects are reported as a percentage. Adverse effects data are obtained from package inserts and are not meant to be comparative or all inclusive. Incidences for the placebo group are indicated in parentheses. nr = not reported.

For eszopiclone (Lunesta), 16% to 34% of patients reported a dose-related unpleasant taste as compared to 3% of placebo patients. Dose-related respiratory infection has been reported in 5% to 10% of patients taking eszopiclone compared to 3% of patients taking placebo. Anxiety has been

reported in 1% to 3.7% of patients receiving eszopiclone compared to zero patients taking placebo in one 6-week placebo controlled trial.

Nightmares have been reported with the use of tasimelteon capsules for N24SWD (Hetlioz) and zaleplon, and abnormal dreams have been reported with suvorexant (Belsomra). Abnormal dreams and nightmares have been reported in clinical trials for patients taking lemborexant (Dayvigo) as well as sleep paralysis, hypnagogic hallucinations, and complex sleep behavior. Additionally, postmarketing reports for suvorexant have identified several possible adverse reactions, including palpitations, tachycardia, psychomotor hyperactivity, anxiety, pruritis, nausea and vomiting.

In a crossover study in patients with SMS with nighttime sleep disturbances, patients 3 to 15 years of age (n=11) received tasimelteon oral suspension (Hetlioz LQ) and those ≥ 16 years old (n=14) received tasimelteon capsules (Hetlioz). Adverse effects were similar between the 2 age groups and were also similar to those observed in studies for N24SWD.

SPECIAL POPULATIONS[124,125,126,127,128,129,130,131,132,133,134,135,136,137,138]

Pediatrics

Tasimelteon oral suspension (Hetlioz LQ) is approved for use in pediatric patients 3 years of age to 15 years of age for the treatment of nighttime sleep disturbances associated with SMS, and tasimelteon capsule (Hetlioz) is approved for patients with nighttime sleep disturbances in SMS in patients ≥ 16 years old. Safety and efficacy of tasimelteon for the treatment of non-24 in pediatric patients have not been established. Safety and effectiveness of the remaining agents in this class review have not been established in pediatric patients.

In an 8-week study, in patients aged 6 to 17 years with insomnia associated with attention-deficit/hyperactivity disorder (ADHD), zolpidem oral solution at a dose of 0.25 mg/kg at bedtime did not decrease sleep latency compared to placebo. The most common treatment-related adverse effects reported were (> 5%) with zolpidem versus placebo and included dizziness (23.5% versus 1.5%), headache (12.5% versus 9.2%), and hallucinations (7% versus 0%).

Eszopiclone (Lunesta) failed to demonstrate efficacy in controlled clinical studies of pediatric patients with ADHD-associated insomnia.

A survey of 671 primary care pediatricians found that more than 75% had prescribed nonprescription medications, and more than half had prescribed prescription medications for pediatric insomnia.[139] Most commonly, these agents were prescribed for acute pain and travel, followed by children with special needs. Antihistamines were the most common nonprescription medications for sleep, followed by melatonin and herbal remedies. Alpha-agonists were the most frequently prescribed prescription sleep medication.

Pregnancy

Some zolpidem formulations (zolpidem sublingual, Zolpimist) are Pregnancy Category C. Doxepin (Silenor), eszopiclone (Lunesta), flurazepam, ramelteon (Rozerem), quazepam (Doral), suvorexant (Belsomra), tasimelteon (Hetlioz, Hetlioz LQ), zaleplon, and the remaining zolpidem formulations (Ambien, Ambien CR, Edluar) were previously Pregnancy Category C and have now been updated to contain descriptive text in compliance with the Pregnancy and Lactation Labeling Rule (PLLR). Available data for these agents are insufficient to identify a risk of major birth defects or miscarriage due to

exposure to these drugs. There have been reports of respiratory depression and sedation in neonates born to mothers using zolpidem during the third trimester of pregnancy. In addition, there are risks of poor neonatal adaptation with exposure to tricyclic antidepressants, including doxepin, during pregnancy.

Lemborexant (Dayvigo) was approved with descriptive text indicating there are insufficient data to advise of the drug-associated maternal or fetal risk. Pregnant women exposed to lemborexant are encouraged to register with the pregnancy exposure registry so that information can be collected and outcomes monitored during pregnancy.

Triazolam (Halcion) was previously Pregnancy Category X with benzodiazepine hypnotics, estazolam and temazepam, and has been updated to contain the PLLR descriptive text. There is a National Pregnancy Registry that monitors pregnancy outcomes in women exposed to triazolam as well as other psychiatric medications. There is no clear evidence that early pregnancy exposure causes major birth defects, however there is a risk for sedation and neonatal withdrawal in infants born to mothers using benzodiazepines in later stages of pregnancy.

Hepatic Impairment

Patients with hepatic impairment may display higher doxepin (Silenor) concentrations than healthy patients. Patients with hepatic impairment should initiate treatment at the lowest recommended daily dosage and monitor for adverse daytime effects.

In patients with severe hepatic impairment, the bioavailability of eszopiclone is increased 2-fold compared with healthy volunteers; time-to-peak and peak concentrations remain unchanged.

In patients receiving lemborexant (Dayvigo), the maximum dose is 5 mg once per night in patients with moderate hepatic impairment (Child-Pugh Class B) as exposure and the half-life were increased in these patients. Lemborexant is not recommended in patients with severe hepatic impairment. Exposure to lemborexant is increased in patients with mild hepatic impairment (Child-Pugh Class A); these patients do not require a dose adjustment but should be monitored for increased somnolence.

Exposure to ramelteon was increased nearly 4 times normal amounts when given to patients with mild hepatic impairment and 10 times normal amounts in those with moderate impairment. Ramelteon should be used with caution in patients with moderate hepatic impairment and should not be used in those with severe impairment.

Dose adjustment of suvorexant (Belsomra) is not required in patients with mild or moderate hepatic impairment. Suvorexant is not recommended in patients with severe hepatic impairment.

Dose adjustment of tasimelteon (Hetlioz, Hetlioz LQ) is not necessary in patients with mild or moderate hepatic impairment. Tasimelteon has not been studied in patients with severe hepatic impairment (Child-Pugh Class C). Therefore, tasimelteon is not recommended for use in patients with severe hepatic impairment.

