Therapeutic Class Overview
Sedative Hypnotics

Therapeutic Class

- **Overview/Summary:**
  Insomnia is the most common sleep disorder in adulthood, affecting 33 to 69% of the population. It is estimated that five to ten percent of adults experience specific insomnia disorders.[1,2] Insomnia is a disorder that results from a difficulty in initiating or maintaining sleep, waking too early, or sleep that is considered nonrestorative or poor quality.[1-3] Furthermore, individuals with insomnia must also report at least one of the following types of daytime impairment as a result of the difficulties experienced with sleep: fatigue/malaise; impairment in memory, attention, or concentration; social or work-related dysfunction; poor school performance; irritability; day time sleepiness; loss of motivation, energy, or initiative; increased tendency for work or driving related accidents/errors; tension headaches; gastrointestinal symptoms; or concerns/worries about sleep. In individuals with insomnia, these complaints occur despite having sufficient opportunity and circumstances for sleep.[1,2] According to the International Classification of Sleep Disorders, insomnia may be classified as one of the following: short-term insomnia, chronic insomnia or other insomnia (defined as patients who experience difficulty initiating or maintaining sleep but do not meet all of the criteria for either short-term or chronic insomnia).[2]

  There are several classes of medications available for the management of insomnia.[4-6] Doxepin (Silenor®) is a tricyclic antidepressant that is Food and Drug Administration (FDA)-approved for the treatment of insomnia characterized by difficulties with sleep maintenance. The exact mechanism by which doxepin exerts its therapeutic effect on insomnia has not been elucidated; however, it is most likely due to antagonism of the histamine-1 receptor.[7] Ramelteon (Rozerem®) is a melatonin agonist that binds to melatonin receptors with much higher affinity compared to melatonin.[8] Similar to ramelteon, tasimelteon (Hetlioz®) is also a melatonin agonist and it is indicated for the treatment non-24 hour sleep-wake disorder, a disorder that is characterized by the extension of the natural sleep-wake cycle beyond 24 hours.[9] Suvorexant (Belsomra®) belongs to a novel class of orexin receptor antagonists and is thought to suppress the wake-drive by blocking the binding of wake-promoting neuropeptides.[10] Doxepin, ramelteon, tasimelteon and suvorexant are not available generically; however; doxepin is available generically in higher doses that are approved for the treatment of depression and anxiety.[6] Benzodiazepines relieve insomnia by reducing sleep latency and increasing total sleep time. Benzodiazepines increase stage two sleep while decreasing rapid eye movement sleep, stage three and stage four sleep.[5] The benzodiazepines bind to γ-aminobutyric acid subtype A ($GABA_A$) receptors in the brain, thereby stimulating GABAergic transmission and hyperpolarization of neuronal membranes.[5] The benzodiazepines primarily differ in their duration of action. Triazolam (Halcion®) has a short duration of action, while estazolam (ProSom®) and temazepam (Restoril®) are intermediate-acting agents. Flurazepam (Dalmane®) and quazepam (Doral®) are generally considered long-acting benzodiazepines.[11-15] All of the benzodiazepines are available generically with the exception of quazepam.[6] The nonbenzodiazepine sedative hypnotics are structurally distinct from the benzodiazepines resulting in more specific activity at the $GABA_A$ receptor. As a result, the nonbenzodiazepine sedative hypnotics are associated with less anxiolytic and anticonvulsant activity compared to the benzodiazepines.[4] Zaleplon (Sonata®) has a duration of approximately one hour, and thus is an effective treatment for patients with difficulty falling asleep.[16] Zolpidem has a duration of less than two and a half hours and may also be useful for patients with difficulties initiating sleep. Zolpidem is available in as an immediate-release tablet (Ambien®), oral spray (Zolpimist®), sublingual tablet (Edluar® and Intermezzo®) and extended-release tablet (Ambien CR®). The sublingual tablet (Intermezzo®) is the only zolpidem formulation that is approved for the treatment of insomnia due to middle-of-the-night awakenings.[17-21] Of the nonbenzodiazepine sedative hypnotics, eszopiclone (Lunesta®) has the longest half-life (approximately five to seven hours); therefore it is effective in treating sleep onset insomnia and sleep maintenance insomnia.[22] Currently zaleplon, eszopiclone and zolpidem (immediate-release and extended-release tablets) are available generically.[6]

Table 1. Current Medications Available in the Therapeutic Class[7-21]

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
Doxepin (Silenor®)	Treatment of insomnia characterized by difficulties with sleep maintenance	Tablet: 3 mg 6 mg	-
Estazolam (ProSom®*)	Short-term treatment of insomnia characterized by difficulty in falling asleep, frequent nocturnal awakenings, and/or early morning awakenings	Tablet: 1 mg 2 mg	✔
Eszopiclone (Lunesta®)	Treatment of insomnia	Tablet: 1 mg 2 mg 3 mg	-
Flurazepam (Dalmane®*)	Treatment of insomnia characterized by difficulty in falling asleep, frequent nocturnal awakenings, and/or early morning awakenings	Capsule: 15 mg 30 mg	✔
Quazepam (Doral®)	Treatment of insomnia characterized by difficulty in falling asleep, frequent nocturnal awakenings, and/or early morning awakenings	Tablet: 15 mg	-
Ramelteon (Rozerem®)	Treatment of insomnia characterized by difficulty with sleep onset	Tablet: 8 mg	-
Suvorexant (Belsomra®)	Treatment of insomnia characterized by difficulties with sleep onset and/or sleep maintenance	Tablet: 5 mg 10 mg 15 mg 20 mg	-
Tasimelteon (Hetlioz®)	Treatment of non-24-hour sleep-wake disorder	Capsule: 20 mg	-
Temazepam (Restoril®*)	Short-term treatment of insomnia	Capsule: 7.5 mg 15 mg 22.5 mg 30 mg	✔
Triazolam (Halcion®*)	Short-term treatment of insomnia	Tablet: 0.125 mg 0.25 mg	✔
Zaleplon (Sonata®*)	Short-term treatment of insomnia	Capsule: 5 mg 10 mg	✔
Zolpidem (Ambien®*, Ambien CR®*, Edluar®, Intermezzo®, Zolpimist®)	Short-term treatment of insomnia characterized by difficulties with sleep initiation†, treatment of insomnia characterized by difficulties with sleep onset and/or sleep maintenance‡, treatment of insomnia when a middle-of-the-night awakening is followed by difficulty returning to sleep§	Extended-release tablet: 6.25 mg 12.5 mg Immediate-release tablet: 5mg 10 mg Sublingual tablet: 5 mg* 10 mg* 1.75 mg†	✔

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
		3.5 mg† Oral mist: 5 mg/ actuation	

*Generic available in at least one dosage form or strength.
†Ambien® (zolpidem), Edluar® (zolpidem sublingual), and Zolpimist® (zolpidem oral mist).
‡ Intermezzo® (zolpidem sublingual).
§ Ambien CR® (zolpidem extended-release).

Evidence-based Medicine

- The result of clinical studies consistently demonstrate that the sedative hypnotics are more effective compared to placebo in patients experiencing insomnia.[22-84]
- The result of several meta-analyses have demonstrated that the benzodiazepine significantly improve sleep latency and total sleep time in patients with insomnia.[77,78,80,81,84]
- Some studies indicate that zaleplon may result in less residual effects and rebound insomnia when compared to zolpidem.[63,65]
- Several agents have demonstrated efficacy in the presence of various comorbidities or specific subpopulations. Eszopiclone and ramelteon have been found to be beneficial across multiple symptoms, including sleep disturbances, mood disturbances, anxiety and hot flashes in peri- and postmenopausal women.[55,35] Eszopiclone has also been found to improve sleep-related symptoms in patients with depression, Parkinson disease, and post-traumatic stress disorder.[29,32,33] Ramelteon has demonstrated efficacy in patients with comorbid generalized anxiety disorder and also in patients with substance abuse.[41,57] Zolpidem extended-release has demonstrated efficacy, when coadministered with escitalopram, in patients with both major depressive disorder as well as generalized anxiety disorder.[70,71] Zolpidem and zaleplon have both demonstrated safety and efficacy in patients with nonpsychotic psychiatric disorders.[66] Efficacy has also been established in populations of elderly patients. Doxepin has demonstrated safety and efficacy in elderly patients through 12 weeks, without causing residual sedation or increasing the risk of complex sleep behaviors.[24,28] Eszopiclone has demonstrated safety and efficacy over two weeks in elderly patients and ramelteon over five weeks.[36,50]
- Furthermore, efficacy of the Furthermore, efficacy of the non-benzodiazepine hypnotics has been demonstrated to be sustained for up to one year. Eszopiclone and zolpidem extended-release have demonstrated sustained efficacy through six months while ramelteon and zolpidem immediate-release have demonstrated sustained efficacy over the course of a year.[30,37,38,56,69,76]

Key Points within the Medication Class

- According to Current Clinical Guidelines:
  - Guidelines do not recommend one sedative hypnotic over another.[1]
  - All agents have been shown to result in positive effects on sleep latency, total sleep time and wake time after sleep onset. Selection of an agent should take into consideration the patient's specific symptom pattern, patient preferences, any comorbid disease states and concurrent medications, as well as the individual side effect profile for each option. Zaleplon and ramelteon have short half-lives, work well to reduce sleep latency and are unlikely to result in residual sedation; however, they have little effect on waking after sleep onset.[1]
  - Eszopiclone and temazepam have longer half-lives, are more likely to improve sleep maintenance, and are more likely to produce residual sedation.[1]
  - Triazolam has been associated with rebound anxiety and is not considered a first-line treatment.[1]
  - The use of doxepin for insomnia in the absence of co-morbid depression is not addressed in clinical guidelines, as the low-dose formulation was not available when these guidelines were published.[1]

- Depending on the patient's specific complaint of sleep initiation or sleep maintenance, consideration should be given to the pharmacokinetic parameters of the available hypnotics. Agents with a longer half-life may be preferred in those with sleep maintenance issues, while agents with a shorter time to maximum concentration may be preferred in patients with sleep initiation complaints. If a patient does not respond to the initial agent, a different agent within the same class is appropriate after evaluating the patient's response to the first agent.[1]

Other Key Facts:

- Currently, estazolam, eszopiclone, flurazepam, temazepam, triazolam, zaleplon and zolpidem (immediate-release and extended-release tablets) are available generically.[6]
- However; doxepin is available generically in higher doses that are approved for the treatment of depression and anxiety.[6]

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Sedative Hypnotics

Overview/Summary

Insomnia is the most common sleep disorder in adulthood, affecting 33 to 69% of the population. It is estimated that five to ten percent of adults experience specific insomnia disorders.[1,2] Insomnia is a disorder that results from a difficulty in initiating or maintaining sleep, waking too early, or sleep that is considered nonrestorative or poor quality.[1-3] Furthermore, individuals with insomnia must also report at least one of the following types of daytime impairment as a result of the difficulties experienced with sleep: fatigue/malaise; impairment in memory, attention, or concentration; social or work-related dysfunction; poor school performance; irritability; day time sleepiness; loss of motivation, energy, or initiative; increased tendency for work or driving related accidents/errors; tension headaches; gastrointestinal symptoms; or concerns/worries about sleep. In individuals with insomnia, these complaints occur despite having sufficient opportunity and circumstances for sleep.[1,2] According to the International Classification of Sleep Disorders, insomnia may be classified as one of the following: short-term insomnia, chronic insomnia or other insomnia (defined as patients who experience difficulty initiating or maintaining sleep but do not meet all of the criteria for either short-term or chronic insomnia).[2]

There are several classes of medications available for the management of insomnia.[4-6] Doxepin (Silenor®) is a tricyclic antidepressant that is Food and Drug Administration (FDA)-approved for the treatment of insomnia characterized by difficulties with sleep maintenance. The exact mechanism by which doxepin exerts its therapeutic effect on insomnia has not been elucidated; however, it is most likely due to antagonism of the histamine-1 receptor.[7] Ramelteon (Rozerem®) is a melatonin agonist that binds to melatonin receptors with much higher affinity compared to melatonin.[8] Similar to ramelteon, tasimelteon (Hetlioz®) is also a melatonin agonist and it is indicated for the treatment non-24 hour sleep-wake disorder, a disorder that is characterized by the extension of the natural sleep-wake cycle beyond 24 hours.[9] Suvorexant (Belsomra®) belongs to a novel class of orexin receptor antagonists and is thought to suppress the wake-drive by blocking the binding of wake-promoting neuropeptides.[10] Doxepin, ramelteon, tasimelteon and suvorexant are not available generically; however; doxepin is available generically in higher doses that are approved for the treatment of depression and anxiety.[6]

Benzodiazepines have been a mainstay of pharmacological treatment for anxiety disorders and insomnia since they were first introduced in the 1960s. Benzodiazepines relieve insomnia by reducing sleep latency and increasing total sleep time. Benzodiazepines increase stage two sleep while decreasing rapid eye movement sleep, stage three and stage four sleep.[5] The benzodiazepines bind to γ-aminobutyric acid subtype A ($GABA_A$) receptors in the brain, thereby stimulating GABAergic transmission and hyperpolarization of neuronal membranes.[5] The benzodiazepines primarily differ in their duration of action. Triazolam (Halcion®) has a short duration of action, while estazolam (ProSom®) and temazepam (Restoril®) are intermediate-acting agents. Flurazepam (Dalmane®) and quazepam (Doral®) are generally considered long-acting benzodiazepines.[11-15] All of the benzodiazepines are available generically with the exception of quazepam.[6]

The nonbenzodiazepine sedative hypnotics are structurally distinct from the benzodiazepines resulting in more specific activity at the $GABA_A$ receptor. As a result, the nonbenzodiazepine sedative hypnotics are associated with less anxiolytic and anticonvulsant activity compared to the benzodiazepines.[4] Zaleplon (Sonata®) has a duration of approximately one hour, and thus is an effective treatment for patients with difficulty falling asleep.[16] Zolpidem has a duration of less than two and a half hours and may also be useful for patients with difficulties initiating sleep. Zolpidem is available in as an immediate-release tablet (Ambien®), oral spray (Zolpimist®), sublingual tablet (Edluar® and Intermezzo®) and extended-release tablet (Ambien CR®). The sublingual tablet (Intermezzo®) is the only zolpidem formulation that is approved for the treatment of insomnia due to middle-of-the-night awakenings.[17-21] Of the nonbenzodiazepine sedative hypnotics, eszopiclone (Lunesta®) has the longest half-life (approximately five to seven hours); therefore it is effective in treating sleep onset insomnia and sleep maintenance

insomnia.[22] Currently zaleplon, eszopiclone and zolpidem (immediate-release and extended-release tablets) are available generically.[6]

Current treatment for insomnia includes behavioral therapy as well as various pharmacologic interventions. The FDA-approved treatments include various benzodiazepine receptor agonists, a low-dose sedating antidepressant, and melatonin receptor agonists. Goals of therapy may include improving sleep quality, improving sleep time and various sleep symptoms, as well as improving insomnia-related next-day complaints.[1,3]

Medications

Table 1. Medications Included Within Class Review[7-22]

Generic Name (Trade name)	Medication Class	Generic Availability
Doxepin (Silenor®)	Tricyclic antidepressant	-
Estazolam (ProSom®*)	Benzodiazepine	✔
Eszopiclone (Lunesta®)	Nonbarbiturate hypnotic	✔
Flurazepam (Dalmane®*)	Benzodiazepine	✔
Quazepam (Doral®)	Benzodiazepine	-
Ramelteon (Rozerem®)	Melatonin receptor agonist	-
Suvorexant (Belsomra®)	Orexin receptor antagonist	-
Tasimelteon (Hetlioz®)	Melatonin receptor agonist	-
Temazepam (Restoril®*)	Benzodiazepine	✔
Triazolam (Halcion®*)	Benzodiazepine	✔
Zaleplon (Sonata®*)	Nonbarbiturate hypnotic	✔
Zolpidem (Ambien®*, Ambien CR®*, Edluar®, Intermezzo®, Zolpimist®)	Nonbarbiturate hypnotic	✔

*Generic available in at least one dosage form or strength.

Indications

Table 2. Food and Drug Administration Approved Indications[7-23]

Indication	Doxepin	Estazolam	Eszopiclone	Flurazepam	Quazepam	Ramelteon	Suvorexant	Tasimelteon	Temazepam	Triazolam	Zaleplon	Zolpidem
Short-term treatment of insomnia									✔	✔	✔	
Short-term treatment of insomnia characterized by difficulties with sleep initiation												✔ *
Short-term treatment of insomnia characterized by difficulty in falling asleep, frequent nocturnal awakenings, and/or early morning awakenings		✔										
Treatment of insomnia			✔									
Treatment of insomnia characterized by difficulties with sleep maintenance	✔											
Treatment of insomnia characterized by difficulties with sleep onset and/or sleep maintenance							✔					✔ †
Treatment of insomnia characterized by difficulty with sleep onset						✔						
Treatment of insomnia characterized by difficulty in falling asleep, frequent nocturnal awakenings, and/or early morning awakenings				✔	✔							
Treatment of insomnia when a middle-of-the-night awakening is followed by difficulty returning to sleep												✔ ‡
Treatment of non-24-hour sleep-wake disorder								✔				

* Ambien® (zolpidem), Edluar® (zolpidem sublingual), and Zolpimist® (zolpidem oral mist).
† Ambien CR® (zolpidem extended-release).
‡ Intermezzo® (zolpidem sublingual).

Pharmacokinetics

Table 3. Pharmacokinetics[7-23]

Generic Name	Bioavailability (%)	Absorption (%)	Renal Excretion (%)	Active Metabolites	Serum Half-Life (hours)
Doxepin	Not reported	Not reported	<3*	N-des-methyldoxepin	15.3
Estazolam	Not reported	Not reported	<5*	Not reported	10 to 24
Eszopiclone	Not reported	Not reported	<10*	(S)-N-des-methylzopiclone	6
Flurazepam	Not reported	Not reported	22 to 55	N-1-hydroxy-ethylflurazepam, N-1-des-alkylflurazepam	2.3
Quazepam	Not reported	Not reported	31	2-oxoquazepam, N-desalkyl-2-oxoquazepam	39 to 73
Ramelteon	1.8	Not reported	<0.1*	M-II	1.0 to 2.6
Suvorexant	82	Not reported	23	None	12
Tasimelteon	38.3	Not reported	<1*	Present, not otherwise specified	1.3 to 3.7
Temazepam	Not reported	Not reported	80 to 90	None	3.5 to 18.4
Triazolam	Not reported	Not reported	79.9	alpha-hydroxytriazolam	1.5 to 5.5
Zolpidem	70†	Not reported	48 to 67	None	2.8 (CR) 2.5 to 2.6 (IR) 2.50 to 2.85 (SL) 2.7 to 3.0‡
Zaleplon	30	Not reported	<1*	None	1

CR=controlled-release, IR=immediate-release, SL=sublingual tablets
*Percentage excreted as parent compound
† Immediate-release tablets.
‡ Oral spray.

Clinical Trials

Clinical trials demonstrating the safety and efficacy of the insomnia agents in their respective FDA-approved indications are outlined in Table 4.[24-84]

In general, data consistently demonstrates the superiority of these agents, when compared to placebo, for patients experiencing insomnia.[24-74,76-78,81-83] The results of multiple meta-analyses have demonstrated that the benzodiazepines significantly improve sleep latency and total sleep time in patients with insomnia.[77,78,80,81,84] Studies suggest that the comparative efficacy of the agents included within this review may vary, with no consistently superior intervention identified.[34,62] However, some studies indicate that zaleplon may result in less residual effects and rebound insomnia when compared to zolpidem.[63,65]

Several agents included in this review have demonstrated efficacy in the presence of various comorbidities or specific subpopulations. Eszopiclone and ramelteon have been found to be beneficial across multiple symptoms, including sleep disturbances, mood disturbances, anxiety and hot flashes in peri- and postmenopausal women.[55,35] Eszopiclone has also been found to improve sleep-related symptoms in patients with depression, Parkinson disease and post-traumatic stress disorder.[29,32,33]

Ramelteon has demonstrated efficacy in patients with comorbid generalized anxiety disorder and also in patients with substance abuse.[41,57] Zolpidem extended-release has demonstrated efficacy, when coadministered with escitalopram, in patients with both major depressive disorder as well as generalized anxiety disorder.[70,71] Zolpidem and zaleplon have both demonstrated safety and efficacy in patients with nonpsychotic psychiatric disorders.[66] Efficacy has also been established in populations of elderly patients. Doxepin has demonstrated safety and efficacy in elderly patients through 12 weeks, without causing residual sedation or increasing the risk of complex sleep behaviors.[24,28] Eszopiclone has demonstrated safety and efficacy over two weeks in elderly patients and ramelteon over five weeks.[36,50]

Furthermore, efficacy of the non-benzodiazepine hypnotics has been demonstrated to be sustained for up to one year. Eszopiclone and zolpidem extended-release have demonstrated sustained efficacy through six months while ramelteon and zolpidem immediate-release have demonstrated sustained efficacy over the course of a year.[30,37,38,56,69,76]

