

Review Article

Clinical Pharmacology in Sleep Medicine

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The basic treatment goals of pharmacological therapies in sleep medicine are to improve waking function by either improving sleep or by increasing energy during wakefulness. Stimulants to improve waking function include amphetamine derivatives, modafinil, and caffeine. Sleep aids encompass several classes, from benzodiazepine hypnotics to over-the-counter antihistamines. Other medications used in sleep medicine include those initially used in other disorders, such as epilepsy, Parkinson's disease, and psychiatric disorders. As these medications are prescribed or encountered by providers in diverse fields of medicine, it is important to recognize the distribution of adverse effects, drug interaction profiles, metabolism, and cytochrome substrate activity. In this paper, we review the pharmacological armamentarium in the field of sleep medicine to provide a framework for risk-benefit considerations in clinical practice.

1. Introduction

Given the high prevalence of sleep complaints in the general population and in patients with a variety of comorbid disorders, the pharmacological treatment options for sleep disorders are common considerations for sleep specialists and nonspecialists alike [1–4]. Clinical pharmacology in sleep medicine can be loosely classified into drugs aimed at treating sleepiness, sleeplessness, and sleep-related movements. Although most of these are available by prescription only, the stimulant caffeine and the antihistamine diphenhydramine are common over-the-counter options for sleepiness and sleeplessness, respectively.

The primary hypersomnias are uncommon compared to disorders that include sleepiness as a secondary symptom to sleep disruption [5]. When presented with the patient reporting sleepiness, it is critical to investigate potential primary causes, such as sleep apnea or insomnia. Pain syndromes, mood disorders, and general medical problems may be comorbid with sleep apnea and/or disrupted sleep. However, residual daytime symptoms persist in some patients despite optimized management of potential primary causes, leading to consideration of stimulant agents in the appropriate clinical setting. Primary hypersomnias such as narcolepsy

and idiopathic hypersomnia are also treated primarily with stimulants.

Insomnia can be considered a constellation of symptoms with a variety of underlying causes [6]. As a symptom, it can be secondary to disorders of mood, pain, or a variety of other neurological and general medical disorders. It can be primary in the sense that it exists in the absence of other identifiable causes, such as insomnia from psychophysiological associations, or secondary to a number of other medical and psychiatric issues [7–13]. One of the most intriguing yet poorly understood aspects of insomnia is the misperception phenotype, in which patients underestimate their sleep times compared to objective measurements [14]. Insomnia can also be the presenting feature of circadian phase disorders—most commonly delayed circadian phase [15]. The primary challenge in regards to the diagnosis and treatment of insomnia is that both depend entirely on the clinical history, with no basis in objective testing.

Restless leg syndrome and periodic limb movements of sleep are the most common movement disorders resulting in sleep disturbance [16, 17]. The former is a strictly clinical diagnosis, while the latter is a polysomnographic finding. Both are treated similarly, often beginning with interrogation of iron stores and oral repletion when needed, followed by

dopaminergic medications, as well as off-label use of other classes. REM behavior disorder is most commonly treated with hypnotic benzodiazepines [18].

The purpose of this paper is to provide an overview of the medications most commonly encountered in sleep medicine. It is not intended as a clinical guideline and prescription decisions should be undertaken with appropriate expertise, consultation, and consideration of available information about adverse effects, interactions, and safety issues. The organization of tables and figures includes basic information about each drug such as half-life, excretion (renal or hepatic), pregnancy class and lactation considerations, and interactions with food, herbals, and smoking (Tables 1–4). In Table 1, the generic names of a variety of sleeping pills are shown along with the biological half-life, primary mode of excretion, pregnancy class, presence in breast milk, and interactions with food, herbs, and smoking tobacco. The FDA defines pregnancy categories as follows: (A) adequate and well-controlled studies failed to demonstrate fetal risk in the first trimester (and there is no evidence of risk in later trimesters); (B) animal reproduction studies have failed to demonstrate fetal risk and there are no adequate and well-controlled studies in pregnant women, or human data reassuring despite animal studies showing risk; (C) animal reproduction studies are either not available or have shown adverse fetal effects and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks; (D) there is positive evidence of human fetal risk, but potential benefits may warrant use of the drug in pregnant women despite potential risks; (X) evidence of human fetal risk, and the risks involved in use of the drug in pregnant women clearly outweigh potential benefits.

In Table 2, the generic names of a variety of stimulants are shown along with the biological half-life, primary mode of excretion, pregnancy class, presence in breast milk, and interactions with food, herbs, and smoking tobacco. Lisdex-amphetamine is metabolized rapidly to dextroamphetamine and the half-life reflects this metabolite's kinetics (indicated with asterisk).

In Table 3, the generic names of miscellaneous sleep-related drugs are shown along with the biological half-life, primary mode of excretion, pregnancy class, presence in breast milk, and interactions with food, herbs, and smoking tobacco.

In Table 4, major contraindications, beyond allergy to the medication or any of its components/metabolites, are given for hypnotics, stimulants, and other agents. Note that coadministration of multiple CNS depressant agents should always be undertaken with substantial caution. * indicates that the only listed contraindication on UpToDate was hypersensitivity reaction. Adverse effect profiles are then listed according to major clinical categories: neuropsychiatric systems, Figure 1; cardiovascular system, Figure 2; endocrine/metabolic, Figure 3; gastrointestinal and urinary, Figure 4. Finally, a summary of cytochrome P450 system interactions is given in Figure 5. Information contributing to the text, figures, and tables were assembled from the listed references as well as several review resources [19–21],

which include UpToDate and Micromedex. Interested readers seeking further detail are directed to these sources.