The bioavailability of zaleplon is increased up to 400% in patients with compensated cirrhosis and 700% with decompensated cirrhosis. Zaleplon is not recommended for use in patients with severe hepatic impairment; dose reductions should be employed with mild to moderate impairment.

In patients receiving zolpidem (Ambien, Edluar, Zolpimist) who have hepatic insufficiency, the daily dose should not exceed 5 mg and, for the controlled-release zolpidem tablet (Ambien CR), the maximum dose should not exceed 6.25 mg. Ambien CR should be avoided in patients with severe

hepatic impairment as it may precipitate hepatic encephalopathy. For zolpidem sublingual in those with hepatic insufficiency, the maximum once daily dose should not exceed 1.75 mg.

Ethnicity

In Japanese adults, the maximum plasma concentration of zaleplon is increased by 37%. The effect of other ethnic groups has not been widely studied.[140]

Geriatrics[141,142,143]

Patients over the age of 65 years may demonstrate an increase in total exposure to sedative/hypnotic agents. Dosing for the benzodiazepines should commonly begin at the lowest effective dose for these patients. Ramelteon and doxepin may be exceptions as they did not show any overall differences in safety and efficacy between elderly and younger adult patients.

Smokers

The clearance of benzodiazepines is accelerated in smokers compared to nonsmokers.

Smoking causes induction of CYP1A2 levels; exposure to tasimelteon (Hetlioz, Hetlioz LQ) in smokers was lower than in non-smokers and, therefore, the efficacy of tasimelteon may be reduced in smokers.

DOSAGES[144,145,146,147,148,149,150,151,152,153,154,155,156,157,158,159,160,161,162]

Drug	Bedtime Dose	Dose Adjustment	Availability
doxepin (Silenor)	6 mg Take 30 minutes before bedtime and not within 3 hours of a meal	Elderly: begin with 3 mg and increase to 6 mg, if required; 3 mg if clinically indicated for individual patients	Tablet: 3 mg, 6 mg
estazolam	1 mg to 2 mg	Elderly, underweight, or debilitated: 0.5 mg to 1 mg	Tablet: 1 mg, 2 mg
eszopiclone* (Lunesta)	1 mg	Dosing can be raised to 2 mg or 3 mg if clinically indicated Elderly: total dose not to exceed 2 mg Severe hepatic impairment: should not exceed 2 mg Concurrent use with strong CYP 3A4 inhibitor: should not exceed 2 mg	Tablet: 1 mg, 2 mg, 3 mg
flurazepam	**Men**: either 15 mg or 30 mg **Women**†: 15 mg	Women: may increase to 30 mg Elderly or debilitated patients: 15 mg	Capsule: 15 mg, 30 mg
lemborexant (Dayvigo)*	5 mg Take immediately before going to bed, with ≥ 7 hours remaining before the planned time to awaken	Dose can be increased to 10 mg if the 5 mg dose is well-tolerated but not effective Moderate hepatic impairment or concurrent use with weak CYP3A inhibitor: max of 5 mg once per night	Tablet: 5 mg, 10 mg
quazepam (Doral)	Initial dose: 7.5 mg	May be increased to 15 mg	Tablet: 15 mg

* Should be taken on empty stomach to avoid delayed onset of action.

† The recommended initial doses for women and men are different because clearance is lower in women.

Dosages (continued)

Drug	Bedtime Dose	Dose Adjustment	Availability
ramelteon (Rozerem)‡	8 mg 30 minutes prior to going to bed	--	Tablet: 8 mg
suvorexant (Belsomra)	10 mg Take within 30 minutes of going to bed, with ≥ 7 hours remaining before the planned time of awakening	Dose can be increased to 20 mg if the 10 mg dose is well-tolerated but not effective	Tablet: 5 mg, 10 mg, 15 mg, 20 mg
tasimelteon (Hetlioz, Hetlioz LQ)	**N24SWD in adults:** 20 mg capsule **SMS:** *Ages ≥ 16 years:* 20 mg capsule *Ages 3 to 15 years weighing > 28 kg:* 20 mg oral suspension *Ages 3 to 15 years weighing ≤ 28 kg:* 0.7 mg/kg oral suspension Administer dose 1 hour before bedtime, at the same time every night; Take without food	--	Capsule: 20 mg Oral suspension: 4 mg/mL Capsules and oral suspension are not interchangeable
temazepam (Restoril)	7.5 mg to 30 mg	Elderly and debilitated: start at 7.5 mg until responses are determined	Capsule: 7.5 mg, 15 mg, 22.5 mg, 30 mg
triazolam (Halcion)	0.125 mg to 0.5 mg	Elderly or debilitated: 0.125 mg to 0.25 mg	Tablet: 0.125 mg (generic only), 0.25 mg
zaleplon¶	10 mg to 20 mg; may use 5 mg for low-weight patient May be taken immediately before bedtime or after in bed and having difficulty falling asleep	Elderly, low-weight, or hepatic impairment: 5 mg to 10 mg Use with cimetidine: 5 mg (initially) Mild to moderate hepatic impairment: 5 mg	Capsule: 5 mg, 10 mg
zolpidem* (Ambien, Edluar, Zolpimist)	**Men:** 5 mg or 10 mg **Women†:** 5 mg Use the lowest dose effective for patient. Should be taken immediately before bedtime with at least 7–8 hours remaining before the planned time of awakening The 5 mg dose can be increased to 10 mg, if needed, but the higher dose is more likely to impair next morning driving and other activities that require full alertness. The total dose should not exceed 10 mg once daily.	Elderly, debilitated, or hepatic insufficiency: 5 mg once daily in both men and women immediately before bedtime Concurrent CNS depressants: dosage adjustment may be necessary	Tablet: 5 mg, 10 mg Sublingual Tablet: 5 mg, 10 mg Oral Spray: 5 mg (30 and 60 metered-doses)

* Should be taken on empty stomach to avoid delayed onset of action.

† The recommended initial doses for women and men are different because clearance is lower in women.

‡ Due to a 31% increase in bioavailability when given with a high-fat meal, ramelteon (Rozerem) should not be taken with or immediately after such a meal.

¶Taking zaleplon or eszopiclone (Lunesta) with or immediately after a heavy, high-fat meal results in slower absorption and would be expected to reduce its effect on sleep latency.

