Pharmacotherapy for insomnia in adults

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Literature review current through: **Sep 2023.**
This topic last updated: **Aug 22, 2023.**

INTRODUCTION

Insomnia is one of the most common symptoms for which adults seek medical advice. While pharmacotherapy should not be the sole treatment for insomnia, medication may be part of an integrated approach that includes behavioral strategies and treatment of relevant comorbidities.

A range of medications and substances are used to treat insomnia in adults, spanning the following categories:

- Medications with regulatory approval for treatment of insomnia
- Off-label prescription medications prescribed for insomnia
- Over-the-counter (OTC) sleep aids (eg, diphenhydramine and doxylamine, alone or in "PM" formulated medications)
- Dietary supplements (eg, melatonin)

Clinical trial data typically are available only for individuals meeting insomnia disorder criteria (table 1). Chronic insomnia disorder requires sleep disturbances and associated daytime symptoms at least three times a week for at least three months despite adequate opportunity and circumstances for sleep. When sleep medications are used for sleep disturbances related to other causes, supporting evidence is indirect. Little or no supportive evidence exists for sleep aids other than the medications with regulatory approval specifically for insomnia.

Both pharmacodynamic and pharmacokinetic characteristics should be considered in selecting a medication to promote improved sleep. The mechanism and duration of action are critical concerns for safety and efficacy. The variety of available insomnia medications allows for a highly individualized treatment approach.

Additional topics on the treatment of insomnia include:

- (See "Overview of the treatment of insomnia in adults".)
- (See "Cognitive behavioral therapy for insomnia in adults".)
- (See "Poor sleep and insomnia in hospitalized adults".)
- (See "Insomnia in patients with a substance use disorder".)
- (See "Sleep-wake disturbances and sleep disorders in patients with dementia".)
- (See "Insomnia in palliative care".)

DRUG SELECTION

Our approach — Pharmacotherapy should not be the sole treatment of insomnia. Cognitive behavioral therapy for insomnia (CBT-I) is the preferred first-line treatment for chronic insomnia in adults and has been endorsed as first-line therapy by multiple societies and guideline panels [1-5]. Overall, the evidence base is stronger for CBT-I than for medications. When used, medications should be combined with healthy sleep habits and CBT-I, when appropriate and available [1,2,6]. (See "Overview of the treatment of insomnia in adults", section on 'Approach to chronic insomnia'.)

Medications with regulatory approval for treatment of insomnia disorder fall into four categories of mechanism of action:

- Benzodiazepine receptor agonists (BZRAs), which include the nonbenzodiazepine BZRAs (eszopiclone, zaleplon, and zolpidem) and five benzodiazepine hypnotics (estazolam, flurazepam, temazepam, triazolam, and quazepam)
- Dual orexin receptor antagonists (DORAs: daridorexant, lemborexant, and suvorexant)
- Low-dose doxepin (a histamine receptor antagonist)
- Ramelteon (a melatonin receptor agonist)

All of the approved medications have been evaluated for efficacy and safety in short-term placebo-controlled randomized trials in adults with insomnia disorder [1]. There are very few studies comparing one agent or class directly with another [7]. This was illustrated by a 2022

systematic review and network meta-analysis, which identified 154 double-blind, placebo-controlled randomized trials of 30 different medications for insomnia in nearly 45,000 participants, of which only five trials were longer than four weeks, and nearly all comparisons relied on indirect evidence and a small subset of the total number of studies [8]. The study concluded that eszopiclone and lemborexant appeared to be the most favorable medications based on overall efficacy, acceptability, and tolerability, but this conclusion was limited by known adverse effects of eszopiclone and inconclusive safety data for lemborexant. While other drugs were found to be effective for treating insomnia, they appeared to have either greater side effects or less evidence of long-term efficacy. Confidence is also tempered by the difficulties of generalizing data obtained in narrowly defined clinical trial participants to the broader population of patients with insomnia seen in clinical practice [9].

Among the major categories and classes, we consider all appropriate to prescribe as first-line pharmacotherapy **except** for the benzodiazepine hypnotics. We see few reasons to start with benzodiazepine hypnotics for insomnia, based on their longer half-lives (especially estazolam, flurazepam, and quazepam), higher risk of dependence and habituation, and the availability of safer options. Of the benzodiazepine hypnotics, temazepam has the most favorable safety profile for use in insomnia.

The discussion that follows outlines an approach to choosing among the remaining categories, organized by the predominant sleep complaint (ie, difficulties with sleep-onset, sleep-maintenance, or both) (algorithm 1). However, medication selection is highly individualized and takes into consideration not only symptom pattern but also past treatment response, medication availability and cost, side effects and contraindications, comorbidities, and patient preference. (See 'Patients with isolated sleep-onset insomnia' below and 'Patients with sleep-maintenance or mixed insomnia' below.)

It is important to keep in mind that while considerable evidence supports the efficacy of medications for insomnia, most patients do not experience full remission of their insomnia symptoms, and adjunctive nonpharmacologic strategies must go hand-in-hand. One study examined subjective assessments of insomnia patients chronically treated with BZRA hypnotics and found that while the majority of patients experienced some degree of therapeutic response, less than half met criteria for remission from their insomnia [10]. The remission rates were lowest for patients with medical and psychiatric comorbidities.

Use of other sedating medications for insomnia should be considered for patients who do not have an adequate therapeutic response to first-line medications with regulatory approval for insomnia, when a different mechanism of action is desired, or when there is a specific reason to avoid BZRAs. Medications with sedating effects, such as trazodone, mirtazapine, and

gabapentin, when used at much lower doses than those studies and approved for other indications, may represent a relatively safe alternative to BZRAs in selected patients, even if the evidence base for efficacy is not as robust. For such patients who have not responded to CBT-I, the risks of untreated insomnia also factor into decision-making. (See 'Antidepressants' below.)

Over-the-counter (OTC) sleep aids and dietary supplements are commonly used by individuals prior to seeking medical attention for insomnia. Aside from melatonin, which has a similar role as ramelteon but weaker evidence, nonprescription therapies are rarely a first-line option by the time an individual seeks medical advice.

Patients with isolated sleep-onset insomnia — For patients with predominantly sleep-onset complaints (eg, difficulty falling asleep at desired time, spending >30 minutes awake before falling asleep, but once asleep, little difficulty maintaining sleep later in the night), we choose from among the following medications: a nonbenzodiazepine BZRA (zaleplon, zolpidem, eszopiclone, and zopiclone) (table 2), a DORA (daridorexant, lemborexant, and suvorexant), or the melatonin agonist, ramelteon (table 3). Among these, the agents with a dual indication for sleep onset and sleep maintenance difficulties (DORAs, zolpidem extended release, eszopiclone, and zopiclone) should be used with caution as they have a higher risk of next-morning residual sedation.

When there is a desire to avoid the side effects and risks of BZRAs, for example in older adults or those with cognitive dysfunction, we generally start with a DORA, ramelteon, or melatonin (algorithm 1 and figure 1). Ramelteon and melatonin are not particularly potent and probably work primarily to augment endogenous circadian signaling, allowing natural homeostatic mechanisms to play out; they will not help maintain sleep later in the night. However, for some individuals, particularly those with mildly delayed circadian rhythms ("night owl" tendencies), ramelteon is sufficient and represents a safe first-line choice. Melatonin works similarly and is discussed below as an alternative herbal supplement. (See 'Ramelteon' below and 'Melatonin' below.)

For younger adults with few comorbidities, a nonbenzodiazepine BZRA is a reasonable first-line choice for sleep-onset insomnia, provided there are no major reasons to avoid a BZRA (eg, opioid use, substance use disorder) and they are able to adhere to precautions for next-morning residual effects (figure 1). The specific medication and formulation can be individualized based on pharmacokinetics, patient preferences, and cost/formulary constraints. (See 'Nonbenzodiazepine BZRAs' below.)

Patients with sleep-maintenance or mixed insomnia — For patients with predominantly sleep-maintenance complaints (ie, middle-of-the-night awakenings for >30 minutes, waking up

>30 minutes before desired time) or mixed symptoms (both sleep-onset and sleep-maintenance problems), we choose from among medications with an appropriately long duration of action: a nonbenzodiazepine BZRA (all except zaleplon) (table 2), a DORA, or low-dose doxepin (for sleep-maintenance only) (table 3). For patients with only sleep maintenance issues, middle-of-the-night dosing is also an option for certain nonbenzodiazepine BZRAs (zaleplon, zolpidem middle-of-the-night), particularly if nightly dosing of medication at bedtime is not required or desired. The choice among these is individualized, with examples as follows:

- When there is a desire to avoid the side effects and risks of BZRAs, low-dose doxepin and a DORA are both reasonable options with appropriate pharmacokinetics to cover the full night (algorithm 1). When used at the low doses approved for insomnia, doxepin can be a safe initial choice in such patients. Although not particularly potent, it can be an effective therapy in some patients based on its antihistamine effects (see 'Low-dose doxepin' below).

- Depending on comorbidities, some patients may benefit from other medications with sedating side effects, such as trazodone or possibly gabapentin, for sleep maintenance; however, as discussed below, off-label prescribing must be done with caution as the risk-benefit ratio in treating sleep disturbances may be very different from that of the indicated disorder. (See 'Medications prescribed off-label for insomnia' below.)

- DORAs are probably similar in potency to the BZRAs for sleep-maintenance insomnia, with a slightly better safety profile since they do not appear to carry risks of respiratory depression. Cost may be a limiting factor for some patients. (See 'Dual orexin receptor antagonists' below.)

- For younger adults with few major comorbidities, a nonbenzodiazepine BZRA is also a reasonable first-line choice for sleep-maintenance insomnia, provided there are no major reasons to avoid a BZRA (eg, opioid use, substance use disorder) and they are able to adhere to precautions for next-morning residual effects. (See 'Nonbenzodiazepine BZRAs' below.)

  For such patients with poorly controlled anxiety contributing to distress, a benzodiazepine with an intermediate half-life and anxiolytic effects (eg, lorazepam) is often a better choice than a nonbenzodiazepine BZRA. (See 'Benzodiazepine hypnotics' below and 'Anxiolytics' below.)

Special populations

- **Older adults and those with cognitive impairment** – Older adults are at increased risk for adverse drug reactions and may have elevated medication serum levels with prolonged effects due to decreased hepatic metabolism [11]. They are particularly vulnerable to excessive sedation, cognitive impairment, delirium, and balance problems [12-15]. An increased risk of falls with severe consequences, including traumatic brain injury and hip fracture, has been observed in association with both benzodiazepines and nonbenzodiazepine BZRAs in older adults [13,16,17]. All BZRAs are considered potentially inappropriate medications in older adults based on risk of adverse effects [11]. (See "Drug prescribing for older adults".)

  Accordingly, there is broad agreement that BZRAs should not be used to treat insomnia in older adults. Selection among the remaining options should be individualized using the same considerations as described above (see 'Our approach' above). Except for benzodiazepines and nonbenzodiazepine BZRAs, all of the other medications approved by the US Food and Drug Administration (FDA) for insomnia have been evaluated for efficacy and safety in older adults with insomnia [18-22] and in adults with cognitive impairment due to mild to moderate dementia [7,18,23].

  While the nonbenzodiazepine BZRAs should generally be avoided as first-line medications in older adults in agreement with Beers criteria [11], selected older adults may be appropriate candidates for low doses, after a careful assessment of risks and benefits. Dosing recommendations for older adults are included in the prescribing information; for most medications, the lowest available dose should be used and not exceeded (table 2 and table 3).