2. Insomnia

Multiple drug treatments exist for the treatment of insomnia, ranging from dedicated hypnotics, such as zolpidem, to multifunctional benzodiazepines [3, 22]. Other drugs have been used for insomnia on account of drowsiness as a prominent side effect such as antihistamines and trazodone, as well as over-the-counter use of the hormone melatonin [23]. In the United States, the Food and Drug Administration has approved the nonbenzodiazepine ligands (zolpidem, eszopiclone, and zaleplon), ramelteon, doxepin, and certain benzodiazepines. Other sleep aids shown in this paper are considered off-label. The use of drug treatments is recommended only in the short term, meaning usually 7–10 nights. Long-term pharmacological treatment is not suggested, and only the newer agents such as zolpidem have even been studied in clinical trials lasting more than a few weeks. Despite this practice recommendation, patients with chronic insomnia may not achieve spontaneous, behavioral modification, or drug-assisted remission, and appropriate treatment in these cases remains uncertain.

The main nonpharmacological approaches span the general categories of (1) treating the underlying contributors (such as pain or mood disorders), (2) optimizing sleep hygiene, and (3) cognitive behavioral therapy. Although the efficacy of improving sleep hygiene recommendations is not well understood [3], that of cognitive behavioral therapy is well known to be at least as effective as hypnotic medication, and may be longer lasting [24–26].

Despite the widespread use of medications to facilitate sleep, fundamental questions remain largely unanswered, such as whether the drugs recapitulate normal sleep physiology. Uncertainty in this area stems in part from the poor understanding of which sleep stages (rapid eye movement (REM) sleep or non-REM (NREM) sub-stages), or other aspects of sleep physiology (such as autonomic or EEG patterns) are most important for the rejuvenating aspects of sleep. To further complicate matters, many drugs used to induce sleep in patients with insomnia may in fact demonstrate suppressive effects on aspects of sleep felt by many to be fundamentally important, such as slow-wave sleep (also known as “deep” sleep or, more formally, as stage N3) and REM sleep, especially the majority of antidepressants as well as traditional benzodiazepines. In a typical night of normal sleep, REM and NREM alternate every approximately 90 minutes; the proportion of time spent in N3 tends to favor the early part of sleep, while the amount of REM sleep tends to increase gradually with each cycle through the night. Beyond these mechanistic questions, important concerns surround the adverse effect profiles of sleeping pills, ranging from “hangover” effect upon waking, to induction of parasomnia, to the potential even for increased morbidity and mortality through a variety of potential mechanisms [27].

Here, we review the major clinical considerations in the use of sleeping pills of a variety of classes.

TABLE 1: Sleeping pill characteristics.

Generic	Half-life	Excretion	Pregnancy and lactation	Interactions with food, herbs, smoking
Alprazolam	11.2 h	Renal	Pregnancy class D Enters breast milk	Smoking and St. John's Wort may decrease levels
Amitriptyline	9–27 h	Renal	Pregnancy class C Enters breast milk	Grapefruit juice may inhibit metabolism; St. John's wort may decrease levels
Chloral hydrate	8–11 h	Hepatic	Pregnancy class C Enters breast milk	
Clonazepam	19–50 h	Hepatic	Pregnancy class D Enters breast milk	St. John's Wort may decrease levels
Diazepam	20–50 h	Hepatic	Pregnancy class D Enters breast milk	Food and grapefruit juice may increase levels; St. John's Wort may decrease levels
Dihydrochloride	2–10 h	Renal	Pregnancy class B Enters breast milk	
Doxepin	15 h	Hepatic	Pregnancy class C Enters breast milk	High-fat meal increases bioavailability but delays peak level timing
Estazolam	10–24 h	Hepatic	Pregnancy class X breast milk: unknown	Grapefruit juice may increase serum levels
Eszopiclone	6 h	Hepatic	Pregnancy class C breast milk: unknown	Large meals may delay absorption
Flurazepam	2.3 h	Hepatic	Pregnancy unclassified breast milk: unknown	Grapefruit juice may increase serum levels
Lorazepam	12.9 h	Hepatic	Pregnancy class D Enters breast milk	
Mirtazepine	20–40 h	Hepatic	Pregnancy class C Enters breast milk	St. John's Wort may decrease levels
Nefazodone	2–4 h	Hepatic	Pregnancy class C Enters breast milk	Food decreases availability
Nortriptyline	28–31 h	Renal	Pregnancy unclassified Enters breast milk	
Oxazepam	3–6 h	Renal	Pregnancy unclassified breast milk: unknown	
Quetiapine	6–7 h	Hepatic	Pregnancy class C Enters breast milk	Food increases absorption rate; St. John's Wort may decrease levels
Ramelteon	1–2.6 h	Hepatic	Pregnancy class C breast milk: unknown	
Temazepam	9–12 h	Hepatic	Pregnancy class X Enters breast milk	Grapefruit juice may increase levels; St. John's Wort may decrease levels
Trazodone	7–10 h	Hepatic	Pregnancy class C Enters breast milk	Food increases absorption rate
Triazolam	1.5–6 h	Renal	Pregnancy class X breast milk: unknown	Grapefruit juice may increase levels; St. John's Wort may decrease levels
Zaleplon	1 h	Hepatic	Pregnancy class C Enters breast milk	St. John's Wort may decrease levels
Zolpidem	2.5–3 h	Hepatic	Pregnancy class C Enters breast milk	Food and St. John's Wort decrease availability; grapefruit juice may decrease metabolism

