

INTRODUCTION

- Generalized anxiety disorder (GAD) is a common form of anxiety disorder characterized by excessive and uncontrollable worry that may manifest itself in a number of psychic and somatic symptoms such as irritability, difficulty concentrating, muscle tension, **fatigue, and sleep disturbance**. To meet Diagnostic and Statistical Manual of Mental Disorders (DSM)-V criteria, worry and other associated symptoms must be present more days than not for at least 6 months and must adversely affect the patient's life (*Baldwin et al 2018, DSM-V criteria*).
 - According to the National Institutes of Mental Health (NIMH), the 12-month prevalence of GAD is **2.7%** in the United States (US) population (*NIMH Web site 2017*).
 - The onset of GAD symptoms may occur before the age of **20**. GAD is twice as common in females compared to males, **and is the most common anxiety disorder among older patients** (*Baldwin et al 2018*).
- Social anxiety disorder (SAD) is characterized by the persistent fear of being observed or evaluated negatively by others in social performance or interaction situations. Patients with **SAD** often avoid social interactions or endure them with intense anxiety or distress (*Bandelow et al 2012*).
- Panic disorder is a form of anxiety disorder that is characterized by episodic, unexpected panic attacks that occur without a clear trigger. Panic attacks are defined by the rapid onset of intense fear (typically peaking within about 10 minutes) with at least 4 of the physical and psychological symptoms listed in the DSM-V diagnostic criteria (ie, palpitations, sweating, trembling/shaking, sensations of shortness of breath, feelings of choking, chest pain/discomfort, nausea, feeling dizzy or unsteady, chills or heat sensations, paresthesias, derealization, fear of losing control, and fear of dying) (*Locke et al 2015*).
- Effective treatments for GAD include cognitive-behavioral therapy, **applied relaxation**, and medications such as selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) (*Baldwin et al 2018*). Other agents, such as buspirone and hydroxyzine are also recommended as treatment options in clinical guidelines. The medication choice should be made based on several factors, such as efficacy, possible adverse events (AEs), contraindications, and drug interactions (*Bandelow et al 2015*).
 - Benzodiazepines (BZDs) have been widely used in managing GAD because of their rapid onset of action and proven efficacy. They can be helpful as short-term treatment during the period before antidepressants take effect and to help alleviate the restlessness and agitation that can occur with initiation of antidepressant therapy. All of the BZDs are considered to be of equal efficacy for the treatment of GAD (*Gliatto 2000, Locke et al 2015*).
 - BZDs exert their effects through their activity at the gamma-aminobutyric acid type A (GABA) receptors, potentiating the effects of endogenous GABA, the main inhibitory neurotransmitter.
- Insomnia is defined as a complaint of trouble initiating or maintaining sleep, which is associated with daytime consequences and is not attributable to environmental circumstances or inadequate opportunity to sleep (*Sateia et al 2017*).
 - Insomnia is considered chronic when it has persisted for at least 3 months at a frequency of at least 3 times per week. The prevalence of chronic insomnia in industrialized nations is estimated to be at least 5% to 10%.
 - Insomnia is considered short-term when the disorder meets symptom criteria but has persisted for less than 3 months. Occasional, short-term insomnia is thought to affect 30% to 50% of the population.
- Insomnia often occurs with comorbid disorders, including depression, anxiety, and substance abuse (*Schutte-Rodin et al 2008*).
 - Certain medical or psychiatric disorders may also increase the risk of insomnia; psychiatric and chronic pain disorders have been associated with insomnia in as many as 50 to 75% of patients.
 - Insomnia is also associated with an increased risk of suicide and may result in relapse among prior substance abusers.
- The primary treatment goals are to improve sleep quality and quantity and to improve insomnia-related daytime impairments (*Schutte-Rodin et al 2008*).