Table 4. Clinical Trials

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Insomnia				
Lankford et al[24] Doxepin 6 mg vs placebo	DB, PC, RCT Elderly adults with primary insomnia	N=255 4 weeks	Primary: sTST at week one Secondary: LSO, sTST at weeks two through four, subjective NAW after sleep onset, sleep quality, CGI, PGI and ISI, safety	Primary: At week one sTST was significantly increased for doxepin 6 mg compared to placebo (335.2 vs 316.7; P<0.01). Secondary: The two treatment groups did not differ significantly on the LSO endpoint at any time during this study. During weeks two through four, sTST was significantly increased with doxepin 6 mg compared to placebo (346.1 vs 336.4; P<0.01). Sleep quality was significantly improved at weeks one, three, and four for doxepin 6 mg compared to placebo, with a trend towards significance at week two (P=0.0511). The subjective NAW after sleep onset was not significantly different from placebo at any time point. The ISI was significantly improved with doxepin, compared to placebo, at all four weeks (all P values <0.02). Doxepin 6 mg produced significant improvements in the CGI-Severity and CGI-Improvement scale scores when compared to placebo at weeks one and two. At weeks three and four, treatment with doxepin resulted in improvements over baseline, but these improvements were not statistically significant. The PGI was significantly improved for patients receiving doxepin on almost all of the five therapeutic effect items at each visit, with this improvement reaching statistical significance, compared to placebo, in four out of five items by the final study visit for patients receiving doxepin. Overall, doxepin was well tolerated with rates of treatment emergent adverse events similar between the doxepin and placebo groups (31 vs 27%, respectively). There were no reports of complex sleep behaviors, memory impairment, or cognitive disorder in any doxepin-treated patient.
Scharf et al[25] Doxepin 1, 3, or 6 mg vs placebo	DB, MC, PC, XO Elderly adults (>65 years of age) with primary insomnia	N=76 This was a 4 period XO; each period lasted 2 nights with a	Primary: WTDS Secondary: Safety	Primary: Doxepin 1, 3 and 6 mg resulted in significant reductions in WTDS when compared to placebo (1 mg: 69.60±32.61 vs 85.80±38.39 minutes; P<0.0001, 3 mg: 64.80±31.96 vs 85.80±38.39 minutes; P<0.0001, and 6 mg: 59.5±28.3 vs 85.80±38.39 minutes; P<0.0001). Secondary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
		5- to 12-day washout period between study drugs		There were 32 adverse events reported during the study. The only event that was reported by more than one patient was headache, occurring in two patients during the placebo treatment period. Seven patients (10%) experienced at least one adverse event during the placebo treatment period, and 9 (12%), 6 (8%), and 5 (7%) patients experienced at least one adverse event during treatment with doxepin 1, 3, and 6 mg, respectively. All reported adverse events were mild or moderate, except for one incident of chest pain that required hospitalization and was determined to be unrelated to the study drug.
Krystal et al[26] Doxepin 3 or 6 mg vs placebo	DB, PC, PG, RCT Patients 18 to 64 years of age with primary insomnia who reported sleep maintenance difficulty	N=229 35 nights of treatment followed by 2 nights of SB placebo	Primary: WASO on night one (assessed by PSG) Secondary: PSG measures: WASO, LPS, NAW after sleep onset, TST, SE, and WASP; patient-reported measures: LSO, WASO, TST, NAW after sleep onset, and sleep quality, safety	Primary: On night one, WASO was significantly improved with doxepin 3 and 6 mg (41.4 and 36.3 minutes for 3 mg and 6 mg, respectively, vs 66.8 minutes with placebo; P<0.0001 for both vs placebo). Secondary: PSG-evaluated outcomes Treatment with doxepin 3 and 6 mg also resulted in significant improvements in WASO over placebo at night 15 (3 mg: 44.7 vs 60.5 minutes; P=0.0053, 6 mg: 41.7 vs 60.5 minutes; P=0.0023) and night 29 (3 mg: 47.2 vs 60.5 minutes; P=0.0299, 6 mg: 40.7 vs 60.5 minutes; P=0.0012). It was found that improvement in WASO on night one for both doses of doxepin did not differ between African Americans and Caucasians. Treatment with both 3 and 6 mg of doxepin resulted in significant improvements over placebo in TST, and consequently SE, at night one (3 mg: 415.3 vs 373.9 minutes, 6 mg: 420.5 vs 373.9 minutes; P<0.0001 for both doses vs placebo) and night 29 (3 mg: 408.0 vs 391.5 minutes; P=0.0262, 6 mg: 419.5 vs 391.5 minutes; P=0.0003). TST and SE were also significantly improved over placebo with 6 mg of doxepin at night 15 (411.5 vs 389.2 minutes; P=0.0157). There were no significant differences in the NAW after sleep onset for any dose at any time point. It was found that SE in the last quarter of the night was significantly improved over placebo with doxepin 3 mg on night one (88.3 vs 79.9%; P=0.0008) and night 15 (86.6 vs 81.2%; P=0.0220), and with doxepin 6 mg on night one (89.8 vs 79.9%; P<0.0001), night 15 (87.4 vs 81.2%; P=0.0239), and night 29 (87.8 vs 80.7%; P=0.0029).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				LPS was significantly improved over placebo on night one for both doxepin 3 and 6 mg (3 mg: 26.7 vs 44.8 minutes; P=0.0047, 6 mg: 27.1 vs 44.8 minutes; P=0.0007). Patient reported outcomes Significant improvements in WASO for doxepin 3 and 6 mg, compared to placebo, were observed at night one (P=0.0003 and P=0.0004, respectively). Significant improvements in WASO over placebo were also seen on the DB average across nights one, 15, and 29 for doxepin 3 and 6 mg (P=0.0088 and P=0.0178, respectively). When compared to placebo, there were also significant improvements in TST for doxepin 3 and 6 mg (P=0.0088 and P=0.0135, respectively). Sleep quality was also significantly improved compared to placebo with doxepin 3 and 6 mg at night one (P=0.0068 and P<0.0001, respectively). Sleep quality was also significantly improved over placebo with doxepin 6 mg for the double-blind average (P=0.0028). Treatment with doxepin 6 mg also resulted in a significant improvement over placebo in LPS at night one (P=0.0492). The average WASO remained improved relative to baseline for both doses of doxepin on both of the two discontinuation nights. The percentage of patients meeting PSG-defined rebound insomnia criteria was similar across groups over both discontinuation nights (1 and 4% in the doxepin 3 and 6 mg groups, respectively vs 1% in the placebo group; P value not reported). There were no significant differences between placebo and either dose of doxepin on any of the measures assessing psychomotor function or next-day alertness at any time point (P value not reported). Overall incidence of adverse events was low with 20 (27%), 26 (35%), and 23 (32%) patients experiencing an adverse event in the placebo, doxepin 3 mg and doxepin 6 mg groups, respectively. The most common adverse events were headache, somnolence/sedation, and nausea.
Roth et al[27] Doxepin 6 mg vs	DB, PC, PG, RCT Healthy adults; the study utilized a first-night effect and 3 hour phase	N=565 1 night	Primary: LPS (assessed via PSG) Secondary: PSG endpoints	Primary: Treatment with doxepin 6 mg demonstrated statistically significant improvements in LPS (13 minute decrease over placebo; P<0.0001). Secondary: Doxepin 6 mg reduced WASO by 39 minutes and improved TST by 51 minutes over

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
placebo	advance model to induce transient insomnia		include WASO, TST, WTAS, and SE; subjective endpoints include LSO, WASO, TST, and sleep quality, safety	placebo (P<0.0001 for both). Doxepin also resulted in a statistically significant improvement over placebo in WTAS (P<0.0001), overall SE (P<0.0001), SE in each quarter of the night (P<0.0001), and SE in each of the eight hours evaluated (P≤0.0003). Doxepin also resulted in significant improvements in subjective variables over placebo including a shorter LSO (P<0.0001), a 10.6 minute reduction in WASO (P=0.0063), a 51.1 increase in TST (P<0.0001), a 0.4 point increase in sleep quality (P=0.0004). There was no consistent evidence of next-day residual sedation and minor sleep stages alterations. The incidence of adverse events with doxepin 6 mg was comparable to placebo (8 vs 7%, respectively; P value not reported).
Krystal et al[28] Doxepin 1 or 3 mg vs placebo	DB, PC, PG, RCT Elderly patients with chronic primary insomnia	N=240 12 weeks Supervised administra-tion of study drug in a sleep laboratory was conducted on nights 1, 15, 29, 57, and 85; patients took study drug nightly at home between visits to sleep laboratory	Primary: WASO on night one Secondary: PSG evaluated endpoints include WASO at other time points, LPS, NAW after sleep onset, TST, SE, and WTAS; patient-reported IVRS endpoints include LSO, TST, and sleep quality, safety	Primary: Treatment with both doxepin 1 and 3 mg led to significant improvement over treatment with placebo in WASO on night one (1 mg: 91.8 vs 108.9 minutes; P=0.0053, 3mg: 74.5 vs 108.9 minutes; P<0.0001). Secondary: Treatment with doxepin 1 mg led to an increase over placebo in WASO on night 85 (97.0 vs 109.2 minutes; P<0.0330). Treatment with doxepin 3 mg led to an increase over placebo in WASO on night 29 and night 85 (84.3 vs 104.6 minutes; P=0.0005 and 75.7 vs 109.2 minutes; P<0.0001, respectively). TST was significantly increased over placebo in the doxepin 1 mg group on night one and night 85 (359.1 vs 339.7 minutes; P=0.0119 and 360.5 vs 343.7 minutes; P=0.0257, respectively). TST was also significantly increased over placebo in the doxepin 3 mg group on night one, night 29, and night 85 (382.9 vs 339.7 minutes; P<0.0001, 363.9 vs 345.0 minutes; P=0.0161, and 373.7 vs 343.7 minutes; P=0.0007). Treatment with doxepin 3 mg resulted in a significant improvement in overall SE when compared to treatment with placebo (P<0.0001). SE in the last quarter of the night was significantly increased over placebo on night one in the doxepin 1 mg group (72.5 vs 62.1%; P=0.0011). In the doxepin 3 mg group, SE in the last quarter of the night was significantly increased over placebo on night one, night 29, and night 85 (76.6 vs 62.1%; P<0.0001, 75.7 vs 64.7%; P=0.0004, and 76.1 vs 65.0%; P=0.0014). SE in hour eight was significantly increased over placebo on night one in the doxepin

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				1 mg group (P=0.0211) and on nights one (P<0.0001) and 29 (P=0.0029) in the doxepin 3 mg group. The NAW was significantly reduced when compared to placebo in the doxepin 1 mg group on nights 29 and 85 (14.9 vs 12.6; P<0.05 and 14.9 vs 11.9; P<0.01). LPS was not significantly reduced when compared to placebo for either dose of doxepin at any time point. Treatment with doxepin also resulted in significant improvements in several patient-reported endpoints. Patient-reported LSO was significantly decreased compared to placebo at weeks one, four, and 12 with doxepin 3 mg (40.0 vs 59.7 minutes; P=0.003, 48.6 vs 56.5 minutes; P=0.0397, and 39.9 vs 55.5 minutes; P=0.0464), and at weeks four and 12 with doxepin 1 mg (45.2 vs 56.5 minutes; P=0.0116, and 37.5 vs 55.5 minutes; P=0.0028). Treatment with doxepin resulted in a significant increase in patient-reported TST over placebo at weeks four and 12 in the 1 mg group (348.8 vs 317.5 minutes; P<0.05 and 371.5 vs 326.0 minutes; P<0.01) and at weeks one, four and 12 in the 3 mg group (356.8 vs 316.2 minutes; P<0.01, 362.5 vs 317.5 minutes; P<0.01, and 389.4 vs 326.0 minutes; P<0.001). Sleep quality was improved over placebo at weeks four and 12 in the doxepin 1 mg group (0.5 vs 0.1; P<0.05 and 0.8 vs 0.2; P<0.05) and at weeks one, four and 12 in the doxepin 3 mg group (0.6 vs 0.0; P<0.001, 0.7 vs 0.1; P<0.001, and 0.9 vs 0.2; P<0.001). There was significant improvement over placebo after two (P=0.0047), four (P=0.0356), and 12 weeks (P=0.0005) on the CGI-Severity scale score for doxepin 3 mg and after 12 weeks (P=0.0101) for doxepin 1 mg. There was significant improvement after two (P=0.0060), four (P=0.0334), and 12 weeks (P=0.0008) on the CGI-Improvement scale score with doxepin 3 mg and after 12 weeks (P=0.0082) for doxepin 1 mg. There was significant improvement, compared to placebo, on the ISI total score at night 15 (P=0.0216), night 29 (P=0.0068), and night 85 (P=0.0056) for doxepin 3 mg. After 12 weeks, there was significant improvements for both doxepin groups,

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				compared to placebo, on all five items of the ISI (P<0.05 for all comparisons). Daytime function ratings were significantly improved, compared to placebo, with doxepin 1 and 3 mg on night one (P=0.0192 and P=0.0282, respectively) as well as on night 85 (P=0.0102 and P=0.0028, respectively). There were no significant differences between placebo and either dose of doxepin on any of the measures assessing objective psychomotor function, subjective next-day alertness or drowsiness at any time. Rates of treatment-emergent adverse events were lower in subjects treated with doxepin 1 and 3 mg compared to subjects treated with placebo (40 and 38 vs 52%, respectively; P value not reported). The most common adverse events were headache and somnolence.
McCall et al[29] Eszopiclone 3 mg vs placebo All patients started with one week of OL fluoxetine; patients experiencing insomnia after this period were randomized to 8 weeks of eszopiclone or placebo in addition to the OL fluoxetine.	DB, PC, RCT Patients 18 to 70 years of age with depression and insomnia	N=60 8 weeks	Primary: DLRF subscale of the Basis-32 Secondary: Safety	Primary: Final DLRF scores were better (lower) in the eszopiclone group than in the placebo group (0.81±0.64 vs 1.2±0.72, ES 0.62). Secondary: The only meaningful adverse event reported, was unpleasant taste, and it occurred in 46% of patients treated with eszopiclone.
Zammit et al[30] Eszopiclone 2 or 3 mg vs	DB, MC, PC, RCT Adults 21 to 64 years of age with chronic primary insomnia	N=308 6 weeks	Primary: Efficacy (PSG and patient reports), next day residual effects (DSST), tolerance,	Primary: Eszopiclone 2 and 3 mg had significantly less time to sleep onset (P≤0.001 and P≤0.0001, respectively), more TST (P≤0.01 and P≤0.0001), better SE (P≤0.001 and P≤0.0001), and enhanced quality and depth of sleep (both P<0.05) across the DB period compared to placebo. Eszopiclone 3 mg (P≤0.01) but not 2 mg significantly improved sleep maintenance compared to placebo.

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placebo			rebound insomnia, safety Secondary: Not reported	Median DSST scores showed no decrement in psychomotor performance relative to baseline and did not differ from placebo in either eszopiclone group. There was no evidence of tolerance or rebound insomnia after therapy discontinuation. Treatment was well tolerated; unpleasant taste was the most common adverse event reported with eszopiclone. Secondary: Not reported
Ancoli-Israel et al[31] Eszopiclone 2 mg vs placebo	DB, MC, PC, RCT Patients 65 to 85 years of age with primary insomnia	N=388 12 weeks Treatment was followed by a two week, SB run out period	Primary: Change from baseline sTST Secondary: Change from baseline in sSL and WASO	Primary: After 12 weeks, the mean sTST was 360.08 minutes with eszopiclone compared to 297.86 minutes at baseline (mean change of 63.24 minutes). This was significantly greater than placebo (P<0.0001). Secondary: There was a greater improvement in sSL with eszopiclone compared to placebo (mean decrease of 24.62 minutes vs 19.92 minutes; respectively; P=0.0014). Patients receiving eszopiclone experienced a greater decrease in WASO compared to those receiving placebo (mean decrease of 36.4 minutes vs 14.8 minutes; P<0.0001). The reported NAW per night was reduced (P≤0.01), and the quality (P<0.001) and depth of sleep (P≤0.001) was improved at all time points with eszopiclone compared to placebo. There was a significantly greater decrease in naps per week over the first three weeks of treatment with eszopiclone (1.2 naps per week decrease) vs placebo (0.4 naps per week; P=0.006), but not at subsequent time points. Similar results were obtained for total nap time per week. Patients receiving eszopiclone had significantly greater improvements in ISI total scores than those receiving placebo at all time points (all P<0.001). The percentage of patients with ISI total scores categorized as "no insomnia" and "sub-threshold

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				insomnia" was greater in the eszopiclone group (78.0% at week 12) than in the placebo group (61.1%; P<0.05). Changes in self-reported daytime alertness, ability to function, ability to concentrate, and sense of physical well-being were significantly increased with eszopiclone compared to placebo at all times points (all P≤0.001). Patients receiving eszopiclone had significant improvements in the vitality scale of the SF-36 at week six (P=0.04) and week 12 (P=0.008), and in the general health scale at week 12 (P=0.009) compared to placebo. There were no significant differences on the other SF-36 individual scale scores, or on the mental or physical component summary scores among the treatment groups. On the SDS, there were significant improvements observed in the eszopiclone group compared to the placebo group for the social life and family life/home responsibilities items (both P≤0.03) at week six, but not at week 12. There was no significant difference on the work/school item at either time point. The overall incidence of adverse events was 59.3% for eszopiclone and 50.5% for placebo. The most common adverse events reported in the eszopiclone group were headache (13.9 vs 12.4% for placebo), unpleasant taste (12.4 vs 1.5% for placebo), and nasopharyngitis (5.7 vs 6.2% for placebo).
Menza et al[32] Eszopiclone 2 to 3 mg vs placebo This was a fixed-dose study; patients <65 years of age received 3 mg and patients ≥65 years of	DB, MC, PC, PG, RCT Patients 35 to 85 years of age with Parkinson's disease and sleep maintenance insomnia or SL insomnia, as well as clinically significant daytime distress or impairment	N=30 6 weeks	Primary: Patient-reported TST Secondary: WASO, NAW and SII, quality of sleep, quality of life (assessed via PDQ-8), motor function (assessed via UPDRS), severity and change	Primary: There was no significant difference in the improvement seen in TST among the groups (66.5 minutes with eszopiclone vs 47.0 minutes with placebo; P=0.1099). Secondary: There were significant differences in NAW (P=0.035), quality of sleep (P=0.018), and CGI-improvement in sleep (P=0.035) among the groups. There was no significant difference in WASO (P=0.071). There were no differences in the UPDRS motor, activities of daily living, therapeutic complications, mood or Schwab subscales. There were no significant differences in SL, FSS, SII, PDQ-8, Ability to Function Scale, the MCBI caregiver burden, the CES-D, or the Daytime Alertness Scale.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
age received 2 mg of eszopiclone.	secondary to insomnia		(assessed via CGI), ability to function, daytime alertness, fatigue severity (assessed via FSS), caregiver quality of life and depression (assessed via MCBI and CES-D)	Overall, 30% of patients reported adverse events; 33% of patients receiving eszopiclone and 27% of patients receiving placebo.
Pollack et al[33] Eszopiclone 3 mg vs placebo Each treatment was administered for three weeks and separated by a one-week washout period.	DB, PC, RCT, XO Patients 18 to 64 years of age with PTSD with associated sleep disturbance	N=24 7 weeks	Primary: Changes in scores on the SPRINT and PSQI scales Secondary: CAPS, SL and TST	Primary: Eszopiclone was associated with significant improvement in PTSD symptomatology as measured by the SPRINT compared to placebo (P=0.032). Eszopiclone was associated with a significantly greater reduction in PSQI score compared to placebo (P=0.011). Secondary: In phase 1, the CAPS was also significantly reduced with eszopiclone compared to placebo (P=0.003). SL was significantly reduced with eszopiclone compared to placebo (P=0.044). There was no significant difference in TST among the treatment groups (P=0.061). Adverse events with eszopiclone were of mild to moderate severity, with the most common comprising unpleasant taste (32%), sedation (16%), and headaches (12%).
Erman et al[34] Eszopiclone 1 mg for 2 nights vs	MC, RCT, XO Patients 21 to 64 years of age with primary insomnia; with a 3 to 7 day washout between	N=65 2 nights for each treatment	Primary: LPS Secondary: SE, WASO, WTDS, NAW, and patient-	Primary: All active treatments reduced median LPS by 42 to 55% compared to placebo (P<0.05). The median LPS was 13.1 minutes for eszopiclone 3 mg and zolpidem 10 mg. The median LPS was 29.0, 16.8, 15.5, and 13.8 minutes for the placebo, eszopiclone 1, 2, and 2.5 mg dose groups, respectively. The two highest doses of eszopiclone (2.5 mg and 3 mg) and zolpidem demonstrated significantly lower LPS when compared to eszopiclone 1 mg (P<0.05).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
eszopiclone 2 mg for 2 nights vs eszopiclone 2.5 mg for 2 nights vs eszopiclone 3 mg for 2 nights vs zolpidem 10 mg for 2 nights vs placebo for 2 nights	XO treatments		reported variables	Secondary: Significant differences were found between all active treatments in SE compared to placebo (P<0.05). Eszopiclone 2, 2.5, and 3 mg, and zolpidem 10 mg demonstrated significantly higher SE when compared to eszopiclone 1 mg (P<0.05). Treatment with eszopiclone 3 mg resulted in significant differences compared to treatment with placebo for WASO, WTDS, and NAW. Eszopiclone 2.5 mg demonstrated significant differences compared to placebo for WASO and WTDS. Neither of the lower doses of eszopiclone nor zolpidem 10 mg was different from placebo for WASO or WTDS. Comparisons of eszopiclone 3 mg and zolpidem 10 mg were not significantly different for WASO (P=0.12), for WTDS (P=0.07), or for NAW (P=0.10). Treatment with eszopiclone 2 and 3 mg and zolpidem 10 mg showed improvements in patient-reported measures of sleep relative to placebo. Both doses of eszopiclone and zolpidem 10 mg significantly improved sSL, sTST, quality of sleep, and depth of sleep relative to placebo (P<0.05). Eszopiclone 2 and 3 mg and zolpidem 10 mg were significantly different from placebo for subject reported NAW and sWASO (P<0.05). Morning sleepiness was significantly less with eszopiclone 3 mg compared to placebo (P<0.05). Evening ratings of daytime alertness were significantly increased with eszopiclone 2 mg and with zolpidem 10 mg compared to placebo (P<0.05), and daytime ability to function was significantly improved for eszopiclone 2 and 3 mg and zolpidem 10 mg compared to placebo (P<0.05). The most common adverse events were headache, unpleasant taste, somnolence, dizziness, and nausea. The overall rate of central nervous system adverse events was 7.9% for placebo, 6.2 to 12.5% for the eszopiclone groups, and 23.4% for zolpidem 10 mg.
Joffe et al[35] Eszopiclone 3 mg for 4 weeks vs	DB, PC, RCT, XO Perimenopausal and postmenopausal women 40 to 65 years of age with	N=59 11 weeks Each treatment period was	Primary: Changes in the ISI scale Secondary: Diary-based sleep parameters	Primary: The ISI score was reduced by 8.7 more points with eszopiclone than with placebo (P<0.0001). The ISI score was 7 or less after four weeks of treatment in 87% of women on eszopiclone and in 34% of women on placebo. Secondary: SL was reduced by 17.8 more minutes with eszopiclone than with placebo (P=0.04).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
placebo for 4 weeks	sleep-onset and/or sleep-maintenance insomnia co-occurring with hot flashes and depressive and/or anxiety symptoms	separated by a 2-week washout period	(WASO, SE, sleep-onset latency, TST, NAW); number of hot flashes/night sweats, depressive symptoms (via MADRS), anxiety symptoms (assessed via BAI), MENQOL, and functional impairment, safety	For both treatment periods together, WASO was reduced by 37.7 minutes more with eszopiclone than placebo (P=0.05), SE improved by 14.6% more with eszopiclone than with placebo (P=0.01), and TST increased by 66.5 minutes more with eszopiclone than with placebo (P=0.01). Among patients with anxiety symptoms at baseline, BAI scores were reduced by a mean of 1.5 more with eszopiclone than with placebo (P=0.03). Quality of life (P=0.0002) and functional disability (P=0.09) improved more on eszopiclone than on placebo. Among those with depressive symptoms at baseline, MADRS scores were reduced by a mean of 7.4 more points with eszopiclone than with placebo (P=0.0004). Compared to placebo, eszopiclone had a significant effect on depressive symptoms during the second (P=0.003), but not first, treatment period. There was a significant reduction in nighttime hot flashes with eszopiclone compared to placebo (reduction by 1.5 nighttime hot flashes; P=0.047), but the effect on daytime symptoms was not different. Compared to placebo, eszopiclone had a significant effect on nighttime hot flashes during the second (P=0.0006), but not first, treatment period. Overall, the treatment was well tolerated. The only adverse event occurring in >5% of the population was metallic taste on eszopiclone (25%).
Scharf et al[36] Eszopiclone 1 or 2 mg vs placebo	DB, MC, PC, RCT Community-dwelling elderly patients (mean age 72.3 years) with primary insomnia	N=231 2 weeks	Primary: Patient-reported efficacy (SL, TST) Secondary: WASO, NAW, number and length of naps, quality of sleep, depth of sleep, ratings of daytime	Primary: Patients treated with eszopiclone 1 and 2 mg had a significantly shorter SL compared to placebo (P<0.05 and P=0.0034, respectively). The eszopiclone 2-mg group (P=0.0003) but not the 1-mg group (P>0.1) had significantly longer TST compared to placebo. Secondary: Compared to placebo, patients receiving eszopiclone 2 mg had significantly less WASO but similar NAW per night (P>0.1). Patients receiving eszopiclone 2 mg had significantly fewer (P=0.028) and shorter in duration (P=0.011) daytime naps, higher ratings of sleep quality (P=0.0006) and

