

Sedatives & hypnotics 2

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BCPS

OTHER ANXIOLYTIC AGENTS

Antidepressants

Many antidepressants are effective in the treatment of chronic anxiety disorders and should be considered as first-line agents, especially in patients with concerns for addiction or dependence. Selective serotonin reuptake inhibitors (SSRIs, such as *escitalopram* or *paroxetine*) or serotonin/norepinephrine reuptake inhibitors (SNRIs, such as *venlafaxine* or *duloxetine*) may be used alone or prescribed in combination with a benzodiazepine during the first weeks of treatment. After 4 to 6 weeks, when the antidepressant begins to produce an anxiolytic effect, the benzodiazepine dose can be tapered. While only certain SSRIs or SNRIs have been approved for the treatment of anxiety disorders such as GAD, the efficacy of these drugs is most likely a class effect. Long-term use of antidepressants and benzodiazepines for anxiety disorders is often required to maintain ongoing benefit and prevent relapse.

OTHER ANXIOLYTIC DRUGS

Antidepressants

Buspirone

Meprobamate

Buspirone

Buspirone is a nonbenzodiazepine partial agonist at serotonin receptors. The actions of *buspirone* appear to be mediated by serotonin (5-HT_{1A}) receptors, although it also displays some affinity for D₂ dopamine receptors and 5-HT_{2A} serotonin receptors. Thus, its mode of action differs from that of the benzodiazepines. *Buspirone* is useful for the chronic treatment of generalized anxiety disorder (GAD) and has an efficacy comparable to that of benzodiazepines as it is devoid of sedation, hypnosis, and general CNS depression or drug abuse liability of benzodiazepines. It has a slow onset of action and is not effective for short-term or “as-needed” treatment of acute anxiety. In addition, *buspirone* lacks the anticonvulsant and muscle-relaxant properties of the benzodiazepines. *Buspirone* usually requires therapy of 3 to 6 weeks to demonstrate efficacy. The frequency of adverse effects is low, with the most common effects being headache, dizziness, nervousness, nausea, and light-headedness. Sedation and psychomotor and cognitive dysfunction are minimal, and dependence is unlikely, a benefit that is particularly important in elderly patients. *Buspirone* does not potentiate the CNS depression of alcohol.

BARBITURATES

Amobarbital
Pentobarbital
Phenobarbital
Secobarbital

BARBITURATES

The barbiturates were formerly the mainstay of treatment to sedate patients or to induce and maintain sleep. They have been largely replaced by the benzodiazepines, primarily because barbiturates induce tolerance and physical dependence, are lethal in overdose, and are associated with severe withdrawal symptoms. All barbiturates are controlled substances.

Mechanism of action

The sedative–hypnotic action of the barbiturates is due to their interaction with GABAA receptors, which enhances GABAergic transmission. The binding site of barbiturates on the GABA receptor is distinct from that of the benzodiazepines. Barbiturates potentiate GABA action on chloride entry into the neuron by prolonging the duration of the chloride channel openings. In addition, barbiturates can block excitatory glutamate receptors. These molecular actions lead to decreased neuronal activity.

At low doses, the barbiturates produce sedation (have a calming effect and reduce excitement). At higher doses, the drugs cause hypnosis, followed by anesthesia (loss of feeling or sensation) and, finally, coma and death. Thus, any degree of depression of the CNS is possible, depending on the dose. Barbiturates do not raise the pain threshold and have no analgesic properties. They may even exacerbate pain. Chronic use leads to tolerance.

Adverse effects

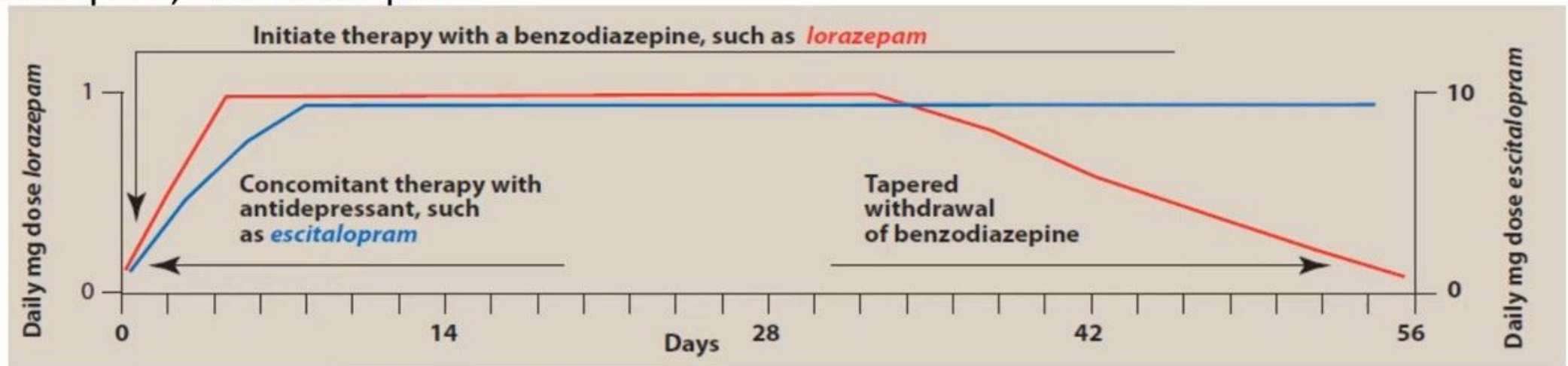
Barbiturates cause drowsiness, impaired concentration, and mental and psychomotor impairment. The CNS depressant effects of barbiturates synergize with those of *ethanol*. Hypnotic doses of barbiturates produce a drug “hangover” that may lead to impaired ability to function normally for many hours after waking. Occasionally, nausea and dizziness occur.