- General treatment measures for insomnia include the treatment of comorbid medical and psychiatric conditions, modifying sleep-interfering medications and substances, and optimizing the sleep environment. Part of the initial approach to treatment should include cognitive behavioral therapy (*Sateia et al 2017, Schutte-Rodin et al 2008*).
- Prior to the introduction of BZDs, barbiturates and related compounds were commonly used for the management of anxiety and sleep disturbance. The first BZD, chlordiazepoxide, was introduced to the US market in 1963, followed shortly by diazepam. Flurazepam, the first BZD approved as a hypnotic, became available in 1970 and rapidly supplanted the use of barbiturates and other related compounds for the treatment of insomnia. Zolpidem, the first non-BZD hypnotic approved in the US, became available in 1992 and remains the most widely prescribed hypnotic medication (*Sateia et al 2017*).
- Other than zolpidem, the non-BZD sedative hypnotics used to treat insomnia are doxepin (Silenor), eszopiclone (Lunesta), ramelteon (Rozerem), **lemborexant (Dayvigo)**, suvorexant (Belsomra), tasimelteon (Hetlioz), and zaleplon (Sonata).
 - Ramelteon and tasimelteon are melatonin receptor agonists that possess affinity for the MT1 and MT2 receptors vs. the MT3 receptor. Tasimelteon has a unique indication for treatment of Non-24-Hour Sleep-Wake Disorder (Non-24), a circadian rhythm sleep disorder found predominantly in the blind and characterized by excessive sleepiness during the day and an inability to sleep at night.
 - Doxepin's mechanism of action is not fully understood, but it is thought that antagonism of the H1 receptor is the most likely mechanism by which doxepin exerts its sleep maintenance effect.
 - The remaining agents act at the GABA-receptor.
- All of the agents in this review (with the exception of tasimelteon) have been shown to result in positive effects on sleep latency, total sleep time (TST) and/or wake time after sleep onset (WASO). The BZDs have been shown to be effective in improving sleep latency and TST. Other agents such as zaleplon and ramelteon are effective in reducing sleep latency, whereas medications such as eszopiclone and temazepam are more likely to improve sleep maintenance (*Schutte-Rodin et al 2008*).
- Although a substantial number of Food and Drug Administration (FDA)- and non FDA-approved anxiolytics and sedative hypnotics are available, the focus of this review will be on BZDs and non-BZDs agents. Other classes of agents such as barbiturates, SNRIs, SSRIs, and tricyclic antidepressants (TCAs) are also utilized in these settings but will not be the focus of this review.
- Several BZDs **and some non-BZDs** have additional FDA-approved indications such as alcohol withdrawal, seizure disorder, muscle relaxation, **and depression**. These indications are outside the scope of this review, and therefore will not be addressed in this review.

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Benzodiazepines	
Xanax (alprazolam), alprazolam Intensol , alprazolam ODT , Xanax XR (alprazolam extended-release)	✓
chlordiazepoxide	✓ §
Klonopin (clonazepam)	✓
Tranxene-T (clorazepate)	✓
Valium (diazepam), diazepam Intensol	✓
estazolam	✓ §
flurazepam	✓ §
Ativan (lorazepam), lorazepam Intensol	✓
oxazepam	✓ §
Restoril (temazepam)	✓
Halcion (triazolam)	✓
Doral (quazepam)	✓
Non-benzodiazepines	
bupirone	✓ §

Data as of **April 2, 2020 JA-U/MG-U/DKB**

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Drug	Generic Availability
Silenor (doxepin)	✓
Lunesta (eszopiclone)	✓
Dayvigo (lemborexant)	-
meprobamate	✓
Rozerem (ramelteon)	✓
Belsomra (suvorexant)	-
Hetlioz (tasimelteon)	-
Sonata (zaleplon)	✓
Ambien, Edluar, Intermezzo, Zolpimist (zolpidem)	✓ *
Ambien CR (zolpidem extended-release)	

* Zolpimist is not available as generic

§ Buspar (buspirone), Dalmene (flurazepam), Librium (chlordiazepoxide), Prosom (estazolam), and Serax (oxazepam) are brands that are no longer marketed

(Drugs@FDA 2020, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2020)

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

Indication	BZDs											Non-BZDs											
	alprazolam	chlordiazepoxide	clonazepam	clorazepate	diazepam	estazolam	flurazepam	lorazepam	oxazepam	temazepam	triazolam	quazepam	buspirone	doxepin	eszopiclone	lemborexant	meprobamate	ramelteon	suvorexant	tasimelteon	zaleplon	zolpidem	
Short term treatment of insomnia characterized by difficulties with sleep initiation/onset																		✓					✓ (Ambien, Edluar, Zolpimist)
Treatment of insomnia, characterized by difficulties with sleep maintenance														✓									
Treatment of insomnia, characterized by difficulties with sleep onset and/or sleep maintenance																✓			✓				✓ (Ambien CR)

Treatment of insomnia characterized by difficulty falling asleep, frequent nocturnal awakenings, and/or early morning awakenings						✓*	✓				✓										
Short-term treatment of insomnia									✓	✓											✓
Treatment of insomnia																					✓
Treatment of non-24-hour sleep-wake disorder																					✓
As needed treatment of insomnia when a middle-of-the-night awakening is followed by difficulty returning to sleep																					✓ (Intermezzo)
Management of anxiety disorder or short-term relief of symptoms of anxiety	✓ (alprazolam Intenso!, Xanax)	✓		✓	✓			✓	✓			✓									✓
Treatment of generalized anxiety disorder	✓ (alprazolam ODT)																				
Treatment of panic disorder, with or without agoraphobia	✓ (alprazolam Intenso!, alprazolam ODT, Xanax, Xanax XR)		✓																		
Preoperative apprehension and anxiety		✓																			
Pre-anesthesia to produce sedation, relief of anxiety, and decreased ability to recall events related to surgery									✓												

*** Short-term use**

(Prescribing information: **alprazolam Intenso! 2017, alprazolam ODT 2019, Ambien 2019, Ambien CR 2019, Ativan 2018, Belsonra 2020, buspirone 2017, chlordiazepoxide 2016, Dayvigo 2019, diazepam Intenso! 2016, Doral 2019, Edluar 2019, estazolam 2019, flurazepam 2018, Halcion 2019, Hetlioz 2019, Intermezzo 2019, Klonopin 2017, lorazepam**