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			alertness, sense of physical well-being, morning sleepiness, ability to function, quality of life (Q-LES-Q), safety	depth (P=0.0015), better daytime alertness (P=0.022) and sense of physical well-being (P=0.047) compared to patients receiving placebo. The differences between eszopiclone 2 mg and placebo were marginally significant for morning sleepiness (P=0.055) and ability to function (P=0.058). Duration of nap was significantly shorter in the eszopiclone 1-mg group compared to the placebo group (P<0.05); however, there were no other significant differences in any other secondary efficacy endpoints. Compared to placebo, the eszopiclone 2-mg group had significantly higher quality of life scores on five of the 16 Q-LES-Q domains (physical health, mood, household activities, leisure time activities and medications; P<0.05). The differences between eszopiclone 2 mg and placebo were marginally significant for the Q-LES-Q global score (P=0.064). There were no significant differences between eszopiclone 1 mg and placebo for any of the Q-LES-Q dimensions. Eszopiclone was well tolerated with unpleasant taste reported as the most frequent treatment-related adverse event.
Krystal et al[37] Eszopiclone 3 mg vs placebo	DB, MC, PC, RCT Adults with chronic insomnia	N=788 6 months	Primary: SL, WASO, NAW, TST, quality of sleep, next-day ratings of ability to function, daytime alertness, sense of physical well-being, safety Secondary: Not reported	Primary: At the first week and each month for the study duration, eszopiclone produced significant and sustained improvements in SL, WASO, NAW, number of nights awakened per week, TST, and quality of sleep compared to placebo (all P≤0.003). Monthly ratings of next-day function, alertness, and sense of physical well-being were also significantly better with the use of eszopiclone than with placebo (all P≤0.002). There was no evidence of tolerance and the most common adverse events were unpleasant taste and headache. Secondary: Not reported
Walsh et al[38] Eszopiclone 3 mg	DB, MC, PC, RCT Adults 21 to 64 years of age with	N=830 26 weeks	Primary: Patient-reported sleep measures (SL, WASO,	Primary: Patient-reported sleep and daytime function improved more with eszopiclone than with placebo at all months (P<0.001).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs placebo	primary insomnia		TST, NAW, sleep quality, daytime alertness, ability to concentrate, physical well-being, and ability to function), ISI, FSS, ESS, Medical Outcomes Study SF-36, Work Limitations Questionnaire, safety (assessments performed at baseline, treatment months one to six, and two weeks after discontinuation of treatment) Secondary: Not reported	Eszopiclone reduced ISI scores to below clinically meaningful levels for 50% of patients (vs 19% of patients with placebo; P<0.05) at six months. Lower mean scores on the FSS and the ESS were observed in the eszopiclone group relative to placebo for each month and the month one to six average (P<0.05). SF-36 domains of Physical Functioning, Vitality, and Social Functioning were improved with eszopiclone vs placebo for the month one to six average (P<0.05). Similarly, improvements were observed for all domains of the Work Limitations Questionnaire with eszopiclone vs placebo for the month one to six average (P<0.05). There was no evidence of rebound insomnia after discontinuation of eszopiclone as SL, WASO and TST remained significantly improved from baseline (all P<0.001). There were no between-treatment differences observed during the discontinuation period except for a significantly greater SL on the first night after discontinuation with eszopiclone vs placebo (45 vs 30 minutes; P=0.015). No significant group differences were observed in mean Benzodiazepine Withdrawal Symptom Questionnaire scores (3.0 with eszopiclone and 2.3 with placebo; P=0.12), or overall adverse event rates (15.2% for eszopiclone and 11.1% for placebo; P value not reported). Unpleasant taste (19.7 vs 1.1%; P<0.001), somnolence (8.8 vs 3.2%; P=0.0029), and myalgia (6.0 vs 2.9; P=0.047) were reported in significantly more patients receiving eszopiclone than those receiving placebo. Secondary: Not reported
Rosenberg et al[39] Eszopiclone 1, 2, 3 or 3.5 mg vs placebo	DB, PC, RCT Healthy adult volunteers with transient insomnia	N=436 1 night	Primary: Efficacy and next-morning effects evaluated by PSG, DSST and self report Secondary: Not reported	Primary: Patients treated with eszopiclone had significantly less PSG LPS (all doses except 1 mg; P≤0.0001), WASO (all doses; P≤0.05) and NAW (3 and 3.5 mg doses; P<0.005), and greater SE (all doses; P≤0.02) compared to placebo. Self-reported efficacy results were similar to PSG. Self-reported morning sleepiness scores were significantly better for eszopiclone 3 and 3.5 mg compared to placebo (P<0.05). Treatment was well tolerated by patients, and the most common treatment-related

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				adverse event was unpleasant taste. Secondary: Not reported
Uchimura et al[40] Eszopiclone 1, 2 or 3 mg vs zolpidem 10 mg vs placebo	DB, PC, RCT, XO Japanese patients 21 to 64 years of age with primary insomnia	N=72 10 nights	Primary: LPS based on PSG and SL based on subjective patient reports Secondary: PSG-determined TST, WASO, SE and NAW; subjective estimates of TST, WASO, NAW, sleep quality and sleep depth	Primary: All active treatments produced significant improvement in objective and subjective SL compared to placebo (P<0.05 for all comparisons); linear dose-response relationships were observed for eszopiclone. Secondary: PSG-determined WASO, SE, NAW and patient-reported measures of WASO, NAW, sleep quality, sleep depth and daytime functioning significantly improved following treatment with eszopiclone 2 and 3 mg and zolpidem 10 mg vs placebo (P<0.05). Eszopiclone at all doses increased TST and stage 2 sleep time (P<0.001 for both comparisons), but did not alter REM or slow-wave sleep.
Johnson et al[41] Ramelteon 16, 80 or 160 mg vs triazolam 0.25 mg, 0.5 mg or 0.75 mg vs placebo	DB, XO Adults with history of sedative abuse	N=14 18 days	Primary: Subject-rated measures (drug liking, street value, pharm-acological classification), observer-rated measures (sedation, impairment), motor and cognitive performance (balance task, DSST, word	Primary: Compared to placebo, all doses of ramelteon showed no significant effect on any of the subjective effect measures, including those related to potential for abuse (all P>0.05). In the pharmacological classification, 79% of subjects identified the highest dose of ramelteon as placebo. Compared to placebo, ramelteon had no effect at any dose on any observer-rated or motor and cognitive performance measure (all P>0.05). Triazolam showed dose-related effects on subject-rated, observer-rated, and motor and cognitive performance measures. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			recall) Secondary: Not reported	
Roth et al[42] Ramelteon 16 mg vs ramelteon 64 mg vs placebo Doses were given 30 minutes before bedtime.	DB, PC, MC, RCT Healthy adult volunteers with transient insomnia (35 to 60 years of age with total sleep duration 6.5 to 8.5 hours, a usual SL of 30 minutes or less, a habitual bedtime between 8:30 PM and midnight)	N =375 1 night	Primary: Mean LPS as measured by PSG Secondary: TST, WASO, percentage of sleep time in each sleep stage, NAW, residual effects assessed by DSST and postsleep questionnaire, safety	Primary: Participants who had received either ramelteon dosage had significantly shorter LPS relative to placebo (both P<0.001). Secondary: Participants who had received ramelteon 16 or 64 mg had significantly longer TST compared to participants who had received placebo (P=0.007 and P=0.033, respectively). There were no significant differences between the ramelteon groups and placebo with regard to WASO, percentage of sleep time in each sleep stage, and NAW. No significant differences in DSST scores were reported among the groups, but ramelteon 64 mg was associated with statistically significant declines in subjective levels of alertness (P=0.020) and ability to concentrate (P=0.043) compared to placebo. No serious adverse events were reported.
Mayer et al[43] Ramelteon 8 mg vs placebo	DB, PC, RCT Patients ≥18 years of age with chronic primary insomnia	N=451 6 months	Primary: LPS (measured by PSG) Secondary: TST (measured by PSG), total time spent in each sleep stage, latency to REM, self-reported efficacy	Primary: Greater reductions in LPS occurred with ramelteon compared to placebo (P<0.05 for each time point). A greater change from baseline occurred with ramelteon (54 to 56%) compared to placebo (30 to 47%). Secondary A greater increase in TST occurred with ramelteon (381.1 minutes) compared to placebo (365.7 minutes) at week one (P<0.001), but not at any other time points. There were no significant changes in percent of time spent in Stage 1 or REM sleep with ramelteon vs placebo. There was a significant increase in percent of time spent in Stage 2 sleep and a significant decrease in time spent in Stage 3/4 with ramelteon compared to placebo (P values not reported).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				There was a greater reduction in subjective SL with ramelteon compared to placebo at week one, as well as months one and five (P<0.05). There were no significant reductions at other time points between the treatment groups. There were no significant differences between ramelteon and placebo at any time point on the following measures: subjective TST, subjective NAW and sleep quality. No significant differences in sWASO was observed between ramelteon (90.89 minutes) and placebo (79.54 minutes) at any time point except month six (P=0.036). There were no significant differences on measures of morning level of alertness and ability to concentrate, or immediate/delayed morning recall between the treatment groups. No rebound insomnia was observed during the placebo run-out period. There were no differences between the treatment groups with regards to measures of withdrawal during the placebo run-out period.
Uchiyama et al[44] Ramelteon 8 mg vs placebo	DB, MC, PC, RCT Japanese patients 20 to 85 years of age with primary insomnia	N=1,605 2 weeks	Primary: Mean patient-reported SL during week one of treatment Secondary: Mean SL during week two of treatment, mean patient-reported TST for week one and for week two, patient's global impression of treatment, rebound insomnia, and safety	Primary: The mean SL was reduced in week one in both the ramelteon and placebo groups (-15.98 and -11.73 minutes, respectively; P=0.0010). Secondary: The mean SL decreased further in week two in both groups; however, the difference between the groups of -2.36 minutes in favor of ramelteon did not achieve statistical significance (P=0.1093). Ramelteon increased TST significantly more than placebo at week one (difference in LS mean, 4.2 minutes; P=0.0484), but not at week two (2.4 minutes; P=0.2378). The mean NAW reported by patients in the ramelteon group was significantly less than that in the placebo group at week 2 (difference in LS mean of -0.07; P=0.0469) but not for week 1 (-0.04; P=0.2592). The mean sleep quality score with ramelteon was significantly smaller than that with placebo for week one (difference in LS mean, -0.12; P=0.0174), but not week two (-0.06; P=0.2059).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				There was no evidence of rebound insomnia with ramelteon during the run-out period. The mean total score for patients' global impression of treatment improved significantly with ramelteon compared to placebo at the end of week one (1.52 vs 1.59; P=0.0041) and week two (1.45 vs 1.53; P=0.0028). The proportion of patients scoring individual items as "improved" was significantly higher for ramelteon than placebo at weeks one and two for time to fall asleep (week one, 53.1 vs 44.3%; P=0.0100, week two, 58.3 vs 52.5%; P=0.0434), TST (week one, 42.0 vs 34.0%; P=0.0121, week two, 47.6 vs 38.8%; P=0.0031), sleep quality (week one, 56.4 vs 48.2%; P=0.0115, week two, 62.5 vs 56.1%; P=0.0463), and usefulness of treatment (week one, 58.2 vs 47.6%; P=0.0008, week two, 64.6 vs 56.8%; P=0.0123), but not for daytime distress (week one, 33.4 vs 31.9%; P=0.9116, week two, 42.7 vs 37.7%; P=0.0881). A total of 26.4% of patients in the ramelteon group and 20.5% of patients in the placebo group reported at least one treatment-emergent adverse event. All events were mild or moderate in severity. The most common adverse event leading to discontinuation was nasopharyngitis.
Uchiyama et al[45] Ramelteon 4 to 16 mg From week four onward, if patient did not improve in the PGI rating, the dosage could be titrated up to a maximum of 16 mg.	MC, SB Japanese patients 20 to 85 years of age with primary insomnia	N=222 24 weeks	Primary: Adverse events, residual effects, rebound insomnia, withdrawal symptoms, and dependence Secondary: Subjective SL and TST	Primary: During the study, 77.4% of patients reported adverse events. The most frequent reported adverse events were nasopharyngitis, inflammation of upper respiratory tract, eczema, elevated γ-glutamyltransferase, laryngopharyngitis, and headache. Endocrine adverse events that were considered drug-related included metrorrhagia, dysmenorrhea, polymenorrhea, increased estradiol, increased cortisol, and decreased cortisol. The mean change in next-morning residual scores significantly improved from baseline with ramelteon (P<0.05). The mean change from baseline in SL at week 24 and the placebo run-out period using the full analysis set with 8 mg were -30.4 and -28.6 minutes in the group continuously treated with ramelteon, which confirms the lack of rebound insomnia. Ramelteon was not associated with withdrawal symptoms and there was no evidence of dependence.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Secondary: Mean subjective SL decreased significantly during the study. In the group that continuously received ramelteon 8 mg, it decreased from a baseline of 70.5 to 54.4 minutes after one week (P<0.0001) and 33.8 minutes after 20 weeks (P<0.0001), then plateaued until the end of the study. The mean subjective TST was 5.52 hours at baseline, increasing to 5.78 hours at week one (P<0.0001) and 6.30 hours at week 20 (P<0.0001), and remained stable until the end of the study.
Gooneratne et al[46] Ramelteon 8 mg vs placebo	DB, PC, RCT Patients ≥60 years of age with obstructive sleep apnea and insomnia symptoms	N=21 4 weeks	Primary: Objective change in SOL using PSG Secondary: Global perception of sleep quality (PSQI), insomnia severity (ISI), daytime functioning (FOSQ), quality of life (SF-36), and APAP adherence	Primary: Using PSG, there was a 10.7 minute decrease in SOL in the ramelteon arm compared to a 17.8 minute increase in the placebo arm (difference, 28.5 minutes; P=0.008). For self-reported SOL, there was no significant difference among the two study arms (−1.3 minutes; P=0.9). Neither objective nor subjective SE differed significantly between study arms. Secondary: There were no significant differences in the PSQI, ISI, FOSQ, or SF-36 among the treatment groups. APAP adherence did not differ significantly between the ramelteon and placebo groups (159.1 vs 226.9 minutes; P=0.4). APAP adherence (≥4 hours of use for ≥4 nights per week) was 47.1% and was not affected by the treatment used. The adverse events reported with ramelteon were diarrhea, skin ulcer, sinusitis, and fracture after being hit by a bicyclist. For placebo, the adverse events were abdominal pain and nausea. All adverse events were thought to be unrelated to study drug treatments, and none were serious adverse events.
Uchimura et al (abstract)[47] Ramelteon 4 and 8 mg	DB, PC, RCT Japanese adults with chronic insomnia	N=1,130 Duration not reported	Primary: Not reported Secondary: Not reported	Primary: Not reported Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs placebo				There was no statistically significant difference between ramelteon and placebo in the change in subjective SL (P value not reported). Significant improvement was observed in the change in subjective TST with ramelteon 8 mg at week one (P value not reported). Post hoc analyses indicated that treatment with ramelteon 8 mg resulted in a reduction in subjective SL in individuals with smaller fluctuations (within ±30 minutes) of subjective SL at baseline, in those with a shorter (<1 year) history of insomnia, and in individuals who had not used benzodiazepines (P value not reported). Ramelteon was safe and well tolerated up to 16 mg nightly.
Kohsaka et al (abstract)[48] Ramelteon 4, 8, 16, or 32 mg vs placebo	DB, PC, XO Japanese patients with chronic insomnia	N=65 Each dose was given for two nights over five study periods	Primary: Not reported Secondary: Not reported	Primary: Not reported Secondary: Not reported Ramelteon 8 and 32 mg significantly shortened the mean LPS when compared to placebo (P value not reported). Overall changes in sleep architecture were modest (<3% changes vs placebo; P value not reported), with increases in stage 1 and decreases in stage 3/4. When compared to SL data from a similarly designed United States study, there was no evidence of any ethnic differences in the efficacy of ramelteon between Japanese and United States patients. Overall, ramelteon 8 mg showed the most favorable balance between sleep-promoting effects and tolerability (P value not reported). Ramelteon was well tolerated, the most common adverse effect was somnolence, which was similar to placebo at doses up to 8 mg, but increased with higher doses (P value not reported). Next-day residual effects occurred no more frequently with ramelteon at any dose than with placebo (P value not reported).
Wang-Weigand et al[49] Ramelteon 8 mg	PC, RCT Adults 18 to 64 years of age with chronic insomnia	N=552 Nightly treatment for 3 weeks with	Primary: Patient reported SL at week three Secondary:	Primary and secondary: There was a reduction in the average patient reported SL (as measured by the PSQ-IVRS) at weeks one, two, and three, when compared to placebo; however, none of these reductions reached statistical significance (P value not reported). There were no significant differences seen between ramelteon and placebo at any time point

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs placebo		a one week, placebo run-out period to assess rebound insomnia	Patient reported SL at week one and two, patient reported TST, patient reported WASO, patient reported NAW, and sleep quality (all assessed each week), safety	regarding the following patient-reported parameters: TST, WASO, NAW, or sleep quality (P value not reported). There was no evidence of rebound insomnia detected during the placebo run-out period for the groups that had received placebo or ramelteon. Headache and somnolence occurred in more than 3% of subjects in either group. Overall, the proportion of subjects with any treatment-related adverse events was similar between the ramelteon and placebo-groups (16.5 vs 15.4%, respectively; P value not reported).
Roth et al[50] Ramelteon 4 mg vs ramelteon 8 mg vs placebo Doses were given at night.	DB, PC, RCT Patients 64 to 93 years of age with chronic primary insomnia	N=829 5 weeks	Primary: SL at week one Secondary: TST at weeks one, three and five; reductions in SL at weeks three and five; sleep diaries; rebound insomnia and withdrawal effects during the seven-day placebo run out	Primary: Significant reductions in SL at week one were reported with both ramelteon 4 mg (70.2 vs 78.5 minutes; P=0.008) and 8 mg (70.2 vs 78.5 minutes; P=0.008) compared to placebo. Secondary: Patients continued to report reduced SL at week three with ramelteon 8 mg (P=0.003) and at week five with ramelteon 4 and 8 mg (P=0.028 and P<0.001, respectively) compared to placebo. Patient-reported TST at weeks one and three was significantly longer compared to placebo for ramelteon 4 mg (324.6 vs 313.9 minutes; P=0.004 and 336.0 vs 324.3 minutes; P=0.007, respectively). TST for ramelteon 4 mg at five weeks and for ramelteon 8 mg at weeks one, three and five were longer than placebo but did not reach statistical significance (P values >0.05). Analyses of other sleep parameters obtained via sleep diaries (e.g., NAW, ease of falling back asleep after an awakening and sleep quality) yielded no statistically significant differences among groups at weeks one, three and five. There was no evidence of significant rebound insomnia or withdrawal effects following treatment discontinuation. Incidence of adverse events was 51.5, 54.8 and 58.0% of patients in the placebo, 4 and 8 mg ramelteon groups, respectively.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Erman et al[51] Ramelteon 4, 8, 16 or 32 mg vs placebo Patients received all 5 treatments, with a 5- to 12-day washout between treatments. Medication was administered 30 minutes before bedtime.	DB, MC, PC, RCT, 5-period XO Men and non-pregnant, non-lactating women 18 to 64 years of age with chronic insomnia	N=107 2 nights per treatment	Primary: Mean LPS Secondary: TST, WASO, percentage of sleep time in each sleep stage, subjective sleep quality, next-day performance and alertness, safety	Primary: All tested doses of ramelteon resulted in statistically significant reductions in LPS compared to placebo (P<0.001). Secondary: All tested doses of ramelteon resulted in statistically significant increases in TST compared to placebo (P=0.001). No significant differences in WASO (P=0.470), percentage of time spent in the different sleep stages and subjective sleep quality (P=0.525) were reported between the ramelteon groups and the placebo group. There were no differences between the placebo group and any ramelteon dose group on next-day performance and alertness (P values not reported). The safety of ramelteon at each dose was similar to that of placebo and the most commonly reported adverse events were headache, somnolence, and sore throat.
Wang-Weigand et al[52] Ramelteon 8 mg vs placebo	DB, PC, RCT (pooled analysis of 4 trials) Patients 18 to 83 years of age with chronic insomnia	N=1,122 Duration varied among included trials	Primary: LS mean LPS for nights one and two for each included trial Secondary: Safety	Primary: At nights one and two, mean LPS was 43.3 minutes (SE, 1.2 minutes) for the placebo group and 30.2 minutes (SE, 1.19 minutes), resulting in a between-group difference of 13.1 minutes (P<0.001). Secondary: The total number of adverse events was similar for ramelteon 8 mg (209 [36.5%]) and placebo (192 [34.3%]) (P value not reported). The most common adverse events were headache and somnolence.
Zammit et al[53] Ramelteon 8 or 16 mg vs placebo	DB, MC, PC, RCT, SD Healthy patients 18 to 64 years of age	N=289 1 night	Primary: LPS assessed by PSG Secondary: PSG assessed endpoints include TST, WASO, and NAW after	Primary: Treatment with ramelteon 8 mg resulted in a significant decrease in LS mean LPS when compared to placebo (12.2 vs 19.7 minutes; P=0.004). Treatment with ramelteon 16 mg resulted in a numeric decrease in LS mean LPS when compared to placebo; however, this decrease did not reach statistical significance (14.8 vs 19.7 minutes; P=0.065). Secondary: Treatment with ramelteon 8 and 16 mg resulted in significant increases in the LS

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			persistent sleep onset; subjective measures include SL, TST, WASO, NAW after persistent sleep onset, and overall sleep quality, safety	mean TST when compared to placebo (8 mg: 436.8 vs 419.7 minutes; P=0.009 and 16 mg: 433.1 vs 419.7 minutes; P=0.043). There were no significant changes in any other objective or subjective measures of sleep. A total of 31 subjects (10.7%) reported at least one adverse event during the study. The incidence rates were 12.4, 13.3, and 6.4% for the placebo, ramelteon 8 and 16 mg groups, respectively. Most adverse events were mild or moderate in severity and the most commonly reported adverse event was somnolence.
Zammit et al[54] Ramelteon 8 mg vs zolpidem 10 mg vs placebo Subjects were administered the study drug 30 minutes prior to bedtime and were awakened 2 hours after dosing to evaluate balance.	DB, MC, PC, XO Adults over the age of 65 with self-reported chronic insomnia	N=33 Each study drug was taken for one night each with a 4 to 10 day washout period between treatments.	Primary: SOT composite score Secondary: Equilibrium scores on the SOT, SOT ratios, SQTT scores, and memory tests, safety	Primary: There were no differences between placebo and ramelteon on the SOT (P=0.837). Secondary: There were no significant differences between placebo and ramelteon on turn time (P=0.776) or turn sway (P=0.982). Treatment with zolpidem, the positive control, did result in significant impairments on the SOT, turn time, and turn sway (P<0.001 for all). Immediate and delayed memory recall were not significantly different with ramelteon (P=0.683 and P=0.650, respectively); however, immediate recall declined significantly with zolpidem (P=0.002). Adverse events were infrequent and none were serious. The same proportion of subjects in the ramelteon and placebo groups reported adverse events (21.2%) compared to 39.4% of subjects in the zolpidem group. Adverse events that occurred in at least two subjects in any group include dizziness, headache, nausea, and somnolence.
Dobkin et al[55] Ramelteon 8 mg	OL, PRO Patient population not specified	N=20 6 weeks	Primary: Patient reported LPS Secondary: Patient reported endpoints include	Primary: Treatment with ramelteon resulted in improvements in LPS at week six when compared to baseline (24.0±15.0 vs 46.2±19.8 minutes; P<0.001). The average improvement across all participants was 22 minutes. Secondary: Treatment with ramelteon 8 mg resulted in improvements at week six when compared

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			TST, WASO, total number of nighttime awakenings, SE, and number of hot flashes/ night sweats; other secondary endpoints include sleep impairment (assessed via the SII), daytime functioning, daytime alertness, quality of life (assessed via the MENQOL), mood (assessed via the BDI), CGI-S, and CGI-I, safety	to baseline in the following parameters: TST (420±38 vs 336±62 minutes; P<0.001), SE (0.91±0.06 vs 0.80±0.10; P<0.001), night time awakenings (1.86±1.53 vs 2.32±1.36; P<0.05), and hot flashes (1.52±1.32 vs 2.31±1.95; P<0.05). There were no significant improvements in WASO at any time period throughout the study when compared to baseline. Significant improvements were observed in patient reported sleep quality (P<0.001), daytime dysfunction (P<0.01), daytime alertness (P<0.001), SII scores (P<0.001), MENQOL scores (P<0.01), BDI scores (P<0.001), and anxiety (P<0.001). At the end of this trial, 55% of women were considered "responders" according to the CGI-I scale. Insomnia severity, assessed by the CGI-S, also improved over baseline (3.14 vs 4.65; P<0.001). Of the subjects treated with ramelteon in this trial, 40% reported side effects. The most frequently reported side effects included headaches, daytime fatigue/fogginess, dry mouth, lightheadedness, and dizziness. Most side effects were mild and transient.
Richardson et al[56] Ramelteon 8 or 16 mg Subjects >65 years of age received 8 mg/day, subjects 18 to 64 years of age received 16 mg/day.	OL, PRO Adults with primary insomnia	N=1,213 48 weeks	Primary: Adverse events, changes in vital signs, laboratory values, 12-ECG, and results of physical examination Secondary: Safety	Primary: There were no noteworthy changes in vital signs, physical examinations, clinical chemistry, hematology, or urinalysis values. There were also no ECG changes to suggest adverse cardiac effects. Consistent statistically significant (P≤0.05) decreases in free thyroxine and free testosterone (in older men) were detected. Duration of menses increased by approximately one day. In both groups, those older and younger than 65, subjective SL and TST improved by month one and was sustained during the one-year period. At six months and one year, CGI indices were improved. During the placebo run-out period, SL did increase but did not return to baseline. Secondary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				A total of 69.8% of patients reported at least one adverse event. There was no difference in adverse event incidence between those older and younger than 65 (P value not reported). The overall incidence of adverse events was similar at six months and one year.
Gross et al[57] Ramelteon 8 mg All patients continued to take their antidepressant; dose reductions were permitted at any time but no dose increases were permitted during the study period.	OL, PRO Patients 18 to 80 years of age with GAD and related insomnia	N=27 10 weeks	Primary: CGI-I, CGI-S, daytime sleepiness (assessed via ESS), HAMA, and patient reported sleep diaries Secondary: Safety	Primary: The addition of ramelteon 8 mg resulted in significant improvement over baseline in the following study parameters: time to fall asleep (34.67±29.26 vs 77.52±47.73 minutes; P<0.001), TST (7.52±1.22 vs 5.02±0.96 hours; P<0.001), CGI-S Insomnia (1.67±0.73 vs 4.30±0.47; P<0.001), CGI-I Insomnia (1.59±0.64 vs 3.85±0.36; P<0.001), HAMA (3.96±2.97 vs 8.26±2.94; P<0.001), ESS (5.48±3.27 vs 11.56±2.14; P<0.001), CGI-S Anxiety (1.25±0.64 vs 2.85±0.66; P<0.001), CGI-I Anxiety (1.41±0.50 vs 2.33±0.78; P<0.001). Secondary: The most common adverse events regarding ramelteon use were headache upon stopping ramelteon (7.4%), daytime tiredness (3.7%), and depression (3.7%). All side effects were reported as transient.
Herring WJ et al[58] Suvorexant high-dose (40 mg in patients <65 years and 30 mg in patients ≥65 years) vs suvorexant low-dose (20 mg in patients <65 years and 15 mg in patients ≥65 years) vs placebo	DB, MC, PC, PG, RCT Patients ≥18 years of age who met DSM-IV-TR criteria for primary insomnia	Study One: N=1,021 3 months Study Two: N=1,009 3 months	Primary: Change from baseline with high-dose therapy in sTST, sTSO, WASO and LPS at months one and three Secondary: Change from baseline with high-dose (both studies) or low-dose therapy (Study One only) in sTST and sTSO at week	Primary: Study One: Compared to placebo, patients in the suvorexant high-dose group experienced a significant increase in sTST from baseline to month one (19.6 minutes; 95% CI, 12.0 to 27.1; P<0.001) and to month three (19.7 minutes; 95% CI, 11.9 to 27.6; P<0.001). Patients in the suvorexant high-dose group also experienced a significant decrease in sTSO from baseline to month one (-7.4 minutes; 95% CI, -12.3 to -2.5; P<0.01) and to month three (-8.4 minutes; 95% CI, -12.8 to -4.0; P<0.01), compared to placebo. Compared to placebo, patients in the suvorexant high-dose group experienced a significant decrease in LPS from baseline to month one (-11.2 minutes; 95% CI, -16.3 to -6.1; P<0.001) and to month three (-9.4 minutes; 95% CI, -14.6 to -4.3; P<0.001). Patients in the suvorexant high-dose group also experienced a significant decrease in WASO from baseline to month one (-26.3 minutes; 95% CI, -33.5 to -19.2; P<0.001) and to month three (-22.9 minutes; 95% CI, -30.3 to -15.4; P<0.001). Study Two: Compared to placebo, patients in the suvorexant high-dose group experienced a significant increase in sTST from baseline to month one (26.3 minutes; 95% CI, 18.3