Dosages (continued)

Drug	Bedtime Dose	Dose Adjustment	Availability
zolpidem ER (Ambien CR)*	**Men:** 6.25 mg or 12.5 mg **Women:** 6.25 mg Use the lowest dose effective for patient. Should be taken immediately before bedtime with at least 7 to 8 hours remaining before the planned time of awakening The 6.25 mg dose can be increased to 12.5 mg, if needed, but the higher dose is more likely to impair next morning driving and other activities that require full alertness. The total dose should not exceed 12.5 mg daily.	Elderly, debilitated, or hepatic insufficiency: 6.25 mg once daily in both men and women immediately before bedtime Concurrent CNS depressants: dosage adjustment may be necessary	Tablet: 6.25 mg, 12.5 mg
zolpidem sublingual*	**Men:** 3.5 mg **Women:** 1.75 mg Take if there is more than 4 hours remaining before planned time of waking	Elderly, hepatic insufficiency, concurrent CNS depressants: 1.75 mg	Sublingual Tablets: 1.75 mg, 3.5 mg

* Should be taken on empty stomach to avoid delayed onset of action.

Since many of the adverse effects to the sedative/hypnotics appear to be dose-related, therapy should usually be initiated with a low dose and then maintained at the lowest effective dose, especially in the elderly.

Continuous use should be avoided; patients should be encouraged to use these medications only when necessary. Use for more than 3 weeks should be avoided and monitored if a longer duration is necessary. These drugs should never be combined with alcohol consumption.

CLINICAL TRIALS

Search Strategies

Articles were identified through searches performed on PubMed and review of information sent by manufacturers. Search strategy included the use of all drugs in this class. Randomized, controlled comparative trials for FDA-approved indications are considered the most relevant in this category. Studies included for analysis in the review were published in English, performed with human participants, and randomly allocated participants to comparison groups. In addition, studies must contain clearly stated, predetermined outcome measure(s) of known or probable clinical importance, use data analysis techniques consistent with the study question, and include follow-up (endpoint assessment) of ≥ 80% of participants entering the investigation. Despite some inherent bias found in all studies including those sponsored and/or funded by pharmaceutical manufacturers, the studies in this therapeutic class review were determined to have results or conclusions that do not suggest systematic error in their experimental study design. While the potential influence of manufacturer sponsorship and/or funding must be considered, the studies in this review have also been evaluated for validity and importance. Many of the trials with agents in this class were performed in an open-label manner; introduction of bias must be considered when evaluating study findings.

Comparisons of Benzodiazepines

estazolam versus flurazepam

The hypnotic efficacy of estazolam 1 mg and 2 mg was compared to flurazepam 30 mg and placebo in a randomized, double-blind, 7-night study that involved 223 patients with insomnia.[163] On subjective assessments of the patients, no differences were noted between estazolam 2 mg and flurazepam 30 mg on any of 6 sleep parameters. Patients who received estazolam 1 mg rated their sleep significantly better than did patients who were receiving placebo on all parameters except sleep onset latency (SOL). Global evaluation of the physicians indicated significant improvement in quality of sleep, sleep duration, and nocturnal awakenings in all 3 active treatment groups; estazolam 2 mg and flurazepam 30 mg decreased SOL significantly. Adverse events were reported by 54% of patients receiving estazolam 1 mg, 58% of those receiving estazolam 2 mg, and 68% of those receiving flurazepam 30 mg. The incidence of adverse events in the placebo group was 43%.

In a double-blind trial, 229 patients with insomnia were randomized to receive estazolam 2 mg, flurazepam 30 mg, or placebo for 7 consecutive nights.[164] The analysis of efficacy was based on patients' daily assessments of sleep and investigators' global evaluations. The patient subjective questionnaire indicated that estazolam and flurazepam significantly improved all parameters ($p<0.05$) as compared to placebo. A marked or moderate improvement in sleep was reported by 81%, 78%, and 36% estazolam, flurazepam, and placebo recipients, respectively. There were no significant differences in hypnotic effect between estazolam and flurazepam. All efficacy parameters of the investigators' global evaluation, except quality of sleep, improved significantly more ($p<0.05$) for patients receiving estazolam or flurazepam than for those receiving placebo. The percentage of patients reporting any adverse experience was 59% for estazolam, 72% for flurazepam, and 43% for placebo. Somnolence and hypokinesia were the most commonly reported adverse events. An analysis of the global evaluation of side effects showed that flurazepam had a significantly worse side effect profile than estazolam ($p<0.05$) or placebo ($p=0.001$).

flurazepam versus quazepam (Doral)

Daytime residual drowsiness and psychomotor performance were assessed for quazepam and flurazepam in 2 randomized, parallel, double-blind studies in insomniacs.[165] In the first study, 17 middle-aged patients took quazepam 15 mg or 30 mg or flurazepam 30 mg nightly for 4 weeks. Subjects were given placebo for 4 nights before and 15 nights after active treatment. In the second study, 48 geriatric patients took quazepam 15 mg, flurazepam 15 mg, or placebo nightly for 1 week. Subjects were given placebo for 1 night before and 7 nights after active treatment. In the first study, flurazepam patients were significantly ($p<0.05$) sleepier the day after the 7th and 14th treatment nights when compared to baseline, whereas quazepam patients were not. In the second study, flurazepam patients were sleepier in the late afternoon ($p<0.05$) after the 7th treatment night than were quazepam and placebo patients. There were no significant differences among the groups in the performance test results.

quazepam versus triazolam (Halcion)

In a double-blind study, 45 patients were randomized to receive either quazepam 15 mg to 30 mg (median 15 mg) or triazolam 0.25 mg to 0.5 mg (median 0.25 mg) for 4 weeks.[166] The subjects, who had insomnia based on a mild to moderate generalized anxiety disorder, received placebo for 1 week before and 2 weeks after treatment with active drug. Anxiety improved significantly with both drugs

and remained improved throughout the 2-week post-drug placebo phase; quazepam was slightly superior to triazolam. Polysomnography, an objective measure of SOL, demonstrated a shortened sleep onset only after quazepam. Sleep efficiency improved after acute administration of both drugs, but improvement was maintained only by quazepam as tolerance developed to triazolam. Rebound insomnia was observed only in the first post-triazolam placebo night. Subjective sleep quality behaved very similarly to objective sleep efficiency. Awakening quality improved after acute therapy with both drugs. Somatic complaints were reported only with quazepam.