Intensol 2019, Lunesta 2019, meprobamate 2016, oxazepam 2016, Restoril 2018, Rozerem 2018, Silenor 2019, Sonata 2019, Tranxene-T 2018, Valium 2017, Xanax 2017, Xanax XR 2016, Zolpimist 2019)

- Information on indications, mechanism of action, pharmacokinetics, dosing, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

CLINICAL EFFICACY SUMMARY

- A meta-analysis that examined 105 randomized, double-blind (DB), placebo-controlled (PC) trials was conducted to evaluate safety and efficacy of drug treatments for chronic insomnia in adults. Of these trials, 52 involved BZDs, 48 involved non-BZDs, and 8 involved antidepressants (ADPs). Most of the studies had short-treatment duration (≤ 4 weeks) in the non-elderly population. The primary efficacy measure was sleep onset latency, with WASO as the secondary outcome measure (*Buscemi et al 2007*).
 - Sleep onset latency was significantly decreased, as compared to placebo, when measured by polysomnography (PSG) for the BZDs (weighted mean difference [WMD]: -10.0 minutes; 95% confidence interval [CI], -16.6 to -3.4), non-BZDs (WMD -12.8 minutes; 95% CI, -16.9 to -8.8) and ADPs (WMD -7.0 minutes; 95% CI, -10.7 to -3.3) as well as when measured by sleep diary (WMD -19.6 minutes; 95% CI, -23.9 to -15.3; WMD -17.0 minutes; 95% CI, -20.0 to -14.0; WMD: -12.2 minutes; 95% CI, -22.3 to -2.2, respectively).
 - WASO, sleep efficiency, TST, and sleep quality were evaluated and subcategorized by PSG and sleep diary. All results were statistically significant and favored BZDs and non-BZDs except for the PSG studies measuring WASO and TST, which were just below the range of significance. The PSG results significantly favored the antidepressants, and the sleep diary results, which were fewer, favored the antidepressants for WASO. Placebo was favored for TST, however, the results did not achieve statistical significance.
 - All treatment groups had a statistically significant incidence of AEs compared to placebo (BZDs risk difference [RD]: 0.15; non-BZDs RD: 0.07; and antidepressants RD: 0.09), although the most commonly reported AEs were considered minor. The most common AEs reported in the BZD group were headache, somnolence, dizziness, nausea, and fatigue while the most common AEs in the non-BZD and ADP groups were headache, dizziness, nausea, and somnolence. Indirect comparisons suggest that BZDs and non-BZDs have similar effects, but that non-BZDs may be safer.
 - The authors noted substantial heterogeneity of data, which was reduced in subgroup analyses by type of drug. Overall, BZDs and non-BZDs were not significantly different with respect to efficacy.
- A meta-analysis of 22 randomized, DB, PC trials evaluated the safety and efficacy of short-term (14 days) BZDs or zolpidem in the treatment of insomnia in adults < 65 years of age ($n = 1894$). The treatment duration was ≤ 35 days. It was found that BZDs and zolpidem produced significant improvements in the primary outcomes (as measured by PSG and self-reporting) of sleep onset latency, number of awakenings, TST, and sleep quality compared to placebo ($p < 0.001$) and their effect sizes were moderate (*Nowell et al 1997*).
- A 2012 meta-analysis that was published using data on the FDA website examined the efficacy and safety of non-BZDs (eszopiclone, zaleplon, zolpidem) using 13 randomized, DB, parallel-group (PG), PC clinical trials ($n = 4378$). Non-BZDs showed a small, but significant, improvement (reduction) of 22 minutes (95% CI, -33 to -11) in the primary endpoint of PSG sleep latency. For the other primary outcome of subjective sleep latency, non-BZDs showed a small but statistically significant improvement of 7 minutes, compared to placebo. The analyses of effects size showed significant but small to medium differences in PSG sleep latency (WMD -0.36; 95% CI, -0.57 to -0.16) and subjective sleep latency (WMD -0.33; 95% CI, -0.62 to -0.04). The secondary outcomes of TST, PSG and subjective number of awakenings, subjective sleep onset, and sleep quality did not show significant differences, which may have been due to limited data and reporting in the clinical trials (*Huedo-Medina et al 2012*).
- A 2017 meta-analysis of 31 randomized, PG, PC trials with BZDs, non-BZDs (eszopiclone, zaleplon, zolpidem), melatonin agonists, ADPs and other sedating medications was conducted to compare the efficacy of these medications for treatment of primary insomnia. In this meta-analysis, both BZDs and non-BZDs were significantly more effective than ADPs (including low-dose doxepin) in reducing objective sleep onset latency. Also, BZDs were found to be significantly more effective than non-BZDs in reducing subjective sleep onset latency. Non-BZDs demonstrated higher effect sizes for the primary outcomes of objective sleep onset latency and objective TST. Additionally, the pooled effect sizes for all of the outcome variables were statistically significant, indicating small to medium effects (*Winkler and Doering 2014*).
- A meta-analysis that evaluated 234 studies ($n = 37,333$) was conducted to determine the most efficacious pharmacological treatments for GAD, panic disorder, and SAD. The authors concluded that various studies with SSRIs

and SNRIs show that they can be efficacious in the management of anxiety. There was also some evidence for the efficacy of certain BZDs, buspirone, imipramine, hydroxyzine and trifluoperazine. BZDs, however, may cause dependency and are therefore not recommended for routine use (*Baldwin and Polkinghorn 2005*).