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			one and in WASO and LPS at night one	to 34.3; P<0.001) and to month three (25.1 minutes; 95% CI, 16.0 to 34.2; P<0.001). Patients in the suvorexant high-dose group also experienced a significant decrease in sTSO from baseline to month one (-12.8 minutes; 95% CI, -18.8 to -6.9; P<0.001) and to month three (-13.2 minutes; 95% CI, -19.4 to -7.0; P<0.001) compared to placebo. Compared to placebo, patients in the suvorexant high-dose group experienced a significant decrease in LPS from baseline to month one (-12.1 minutes; 95% CI, -17.8 to -6.4; P<0.001) but the decrease observed from baseline to month three was not significant (-3.6 minutes; 95% CI, -10.1 to 2.8; P value not reported). Patients in the suvorexant high-dose group also experienced a significant decrease in WASO from baseline to month one (-29.4 minutes; 95% CI, -36.6 to -22.3; P<0.001) and to month three (-29.4 minutes; 95% CI, -36.7 to -22.1; P<0.001). Secondary: Study One: Compared to placebo, patients in the suvorexant high-dose group experienced a significant increase in sTST (21.4 minutes; 95% CI, 15.5 to 27.4; P<0.001) as well as a significant decrease in sTSO (-5.7 minutes; 95% CI, -9.7 to -1.6; P<0.01) from baseline to week one. Patients in the suvorexant low-dose group also experienced a significant increase in sTST (13.6 minutes; 95% CI, 6.9 to 20.3; P<0.001) and a significant decrease in sTSO (-5.6 minutes; 95% CI, -10.2 to -1.1; P<0.05) from baseline to week one, compared to placebo. Compared to placebo, patients in the suvorexant high-dose group experienced a significant decrease in LPS (-10.3 minutes; 95% CI, -15.0 to -5.5; P<0.001) and WASO (-38.4 minutes; 95% CI, -44.5 to -32.3; P<0.001) from baseline to night one. Patients in the suvorexant low-dose group also experienced a significant decrease in LPS (-9.6 minutes; 95% CI, -14.9 to -4.3; P<0.001) and WASO (-32.5 minutes; 95% CI, -39.3 to -25.7; P<0.001). Study Two: Compared to placebo, patients in the suvorexant high-dose group experienced a significant increase in sTST (26.4 minutes; 95% CI, 19.8 to 33.1; P<0.001) as well as a significant decrease in sTSO (-13.1 minutes; 95% CI, -17.7 to -8.4; P<0.001) from baseline to week one.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Compared to placebo, patients in the suvorexant high-dose group experienced a significant decrease in LPS (-21.7 minutes; 95% CI, -28.6 to -14.9; P<0.001) and WASO (-42.0 minutes; 95% CI, -48.6 to -35.3; P<0.001) from baseline to night one.
Michelson et al[59] Suvorexant (40 mg in patients <65 years and 30 mg in patients ≥65 years) vs placebo	DB, MC, PC, PG, RCT Patients ≥18 years who met criteria for primary insomnia assessed by a clinical interview and a structured sleep diagnostic interview	N=781 1 year	Primary: Safety and tolerability of suvorexant Secondary: STSTM and STSOM during the first month of treatment	Primary: Patients treated with suvorexant (69.5%) had a similar incidence of adverse events compared to those treated with placebo (63.6%) (95% CI, -1.1 to 13.1). There was a greater incidence of drug-related adverse events, as established by the investigator, in patients treated with suvorexant (34.9%) compared to those treated with placebo (20.5%) (95% CI, 7.8 to 20.6). The incidence of serious adverse events was similar between the suvorexant (5.2%) and placebo (6.6%) treatment groups (95% CI, -5.5 to 1.9). Incidence of discontinuation due to adverse events was similar between the suvorexant (11.7%) and placebo (8.5%) treatment groups (95% CI, -1.5 to 7.4). Somnolence was the adverse event with the highest incidence in the suvorexant treatment group (13.2%) and had greater incidence in the active treatment group compared to placebo (2.7%) (95% CI, 6.8 to 14.1). Secondary: The suvorexant group showed significant improvements in the STSTM compared with the placebo group at week one (P<0.0001), week two (P<0.0001), week three (P<0.0001), week four (P<0.0001) and at the end of month one (P<0.0001). The suvorexant group showed significant improvements in the STSOM compared with the placebo group at week one (P=0.0001), week two (P=0.0077), week three (P=0.0047) and week four (P=0.0004) and at the end of month one (P=0.0002).
Sun et al[60] Suvorexant 10 mg, 50 mg and 100 mg vs placebo	DB, PC, RCT, XO Healthy male subjects 18 to 45 years of age	N=20 2 nights	Primary: SWA Secondary: PSG sleep parameters (LPS, WASO, SE, TST); sleep architecture; psychomotor performance (assessed via SRT, CRT and	Primary: Compared to placebo, there was no statistically significant effect of suvorexant on SWA during the first half of the night with similar findings across the entire night compared to placebo (P=NS). Secondary: Patients treated with suvorexant 50 mg and 100 mg experienced significantly decreased LPS (50 mg: 90% CI, 0.21 to 0.60; P<0.05; 100 mg: 90% CI, 0.14 to 0.39; P<0.05) and WASO (50 mg: 90% CI, 0.60 to 0.81; P<0.05; 100 mg: 90% CI, 0.59 to 0.79; P<0.05) and significantly increased SE (50 mg: 90% CI, 1.02 to 1.05; P<0.05; 100 mg: 90% CI, 1.03 to 10.6; P<0.05) and TST (90% CI, 1.03 to 10.6; P<0.05 for both doses) compared to placebo.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			DSST); subjective residual effects	There were no consistent statistically significant effects of suvorexant on PSG sleep architecture over the entire eight hour PSG-recording session compared to placebo. There was no statistically significant effect of suvorexant on NSS compared to placebo suggesting that suvorexant treatment does not lead to an imbalance in sleep stage changes or cause sleep fragmentation (P=NS) Compared to placebo, in patients treated with suvorexant 100 mg, there was an increase in reaction time for both SRT (90% CI, 4.02 to 23.26; P<0.05) and CRT (90% CI, 5.46 to 33.52; P<0.05) but not DSST (90% CI, -6.05 to 0.45; P=NS). There were no significant changes on SRT, CRT and DSST in patients treated with suvorexant 10 mg and 50 mg, compared to placebo (P=NS). With regards to subjective residual effects, patients treated with suvorexant 50 mg and 100 mg demonstrated a significant effect compared to placebo on "pattern of wakening" (50 mg: 90% CI, -20.77 to -5.13; P<0.05; 100 mg: 90% CI, -21.24 to -5.61; P<0.05) and "behavior on waking" (50 mg: 90% CI, -18.55 to -7.45; P<0.05; 100 mg: 90% CI, -20.95 to -9.85; P<0.05) at 10 hours post dose, suggesting less ease in waking up and less alertness following waking, compared to placebo. No significant differences were observed in the parameters "getting to sleep" and "quality of sleep" (P=NS).
Rajaratnam et al[61] Study One: Tasimelteon 10, 20, 50 or 100 mg vs placebo Study Two: Tasimelteon 20 mg, 50 mg or 100 mg vs	DB, PC, PG, RCT Study One: Patients 18 to 50 years of age in good health and without major sleep disorders Study Two: Patients 21 to 50 years of age in good health and without major sleep disorders with induced	Study One: N=39 7 nights Study Two: N=412 Duration not specified	Primary: Study One: SE (assessed via TST) and $DLMO_{25\%}$ Study Two: LPS Secondary: Study One: WASO; latency to sleep onset; LPS; percentage of REM sleep relative to total	Primary: Study One: Patients treated with tasimelteon at all doses experienced an increase in SE during the middle third of the night (P<0.05 for all doses). There was no significant difference with regards to SE in the first and final third of the sleep episode between the tasimelteon and placebo groups (P value not reported). Patients in the tasimelteon groups slept 35 to 104 minutes more than the placebo group (P<0.05 for tasimelteon 20 mg, 50 mg and 100 mg groups). $DLMO_{25\%}$ occurred earlier on treatment day one compared to baseline for all treatment groups, indicating that the circadian melatonin rhythm had advanced. Only patients treated with tasimelteon 100 mg shifted $DLMO_{25\%}$ significantly earlier than did placebo (P=0.001). Study Two: Compared to placebo, patients treated with tasimelteon experienced shorter LPS

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
placebo	transient insomnia		scored data Study Two: WASO	(P<0.001 for all groups). Secondary: Study One: In patients treated with tasimelteon, there was no significant difference in WASO compared to placebo (P value not reported); however, patients treated with tasimelteon experienced a decrease in latency to sleep onset (P<0.05 for all groups) and LPS (P<0.05 for tasimelteon 10 mg, 50 mg and 100 mg). On treatment day one, REM sleep accumulated more rapidly in patients treated with tasimelteon 20 mg, 50 mg and 100 mg compared to placebo or tasimelteon 10 mg (P value not reported). REM sleep relative to total sleep scored data from baseline to treatment day one did not differ significantly in groups receiving tasimelteon 20 mg, 50 mg or 100 mg (P value not reported). Study Two: Patients treated with tasimelteon 20 mg and 50 mg experienced reduced WASO compared to patients treated with placebo (P<0.05 for both groups).
Package insert[9] SET Tasimelteon 20 mg vs placebo	DB, MC, PC, PG, RCT Patients with a median age of 54 years who are totally blind with non-24 hour sleep-wake disorder	N=84 6 months	Primary: Nighttime total sleep time on 25% most symptomatic nights; daytime nap duration on 25% most symptomatic days Secondary: Not reported	Primary: At baseline, patients in the tasimelteon group had an average of 195 minutes of nighttime sleep and 137 minutes of daytime sleep on the 25% of most symptomatic nights and days, respectively. Patients treated with tasimelteon increased nighttime total sleep time by 50 minutes and decreased daytime sleep by 49 minutes, compared to an increase of 22 minutes and a decrease of 22 minutes, respectively, for patients who received placebo (P values not reported). A responder analysis was conducted for patients with both a ≥45-minute increase in nighttime sleep and a ≥45-minute decrease in daytime nap time. Of patients treated with tasimelteon, 29% (N=12) met the responder criteria compared to 12% (N=5) in the placebo group (P values not reported). Secondary: Not reported.
Package insert[9] RESET	DB, MC, PC, PG, RCT, WT	N=40 20 weeks	Primary: Nighttime total sleep time on	Primary: Patients treated with tasimelteon experienced a decrease in nighttime total sleep of 7 minutes and an additional decrease in daytime nap time of 9 minutes, compared to a

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Tasimelteon 20 mg vs placebo	Patients with a median age of 55 years who are totally blind with non-24 hour sleep-wake disorder		25% most symptomatic nights; daytime nap duration on 25% most symptomatic days Secondary: Not reported	decrease of 74 minutes and an increase of 50 minutes, respectively, for patients who received placebo (P value not reported). Secondary: Not reported.
Huang et al[62] Zaleplon 10 mg vs zolpidem 10 mg	AC, DB, RCT Patients 20 to 65 years of age with primary insomnia	N=48 2 weeks	Primary: Change in subjective SL from baseline to week two Secondary: Sleep duration, NAW, sleep quality and incidence of rebound insomnia	Primary: There was a significant reduction in subjective SL in the zaleplon group (reduced from 63.0 minutes to 31.6 minutes; P<0.05) and zolpidem group (reduced from 61.9 minutes to 30.0 minutes; P<0.05). There was no significant difference between the zaleplon group and zolpidem group in SL (P=0.084). Secondary: There was no significant difference in sleep duration, NAW, or sleep quality among the groups. None of the patients experienced rebound insomnia. The most frequently reported adverse effects were headache, dizziness, anxiety and urinary tract infection. There was no significant difference in the frequency of each adverse effect between the zaleplon and zolpidem groups.
Danjou et al[63] Zaleplon 10 mg vs zolpidem 10 mg vs placebo	DB, XO Healthy volunteers, mean age 29.5 years	N=36 13 days	Primary: Subjective and objective measurements of residual effects when study drug was given five, four, three, or two hours before morning awakening, tests included DSST, CFF threshold,	Primary: No residual effects were demonstrated after zaleplon 10 mg, when administered as little as two hours before waking, on either subjective or objective assessments. Zolpidem 10 mg showed significant residual effects on DSST and memory after administration up to five hours before waking and CRT, CFF threshold and Sternberg Memory Scanning Task after administration up to four hours before waking. Residual effects of zolpidem were apparent in all objective and subjective measurements when the drug was administered later in the night. There were no serious adverse experiences during the study; all adverse events were mild-to-moderate. Overall, the number of subjects who reported any adverse experience after administration of study drug was similar for zaleplon and placebo (11

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			CRT, Memory Test, Sternberg Memory Scanning Task, LARS, LSEQ, adverse events Secondary: Not reported	and 33% regardless of the time of drug administration) but was significantly higher following zolpidem (56 to 72%) when zolpidem was administered two, three, four, and five hours before awakening (P values not reported). Secondary: Not reported
Verster et al[64] Zaleplon 10 mg vs zaleplon 20 mg vs zolpidem 10 mg vs zolpidem 20 mg vs placebo This was a 2-part study with the first part evaluating the effect of ethanol and the second part evaluating the effects of zaleplon and	DB, XO Healthy volunteers with mean age 24.0 years	N=30 Single dose with at least a 5-day washout period	Primary: Driving ability (standard deviation of the lateral position, standard deviation of speed, memory, psychomotor performance) (subjects given study medication five hours after going to bed and awakened three hours after dose, driving test performed four hours after awakened, memory and psychomotor tests performed six hours after awakened) Secondary:	Primary: Zaleplon 10 and 20 mg did not significantly impair driving ability four hours after middle-of-the-night administration (significant difference defined as P<0.0125). Relative to placebo, after zolpidem 10 mg, standard deviation of the lateral position (amount of weaving of the car) was significantly elevated but the magnitude of the difference was small and not likely to be of clinical importance (difference, 2.87 cm; P<0.005). Standard deviation of speed (speed variability) was not significantly different for zolpidem 10 mg than placebo (P=0.256). Zolpidem 20 mg significantly increased SDLP and speed variability (both P<0.001). Memory and psychomotor test performances were unaffected after both doses of zaleplon and zolpidem 10 mg. Zolpidem 20 mg significantly impaired performance on psychomotor and memory tests. (Note: the recommended dose for zolpidem is 10 mg immediately before bedtime.) Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
zolpidem. Only the second part of the study was reported in this review.			Not reported	
Dundar et al[65] Zaleplon 5 to 20 mg vs zolpidem 5 to 10 mg The complete MA included 24 studies in 3,909 patients of which 17 studies compared zaleplon, zolpidem or zopiclone* to a benzodiazepine, 1 study compared zolpidem to zopiclone* and 6 studies compared zaleplon to zolpidem. Only the results of the studies comparing zaleplon to zolpidem are included in this review.	DB, MA, PG, RCT, XO Patients 16 to 85 years of age with insomnia	6 trials N=1,539 Duration varied (2 nights to 4 weeks)	Primary: SOL, TST, quality of sleep, adverse events, rebound insomnia Secondary: Not reported	Primary: Of the two studies that directly compared SOL, one study reported a significantly shorter SL with zaleplon (P<0.001), whereas the other study reported results in favor of zolpidem (P=0.03). Of the two studies that directly compared TST, one study reported that sleep duration was significantly less in the zaleplon group (290.7 vs 308.6 minutes for zolpidem; P=0.05) but another study found no difference (eight hours for zaleplon vs 8.3 hours for zolpidem; P value not reported). Patients on zaleplon were less likely to experience an improvement in sleep quality than those on zolpidem (OR, 0.66; 95% CI, 0.51 to 0.87). There was no statistically significant difference in the frequency of treatment-emergent adverse events (OR, 0.86; 95% CI, 0.62 to 1.20). One study reported that patients taking zaleplon were less likely to suffer withdrawal symptoms on the first night of the placebo run-out phase than those on zolpidem (1.5 and 7.1% respectively; P=0.01). Combined results from two trials noted that patients receiving zaleplon were less likely to experience rebound insomnia compared to those receiving zolpidem (SL OR, 0.27; 95% CI, 0.17 to 0.44; sleep duration OR, 0.25; 95% CI, 0.15 to 0.41; and NAW OR, 0.34; 95% CI, 0.18 to 0.61). In a XO, 62.3% of patients favored zolpidem compared to 37.7% of patients who favored zaleplon (P=0.08). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Elie et al[66] Zaleplon 5, 10 or 20 mg or zolpidem 10 mg vs placebo After 28 days, all treatments were followed by placebo for 3 nights.	DB, MC, PC, RCT Adults with primary insomnia or insomnia associated with mild nonpsychotic psychiatric disorders	N=615 4 weeks	Primary: Patient's assessment of SL Secondary: Patient's assessment of sleep duration, sleep quality, NAW, rebound insomnia, withdrawal effects, safety	Primary: Median SL was significantly lower with zaleplon 10 and 20 mg than with placebo during all four weeks of treatment, and with zaleplon 5 mg and zolpidem 10 mg for the first three weeks. Secondary: Zaleplon 20 mg significantly ($P \leq 0.05$) increased sleep duration compared to placebo in all but week three of the study, while zolpidem 10 mg significantly ($P \leq 0.05$) increased sleep duration at all time points. Mean scores for sleep quality were significantly ($P \leq 0.05$) better than with placebo during week one with zaleplon 10 and 20 mg, and for all weeks with zolpidem 10 mg. No significant differences were observed in NAW between the placebo and active treatment groups (P values not reported). The number of patients treated with zaleplon showing rebound insomnia was not significantly different from placebo on the first night after discontinuation of four weeks of treatment. Significant differences in SL ($P \leq 0.05$) and NAW ($P \leq 0.01$) were noted in patients treated with zolpidem 10 mg. On the second night after discontinuation of treatment, there were significantly more patients ($P \leq 0.05$) showing rebound insomnia for the NAW with zaleplon 10 and 20 mg than with placebo, and on the third night there were significantly fewer patients ($P \leq 0.05$) showing rebound for the NAW with zaleplon 20 mg. There was no evidence of withdrawal symptoms after discontinuation of four weeks of zaleplon treatment. Significantly more patients who had received zolpidem than placebo reported withdrawal effects on the first night after treatment was discontinued; however, there was no statistically significant difference on the second or third night between the two groups. The frequency of adverse events in the active treatment groups did not differ significantly from that in the placebo group.
Zammit et al[67]	DB, PC, RCT, XO	N=37	Primary: LPS; TST;	Primary: LPS after the administration of zaleplon 10 mg, zolpidem 10 mg and placebo was

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Zaleplon 10 mg vs zolpidem 10 mg vs placebo	Patients 18 to 65 years of age with primary sleep-maintenance insomnia	2 nights	daytime SL Secondary: Not reported	14.9, 11.7, and 42.2 minutes, respectively (overall P<0.001), which made the LPS with active agents shorter by approximately 27 and 31 minutes (P<0.001 for both comparisons). TST was significantly longer with zaleplon 10 mg and zolpidem 10 mg than placebo by approximately 22 and 30 minutes, respectively (overall P<0.001). Daytime SL was not significantly different between the zaleplon 10 mg and placebo groups (P>0.136); however, it was shorter with zolpidem 10 mg compared to placebo (overall P<0.001) when tested at four (P<0.001), five (P<0.001) and seven (P<0.05) hours, respectively, after dose administration. Secondary: Not reported
Hindmarch et al[68] Zolpidem, modified release 6.25 mg vs zolpidem modified release 12.5 mg vs flurazepam 30 mg vs placebo	DB, DD, RCT, XO Healthy volunteers at least 65 years of age	N=24 Single dose, treatment visits lasted 2 days and were separated by 28 to 42 days washout	Primary: Psychometric tests performed eight hours after study medication (CFF, CRT, word recall, CTT, DSST), subjective evaluation of sleep (LSEQ), safety, pharm-acokinetics (zolpidem modified release only) Secondary: Not reported	Primary: There were no significant differences in psychometric tests between either dose of zolpidem modified release and placebo (P<0.05). Psychometric performance was significantly impaired (P<0.05) with flurazepam compared to placebo for all tests with the exception of the DSST (P=0.0526). Ease of falling asleep and sleep quality were significantly improved with both doses of zolpidem modified release and with flurazepam (all P<0.05). Neither zolpidem modified release nor flurazepam modified perception of well-being on awakening (P values not reported). The frequency of adverse events was similar in all four groups. None of the adverse events was serious or led to withdrawal from the study. The plasma concentration ratio was 1.96 between the two doses of zolpidem modified-release, which is consistent with dose linearity. Secondary: Not reported
Krystal et al[69]	DB, MC, PC, RCT	N=1,025	Primary: Score on the	Primary: At week 12, PGI, Item 1 (aid to sleep) was scored as favorable (i.e., “helped me