  Extra caution is necessary with off-label prescribing in older adults [19]. Antidepressants prescribed for insomnia (eg, trazodone) may have unintended consequences in older adults, such as a hypotensive effect that increases fall risk [24]. OTC antihistamines with anticholinergic activity may cause confusion and other undesired effects in older patients [11,25].

- **Hepatic impairment** – All of the approved insomnia medications undergo hepatic metabolism. Prescribing guidelines differ among the medications and are highlighted where appropriate with each medication. Generally, mild to moderate hepatic impairment may require a lower dose, while severe impairment may require a lower dose or avoidance of the medication. None of the FDA-approved insomnia medications at recommended doses is known to cause hepatic injury.

- **Renal impairment** – The pharmacokinetics of approved insomnia medications are minimally affected by renal impairment. No dosage adjustments are required.

  A retrospective cohort study of patients with sleep disorders undergoing continuous ambulatory peritoneal dialysis did not find an association between sedative-hypnotic use and all-cause mortality [26].

- **Pulmonary disease** – There is minimal potential for respiratory depression with the FDA-approved insomnia medications at recommended doses; however, caution is advised in patients with compromised respiratory function. The greatest risk of lethal respiratory depression is with benzodiazepines used concomitantly with opioids. Caution is also advised in patients taking concurrent gabapentin or pregabalin [27] and those with untreated moderate to severe obstructive or central sleep apnea [28].

- **Substance use disorders** – All of the BZRAs and DORAs are Schedule IV controlled substances (relatively low abuse potential, limited dependence risk). Ramelteon and low-dose doxepin have no abuse potential. The choice of whether to prescribe an insomnia medication and what medication to select should be influenced by the type of substance use and whether it is active use or a remote history. Treatment of insomnia in patients with substance abuse is discussed in more detail separately. (See "Insomnia in patients with a substance use disorder", section on 'Management'.)

- **Hospitalized patients** – Acute sleep disturbance in the hospital setting is common. Illness-related stress, environmental factors (eg, light, noise), scheduling of assessments and therapies, and side effects of medications all may undermine the quality of sleep. (See "Poor sleep and insomnia in hospitalized adults", section on 'Contributing factors'.)

  Increased caution is necessary when considering sleep-promoting medications to avoid adverse effects related to disease-specific factors influencing a medication's pharmacodynamic and kinetic actions, and those potentially resulting from medication interactions. Special concern should be given to a medication's effects on cognition, balance, and blood pressure [29]. (See "Poor sleep and insomnia in hospitalized adults", section on 'Pharmacotherapy'.)

- **Individuals with nonstandard schedules** – Many people doing shift work experience impairment in their ability to achieve adequate sleep, as well as optimum alertness during working hours [30,31]. Short-acting hypnotics may help people sleep more during the daytime between nighttime shifts. Evening melatonin may facilitate a more rapid readjustment to nighttime sleep following a shift change. Melatonin is also sometimes

used for daytime sleep in night shift workers. (See "Sleep-wake disturbances in shift workers", section on 'Improving daytime sleep'.)

PRESCRIBING AND MONITORING

Shared warnings and precautions — All medications approved for the treatment of insomnia share risks related to the following common side effects:

- **Central nervous system (CNS) depressant effects**, including impaired alertness, motor incoordination, and next-morning impairment. These risks are generally highest with the benzodiazepine receptor agonists (BZRAs), intermediate for dual orexin receptor antagonists (DORAs), and lowest for low-dose doxepin and ramelteon. In addition, the benzodiazepines are respiratory depressants that can worsen hypoventilation and obstructive sleep apnea.

  Risks are increased when medications for insomnia are combined with other CNS depressant medications or alcohol. We do **not** prescribe benzodiazepine hypnotics for insomnia in patients taking opioids due to risk of respiratory depression. In addition, recent prescription of opioids is a marker of increased risk of overdose in young adults prescribed benzodiazepines for sleep disorders [32]. Nonbenzodiazepine BZRAs are not strictly prohibited but require caution and should generally be avoided as first-line medications in patients taking opioids, as they have also been associated with increased risk of overdose when co-prescribed with opioids [33]. DORAs, doxepin, and ramelteon are safer initial choices in this setting (figure 1).

- **Abnormal thinking and behavioral changes**, including bizarre behavior, hallucinations, agitation, and amnesia.

- **Complex sleep-related behaviors** such as sleepwalking, driving, making telephone calls, eating, and having sex while not fully awake. These events have been reported with all insomnia medications but appear to be more common with zolpidem, zaleplon, eszopiclone, and triazolam than other medications used for sleep [34]. (See "Disorders of arousal from non-rapid eye movement sleep in adults", section on 'Clinical features' and "Approach to abnormal movements and behaviors during sleep".)

  The incidence and risk factors for complex sleep-related behaviors are not well characterized, even for nonbenzodiazepines. Across studies, estimates for sleep-related behaviors of any severity related to nonbenzodiazepine hypnotics range widely, from 3 to 25 percent, with rates in the higher end of the range primarily associated with doses

exceeding recommended levels [35-38]. While most events are non-serious, rare cases of injury and even death have been described via mechanisms such as accidental overdose, motor vehicle crash, and drowning. Higher dose appears to be a risk factor for complex sleep-related behaviors, although in at least one study, higher doses were associated with risk in younger adults but not older adults [35].

- **Risk of worsening depression and suicidal ideation**. In the United States, all approved insomnia medications carry warnings or cautions about suicide risk in patients with depression. Insomnia is associated with increased risk for suicide, which may be primarily mediated by underlying depression [39]. However, insomnia has been shown to be an independent risk factor for suicide. Accordingly, all people with insomnia should be assessed for suicidal ideation and behavior.

  Patients with comorbid depression should be assessed for suicidal ideation before prescribing hypnotics and if present, monitored closely. Limited data suggest that treatment of insomnia with a BZRA in such patients does not worsen, and may even reduce suicidal ideation in patients with comorbid depression and severe insomnia [40]. (See "Unipolar depression in adults: Assessment and diagnosis", section on 'Suicide risk' and "Suicidal ideation and behavior in adults", section on 'Patient evaluation'.)

  A 2017 systematic review identified several retrospective and prospective observational studies showing a positive association between suicidal ideation and behavior and use of hypnotics but concluded that none of the studies adequately controlled for depression or other psychiatric disorders that may be linked with insomnia [41]. Other studies suggest that treating insomnia in patients with depression in some cases hastens recovery from depression [42,43], and in other cases at least improves insomnia and next-day functioning, if not necessarily impacting depression severity [44,45].

  Risks factors are not well established, and further studies are needed. In one administrative claims database study that included more than 350,000 patients treated with an insomnia medication, the adjusted hazard of a suicide attempt was 61 percent greater with trazodone (doses <200 mg) compared with zolpidem [46]. The study also found that the risk for suicide attempt was lower for patients continued on an insomnia medication for over 120 days, compared with those prescribed doses for 30 days or less. Another claims database study of depressed patients with insomnia who were prescribed zolpidem found that the relative risk of suicide attempts increased immediately before prescription of zolpidem, but subsequently declined, suggesting that the medication did not contribute to additional suicide risk [47].

Safe prescribing practices — Pharmacotherapy should not be the sole treatment for insomnia. CBT-I is recommended as first-line treatment for chronic insomnia [1-4]. When used, medications should be part of a holistic approach that includes healthy sleep habits, adequate opportunity for sleep, treatment of relevant comorbidities, and CBT-I when appropriate and available.

While not studied or validated formally, safe prescribing practices that may help to mitigate common risks of insomnia medications include the following (table 4) [41]:

- Prescribe the lowest possible effective dosage
- Avoid prescribing a dosage greater than the maximum recommended dosage
- Avoid providing refills until continued need, efficacy, and tolerability are established
- Avoid combining with alcohol or other sedatives, including opioids
- Use increased caution in older adults and patients with renal and liver dysfunction
- In patients with comorbid depression, assess for suicidal ideation before prescribing and, if present, monitor closely while treating insomnia
- Instruct patients on proper timing of the medication in relation to desired sleep onset
- Instruct patients on medication half-life and expected duration of effect
- Advise against use if there is insufficient time for medication elimination between planned bedtime and rise time
- Discuss risk of next-day impairment in alertness, memory, coordination, and driving
- Discuss risk of complex sleep-related behaviors such as sleepwalking, eating, and driving
- Schedule regular follow-up to review efficacy, side effects, nonpharmacologic options, and assess ongoing need for medication

Initial doses and adjustments — Most of the approved insomnia medications have at least two dosage options, usually with a low recommended starting dose for older adults and, in the case of zolpidem, for females (table 2 and table 3). Under most circumstances, treatment should be initiated at the lowest dose to assess tolerability and then cautiously advanced to a higher dose only when necessary for greater efficacy. Rarely should doses beyond the prescribing guidelines be considered [28].

There is considerable intraindividual variation in how quickly medications are metabolized and continue to exert a sleep-promoting effect. The indications represent a general guide (sleep-onset versus sleep-maintenance); however, some medication and dose adjustments may be necessary for an optimum balance of efficacy and undesired residual effects.

Advice on taking the medication daily or intermittently should be individualized and may change over time. For patients with high levels of distress, we may suggest taking a medication nightly for the first one to two weeks to assess efficacy before making adjustments. Patients with a lower level of distress may be instructed to use as needed up to daily; knowledge that a medication is available can be reassuring and build confidence in nonpharmacologic strategies.

Response assessment — The effectiveness and safety of medications prescribed for insomnia must be monitored regularly. We generally recommend a clinical visit or phone follow-up within a few weeks of an initial prescription to review effectiveness, pattern of use, and adverse effects [6]. Patients should be able to contact the prescriber quickly to report adverse events.

The frequency of visits thereafter can be individualized depending on the patient's risks for side effects, medication adjustments, and ongoing need for medication. When scheduled medications are prescribed or refilled for insomnia symptoms, recent dispensing of other scheduled medications (eg, opioids) and sedating medications must be reviewed.

Patients with inadequate response — Medications for insomnia may need to be titrated or switched to achieve optimal results. Changes among insomnia medications can be made within the same class or to one with a different mechanism of action, depending on the perceived reason for failure.

Switching to an alternate within-class medication is primarily relevant for nonbenzodiazepine BZRAs and is typically done for pharmacokinetic (half-life) reasons, choosing a medication with a shorter or longer duration of action depending on a patient's response (see 'Nonbenzodiazepine BZRAs' below). Switching to a medication with a different mechanism of action is typically done for insufficient efficacy or the presence of side effects.

Asking targeted questions and reviewing sleep diaries may reveal one or more of the following addressable issues:

- The medication dose may be too low or taken inappropriately (too early or too late).
- The medication may have an inappropriate duration of action for the specific sleep complaint, lasting not long enough, or too long and producing daytime sedation. Duration

of action can be adjusted by modifying the dose of the medication or its time of administration, or changing to a medication with a different half-life.

- Daytime sedation, if not excessive, may improve over the first week of administration. However, patients should always be cautioned to not drive in the morning after the first few doses until they can assess the side effects of the medication.

Treatment duration — The duration of medication treatment for insomnia should be individualized. The majority of placebo-controlled studies provide direct safety and efficacy data only for relatively short-term use. The aim is to treat for long enough to improve symptoms and build confidence in nonpharmacologic strategies but to avoid treating for longer than is needed, in order to avoid unnecessary risk and side effects.

While most patients find that their insomnia symptoms are well controlled following the use of an insomnia medication for a few weeks, others continue to benefit over extended periods. This is especially the case with individuals with chronic comorbid conditions that contribute to their impaired sleep. Ongoing monitoring for efficacy and side effects is necessary when prescribing medications long term. Periodic attempts can be made to assess the efficacy of lower medication doses and/or discontinuation of the drug.