- A meta-analysis of 8 randomized controlled trials (n = 152) compared the effects of acetazolamide, temazepam, zolpidem, zaleplon, or theophylline on sleep quality in patients with acute exposure to high altitudes. The meta-analysis concluded that zaleplon and zolpidem improved the TST, sleep efficiency index, and stage 4 sleep duration, and these agents decreased WASO compared to placebo or no-treatment. Temazepam showed similar outcomes to placebo for the onset of sleep and sleep quality (*Kong et al 2018*).
- Two 6-month DB, PC, randomized trials (SET and RESET) of tasimelteon in totally blind patients with Non-24 (n = 84) demonstrated that tasimelteon 20 mg given 1 hour before bedtime at the same time every day was well tolerated and entrained the master body clock to a 24-hour clock as measured by urinary 6-sulfatoxymelatonin (aMT6s) and cortisol. During the SET clinical trial, the primary endpoint of sleep entrainment (as measured by aMT6s) was achieved by 20% (8 out of 40) of patients in the tasimelteon group vs. 3% (1 out of 38) of patients in the placebo group (difference of 17%, 95% CI: 3.2 to 31.6, p = 0.0171). A responder analysis demonstrated that 29% of subjects treated with tasimelteon demonstrated clinical response as measured by a ≥ 45-minute improvement in both nighttime and daytime sleep. During the RESET trial, 90% (9 out of 10) of patients in the tasimelteon group vs. 20% (2 out of 10) of patients in the placebo group maintained entrainment (*Lockley et al 2015*).
- A 12-month DB, PG, randomized clinical trial evaluated the safety and efficacy of suvorexant compared to placebo in patients with primary insomnia (n = 781). At Month 1, suvorexant showed greater efficacy than placebo in improving subjective sleep maintenance (TST 22.7 min, 95% CI: 16.4 to 29, p < 0.0001) and subjective time to sleep onset (TSO) (TSO -9.5 min, 95% CI: -14.6 to -4.5, p = 0.0002). These improvements were maintained throughout the 1-year phase (27.5 min in subjective TST, 95% CI: 16.2 to 38.8, p < 0.0001; -9.7 min in subjective TSO, 95% CI: -16.5 to -2.9, p = 0.0055). Over the course of 1 year, the proportion of patients with discontinuation due to AEs or serious AEs was similar among the treatment groups and there was no clinically important difference. The most common AE, somnolence, was reported for 13% of patients who received suvorexant and 3% who received placebo (difference of 10.5%, 95% CI: 6.8 to 14.1) (*Michelson et al 2014*).
- A meta-analysis of 4 randomized controlled trials (n = 3076) revealed improved TSO, subjective TST, and subjective quality of sleep at months 1 and 3 with suvorexant compared with placebo. At 12 months, suvorexant increased subjective TST, quality of sleep, but not TSO. Comparative trials of suvorexant to other agents are lacking (*Kuriyama et al 2017*).
- Two DB, PC, randomized studies evaluated the efficacy of lemborexant in patients with insomnia.
 - SUNRISE 1 randomized 1006 patients to lemborexant (5 mg or 10 mg), zolpidem CR, or placebo for 1 month. Compared with placebo, both doses of lemborexant displayed improved sleep onset from baseline (least squares means [LSM] treatment ratio 0.77; 95% CI, 0.67 to 0.89; p < 0.001 for lemborexant 5 mg, and LSM treatment ratio 0.72; 95% CI, 0.63 to 0.83; p < 0.001 for lemborexant 10 mg) and improved sleep efficiency (LSM treatment difference vs placebo 7.1%; 95% CI, 5.6% to 8.5%; p < 0.001 for lemborexant 5 mg, and LSM difference 8.0%; 95% CI, 6.6% to 9.5%; p < 0.001 for lemborexant 10 mg). Compared with zolpidem, both doses of lemborexant improved wake-after-sleep onset in the second half of the night (LSM treatment difference vs zolpidem -6.7 min; 95% CI, -11.2 to -2.2 min; p = 0.004 for lemborexant 5 mg, and LSM treatment difference -8.0 min; 95% CI, -12.5 to -3.5 min; p < 0.001 for lemborexant 10 mg) (*Rosenberg et al 2019*).
 - In the second study, 971 patients received lemborexant 5 mg, lemborexant 10 mg, or placebo. At 6 months, both doses of lemborexant demonstrated improvement in sleep onset, sleep efficiency, and WASO compared with placebo (p < 0.05 for all comparisons of lemborexant doses vs placebo) (*Dayvigo prescribing information 2019*).
- A meta-analysis with 48 studies was conducted to evaluate the efficacy of pharmacological treatments in GAD. The main drug classes compared were the BZDs (diazepam, lorazepam, alprazolam) and the azapirones (buspirone). The BZDs and azapirones were equally effective for anxiety (effect size for BZDs of 0.32, effect size for azapirones of 0.30), although the compliance rate was higher for the BZDs (24.4% drop-out rate vs. 30.7%, respectively, p < 0.05). The author concluded that BZDs and azapirones are effective for the short-term treatment of anxiety, but no drug class is superior in reducing symptoms (*Mitte et al 2005*).
- A Cochrane review of 24 randomized studies (n = 4233) concluded a possible superiority of BZDs for a response to treatment (risk ratio [RR] 1.65, 95% CI, 1.39 to 1.96) and dropout rate (RR 0.50; 95% CI, 0.39 to 0.64) compared with placebo among adult patients with panic disorder. The quality of the evidence was rated low for both outcomes (*Breilmann et al 2019*).