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Zolpidem ER 12.5 mg vs placebo Treatments were taken 3 to 7 nights per week.	Patients 18 to 64 years of age with chronic primary insomnia	26 weeks	PGI, Item 1, (aid to sleep) at week 12 of the treatment period in the ITT population Secondary: Scores on CGI-I, PGI, PMQ, TST, WASO, SOL, quality of sleep, and NAW in the ITT population	sleep") by 89.8% of zolpidem patients vs 51.4% of placebo patients (P<0.0001). Secondary: The percentage of patients who reported a treatment benefit on the PGI (Items 1 to 4) was higher in the zolpidem ER group compared to placebo at each four-week interval during the 24-week treatment period (all P<0.0001). The percentage of patients who obtained a positive evaluation on the CGI-I scale was greater in the zolpidem ER group compared to the placebo group at all four-week intervals during the 24-week treatment period (all P<0.0001). At every time point, results on the PMQ were greater for patients in the zolpidem ER group compared to the placebo group for the TST (P<0.0001), WASO (P<0.0001), SOL (P≤0.0014), quality of sleep (P<0.0001), and NAW (month one; P=0.0515, months two to six; P<0.0001). Patients in the zolpidem ER group demonstrated improvements in their ability to concentrate in the morning at each month throughout the treatment period, as compared to those in the placebo group (months 1 to 5, P<0.0001; month 6, P=0.0014). Patients in the zolpidem ER group had sustained reductions in their level of sleepiness in the morning compared to placebo at each month throughout the treatment period (P<0.0001). The most common adverse events occurring at a higher frequency in the zolpidem extended-release group than in the placebo group were headache, anxiety, somnolence, dizziness, fatigue, disturbance inattention, irritability, nausea, and sinusitis.
Fava et al[70] Zolpidem ER 12.5 mg vs	DB, MC, PC, PG, RCT Patients 21 to 64 years of age with major depressive disorder and	N=358 24 weeks Two phases were included	Primary: Change from baseline in subjective TST Secondary: Subjective LSO,	Primary: Phase 1 During phase 1, treatment with zolpidem ER led to significantly greater improvements in TST when compared to treatment with placebo (P<0.0001). Phase 2 During phase 2, treatment with zolpidem ER led to improvements in TST that were

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
placebo Patients were also receiving OL escitalopram 10 mg daily.	associated insomnia	Phase 1 was 8 weeks; responders (≥50% in 17-item $HDRS_{17}$) at week 8 continued to receive an additional 16 weeks of therapy in phase 2	NAW, WASO, sleep quality, sleep-related next-day functioning, $HDRS_{17}$ SIS score, PGI-IT, CGI-I, CGI-S, MGH-CPFQ, Q-LES-Q, safety	significant at weeks 12 and 16 (P<0.05 for both), but not at weeks 20 and 24 (P value not reported). Secondary: Phase 1 Treatment with zolpidem ER led to significantly greater improvement in TST at each assessment. The LSM difference between the treatment groups in the change from baseline TST ranged from 37.9 to 45.5 minutes (P<0.0001 for all comparisons). The group receiving zolpidem ER had a TST of approximately seven hours at week eight, compared to approximately five hours at baseline (P<0.0001 vs placebo for improvement over baseline). Treatment with zolpidem ER led to significantly greater improvements in WASO, LSO, NAW, and sleep quality when compared to treatment with placebo (P<0.001 for all comparisons at all time points). Total improvement in insomnia-only $HDRS_{17}$ was also significantly greater in the group receiving zolpidem ER compared to those receiving placebo (P<0.001 for all time points). Treatment with zolpidem ER also produced favorable results on all domains of the SIS, except mental fatigue, when compared to treatment with placebo at week eight (P<0.05). There were no significant differences at week eight between the two groups on the improvement in functioning and quality of life on the Q-LES-Q; however, at week eight, there were greater improvements seen in the MGH-CPFQ total score, wakefulness/alertness, energy, memory/recall, and mental acuity in those patients receiving zolpidem ER compared to those receiving placebo (P<0.05). There were no significant improvements found with zolpidem ER compared to placebo on motivation/enthusiasm, attention focus/sustain, or ability to find words, at week eight. Treatment with zolpidem ER was also associated with greater improvements than placebo in some aspects of sleep-related next-day functioning, including morning energy, sleep impact on daily activities, and morning concentration ability. Decreases seen in the $HDRS_{17}$ scores at week eight were comparable between the two treatment groups; at the end of phase 1 58.4 and 63.7% of patients in the placebo and zolpidem ER groups, respectively, met the criteria for depression treatment response.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				PGI-IT scores were superior in the group receiving zolpidem ER compared to those in the placebo group (P<0.001) and both CGI-S and CGI-I scores were comparable between the groups throughout phase 1. Phase 2 During phase 2, treatment with zolpidem ER continued to show significantly greater improvement at each visit in the NAW and sleep quality, when compared to treatment with placebo (P value not reported). For WASO, treatment with zolpidem ER resulted in significant improvements over treatment with placebo at weeks 16 and 20 and there were no significant differences between the treatment groups in LSO during phase 2 (P value not reported). The $HDRS_{17}$ total score of insomnia-only items demonstrated significantly greater improvement in the zolpidem ER group throughout phase 2 (P<0.05 for all time points). Treatment with zolpidem ER was associated with significant differences on all of the SIS domain scores at week 24, except mental fatigue (P<0.05). There were no differences between the groups in any of the MGH-CPFQ subscales at week 24 (P value not reported). Treatment with zolpidem ER resulted in improvements over placebo on the physical health/activities and medication satisfaction subscales of Q-LES-Q (P<0.05); however, treatment with placebo resulted in improvements over zolpidem ER on the school/course work subscale (P<0.05). Both groups experienced improvements in depression treatment remission and depression symptoms; however, these improvements were not significantly different between groups (P value not reported). PGI-IT scores indicated insomnia treatment was rated higher with zolpidem ER compared to placebo (P<0.001). Ratings of severity and mental illness by clinicians were comparable between the two groups throughout phase 2. A greater percentage of patients treated with zolpidem ER experienced at least one adverse event during phase 1 when compared to patients treated with placebo (72.9 vs 66.3%; P value not reported). The most common adverse events that occurred more frequently in the group receiving zolpidem ER, compared to the placebo group,

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				include nausea, somnolence, dry mouth, dizziness, fatigue, upper respiratory tract infection, and decreased libido. During phase 2, 57.3% of zolpidem ER-treated patients and 60% of placebo-treated patients experienced an adverse event (P value not reported). The most frequently reported events among both treatment groups include headache, diarrhea, and nasopharyngitis.
Fava et al[71] Zolpidem ER 12.5 mg vs placebo All patients received OL escitalopram 10 mg/day.	DB, MC, PC, PG, RCT Patients 21 to 64 years of age with insomnia and comorbid GAD	N=383 8 weeks	Primary: Change from baseline to week eight in subjective TST Secondary: Subjective SOL, NAW, WASO, sleep quality, HAMA, BAI, SIS, MGH-CPFQ, SDS, safety	Primary: At week eight, the mean TST increased from baseline by 106 minutes in the group receiving zolpidem ER and by 68.2 minutes in the placebo group (LSM in the change from baseline between groups 39.4 minutes, 90% CI, 24.81 to 53.99; P<0.0001). Secondary: From week one through week eight, mean TST was significantly greater in the group receiving zolpidem ER when compared to those receiving placebo (P<0.0001). Significant improvements in SOL, WASO, NAW, and quality of sleep were observed throughout the treatment period with zolpidem ER vs placebo based on the difference in LSM change from baseline (P<0.0001 for all comparisons). Significant improvements were also seen with MSQ measures of sleep-related next-day symptoms, including morning energy, morning concentration, and impact of sleep on daily activities (P<0.0001 for all comparisons). The change from baseline in PGI-IT for the zolpidem ER-treated group was significantly greater when compared to the placebo-treated group (P<0.0001 for all comparisons). At week two, there was a significant difference in favor of treatment with zolpidem ER on all seven items of the SIS (P<0.0001 for six comparisons; P<0.01 for one comparison). This improvement was sustained to week eight on four of the seven items: daily activities (P=0.107), emotional impact (P<0.0001), energy/fatigue (P<0.001), and satisfaction with sleep (P<0.0001). Between group differences in the total MGH-CPFQ score were significant at week four but not at week eight (P=0.0586). There were statistically significant differences between groups at one or both of the time points for three of seven items. There was statistically significantly greater improvement in the zolpidem ER group on three items (motivation, wakefulness/alertness, and energy) at week four (P<0.05) and on two items (wakefulness/alertness and energy) at week eight (P<0.01). The mean HAMA total scores decreased for both groups throughout the study. At

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				week eight, HAMA total scores for both the group receiving zolpidem ER and the group receiving placebo showed comparable reductions (-13.3 vs -12.5, respectively; P=0.4095). Rates of treatment response in the group receiving zolpidem ER and the group receiving placebo were similar at week eight (63.4 vs 64.2%, respectively; P=0.8564). Both treatment groups demonstrated at least a 40% reduction in the BAI at week one and continued to improve throughout the study. By week six, there was a difference in favor of the placebo group that as also present at week eight. There were no significant differences in Q-LES-Q between groups at week eight and there were no significant differences between groups in SDS scores at any time point measured. Treatment-emergent adverse events that occurred in at least 10% of patients and either group but with a higher incidence in the group receiving zolpidem ER included dizziness, nausea, and fatigue. Six patients receiving zolpidem ER experienced seven events of non-global amnesia between two and 59 days of taking the study medication. One patient in each group experienced one serious adverse event. Laboratory values, vital signs, and physical examination findings revealed no meaningful changes or clinically relevant differences between groups.
Erman et al[72] zolpidem ER 12.5 mg vs placebo Zolpidem ER or placebo was to be taken nightly or at least 3 times per week.	DB, PC, RCT (subset analysis) Adults under 65 years of age with chronic insomnia	N=1,012 24 weeks	Primary: Change from baseline to week 12 in the Time Management and Output scales of the WLQ Secondary: Change from baseline to week four and to week 24 in the Time Management and Output scales of	Primary: At week 12, treatment with zolpidem ER 12.5 resulted in a 4.86 point reduction in the Output Scale (95% CI, -8.37 to -1.36; P=0.0066; ES, -0.21) and a 7.29 point reduction in the Time Management Scale (95% CI, -10.77 to -3.81; P<0.0001; ES, -0.31) vs placebo. Secondary: At week four, scores for the Output Scale and the Time Management Scale were significantly lower than at baseline (P value not reported). The decrease was significantly greater with zolpidem ER than for placebo for both the Output Scale (-9.59; SE, 1.44 vs -2.16; SE, 1.61; P<0.0001, ES, -0.33) and the Time Management Scale (-12.22; SE, 1.49 vs -3.85; SE, 1.68; P<0.0001, ES, -0.36).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			the WLQ, or premature discontinuation	
Roth et al[73] Zolpidem 1.75 or 3.5 mg sublingual vs placebo Subjects were awakened 4 hours after lights out, dosed with zolpidem sublingual or placebo, kept awake for 30 minutes, and then returned to bed for 30 minutes.	DB, PC, XO Adults with insomnia characterized by difficulty returning to sleep following MOTN awakenings	82 subjects 3 2-night treatment periods Each treatment period consisted of 2 consecutive nights of dosing separated by a washout of 5 to 12 days.	Primary: LPS following MOTN comparing zolpidem sublingual 3.5 mg to placebo Secondary: TST, SE, sleep quality, subjective SOL, subjective TST, and mean LPS for zolpidem sublingual 1.75 compared to placebo (all assessed after MOTN); according to the statistical analysis plan, if any test of a secondary endpoint did not attain statistical significance, then inferential analyses of secondary endpoints would cease and no	Primary: Treatment with zolpidem sublingual 3.5 mg resulted in a significant improvement in LPS after MOTN compared to treatment with placebo (9.69 vs 28.12 minutes; P<0.001 vs placebo, P<0.001 vs zolpidem sublingual 1.75 mg). Secondary: Treatment with zolpidem sublingual 1.75 mg resulted in a significant improvement in LPS after MOTN compared to treatment with placebo (16.89 vs 28.12 minutes; P<0.001). Treatment with zolpidem sublingual 1.75 mg resulted in improvements in the following parameters: TST after MOTN (197.80 vs 183.12 minutes; P<0.001), subjective SOL after MOTN (28.58 vs 40.43 minutes; P<0.001), and subjective TST after MOTN (162.36 vs 148.61 minutes; P<0.011). Treatment with zolpidem sublingual 3.5 mg resulted in improvements in the following parameters: TST after MOTN (208.99 vs 183.12 minutes; P<0.001 vs placebo, P=0.005 vs zolpidem sublingual 1.75 mg), subjective SOL after MOTN (25.23 vs 40.43 minutes; P<0.001), and subjective TST after MOTN (172.51 vs 148.61 minutes; P<0.011). The endpoints of WASO after MOTN and NAW after MOTN failed to reach significance for either dose of zolpidem sublingual compared to placebo. Treatment with zolpidem sublingual 3.5 mg resulted in the greater improvement in sleep quality compared to treatment with placebo (P<0.001) and compared to treatment with zolpidem sublingual 1.75 mg (P=0.018). Sleep quality ratings in the group receiving zolpidem sublingual 1.75 mg were not significantly different than the group receiving placebo. No serious adverse events occurred and no subject discontinued the study due to an adverse event. Out of the 82 included subjects, 14 reported an adverse event. All adverse events were mild in severity and transient.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			further inferential assessment of remaining secondary endpoints would be made, safety	
Staner et al[74] Zolpidem 5 mg sublingual tablet vs zolpidem 10 mg sublingual tablet vs zolpidem 10 mg tablet	OL, RCT, XO Healthy volunteers in a post-nap model of insomnia	N=21 Single dose	Primary: LPS, SOL, latency to stage 1, TST, SE, awakening after sleep onset, REM SL, stage 4 duration Secondary: Not reported	Primary: For zolpidem 10 mg sublingual tablets, LPS was significantly decreased by 6.11 minutes as compared to zolpidem 10 mg tablets (P<0.05). Zolpidem 10 mg sublingual tablets decreased SOL by 5.81 minutes as compared to zolpidem 10 mg tablets (P<0.05). Zolpidem 10 mg sublingual tablets decreased latency to stage 1 by 6.17 minutes as compared to zolpidem 10 mg tablets (P<0.05). Similar differences were demonstrated for sleep initiation parameters between zolpidem 5 mg and 10 mg sublingual tablets (7.28 minute difference for LPS, 6.69 minute difference for SOL and 6.06 minute difference for latency to stage 1; all P<0.05). There were no significant differences in the three sleep initiation parameters between zolpidem 5 mg and 10 mg sublingual tablets. There were no significant differences between the three treatments for sleep maintenance parameters, including TST, SE or awakening after sleep onset. There were no differences in sleep maintenance between zolpidem 5 mg and 10 mg sublingual tablets. Significant treatment effects were evidenced for REM SL and stage 4 duration. Both REM SL and stage 4 duration were similar with zolpidem 5 mg and 10 mg sublingual tablets. Both parameters were significantly shorter in patients receiving zolpidem 5 mg sublingual tablets compared to zolpidem 10 mg tablets (REM SL, -19.22 minutes; P<0.01, stage 4 duration, -11.89 minutes; P<0.01). There were no differences in sleep architecture between zolpidem 5 mg and 10 mg sublingual tablets. No differences were detected in subjective sleep parameters as indicated by a lack of significant treatment effect on any of the LSEQ variables. Next-day residual effects

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				were comparable between treatments. Vigilance, psychomotor performances, attention and concentration were comparable between treatments. The most frequent adverse events were somnolence, headache and fatigue. All were of moderate or mild intensity and resolved spontaneously. Secondary: Not reported
Staner et al[75] Zolpidem 10 mg sublingual tablet vs zolpidem 10 mg tablet	DB, MC, RCT, XO Patients 18 to 65 years of age with primary insomnia	N=70 Single dose	Primary: LPS, SOL, time spent in sleep stage 1 Secondary: TST, WASO, SE index, total time spent awake, time spent in stage 2, time spent in slow wave sleep; time spent in REM sleep; REM SL, LSEQ, DSST, CFF Test	Primary: Zolpidem sublingual shortened the LPS by about 34% or 10.3 minutes (P=0.001), SOL with about 8.6 minutes (P<0.01) and time spent in sleep stage 1with about 7.4 minutes (P<0.01) compared to zolpidem. Secondary: There were no significant differences on in TST and WASO among the treatment groups. The TST was 432 minutes for zolpidem sublingual and 425 minutes for zolpidem. WASO was 31 and 30 minutes for zolpidem sublingual and zolpidem, respectively. There was a significant difference in SE index (P<0.05) and total time spent awake (P<0.05), favoring zolpidem sublingual. No differences were found between the treatments for the sleep architecture parameters time spent in sleep stage 1, slow wave sleep, REM and REM SL. The difference found for time spent in stage 2 reached statistical significance (P<0.05), favoring zolpidem sublingual. There were no significant differences in LSEQ scores among the treatment groups. There were no significant differences in the way patients rated their subjective feelings of alertness, contentedness and calmness on the visual analog scale. There were no significant differences in DSST between the two treatments. CFF Test results indicated that, during the descending runs, patients had a lower flicker fusion threshold after zolpidem sublingual than after zolpidem (P<0.05). There were no between-treatment differences for the ascending runs. Both routes of administration were well tolerated with a similar overall incidence of adverse events. The most common adverse events with zolpidem sublingual were

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				somnolence and dysgeusia. Nausea, dysgeusia, somnolence and dizziness were the most common adverse events with zolpidem.
Roehrs et al[76] Zolpidem 10 mg vs placebo	DB, PC, RCT Patients 21 to 70 years of age with primary insomnia	N=33 12 months	Primary: Number of zolpidem or placebo choices made, total number of zolpidem or placebo capsules chosen, and given a placebo or zolpidem choice on a given night, the nightly number of capsules taken Secondary: Not reported	Primary: On weekly telephone interviews, patients reported taking 73 to 89% of the single nightly capsules each month while at home. The groups did not differ in the average percentage of capsules used over the 12 months (placebo, 81% vs zolpidem, 84%). Over the three one-week laboratory self-administration assessments, the zolpidem group selected zolpidem (80.3%) more often than placebo (P<0.020). The placebo group showed no color preference, choosing the red capsule 51% of opportunities and the blue capsule 49% of opportunities. Overall, the zolpidem group self-administered more zolpidem capsules than placebo capsules (P<0.001). In the zolpidem group, the total number of capsules chosen, whether placebo or zolpidem, did not differ over months one, four, and 12. The total number of placebo capsules self-administered by the placebo group increased significantly during month four and month 12 compared to month one (P<0.02). Within the zolpidem group, the nightly number of placebo vs zolpidem capsules self-administered each month did not differ. On average, the zolpidem group self-administered a 9.1 mg dose nightly in month one, a 9.4 mg dose in month four, and a 9.4 mg dose in month 12. In the placebo group, the nightly number of capsules increased over time (P<0.02). The percent of patients increasing the dose did not differ between the zolpidem and placebo groups and did not change from month four to month 12. A significantly greater percent of patients receiving zolpidem compared to placebo decreased the dose they self-administered in month four and month 12 compared to month one (P<0.001). The self-administration rates did not differ when at the laboratory vs at home for patients receiving zolpidem. These rates also did not differ over the three assessments. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Roth et al[77] Zolpidem 5, 7.5, 10, 15, 20 mg vs placebo Statistical analyses were primarily performed between zolpidem 7.5 and 10 mg and placebo.	DB, PC, PG, RCT Healthy adult volunteers with transient insomnia	N=462 Single dose	Primary: SL, sleep duration, SE (TST divided by time in bed) NAW (sleep maintenance), effect on sleep stages, next day psychomotor performance and alertness (DSST, Symbol Copying Tests, Visual Analog Scales on the Morning Questionnaire) Secondary: Not reported	Primary: Compared to placebo, zolpidem 7.5 and 10 mg significantly decreased SL, increased sleep duration and efficiency, and reduced the NAW (all P<0.05). Subjective quality of sleep was also rated significantly better with both doses of zolpidem compared to placebo (both P<0.001). Increasing the dose above 10 mg did not result in a corresponding increase in hypnotic efficacy. Treatment with zolpidem had no effect on stage 1, stage 2 and stages 3 to 4 sleep. Significantly less REM sleep was reported in the zolpidem groups compared to the placebo group (both P<0.001). Zolpidem 7.5 or 10 mg had no significant effect on next day psychomotor performance and alertness. No statistically significant differences in the overall side effects were found between zolpidem doses of 7.5 mg (4.9%) or 10 mg (6.7%) and placebo (7.8%). Higher doses of zolpidem were associated with more side effects (17.6% with 15 mg [P=0.069 vs placebo] and 31.4% with 20 mg [P<0.001 vs placebo]). Secondary: Not reported
Scharf et al[78] Zolpidem 10 or 15 mg vs placebo Patients were randomized to receive either zolpidem or placebo for 35 nights, followed by placebo	DB, MC, PC, PG, RCT Adults with chronic insomnia	N=75 5 weeks	Primary: LPS, SE, sleep maintenance, sleep quality, effects on sleep stages, residual drug effects, safety Secondary: Not reported	Primary: Zolpidem had a significant (P<0.05) effect on LPS and SE from weeks two through five in the 10-mg group and at weeks two through six in the 15-mg group. Polysomnographic measures of sleep maintenance were not significantly different among the three treatment groups (P>0.05). Patients receiving zolpidem 15 mg reported significantly better quality of sleep than those receiving the 10 mg dose at week two and placebo at week five. Stages 1, 2, and 3 to 4 sleep were not significantly affected by either the 10- or 15-mg doses of zolpidem compared to placebo. However, there were significant (P<0.05) decreases in REM sleep at weeks three and four with zolpidem 15 mg compared to placebo.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
for 3 additional nights.				There was no evidence of residual effect with zolpidem 10 or 15 mg. There was no evidence of tolerance at either dose. The only significant treatment difference was in the percent of time in Stage 3 to 4 sleep (P<0.05 for both zolpidem doses compared to placebo). There were no significant treatment differences between the 10-mg zolpidem group and the placebo group in LPS, SE, WTDS or sleep quality during the post treatment period when zolpidem was discontinued. The 15-mg zolpidem group did not differ significantly from the placebo group on LPS or SE on the first night post treatment, but did result in a significantly greater WTDS and poorer quality of sleep (P<0.05 compared to placebo) during the first night post treatment. Comparison of the subsequent two nights post treatment showed no significant differences between zolpidem 15 mg and placebo on any of these variables. Overall, the incidence of treatment emergent adverse events in the zolpidem groups was similar to those in the placebo group. While none of the adverse events were severe, two patients in the 15-mg zolpidem group withdrew from the study: one patient experienced drowsiness, dizziness, and nausea; and one patient experienced visual disturbance and over sedation. The 15-mg zolpidem dosage provided no clinical advantage over the 10 mg zolpidem dosage. Secondary: Not reported
Valente et al[79] Zolpidem 5 and 10 mg sublingual tablet vs zolpidem 10 mg oral tablet	DB, DD, OL, RCT Healthy volunteers	N=58 Duration not specified	Primary: PSG; post-sleep questionnaires Secondary: Not reported	Primary: A significant main treatment effect was evident considering the SOL and persistent SL. An earlier sleep onset was induced by sublingual zolpidem 10 mg (SOL: P<0.004; persistent SL: P<0.006) and sublingual zolpidem 5 mg (SOL: P<0.025; persistent SL: P<0.046) compared to oral zolpidem 10 mg. Subjects that received sublingual zolpidem 10 mg reported an earlier sleep onset (latency to sleep and LPS) when compared to subjects from other groups (P<0.005). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Holbrook et al[80] Benzodiazepines (triazolam: 16 trials, flurazepam: 14 trials, temazepam: 13 trials, midazolam: 5 trials, nitrazepam*: 4 trials, estazolam: 2 trials, lorazepam, diazepam, brotizolam*, quazepam, loprazolam* and flunitrazepam*: 1 trial) vs zopiclone*: 13 trials or diphenhydramine, glutethimide, promethazine: 1 trial or cognitive behavioral therapy: 1 trial or placebo: 4 trials	MA Patients with insomnia receiving benzodiazepines as compared to placebo or an active agent	45 trials N=2,672 Duration varied (1 day to 6 weeks, mean 12.2 days)	Primary: Sleep latency, total sleep duration, adverse effects, dropout rates, cognitive function decline Secondary: Not reported	Primary: Using sleep records, benzodiazepines demonstrated a decrease in sleep latency by 4.2 minutes compared to placebo, though not significant (95% CI, -0.7 to 9.2). Benzodiazepines demonstrated a significant increase in sleep duration compared to placebo by 61.8 minutes (95% CI, 37.4 to 86.2). Benzodiazepines were more likely than placebo to be associated with complaints of daytime drowsiness (OR, 2.4; 95% CI, 1.8 to 3.4), dizziness or lightheadedness (OR, 2.6; 95% CI, 0.7 to 10.3); no difference was observed in dropout rates between the two groups. Pooled results from 3 trials indicated there was no significant difference between benzodiazepines and zopiclone in sleep latency, but benzodiazepine therapy may lead to a longer sleep by 23.1 minutes (95% CI, 5.6 to 40.6). There was a nonsignificant difference in terms of adverse events (OR, 1.5; 95% CI, 0.8 to 2.9). Comparisons between benzodiazepines and antihistamines did not detect any significant differences on sleep outcomes. In 1 trial where a benzodiazepine was compared to behavioral therapy, triazolam was found to be more effective in reducing sleep latency early in the trial, but efficacy decreased by the second week of treatment. Behavioral therapy efficacy was maintained throughout the 9-week follow-up. Secondary: Not reported
Smith et al[81]	MA	21 trials	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Benzodiazepines (flurazepam, quazepam, triazolam, lorazepam, midazolam): 6 trials or benzodiazepine receptor agonists (zolpidem, zopiclone*): 2 trials vs behavioral treatment: 14 trials vs placebo One trial directly compared pharmacotherapy with a benzodiazepine (temazepam) and behavioral therapy.	Patients with primary insomnia for 1 month or longer	N=470 Duration varied (<1 week to 10 weeks)	SL, TST, NAW, WASO, and sleep quality before and after treatment Secondary: Not reported	SL was reduced by 30% with pharmacological treatment compared to 43% with behavioral interventions. Pharmacotherapy increased TST by 12% and behavior therapy by 6%. Both pharmacotherapy and behavior therapy reduced NAW per night by 1. WASO was reduced by 46% with pharmacotherapy and by 56% with behavior therapy. Pharmacotherapy improved sleep quality by 20% and behavior therapy by 28%. Overall, there were no differences in TST, NAW, WASO, and sleep quality between benzodiazepine receptor agonists and behavioral therapy. The behavioral therapy group had a greater reduction in LSO than the group that took the benzodiazepine receptor agonists (95% CI, 0.17 to 1.04) Secondary: Not reported
Nowell et al[82] Benzodiazepines (estazolam: 6 trials, flurazepam: 10 trials, lorazepam: 1 trial,	MA of 22 trials (from 1978-1996); DB, PC, RCT, XO Adults <65 years of age with	22 trials N=1,894 Median duration of 7	Primary: SL, TST, NAW, sleep quality Secondary: Not reported	Primary: Zolpidem and benzodiazepines were significantly more effective than placebo with regard to SL, TST, NAW and sleep quality (P<0.001). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
quazepam: 3 trials, temazepam: 3 trials, triazolam: 4 trials) or zolpidem: 5 trials) vs placebo	chronic insomnia	days, range 4 to 35 days		Note: This MA did not compare the efficacy of zolpidem to benzodiazepines.
Buscemi et al[83] Benzodiazepines (52 trials including brotizolam‡, estazolam, flunitrazepam*, flurazepam, loprazolam*, lorazepam, lormetazepam*, nitrazepam*, quazepam, temazepam and triazolam) or nonbenzodiazepines (48 trials including eszopiclone, gaboxadol*, indiplon*, zaleplon, zolpidem and zopiclone*) or	MA of 105 trials (up to July 2006); DB, PC, RCT Adults with chronic insomnia	105 trials N varied, range 6 to 1,507 Duration varied (1 night to 6 months)	Primary: SL, WASO, SE, sleep quality, TST, adverse events Secondary: Not reported	Primary: SL assessed by PSG was significantly decreased for benzodiazepines (WMD, -10.0 minutes; 95% CI, -16.6 to -3.4), nonbenzodiazepines (WMD, -12.8 minutes; 95% CI, -16.9 to -8.8) and antidepressants (WMD, -7.0 minutes; 95% CI, -10.7 to -3.3). SL assessed by sleep diaries was also significantly improved for benzodiazepines (WMD, -19.6 minutes; 95% CI, -23.9 to -15.3), nonbenzodiazepines (WMD, -17.0 minutes; 95% CI, -20.0 to -14.0) and antidepressants (WMD, -12.2 minutes; 95% CI, -22.3 to -2.2). MA for WASO, SE, sleep quality and TST measured by PSG and sleep diary were statistically significant and favored benzodiazepines and nonbenzodiazepines vs placebo with the exception of PSG studies measuring WASO and TST, which were marginally nonsignificant. In contrast, PSG results significantly favored antidepressants vs placebo, but sleep diary results were fewer and nonsignificantly favored antidepressants for WASO and nonsignificantly favored placebo for TST (P values were not reported). Indirect comparisons between benzodiazepines and nonbenzodiazepines resulted in no significant difference in SL; however, benzodiazepines were associated with more adverse events (P value not reported). Indirect comparisons between benzodiazepines and antidepressants resulted in no significant difference in SL or adverse events (P values not reported). Indirect comparisons between nonbenzodiazepines and antidepressants resulted in a significantly greater SL assessed by PSG but not by sleep diary for nonbenzodiazepines. There was no significant difference in adverse events (P values