Medication discontinuation — Patients may experience rebound insomnia (worse sleep compared with the person's baseline prior to starting the medication) for several days following abrupt discontinuation of any insomnia medication, most commonly with BZRA hypnotics [28]. A gradual taper over a few days to weeks should limit rebound effects, depending on the specific drug and dose. Note that patients may return to baseline insomnia symptoms when stopping their insomnia medications. New withdrawal symptoms (eg, seizures) are not likely to occur when discontinuing the US Food and Drug Administration (FDA)-approved insomnia medications at recommended doses.

There is increasing evidence to support the role of cognitive behavioral therapy for insomnia (CBT-I) to facilitate discontinuation of chronic medications for insomnia. (See "Cognitive behavioral therapy for insomnia in adults", section on 'CBT-I to facilitate discontinuation of hypnotics'.)

MEDICATIONS WITH REGULATORY APPROVAL FOR INSOMNIA

Medications discussed below are listed in alphabetical order. Our approach to choosing among the medications for insomnia is reviewed above. (See 'Drug selection' above.)

Benzodiazepine receptor agonists — Benzodiazepine receptor agonists (BZRAs) for insomnia include five older benzodiazepines (based on their characteristic benzene and diazepine rings) and three nonbenzodiazepine BZRAs, with alternate structures but similar mechanism of action.

In the United States, all BZRAs are subject to federal regulation based on their potential for abuse, misuse, and diversion. Both benzodiazepines and nonbenzodiazepine BZRAs are listed as Schedule IV substances (table 5), indicating a low potential for abuse and diversion compared with most other controlled substances (eg, opioids).

Benzodiazepine hypnotics — As discussed above, we generally avoid use of hypnotic benzodiazepines for treatment of insomnia based on the longer half-lives of many of them, higher risk of dependence and habituation, and the availability of safer options. This is particularly true for estazolam, flurazepam, and quazepam. (See 'Our approach' above.)

The benzodiazepine medications approved for insomnia treatment in the United States are estazolam, flurazepam, quazepam, temazepam, and triazolam (table 6). Among these, temazepam may have the best safety profile for use in insomnia. Several other benzodiazepines are marketed for insomnia outside the United States (eg, brotizolam, camazepam, flunitrazepam, loprazolam, lormetazepam, and nitrazepam). We use the term "hypnotic" benzodiazepine to distinguish the benzodiazepines approved for insomnia from those used for other purposes, such as anxiety (see 'Anxiolytics' below).

- **Mechanism of action** – Benzodiazepines promote sedation by enhancing the normal inhibitory action of gamma-aminobutyric acid (GABA) at the GABA-A receptor complex. They are allosteric modulators of the GABA-A receptor complex, with a separate recognition site from the GABA site. When a BZRA is attached, more chloride ions can enter the cell to promote a greater inhibitory (sedative) effect.

- **Dosing** – Dose ranges for the hypnotic benzodiazepines are listed in the table (table 6).

- **Metabolism and interactions** – With the exception of triazolam, the benzodiazepine hypnotics have moderate to very long half-lives (table 6), potentially several days in some cases. They should be avoided in combination with strong CYP3A4 inhibitors such as ketoconazole (table 7) and used with caution with moderate CYP3A4 inhibitors due the risk of marked increase in the hypnotic blood level. Specific interactions may be determined using the Lexicomp drug interactions tool (Lexi-Interact) included in UpToDate.

- **Side effects** – The most common side effects are somnolence, drowsiness, and dizziness. The risk for ataxia also should be considered.

The benzodiazepines have a boxed warning regarding the concomitant use of opioid medications due to the increased risk of sedation, respiratory depression, coma, and death [48]. Withdrawal effects are possible with rapid or abrupt discontinuation. Rare severe anaphylactic and anaphylactoid reactions have been reported. (See "Benzodiazepine use disorder", section on 'Withdrawal'.)

- **Efficacy** – Meta-analyses of randomized, placebo-controlled trials indicate that benzodiazepines decrease sleep latency and the number of awakenings, while improving sleep duration and sleep quality [49-52]. Typical changes associated with these medications include decreases in the duration to sleep onset by approximately 10 minutes and increases in the total sleep time of 30 to 60 minutes [49,50].

Nonbenzodiazepine BZRAs — The nonbenzodiazepine BZRA insomnia medications in the United States are eszopiclone, zaleplon, and zolpidem (table 2). Only zolpidem is marketed with alternate formulations. Zopiclone is available in selected countries.

Among the three nonbenzodiazepine BZRAs and their various formulations, zolpidem (immediate release) is often a good first choice for either sleep-onset or sleep-maintenance complaints. Although the half-life is relatively short, effects in patients are variable, and in the author's experience, many patients experience adequate full-night effects. For patients who tolerate the drug but continue to wake up in the middle of the night or too early in the morning, we may switch to zolpidem extended release or eszopiclone. For patients with persistent hangover effects in the morning but who are otherwise satisfied with efficacy, we may try zaleplon, which has the shortest half-life of the three choices.

- **Mechanism of action** – As BZRAs, nonbenzodiazepine BZRAs promote sedation by enhancing the inhibitory action of GABA at the GABA-A receptor complex. Compared with benzodiazepines, nonbenzodiazepine BZRAs appear to have greater selectivity for certain GABA-A subunit subtypes, which may limit the range of side effects as well as therapeutic effects (eg, less anxiolytic effect).

- **Dosing**

  - **Eszopiclone** – Eszopiclone has the longest half-life of the nonbenzodiazepines (approximately six hours, longer in older adults) and can be used for either sleep onset or sleep maintenance insomnia. The starting dose is 1 mg nightly, with a maximum of 3 mg in younger adults and 2 mg in older adults.

  - **Zaleplon** – Zaleplon has the shortest half-life of the nonbenzodiazepines and is primarily indicated for sleep-onset symptoms. Due to the very short half-life

(approximately one hour), the potential for hangover sleepiness is minimal after normal sleep periods. The usual starting dose is 5 mg, and the maximum dose is 20 mg. The starting and maximum dose in older adults is 5 mg. Zaleplon may be used in the middle of the night as long as the patient has at least four hours to remain in bed.

- **Zolpidem** – Zolpidem has an intermediate half-life of 1.5 to 4.5 hours and is indicated for either sleep-onset or sleep-maintenance insomnia. Because many patients find adequate coverage for the full night, we typically start with immediate release in all patients, even those with sleep-maintenance complaints. An extended-release formulation can be tried in those who do not have adequate effect with the immediate-release formulation.

  For immediate-release zolpidem formulations, the starting dose is 5 mg in females and 5 to 10 mg in males; a higher dose (10 mg) can be used in younger adults, but the maximum recommended dose is 5 mg for older adults. A low-dose sublingual tablet (1.75 to 3.5 mg) is marketed for middle-of-the-night use, with the requirement that at least four hours be available to sleep after administration and at least five hours be available prior to driving. The starting dose of zolpidem extended release is 6.25 mg in females and 6.25 to 12.5 mg in males.

- **Metabolism and interactions** – The nonbenzodiazepine BZRA half-lives are considerably shorter than those of benzodiazepine hypnotics (with the exception of triazolam), ranging from about one hour to about six hours. The shorter half-lives reduce their risk for causing daytime sedation and impairment compared with benzodiazepines. Concomitant use with a strong CYP3A inhibitor (table 7) may require a dose reduction of the nonbenzodiazepine. Specific interactions may be determined using the Lexicomp drug interactions tool (Lexi-Interact) included in UpToDate.

- **Side effects** – The most common side effects are somnolence, drowsiness, and dizziness. The risk for ataxia also should be considered. While caution with concomitant opioids is advised with nonbenzodiazepines, there is no boxed warning in this regard. All are Schedule IV controlled substances; however, the nonbenzodiazepines do not appear to be common choices for recreational use.

  The US Food and Drug Administration (FDA) added a boxed warning in 2019 on the risk of rare but serious complex sleep-related behaviors. The boxed warning was added to all formulations of zolpidem, zaleplon, and eszopiclone, along with the following information and guidance [34]:

- These events can occur with just one dose of these medicines as well as after a longer duration of treatment. Events have been reported both with and without prior alcohol or other central nervous system (CNS) depressant use. These events can occur without a prior history of such events.

- Eszopiclone, zaleplon, and zolpidem are contraindicated in patients who report an episode of complex sleep behavior after taking these insomnia medicines.

- Tell patients to discontinue their insomnia medicine if they experience an episode of complex sleep behavior even if it did not result in a serious injury.

- When starting patients on eszopiclone, zaleplon, or zolpidem, follow the dosing recommendations in the prescribing information and start with the lowest possible dose.

- **Efficacy** – Meta-analyses of randomized, placebo-controlled trials indicate that nonbenzodiazepines decrease sleep latency and the number of awakenings, while improving sleep duration and sleep quality [1,49-54]. Typical effects include a decrease of 5 to 15 minutes in sleep onset time compared with placebo, a 30- to 60-minute increase in total sleep time, and moderate to large improvement in subjective sleep quality.

Dual orexin receptor antagonists — Daridorexant, lemborexant, and suvorexant are dual orexin receptor antagonists (DORAs). All three are indicated for insomnia characterized by difficulty with sleep onset and/or sleep maintenance (table 3).

- **Mechanism of action** – The orexin (also called hypocretin) system promotes and stabilizes wakefulness with projections from the hypothalamus to the cortex and to the nuclei of multiple wake-promoting neurotransmitters (histamine, acetylcholine, dopamine, serotonin, and norepinephrine). These medications have antagonist activity at both of the orexin receptors (OX1R and OX2R), thereby facilitating sleep by decreasing the wake drive [55].

- **Dosing** – For all three medications, a recent meal may delay the onset of action, and clinicians should be aware of dose modifications related to use of CYP3A inhibitors and/or inducers (see metabolism and interactions below) (table 3).

  - Lemborexant – The recommended starting dose of lemborexant for adults and older adults is 5 mg immediately before bedtime and having at least seven hours available before the planned time of awakening. The dose may be advanced to 10 mg based on clinical response and tolerability.

- Suvorexant – The recommended starting dose of suvorexant for adults and older adults is 10 mg within 30 minutes of going to bed and having at least seven hours remaining before the planned time of awakening. If the 10 mg dose is well tolerated, the dose may be increased to a maximum of 20 mg.

- Daridorexant – The recommended dose of daridorexant is 25 or 50 mg within 30 minutes of going to bed and having at least seven hours available before the planned time of awakening. Based on safety and efficacy data, 50 mg is an appropriate initial dose that appears to be equally safe and somewhat more effective than 25 mg [56].

- **Metabolism and interactions** – Among the DORAs, lemborexant has the longest approximate half-life (17 to 19 hours), followed by suvorexant (12 hours) and daridorexant (8 hours). For all three drugs, concomitant use with strong CYP3A **inhibitors** is not recommended (table 7). For lemborexant, moderate CYP3A inhibitors should also be avoided, and a maximum dose of 5 mg is recommended in combination with mild CYP3A inhibitors; for suvorexant and daridorexant, lower doses are recommended with moderate CYP3A inhibitors to reduce the risk of toxicity. Daridorexant should be avoided in combination with strong or moderate **inducers** of CYP3A as well. All DORAs should be avoided in patients with severe hepatic impairment. Specific interactions may be determined using the Lexicomp drug interactions tool (Lexi-Interact) included in UpToDate.