A randomized, double-blind, 3-compartment, parallel-group study comparing quazepam 15 mg, triazolam 0.5 mg, and placebo was conducted in 65 insomniac subjects over 5 weeks.[167] Using sleep questionnaires for evaluation, no differences were noted between quazepam and triazolam on treatment nights. Evidence of carryover effectiveness with quazepam and rebound effects with triazolam was noted on off-treatment nights.

Comparisons of Benzodiazepines and Non-benzodiazepines

temazepam versus zolpidem (Ambien)

A randomized, double-blind trial compared zolpidem 10 mg to temazepam 20 mg with respect to subjective rebound insomnia after cessation of 4 weeks of treatment of 163 patients with chronic insomnia.[168] Both agents improved total sleep time (TST), as well as SOL significantly during the 4 treatment weeks. Prevalence rates for rebound insomnia, defined as a worsening of TST or SOL of more than 40% compared to baseline, were 27% for TST and 53% for SOL in the zolpidem group and 26% and 58%, respectively, in the temazepam group. No significant differences were found between the agents for rebound insomnia, nor with respect to their efficacy or safety.

triazolam versus zaleplon

Zaleplon and triazolam were compared in a double-blind, placebo-controlled trial enrolling 132 patients with primary insomnia.[169] Patients received zaleplon 5 mg or 10 mg, triazolam 0.25 mg, or placebo for 14 nights. Median SOL was shorter in both zaleplon groups and triazolam group compared to placebo during the first week of therapy, but not during the second week due to a significant placebo effect. The effects of zaleplon on SOL were similar in the first and second weeks. Total sleep time did not differ between zaleplon and placebo groups. Total sleep time was increased during the first week of triazolam treatment, but not the second. On subjective assessment of SOL, zaleplon 10 mg and triazolam were more effective than placebo during the first week. Only zaleplon 10 mg produced lower subjective SOL during the second week. On the last night of assessment, none of the active treatments were judged more effective than placebo. Negative residual morning psychomotor or memory effects were not observed in any treatment group.

triazolam versus zolpidem (Ambien)

In a parallel-group, double-blind, placebo-controlled, polysomnographic study, the possible occurrence of rebound insomnia was evaluated in 24 patients suffering from moderate to severe chronic insomnia. Patients were randomized to either triazolam 0.5 mg, zolpidem 10 mg, or placebo.[170] Treatment duration was 27 nights, followed by 3 placebo-controlled withdrawal nights. Both drugs showed significant efficacy compared to placebo during the active treatment period. A trend toward tolerance was noted in the triazolam group but not in the zolpidem group. The increase in total sleep time in the zolpidem group was accompanied by an increase in the number of sleep cycles. When active treatment

was discontinued, clear rebound insomnia was present in the triazolam group while it was not possible to observe any rebound in the placebo and zolpidem groups. Subjective feelings of the patients assessed by means of visual analog scale correlated well with polysomnographic data.

Comparisons of Non-benzodiazepines

lemborexant (Dayvigo) versus zolpidem ER (Ambien CR)

A randomized, double-blind, parallel-group, placebo-controlled, active-comparator study (SUNRISE 1, NCT02783729) evaluated patients with a DSM-5 diagnosis of insomnia who reported sleep maintenance difficulties, with or without sleep onset difficulties.[171] Notably, the study included females ≥ 55 years of age and males ≥ 65 years of age. Patients were randomized for 1 month to receive placebo (n=208), zolpidem tartrate extended release (6.25 mg, n=263), or lemborexant (5 mg, n=266; 10 mg, n=269) nightly. The primary endpoint was the change from baseline in transformed latency to persistent sleep (LPS), as assessed by polysomnography, for lemborexant versus placebo. Secondary endpoints included changes from baseline in sleep efficiency (SEF) and wake after sleep onset (WASO) versus placebo as well as WASO in the second half of the night versus zolpidem. Lemborexant demonstrated statistical significance in sleep onset measured by LPS on nights 29 and 30 over placebo (lemborexant 5 mg treatment ratio, 0.77 [95% CI, 0.67 to 0.89; p<0.001]; lemborexant 10 mg treatment ratio, 0.72 [95% CI, 0.63 to 0.83; p<0.001]). There was a statistically significant improvement in SEF over placebo for both strengths of lemborexant as well as a reduction in WASO versus placebo. In the second half of the night, WASO also improved in patients treated with lemborexant versus zolpidem extended-release (lemborexant 5 mg LSM treatment difference versus zolpidem, -6.7 min [95% CI -11.2 to -2.2; p=0.004]; lemborexant 10 mg LSM treatment difference versus zolpidem, -8 min [95% CI, -12.5 to -3.5; p<0.001].

zaleplon versus zolpidem (Ambien)

In a double-blind study, 615 patients were randomized to receive zaleplon 5 mg, zaleplon 10 mg, or zaleplon 20 mg, zolpidem 10 mg, or placebo.[172] The 4-phase study consisted of a pre-study washout period (1-3 weeks), a single-blind placebo run-in period (7 nights), a double-blind treatment period (28 nights), and a single-blind placebo run-out period (3 nights). In the 574 patients who completed the study, zolpidem significantly reduced SOL during weeks 1 through 3, as did zaleplon 5 mg. Zaleplon 20 mg and zolpidem 10 mg significantly increased sleep duration during all 4 weeks of the double-blind treatment. No significant differences were observed in number of awakenings between the placebo and active treatment groups during the double-blind treatment periods. Scores for sleep quality were significantly better than placebo during week 1 with zaleplon 10 and 20 mg and for all weeks with zolpidem 10 mg. On the first night after treatment discontinuation, significantly more patients who received zolpidem experienced longer SOL relative to baseline and reported withdrawal effects (depressed mood, pain in muscles, peculiar taste, loss of memory, olfactory sensitivity). The most common adverse event in all treatment groups was headache. There were no significant differences in the frequency of treatment-emergent adverse events among the active treatment groups and the placebo group.