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
antidepressants (8 trials including doxepin, pivagabine*, trazodone and trimipramine) vs placebo (105 trials) Some trials had multiple treatment arms.				were not reported). All drug groups had a statistically significant higher risk of harm (more adverse events) compared to placebo, although the most commonly reported adverse events were minor. Risk differences were 0.15, 0.07 and 0.09 for the benzodiazepines, nonbenzodiazepines and antidepressants, respectively, compared to placebo. The adverse events most commonly reported in these studies were headache, drowsiness, dizziness and nausea. Secondary: Not reported
Winkler et al[84] Antidepressants (4 trials including doxepin and trimipramine) vs antiepileptic drugs (2 trials including tiagabine) vs antihistamines (1 trial including diphenhydramine and valerian plus hops) vs benzodiazepines (6	MA Patients with primary insomnia	31 trials N=3,820 Duration varied (<3 months, 168 days or 224 days)	Primary: TST and sTST Secondary: SOL, sSOL, WASO, sWASO, SE, sSE, SQ	Primary: Comparisons for benzodiazepines to placebo were significant for TST (95% CI, 0.12 to 1.16; P=0.015) but not sTST (95% CI, -0.07 to 1.73; P=0.071). Comparisons between benzodiazepine receptor agonists and placebo were significant for all outcome variables (TST: 95% CI, 0.33 to 0.71; P<0.001 and sTST: 95% CI, 0.08 to 0.42; P=0.003). Comparisons between antidepressants and placebo were significant for all outcome variables (TST: 95% CI, 0.29 to 0.59; P<0.001 and sTST: 95% CI, 0.22 to 0.66; P<0.001). Secondary: Comparisons for benzodiazepines to placebo were significant for all secondary outcomes (P<0.05). Comparisons between benzodiazepine receptor agonists and placebo were significant for all outcome variables (P<0.05) with the exception of sWASO and sSE. Comparisons between antidepressants and placebo were significant for all outcome variables (P<0.05) with the exception of sSOL. With regards to SOL, benzodiazepines and benzodiazepine receptor agonists were significantly more effective than antidepressants (P value not reported). With regards to sSOL, benzodiazepines were significantly more effective than benzodiazepine receptor agonists (P value not reported).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
trials including flurazepam, lormetazepam*, temazepam, triazolam, quazepam) vs benzodiazepine receptor agonists (14 trials including eszopiclone, zaleplon and zolpidem), vs hormones (1 trial including prolonged-release melatonin), vs melatonin receptor agonists (2 trials including ramelteon), vs narcotics (1 trial including propofol) vs neuropeptides (1 trial				With regards to SQ, while a Q test demonstrated that benzodiazepines were significantly more effective than benzodiazepine receptor agonists, there was an insignificant Q test for the heterogeneity between the treatment conditions (P value not reported).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
including DSIP) vs placebo				

*****Not available in the United States.
Drug regimen abbreviations: ER=extended release
Study abbreviations: AC=active control, CI=confidence interval, DB=double-blind, DD=double dummy, ITT=intent to treat, MA=meta-analysis, MC=multicenter, NS=not significant, OL=open-label, OR=odds ratio, PC=placebo-controlled, PG=parallel-group, PRO=prospective, RCT=randomized controlled trial, SB=single-blind, SD=single dose, XO=crossover, WMD=weighted mean difference
Miscellaneous abbreviations: APAP=auto-titrating positive airway pressure, BAI=Beck Anxiety Inventory, CAPS=Clinician Administered PTSD Scale, CES-D=Center for Epidemiologic Studies Depression Scale, CFF=Critical Flicker Fusion, CGI=Clinical Global Impression, CGI-I=Clinical Global Impression-Improvement, CGI-S=Clinical Global Impressions-Severity, CRT=Choice Reaction Time, CTT=Continuous Tracking Test, DLMO=dim light melatonin onset, DLRF=Daily Living and Role Functioning, DSM-IV-TR=Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision, DSST=Digit-Symbol Substitution Test, ECG=electrocardiogram, ES=effect size, ESS=Epworth Sleepiness Scale, FOSQ=Functional Outcomes of Sleepiness Questionnaire, FSS=Fatigue Severity Scale, GAD=Generalized Anxiety Disorder, HAMA=Hamilton Rating Scale for Anxiety, HAM-D=Hamilton Rating Scale for Depression, $HDRS_{17}$=Hamilton Depression Rating Scale 17-item, HRQOL=health-related quality of life, ISI=Insomnia Severity Index, IVRS=interactive voice response system, LARS=Leeds Analogue Rating Scales, LPS=latency to persistent sleep, LSAS=Liebowitz Social Anxiety Scale, LSEQ=Leeds Sleep Evaluation Questionnaire, LSM=least squares mean, LSO=latency to sleep onset, MADRS=Montgomery-Åsberg Depression Rating Scale, MCBI=Multidimensional Caregiver Burden Inventory, MENQOL=Menopause-Related Quality of Life, MGH-CFPQ=Massachusetts General Hospital Cognitive and Physical Functioning Questionnaire, MOTN=middle-of-the-night awakening, MSQ=Morning Sleep Questionnaire, NAW=number of awakenings, PDQ-8=Parkinson Disease Questionnaire Short Form, PGI=Patient Global Impression, PGI-IT= Patient Global Impression of Insomnia Treatment, PMQ=Patient Morning Questionnaire, PSG=polysomnography, PSQI=Pittsburg Sleep Quality Index, PSQ-IVRS=Post-Sleep Questionnaire Interactive Voice Response System, PTSD=posttraumatic stress disorder, Q-LES-Q=Quality of Life Enjoyment and Satisfaction Questionnaire, REM=rapid eye movement, SDS=Sheehan Disability Scale, SE=sleep efficiency, SF-36=Short Form-36, SII=Sleep Impairment Index, SIS=Sleep Impact Scale, SL=sleep latency, SOL=sleep onset latency, SOT=Sensory Organization Test, SPRINT=Short PTSD Rating Interview, SQ=sleep quality, SQTT=Step Quick Turn Test, SRT=simple reaction time, sSE=subjective sleep efficiency, sSL=subject reported sleep latency, sSOL=subjective sleep onset latency, SSRI=selective serotonin-reuptake inhibitor, STSOM=subjective time to sleep onset in minutes, sTST=subject reported total sleep time, STSTM=subjective total sleep time in minutes, SWA=slow wave activity, sWASO=subjective wake time after sleep onset, TST=total sleep time, UPDRS=Unified Parkinson Disease Rating Scale, WASO=wake time after sleep onset, WLQ=Work Life Questionnaire, WTAS= wake time after sleep (time from last epoch of sleep until the end of 8 hour recording period), WTDS=wake time during sleep

Special Populations

Table 5. Special Populations[7-23]

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
Doxepin	In the elderly reduce dose to 3 mg; can increase to 6 mg, if clinically indicated. Safety and efficacy in children have not been established.	Effects have not been evaluated.	Patients may display higher concentrations of doxepin than healthy patients; initiate treatment with 3 mg and monitor closely for adverse daytime effects.	C	Yes; use with caution.
Estazolam	No overall differences in safety or efficacy observed between elderly and younger adult subjects. Safety and efficacy in patients <18 years old have not been established.	Not studied in renal dysfunction.	Not studied in hepatic dysfunction.	X	Unknown; use is not re-commended.
Eszopiclone	For elderly patients with primary complaint of difficultly falling asleep, start with 1 mg and increase to 2 mg if clinically indicated; for those with a primary complaint of difficulty staying asleep, use 2 mg. Safety and efficacy in patients <18 years old have not been established.	No dosage adjustment required.	Severe hepatic impairment; use with caution; start with 1 mg and do not increase above 2 mg. Mild-to-moderate impairment; no dosage adjustment required.	C	Unknown; use with caution.
Flurazepam	Recommended dose is 15 mg for the elderly. Safety and efficacy in children have not been established.	No dosage adjustment required.	Recommended dose is 15 mg.	C	Unknown; use with caution.
Quazepam	Begin dosing on lower end of dosing range for the elderly.	Not studied in renal dysfunction.	Not studied in hepatic dysfunction.	C	Yes; use with caution.

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
	Safety and efficacy in patients <18 years old have not been established.				
Ramelteon	No overall differences in safety or efficacy observed between elderly and younger adult subjects. Safety and efficacy in children have not been established.	No dose adjustment required.	Severe hepatic impairment; use is not recommended. Moderate hepatic impairment; use with caution.	C	Unknown; use with caution.
Suvorexant	No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients. Safety and efficacy in children have not been established.	No dosage adjustment required.	Severe hepatic impairment; use is not recommended. Mild to moderate hepatic impairment; no dosage adjustment required.	C	Unknown; use with caution.
Tasimelteon	The risk of adverse reactions may be greater in patients >65 years of age than younger patients because exposure to tasimelteon is increased by approximately 2-fold compared with younger patients. Safety and efficacy in children have not been established.	No dosage adjustment required.	Not studied in severe hepatic dysfunction. Mild to moderate hepatic impairment; no dosage adjustment required.	C	Unknown; use with caution.
Temazepam	Recommended dose is 7.5 mg in patients ≥65 years of age. Safety and efficacy in children have not been established.	No dosage adjustment required.	No dosage adjustment required.	X	Yes; use with caution.
Triazolam	The recommended dose in the elderly is 0.125 mg; may increase to a	Not studied in renal dysfunction.	Not studied in hepatic dysfunction.	X	Yes; use is not re-commended.

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
	maximum of 0.25 mg. Safety and efficacy in patients <18 years old have not been established.				
Zaleplon	Recommended dose in the elderly is 5 mg; doses over 10 mg are not recommended. Safety and efficacy in children have not been established.	No dosage adjustment required.	Severe hepatic impairment; use is not recommended. Mild to moderate hepatic impairment; use 5 mg.	C	Yes; use is not re-commended.
Zolpidem	Recommended dose is 5 mg*, 6.25 mg†, or 1.75 mg‡; monitor patients closely. Safety and efficacy in children have not been established.	No dose adjustment required.	Recommended dose is 5 mg*, 6.25 mg†, or 1.75 mg‡.	C	Yes; use with caution.

* Ambien® (zolpidem), Edluar® (zolpidem sublingual), and Zolpimist® (zolpidem oral mist).
† Ambien CR® (zolpidem extended release).
‡ Intermezzo® (zolpidem sublingual); dose provided is for both men and women.
Pregnancy Category C=Risk cannot be ruled out. Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.

Adverse Drug Events

Table 6. Adverse Drug Events (%)[7-23]

Adverse Event(s)	Doxepin	Estazolam	Eszopiclone	Flurazepam	Quazepam	Ramelteon	Suvorexant	Tasimelteon	Temazepam	Triazolam	Zaleplon	Zolpidem
Cardiovascular Disorders												
Arrhythmia	-	✔	-	-	-	-	-	-	-	-	-	-
Blood pressure increased	-	-	-	-	-	-	-	-	-	-	-	1*
Chest discomfort	-	-	-	-	-	-	-	-	-	-	-	1*
Chest pain	-	1	-	✔	-	-	-	-	-	-	-	1[‡§]
Electroencephalogram changes	-	✔	-	-	-	-	-	-	-	-	-	-
Hypertension	<1 to 1	-	-	-	-	-	-	-	-	-	-	-
Hypotension	-	-	-	✔	-	-	-	-	-	-	-	-
Palpitations	-	✔	-	✔	-	-	-	-	-	-	-	2[†‡§]
Tachycardia	-	-	-	-	-	-	-	-	-	0.5 to 0.9	-	-
Infections and Infestations												
Infection	-	-	5 to 10	-	-	-	-	-	-	-	-	-
Influenza	-	-	-	-	-	-	-	-	-	-	-	3*
Influenza-like illness	-	-	-	-	-	-	-	-	-	-	-	1[†], 2[‡§]
Viral infection	-	-	3	-	-	-	-	-	-	-	-	-
Eye Disorders												
Abnormal vision	-	-	-	-	-	-	-	-	-	-	<1 to 2	-
Altered visual depth perception	-	-	-	-	-	-	-	-	-	-	-	1*
Asthenopia	-	-	-	-	-	-	-	-	-	-	-	1*
Diplopia	-	-	-	-	-	-	-	-	-	-	-	-
Eye pain	-	-	-	-	-	-	-	-	-	-	3 to 4	-
Eye redness	-	-	-	-	-	-	-	-	-	-	-	2*
Hyperacusis	-	-	-	-	-	-	-	-	-	-	1 to 2	-
Visual disturbance	-	-	-	-	-	-	-	-	-	0.5 to 0.9	-	3*
Vision blurred	-	-	-	✔	-	-	-	-	1.3	-	-	2*
Ear and Labyrinth Disorders												
Ear pain	-	-	-	-	-	-	-	-	-	-	<1 to 1	-
Labyrinthitis	-	-	-	-	-	-	-	-	-	-	-	1*
Otitis externa	-	-	-	-	-	-	-	-	-	-	-	1[†]
Vertigo	-	-	-	-	-	-	-	-	-	-	-	2*
Tinnitus	-	-	-	-	-	-	-	-	-	<0.5	-	1*
Endocrine and Metabolic Disorders												
Appetite disorder	-	-	-	-	-	-	-	-	-	-	-	1*
Dysmenorrhea	-	-	3[‖]	-	-	-	-	-	-	-	3 to 4	-

Adverse Event(s)	Doxepin	Estazolam	Eszopiclone	Flurazepam	Quazepam	Ramelteon	Suvorexant	Tasimelteon	Temazepam	Triazolam	Zaleplon	Zolpidem
Gynecomastia	-	-	3[¶]	-	-	-	-	-	-	-	-	-
Menorrhagia	-	-	-	-	-	-	-	-	-	-	-	1*
Peripheral edema	-	-	-	-	-	-	-	-	-	-	<1 to 1	-
Gastrointestinal Disorders												
Abdominal discomfort	-	-	-	-	-	-	-	-	1.5	-	-	1*
Abdominal pain	-	1	-	-	-	-	-	-	-	-	6	2[‡§]
Abdominal tenderness	-	-	-	-	-	-	-	-	-	-	-	1*
Anorexia	-	-	-	✔	-	-	-	-	-	-	<1 to 2	-
Colitis	-	-	-	-	-	-	-	-	-	-	<1 to 2	-
Constipation	-	-	-	✔	-	-	-	-	-	<0.5	-	2*[‡§]
Cramps		-	-	-	-	-	-	-	-	0.5 to 0.9	-	-
Diarrhea	-	-	2 to 4[#]	✔	-	-	2	-	1.7	<0.5	-	3[‡§]
Dyspepsia	-	2	4 to 5, 2 to 6[#]	✔	1	-	-	-	-	-	-	-
Flatulence	-	-	-	-	-	-	-	-	-	-	-	1[†]
Frequent bowel movements	-	-	-	-	-	-	-	-	-	-	-	1*
Gastrointestinal pain	-	-	-	✔	-	-	-	-	-	-	-	-
Gastroenteritis	-	-	-	-	-	-	-	-	-	-	-	1*
Gastrointestinal disorders	0 to 2	-	-	-	-	-	-	-	-	-	-	4**
Gastroesophageal reflux disease	-	-	-	-	-	-	-	-	-	-	-	1*
Nausea	2	4	4 to 5	✔	-	2	-	-	3.1	4.6	6 to 8	7*, 1**
Vomiting	-	-	3	✔	-	-	-	-	-	4.6	-	1*[†]
Musculoskeletal												
Arthralgia	-	-	-	-	-	-	-	-	-	-	-	2[†]
Back pain	-	2	-	-	-	-	-	-	-	-	-	4*, 3[‡§]
Body pain	-	-	-	-	-	-	-	-	-	-	-	-
Joint pain	-	-	-	✔	-	-	-	-	-	-	-	-
Myalgia	-	-	-	-	-	-	-	-	-	-	-	4*
Muscle cramp	-	-	-	-	-	-	-	-	-	-	-	2[†]
Muscle stiffness	-	1	-	-	-	-	-	-	-	-	-	-
Neck injury	-	-	-	-	-	-	-	-	-	-	-	1[†]
Neck pain	-	-	-	-	-	-	-	-	-	-	-	1*, 2[†]
Pain	-	-	-	✔	-	-	-	-	-	0.5 to 0.9	-	-
Nervous System Disorders												
Abnormal coordination	-	4	-	-	-	-	-	-	-	-	-	-

Adverse Event(s)	Doxepin	Estazolam	Eszopiclone	Flurazepam	Quazepam	Ramelteon	Suvorexant	Tasimelteon	Temazepam	Triazolam	Zaleplon	Zolpidem
Abnormal dreams	-	2	1 to 3[#]	-	-	-	2	7	1.2	<0.5	-	1[‡§]
Abnormal thoughts	-	2	-	-	-	-	-	-	-	-	-	-
Agitation	-	✔	-	-	-	-	-	-	-	-	-	-
Amnesia	-	✔	-	-	-	-	-	-	-	-	2 to 4	1[‡§]
Apprehension	-	✔	-	✔	-	-	-	-	-	-	-	-
Anxiety	-	✔	1 to 3	-	-	-	-	-	2	-	-	2*, 3[†]
Apathy	-	✔	-	-	-	-	-	-	-	-	-	1[†]
Ataxia	-	✔	-	✔	-	-	-	-	-	4.6	-	1*
Balance disorder	-	-	-	-	-	-	-	-	-	-	-	2*
Binge eating	-	-	-	-	-	-	-	-	-	-	-	1*
Bitter taste	-	-	-	✔	-	-	-	-	-	-	-	-
Burning sensation	-	-	-	-	-	-	-	-	-	-	-	1[†]
Circumoral paresthesia	-	✔	-	-	-	-	-	-	-	-	-	-
Confusion	-	2	3	✔	-	-	-	-	1.3	0.5 to 0.9	<1 to 1	-
Daytime drowsiness	-	-	-	-	12	-	-	-	-	-	-	-
Decreased libido	-	✔	3	-	-	-	-	-	-	-	-	-
Decreased reflexes	-	✔	-	-	-	-	-	-	-	-	-	-
Depersonalization	-	-	-	-	-	-	-	-	-	-	<1 to 2	1*
Depressed mood	-	-	-	-	-	-	-	-	-	-	-	1[†]
Depression	-	2	1 to 4	✔	-	-	-	-	1.7	0.5 to 0.9	-	2*[‡§]
Difficulty focusing	-	-	-	✔	-	-	-	-	-	-	-	-
Disinhibition	-	-	-	-	-	-	-	-	-	-	-	1*
Disorientation	-	-	-	-	-	-	-	-	-	-	-	3*
Disturbance in attention	-	-	-	-	-	-	-	-	-	-	-	2*
Dizziness	-	7	5 to 7, 1 to 6[#]	✔	2	3	3	-	4.5	7.8	7 to 9	12*, 8[†], 5[‡§]
Dizziness, postural	-	-	-	-	-	-	-	-	-	-	-	1[†]
Drowsiness	-	-	-	-	-	-	-	-	9.1	14	-	8[‡§]
Drugged feeling	-	-	-	-	-	-	-	-	-	-	-	3[‡§]
Dysesthesia	-	-	-	-	-	-	-	-	-	<0.5	-	-
Euphoric mood	-	-	-	✔	-	-	-	-	1.5	0.5 to 0.9	-	1*
Excitement	-	-	-	✔	-	-	-	-	-	-	-	-
Fatigue	-	-	-	-	2	2	-	-	-	-	-	3*, 1**
Hallucinations	-	-	1 to 3	✔	-	-	-	-	-	-	<1 to 1	4*
Hangover	-	3	-	-	-	-	-	-	2.5	-	-	-
Headache	-	16	17 to 21, 13	✔	5	-	7	17	8.5	9.7	30 to 42	19*, 14[†],