- **Side effects** – The most common side effect of DORAs is somnolence [57]. Some patients may experience dose-dependent impairment in driving the morning following bedtime dosing. Patients should not drive if they do not feel fully alert. Very rarely, people might experience sleep paralysis, hypnagogic or hypnopompic hallucinations, and cataplexy-like symptoms.

  DORAs are contraindicated in narcolepsy. All DORAs are Schedule IV controlled substances (very low abuse potential, no evidence of physical dependence). They do not appear to cause respiratory depression or, in short-term studies of lemborexant, clinically significant changes in respiratory function in patients with preexisting chronic obstructive lung disease or obstructive sleep apnea [58].

- **Efficacy** – A meta-analysis of four trials including 3076 patients (mean age 56 years) with primary insomnia found that suvorexant decreased subjective sleep latency by approximately 7 minutes at 1 and 3 months, increased subjective sleep time by approximately 18 minutes at 1, 3, and 12 months, and improved subjective sleep quality at 1, 3, and 12 months [59]. Suvorexant has also been studied in patients with mild to

moderate Alzheimer disease. (See "Sleep-wake disturbances and sleep disorders in patients with dementia", section on 'Pharmacotherapy'.)

Lemborexant has been shown to improve both objective and subjective outcomes for sleep onset and sleep maintenance when compared with placebo [60,61] as well as with zolpidem extended release in adults age 55 years and older [7]. For lemborexant, safety data are available for up to 12 months of continuous use [62]. Effects on sleep appear to be maintained with long-term use, with no clear evidence of withdrawal or rebound in the two weeks following drug discontinuation.

Daridorexant has been studied in two phase 3 randomized trials including over 1800 adults with insomnia ranging from 18 to 88 years of age at doses of 10, 25, and 50 mg [56,63-65]. Trials have shown dose-dependent improvements in objective (sleep onset and wake after sleep onset) and subjective (sleep onset and total sleep time) measures with doses of 25 and 50 mg compared with placebo, without a clear increase in adverse effects with doses up to 50 mg. Based on an open-label extension study of 801 patients, efficacy and safety appear to be maintained with up to 12 months of continuous use [66].

Low-dose doxepin — Doxepin at very low doses (3 and 6 mg) is approved for the treatment of sleep-maintenance insomnia in adults (table 3).

- **Mechanism of action** – Doxepin is a tricyclic antidepressant medication that is unique in this class in having antihistaminic activity that enhances sleep maintenance. Doxepin has very high selectivity for the postsynaptic histamine H1 receptor, where it functions as a histamine antagonist and thereby produces a sedating effect [67]. At these very low doses, there is limited activity at additional receptors that may result in side effects from doxepin prescribed at higher doses, including those approved for major depressive disorder (up to 300 mg daily).

- **Dosing** – Prescribing guidelines recommend starting doses of 6 mg for adults and 3 mg for older adults to be taken within 30 minutes of bedtime and not within three hours of a meal. While only the 3 and 6 mg doxepin tablets are approved by the FDA for treating insomnia, low doses also can be prescribed with the liquid formulation of doxepin. The lowest dose of the generic capsule formulation of doxepin (10 mg) is sometimes used for cost reasons. There are inadequate safety and efficacy data to recommend doses higher than 10 mg nightly for insomnia.

- **Metabolism and interactions** – The elimination half-life of doxepin is approximately 15 hours. It should not be used with monoamine oxidase inhibitors. Specific interactions may

be determined using the Lexicomp drug interactions tool (Lexi-Interact) included in UpToDate.

- **Adverse effects** – The most common side effects are somnolence/sedation, nausea, and upper respiratory tract infection. As a tricyclic antidepressant, it should be avoided in patients with untreated angle-closure glaucoma or severe urinary retention. It has no abuse potential.

- **Efficacy** – A systematic review of low-dose doxepin for insomnia identified five placebo-controlled trials in 867 adults with chronic insomnia [68]. In two trials in adults up to 64 years of age (n = 296), doxepin improved objective total sleep time by 25 and 30 minutes for 3 mg and 6 mg doses, respectively, compared with placebo [68]. Similarly, in three trials in adults ≥65 years (n = 571), total sleep time improved by 30 and 38 minutes for 3 mg and 6 mg doses, respectively. Sleep maintenance improvements were noted into the final quarter of the night. Patient-reported subjective assessments paralleled the sleep study findings.

Ramelteon — Ramelteon is a melatonin receptor agonist approved for the treatment of insomnia in the United States and Japan but not Europe (table 3). It is indicated for insomnia characterized by difficulty with sleep onset. Ramelteon is unlikely to improve sleep maintenance.

- **Mechanism of action** – Ramelteon has agonist activity at the melatonin MT1 and MT2 receptors, which are prominent in the hypothalamic suprachiasmatic nucleus (SCN; master circadian rhythm timekeeper) [69]. Like melatonin, ramelteon facilitates sleep onset by decreasing the typical evening SCN-driven arousal (MT1), and apparently helps to reinforce circadian periodicity (MT2). An active metabolite (M-II) has much lower receptor affinity and potency, although it has much greater systemic exposure than the parent compound.

- **Dosing** – Ramelteon is available in a single 8 mg dose, to be taken within 30 minutes of going to bed. Avoid taking with or soon after a high-fat meal.

- **Metabolism and interactions** – Elimination half-life approximately 1 to 2.6 hours. Ramelteon should not be used in combination with fluvoxamine, a strong CYP1A2 inhibitor that may markedly increase ramelteon blood levels. It should be avoided in patients with severe hepatic impairment. Specific interactions may be determined using the Lexicomp drug interactions tool (Lexi-Interact) included in UpToDate.

- **Adverse effects** – The most common side effects are somnolence, dizziness, fatigue, nausea, and exacerbation of insomnia. There are rare reports of decreased testosterone

and increased prolactin. There is no abuse potential.

- **Efficacy** – In randomized trials, short-term use of ramelteon is associated with improvement in sleep onset in patients with insomnia, but the effect size is relatively small and may not be clinically significant [1]. A meta-analysis that included 11 trials and over 5700 patients found that ramelteon was associated with improvement in subjective sleep latency (-4.6 minutes) and total sleep time (7.3 minutes) compared with placebo but no significant difference in other parameters, including subjective total sleep time, number of awakenings, and wakefulness after sleep onset [70]. Although most studies examined short-term treatment and outcome in middle-aged adults [70], a small number of individual trials have demonstrated persistence of subjective benefit for at least six months, and improvement in older adults [71-75]. Subjective efficacy extended to one year in an open label trial [76].

MEDICATIONS PRESCRIBED OFF-LABEL FOR INSOMNIA

A wide variety of sedating prescription medications that are not specifically indicated for the treatment of insomnia are in relatively widespread use in patients with sleep-onset and/or sleep-maintenance complaints. Even when patients have a comorbid condition for which the sedating medication is indicated (eg, depression or epilepsy), often the medication is intended solely to treat insomnia symptoms and used at doses that may not be therapeutic for the relevant comorbidity.

As discussed above, none of these medications is routinely recommended for first-line use due to the absence of good efficacy evidence and inadequate safety evaluations for insomnia patients. They should be considered primarily for patients who do not have an adequate therapeutic response to first-line medications with regulatory approval for insomnia, when a different mechanism of action is desired, or when there is a specific reason to avoid benzodiazepine receptor agonists (BZRAs).

Extra care is required with off-label prescribing for insomnia since the risk-benefit ratio in treating sleep disturbances may be very different from that of the indicated disorder [11]. With all of these sedating prescription medications, a shared possible side effect is daytime sleepiness and impairment. There are additional contraindications, warnings, and common side effects for each medication.

Antidepressants — Despite their modest sleep-promoting effects, routine use of sedating antidepressants other than low-dose doxepin is **not** recommended to treat insomnia in patients

who are not depressed because the sedating effect tends to be short-lived and other side effects are common [77-79]. In addition, the doses of antidepressants used for insomnia are generally well below therapeutic doses for depression.

The American Academy of Sleep Medicine (AASM) practice guideline includes doxepin among the drugs listed as options for management of sleep maintenance in chronic insomnia but suggests against use of trazodone based on paucity of data and the small effect sizes observed in a single randomized trial in patients with primary insomnia [1].

Nonetheless, antidepressant medications with sedating side effects are by far the most common off-label prescriptions for insomnia. Examples include trazodone (see 'Trazodone' below), mirtazapine, and amitriptyline [79].

Trazodone — Trazodone is highlighted here due to its widespread use for insomnia (table 3) [80,81], although the AASM practice guideline suggests against its use for this purpose [1].

- **Mechanism of action** – Trazodone is an antidepressant with three main actions: serotonin reuptake inhibition, antagonism of 5-HT2A, 5-HT2B, alpha-1A, and alpha-2C receptors, and partial agonism at 5-HT1A [82]. The sedative effect is probably mediated through multiple receptors, including 5-HT2A.

- **Dosing** – Doses of trazodone studied for insomnia range from 50 to 150 mg nightly [80]. The usual adult dose is 50 to 100 mg, with a lower starting dose suggested in older adults. Titration to doses above 150 mg nightly is unlikely to help insomnia symptoms and is not advised due to increased risk of adverse effects. Gradual dose reduction is recommended on discontinuation rather than abrupt withdrawal.

- **Metabolism and interactions** – Trazodone has an elimination half-life of approximately five to nine hours, which may be prolonged in patients with obesity. The active metabolite is m-chlorophenylpiperazine (mCPP). It cannot be used with monoamine oxidase inhibitors (MAOIs). Specific interactions may be determined using the Lexicomp drug interactions tool (Lexi-Interact) included in UpToDate.

- **Side effects** – The most common problematic side effects are syncope, edema, blurred vision, diarrhea, nasal congestion, and weight loss. It has the potential to cause cognitive and motor impairment. As an antidepressant, it carries a boxed warning about the risk of suicidal ideation and behavior in children and young adults. (See "Effect of antidepressants on suicide risk in adults".)

  Additional precautions include the following:

- Serotonin syndrome – Risk is increased when used concomitantly with other serotonergic agents [83].
- Cardiac arrhythmias – Trazodone is associated with prolongation of the QT interval [82]. It should be avoided with medications that also increase the QT interval.
- Orthostatic hypotension and syncope – Hypotension can occur, likely as a result of alpha-1 antagonism [24].
- Increased risk of bleeding – Use with aspirin, nonsteroidal antiinflammatory medications (NSAIDs), warfarin, and antiplatelet and anticoagulant medications may increase bleeding risk.
- Priapism – Male patients should be cautioned about risks associated with a painful prolonged penile erection. Analogous discomfort has been reported in females due to persistent clitoral engorgement [84].
- Psychiatric – Trazodone is associated with a risk of activation of mania or hypomania.
- Angle-closure glaucoma – Trazodone should be avoided in patients with risk factors for primary angle-closure glaucoma. (See "Angle-closure glaucoma", section on 'Epidemiology and risk factors'.)

- **Efficacy** – A systematic review identified seven randomized trials of trazodone in 429 patients with insomnia using doses ranging from 50 to 150 mg nightly for one to four weeks [80]. Trazodone improved subjective sleep quality and number of awakenings but did not have an effect on any other objective sleep measures compared with placebo. There was significant heterogeneity in patient populations, and the overall quality of the evidence was rated as low to moderate. In the largest trial, 306 nondepressed patients with insomnia were randomly assigned to receive trazodone (50 mg), zolpidem (10 mg), or placebo for two weeks [85]. After one week of therapy, trazodone modestly improved subjective sleep latency, sleep duration, wake time after sleep onset, and number of awakenings compared with placebo. However, after two weeks, the trazodone group did not differ significantly from the placebo group. In a separate trial, trazodone showed a trend towards benefit as a second-line strategy in patients who failed to remit with first-line zolpidem [86].