A randomized, double-blind, placebo-controlled, 3-period, crossover design was used to study 37 adults with insomnia who received treatment during an experimental awakening 4 hours after bedtime.[173] The study objective was to assess the efficacy of zaleplon 10 mg and zolpidem 10 mg administered during experimental middle-of-the-night awakenings in patients with sleep maintenance insomnia using

objective polysomnographic measures and to assess daytime residual sedation 4 to 7 hours after dosing using sleep latency testing. Latency to persistent sleep and total sleep time before and after awakening were recorded. Compared with placebo, latency to persistent sleep after both zaleplon and zolpidem was shorter and total sleep time after administration of the drugs was longer. Significant differences from placebo were not found with zaleplon in daytime sedation measures. At 4, 5, and 7 hours after zolpidem, sleep onset, measured by sleep latency testing, was shorter than after placebo. Self-reported measures of concentration and alertness and Digit Symbol Substitution Test scores after zolpidem were also lower than placebo. Zaleplon 10 mg and zolpidem 10 mg effectively shorten sleep latency and lengthen sleep duration after dosing when administered during experimental nocturnal awakening. Residual sedation was not detected as little as 4 hours after zaleplon 10 mg, but was detected with zolpidem 10 mg up to 7 hours after treatment.

Placebo-controlled Trials of Non-benzodiazepines

doxepin (Silenor) versus placebo

A randomized, double-blind, parallel-group, placebo-controlled study was conducted in healthy adults with transient insomnia.[174] Subjects received a single nighttime dose of placebo (n = 282) or doxepin 6 mg (n = 283) in a sleep laboratory. Efficacy was evaluated objectively by polysomnography and subjectively by morning questionnaire. The primary endpoint was latency to persistent sleep (LPS). Secondary polysomnography endpoints included wake after sleep onset (WASO), total sleep time (TST), wake time after sleep (WTAS), and sleep efficiency (SE). Doxepin demonstrated statistically significant improvements in LPS (13-minute decrease; $p<0.0001$), WASO (39 minutes less; $p<0.0001$), TST (51 minutes more; $p<0.0001$), WTAS ($p<0.0001$), overall SE ($p<0.0001$), and SE in each quarter of the night ($p<0.0001$), all versus placebo. There was no consistent evidence of residual sedation or minor sleep stage alterations. The incidence of doxepin adverse events was comparable to placebo.

A randomized, double-blind, parallel-group, 5-week placebo-controlled trial was conducted in adults diagnosed with primary insomnia and reported difficulty maintaining sleep (n = 229).[175] Wake time after sleep onset (WASO) on the first night was identified as the primary outcome measure, and both active doses (3 mg and 6 mg) resulted in statistically significant reductions in WASO ($p< 0.0001$). Subsequent WASO measurements were also statistically significant including on night 15 (3 mg $p=0.0025$; 6 mg $p=0.0009$), and night 29 (3 mg $p=0.00248$; 6 mg $p=0.0009$). Other secondary endpoints with significant improvement compared to placebo included latency to persistent sleep (3 mg $p=0.0047$; 6 mg $p=0.0007$) on night 1 only, and Total Sleep Time on nights 1 (both doses $p<0.0001$), and 29 (3 mg $p=0.0261$; 6 mg $p<0.0001$). Although most measures were statistically significant, 2 measures did not reach significance for the 3 mg capsule. Both Sleep efficiency (SE) on the 29th night and total sleep time on night 15 did not reach statistical significance. In contrast to benzodiazepine and other non-benzodiazepine hypnotics, there was no evidence of rebound insomnia when doxepin was discontinued.

eszopiclone (Lunesta) versus placebo

A double-blind study enrolled 308 patients, 21 to 64 years of age, with primary chronic insomnia.[176,177] Patients were randomized to receive eszopiclone 2 mg, eszopiclone 3 mg, or placebo for 44 consecutive nights followed by 2 nights of single-blind placebo. Treatment with either dose of eszopiclone resulted in an approximate 45-minute improvement in the primary endpoint of SOL (placebo 58 minutes; $p<0.001$ for both doses). Eszopiclone also significantly improved the secondary

endpoint of sleep efficiency (p<0.0001 for both doses compared to placebo). Another secondary endpoint, wake time after sleep onset (WASO), was reduced only by the higher dose of eszopiclone (41.2 minutes) compared to placebo (49.1 minutes; p=0.02). There was no evidence of tolerance or rebound insomnia after therapy discontinuation. There was no decrement in psychomotor performance relative to baseline, nor was there a difference between eszopiclone and placebo. The most common adverse event related to eszopiclone was unpleasant taste.

A double-blind study randomized 231 patients, 65 to 85 years of age, with chronic insomnia to receive either eszopiclone 1 mg, eszopiclone 2 mg, or placebo nightly for 2 weeks.[178,179,180] In the study, the higher dose of eszopiclone improved sleep maintenance (p<0.05), total sleep time (by 40 minutes; p<0.001), quality of sleep (p<0.001), depth of sleep (p<0.002), and reduced the number of naps (median 0 versus 2, p<0.05) compared to placebo. Patients receiving the higher dose also reported significant improvements in daytime alertness, daytime ability to function, sense of well-being, and reduced morning sleepiness (p<0.05 for all comparisons to placebo). Both doses of eszopiclone were effective at decreasing SOL (p<0.004 compared to placebo) and reducing total nap time (p<0.05 compared to placebo).

In a double-blind study, 264 patients, 65 to 85 years of age, with a diagnosis of primary insomnia were randomized to receive eszopiclone 2 mg or placebo nightly for 2 weeks.[181] Compared with placebo, eszopiclone 2 mg significantly reduced objective (polysomnographic) and subjective SOL ([p<0.0001 for both measurements] and [p<0.05 and p=0.0019, respectively]). Subjective improvement was also noted in sleep efficiency (p<0.04), total sleep time (p<0.0001), and the cumulative number and duration of naps among patients who napped (p=0.03) compared to placebo. Eszopiclone also produced improvements in the quality of sleep and in physical functioning. There was no rebound insomnia after treatment withdrawal, and the most common adverse event was unpleasant taste.

In a double-blind study, investigators randomized 545 patients with insomnia and major depressive disorder to receive, in addition to daily fluoxetine, eszopiclone 3 mg or placebo nightly.[182] In the 8-week study, patients treated with eszopiclone showed improvements in the primary endpoint, wake time after sleep onset ($p \leq 0.002$), compared to those receiving placebo. The active treatment was also more effective than placebo in improving the secondary endpoints of SOL ($p \leq 0.0001$) and TST ($p \leq 0.0004$). Patients in the eszopiclone group reported superior subjective improvements in sleep quality ($p \leq 0.0002$), depth of sleep ($p \leq 0.0007$), daytime alertness (p=0.03), clarity of thought and concentration (p=0.02), and ability to function (p=0.007). Patients in the eszopiclone group demonstrated significantly greater improvement in symptoms of depression, as measured by HAM-D17 (Hamilton Depression Rating Scale), at weeks 4 (p=0.01) and 8 (p=0.002). HAM-D17 response were noted in 59% of patients in the eszopiclone group compared to 48% of patients in the placebo group; remission rates were 42% and 33%, respectively (p=0.03). Study completion rates and treatment tolerability were similar between groups.