CLINICAL GUIDELINES**Anxiety**

- American Academy of Family Physicians (AAFP) Diagnosis and Management of Generalized Anxiety Disorder and Panic Disorder in Adults (*Locke et al 2015*)
 - First-line pharmacologic therapies
 - SSRIs
 - SNRIs (duloxetine and venlafaxine ER)
 - buspirone
 - Second-line pharmacologic therapies
 - TCAs
 - pregabalin
 - quetiapine
 - hydroxyzine
 - Third-line pharmacologic therapies
 - Monoamine oxidase inhibitors (MAOIs)
 - The above therapies can be augmented with the addition of BZDs such as alprazolam, clonazepam, diazepam, and lorazepam.
- World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for the pharmacological treatment of anxiety, obsessive-compulsive and post-traumatic stress disorders (*Bandelow et al 2012*)
 - GAD
 - Recommendations, grade 1 (full evidence from controlled studies and good risk-to-benefit ratio)
 - First-line therapy
 - SSRIs (escitalopram, paroxetine, and sertraline)
 - SNRIs (venlafaxine, duloxetine)
 - pregabalin
 - Recommendations, grade 2 (full evidence from controlled studies and moderate risk-to-benefit ratio)
 - Imipramine is recommended as second-line therapy
 - BZDs (alprazolam, diazepam) are recommended for patients without a history of dependency
 - Hydroxyzine may be an effective option, although it can cause sedation
 - Recommendations, grade 3 (limited positive evidence from controlled studies)
 - In treatment-refractory GAD patients, augmentation of SSRI treatment with atypical antipsychotics (risperidone or olanzapine) may be used.
 - SAD
 - Recommendations, grade 1 (full evidence from controlled studies and good risk-to-benefit ratio)
 - First-line therapy
 - SSRIs (escitalopram, fluvoxamine, paroxetine, and sertraline)
 - venlafaxine
 - Recommendations, grade 2 (full evidence from controlled studies and moderate risk-to-benefit ratio)
 - The MAOI phenelzine is effective but less well tolerated than other antidepressants.
 - Recommendations, grade 3 (limited positive evidence from controlled studies)
 - In treatment-resistant cases, BZDs (clonazepam) may be used in patients without a history of dependency.
 - Recommendations, grade 4 (evidence from uncontrolled studies)
 - In treatment-resistant cases, the addition of buspirone to an SSRI was effective according to an open study.
- American Psychiatric Association practice guideline for the treatment of patients with panic disorder (second edition) (*Stein et al 2009*)
 - SSRIs, SNRIs, TCAs, and BZDs appear roughly comparable with regard to efficacy for panic disorder; however, SSRIs and SNRIs are recommended as first-line agents due to their relatively favorable safety profile.
 - BZDs may be used adjunctively with antidepressants to treat residual anxiety. BZDs may also be used as monotherapy or in combination with antidepressants for patients who are experiencing distressing symptoms that require rapid symptom control.
 - TCAs should be avoided in patients with acute narrow angle glaucoma or clinically significant prostatic hypertrophy. They may also increase the risk of falls in the elderly.