Mirtazapine — Mirtazapine is an antidepressant with regulatory approval for the treatment of major depressive disorder; however, it is often prescribed for insomnia symptoms due to its sedating properties. Minimal evidence supports its use for insomnia disorder, although it is

commonly prescribed, and some experts find it useful in certain patients. Due to insufficient evidence regarding mirtazapine as a monotherapy in the treatment of insomnia, it was not included in a 2018 systematic review of antidepressants used for insomnia in adults [79]. It is also not reviewed in the AASM practice guideline on chronic insomnia [1].

- **Mechanism of action** – Mirtazapine is a tetracyclic antidepressant, which functions as an antagonist at the alpha-2 adrenergic inhibitory autoreceptors and heteroreceptors, as well as at serotonin 5-HT2 and 5-HT3 receptors. In addition, there is antagonist activity at the peripheral alpha-1 adrenergic and muscarinic receptors, and inverse agonist effects at histamine H1 receptors. Multiple receptor effects likely contribute to sedation, especially the specific serotonin and histamine receptor interactions.

- **Dosing** – The typical dose range for depression is 15 to 45 mg in the evening. Lower mirtazapine doses (7.5 to 15 mg) tend to be prescribed to promote sleep due to concern about excessive activation at higher doses; however, this has not been demonstrated in clinical trials in people with insomnia.

- **Metabolism and interactions** – Mirtazapine has an elimination half-life in the range of 20 to 40 hours [87]. It is contraindicated within 14 days of MAOI use. Specific interactions may be determined using the Lexicomp drug interactions tool (Lexi-Interact) included in UpToDate.

- **Side effects** – The most common side effect complaints are somnolence, increased appetite, weight gain, and dizziness. There may be impairment in judgment, thinking, and motor skills. As an antidepressant, mirtazapine carries a boxed warning about the risk of suicidal ideation and behavior in children and young adults. (See "Effect of antidepressants on suicide risk in adults".)

  Additional selected warnings and precautions include the following:

  - Hematologic – Agranulocytosis has been reported with mirtazapine.

  - Serotonin syndrome – Risk is increased when used concomitantly with other serotonergic agents.

  - Angle-closure glaucoma – Patients with untreated narrow angles taking antidepressants have increased risk for developing angle-closure glaucoma. (See "Angle-closure glaucoma", section on 'Epidemiology and risk factors'.)

  - QT prolongation – Caution is advised in patients with risk factors for QT prolongation.

- Activation of mania or hypomania – Patients should be screened for bipolar disorder.
- Seizures – Caution is advised in patients with seizure disorders.
- Cardiovascular – Cholesterol and triglyceride elevation can occur.
- Hyponatremia – Low sodium may occur with antidepressants including mirtazapine.
- Transaminase elevations – Use with caution in patients with hepatic impairment.

- **Efficacy** – Most studies of the effects of mirtazapine on sleep have been performed in patients diagnosed with major depression who also have insomnia symptoms. A 2012 systematic review of the use of mirtazapine in patients with depression and insomnia identified 23 eligible trials, of which 12 were blinded, randomized, and placebo controlled [88]. The eight trials with detailed sleep measures showed significant improvement in total sleep time, sleep efficiency, and sleep quality. A subsequent cross-over study in 19 healthy adults assessed the subjective and polysomnographic effects of mirtazapine 7.5 mg on normal sleep and transient insomnia using an acoustic stress model [89]. Compared with placebo, the use of mirtazapine during acoustic stress was associated with increased total sleep time, fewer awakenings, and increased N3 sleep.

Amitriptyline — Amitriptyline is an antidepressant with regulatory approval for the treatment of major depressive disorder; however, it often has been prescribed for insomnia symptoms due to its sedating properties, though less commonly than in past decades. Minimal evidence supports its use for insomnia disorder, although some experts still find it useful in certain patients. Due to insufficient evidence regarding amitriptyline as a monotherapy in the treatment of insomnia, it was not included in a 2018 systematic review of antidepressants used for insomnia in adults [79]. It is also not reviewed in the AASM practice guideline on chronic insomnia [1].

- **Mechanism of action** – Amitriptyline is a tertiary tricyclic antidepressant, which functions as a membrane pump reuptake inhibitor of norepinephrine and serotonin. In addition, there is antagonist activity at the alpha-1 adrenergic, histamine H1, and muscarinic M1 receptors. Multiple receptor activities likely contribute to sedation, especially the serotonin and histamine effects.
- **Dosing** – The typical total daily dosing range for depression is 25 mg to a maximum of 300 mg. Doses in the range of 10 to 50 mg are typically prescribed for insomnia symptoms.
- **Metabolism and interactions** – Amitriptyline is metabolized to nortriptyline, which also has antidepressant properties. Amitriptyline has an elimination half-life in the range of 13

to 36 hours [90]. There are numerous potential serious drug interactions. It is contraindicated within 14 days of MAOI use. It is not recommended during the acute recovery phase following a myocardial infarction or in the presence of congestive heart failure. Specific interactions may be determined using the Lexicomp drug interactions tool (Lexi-Interact) included in UpToDate.

- **Side effects** – The most common side effect complaints are somnolence, weight gain, dry mouth, constipation, dizziness, and headache. As an antidepressant, it carries a boxed warning about the risk of suicidal ideation and behavior in children and young adults. (See "Effect of antidepressants on suicide risk in adults".)

  Prescribers should be especially attuned to the risks of anticholinergic side effects (eg, blurred vision, dry mouth, urinary retention, confusion, and delirium), antihistamine effects (eg, sedation, increased appetite, and weight gain), orthostatic hypotension, dizziness, and falls. Additional warnings and precautions include:

  - Hematologic – Agranulocytosis has been reported with amitriptyline.
  - Serotonin syndrome – Risk is increased when used concomitantly with other serotonergic agents.
  - Angle-closure glaucoma – Patients with untreated narrow angles taking antidepressants have increased risk for developing angle-closure glaucoma. (See "Angle-closure glaucoma", section on 'Epidemiology and risk factors'.)
  - Cardiac conduction abnormalities – Caution is strongly advised in patients with risk factors for arrhythmias, especially with QT prolongation.
  - Activation of mania or hypomania – Patients should be screened for bipolar disorder.
  - Seizures – Amitriptyline may decrease the seizure threshold.
  - Hyponatremia – Low sodium may occur with antidepressants including amitriptyline.
  - Transaminase elevations – Use with caution in patients with hepatic impairment.

- **Efficacy** – The few studies of the effects of amitriptyline for treating insomnia have been in populations of patients with depression. Quality studies of amitriptyline monotherapy for insomnia disorder are lacking. Polysomnographic studies among depressed patients have shown amitriptyline to be associated with decreased sleep latency, increased sleep continuity, decreased amount and percentage of REM sleep, and increased phasic eye

movements during REM [91]. (See "The effects of medications on sleep quality and sleep architecture", section on 'Antidepressants'.)

Antiepileptics — Limited evidence has shown improvement in sleep duration with gabapentin [92,93]. The most appropriate use may be in patients with substance use disorders such as alcohol use disorder and with chronic pain syndromes [94]. (See "Insomnia in patients with a substance use disorder".)

Antihypertensives — There is anecdotal support for the use of clonidine for sleep, especially among children and adolescents. (See "Pharmacotherapy for insomnia in children and adolescents: A rational approach", section on 'Alpha-adrenergic agonists'.)

Antipsychotics — Quetiapine is by far the most common antipsychotic medication prescribed for insomnia symptoms. Relatively low doses (25 to 100 mg) are usually prescribed when intended for sleep difficulty in patients without a comorbid mental health disorder [95]. However, we generally advise against use of antipsychotics for insomnia in patients without a comorbid psychiatric diagnosis (eg, schizophrenia, bipolar disorder) based on the availability of safer options.

Anxiolytics — Anxiolytic benzodiazepines such as alprazolam, clonazepam, and lorazepam are not well studied for safety and efficacy for the indication of insomnia. Their most appropriate use is as adjunctive or bridge therapy in patients with insomnia as a result of anxiety or depression. (See "Bipolar major depression in adults: Choosing treatment", section on 'Anxiety, insomnia, or agitation' and "Generalized anxiety disorder in adults: Management".)

OVER-THE-COUNTER SLEEP AIDS

Over-the-counter (OTC) sleep aids are fully regulated by the US Food and Drug Administration (FDA), including composition, doses, indications, manufacture, and marketing. One of two approved sleep aids (diphenhydramine, doxylamine) are in these products, and they are marketed solely for sleep or combined with analgesics (acetaminophen, ibuprofen) as "PM" formulations.

Benefits of these sleep aids are the easy OTC access and relative safety; however, caution is necessary when recommending these medications, especially with long-term use or with older adults or when used concomitantly with medications having sedating or anticholinergic properties [11]. Tolerance may develop with extended use. Some individuals take very large amounts attempting to attain sedating effects.

Due to possible anticholinergic effects, they should be used very cautiously in older adults because of confusion and delirium risk [96].

- **Mechanism of action** – Intended sedation is due to postsynaptic histamine H1 receptor antagonism. Postsynaptic muscarinic antagonism may cause undesired anticholinergic effects [25,67].
- **Dosing** – Most preparations contain the following recommended doses. It is best to use lowest effective dose.
  - Diphenhydramine – 25 to 50 mg at bedtime
  - Doxylamine – 25 mg 30 minutes before bedtime
- **Metabolism and interactions** – The approximate elimination half-life of diphenhydramine is 9 to 10 hours and slightly longer for doxylamine (10 to 12 hours). Half-lives may be shorter in children and longer in older adults.
- **Side effects** – The most common side effects are sedation, dizziness, disturbed coordination, epigastric distress, and thickening of bronchial secretions. Warnings/contraindications include narrow-angle glaucoma, stenosing peptic ulcer, pyloroduodenal obstruction, symptomatic prostatic hypertrophy, and bladder-neck obstruction.
- **Efficacy** – Diphenhydramine is associated with a mean reduction in sleep onset of approximately eight minutes compared with placebo and a 12-minute improvement in total sleep time [1]. Contemporary data are not available for doxylamine [97,98].

DIETARY SUPPLEMENTS

Many products marketed as sleep aids are classed as dietary supplements, which are regulated in the United States as a subcategory of food under the Dietary Supplement Health and Education Act of 1994 (DSHEA). Dietary supplements can be formulated with active pharmacologic ingredients and marketed with a variety of health claims [99], and the concentration and purity of the ingredients are not guaranteed. (See "High-risk dietary supplements: Patient evaluation and counseling", section on 'Regulation of dietary supplements'.)

Dietary sleep aid products may have single or multiple supposedly active ingredients. There is little to no evidence to support the use of these products in the treatment of insomnia, although

most are generally regarded as safe [1,100]. The best evidence is for melatonin, although even that is weak.

Melatonin — Exogenous melatonin may be useful for sleep-onset insomnia in some patients. Circadin is a prescription-required melatonin formulation available outside of the United States in certain countries.

Similar to the melatonin agonist, ramelteon, exogenous melatonin is not a very potent hypnotic and does not help maintain sleep later in the night. It probably works best when taken a few hours before bedtime, when it can help to augment natural circadian alignment.

- **Mechanism of action** – Melatonin is an agonist at melatonin receptors, including those in the suprachiasmatic nucleus (SCN). Relevant to insomnia, melatonin facilitates sleep onset by decreasing the typical evening SCN-driven arousal, and it helps to reinforce circadian periodicity [69].