Adverse Event(s)	Doxepin	Estazolam	Eszopiclone	Flurazepam	Quazepam	Ramelteon	Suvorexant	Tasimelteon	Temazepam	Triazolam	Zaleplon	Zolpidem
			to 15[#]									7[‡§], 3**
Insomnia	-	-	-	-	-	2	-	-	-	<0.5	-	-
Involuntary muscle contractions	-	-	-	-	-	-	-	-	-	-	-	1[†]
Irritability	-	-	-	✔	-	-	-	-	-	-		-
Hypertonia	-	-	-	-	-	-	-	-	-	-	1	-
Hypoesthesia	-	-	-	-	-	-	-	-	-	-	<1 to 2	2*
Hypokinesia	-	8	-	-	-				-	-	-	-
Lethargy	-	-	-	✔	-	-	-	-	4.5	-	-	3[‡§]
Lightheadedness	-	-	-	✔	-	-	-	-	-	4.9	-	2[‡§]
Malaise	-	5	-	-	-	-	-	-	-	-	<1 to 2	-
Memory disorders/impairment	-	-	-	-	-	-	-	-	-	0.5 to 0.9	-	3*, 1[†]
Mood swings	-	-	-	-	-	-	-	-	-	-	-	1*
Nervousness	-	8	5, 2[#]	✔	-	-	-	-	4.6	5.2	-	-
Nervous system disorders	-	-	-	-	-	-	-	-	-	-	-	5**
Neuralgia	-	-	3[#]	-	-	-	-	-	-	-	-	-
Pain	-	-	4 to 5[#]	-	-	-	-	-	-	-	-	-
Paresthesia	-	-	-	-	-	-	-	-	-	<0.5	3	1*[†]
Photosensitivity reaction	-	-	-	-	-	-	-	-	-	-	<1	-
Psychomotor retardation	-	-	-	-	-	-	-	-	-	-	-	2*[†]
Pyrexia	-	-	-	-	-	-	-	-	-	-	-	1[†]
Restlessness	-	-	-	✔	-	-	-	-	-	-	-	-
Sedation	-	-	-	✔	-	-	-	-	-	-	-	-
Sleep disorder	-	-	-	-	-	-	-	-	-	-	-	1[‡§]
Slurred speech	-	-	-	✔	-	-	-	-	-	-	-	-
Somnolence	6 to 9	42	8 to 10	✔	-	2	7		-	-	5 to 6	15*, 6[†], 8[‡]
Stress symptoms	-	-	-	-	-	-	-	-	-	-	-	1*
Syncope	-	✔	-	-	-	-	-	-	-	-	-	-
Talkativeness	-	-	-	✔	-	-	-	-	-	-	-	-
Tiredness	-	-	-	-	-	-	-	-	-	0.5 to 0.9	-	-
Tremor	-	-	-	-	-	-	-	-	-	-	2	1[†]
Weakness	-	-	-	✔	-	-	-	-	1.4	<0.5	-	-
Vertigo	-	-	-	-	-	-	-	-	1.2	-	<1 to 1	-
Respiratory Disorders												

Adverse Event(s)	Doxepin	Estazolam	Eszopiclone	Flurazepam	Quazepam	Ramelteon	Suvorexant	Tasimelteon	Temazepam	Triazolam	Zaleplon	Zolpidem
Congestion	-	-	-	-	-	-	-	-	-	<0.5	-	-
Chest congestion	-	3	-	-	-	-	-	-	-	-	-	-
Cough	-	-	-	-	-	-	2	-	-	-	-	-
Epistaxis	-	-	-	-	-	-		-	-	-	<1 to 1	-
Lower respiratory tract infection	-	-	-	-	-	-	-	-	-	-	-	1[†]
Nasopharyngitis	-	-	-	-	-	-	-	-	-	-	-	6[†]
Pharyngitis	-	1	-	-	-	-	-	-	-	-	-	3[‡§]
Shortness of breath	-	-	-	✔	-	-	-	-	-	-	-	-
Sinusitis	-	-	-	-	-	-	-	-	-	-	-	4[‡§]
Throat irritation	-	-	-	-	-	-	-	-	-	-	-	1*
Upper respiratory tract infection	2 to 4	-	-	-	-	-	2	7	-	-	-	1[†]
Skin and Subcutaneous Tissue Disorders												
Allergic skin reaction	-	-	-	-	-	-	-	-	-	<0.5	-	-
Dermatologic symptoms	-	-	-	✔	-	-	-	-	-	<0.5	-	-
Flushing	-	✔	-	✔	-	-	-	-	-	-	-	-
Pruritus	-	1	1 to 4[#]	-	-	-	-	-	-	-	-	-
Rash	-	-	3 to 4	✔	-	-	-	-	-	-	-	2[‡§], 1*[†]
Skin wrinkling	-	-	-	-	-	-	-	-	-	-	-	1*
Urticaria	-	-	-	-	-	-	-	-	-	-	-	1*[†]
Other												
Accidental injury	-	-	3[#]	-	-	-	-	-	-	-	-	-
Allergy	-	-	-	-	-	-	-	-	-	-	-	4[‡§]
Asthenia	-	11	-	-	-	-	-	-	-	-	5 to 7	1*
Body temperature increased	-	-	-	-	-	-	-	-	-	-	-	1*
Contusion	-	-	-	-	-	-	-	-	-	-	-	1*
Dry mouth	-	✔	5 to 7, 3 to 7[#]	✔	2	-	2	-	1.7	<0.5	-	3[‡§]
Dry throat	-	-	-	-	-	-	-	-	-	-	-	1[†]
Dysuria	-	-	-	-	-	-	-	-	-	-	-	1[†]
Elevated alkaline phosphatase	-	-	-	✔	-	-	-	-	-	-	-	-
Elevated alanine aminotransferase	-	-	-	-	-	-	-	10	-	-	-	-
Elevated bilirubin, direct	-	-	-	✔	-	-	-	-	-	-	-	-

Adverse Event(s)	Doxepin	Estazolam	Eszopiclone	Flurazepam	Quazepam	Ramelteon	Suvorexant	Tasimelteon	Temazepam	Triazolam	Zaleplon	Zolpidem
Elevated bilirubin, total	-	-	-	✔	-	-	-	-	-	-	-	-
Elevated cholesterol	-	-	-	-	-	-	✔	-	-	-	-	-
Elevated serum glutamic oxaloacetic transaminase	-	-	-	✔	-	-	-	-	-	-	-	-
Elevated serum glutamic pyruvic transaminase	-	-	-	✔	-	-	-	-	-	-	-	-
Erythema, sublingual	-	-	-	-	-	-	-	-	-	-	-	✔ ‡
Exposure to poisonous plant	-	-	-	-	-	-	-	-	-	-	-	1*
General disorders and administration site conditions	-	-	-	-	-	-	-	-	-	-	-	3**
Genitourinary complaints	-	-	-	✔	-	-	-	-	-	-	-	-
Granulocytopenia	-	-	-	✔	-	-	-	-	-	-	-	-
Hepatic failure resulting in death	-	-	-	-	-	-	-	-	-	<0.5	-	-
Leukopenia	-	-	-	✔	-	-	-	-	-	-	-	-
Parosmia	-	-	-	-	-	-	-	-	-	-	<1 to 2	-
Tongue paresthesia	-	-	-	-	-	-	-	-	-	-	-	✔ ‡
Taste alterations	-	-	-	-	-	-	-	-	-	<0.5	-	-
Unpleasant taste	-	-	17 to 34, 8 to 12#	-	-	-	-	-	-	-	-	-
Urinary tract infection	-	-	3#	-	-	-	-	7	-	-	-	-
Vulvovaginal dryness	-	-	-	-	-	-	-	-	-	-	-	1†

* Ambien CR® (zolpidem extended-release).
† Ambien CR® (zolpidem extended-release), elderly patients (age not specified).
‡ Edluar® (zolpidem sublingual)
§ Ambien® (zolpidem) and Zolpimist® (zolpidem oral mist).
‖ Gender-specific adverse event in females.
¶ Gender-specific adverse event in males.
# Adverse event rate in elderly patients.
** Intermezzo® (zolpidem sublingual).

Contraindications

Table 7. Contraindications[7-23]

Contraindication	Doxepin	Estazolam	Eszopiclone	Flurazepam	Quazepam	Ramelteon	Suvorexant	Tasimelteon	Temazepam	Triazolam	Zaleplon	Zolpidem
Coadministration with monoamine oxidase inhibitor	✔	-	-	-	-	-	-	-	-	-	-	-
Do not take in conjunction with fluvoxamine	-	-	-	-	-	✔	-	-	-	-	-	-
Hypersensitivity to doxepin, any of its inactive ingredients, or other dibenoxepines	✔	-	-	-	-	-	-	-	-	-	-	-
Hypersensitivity to the active ingredient or any excipients in the formulation	-	✔	✔	✔	✔	-	-	-	✔	✔	✔	✔
Patients who develop angioedema after treatment should not be rechallenged	-	-	-	-	-	✔	-	-	-	-	-	-
Patients with narcolepsy	-	-	-	-	-	-	✔	-	-	-	-	-
Strong inhibitors of cytochrome P450 3A4	-	-	-	-	-	-	-	-	-	✔	-	-
Suspected or established sleep apnea or pulmonary insufficiency	-	-	-	-	✔	-	-	-	-	-	-	-
Untreated narrow angle glaucoma or severe urinary retention	✔	-	-	-	-	-	-	-	-	-	-	-
Women who are or may become pregnant	-	✔	-	-	✔	-	-	-	✔	✔	-	-

Boxed Warnings

Boxed Warning for Silenor® (doxepin)[7]

WARNING
Suicidality in children and adolescents: Antidepressants increased the risk of suicidal thinking and behavior (suicidality) in short-term studies in children and adolescents with major depressive disorder and other psychiatric disorders. Anyone considering the use of doxepin or any other antidepressant in a child or adolescent must balance this risk with the clinical need. Patients who are started on therapy should be observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. Doxepin is not approved for use in pediatric patients. Pooled analyses of short-term (four to 16 weeks), placebo-controlled trials of nine antidepressant drugs (selective serotonin reuptake inhibitor and others) in children and adolescents with major depressive disorder, obsessive-compulsive disorder, or other psychiatric disorders (a total of 24 trials involving more than 4,400 patients) have revealed a greater risk of adverse reactions representing suicidal thinking or behavior (suicidality) during the first few months of treatment in those receiving antidepressants. The average risk of such reactions in patients receiving antidepressants was 4%, twice the placebo risk of 2%. No suicides occurred in these trials.

Warnings and Precautions

Table 8. Warnings and Precautions[7-23]

Warning/Precaution	Doxepin	Estazolam	Eszopiclone	Flurazepam	Quazepam	Ramelteon	Suvorexant	Tasimelteon	Temazepam	Triazolam	Zaleplon	Zolpidem
A variety of abnormal thinking and behavior changes have been reported to occur in association with the use of sedative-hypnotics	-	-	✔	-	✔	✔	✔	-	✔	✔	-	✔
Abnormal thinking and behavior changes; the emergence of any new behavioral sign or symptom of concern required careful and immediate evaluation	✔	-	✔	-	-	-	-	-	✔	✔	✔	✔
Anterograde amnesia of varying severity and paradoxical reactions have been reported following therapeutic doses	-	-	-	-	-	-	-	-	-	✔	-	-
Central nervous system depressant effects; caution patients about concomitant ingestion of alcohol and other central nervous system depressant drugs	-	-	-	-	-	-	-	-	-	✔	-	-
Central nervous system depressant effects; daytime	-	-	-	-	-	-	✔	-	-	-	-	-

Warning/Precaution	Doxepin	Estazolam	Eszopiclone	Flurazepam	Quazepam	Ramelteon	Suvorexant	Tasimelteon	Temazepam	Triazolam	Zaleplon	Zolpidem
wakefulness may be impaired even when used as prescribed. Monitor for somnolence and CNS depressant effects												
Central nervous system depressant effects; dose should be discontinued or decreased in patients who drive if daytime somnolence develops	-	-	-	-	-	-	✔	-	-	-	-	-
Central nervous system depressant effects; due to the rapid onset of action, should only be taken immediately prior to going to bed or after the patient has going to bed and has experienced difficulty falling asleep	-	-	-	-	-	-	-	-	-	-	✔	-
Central nervous system depressant effects; should not be taken with alcohol and dose adjustments may be required when co-administered with other central nervous system depressants	-	✔	✔	-	✔	-	✔	-	✔	-	✔	✔
Central nervous system depressant effects; use caution if driving or performing activities requiring complete mental alertness	-	-	-	-	-	-	✔	-	-	✔	-	-
Central nervous system depressant effects; use with other sedative-hypnotics at bedtime or in the middle of the night is not recommended	-	-	✔	-	-	-	-	-	-	-	-	✔
Central nervous system effects; patients should avoid engaging in hazardous activities that require concentration, should confine their activities to those necessary to prepare for bed, and should not consume alcohol in combination	✔	✔	-	✔	-	✔	-	-	✔	-	-	-

Warning/Precaution	Doxepin	Estazolam	Eszopiclone	Flurazepam	Quazepam	Ramelteon	Suvorexant	Tasimelteon	Temazepam	Triazolam	Zaleplon	Zolpidem
Co-administration with potent cytochrome P450 3A4 inhibitors; dose should be reduced	-	-	✔	-	-	-	-	-	-	✔	-	-
Complex behaviors such as “sleep driving”* and other complex behaviors have been reported; discontinuation should be strongly considered for patients who report any complex sleep behavior	-	-	-	-	✔	✔	✔	-	-	✔	-	-
Complex behaviors such as “sleep driving”* have been reported with sedative-hypnotics; discontinuation should be strongly considered for patients who report a “sleep driving” episode	✔	-	✔	-	-	-	-	-	✔	-	✔	✔
Daytime function may be impaired even when used as prescribed. Monitor for excess depressant effects. Caution patients against driving or engaging in other hazardous activities or activities requiring complete mental alertness	-	-	✔	-	✔	-	-	-	-	-	-	✔ §
Daytime anxiety has been reported with continued used in some patients	-	-	-	-	-	-	-	-	-	✔	-	-
Impaired motor/cognitive performance may occur following several days of repeated use due to accumulation of the active drug and its metabolites	-	✔	-	-	-	-	-	-	-	-	-	-
In primarily depressed patients, worsening of depression, including suicidal thoughts and actions, has been reported	✔	✔	✔	-	-	-	✔	-	-	✔	-	✔
May worsen depression; consider appropriate precautions	-	-	-	-	✔	-	-	-	-	-	-	-

Warning/Precaution	Doxepin	Estazolam	Eszopiclone	Flurazepam	Quazepam	Ramelteon	Suvorexant	Tasimelteon	Temazepam	Triazolam	Zaleplon	Zolpidem
Need to evaluate for co-morbid diagnoses; symptomatic treatment of insomnia should be initiated only after a careful evaluation of the patient	✔	-	✔	✔	✔	✔	✔	-	✔	✔	✔	✔
Patients with compromised respiratory function; precautions should be taken due to potential for depression of respiratory drive	-	✔	✔	-	-	-	✔	-	-	-	✔	✔
Patients with sleep apnea syndrome or myasthenia gravis; use with caution	-	-	-	-	-	-	-	-	-	-	-	✔
Reproductive effects; associated with an effect on reproductive hormones in adults	-	-	-	-	-	✔	-	-	-	-	-	-
Risk of next day driving impairment; risk increased if used with less than four hours of bedtime remaining, if higher than recommended dose is taken, if co-administered with other drugs that increase blood levels	-	-	✔	-	-	-	-	-	-	-	-	✔ †
Risk of next-day psychomotor impairment is increased if taken with less than a full night of sleep remaining, if higher than recommended dose is taken or if co-administered with other central nervous system depressants	-	-	-	-	✔	-	-	-	-	-	-	-
Risk of next-day psychomotor impairment is increased if taken with less than a full night of sleep remaining, if higher than recommended dose is taken, if co-administered with other central nervous system depressants or if co-administered with other drugs that increase blood levels	-	-	-	-	-	-	-	-	-	-	-	✔ ‡§‖¶

Warning/Precaution	Doxepin	Estazolam	Eszopiclone	Flurazepam	Quazepam	Ramelteon	Suvorexant	Tasimelteon	Temazepam	Triazolam	Zaleplon	Zolpidem
Severe anaphylactic and anaphylactoid reactions, including rare cases of angioedema involving the tongue, glottis or larynx, have been reported in patients taking first or subsequent doses of sedative-hypnotics; patients who develop angioedema after treatment should not be rechallenged with the drug	-	-	✔	-	✔	✔	-	-	✔	✔	✔	✔
Severe hepatic impairment; use not recommended	-	-	-	-	-	✔	-	-	-	-	✔	-
Severe injuries; may cause drowsiness and a decreased level of consciousness, which may lead to falls and consequently to severe injuries	-	-	-	-	-	-	-	-	-	-	-	✔ ‡$
Signs and symptoms similar to those associated with withdrawal from other central nervous system-depressant drugs have been reported following rapid dose decrease or abrupt discontinuation	-	-	✔	-	-	-	-	-	-	-	✔	✔
Sleep apnea; use not recommended	-	-	-	-	-	✔	-	-	-	-	-	-
Sleep paralysis, hypnagogic/hypnopompic hallucinations and mild cataplexy may occur	-	-	-	-	-	-	✔	-	-	-	-	-
Somnolence; due to the potential impairment of activities requiring mental alertness, activities should be limited to preparing for going to bed	-	-	-	-	-	-	-	✔	-	-	-	-
Taking while still up and about may result in short-term memory impairment, hallucinations, impaired coordination, dizziness, and lightheadedness	-	-	✔	-	-	-	-	-	-	-	✔	-
The usual precautions should be observed in patients with	-	-	-	✔	-	-	-	-	✔	✔	-	-

Warning/Precaution	Doxepin	Estazolam	Eszopiclone	Flurazepam	Quazepam	Ramelteon	Suvorexant	Tasimelteon	Temazepam	Triazolam	Zaleplon	Zolpidem
impaired renal or hepatic function and chronic pulmonary insufficiency												
Use in patients with a history of abuse or addiction; use caution due to the risk of habituation and dependence	-	✔	-	-	-	-	-	-	-	-	-	-
Use in patients with concomitant illness; caution is advisable in using in patients with diseases or conditions that could affect metabolism or hemodynamic responses	-	-	✔	-	-	-	-	-	-	-	✔	-
Use in patients with depression; use with caution and use the least amount of drug that is feasible	-	✔	✔	✔	-	-	-	-	✔	✔	✔	✔
Use in the elderly and/or debilitated patients; patients should be closely monitored	-	-	-	-	-	-	-	-	-	-	✔	-
Withdrawal symptoms have been reported following abrupt discontinuation of treatment	-	✔	-	✔	-	-	-	-	✔	✔	-	-
Withdrawal symptoms similar to that from alcohol can occur following abrupt discontinuation. Milder symptoms can occur following abrupt discontinuation of benzodiazepines taken at therapeutic levels for short periods	-	-	-	-	✔	-	-	-	-	-	-	-

***** Sleep driving consists of driving while not fully awake after ingestion of a sedative-hypnotic, with amnesia for the event.
† Intermezzo® (zolpidem sublingual).
‡ Ambien® (zolpidem).
§ Ambien CR® (zolpidem extended-release).
‖ Edluar® (zolpidem sublingual).
¶ Zolpimist® (zolpidem oral mist).

Drug Interactions

Table 9. Drug Interactions[7-23]

Generic Name	Interacting Medication or Disease	Potential Result
Benzo-diazepines (all)	Azole antifungals	Increased and prolonged serum levels, central nervous system depression, and psychomotor impairment have been noted with certain benzodiazepines undergoing oxidative metabolism and may possibly continue for several days after stopping the azole antifungal agent. Consider administering a lower benzodiazepine dose or a benzodiazepine that undergoes glucuronidation (e.g., lorazepam, temazepam) when giving fluconazole. Use of triazolam with itraconazole or ketoconazole is contraindicated.
Benzo-diazepines (all)	Central nervous system depressants	Benzodiazepines produce additive central nervous system depressant effects when co-administered with ethanol or other central nervous system depressants. Downward dose adjustment of the benzodiazepine and/or concomitant central nervous system depressants may be necessary.
Benzo-diazepines (all)	Hydantoins	Serum hydantoin concentrations may be increased and phenytoin may increase the clearance of certain benzodiazepines. Hydantoin levels and effects should be monitored when the benzodiazepine dose is started or stopped.
Benzo-diazepines (all)	Protease inhibitors (amprenavir, atazanavir, darunavir, indinavir, lopinavir-ritonavir, nelfinavir, ritonavir, saquinavir)	Concurrent use may lead to severe sedation and respiratory depression due to inhibition of hepatic metabolism resulting in large increases in serum concentrations of benzodiazepines undergoing oxidative metabolism. Coadministration of these protease inhibitors with benzodiazepines metabolized by cytochrome P450 3A4 is contraindicated.
Benzo-diazepines (all)	Rifamycins	When used with rifamycins, the pharmacologic effects of certain benzodiazepines may be decreased due to an increase in the oxidative metabolism of the benzodiazepine (cytochrome P450). Monitor clinical response when starting or stopping rifamycins and the benzodiazepine dose may be adjusted as needed.
Estazolam, quazepam	Opioid analgesics (buprenorphine, methadone)	Increased sedation and strength of opioid effects have been observed. Patients should be advised against driving or operating machinery while taking these agents simultaneously.
Benzo-diazepines (all)	Alcohol	Increased central nervous system effects and impaired psychomotor function have been observed. Patients should be cautioned to avoid the use of alcohol and benzodiazepines concurrently. With acute ethanol ingestion, increased benzodiazepine absorption and decreased hepatic metabolism is possible.
Doxepin	Cytochrome P450 system	Doxepin is primarily metabolized by cytochrome P450 2D6 (with cytochrome P450 1A2 and cytochrome P450 3A4 as minor pathways). Inhibitors or substrates of cytochrome P450 2D6 (i.e., quinidine, selective serotonin

Generic Name	Interacting Medication or Disease	Potential Result
		reuptake inhibitors) may increase the plasma concentration of doxepin when administered concomitantly. Individuals considered "poor metabolizers" at cytochrome P450 2D6 have higher than expected plasma concentrations of tricyclic antidepressants at usual doses. Drugs that inhibit cytochrome P450 2D6 may make normal metabolizers resemble poor metabolizers. An individual who is stable on a given dose of tricyclic antidepressant may become abruptly toxic when given one of these inhibiting drugs as concomitant therapy. Inhibitors of cytochrome P450 2D6 include some that are not metabolized by the enzyme (quinidine; cimetidine) and many that are substrates for P450 2D6 (many other antidepressants, phenothiazines, and the Type 1C antiarrhythmics propafenone and flecainide). All selective serotonin reuptake inhibitors inhibit cytochrome P450 2D6; however, they may vary in the extent of inhibition.
Doxepin	Drugs that prolong the QT interval (e.g., antiarrhythmic agents, arsenic trioxide, chlorpromazine, cisapride, dolasetron, droperidol, mefloquine, mesoridazine, moxifloxacin, pentamidine, pimozide, tacrolimus, thioridazine, and ziprasidone)	An additive effect of doxepin with other drugs that prolong the QT interval cannot be excluded.
Doxepin	Monoamine oxidase inhibitors	Serious side effects and even death have been reported following the concomitant use with monoamine oxidase inhibitors.
Doxepin	Alcohol	Alcohol ingestion may increase the danger inherent in any intentional or unintentional doxepin over dosage; this is of particular importance in patients with excessive alcohol use.
Doxepin	Cimetidine	Cimetidine has been reported to produce clinically significant fluctuations in steady-state serum concentrations of various tricyclic antidepressants. Serious anticholinergic symptoms have been associated with elevations in the serum levels of tricyclic antidepressants when cimetidine therapy is initiated. Additionally, higher than expected tricyclic antidepressant levels have been observed when treatment is initiated in patients already taking cimetidine. In patients well controlled on tricyclic antidepressant therapy receiving concurrent cimetidine therapy, discontinuation of cimetidine has been reported to decrease established steady-state serum levels of the tricyclic antidepressant and compromise their therapeutic effects.
Doxepin	Tolazamide	A case of severe hypoglycemia has been reported in a

Generic Name	Interacting Medication or Disease	Potential Result
		type 2 diabetes patient maintained on tolazamide (1 g/day) 11 days after the addition of doxepin (75 mg/day).
Eszopiclone	Central nervous system depressants	An additive effect on psychomotor performance was seen with coadministration of eszopiclone and ethanol 0.7 g/kg for up to four hours after ethanol administration.
Eszopiclone	Cytochrome P450 3A4 inducers (e.g., rifampicin)	Coadministration resulted in an 80% reduction in racemic zopiclone exposure; a similar effect would be expected with eszopiclone.
Eszopiclone	Cytochrome P450 3A4 inhibitors (e.g., itraconazole, clarithromycin, nefazodone, troleandomycin, ritonavir, nelfinavir)	The exposure of eszopiclone was increased by coadministration of ketoconazole. Other strong inhibitors of cytochrome P450 3A4 would be expected to behave similarly. Dose reduction of eszopiclone is needed for patients receiving potent cytochrome P450 3A4 inhibitors.
Eszopiclone	Lorazepam	Eszopiclone and lorazepam decrease each other's maximum concentration by 22%.
Eszopiclone	Olanzapine	No pharmacokinetic interaction was detected when eszopiclone was co-administered with olanzapine but a pharmacodynamic interaction was observed on a measure of psychomotor function (decreased Digit-Symbol Substitution Test scores).
Ramelteon	Azole antifungals (e.g., fluconazole, itraconazole, ketoconazole)	When coadministered with ketoconazole, the area under the curve for ramelteon increase by approximately 84% and the maximum concentration of ramelteon increased by 36%. When coadministered with fluconazole, the area under the curve and maximum concentration of ramelteon both increased by about 150%. Similar increases were seen in metabolite M-II exposure.
Ramelteon	Cytochrome P450 system	Ramelteon has a highly variable intersubject pharmacokinetic profile. Cytochrome P450 1A2 is the major isozyme involved in the metabolism; however, the cytochrome P450 2C and 3A4 isozymes are also involved to a lesser extent.
Ramelteon	Alcohol	Coadministration may produce additive central nervous system effects.
Ramelteon	Fluvoxamine	Coadministration resulted in a 190-fold increase in the area under the curve for ramelteon and a 70-fold increase in the maximum concentration for ramelteon.
Ramelteon	Rifampin	Coadministration resulted in an approximate 80-fold decrease in the area under the curve and maximum concentration of ramelteon and metabolite M-II. Ramelteon efficacy may be reduced when coadministered with a strong cytochrome P450 enzyme inducer.
Suvorexant	Central nervous system active agents	Coadministration with alcohol resulted in additive psychomotor impairment.
Suvorexant	Cytochrome P450 3A inducers	Suvorexant exposure can be substantially decreased when co-administered with strong cytochrome P450 3A inducers (e.g., rifampin, carbamazepine and phenytoin). Efficacy of suvorexant may be reduced.