2.1. *Benzodiazepines.* The benzodiazepine family shares multifunctional clinical effects including anticonvulsant, anxiolytic, amnesic, and hypnotic features. All members of the benzodiazepine class bind with high affinity to neuronal GABA_A receptors, which mediate synaptic and extrasynaptic forms of inhibition [28]. By enhancing the conductance of

these (generally inhibitory) ligand-gated chloride channels, the clinical impact of these drugs is attributed to neuronal inhibition.

The benzodiazepines have liabilities in the treatment of insomnia due to concerns for adverse effects, tolerance, and dependence [29]. The pharmacokinetics of these

		Parasomnia	Insomnia	Sleeping/fatigue	Headache	Gait and coordination	Sensory changes	Motor changes	Memory/cognition	Seizure	Psychiatric sx	Depression	Suicide	Dependence/abuse
Sleeping pills	Alprazolam	X	X	X	X	X	X	X	X	X	X	X	X	X
	Amitriptyline	X	X	X	X	X	X	X	X	X	X			
	Chloral hydrate	X		X	X	X		X	X		X			
	Clonazepam	X	X	X	X	X	X	X	X		X	X	X	X
	Diazepam		X	X	X	X		X	X		X	X		X
	Diphenhydramine		X	X	X	X	X	X	X		X			
	Doxepin	X		X	X	X	X	X	X	X	X			
	Estazolam	X		X		X	X	X	X	X	X			X
	Eszopiclone	X		X	X	X	X	X	X		X	X		X
	Flurazepam			X	X	X	X	X	X		X	X		X
	Lorazepam			X	X	X		X	X	X	X	X	X	X
	Mirtazepine	X		X		X	X	X	X	X	X			
	Nefazodone	X	X	X	X	X	X	X	X	X	X			
	Nortriptyline	X	X	X	X	X	X	X	X	X	X			
	Oxazepam			X	X	X		X	X	X	X			X
	Quetiapine	X	X	X	X	X	X	X	X	X	X	X	X	
	Ramelteon		X	X		X	X					X		
	Temazepam	X		X	X	X		X	X		X			X
	Trazodone	X	X	X	X	X	X	X	X	X	X			
	Triazolam	X		X	X	X	X	X	X		X	X		X
	Zaleplon	X		X	X	X	X	X	X		X	X		X
	Zolpidem	X	X	X	X	X	X	X	X		X	X		X
Stimulants	Caffeine		X		X			X			X			
	Dexmethylphenidate		X		X	X		X			X	X		
	Dextroamphetamine				X	X		X			X			X
	Dextroamp/amphet		X	X	X	X		X		X	X			X
	Lisdexamfetamine		X	X	X	X		X			X			X
	Methylphenidate		X	X	X	X	X	X	X		X	X		X
	Modafinil		X	X	X	X	X	X	X		X	X		
Other	Gabapentin			X	X	X	X	X	X		X	X		
	GHB	X	X	X	X	X	X	X	X	X	X	X	X	X
	Pramipexole	X	X	X	X	X	X	X	X		X	X		
	Ropinirole		X	X	X	X	X	X	X	X	X		X	

X	Serious
X	<1%
X	1-10%
X	>10%

FIGURE 1: Neuropsychiatric adverse effect profiles. The frequency of reported adverse effects for each drug is given according to the color key. The categories that included a spectrum of symptoms are as follows: *parasomnia* (abnormal dreams, nightmares, vivid dreams, complex sleep-related behavior, sleep cooking, sleep eating, sleep driving, phone calls, restless legs or leg movements); *sleepiness/fatigue* (drowsy, hangover, hypersomnia, lethargy, sedation, sluggish, somnolence); *gait and coordination* (imbalance, dizziness, dysarthria, falls, motion sickness, vertigo); *sensory change* (hyperesthesia, hypoesthesia, numbness, back pain, myalgia, neuralgia, paresthesia, peripheral neuropathy); *motor change* (akathisia, ataxia, choreiform movements, dysdiadochokinesis, dyskinesia, hyperkinesias, dystonia, tics, extrapyramidal symptoms, hypertonia, hypotonia, muscle spasm, myoclonus, parkinsonism, Tourette's, tremor, twitching); *memory/cognition* (abnormal thinking, attention disturbance, amnesia, cognitive disorder, confusion, mental impairment); *psychiatric change* (anger, anxiety, apathy, dysphoria, emotional lability, irritability, malaise, mood swings, aggression, agitation, disinhibition, hostility, inappropriate behavior, delirium, delusions, depersonalization, derealization, psychosis, hallucinations, mania, nervousness, tension, paranoia, depression).

TABLE 2: Stimulant characteristics.