- **Dosing** – Melatonin is marketed in a variety of formulations, including immediate- and extended-release pills, dissolvable tablets, transdermal patch, and liquids.

  Melatonin is a dietary supplement in the United States but requires a prescription in select countries, including the European Union. Actual quantities of melatonin contained in marketed supplements may vary from what is listed on the label (both higher and lower); products may also contain substances not listed on the label, such as serotonin [101,102]. The regulation of dietary supplements and potential health risks for consumers are discussed in detail separately. (See "High-risk dietary supplements: Patient evaluation and counseling", section on 'Regulation of dietary supplements'.)

  Typical melatonin doses for insomnia are in the 1 to 5 mg range, although some products are as low as 200 mcg and as high as 20 mg. Doses below 1 mg may be as effective as higher amounts. The potential benefits of melatonin use for sleep-onset insomnia may be improved with dosing a few hours prior to bedtime.

- **Metabolism and interactions** – Melatonin is rapidly absorbed, and the elimination half-life is approximately 20 to 50 minutes.

- **Side effects** – Side effects are not well established with controlled studies. The most commonly reported are vivid dreams and nightmares, dizziness, daytime sleepiness, headache, short-term feelings of depression, irritability, and stomach cramps [103]. The safety of long-term melatonin use has not been established with controlled studies.

- **Safe storage** – As with prescription medications, supplements, including melatonin, should be stored safely in locked containers out of the reach of children. Unintentional pediatric ingestions of melatonin have risen in the United States despite declines in unsupervised medication exposures in young children more generally [104,105].

- **Efficacy** – The use of exogenous melatonin as a nighttime sleep aid has been extensively researched with many studies showing possible small benefits for sleep onset and none for sleep maintenance [106,107]. There may be a small net increase in the total sleep time. The potential benefits may vary with the dose, timing of administration and its relation to the individual's circadian predisposition, and age of the person.

  A 2020 systematic review identified 12 meta-analyses of placebo-controlled randomized trials (3 to 13 trials per study, largest analysis included 1315 patients) with quality ranging from moderate to critically low [107]. The authors concluded that melatonin results in a statistically significant but small improvement in sleep latency and total sleep time, with a lack of consensus on whether the effects are clinically meaningful.

Others — Many other dietary supplements are marketed for insomnia; however, there is insufficient evidence to support their efficacy. They are generally regarded as safe, with two notable exceptions: kava and valerian have been associated with severe liver injury in rare cases [77,108,109].

Dietary supplements may include synthetic compounds, plant-derived ingredients, and minerals. Some are homeopathic formulations. Examples of supplements widely marketed for insomnia include chamomile, glycine, Griffonia, hops, hyoscyamus, kava, L-theanine, lavender, magnesium, passionflower, nightshade, skullcap, stramonium, tryptophan, valerian, and wild jujube seeds.

A meta-analysis that included 14 randomized trials in over 1600 patients found no significant difference between any herbal medicine and placebo on any of 13 clinical efficacy measures of insomnia [108]. The majority of the trials (11 out of 14) studied valerian; chamomile, kava, and wuling were studied in one trial each. Unlike the other herbals studied, valerian was associated with a greater number of adverse events per person compared with placebo. Valerian may also produce hepatotoxic effects [77]. (See "Overview of herbal medicine and dietary supplements".)

CANNABINOIDS

Cannabidiol (CBD) and tetrahydrocannabinol (THC) have been recognized as potential therapies for insomnia and other sleep disorders [110]. Available research is limited, however, and studies

have shown mixed results [111-114]. Similarly, anecdotal reports on the value of medical cannabis for insomnia have been mixed. Further research to establish efficacy and safety is necessary before these compounds can be recommended for insomnia treatment.

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Insomnia in adults".)

INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Basics topic (see "Patient education: Insomnia (The Basics)")
- Beyond the Basics topics (see "Patient education: Insomnia (Beyond the Basics)" and "Patient education: Insomnia treatments (Beyond the Basics)")

SUMMARY AND RECOMMENDATIONS

- **Importance of nonpharmacologic therapy** – Pharmacotherapy should not be the sole treatment for insomnia. Cognitive behavioral therapy for insomnia (CBT-I) is the preferred first-line treatment. When used, medications should be combined with healthy sleep habits (table 8) and with CBT-I when appropriate and available. (See "Overview of the treatment of insomnia in adults".)

- **Approved medications** – Medications with regulatory approval for insomnia include benzodiazepine receptor agonists (BZRAs; includes benzodiazepine hypnotics and nonbenzodiazepines); ramelteon, a melatonin receptor agonist; low-dose doxepin, a histamine receptor antagonist; and the dual orexin receptor antagonists (DORAs). All are more effective than placebo in adults with insomnia disorder, and very few comparative studies have been performed. (See 'Drug selection' above.)

- **Avoidance of benzodiazepine hypnotics** – Among the approved insomnia medications, we consider all appropriate to prescribe as first-line pharmacotherapy **except** for the older benzodiazepine hypnotics. We see few reasons to start with benzodiazepine hypnotics for insomnia, based on the longer half-lives of many (especially estazolam, flurazepam, and quazepam), higher risk of dependence and habituation, and the availability of safer options. (See 'Our approach' above.)

- **Medication selection** – Selection of a medication from the remaining categories should be based on the predominant sleep complaint (sleep-onset or sleep-maintenance insomnia) as well as past treatment response, medication availability and cost, side effects and contraindications, comorbidities, and patient preference (algorithm 1 and figure 1).

  - For patients with **isolated sleep-onset insomnia**, we suggest use of a nonbenzodiazepine BZRA (table 2), a DORA, or ramelteon (table 3) (**Grade 2C**). Among these, the agents with a dual indication for sleep onset and sleep maintenance difficulties (DORAs, zolpidem extended release, eszopiclone, and zopiclone) should be used with caution as they have a higher risk of next-morning residual sedation. We avoid first-line use of nonbenzodiazepine BZRAs in most older adults, those with cognitive impairment, and patients with a history of substance use disorder or current opioid use. (See 'Patients with isolated sleep-onset insomnia' above.)

  - For patients with **sleep-maintenance or mixed insomnia**, we suggest use of a nonbenzodiazepine BZRA (all except zaleplon) (table 2), a DORA, or low-dose doxepin (table 3) (**Grade 2C**). The choice among these is individualized; we avoid first-line use of nonbenzodiazepine BZRAs in most older adults, those with cognitive impairment, and patients with a history of substance use disorder or current opioid use. (See 'Patients with sleep-maintenance or mixed insomnia' above.)

  - Off-label use of sedating medications for insomnia is primarily reserved for patients who do not have an adequate response to first-line medications, when a different

mechanism of action is desired, or when there is a specific reason to avoid BZRAs. (See 'Medications prescribed off-label for insomnia' above.)

- **Safe prescribing** – All medications for insomnia share risks related to central nervous system (CNS) depression, abnormal thinking and behavioral changes, complex sleep-related behaviors, and worsening depression and suicidal ideation. Safe prescribing practices may help to mitigate common risks of insomnia medications (table 4). (See 'Shared warnings and precautions' above and 'Safe prescribing practices' above.)

- **Dosing** – Under most circumstances, treatment should start at the lowest available dose (table 2 and table 3 and table 6). Doses should be increased only when necessary for greater efficacy. Doses beyond the prescribing guidelines should rarely be used. (See 'Initial doses and adjustments' above.)

- **Duration** – The duration of medications for insomnia should be individualized based on response and tolerability. The aim is to treat for long enough to improve symptoms and build confidence in nonpharmacologic strategies but to avoid treating for longer than is needed, in order to avoid unnecessary risk and side effects. (See 'Response assessment' above and 'Patients with inadequate response' above and 'Treatment duration' above.)

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Topic 97868 Version 30.0

GRAPHICS

International Classification of Sleep Disorders, third edition (ICSD-3) diagnostic criteria for chronic insomnia disorder

Diagnostic criteria A-F must be met:	
A	The patient reports, or the patient's parent or caregiver observes, one or more of the following: ▪ Difficulty initiating sleep* ▪ Difficulty maintaining sleep¶ ▪ Waking up earlier than desired$^{\Delta}$ ▪ Resistance to going to bed on appropriate schedule ▪ Difficulty sleeping without parent or caregiver intervention
B	The patient reports, or the patient's parent or caregiver observes, one or more of the following related to the nighttime sleep difficulty: ▪ Fatigue/malaise ▪ Attention, concentration, or memory impairment ▪ Impaired social, family, occupational, or academic performance ▪ Mood disturbance/irritability ▪ Daytime sleepiness ▪ Behavioral problems (eg, hyperactivity, impulsivity, aggression) ▪ Reduced motivation/energy/initiative ▪ Proneness to errors/accidents ▪ Concerns about or dissatisfaction with sleep
C	The reported sleep-wake complaints cannot be explained purely by inadequate opportunity (ie, enough time is allotted for sleep) or inadequate circumstances (ie, the environment is safe, dark, quiet, and comfortable) for sleep
D	The sleep disturbance and associated daytime symptoms occur at least three times per week
E	The sleep disturbance and associated daytime symptoms have been present for at least three months
F	The sleep/wake difficulty is not better explained by another sleep disorder

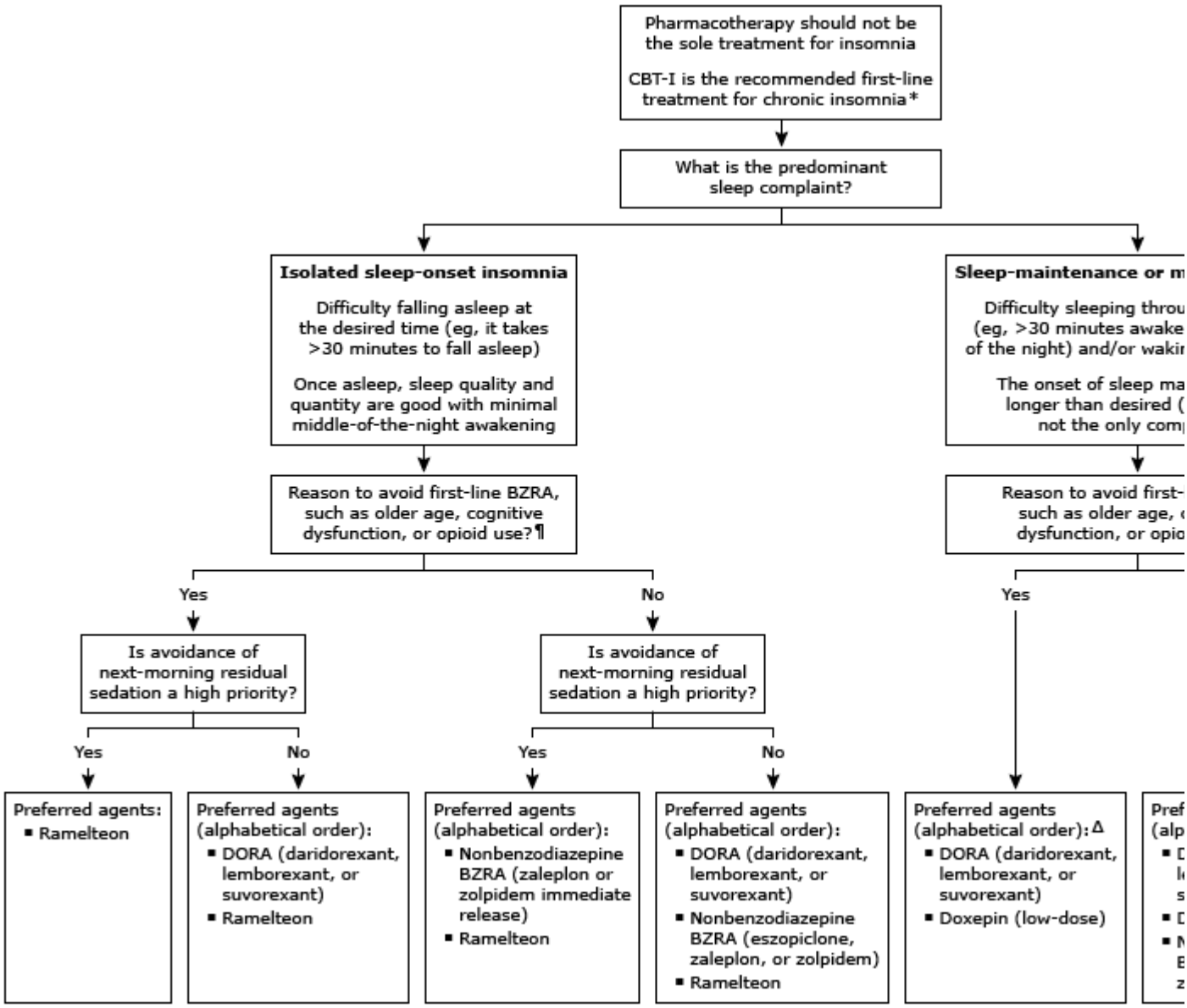
* In general, delays of >20 minutes for children and young adults and >30 minutes for middle-aged and older adults are considered clinically significant.