Barbiturates induce cytochrome P450 (CYP450) microsomal enzymes in the liver. Therefore, chronic barbiturate administration diminishes the action of many drugs that are metabolized by the CYP450 system. Barbiturates are contraindicated in patients with acute intermittent porphyria. Abrupt withdrawal from barbiturates may cause tremors, anxiety, weakness, restlessness, nausea and vomiting, seizures, delirium, and cardiac arrest. Withdrawal is much more severe than that associated with opioids and can result in death. Death may also result from overdose.

Recommended Therapy for Specific Anxiety and Related Disorders

GAD

- a. Antidepressants: These are considered first-line agents. These include the SSRIs (escitalopram, paroxetine, and sertraline) and the SNRIs (duloxetine and venlafaxine).
- b. Benzodiazepines: This class of drugs is rapidly effective; if possible, try to discontinue in 3–4 weeks or once the patient has remittance of symptoms. Long-term therapy is common but not recommended. Benzodiazepines can be taken in combination with either antidepressants or buspirone as a bridge until these drugs begin to take effect. Benzodiazepines are more effective against somatic symptoms than against the underlying psychic pathology. Evidence is strongest for alprazolam, diazepam, and lorazepam.



c. Buspirone: Good when benzodiazepines should be avoided (e.g., in patients with a history of substance use disorder); takes 2–4 weeks to be effective.

Buspirone is considered a second-line agent.

d. Pregabalin: Depending on the guidelines, it is considered a first- or second-line agent (behind antidepressants). Limited data suggest comparable efficacy with venlafaxine and benzodiazepines. Pregabalin can also be used as an adjunct.

e. Not effective: β -Blockers

f. CBT or another type of psychotherapy should be included with pharmacotherapy.

g. In treatment-refractory patients, augmentation with aripiprazole, quetiapine, olanzapine, or risperidone can be tried.

Panic disorder

- a. Antidepressants: First-line therapy. These include the SSRIs (citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine [immediate and CR], sertraline) and venlafaxine XR.
- b. Benzodiazepines: High-potency agents; effective; rapid onset; evidence is strongest for alprazolam, clonazepam, diazepam, and lorazepam
- c. Not effective: Buspirone, β -blockers, antihistamines, trazodone. Bupropion is considered third line in some guidelines and is not recommended in others.
- d. CBT and other psychotherapies are effective.
- e. Patients with panic disorder tend to have a higher sensitivity to physical adverse effects. For this reason, these patients should be initiated on low doses of antidepressants – as low as 25 mg of sertraline or 10 mg of paroxetine.

OCD

- a. Serotonergic agents are effective – SSRIs (escitalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline). Depending on guidelines, clomipramine is considered a first- or second-line agent. Patients tend to require higher doses of antidepressants.
- b. CBT may be effective, but it is secondary to pharmacotherapy.
- c. Alone, SSRIs often fail to control OCD completely. Not many other drugs help. Augmentation with haloperidol or an SGA (aripiprazole, olanzapine, quetiapine, or risperidone) may help. In general, high doses need to be used.