Generic	Half life	Excretion	Pregnancy and lactation	Interactions with food, herbs, smoking
Caffeine	5 hr	Hepatic	Pregnancy class C Enters breast milk	
Dexmethylphenidate	2–4.5 hr	Hepatic	Pregnancy class C breast milk: unknown	High-fat foods may increase absorption rate
Dextroamphetamine	10–13 hr	Renal	Pregnancy class C Enters breast milk	Absorption may be altered by acidic foods, juices, and vitamin C
Dextroamphetamine and amphetamine	10–13 hr	Renal	Pregnancy class C Enters breast milk	Absorption may be altered by acidic foods, juices, and vitamin C
Lisdexamfetamine	10–13 hr*	Hepatic	Pregnancy class C Enters breast milk	High-fat foods may increase absorption rate
Methylphenidate	3–4 hr	Renal	Pregnancy class C Enters breast milk	Food delays absorption; high-fat meals increase Metadate AUC
Modafinil	15 hr	Hepatic	Pregnancy class C breast milk: unknown	

TABLE 3: Miscellaneous sleep medication characteristics.

Generic	Half life	Excretion	Pregnancy and lactation	Interactions with food, herbs, smoking
Gabapentin	5–7 h	Renal	Pregnancy class C Enters breast milk	
GHB	30–60 min	n/a	Pregnancy class B breast milk: unknown	High-fat meals decrease peak serum level
Pramipexole	8.5 h	Renal	Pregnancy class C breast milk: unknown	
Ropinirole	6 h	Hepatic	Pregnancy class C breast milk: unknown	

medications are variable and should be considered in the clinical context as each relates to the timing of dosing and the risk of hangover effects, especially the potential risk of sedation carrying into the waking day and affecting operation of automobiles or other activities [30]. Other important considerations include the clinical context, such as comorbid psychiatric disorders (e.g., cross-tolerance may occur; also, mood changes can occur), and comorbid alcohol abuse advanced age should prompt caution, as paradoxical effects may be observed, and certain side effect issues become particularly important such as gait instability and falls, as well as concern for cognitive impairment.

Benzodiazepines tend to suppress slow-wave sleep (N3) and REM sleep, in favor of increased time spent in stage N2. In addition, the sleep EEG may show increased spindle activity and beta frequency. The clinical importance of these observations remains poorly understood, although it is intriguing that N3 and REM suppression might be expected to impair the restorative value of sleep, as these stages have received the most attention in the literature as important for memory and other functions [31–33].

2.2. Benzodiazepine Site Ligands. This class of new generation hypnotics includes zolpidem, eszopicole, and zaleplon [34, 35]. They differ from traditional benzodiazepines in their chemical structure, but they interact with the benzodiazepine binding site on GABA_A receptors. For this

reason they are sometimes referred to as nonbenzodiazepine hypnotics. An important feature of these medications is the subtype selectivity at the GABA_A receptor complex. For example, zolpidem has $\alpha 1$ selectivity, while eszopicole also interacts with the $\alpha 2$ and $\alpha 3$ subtypes. Transgenic rodent studies have suggested that certain α subtypes mediate certain clinical effects of the benzodiazepines (which are fairly nonselective for $\alpha 1$, $\alpha 2$, $\alpha 3$, and $\alpha 5$ subtypes) [36].

The effects on sleep architecture are subtle and of unknown clinical importance. The major clinical concerns surrounding this class include the risk of parasomnia. These activities may include complex and potentially risky behaviors such as eating and even leaving the home or operating machinery/automobile, without memory of these events. Also worth noting is the pharmacokinetics of these agents. Zaleplon has the shortest half-life, and is most useful for isolated sleep-onset insomnia and may also be considered for awakenings within the night that are too close to final wake time to allow for middle-of-the-night dosing with other agents (for risk of sedation intruding into the waking day).

3. Antidepressants

The tricyclic and heterocyclic antidepressant medications are often associated with sleepiness, probably related to antihistamine and possibly other “off-target” receptor interactions (such as anticholinergic and anti-histamine effects).

TABLE 4: Significant contraindications.