¶ In general, periods of awakening in the middle of the night of >20 minutes for children and young adults and >30 minutes for middle-aged and older adults are considered clinically significant.

Δ In general, waking up >30 minutes before normal awakening time is considered clinically significant.

Graphic 117710 Version 2.0

Medication selection for insomnia in adults



CBT-I: cognitive behavioral therapy for insomnia; DORA: dual orexin receptor antagonist; BZRA: benzodiazep agonist.

* When used, medications should be part of a holistic approach that includes healthy sleep habits, adequate sleep, treatment of relevant comorbidities, and CBT-I when appropriate and available. Treatment selection is based on the nature of the insomnia symptoms, past treatment responses, medication availability and cost, comorbidities, and patient preferences. Duration of effect varies based on elimination half-life, patient age, factors. Refer to UpToDate topic and tables for dosing and administration details.

¶ BZRAs include benzodiazepines and nonbenzodiazepine BZRAs such as zolpidem. Among the benzodiazep approved for insomnia that may be used as second-line therapies, temazepam has the most favorable safet

Δ All patients should be aware of the risk of next morning sedation with insomnia medications. Agents with for sleep onset and sleep maintenance difficulties (eg, DORAs, zolpidem extended release, eszopiclone, zopi higher risk of next-morning residual sedation than other first-line agents such as doxepin.

Graphic 129521 Version 5.0

Nonbenzodiazepine benzodiazepine receptor agonists (BZRAs) in the management of insomnia in adults

Nonbenzodiazepine	Clinical use*	Preparations	Adult dose (initial)¶	Adult dose (max)	Dose in older adults (≥65 years)	Half-lif (hours
Eszopiclone	Sleep onset or sleep maintenance insomnia	Tablet	1 mg	3 mg	1 to 2 mg	Intermedi (6)
Zaleplon	Sleep onset insomnia	Capsule	5 mg	20 mg	5 mg	Short (1)
Zolpidem	Sleep onset or sleep maintenance insomnia	Tablet, capsule, sublingual tablet (5 mg or 10 mg), oral liquid (5 mg per spray)	Males 5 to 10 mg Females 5 mg	10 mg	5 mg	Short (1.4 4.5)
Zolpidem extended release	Sleep onset or sleep maintenance insomnia	Coated tablet	Males 6.25 to 12.5 mg Females 6.25 mg	12.5 mg	6.25 mg	Intermedi (1.6 to 4◇
Zolpidem middle of the night (fast-acting, low dose)	Sleep maintenance insomnia (middle of the night)	Sublingual tablet (1.75 mg or 3.5 mg)	Males 3.5 mg Females 1.75 mg	3.5 mg	1.75 mg	Short (1.4 4.5)
Zopiclone (not available in the United States)	Sleep onset or sleep maintenance insomnia	Tablet	3.75 mg	7.5 mg	3.75 mg	Intermedi (5 to 7)

* Appropriate clinical uses may differ from the US Food and Drug Administration (FDA)-approved indication(s) for a given drug.

¶ Initiate treatment using lowest dose shown for those with low body weight, debilitated patients, and those receiving treatment with opioid analgesics or other central nervous system or cardiorespiratory depressants.

Δ For specific drug interactions, including management recommendations and combinations that should be avoided, use Lexi-Interact drug interactions program included with UpToDate.

◇ Duration of effect longer than predicted by half-life due to sustained release.

Graphic 117510 Version 8.0

Other drugs for the management of insomnia in adults

Other drugs	Mechanism of action	Clinical use*	Adult dose (usual)	Dose in older adults (≥65 years)	Half-life (hours)	Potential for drug interactions¶
Doxepin	Histamine H1 receptor antagonism[Δ]	Sleep maintenance insomnia	3 to 10 mg[◇]	3 to 6 mg	Long (15 drug; 31 active metabolite)	▪ Moderate ▪ Doxepin clearance is largely dependent on CYP2D6 ▪ Avoid use within two weeks of MAOI administration
Ramelteon	Melatonin receptor agonist	Sleep onset insomnia	8 mg	8 mg	Short (1 to 2.6 drug; 2 to 5 active metabolite)	▪ Moderate ▪ Ramelteon clearance is largely dependent on CYP1A2 and CYP2C9
Lemborexant	Dual orexin receptor antagonist (DORA)	Sleep onset or sleep maintenance insomnia	5 to 10 mg	5 mg	Long (17 to 19)	▪ Significant drug interactions ▪ Lemborexant clearance is dependent on CYP3A4 ▪ If used in combination with mild inhibitors of CYP3A4, recommended dose is 5 mg ▪ Avoid use of lemborexant with moderate

						and strong inhibitors and inducers of CYP3A4
Suvorexant	DORA	Sleep onset or sleep maintenance insomnia	10 to 20 mg	10 to 15 mg	Intermediate (12)	▪ Significant drug interactions ▪ Suvorexant clearance is largely dependent on CYP3A ▪ If used in combination with moderate inhibitors of CYP3A, recommended dose is 5 mg; may increase to 10 mg ▪ Avoid use of suvorexant with strong inhibitors or inducers of CYP3A
Daridorexant	DORA	Sleep onset or sleep maintenance insomnia	25 to 50 mg	25 to 50 mg	Intermediate (8)	▪ Significant drug interactions ▪ Daridorexant clearance is largely dependent on CYP3A ▪ If used in combination with moderate inhibitors of CYP3A, recommended dose is 25 mg ▪ Avoid use of daridorexant with strong inhibitors or moderate/strong

						inducers of CYP3A
Trazodone[§]	Serotonin 5-HT2A, alpha-1 adrenergic, and histamine H1 receptor antagonism[Δ]	Sleep onset or sleep maintenance insomnia	50 to 100 mg	25 to 100 mg	Intermediate (10 to 12)	▪ Moderate ▪ Trazodone is metabolized by CYP3A4 to an active metabolite; use with caution in combination with other serotonergic drugs

Dosing in this table is for adult patients with normal organ (eg, kidney, liver) function. For dosage adjustments, refer to Lexicomp drug information included with UpToDate.

CYP: cytochrome P450; MAOI: monoamine oxidase inhibitor; FDA: US Food and Drug Administration.

* Appropriate clinical uses may differ from the FDA-approved indication(s) for a given drug.

¶ For specific drug interactions, including management recommendations and combinations that should be avoided, use Lexi-Interact drug interactions program included with UpToDate.

Δ Although classified as antidepressants, these drugs are not therapeutic for treating depression at the doses used for insomnia.

◇ FDA-approved for insomnia at doses of 3 and 6 mg daily using tablet formulation.

§ Not approved by the FDA for insomnia indication.

Graphic 117512 Version 10.0

Insomnia medication indications and prescribing considerations

Medication	Category or mechanism	Type of insomnia		Clini	
		Isolated sleep onset insomnia	Sleep maintenance or mixed insomnia	High priority to avoid next-morning sedation	Old or c dys
Daridorexant	DORA	✓*	✓	✗	
Lemborexant	DORA	✓*	✓	✗	
Suvorexant	DORA	✓*	✓	✗	
Doxepin (low-dose)	HRA/TCA	✗	✓	✓	
Eszopiclone	nBZRA	✓*	✓	✗	
Zaleplon	nBZRA	✓	✓	⚠	
Zolpidem IR	nBZRA	✓	✓	⚠	
Zolpidem ER	nBZRA	✓*	✓	✗	
Zolpidem MON	nBZRA	✗	✓	✗	
Temazepam	BZRA	✓*	✓	✗	
Triazolam	BZRA	✓	✓	⚠	
Ramelteon	MRA	✓	✗	✓	
Melatonin	MRA	✓	✗	✓	
Trazodone	SAND	✓	✓	⚠	
Mirtazapine	SAND	✓	✓	⚠	
Amitriptyline	TCA	✓	✓	⚠	
Gabapentin	ASD	✗	✓	⚠	

✓	Preferred option.
✓*	If used for isolated sleep-onset insomnia, be aware that the risk of next-morning residual drows preferred options.
⚠	May use but with increased caution.
✗	Contraindicated or better options available.
✓	Off-label or over-the-counter. Off-label prescribing of sedating medications for insomnia should
⚠	do not have an adequate therapeutic response to first-line medications with regulatory approv
✗	mechanism of action is desired, or when there is a specific reason to avoid BZRAs. Doses of suc generally subtherapeutic for the relevant comorbidity.

Pharmacotherapy should not be the sole therapy for insomnia. Cognitive behavioral therapy for insomnia (C treatment for chronic insomnia. This table is intended to complement individualized decision-making for me topics on insomnia treatment for more detailed discussion.

DORA: dual orexin receptor antagonist; TCA: tricyclic antidepressant; HRA: histamine receptor antagonist; nB
benzodiazepine receptor agonist; IR: immediate release; ER: extended release; MON: middle of the night; BZ
MRA: melatonin receptor agonist; SAND: serotonergic antidepressant; ASD: antiseizure drug.

Graphic 141380 Version 1.0

Safe medication prescribing practices for insomnia*

▪ Prescribe the lowest possible effective dose
▪ Avoid prescribing a dose greater than the maximum recommended dose
▪ Avoid providing refills until continued need, efficacy, and tolerability are established
▪ Avoid combining with alcohol or other sedatives, including opioids
▪ Use increased caution in older adults and patients with renal and liver dysfunction
▪ In patients with comorbid depression, assess for suicidal ideation before prescribing and if present, monitor closely while considering other treatment options
▪ Instruct patients on proper timing of the drug in relation to desired sleep onset
▪ Instruct patients on drug half-life and expected duration of effect
▪ Advise against use if there is insufficient time for drug elimination between planned bedtime and rise time
▪ Discuss risk of next-day impairment in alertness, memory, coordination, and driving
▪ Discuss risk of complex sleep-related behaviors such as sleep walking, eating, and driving
▪ Schedule regular follow-up to review efficacy, side effects, non-pharmacologic options, and assess ongoing need for medication

* For detailed prescribing information, clinicians should refer to the individual drug information topics within UpToDate. Comprehensive information on drug-drug interactions can be determined using the drug interactions tool (Lexi-Interact online). This tool can be accessed from the UpToDate online search page or through the individual drug information topics in the section on Drug interactions.