Insomnia

- American Academy of Sleep Medicine (AASM) Clinical Practice Guidelines for the Pharmacologic Treatment of Chronic Insomnia in Adults (*Sateia et al 2017*)
 - Recommendations for the treatment of sleep maintenance insomnia (vs. no treatment) in adults (all recommendations listed are considered of weak strength with varying qualities of evidence as noted below)
 - The pharmacologic agents that are recommended:
 - doxepin (low quality of evidence)
 - suvorexant (low quality of evidence)
 - The pharmacologic agents that are not recommended:
 - melatonin (very low quality of evidence)
 - tiagabine (low quality of evidence)
 - trazodone (moderate quality of evidence)
 - tryptophan (high quality of evidence)
 - valerian (low quality of evidence)
 - Recommendations for sleep onset and sleep maintenance insomnia (vs. no treatment) in adults (all recommendations listed are considered of weak strength with varying qualities of evidence as noted below)
 - The pharmacologic agents that are recommended:
 - eszopiclone (very low quality of evidence)
 - temazepam (moderate quality of evidence)
 - zolpidem (very low quality of evidence)
 - The pharmacologic agent that is not recommended:
 - diphenhydramine (low quality of evidence)
 - Recommendations for sleep onset insomnia (vs. no treatment) in adults (all recommendations listed are considered of weak strength with varying qualities of evidence as noted below)
 - The pharmacologic agents that are recommended include:
 - ramelteon (very low quality of evidence)
 - triazolam (high quality of evidence)
 - zaleplon (low quality of evidence)
 - The pharmacologic agents that are not recommended:
 - melatonin (very low quality of evidence)
 - tiagabine (very low quality of evidence)
 - trazodone (moderate quality of evidence)
 - tryptophan (high quality of evidence)
 - valerian (low quality of evidence)
- American College of Physicians (ACP) Management of Chronic Insomnia Disorder in Adults: A Clinical Practice Guide (*Qaseem et al 2016*)
 - ACP recommends that all adults receive cognitive behavioral therapy for insomnia as the initial treatment for chronic insomnia disorder (Grade: strong recommendation, moderate-quality evidence).
 - ACP also recommends collaboration with the patient to determine whether a pharmacologic therapy should be initiated (Grade: weak recommendation, low-quality evidence).
 - Low-quality evidence shows that both eszopiclone and zolpidem improved global outcomes in the general population, and low- to moderate-quality evidence shows that eszopiclone, zolpidem, and doxepin improved sleep outcomes, such as sleep onset latency, TST, and WASO.
 - Moderate-quality evidence shows that suvorexant improved treatment response and sleep outcomes in mixed general and adult populations.
 - Low-quality evidence shows no statistically significant difference between ramelteon and placebo for sleep outcomes in the general population.
 - In older adults, low-quality evidence shows that eszopiclone improved global and sleep outcomes and both zolpidem and ramelteon decreased sleep onset latency.
 - Moderate-quality evidence shows that doxepin improved Insomnia Severity Index (ISI) scores, and low- to moderate-quality evidence shows that it improved sleep outcomes.
 - BZDs and melatonin were not included in these guidelines.
 - No one sedative hypnotic was recommended over another, due to insufficient evidence.

- Department of Veterans Affairs/Department of Defense (VA/DoD) Clinical Practice Guideline for the Management of Chronic Insomnia Disorder and Obstructive Sleep Apnea (VA/DoD 2019)
 - The VA/DoD guideline recommends cognitive behavioral therapy (strong recommendation) and suggests brief behavioral therapy (weak recommendation) for chronic insomnia disorder. Cognitive behavioral therapy should be the first-line treatment over pharmacotherapy (weak recommendation).
 - Low-dose doxepin (ie, 3 mg or 6 mg) or non-BZD benzodiazepine receptor agonists (ie, zolpidem, zaleplon, eszopiclone) are the recommended pharmacotherapies for short-course treatment of chronic insomnia disorder (weak recommendation).
 - The guideline recommends against using BZDs and trazodone for treating chronic insomnia disorder (weak recommendation).
 - The evidence remains insufficient to make recommendations regarding ramelteon or suvorexant for chronic insomnia disorder.

SAFETY SUMMARY

Contraindications

- MAOIs are contraindicated for concomitant use with buspirone and doxepin (or within 14 days of discontinuing an MAOI).
- Doxepin is contraindicated in patients with untreated narrow angle glaucoma or severe urinary retention.
- Suvorexant and lemborexant are contraindicated in patients with narcolepsy.
- Alprazolam products, estazolam, and triazolam are contraindicated with ketoconazole or itraconazole. Triazolam is also contraindicated with nefazodone and protease inhibitors.
- Alprazolam ODT, clonazepam, clorazepate, diazepam, and lorazepam are contraindicated in patients with acute narrow angle glaucoma.
- Clonazepam is contraindicated in patients with significant liver disease.
- Diazepam is contraindicated in patients with myasthenia gravis, severe respiratory insufficiency, severe hepatic insufficiency, and sleep apnea.
- Quazepam is contraindicated in patients with sleep apnea or chronic pulmonary insufficiency.
- Zolpidem products, eszopiclone, and zaleplon are contraindicated in patients with a prior history of complex sleep behaviors.