Alprazolam	Ketoconazole, itraconazole, narrow-angle glaucoma, significant sleep apnea, myasthenia gravis, respiratory insufficiency, liver failure, and pregnancy
Amitriptyline	Recent or concurrent MAOI use and acute myocardial infarction
Chloral hydrate	Hepatic or renal impairment, gastritis or ulcer, and severe cardiac disease
Clonazepam	Narrow-angle glaucoma, significant sleep apnea, myasthenia gravis, respiratory insufficiency, liver failure, and pregnancy
Diazepam	Narrow-angle glaucoma, significant sleep apnea, myasthenia gravis, respiratory insufficiency, liver failure, and pregnancy
Dihydroxyamine	Acute asthma and breast-feeding
Doxepin	Recent or concurrent MAOI use, narrow angle glaucoma, and urinary retention
Estazolam	Narrow-angle glaucoma, significant sleep apnea, myasthenia gravis, respiratory insufficiency, liver failure, and pregnancy
Eszopiclone	*
Flurazepam	Narrow-angle glaucoma, significant sleep apnea, myasthenia gravis, respiratory insufficiency, liver failure, and pregnancy
Lorazepam	Narrow-angle glaucoma, significant sleep apnea, myasthenia gravis, respiratory insufficiency, liver failure, and pregnancy
Mirtazepine	Recent or concurrent MAOI use
Nefazodone	Active liver disease, recent or concurrent MAOI use, acute myocardial infarction, concurrent use of carbamazepine, cisapride, or pimozide
Nortriptyline	Recent or concurrent MAOI use and acute myocardial infarction
Oxazepam	Narrow-angle glaucoma, significant sleep apnea, myasthenia gravis, respiratory insufficiency, liver failure, and pregnancy
Quetiapine	*
Ramelteon	Concurrent fluvoxamine
Temazepam	Narrow-angle glaucoma, significant sleep apnea, myasthenia gravis, respiratory insufficiency, liver failure, and pregnancy
Trazodone	*
Triazolam	Ketoconazole, itraconazole, narrow-angle glaucoma, significant sleep apnea, myasthenia gravis, respiratory insufficiency, liver failure, and pregnancy
Zaleplon	*
Zolpidem	OSA, respiratory impairment, myasthenia gravis, severe hepatic impairment, and sleepwalking
Caffeine	*
Dexmethylphenidate	Agitation, anxiety, glaucoma, motor tics, history of Tourette's syndrome, and recent or concurrent MAOI use
Dextroamphetamine	Symptomatic cardiovascular/atherosclerotic disease, moderate or severe hypertension, hyperthyroidism, glaucoma, agitation, history of drug abuse, and recent or concurrent MAOI use
Dextroamphetamine and amphetamine	Symptomatic cardiovascular/atherosclerotic disease, moderate or severe hypertension, hyperthyroidism, glaucoma, agitation, history of drug abuse, and recent or concurrent MAOI use
Lisdexamfetamine	Symptomatic cardiovascular/atherosclerotic disease, moderate or severe hypertension, hyperthyroidism, glaucoma, agitation, history of drug abuse, and recent or concurrent MAOI use
Methylphenidate	Agitation, anxiety, glaucoma, motor tics, history of Tourette's syndrome, and recent or concurrent MAOI use
Modafinil	*
Gabapentin	*
GHB	Alcohol and other CNS depressants
Pramipexole	*
Ropinirole	*

		Hypertension	Palpitations	Arrythmia	Chest discomfort	Hypotension	Heart attack
Sleeping pills	Alprazolam		X		X	X	
	Amitriptyline	X	X	X		X	X
	Chloral hydrate						
	Clonazepam		X				
	Diazepam					X	
	Diphenhydramine		X	X	X	X	
	Doxepin	X	X	X	X	X	
	Estazolam		X				
	Eszopiclone	X			X		
	Flurazepam		X		X	X	
	Lorazepam					X	
	Mirtazepine	X				X	
	Nefazodone		X	X		X	
	Nortriptyline	X	X	X		X	X
	Oxazepam						
	Quetiapine	X	X	X	X	X	
	Ramelteon						
	Temazepam						
	Trazodone	X	X	X	X	X	X
	Triazolam		X				
Zaleplon	X	X	X	X	X		
Zolpidem	X	X		X	X		
Stimulants	Caffeine		X	X	X		
	Dexmethylphenidate						
	Dextroamphetamine	X	X				
	Dextroamp/amphet		X				X
	Lisdexamfetamine	X					
	Methylphenidate	X	X	X		X	X
Other	Modafinil	X	X		X		
	Gabapentin						
	GHB	X	X		X	X	
	Pramipexole				X	X	
	Ropinirole	X	X	X	X	X	X

X	Serious
X	<1%
X	1–10%
X	>10%

FIGURE 2: Cardiovascular adverse effect profiles. The frequency of reported adverse effects for each drug is given according to the color key. The categories that included a spectrum of symptoms are as follows: *arrhythmia* (atrial, ventricular, A-V block, bundle branch block, extrasystole); *hypotension* (orthostatic).

Most neuroactive drugs exhibit what has become known as “promiscuity”, that is, interaction with multiple targets, although the clinical implications remain to be fully explored [37–41]. Common tricyclics used as sleeping pills include amitriptyline, nortriptyline (which is itself an active metabolite of amitriptyline), and low doses of doxepin. These agents have high affinity for the 5HT and NE reuptake enzymes as well as 5HT_{2A} receptors, α1 adrenergic receptors, muscarinic

acetylcholine receptors, and histamine H1 receptors. Other traditional antidepressants used as sleeping pills include trazodone, nefazodone, and mirtazepine. Trazodone is a 5HT reuptake inhibitor with antagonism also at 5HT_{1A}, 5HT_{2A}, and α1 adrenergic receptors, with low affinity interaction at histamine H1 receptors. Priapism is a rare but serious side effect of trazodone. Mirtazepine is an antagonist at multiple subtypes of the 5HT₂ receptor, as well as the α2 adrenergic

		Thyroid changes	Blood sugar changes	Weight gain	Weight loss	Appetite changes	Menstrual changes	Sexual dysfunction
Sleeping pills	Alprazolam			X	X	X	X	X
	Amitriptyline			X				
	Chloral hydrate							
	Clonazepam			X	X	X	X	X
	Diazepam							X
	Diphenhydramine					X	X	
	Doxepin		X	X		X		X
	Estazolam					X	X	
	Eszopiclone					X	X	X
	Flurazepam			X	X	X		
	Lorazepam			X	X	X	X	
	Mirtazepine			X	X	X		
	Nefazodone					X		X
	Nortriptyline		X	X	X			X
	Oxazepam						X	X
	Quetiapine	X	X	X		X		X
	Ramelteon							
	Temazepam							X
	Trazodone			X	X	X	X	X
	Triazolam							
Zaleplon	X	X			X	X	X	
Zolpidem		X			X	X		
Stimulants	Caffeine							
	Dexmethylphenidate					X		
	Dextroamphetamine				X	X		X
	Dextroamp/amphet				X	X	X	X
	Lisdexamfetamine				X	X		X
	Methylphenidate				X	X	X	X
Modafinil					X			
Other	Gabapentin		X	X		X		X
	GHB		X	X			X	
	Pramipexole				X	X		X
	Ropinirole	X	X			X		X