A multicenter, randomized, double-blind, placebo-controlled trial evaluating eszopiclone treatment upon patient-reported sleep, fatigue and sleepiness, insomnia severity, quality of life, and work limitations for 6 months.[183] A total of 830 patients with primary insomnia, who reported mean nightly total sleep time $\leq$ 6.5 hours/night and/or mean nightly sleep latency > 30 minutes, were randomized to eszopiclone 3 mg or matching placebo for 6 months. Patient-reported sleep and daytime function, Insomnia Severity Index, Physical Functioning, Vitality, and Social Functioning, and Work Limitations Questionnaire domain scores were improved with eszopiclone versus placebo (all p<0.05).

lemborexant (Dayvigo) versus placebo

A multicenter, randomized, double-blind, placebo-controlled trial (SUNRISE 2, NCT02952820) assessed the efficacy of lemborexant in adult patients with a DSM-5 diagnosis of insomnia.[184] Patients were randomized to placebo (n=325), lemborexant 5 mg (n=323), or lemborexant 10 mg (n=323) once nightly, and patients reported their outcomes in a sleep diary. The primary endpoint was the mean change from baseline to end of treatment at 6 months for patient-reported sleep onset latency (SOL), defined as the estimated number of minutes from the time patient attempted to sleep until onset of sleep. Secondary endpoints included change from baseline to end of treatment for patient-reported sleep efficiency (SEF) and wake after sleep onset (WASO). Lemborexant demonstrated statistical superiority in the primary efficacy measure over placebo at 1 month. Lemborexant improved SOL versus placebo (lemborexant 5 mg SOL treatment effect ratio, 0.7 [95% CI, 0.6 to 0.8; p<0.05]; lemborexant 10 mg SOL treatment effect ratio, 0.7 [95% CI, 0.6 to 0.8; p<0.05]). For the secondary endpoints, lemborexant also showed statistically significant superiority over placebo (lemborexant 5 mg SEF treatment difference from placebo, 4.5% [95% CI, 2.2 to 6.9; p<0.05]; lemborexant 10 mg SEF treatment difference from placebo, 4.7% [95% CI, 2.4 to 7; p<0.05]). There was also a greater improvement in WASO versus placebo (lemborexant 5 mg WASO treatment difference from placebo, -17.5 min [95% CI, -27.3 to -7.6; p<0.05]; lemborexant 10 mg WASO treatment difference from placebo, -12.7 min [95% CI, -22.4 to -3; p<0.05]).

ramelteon (Rozerem) versus placebo

In a double-blind study, investigators randomized 829 elderly patients (mean age 72.4 years) with chronic primary insomnia to either ramelteon 4 mg, ramelteon 8 mg, or placebo nightly for 5 weeks.[185] Administration of ramelteon resulted in a reduction in subjective SOL and an increase in TST at weeks 1, 3, and 5 of the study. Ramelteon did not change subjective sleep quality, the number of night time awakenings, or the ease of falling back to sleep. Withdrawal effects, including rebound insomnia, were not observed.

In a double-blind study, 405 patients (mean age 39.3 years) with primary insomnia were randomized to receive ramelteon 8 mg, ramelteon 16 mg, or placebo nightly for 35 nights.[186] Polysomnography indicated that both doses of ramelteon were associated with a reduction in SOL at each assessment starting on nights 1 and 2. Ramelteon was also associated with an improvement in TST and sleep efficiency on nights 1 and 2.

A 6-month, randomized, double-blind, placebo-controlled, multicenter study evaluated the long-term efficacy of ramelteon for insomnia in 451 adults (age ≥ 18 years) with chronic primary insomnia.[187] Patients were randomized to receive either ramelteon 8 mg or placebo 30 minutes before bedtime nightly for 6 months. Sleep was evaluated by polysomnography and morning questionnaires on the first 2 nights of week 1; the last 2 nights of months 1, 3, 5, and 6; and nights 1 and 2 of the placebo run-out. Next-morning residual effects, as well as adverse effects and vital signs, were recorded at each visit. Rebound insomnia and withdrawal effects were evaluated during placebo run-out. During the 6 months of treatment, ramelteon consistently reduced latency to persistent sleep compared with baseline and with placebo; significant decreases were observed at week 1 and months 1, 3, 5, and 6 (p<0.05). Ramelteon significantly reduced subjective sleep latency relative to placebo at week 1, month 1, and month 5 (p<0.05), with reductions nearing statistical significance at months 3 and 6 (p≤0.08). No significant next-morning residual effects were detected during ramelteon treatment. No withdrawal

symptoms or rebound insomnia were detected after ramelteon discontinuation. Most adverse events were mild or moderate in severity.

suvorexant (Belsomra) versus placebo

In 3 clinical trials, suvorexant was evaluated in patients with insomnia characterized by sleep onset and sleep maintenance difficulties.[188] Non-elderly patients (age 18 to 64) and elderly patients (age ≥ 65) were randomized separately in 2 similarly designed, 3-month, randomized, double-blind, placebo-controlled, parallel-group studies. For the studies together, there were 465 female and 275 male non-elderly adults with a mean age of 46 years treated with 20 mg suvorexant (n = 291) or placebo (n = 449). Elderly patients with a mean age of 71 years including 346 female and 174 male patients were treated with 15 mg suvorexant (n = 202) or placebo (n = 318). In both studies, both suvorexant 15 mg and 20 mg were superior to placebo for sleep latency assessed objectively by polysomnography, as well as subjectively by patient-estimated sleep latency. Efficacy was similar for males and females and for Caucasians and non-Caucasians, based on the limited data. These doses were also superior to placebo for sleep maintenance as assessed objectively by polysomnography, as well as subjectively by patient-estimated total sleep time. In these 2 studies, suvorexant was also evaluated at doses of 30 mg and 40 mg. The higher doses had similar efficacy to the lower doses; however, there were more side effects reported at the higher doses.

The third study was a 1-month crossover study, that involved non-elderly adults, ages 18 to 64 years, with a mean age of 44 years, treated with placebo (n = 249) and suvorexant at a dose of 10 mg (n = 62), 20 mg (n = 61) or up to 80 mg. Both 10 mg and 20 mg were superior to placebo for sleep latency and sleep maintenance, both assessed objectively by polysomnography.