Warnings/Precautions

- Boxed warnings
 - BZDs carry a boxed warning for concomitant use with opioids, as it may result in profound sedation, respiratory depression, coma, and death.
 - Zolpidem products, eszopiclone, and zaleplon carry a boxed warning for complex sleep behaviors such as sleep-walking, sleep-driving, and other activities, which may lead to serious injuries, including death.
 - On April 30, 2019, the FDA mandated the addition of a boxed warning based on 66 cases of complex sleep behaviors with eszopiclone, zaleplon, or zolpidem leading to serious injuries, including death in 20 cases (FDA Drug Safety Communication 2019).
- Daytime somnolence, sleep-walking, nighttime “sleep-driving,” and depression are listed as warnings for the majority of BZDs and non-BZDs in this review.
- Withdrawal effects can be observed after continuous long-term therapy with BZDs. Abrupt withdrawal or discontinuation should be avoided.
 - Withdrawal effects are mainly anxiety symptoms, but can also include autonomic instability (eg, diaphoresis, increased heart rate), insomnia, and sensory hypersensitivity. The most serious withdrawal effects are seizures and delirium tremens, which can occur with abrupt discontinuation.
- Severe anaphylaxis/anaphylactoid reactions (angioedema) have been reported with eszopiclone, flurazepam, quazepam, ramelteon, temazepam, zaleplon, and zolpidem.
- Worsening of symptoms of depression is considered a warning with most BZDs, doxepin, eszopiclone, zaleplon, zolpidem, lemborexant, and suvorexant.
- Pregnancy
 - All BZDs are considered highly teratogenic, especially during the first trimester.
 - Zolpidem use during the third trimester may lead to respiratory depression and sedation in neonates.

- Ramelteon shows a lack of a drug-associated risk for maternal and fetal outcomes based on postmarketing reports.
- Using meprobamate during the first trimester may lead to congenital malformations, and thus, meprobamate should be avoided during pregnancy.
- Other non-BZDs have not been studied in pregnant women and lack information on maternal or fetal outcomes in humans.
- Elderly
 - BZDs should be used cautiously in the elderly, ie, the lowest possible dose with slow dose up-titration should be utilized. Additionally, BZDs with a short half-life (eg, oxazepam) are preferred over those with a long half-life in the elderly patient population (*Gliatto 2000*).
 - Zolpidem increases the risk of dizziness, drowsiness, and diarrhea in elderly patients.
 - Elderly patients have a 2-fold exposure to tasimelteon compared with younger patients.
 - With the non-BZDs, differences in the reported AEs between elderly and younger patients were not noted; however, older patients may be at a higher risk for drowsiness, and consequently, falls.

AEs

- Drowsiness, sedation, fatigue, cognitive impairment, and muscle weakness are the most frequent AEs with BZD use. Rare AEs include bradycardia, hypotension, rash, urticaria, blurred vision, diplopia, flushing, constipation, nausea, vomiting, change in libido, hepatic dysfunction, and abdominal pain.
- BZD use can lead to physiological dependence and tolerance, especially at higher doses and/or when given for a long duration. Treatment with BZDs should be limited to short-term use whenever possible. All BZDs are Schedule IV controlled substances.
- Somnolence/sedation and other central nervous system (CNS)-related AEs have also been reported with the non-BZD sedative hypnotics.

Drug Interactions

- In general, concomitant use of alcohol and other CNS depressants can increase the risk of CNS depression.
- The concomitant use of BZDs and opioids increases the risk of respiratory depression.
- Most BZDs (except lorazepam, oxazepam, and temazepam) are metabolized to some extent by cytochrome P450 (CYP) 3A4. Inhibitors of CYP3A4 (eg, ketoconazole, itraconazole) can increase the risk of toxicity while inducers of CYP3A4 (eg, rifampin) can decrease their effectiveness.
- With the non-BZDs (buspirone, ramelteon, lemborexant, suvorexant, zolpidem), there can be an increased toxicity risk when administered concomitantly with CYP3A4 inhibitors. The efficacy of buspirone, eszopiclone, lemborexant, suvorexant, ramelteon, tasimelteon, zaleplon, and zolpidem may be reduced when these agents are co-administered with CYP3A4 inducers (particularly with rifampin when administered with eszopiclone or ramelteon). Lemborexant may decrease the levels of CYP2B6 substrates (eg, methadone, bupropion).

Recalls

- On October 25, 2019, Mylan voluntarily recalled 1 lot of alprazolam tablets (lot number 8082708) due to the potential presence of foreign substances that may lead to infection (*Mylan Pharmaceuticals 2019*).

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
BZDs				
<i>Alprazolam products</i>				
alprazolam	tablets, oral concentrate, orally disintegrating tablets	Oral	3 times daily	A lower starting dose recommended for elderly, patients with advanced liver disease, and patients with a debilitating disease