X	Serious
X	<1%
X	1-10%
X	>10%

FIGURE 3: Endocrine/metabolic adverse effect profiles. The frequency of reported adverse effects for each drug is given according to the color key. The categories that included a spectrum of symptoms are as follows: *thyroid* (hyper- or hypothyroidism), *blood sugar* (diabetes, increased or decreased blood sugar); *appetite change* (increased or decreased, dysphagia); *menstrual change* (amenorrhea, dysmenorrhea, early menses, menorrhagia, menstrual cramps, menstrual disorders); *sexual dysfunction* (erectile dysfunction, delayed ejaculation, impotence, change in libido, priapism).

receptor, and the histamine H1 receptor. Nefazodone is also an antagonist of 5HT2 receptors, α 2 adrenergic receptors, and the histamine H1 receptors. Hepatotoxicity is a prominent clinical concern for nefazodone. Kidney and liver function may influence the choice of agents in this class.

In contrast to the above antidepressant agents, the newer SSRI and SNRI medications are generally either neutral from an alertness standpoint or are activating and thus unlikely to be prescribed for the purpose of insomnia treatment, except in the indirect setting when the insomnia is felt to

		Abdominal pain	Nausea/vomiting	Diarrhea	Constipation	Acid reflux	Abnormal taste	Liver enzyme elevation	Urinary symptoms	Kidney function changes
Sleeping pills	Alprazolam	X	X	X				X	X	
	Amitriptyline		X	X	X		X		X	
	Chloral Hydrate		X	X						
	Clonazepam	X	X	X	X			X	X	
	Diazepam		X	X	X				X	
	Diphenhydramine		X	X	X				X	
	Doxepin	X	X	X	X	X	X	X	X	
	Estazolam		X		X		X		X	
	Eszopiclone		X	X			X		X	X
	Flurazepam		X	X	X	X	X	X		
	Lorazepam		X							
	Mirtazepine	X	X		X			X	X	
	Nefazodone		X	X	X		X	X	X	X
	Nortriptyline	X	X	X	X		X	X	X	
	Oxazepam								X	
	Quetiapine	X	X		X	X	X	X	X	X
	Ramelteon		X				X			
	Temazepam		X	X						
	Trazodone	X	X	X	X		X	X	X	
	Triazolam		X							
Zaleplon	X	X		X	X	X	X	X		
Zolpidem	X	X	X	X	X		X	X	X	
Stimulants	Caffeine		X							X
	Dexmethylphenidate	X	X							
	Dextroamphetamine			X	X		X			
	Dextroamp/amphet	X	X	X	X				X	
	Lisdexamfetamine	X	X	X						
	Methylphenidate	X	X	X	X			X		X
Other	Modafinil		X	X	X		X	X	X	
	Gabapentin	X	X	X	X				X	
	GHB	X	X	X	X	X	X	X	X	X
	Pramipexole	X	X	X	X				X	
	Ropinirole	X	X	X	X	X		X		X

X	Serious
X	<1%
X	1–10%
X	>10%

FIGURE 4: Gastrointestinal and genitor-urinary adverse effect profiles. The frequency of reported adverse effects for each drug is given according to the color key. The categories that included a spectrum of symptoms are as follows: *change in liver enzymes* (transaminase, bilirubin, hepatic failure, hepatic encephalopathy or coma, hepatitis); *urinary symptoms* (abnormal urine, enuresis, dysuria, pyuria, hematuria, difficulty urinating, nocturia, polyuria, incontinence, retention, change in frequency); change in kidney function (hyponatremia, acute renal failure).

be a consequence of a mood disorder. These drugs may also increase motor activity during sleep; whether shifting daily dosing to the morning improves these nocturnal side effects is patient-specific.

3.1. *Anticonvulsants.* Certain anticonvulsants confer sedation as an adverse effect, and may provide some potential benefit for insomnia complaints, especially if there is already an indication for the medication. For example, gabapentin

	1A2	2A6	2B6	2C8	2C9	2C19	2D6	2E1	3A4
Sleeping pills	Alprazolam								S
	Amitriptyline	S		S	S	S	S		S
	Chloral hydrate							S	
	Clonazepam								S
	Diazepam	S		S	S	S			S
	Diphenhydramine								
	Doxepin	S				S	S		S
	Estazolam								S
	Eszopiclone							S	S
	Flurazepam								S
	Lorazepam*								
	Mirtazepine	S				S	S		S
	Nefazodone						S		S
	Nortriptyline	S					S	S	S
	Oxazepam*								
	Quetiapine							S	S
	Ramelteon	S					S		S
	Temazepam			S		S	S		S
	Trazodone							S	S
	Triazolam								S
Zaleplon								S	
Zolpidem	S				S	S	S		S
Stimulants	Caffeine	S			S	S	S	S	S
	Dextroamphetamine	?					?		?
	Dextroamp/amphet								
	Dexmethylphenidate								
	Lisdexamfetamine	?					?		?
	Methylphenidate								
Other	Modafinil								S
	Gabapentin								
	GHB								
	Pramipexole								
	Ropinirole	S							S