PTSD

- a. PTSD can be combat or non-combat related, and response to therapy may vary depending on the source of trauma.
- b. Psychotherapy is considered the cornerstone of therapy. Effective methods incorporate CBT, including exposure therapy and trauma-based CBT.
- c. Medications are considered adjuncts to psychotherapy. They are preferred if psychotherapists are not readily available.
- d. SSRIs (fluoxetine, sertraline, and paroxetine) and venlafaxine XR are considered first-line agents.
- e. Augment with other agents to treat specific symptoms (e.g., intermittent explosive behavior with β -blockers or mood stabilizers).
 - i. Prazosin is used for PTSD-associated nightmares, despite recent evidence that it may not reduce distressing dreams or improve sleep quality in combat-related PTSD.
 - ii. Anticonvulsants for aggression, anger, and depression (carbamazepine, lamotrigine, topiramate). Valproic acid is not considered effective.
 - iii. Atypical antipsychotics for psychotic symptoms (aripiprazole, quetiapine, risperidone). Some guidelines recommend against the use of olanzapine.
- f. Benzodiazepines are sometimes used acutely for sleep disturbances, but use should be very limited. Most data analyses indicate a lack of efficacy. Benzodiazepines have dissociative and disinhibiting properties and may worsen non-hyperarousal symptoms. Benzodiazepines may also interfere with the fear-conditioning aspects of psychotherapy

Social anxiety disorder

- a. CBT is the most important modality.
- b. Antidepressants: First-line medication for treatment; SSRIs (escitalopram, fluvoxamine (immediate release and CR), paroxetine (immediate release and CR), sertraline), and venlafaxine XR. Response to antidepressants tends to be slow (up to 12 weeks) and has a flat dose-response curve.
- c. Benzodiazepines (alprazolam and clonazepam) are considered second-line agents, but use should be minimized, given the risk of substance use disorders among patients with social anxiety disorder.
- d. Anticonvulsants: Pregabalin is considered a first-line agent, and gabapentin and a second-line agent for the treatment of social anxiety disorder.

Specific phobias

- a. Not treated with medication
- b. Systematic desensitization and other behavioral approaches often effective

INSOMNIA

- Normal Sleep Patterns and Neurochemistry/Physiology of Sleep
- People with sleep problems usually experience one or more of the following: insomnia, daytime sleepiness, or abnormal sleep behaviors.
- The neural networks regulating sleep-wake cycles are located in the brain stem, basal forebrain, and hypothalamus, with projections to the cortex and thalamus.
- The reticular activating system maintains wakefulness, and when activity here declines, sleep occurs.
- Several neurotransmitters are involved in the sleep-wake cycle. Norepinephrine, acetylcholine, histamine, and neuropeptides operate in the hypothalamus during wakefulness. Neuronal systems in the raphe nuclei, solitary tract, ventricular thalamus, anterior hypothalamus, and basal forebrain promote sleep. As the reticular activating system slows down, serotonin neurotransmission in the raphe nuclei reduces sensory input and inhibits motor activity. Norepinephrine is involved in dreaming, whereas serotonin is active during non-dreaming sleep.

Sleep Stages	
State	Characteristics
Wakefulness	Low-voltage EEG, random eye movements, high muscle tone
Non-REM sleep	Low muscle tone, few eye movements
Stage 1	Transition between wakefulness and sleep, low-voltage desynchronized EEG, lasts 0.5–7.0 min
Stage 2	Low-voltage EEG with sleep spindles and K-complexes
Stages 3 and 4	High-amplitude, slow-wave EEG, “delta sleep”
REM sleep	Low-voltage, mixed-frequency EEG, low muscle tone, REMs, autonomic fluctuations in heart rate and perspiration, and dreaming reported in 80%–90% of subjects

EEG = electroencephalogram; REM = rapid eye movement.

Types of Insomnia

Type	Duration (wk)	Likely Causes
Transient	< 1	Acute situational or environmental stressors
Short term	< 4	Continued personal stress
Chronic	> 4	Psychiatric illness, substance use disorder Behavioral causes (poor sleep hygiene) Medical causes, primary sleep disorder (e.g., sleep apnea, restless legs syndrome; these are no longer recognized by the <i>DSM-5</i> as insomnia)

The 4 Stages of Sleep



NREM Stage 1

- transition period between wakefulness and sleep
- lasts around 5 to 10 minutes



NREM Stage 3

- muscles relax
- blood pressure and breathing rate drop
- deepest sleep occurs



NREM Stage 2

- body temperature drops and heart rate begins to slow
- brain begins to produce sleep spindles
- lasts approximately 20 minutes



REM Sleep

- brain becomes more active
- body becomes relaxed and immobilized
- dreams occur
- eyes move rapidly

Benzodiazepine hypnotics decrease the latency to sleep onset and increase stage II of non-rapid eye movement (REM) sleep. Both REM sleep and slow-wave sleep are decreased. In the treatment of insomnia, it is important to balance the sedative effect needed at bedtime with the residual sedation (“hangover”) upon awakening. Short-acting *triazolam* is effective in treating individuals who have problems falling asleep. The risk of withdrawal and rebound insomnia is higher with *triazolam* than with other agents. Intermediate-acting *temazepam* is useful for patients who experience frequent awakenings and have difficulty staying asleep. *Temazepam* should be administered 1 to 2 hours before the desired bedtime. Long-acting *flurazepam* is rarely used, due to its extended half-life, which may result in excessive daytime sedation and accumulation of the drug, especially in the elderly. *Estazolam* and *quazepam* are considered intermediate- and long-acting agents, respectively. In general, hypnotics should be used for only a limited time, usually 1 to 3 weeks. Nonbenzodiazepine agents are now preferred due to reduced potential for tolerance, abuse, and physical dependence.