Adapted from: McCall WV, Benca RM, Rosenquist PB, et al. Hypnotic medications and suicide: Risk, mechanisms, mitigation, and the FDA. Am J Psychiatry 2017; 174:18.

Graphic 113191 Version 4.0

Schedules of controlled substances in the United States*

Schedule	Examples	Medical use?	Potential for abuse/dependence	Prescription
I	Heroin, marijuana, LSD[¶]	No[Δ]	High	Not applicable
II	Narcotics: ▪ Codeine ▪ Fentanyl ▪ Hydrocodone and hydrocodone combinations (eg, with acetaminophen) ▪ Hydromorphone ▪ Morphine ▪ Methadone ▪ Oxycodone and oxycodone combinations (eg, with acetaminophen) ▪ Tapentadol Stimulants: ▪ Amphetamine ▪ Methamphetamine ▪ Methylphenidate Other: ▪ Cocaine ▪ Pentobarbital, secobarbital	Yes	High	Require a written prescription by a licensed practitioner. Refilling of individual prescriptions is prohibited.
III	Narcotics: ▪ Buprenorphine ▪ Combination products with <90 mg codeine/unit (eg, acetaminophen with codeine) Non-narcotics: ▪ Dronabinol	Yes	Less than with Schedule I and II drugs	A prescription for a drug in Schedules III through V must be issued by a licensed practitioner and may be communicated orally, in writing, or by facsimile to

	▪ Ketamine			the pharmacist; may be refilled up to five times
IV	Narcotics:	Yes	Less than with Schedule III drugs	
	▪ Tramadol and combinations (eg, with acetaminophen)			
	Others:			
	▪ Alprazolam ▪ Diazepam ▪ Clonazepam ▪ Lorazepam ▪ Midazolam			
V	Preparations containing limited quantities of certain narcotic and stimulant drugs used for antitussive, antidiarrheal, and analgesic purposes (eg, cough preparation with <200 mg codeine/100 mL [eg, Robitussin AC])	Yes	Lower than with Schedule IV drugs	

* Drugs and other substances that are considered controlled substances under the Controlled Substances Act are divided into five schedules based upon whether they have a currently accepted medical use in the United States and their relative abuse potential and likelihood of causing dependence when abused.

¶ Lysergic acid diethylamide.

Δ Marijuana is classified as a Schedule I controlled substance under federal law. The definition of Schedule I in the law indicates a lack of accepted medical use, and the designation as such in the table reflects this statutory language. Several states have made marijuana legal for medical and/or recreational use under state law. Marijuana's legal status is reviewed in greater detail in the UpToDate content on the epidemiology, comorbidity, health consequences, and medico-legal status of cannabis use and cannabis use disorder.

United States Department of Justice; Drug Enforcement Administration website http://www.deadiversion.usdoj.gov/schedules/#list.

Graphic 66064 Version 9.0

Benzodiazepines in the management of insomnia in adults

Benzodiazepine	Clinical use*	Adult dose (usual)¶	Dose in older adults (≥65 years)	Half-life (hours)	Potential for drug interactionsΔ
Estazolam	Sleep onset or sleep maintenance insomnia	1 to 2 mg	0.5 mg	Intermediate (10 to 24)	CYP3A4 to minimally active metabolite.
Flurazepam	Sleep onset or sleep maintenance insomnia	15 to 30 mg	15 mg	Long (40 to 114; 120 to 160 older adults)	Non-CYP glucuronidation in liver. Active metabolite.
Temazepam	Sleep onset or sleep maintenance insomnia	7.5 to 30 mg	7.5 to 15 mg	Intermediate (8 to 15)	Primarily non-CYP glucuronidation in liver to inactive metabolites. CYP3A4 to active metabolite (minor pathway, clinically insignificant).
Triazolam	Sleep onset insomnia	0.125 to 0.25 mg	0.125 to 0.25 mg	Short (2 to 5)	CYP3A4. No active metabolite.
Quazepam	Sleep onset or sleep maintenance insomnia	7.5 to 15 mg	7.5 mg	Long (39)	CYP3A4, CYP2C9/19. Active metabolites.

* Appropriate clinical uses may differ from the US Food and Drug Administration (FDA)-approved indication(s) for a given drug.

¶ Initiate treatment using lowest dose shown for those with low body weight, debilitated patients, and those receiving treatment with opioid analgesics or other central nervous system or cardiorespiratory depressants.

Δ For specific drug interactions, including management recommendations and combinations that should be avoided, use Lexi-Interact drug interactions program included with UpToDate.

Graphic 117509 Version 5.0

Cytochrome P450 3A (including 3A4) inhibitors and inducers

Strong inhibitors	Moderate inhibitors	Strong inducers	Moderate inducers
▪ Adagrasib ▪ Atazanavir ▪ Ceritinib ▪ Clarithromycin ▪ Cobicistat and cobicistat-containing coformulations ▪ Darunavir ▪ Idelalisib ▪ Indinavir ▪ Itraconazole ▪ Ketoconazole ▪ Levoketoconazole ▪ Lonafarnib ▪ Lopinavir ▪ Mifepristone* ▪ Nefazodone ▪ Nelfinavir ▪ Nirmatrelvir-ritonavir ▪ Ombitasvir-paritaprevir-ritonavir ▪ Ombitasvir-paritaprevir-ritonavir plus dasabuvir ▪ Posaconazole ▪ Ritonavir and ritonavir-containing coformulations ▪ Saquinavir ▪ Tucatinib ▪ Voriconazole	▪ Amiodarone¶ ▪ Aprepitant ▪ Berotralstat ▪ Cimetidine¶ ▪ Conivaptan ▪ Crizotinib ▪ Cyclosporine¶ ▪ Diltiazem ▪ Duvelisib ▪ Dronedarone ▪ Erythromycin ▪ Fedratinib ▪ Fluconazole ▪ Fosamprenavir ▪ Fosaprepitant¶ ▪ Fosnetupitant-palonosetron ▪ Grapefruit juice ▪ Imatinib ▪ Isavuconazole (isavuconazonium sulfate) ▪ Lefamulin ▪ Letermovir ▪ Netupitant ▪ Nilotinib ▪ Ribociclib ▪ Schisandra ▪ Verapamil	▪ Apalutamide ▪ Carbamazepine ▪ Enzalutamide ▪ Fosphenytoin ▪ Lumacaftor ▪ Lumacaftor-ivacaftor ▪ Mitotane ▪ Phenobarbital ▪ Phenytoin ▪ Primidone ▪ Rifampin (rifampicin)	▪ Bexarotene ▪ Bosentan ▪ Cenobamate ▪ Dabrafenib ▪ Dexamethasone$^{\Delta}$ ▪ Dipyrone ▪ Efavirenz ▪ Elagolix, estradiol, and norethindrone therapy pack◇ ▪ Eslicarbazepine ▪ Etravirine ▪ Lorlatinib ▪ Mitapivat ▪ Modafinil ▪ Nafcillin ▪ Pexidartinib ▪ Rifabutin ▪ Rifapentine ▪ Sotorasib ▪ St. John's wort

- For drug interaction purposes, the inhibitors and inducers of CYP3A metabolism listed above can alter serum concentrations of drugs that are dependent upon the CYP3A subfamily of liver enzymes, including CYP3A4, for elimination or activation.
- These classifications are based upon US Food and Drug Administration (FDA) guidance.[1,2] Other sources may use a different classification system resulting in some agents being classified differently.
- Data are for systemic drug forms. Degree of inhibition or induction may be altered by dose, method, and timing of administration.
- Weak inhibitors and inducers are not listed in this table with exception of a few examples. Clinically significant interactions can occasionally occur due to weak inhibitors and inducers (eg, target drug is highly dependent on CYP3A4 metabolism and has a narrow therapeutic index). Accordingly, specific interactions should be checked using a drug interaction program such as the Lexicomp drug interactions program included within UpToDate.
- Refer to UpToDate topics on specific agents and indications for further details.

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* Mifepristone is a significant inhibitor of CYP3A4 when used chronically (eg, for hyperglycemia in patients with Cushing syndrome); not in single-dose use.

¶ Classified as a weak inhibitor of CYP3A4 according to FDA system.[1]

Δ Classified as a weak inducer of CYP3A4 according to FDA system.[1]

◇ The fixed-dose combination therapy pack taken in the approved regimen has moderate CYP3A4 induction effects. When elagolix is used as a single agent, it is a weak CYP3A4 inducer. Norethindrone and estradiol are not CYP3A4 inducers.

References:

1. *Clinical Drug Interaction Studies — Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions Guidance for Industry (January 2020) available at: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/clinical-drug-interaction-studies-cytochrome-p450-enzyme-and-transporter-mediated-drug-interactions.*
2. *US Food & Drug Administration. Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers. Available at: FDA.gov website.*

Graphic 76992 Version 95.0

Sleep hygiene guidelines

Recommendation	Details
Regular bedtime and rise time	Having a consistent bedtime and rise time leads to more regular sleep schedules and avoids periods of sleep deprivation or periods of extended wakefulness during the night.
Avoid napping	Avoid napping, especially naps lasting longer than 1 hour and naps late in the day.
Limit caffeine	Avoid caffeine after lunch. The time between lunch and bedtime represents approximately 2 half-lives for caffeine, and this time window allows for most caffeine to be metabolized before bedtime.
Limit alcohol	Recommendations are typically focused on avoiding alcohol near bedtime. Alcohol is initially sedating, but activating as it is metabolized. Alcohol also negatively impacts sleep architecture.
Avoid nicotine	Nicotine is a stimulant and should be avoided near bedtime and at night.
Exercise	Daytime physical activity is encouraged, in particular, 4 to 6 hours before bedtime, as this may facilitate sleep onset. Rigorous exercise within 2 hours of bedtime is discouraged.
Keep the sleep environment quiet and dark	Noise and light exposure during the night can disrupt sleep. White noise or ear plugs are often recommended to reduce noise. Using blackout shades or an eye mask is commonly recommended to reduce light. This may also include avoiding exposure to television or technology near bedtime, as this can have an impact on circadian rhythms by shifting sleep timing later.
Bedroom clock	Avoid checking the time at night. This includes alarm clocks and other time pieces (eg, watches and smart phones). Checking the time increases cognitive arousal and prolongs wakefulness.
Evening eating	Avoid a large meal close to bedtime. Eat a healthy and filling (but not too heavy) meal in the early evening and avoid late-night snacks.

Graphic 122804 Version 4.0

Contributor Disclosures

David N Neubauer, MD Consultant/Advisory Boards: Eisai [Insomnia]; Idorsia [Insomnia]. All of the relevant financial relationships listed have been mitigated. **Ruth Benca, MD, PhD** Grant/Research/Clinical Trial Support: Eisai [Insomnia]. Consultant/Advisory Boards: Eisai [Insomnia]; Genentech [Mood disorder]; Idorsia [Insomnia]; Jazz Pharmaceuticals [Hypersomnia]; Merck [Insomnia]; Sage [Depression]. All of the relevant financial relationships listed have been mitigated. **Joann G Elmore, MD, MPH** No relevant financial relationship(s) with ineligible companies to disclose. **April F Eichler, MD, MPH** No relevant financial relationship(s) with ineligible companies to disclose.

Contributor disclosures are reviewed for conflicts of interest by the editorial group. When found, these are addressed by vetting through a multi-level review process, and through requirements for references to be provided to support the content. Appropriately referenced content is required of all authors and must conform to UpToDate standards of evidence.

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