Minor inhib
Moderate inhib
Major inhibition
S: minor substr
S: major substr

FIGURE 5: Cytochrome P450 profiles. The metabolism and interactions with the CYP family enzymes is given for each drug. The features of the interaction are given in the color key. ? refers to the substrate interactions being limited to *in vitro* studies.

may be used for certain kinds of pain, and could have beneficial effects for symptomatic relief of RLS and/or insomnia. Gabapentin is thought to act on neuronal calcium channels, but the mechanism(s) of sedation remain uncertain. Peripheral edema and neuropsychiatric side effects remain prominent concerns for gabapentin.

3.2. Neuroleptics. The dopamine antagonists generally cause some degree of sedation, and patients requiring these medications for psychiatric reasons may experience improvement in their comorbid insomnia. Quetiapine may be the most commonly prescribed neuroleptic for the off-label use as a hypnotic. However, this drug has substantial adverse effect burden (including weight gain, blood sugar handling, etc.), with particular concern for older populations. Its binding profile is that of atypical neuroleptics in that it is D2

preferring, but also shows antagonism of 5HT₂ receptors and histamine H1 receptors. The metabolite norquetiapine inhibits NE reuptake.

3.3. Melatonin System. Melatonin is released by the pineal gland through regulation from the suprachiasmatic nucleus, mainly driven by light exposure conveyed by the retinohypothalamic tract [42]. Two receptor types, the MT1 and MT2, mediate the molecular signaling of melatonin. Secretion follows a circadian rhythm, and exogenous administration can alter a patient's circadian rhythm depending on the timing of dosing. For example, early evening administration of melatonin results in a phase advance, which may be implemented to address delayed circadian phase syndrome [15]. Melatonin is available over the counter and has extensive literature supporting its use in circadian rhythm

disorders, although the evidence for its use for insomnia is limited [43]. Ramelteon is a synthetic melatonin receptor agonist, which is nonselective for the two subtypes.

3.4. Antihistamines. The nonselective antihistamines such as diphenhydramine may produce sleepiness as the result of inhibition of central histamine H1 receptors. Histamine is one of several wake-promoting neurotransmitters and is released by the diffuse projections of the tuberomammillary nucleus [44]. Over-the-counter preparations may include combinations of diphenhydramine with analgesics such as ibuprofen and acetaminophen. The main concerns in the use of antihistamines for insomnia are the long half-life (which tends to produce a hangover-like effect), and in those of advanced age, the anticholinergic effects may alter cognition. At high doses, EKG changes become an increasing concern. Prescription antihistamines have also been used off-label, such as hydroxyzine.

4. Sleepiness

Sleepiness is a common daytime complaint, with a diversity of potential etiologies [45]. Although some promote the distinction between sleepiness and fatigue as a gateway to considering etiologies, the language patients use to describe this spectrum of symptoms is as imprecise as the medical profession's ability to quantify them [46–49]. For example, the commonly employed Epworth sleepiness scale has only meager correlation with sleep apnea severity [50–52]. Even objective measures of sleepiness, such as the sleep latency values in the multiple sleep latency test (MSLT), show weak relation to underlying sleep apnea severity [53]. Adding to the complexity of the situation, some patients with effectively treated primary causes of sleepiness, such as sleep apnea, may exhibit persistent or residual sleepiness. It is critical to determine underlying causes for excessive sleepiness before considering countermeasures in the form of stimulant therapy. For example, stimulant treatments may mask symptoms that in fact point to treatable factors such as sleep apnea, insufficient sleep, etc.

4.1. Stimulants. The largest class of stimulants includes amphetamines or amphetamine derivatives, although other options include modafinil and caffeine [54–57]. They are thought to enhance alertness by increasing the release of catecholamines, known to be excitatory and thus increase wakefulness. The pharmacokinetics (half-life) should be considered in treatment strategies, keeping in mind the potential for patient-specific effects. Avoiding consumption later in the day is an important consideration for the potential of inadvertently causing insomnia symptoms. Kidney and liver function may influence the choices in this class.

Modafinil and armodafinil are nonamphetamine stimulants with a mechanism that may involve dopamine signaling among other possibilities [54]. Like the amphetamines, side effects relate to the activating properties. In addition, the rare but serious Stevens-Johnson reaction has been reported with modafinil. For women taking hormonal contraception pills, their levels may be decreased by these agents and

thus they should be avoided unless other backup forms of contraception are used. Patients should also be aware of potential interactions of prescription stimulants with over-the-counter products that contain stimulants such as caffeine, pseudoephedrine, ephedrine.

4.2. Caffeine. Caffeine is contained in a diversity of food and drink and is the most widely used stimulant. Individual differences in the response to caffeine, including sensitivity to side effects, may be due to polymorphisms in the adenosine signaling system [58–61]. Because caffeine can lead to similar cardiovascular and CNS effects as the other stimulants, caution should be exercised in regards to the possibility that patients may augment prescription medications with caffeine-containing products or other over-the-counter agents that may present interaction concerns.