Benzodiazepines for Insomnia

Drug (trade)	Usual Dose (mg)	Half-Life (hr)	Duration
Triazolam (Halcion)	0.125–0.25	2–6	Short
Temazepam (Restoril)	15–30	8–20	Intermediate
Estazolam (Prosom)	1–2	8–24	Intermediate
Flurazepam (Dalmane)	15–30	48–120	Long
Quazepam (Doral)	7.5–15	48–120	Long

Doxepin (Silenor) is a TCA indicated for impaired sleep maintenance. The doses used are lower than those used for depression. Chances for morning effects are high because of the long half-life of both doxepin and its active metabolite, nordoxepin.

Ramelteon (Rozerem): Melatonin agonist (no activity at the GABA or benzodiazepine receptor). Duration is 2–5 hours. To date, there is no evidence that this melatonin agonist is associated with dependence or tolerance, and it may be used long term. This drug can be used long term for chronic insomnia. Ramelteon is primarily metabolized by CYP1A2, but inducers and inhibitors of 2C9 and 3A4 can also affect it.

Suvorexant (Belsomra) is an orexin receptor antagonist. The neuropeptide orexin promotes wakefulness. By blocking the OX1R and OX2R receptors, suvorexant both decreases sleep latency and promotes sleep maintenance. Suvorexant should be taken within 30 minutes of bedtime and with at least 7 hours of sleep time. Suvorexant is metabolized by CYP3A4, and the dose must be decreased in patients taking concomitant 3A4 inhibitors. Suvorexant is contraindicated in patients with narcolepsy.

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Z- HYPNOTICS

Eszopiclone: This non-benzodiazepine is a γ -aminobutyric acid (GABA)_A agonist whose half-life is 6 hours; thus, morning effects can result if it is taken late in the night. Eszopiclone can be used for chronic insomnia. On May 1, 2014, the FDA reduced the starting dose to 1 mg to minimize the amount of next-day impairment. Patients should be counseled to use caution when driving or performing activities that require alertness, particularly with the 2- to 3-mg doses. Eszopiclone should be taken immediately before bed and when the patient will be in bed for at least 7–8 hours. Eszopiclone can cause a metallic taste in the mouth.

Zaleplon: This is a non-benzodiazepine with a pharmacology similar to zolpidem (see the text that follows) and a very short half-life. For patients with sleep maintenance problems, it may not last as long. However, zaleplon has a shorter half-life (about 1 hour) and may cause fewer problems in the morning, especially if given late. Zaleplon shortens onset to sleep but does not prolong sleep time or number of awakenings. Zaleplon is indicated only for short-term treatment of insomnia. Zaleplon has been used in trials for up to 5 weeks.

Zolpidem: This non-benzodiazepine sedative-hypnotic modulates the GABA_A receptor complex.

a. Compared with benzodiazepines, zolpidem lacks anticonvulsant action, muscle-relaxant properties, and respiratory depressant effect; it also has a lower risk of tolerance and withdrawal. Zolpidem should still be avoided in obstructive sleep apnea. Zolpidem is a good choice for patients in whom benzodiazepines should be avoided.

b. Zolpidem is available as an immediate-release tablet (IR), controlled-release tablet (CR), sublingual tablet, and sublingual spray. The pharmacokinetics and indications vary depending on the dosing form. The sublingual spray has a shorter onset of action, but that of the sublingual tablet is comparable with both the IR and the CR tablets.

c. Indications vary by dosage form. All are indicated to decrease sleep latency. The CR tablets are indicated to improve sleep maintenance and can be used for longer-term therapy. Intermezzo is indicated as a “as-needed [prn]” treatment for patients who have difficulty falling back to sleep as long as 4 hours or more remain.

Drug	Half-Life (hr)	Administration (minutes before sleep)	Indications		
			Sleep Onset	Sleep Maintenance	Chronic Therapy
Doxepin (Silenor)	Doxepin: 15.3 Nordoxepin: 31	30		X	
Eszopiclone (Lunesta)	6	Immediately	X	X	X
Ramelteon (Rozerem)	1–2.6	30	X		X
Suvorexant (Belsomra)	12	30	X	X	
Zaleplon (Sonata)	1	Immediately	X		
Zolpidem (Ambien)	1.4–6.5 (see the text that follows)	Immediately	X	X (CR only)	