There were also special safety studies for suvorexant to evaluate effects on driving, next-day memory and balance in elderly and non-elderly patients, middle of the night safety in elderly patients, rebound effects, withdrawal effects, and respiratory safety.

tasimelteon capsule (Hetlioz) versus placebo

The effectiveness of tasimelteon was evaluated in 104 patients in 2 randomized, double-masked, placebo-controlled, clinical trials of totally blind individuals with non-24-hour sleep-wake disorder (non-24) disorder.[189,190] Patients were randomized to receive tasimelteon or placebo 1 hour prior to bedtime, at the same time every night. In Study 1 (Safety and Efficacy of Tasimelteon [SET]), 84 patients with non-24 were randomized to receive tasimelteon 20 mg or placebo, 1 hour prior to bedtime, at the same time every night for up to 6 months. Study 2 (Randomized Withdrawal Study of the Efficacy and Safety of Tasimelteon [RESET]) was a randomized withdrawal trial in that evaluated tasimelteon (n = 10) compared to placebo (n = 10), in patients with non-24 to evaluate the maintenance of efficacy. Patients were treated initially for approximately 12 weeks. Patients in whom the calculated time of peak melatonin level occurred at approximately the same time of day (in contrast to the expected daily delay) during the run-in phase were randomized to receive placebo or continue treatment for 8 weeks. Study 1 and Study 2 evaluated the duration and timing of night time sleep and daytime naps via patient-recorded diaries. Because symptoms of night time sleep disruption and daytime sleepiness are cyclical in patients with non-24, with severity varying, efficacy endpoints for night time total sleep time and daytime nap duration were based on the 25% of nights with the least night time sleep, and the 25% of days with the most daytime nap time. In Study 1, at baseline, patients had an average 195 minutes of night time sleep and 137 minutes of daytime nap time on the 25% of most symptomatic nights and days, respectively. Treatment with tasimelteon resulted in a

significant improvement, compared with placebo. In Study 1, mean total night time sleep was 28 minutes longer and daytime nap time was 27 minutes shorter in the tasimelteon group compared to placebo. In Study 2, synchronization was maintained in 90% of the tasimelteon group versus 20% of placebo. Mean total night time sleep was 67 minutes longer and daytime nap time was 59 minutes shorter in the tasimelteon group compared to placebo. A responder analysis of patients with both ≥ 45 minutes increase in night time sleep and ≥ 45 minutes decrease in daytime nap time was conducted in Study 1: 29% (n = 12) of patients treated with tasimelteon, compared with 12% (n = 5) of patients treated with placebo met the responder criteria.

tasimelteon (Hetlioz, Hetlioz LQ) versus placebo

In a 9-week, double-blind, randomized, placebo-controlled, crossover study in 25 adults and pediatric patients with nighttime sleep disturbances in SMS, patients ≥ 16 years of age received tasimelteon 20 mg capsules and patients 3 to 15 years of age received a weight-based dose of tasimelteon oral suspension.[191] The study consisted of two 4-week periods during which time patients were instructed to take the study drug 1 hour before bedtime. The periods were separated with a 1-week washout interval. The primary endpoints were nighttime total sleep time and nighttime sleep quality as recorded by a parent/guardian. Nighttime sleep quality was rated on a 5-point scale (1=poor, 5=excellent). The efficacy comparisons for both endpoints were based on the 50% of nights with the worst sleep quality and the 50% of nights with the least nighttime sleep. At baseline, the mean quality score was 2.1 and the total sleep time was 6.4 hours, each based on the 50% of nights with worst sleep quality or least nighttime sleep, respectively. At completion of the study, the mean score of worst daily nighttime sleep quality was 2.8 with tasimelteon and 2.4 with placebo, and the difference was statistically significant (difference, 0.4; 95% CI, 0.1 to 0.7). However, the difference in mean worst daily nighttime total sleep time between the groups was not significant (mean, 7 hours with tasimelteon and 6.7 hours with placebo; difference, 0.3 hours; 95% CI, 0 to 0.6).

zolpidem sublingual versus placebo

A randomized, double-blind, placebo-controlled, 3-way crossover study evaluated the efficacy and safety of low-dose, sublingual zolpidem tartrate when taken during a scheduled middle-of-the-night (MOTN) awakening in subjects with insomnia characterized by difficulty returning to sleep following MOTN awakenings.[192] The study was performed at 5 sleep laboratories and enrolled adults (24 males, 58 females, mean age 45.9 years) with a diagnosis of DSM-IV primary insomnia and a history of prolonged MOTN awakenings. Baseline difficulties with MOTN awakenings were confirmed by a 10-day screening sleep diary and polysomnography (PSG) screening. Each treatment period consisted of 2 consecutive nights of dosing separated by a washout period of 5 to 12 days. Subjects were awakened 4 hours after lights out, dosed with sublingual zolpidem 3.5 mg, zolpidem 1.75 mg, or placebo, kept awake for 30 minutes, and then returned to bed for an additional 4 hours. Sleep parameters were assessed by PSG and post-sleep questionnaires. Results demonstrated that low-dose sublingual zolpidem tartrate demonstrated significant dose-related decreases in latency to persistent sleep and total sleep time ($p<0.001$) compared to placebo after MOTN dosing. All subject reports paralleled PSG observations. Neither dose showed next-morning impairment on the digit symbol substitution test (DSST) or ratings of sleepiness. The 3.5-mg dose produced improvements in reports of sleep quality ($p<0.001$), ability to function, and level of refreshed sleep ($p<0.05$ for both dosages) compared to placebo. Sublingual zolpidem tartrate lozenges were generally safe and well tolerated.