5. Sleep-Related Movement Disorders

The medications pramipexole and ropinirole were initially developed for treatment of Parkinson's disease. However, they have been shown to improve RLS symptoms, which are also thought to derive from impaired dopaminergic signaling in the brain [16, 62]. This may underlie the improvement in RLS that may accompany oral iron repletion, as manifested by low serum ferritin, due to iron being a cofactor in the rate-limiting step of brain dopamine synthesis. One main concern with these agents relates to orthostatic hypotension, which may be of particular interest to those with nocturia due to syncope/fall risk during nocturnal awakenings. Although very rare, compulsive behaviors (such as gambling) may occur with the dopaminergic agents. Kidney and liver function may dictate the choice between these two drugs, as pramipexole undergoes renal clearance while ropinirole undergoes hepatic metabolism.

Clonazepam (with or without melatonin) is commonly used for REM sleep behavior disorder [18]. RBD is characterized on the PSG as REM without atonia (and possibly capturing dream enactment), and by the clinical history of dream enactment, which should be distinguished from other nocturnal behaviors such as NREM parasomnias or seizure activity or delirium. RBD episodes may include vocalizations as well as actions, which can be associated with injurious behavior to the patient and/or bed partner. In addition to pharmacological suppression with clonazepam, it may be useful to assess and treat sleep apnea, which may contribute to REM-related arousals.

6. Metabolic Considerations: The Cytochrome P450 System

The cytochrome P450 (CYP) family of heme-containing enzymes is involved in the metabolism of organic molecules, both endogenous and exogenous [63–65]. These proteins, found mainly in the liver, transform their substrates through oxidation, an important step in metabolism. Each CYP enzyme may catalyze the metabolism of multiple drugs, and a single drug may interact with one or more CYP enzymes. Before drugs reach the liver, metabolism may

begin in the intestine primarily via the CYP3A4 isozyme. We summarize the relevant CYP interactions in regards to the drugs mentioned above; like drug-drug interactions, it is suggested that medical databases be consulted for more complete information.

There are two main contexts for considering the CYPs in clinical pharmacology. The most clinically relevant is the effect of certain drugs on enhancing or inhibiting the action of one or more CYP enzymes, which may alter the metabolism of shared substrate drugs. The other context is the increasing recognition that genetic polymorphisms may alter an individual's metabolism of certain drugs. For example, genetic variants of a CYP enzyme yield phenotypic classification into poor metabolizer, extensive metabolizer, and ultrarapid metabolizer phenotypes [64]. Homozygous individuals for the autosomal recessive allele are poor metabolizers, and individuals that are heterozygous or wild type are extensive metabolizers. Duplication or amplification results in the ultrarapid metabolizer phenotype. These phenotypes may have important implications for drug development and clinical trial design as well as clinical care [63, 64]. The impact of drug interactions related to the CYP system range from the need for dose adjustments to the risk of important toxicities. Age is another consideration, as advanced age may be associated with reduced CYP activity [65]. Liver and heart failure may affect the CYP system as well.

Inhibition of a CYP enzyme may be reversible or irreversible. For reversible inhibition, if two drugs are substrates for a CYP enzyme, the drug with the more potent interaction will undergo more extensive metabolism, while the less potent CYP substrates will undergo less metabolism. This form of competitive CYP inhibition will increase serum levels of the less potent drug, which may have important toxicity implications. For prodrugs that require CYP processing to generate an active metabolite, CYP inhibition will actually reduce the amount of the active drug. Irreversible inhibition is less common, and may require increased time after drug discontinuation before the CYP enzyme activity is restored to baseline.

CYP enzyme induction can occur via increased synthesis of the enzyme, or increase in the rate of enzymatic metabolism of existing proteins. CYP1A2, CYP2C9, CYP2E1, and CYP3A4 are inducible. Induction may be gradual if synthesis is involved, unlike inhibition which tends to be more acute.

The CYP metabolism of sleep-wake drugs is shown in Figure 5. In each case, the substrate or inhibitor status is indicated, along with whether this is major or minor (the former obviously requiring closer consideration). Some drugs are both substrates for, and inhibitors of, a single CYP enzyme (e.g., nefazodone with 3A4). For example, most sleeping pills are substrates for CYP 3A4, which is involved in the metabolism of many common drugs (e.g., the statins atorvastatin and simvastatin), a reminder that combination therapy may require adjustment of dose or reassessment of risk-benefit balance. Another example is modafinil and 2C19, which also metabolizes proton pump inhibitors. Because many patients with sleep disorders also have comorbid medical and psychiatric disorders, it is important to

cross-refer CYP considerations shown here with those related to the rest of their medications [63, 64]. It is worth noting that nonprescription drugs and certain food and natural supplement products may influence the CYP system [66]. For example, certain substances found in grapefruit juice inhibit the CYP3A4 isozyme. In addition, the natural supplement St. John's Wort induces CYP3A4 and inhibits CYP1A1, CYP1B1, CYP2D6, and CYP3A4. Smoking tobacco, as well as consumption of char-broiled foods, leads to induction of CYP1A2 isozyme [64]. Less common interactions include the inhibition of CYP2A6 by starfruit, and inhibition of CYP2E1 by watercress.

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