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 and temazepam (Restoril®) are intermediate-acting agents. Flurazepam and quazepam (Doral®) are generally considered long-acting benzodiazepines.[11-15] All of the benzodiazepines sedative-hypnotics are available generically.[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 several zolpidem formulations are available generically.[6]

Table 1. Current Medications Available in the Therapeutic Class[7-22]

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*	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*	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: 7.5 mg 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, generic products are available for all benzodiazepine sedative-hypnotics as well as eszopiclone, zaleplon and several zolpidem formulations.[6]
- Doxepin is available generically in higher doses that are approved for the treatment of depression and anxiety.[6]

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