In a randomized, double-blind, placebo-controlled outpatient as-need study, adults aged 18 to 64 years (n = 295; 201 female; 94 male) with a history of problems returning to sleep after MOTN awakenings were evaluated in a 4-week study using zolpidem tartrate.[193,194] Patients used either 3.5 mg zolpidem tartrate or placebo (as needed) following episodes of MOTN waking with difficulties in returning to sleep. Patients were required to have at least 4 hours of time to remain in bed following zolpidem dosing. The results were patient evaluations of the time to return to sleep following as needed dosing were significantly shorter for zolpidem 3.5 mg than placebo.

zolpidem (Zolpimist) versus placebo

In a double-blind, parallel-group, single-night trial in adults experiencing transient insomnia (n = 462), zolpidem 7.5 mg or 10 mg or placebo were compared.[195] Both zolpidem doses were superior to placebo by measure of sleep latency, sleep duration, and number of awakenings.

zolpidem ER (Ambien CR) versus placebo

Two similar 3-week studies of zolpidem ER were conducted in patients with primary insomnia.[196,197] One study randomized 205 elderly patients (mean age 70.2 years) to zolpidem ER 6.25 mg or placebo while the other randomized 212 adults (mean age 44.3 years) to zolpidem ER 12.5 mg or placebo. In each study, zolpidem ER was found to lead to significant improvement compared to placebo in polysomnographic WASO in the first 6 hours of the night, as well as improvement in SOL and TST. Subjects did not report any residual impairment or sedation.

META-ANALYSES

A meta-analysis of clinical trials submitted to the FDA assessed the efficacy of eszopiclone, zaleplon, and zolpidem compared to placebo for the treatment of insomnia in adults (13 trials; n = 4,378).[198] Overall, these agents had significant but minimal improvements in the following primary outcomes: effect size

Other meta-analyses also have found minimal differences with regard to efficacy of benzodiazepines and the non-benzodiazepine hypnotics, but are limited by treatment duration (e.g., zaleplon, zolpidem, eszopiclone).[199,200,201]

SUMMARY

The selection of a specific hypnotic is based in large part on whether the patient has problems with initiation or maintenance of sleep, co-morbid conditions, side effect tolerance, and availability. Sedative hypnotics should be prescribed at the lowest dose that treats the patients' symptoms.

The assumed increased risk with benzodiazepine medications over non-benzodiazepines is based on indirect comparisons, and there is evidence of publication bias as both groups have increased incidence of adverse risks in patients over 60 years of age.

Benzodiazepines are Scheduled IV controlled substances. In general, the benzodiazepines decrease the time for sleep onset and prolong the duration of sleep, although dependence, tolerance, and abuse may occur. Among the benzodiazepines, the duration of action is the primary variable that may make 1 preferable to another in a given patient. Triazolam (Halcion) has the shortest duration of action, while temazepam (Restoril) and estazolam have intermediate durations. Flurazepam and quazepam (Doral) have long durations of effect and, as a result, should be avoided in the elderly or others in whom daytime impaired function may be a concern.

Eszopiclone (Lunesta), lemborexant (Dayvigo), suvorexant (Belsomra), zaleplon, zolpidem (Ambien, Ambien CR, Edluar, zolpidem sublingual, Zolpimist) are also Scheduled IV controlled substances. Patients with a history of addiction to, or abuse of, drugs or alcohol are at increased risk for misuse, abuse and addiction these agents; patients should be monitored carefully when taking these agents. Doxepin (Silenor), ramelteon (Rozerem), and tasimelteon (Hetlioz) are not controlled substances and are not associated with abuse or physical dependence.

Eszopiclone (Lunesta), zaleplon, and zolpidem (Ambien, Ambien CR, Edluar, zolpidem sublingual, Zolpimist) carry a boxed warning for complex sleep behaviors when used as prescribed. These activities include sleep-walking, sleep-driving, or other complex activities that normally occur with wakefulness, that may lead to serious injury or death. Patients do not usually recall these events. The medication that contributed to the complex sleep behavior should be discontinued and not restarted.

Rebound insomnia may develop when benzodiazepines are abruptly withdrawn and is more likely to occur with the short-acting benzodiazepines. Rebound insomnia can be minimized by using smaller doses and tapering the dosage. Some studies have highlighted concerns with increased falls and hip fractures in the elderly following benzodiazepine use; however, others have found that untreated insomnia itself increases the risk of falls.

Similar to the benzodiazepines, the BZ-1 selective agents decrease sleep latency with duration of action again being the primary difference among these agents. Although dependence, tolerance, and abuse may occur with these agents, next day sedation, rebound insomnia, and drug interactions are generally lessened. For the BZ-1 selective agents, zaleplon is more rapid acting with a shorter duration than zolpidem tablets (Ambien, Ambien CR). Eszopiclone (Lunesta) has a longer half-life than either zaleplon or zolpidem. Specialized formulations of zolpidem (Edluar, zolpidem sublingual, Zolpimist) do not have a significant clinical advantage over tablets. Additionally, due to gender differences in zolpidem clearance, women require lower doses of zolpidem.

Doxepin (Silenor) appears to have some success in treating insomnia, particularly in cases where sleep latency and not sleep initiation is the issue. Patients experiencing problems with sleep latency who have not achieved success with more common sedative/hypnotic agents may benefit from doxepin. However, in general, no data are present to suggest doxepin is superior to other agents in this class.

The melatonin receptor agonist, ramelteon (Rozerem), has demonstrated reduction in sleep latency, but not in sleep maintenance. Patient evaluations are inconsistent, and there are no direct comparative studies. There is a low likelihood of dependence or abuse, and adverse effects are rare.

Tasimelteon (Hetlioz, Hetlioz LQ) is a melatonin receptor agonist pharmacologically similar to ramelteon (Rozerem). Tasimelteon capsule (Hetlioz) is approved for non-24 in totally blind adults and for nighttime sleep disturbances in Smith-Magenis Syndrome (SMS) in patients ≥ 16 years of age. Newly approved tasimelteon oral suspension (Hetlioz LQ) is indicated for nighttime sleep disturbances in SMS in pediatric patients 3 years to 15 years of age only. Tasimelteon capsules (Hetlioz) and oral suspension (Hetlioz LQ) are not interchangeable. Due to differences in circadian rhythms, it can take weeks or months of daily use of tasimelteon before the patient experiences any benefit. Comparisons to ramelteon or melatonin are lacking.

Lemborexant (Dayvigo) and suvorexant (Belsomra), orexin receptor antagonists, have shown better sleep latency and/or sleep maintenance compared to placebo. There is no evidence that suvorexant offers significant advantages over existing drugs. When compared to zolpidem ER, lemborexant

reduced wake after sleep onset, especially in the second half of the night in a clinical trial of patients ≥ 55 years of age; however, there is no clear clinical advantage over other sedative hypnotics for the management of insomnia.

Current treatment guidelines for insomnia do not recommend one agent within this class over another; rather, they suggest that treatment should be individualized.

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