Generic Name	Interacting Medication or Disease	Potential Result
Suvorexant	Digoxin	Concomitant administration of suvorexant with digoxin slightly increased digoxin levels due to inhibition of intestinal P-glycoprotein. Digoxin concentrations should be monitored when co-administering suvorexant with digoxin.
Suvorexant	Moderate cytochrome P450 3A inhibitors	The recommended dose in patients receiving moderate cytochrome P450 3A inhibitors (e.g., amprenavir, aprepitant, atazanavir, ciprofloxacin, diltiazem, erythromycin, fluconazole, fosamprenavir, grapefruit juice, imatinib, verapamil) is 5 mg. The dose can be increased to 10 mg if necessary for efficacy.
Suvorexant	Strong cytochrome P450 3A inhibitors	Concomitant use with strong inhibitors of cytochrome P450 3A (e.g., ketoconazole, itraconazole, posaconazole, clarithromycin, nefazodone, ritonavir, saquinavir, nelfinavir, indinavir, boceprevir, telaprevir, telithromycin and conivaptan) is not recommended.
Tasimelteon	Strong cytochrome P450 1A2 inducers	Avoid use in combination with rifampin or other cytochrome P450 3A4 inducers because of a potentially large decrease in tasimelteon exposure with reduced efficacy.
Tasimelteon	Strong cytochrome P450 1A2 inhibitors	Avoid use in combination with fluvoxamine or other strong cytochrome P450 1A2 inhibitors because of a potentially large increase in tasimelteon exposure and greater risk of adverse reactions.
Triazolam	Macrolides and related antibiotics (clarithromycin, erythromycin, telithromycin)	Increased central nervous system depression and prolonged sedation have been noted with concomitant use of certain benzodiazepines and macrolide related agents. Consider benzodiazepines undergoing conjugative metabolism that are unlikely to interact (e.g., lorazepam, oxazepam, temazepam).
Triazolam	Nonnucleoside reverse transcriptase (NNRT) inhibitors (delavirdine, efavirenz)	NNRT inhibitors may inhibit the hepatic metabolism (cytochrome P450 3A4) of the benzodiazepine. The pharmacologic effects of certain benzodiazepines may be increased and the duration prolonged, leading to protracted sedation and respiratory depression. NNRT inhibitors should not used simultaneously with certain benzodiazepines.
Zaleplon	Cytochrome P450 3A4 inducers (e.g., rifampin)	Coadministration resulted in an approximate 80% reduction in the maximum concentration and area under the curve of zaleplon, which may lead to ineffectiveness.
Zaleplon	Alcohol	Zaleplon may potentiate the central nervous system-impairing effects of alcohol (ethanol 0.75 g/kg) for one hour after alcohol administration.
Zaleplon	Cimetidine	Coadministration resulted in an 85% increase in both the maximum concentration and area under the curve of zaleplon.
Zaleplon	Diphenhydramine	Due to the central nervous system effects with each drug, an additive pharmacodynamic effect is possible.
Zaleplon	Imipramine	Coadministration may produce additive effects on decreased alertness and impaired psychomotor performance for two to four hours after administration.

Generic Name	Interacting Medication or Disease	Potential Result
Zaleplon	Thioridazine	Coadministration may produce additive effects on decreased alertness and impaired psychomotor performance for two to four hours after administration.
Zolpidem	Azole antifungals (e.g., fluconazole, itraconazole, ketoconazole)	Plasma concentrations and therapeutic effects of zolpidem may be increased. Consideration should be given to using a lower dose of zolpidem when ketoconazole and zolpidem are given together.
Zolpidem	Central nervous system depressants (e.g., alcohol)	Co-administration of zolpidem with other central nervous system depressants increases the risk of central nervous system depression. An additive effect on psychomotor performance between alcohol and zolpidem has been demonstrated.
Zolpidem	Cytochrome P450 3A inhibitors	Some compounds known to inhibit cytochrome P450 3A may increase exposure to zolpidem.
Zolpidem	Selective serotonin reuptake inhibitors (e.g., sertraline, fluoxetine)	The onset of action of zolpidem may be shortened and the effect increased. Coadministration with sertraline has been shown to produce a 43% increase in zolpidem maximum concentration and a 53% decrease in zolpidem time to maximum concentration. A 17% increase in zolpidem half-life has been observed after multiple doses of zolpidem and fluoxetine.
Zolpidem	Chlorpromazine	Coadministration may produce an additive effect of decreased alertness and psychomotor performance.
Zolpidem	Flumazenil	The effects of zolpidem may be reversed by flumazenil.
Zolpidem	Imipramine	Coadministration produced a 20% decrease in peak levels of imipramine; however, an additive effect of decreased alertness was seen.
Zolpidem	Rifamycins (e.g., rifampin)	Plasma concentrations and therapeutic effects of zolpidem may be decreased.

Dosage and Administration

Table 10. Dosing and Administration[7-23]

Generic Name	Adult Dose	Pediatric Dose	Availability
Doxepin	Treatment of insomnia characterized by difficulties with sleep maintenance: Tablet: 6 mg once daily	Safety and efficacy in children have not been established.	Tablet: 3 mg 6 mg
Estazolam	Short-term treatment of insomnia characterized by difficulty in falling asleep, frequent nocturnal awakenings, and/or early morning awakenings: Tablet: initial, 1 mg orally at bedtime; maintenance, 1 to 2 mg orally at bedtime	Safety and efficacy in patients <18 years old have not been established.	Tablet: 1 mg 2 mg
Eszopiclone	Treatment of insomnia: Tablet: initial, 1 mg orally at bedtime; maintenance, 1 mg to 3 mg orally at bedtime; maximum, 3 mg orally at bedtime	Safety and efficacy in patients <18 years old have not been established.	Tablet: 1 mg 2 mg 3 mg

Generic Name	Adult Dose	Pediatric Dose	Availability
Flurazepam	Short-term treatment of insomnia characterized by difficulty in falling asleep, frequent nocturnal awakenings, and/or early morning awakenings: Capsule: 30 mg orally at bedtime; however, 15 mg orally at bedtime may suffice in some patients	Safety and efficacy in children have not been established.	Capsule: 15 mg 30 mg
Quazepam	Treatment of insomnia characterized by difficulty in falling asleep, frequent nocturnal awakenings, and/or early morning awakenings: Tablet: initial, 7.5 mg orally; maintenance, 7.5 mg to 15 mg orally	Safety and efficacy in children have not been established.	Tablet: 15 mg
Ramelteon	Treatment of insomnia characterized by difficulty with sleep onset: Tablet: 2 mg immediately before bedtime	Safety and efficacy in children have not been established.	Tablet: 8 mg
Suvorexant	Treatment of insomnia characterized by difficulties with sleep onset and/or sleep maintenance: Tablet: initial, 10 mg orally at bedtime; maintenance, 10 mg to 20 mg orally at bedtime; maximum, 20 mg once daily at bedtime	Safety and efficacy in children have not been established.	Tablet: 5 mg 10 mg 15 mg 20 mg
Tasimelteon	Non-24 Hour Sleep Wake Disorder: Capsule: 20 mg orally at bedtime	Safety and efficacy in children have not been established.	Capsule: 20 mg
Temazepam	Short-term treatment of insomnia: Capsule: initial, 15 mg orally at bedtime; maintenance, 7.5 mg to 30 mg orally at bedtime	Safety and efficacy in children have not been established.	Capsule: 7.5 mg 15 mg 22.5 mg 30 mg
Triazolam	Short-term treatment of insomnia: Tablet: initial, 0.125 mg to 0.25 mg orally at bedtime; maintenance, 0.125 mg to 5 mg orally at bedtime; maximum, 0.5 mg orally at bedtime	Safety and efficacy in patients <18 years old have not been established.	Tablet: 0.125 mg 0.25 mg
Zaleplon	Short-term treatment of insomnia: Capsule: 10 mg	Safety and efficacy in children have not been established.	Capsule: 5 mg 10 mg
Zolpidem	Short-term treatment of insomnia characterized by difficulties with sleep initiation: Immediate release tablet: initial, 5 mg orally at bedtime for women and 5 mg to 10 mg orally at bedtime for men; maintenance, 5 mg to 10 mg orally at bedtime; maximum, 10 mg orally at bedtime Oral mist: 10 mg once daily	Safety and efficacy in children have not been established.	Extended-release tablet: 6.25 mg 12.5 mg Immediate-release tablet: 5 mg 10 mg Sublingual tablet:

Generic Name	Adult Dose	Pediatric Dose	Availability
	Sublingual tablet*: initial, 5 mg orally at bedtime for women and 5 mg to 10 mg orally at bedtime for men; maintenance, 5 mg to 10 mg orally at bedtime; maximum, 10 mg orally at bedtime Treatment of insomnia characterized by difficulties with sleep onset and/or sleep maintenance: Extended release tablet: initial, 6.25 mg orally at bedtime for women and 6.25 mg to 12.5 mg orally at bedtime for men; maintenance, 6.25 mg to 12.5 mg orally at bedtime; maximum, 12.5 mg orally at bedtime Treatment of insomnia when a middle-of-the-night awakening is followed by difficulty returning to sleep: Sublingual tablet†: 1.75 mg orally at bedtime for women and 3.5 mg orally at bedtime for men		5 mg* 10 mg* 1.75 mg† 3.5 mg† Oral mist: 5 mg/actuation

* Edluar® (zolpidem sublingual).
† Intermezzo® (zolpidem sublingual).

Clinical Guidelines

Table 11. Clinical Guidelines

Clinical Guideline	Recommendations

American Academy of Sleep Medicine: **Clinical Guideline for the Evaluation and Management of Chronic Insomnia in Adults (2008)**[1]	General Principles
	• Treatment is recommended when chronic insomnia has significant negative impact on sleep quality, health, comorbid conditions, or daytime function.
	• Comorbid conditions (e.g. major depression, chronic pain) should be addressed and treated.
	  o Behavior and medication that may impair sleep should be identified and modified, when possible (e.g. modifying inappropriate caffeine and alcohol intake as well as and self-medication).
	• The primary treatment goals are to improve sleep quality/quantity and to improve insomnia related daytime impairments.
	  o Other goals include improved insomnia symptoms so that sleep onset latency is less than 30 minutes, wake time after sleep onset is less than 30 minutes, awakenings after sleep onset are decreased, or total sleep time is at least six hours with a sleep efficiency of at least 80 to 85%.
	• Short-term hypnotic treatment should be supplemented with behavioral and cognitive therapies when possible.
	• When pharmacotherapy is utilized, the choice of a specific

Clinical Guideline	Recommendations
	pharmacological agent should be directed by symptom pattern, treatment goals, past treatment responses, patient preference, availability of other treatments, comorbid conditions, contraindications, concurrent medication interactions, and side effects. • For patients with primary insomnia, when pharmacologic treatment is utilized alone or in combination therapy, the recommended sequence of medication trials is as follows: o Short-intermediate acting benzodiazepine receptor agonists or ramelteon: ▪ No specific agent is preferable to the others. Each has been shown to have positive effects on sleep latency, total sleep time, and wake after sleep onset in placebo-controlled trials. ▪ Individual patients may respond differentially to medications within this class. Symptom pattern, past response and patient preference should be considered in selecting a specific agent. ▪ Zaleplon and ramelteon have very short half-lives and are likely to reduce sleep latency but have little effect on waking after sleep onset. They are unlikely to result in residual sedation. ▪ Eszopiclone and temazepam have relatively longer half-lives, are more likely to improve sleep maintenance, and are more likely to produce re-sidual sedation (residual activity is limited to a minority of patients). ▪ Triazolam has been associated with rebound anxiety and is not considered a first-line hypnotic. ▪ Patients who prefer not to use a Drug Enforcement Agency-scheduled drug, and patients with a history of substance use disorders, may be candidates for ramelteon, particularly if the complaint is that of sleep initiation difficulty. o Alternate short-intermediate acting benzodiazepine receptor agonists or ramelteon: ▪ If a patient does not respond to the initial agent, a different agent within the same class is appropriate. ▪ Selection of the alternative drug should be based on the patient's response to the first. For a patient who continues to complain of wake after sleep onset might be prescribed a drug with a longer half-life; a patient who complains of residual sedation might be prescribed a shorter-acting drug. ▪ Flurazepam is rarely used because of its extended half-life. o Sedating low-dose antidepressants: ▪ May be used next when accompanied with comorbid depression or treatment failures. ▪ Examples of these include trazodone, amitriptyline, doxepin, and mirtazapine. No specific agent is recommended as preferable to the others in this group. ▪ Treatment history, coexisting medical conditions,

Clinical Guideline	Recommendations
	side effects, and pharmacokinetics may guide the selection of a specific agent. o Combined benzodiazepine receptor agonists or ramelteon and sedating antidepressants: ▪ A combination of medications from two different classes may improve efficacy by targeting multiple sleep-wake mechanisms while minimizing the toxicity that could occur with higher doses of a single agent. o Other sedating agents: ▪ Examples include anti-epilepsy medications (gabapentin, tiagabine) and atypical antipsychotics (quetiapine and olanzapine). o Prescription drugs – not recommended: ▪ Older approved drugs for insomnia including barbiturates, barbiturate-type drugs and chloral hydrate are not recommended for the treatment of insomnia. o Over-the-counter (OTC) drugs – not recommended: ▪ Antihistamine or antihistamine/analgesic type drugs (OTC "sleep aids"), as well as herbal and nutritional substances (e.g., valerian and melatonin), are not recommended in the treatment of chronic insomnia due to the relative lack of efficacy and safety data. <u>Frequency and Duration of Treatment and Follow-up</u> • Pharmacological treatment should be accompanied by patient education regarding treatment goals, safety concerns, potential side effects and drug interactions, other treatment modalities (cognitive and behavioral treatments), potential for dosage escalation, and rebound insomnia. • Administration may be nightly, intermittent (e.g., three nights per week), or as needed. o Efforts should be made to employ the lowest effective maintenance dosage of medication and to taper medication when conditions allow. • Patients should be followed on a regular basis, every few weeks in the initial period of treatment when possible, to assess for effectiveness, possible side effects, and the need for ongoing medication. • An initial treatment period of two to four weeks may be appropriate, followed by re-evaluation of the continued need for therapy. o Chronic hypnotic medication may be indicated for long-term use in those with severe or refractory insomnia or chronic comorbid illness. If used long-term, schedule regular follow-up visits at least every six months to monitor efficacy, tolerability, safety and periodic attempts to reduce dose and/or dosing frequency should be made. o Long-term prescribing should be accompanied by follow-up, ongoing assessment of effectiveness, monitoring for adverse effects, and evaluation for new onset or exacerbation of comorbid disorders.
The American Academy of Sleep	<u>Timed Melatonin</u> • Appropriately-timed administration of melatonin, in doses of 0.5 to 10

Clinical Guideline	Recommendations
Medicine (AASM): **Circadian Rhythm Sleep Disorders: Part II, Advanced Sleep Phase Disorder, Delayed Sleep Phase Disorder, Free-Running Disorder, and Irregular Sleep-Wake Rhythm (2007)**[85]	mg, has been shown to entrain totally blind patients who have free-running disorder. • Treatment with melatonin must be sustained or relapse will occur. • Entrainment may not occur for weeks or months after treatment initiation, depending on the phase of the patient's melatonin rhythm at treatment initiation and the period of the patient's free-running rhythm. Hypnotic Medications • The safety and efficacy of hypnotic medications for the promotion of sleep in free-running disorder in the blind have not been established. Stimulant Medications • The safety and efficacy of stimulant medications in the promotion of wakefulness in free-running disorder in the blind have not been established.
National Institutes of Health: **Manifestations and Management of Chronic Insomnia in Adults (2005)**[2]	Behavioral and Cognitive Therapies • Behavioral methods include relaxation training, stimulus control, and sleep restriction. • Cognitive therapy methods have been added to behavioral methods and include cognitive restructuring, in which anxiety-producing beliefs and erroneous beliefs about sleep and sleep loss are specifically targeted. • The combination of cognitive methods and behavioral methods has been found to be as effective as prescription medications for short-term treatment of chronic insomnia. The beneficial effects of cognitive methods and behavioral methods may last well beyond the termination of active treatment. Benzodiazepine Receptor Agonists • Benzodiazepine receptor agonists include benzodiazepines (e.g., estazolam, flurazepam, quazepam, temazepam and triazolam) and newer agents that act at benzodiazepine receptors but have a nonbenzodiazepine structure (e.g., eszopiclone, zaleplon and zolpidem). • Results from moderate to high-quality studies indicate that these eight agents are effective in the short-term management of insomnia. With the exception of eszopiclone, the benefits of these agents for long-term use have not been studied using randomized, controlled trials. • The frequency and severity of the adverse effects are much lower for the newer benzodiazepine receptor agonists, most likely because these agents have shorter half-lives. • In the short-term, abuse of the benzodiazepine receptor agonists is not a major problem, but problems associated with their long-term use require further study. • Barbiturates (e.g., phenobarbital) have been used in the treatment of insomnia, however, short-term and long-term studies are lacking; such drugs bear significant risks and are not recommended in the treatment of chronic insomnia. Other Prescription Medications • Other sedating medications have been used in the treatment of insomnia. These include barbiturates and antipsychotics. • Studies demonstrating the usefulness of these medications for either short- or long-term management of insomnia are lacking.

Clinical Guideline	Recommendations
	• All of these agents have significant risks. Thus, their use in the treatment of chronic insomnia cannot be recommended. Antidepressants • Antidepressants (especially trazodone) are often prescribed for insomnia, although they are not Food and Drug Administration (FDA)-approved for this purpose. • In short-term use, trazodone and doxepin have been shown to have some beneficial effects, but there are no studies on long-term use. • Data on other antidepressants (e.g., amitriptyline and mirtazapine) in individuals with chronic insomnia are lacking. • These guidelines were published prior to the FDA approval of ramelteon. Nonprescription Medications • Antihistamines are the most commonly used OTC treatments for chronic insomnia, but there is no systematic evidence for efficacy and there are significant concerns about risks of these medications. • Adverse effects include residual daytime sedation, diminished cognitive function, and delirium, the latter being of particular concern in the elderly. Other adverse effects include dry mouth, blurred vision, urinary retention, constipation, and risk of increased intraocular pressure in individuals with narrow angle glaucoma.

Conclusions

Agents from several drug classes are available for the treatment of insomnia including, tricyclic antidepressants, melatonin receptor agonists, benzodiazepines and nonbenzodiazepine hypnotics as well as orexin receptor antagonists. The benzodiazepines are generally classified based on their duration of action. Triazolam (Halcion®) has a short duration of action, while estazolam (ProSom®) and temazepam (Restoril®) are intermediate-acting agents. Flurazepam (Dalmane®) and quazepam (Doral®) are generally considered long-acting benzodiazepines.[11-15] The nonbenzodiazepine sedative hypnotics have specific activity at the γ-aminobutyric acid subtype A receptors and do not have anxiolytic or anticonvulsant effects.[4] Zaleplon (Sonata®) is a short-acting agent and is effective for patients with difficulty falling asleep.[16] Zolpidem is available in as an immediate-release tablet (Ambien®), oral spray (Zolpimist®), sublingual tablet (Edluar® and Intermezzo®) and extended-release tablet (Ambien CR®). The sublingual tablet (Intermezzo®) is the only zolpidem formulation that is approved for the treatment of insomnia due to middle-of-the-night awakenings.[17-21] Of the nonbenzodiazepine sedative hypnotics, eszopiclone (Lunesta®) has the longest half-life and is effective in treating sleep onset insomnia and sleep maintenance insomnia.[22] Doxepin (Silenor®), an antidepressant, is approved for the treatment of insomnia and likely causes sedation through antagonism of the histamine-1 receptor.[7] Ramelteon (Rozerem®) and tasimelteon (Hetlioz®)are melatonin agonists and ramelteon has a higher affinity for the melatonin receptor compared to endogenous melatonin.[8,9] The duration of effect for ramelteon is up to five hours.[8] Suvorexant (Belsomra®) belongs to the novel class of orexin receptor antagonists and is presumed to promote sleep by suppressing the wake drive.[10] Currently, estazolam, eszopiclone, flurazepam, temazepam, triazolam, zaleplon and zolpidem (immediate-release and extended-release tablets) are available generically.[6]

In general, study results consistently demonstrate that these agents are more effective compared to placebo, for patients experiencing insomnia.[24-74,76-78,81-83] Studies suggest that the comparative efficacy of the agents included within this review may vary, with no consistently superior intervention identified; however, some studies indicate that zaleplon may result in less residual effects and rebound insomnia when compared to zolpidem.[62,63,65] Several agents have demonstrated efficacy in the presence of various comorbidities or specific subpopulations including elderly; peri- and postmenopausal women; patients

with depression, generalized anxiety disorder, Parkinson disease, substance abuse and posttraumatic stress disorder.[29,32,33,41,55-57,70,71] Furthermore, efficacy of the nonbenzodiazepine hypnotics has been demonstrated to be sustained for up to one year. Eszopiclone and zolpidem extended-release have demonstrated sustained efficacy through six months while ramelteon and zolpidem have demonstrated sustained efficacy over the course of a year. [30,37,38,56,69,76]

Currently, guidelines do not recommend one sedative hypnotic over another. All agents have been shown to result in positive effects on sleep latency, total sleep time and wake time after sleep onset. Selection of an agent should take into consideration the patient's specific symptom pattern, patient preferences, any comorbid disease states and concurrent medications, as well as the individual side effect profile for each option. Zaleplon and ramelteon have short half-lives, work well to reduce sleep latency and are unlikely to result in residual sedation; however, they have little effect on waking after sleep onset. Eszopiclone and temazepam have longer half-lives, are more likely to improve sleep maintenance, and are more likely to produce residual sedation. Triazolam has been associated with rebound anxiety and is not considered a first-line treatment. The use of doxepin for insomnia in the absence of co-morbid depression is not addressed in clinical guidelines, as the low-dose formulation was not available when these guidelines were published. Depending on the patient's specific sleep complaint of sleep initiation or sleep maintenance, consideration should be given to the pharmacokinetic parameters of the available hypnotics. Agents with a longer half-life may be preferred in those with sleep maintenance issues, while agents with a shorter time to maximum concentration may be preferred in patients with sleep initiation complaints. If a patient does not respond to the initial agent, a different agent within the same class is appropriate after evaluating the patient's response to the first agent.[1]

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