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Xanax XR	Extended-release tablets	Oral	Once daily	Administer in the morning; a lower starting dose recommended for elderly, patients with advanced liver disease, and patients with a debilitating disease
Other BZDs				
chlordiazepoxide	Capsules	Oral	2 to 4 times daily	
clonazepam	Tablets	Oral	Twice daily	
clorazepate	Tablets	Oral	In divided doses or a single dose at bedtime	
diazepam	Tablets, oral concentrate, oral solution, injection	Oral, IV	2 to 4 times daily	
estazolam	Tablets	Oral	At bedtime	
flurazepam	Capsules	Oral	Before retiring	A lower dose is recommended for women, since they clear flurazepam from the body at a lower rate than men
lorazepam	Tablets, oral concentrate, injection	Oral, IV	2 to 3 times daily for anxiety or a single dose at bedtime for insomnia	
oxazepam	Capsules	Oral	3 to 4 times daily	
temazepam	Capsules	Oral	Before retiring	
triazolam	Tablets	Oral	Before bedtime	
quazepam	Tablets	Oral	At bedtime	
Non-BZDs				
bupirone	Tablets	Oral	Twice daily	Not recommended in patients with severe renal or hepatic impairment
doxepin	Tablets	Oral	Within 30 minutes of bedtime	A lower starting dose is recommended in the elderly
eszopiclone	Tablets	Oral	Immediately before bedtime, with at least 7 to 8 hours remaining before the planned time of awakening	Do not exceed 2 mg in patients with severe hepatic impairment
lemborexant	Tablets	Oral	Immediately before bedtime, with at least 7 hours remaining before the planned time of awakening	Not recommended in patients with severe hepatic impairment
meprobamate	Tablets	Oral	3 to 4 times daily	Not recommended in children < 6 years of age
ramelteon	Tablets	Oral	Within 30 minutes of bedtime	Not recommended in patients with severe hepatic impairment
suvorexant	Tablets	Oral	Within 30 minutes of going to bed, with at least 7 hours remaining before the planned time of awakening	Not recommended in patients with severe hepatic impairment

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
tasimelteon	Capsules	Oral	Before bedtime, at the same time every night	Not recommended in patients with severe hepatic impairment
zaleplon	Capsules	Oral	Immediately before bedtime or after the patient has gone to bed and has experienced difficulty falling asleep	Not recommended in patients with severe hepatic impairment
<i>zolpidem products</i>				
Edluar	Tablets	SL	Immediately before bedtime with at least 7 to 8 hours remaining before the planned time of awakening	A lower dose is recommended for women than for men, since they clear zolpidem from the body at a lower rate than men
Intermezzo	Tablets	SL	Should be administered when patient wakes in the middle of the night, but has at least 4 hours of bedtime remaining before the planned time of awakening	A lower dose is recommended for women than for men, since they clear zolpidem from the body at a lower rate than men
Zolpimist	Oral spray	Oral	Immediately before bedtime with at least 7 to 8 hours remaining before the planned time of awakening	A lower dose is recommended for women than for men, since they clear zolpidem from the body at a lower rate than men
Ambien	Tablets	Oral	Immediately before bedtime with at least 7 to 8 hours remaining before the planned time of awakening	A lower dose is recommended for women than for men, since they clear zolpidem from the body at a lower rate than men
Ambien CR	Extended-release tablets	Oral	Immediately before bedtime with at least 7 to 8 hours remaining before the planned time of awakening	A lower dose is recommended for women than for men, since they clear zolpidem from the body at a lower rate than men

Abbreviations: IV = intravenous; SL = sublingual

See the current prescribing information for full details

CONCLUSION

- No specific sedative hypnotic in this review is considered preferable to the others, as each has been shown to have positive effects on sleep latency, TST, and/or WASO in placebo-controlled trials.
- Individual patients may respond differently to these medications and therapy selection, therefore, should be based on consideration of the patient's specific symptom pattern, patient preferences, comorbid disease states, concurrent medications, and the side effect profile for each option (*Schutte-Rodin et al 2008*).
- Depending on the patient's specific complaint of sleep initiation or sleep maintenance, consideration should be given to the pharmacokinetic parameters of the available hypnotics. Agents with a longer half-life may be preferred in those with sleep maintenance issues, while agents with a shorter time to maximum concentration may be preferred in patients with sleep initiation complaints. If a patient does not respond to the initial agent, a different agent within the same class is appropriate after evaluating the patient's response to the first agent (*Schutte-Rodin et al 2008*).
- Tasimelteon is the only FDA-approved prescription product with proven efficacy for the treatment of Non-24 in totally blind patients.
- The recommended treatments for GAD include cognitive-behavioral therapy, applied relaxation, and preferred medications such as SSRIs and SNRIs (*Baldwin et al 2018*).
- Although numerous meta-analyses have been conducted with the anxiolytic and sedative hypnotic classes, they are limited by lack of availability of high quality evidence and considerable variability in design and methodology across clinical trials (*Sateia et al 2017*).

- The 2019 VA/DoD guideline recommends low-dose doxepin or non-BZD benzodiazepine receptor agonists (ie, zolpidem, zaleplon, eszopiclone) for short-course treatment of chronic insomnia disorder (VA/DoD 2019).
- All of the BZDs and many of the non-BZD agents are Schedule IV controlled substances due to their propensity to cause physiological dependence. Withdrawal effects can be observed after continuous long-term therapy with many of these agents; therefore, abrupt withdrawal or discontinuation should be avoided.

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