Drug-induced sleep disorders

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Introduction

This article includes discussion of drug-induced sleep disorders, daytime sleepiness, drug-induced insomnia, restless legs syndrome, sleep apnea, and vivid dreams and nightmares. The foregoing terms may include synonyms, similar disorders, variations in usage, and abbreviations.

Overview

A large number of drugs are associated with sleep disorders. This article starts with a classification of various drug-induced sleep disorders and lists drugs associated with each. Some sleep disorders, such as sleepwalking, have been associated with the use of hypnotics for insomnia. Pathomechanism is described when known. This knowledge may help in the modification of drug therapy or alternative medications.

Key points

• Several sleep disorders have been reported as secondary to adverse effects of drugs.
• Excessive daytime sleepiness and insomnia are the most common of these adverse effects but disorders of breathing and movement during sleep may also occur.
• Insomnia may occur due to use of prescription or recreational drugs as well as caffeine and alcohol.
• Recognition of drug-induced sleep disorders and their distinction from primary sleep disorders and sleep disturbances that occur during the course of neurologic diseases is important for the management of patients.

Historical note and terminology

Sleep disorders, particularly insomnia, and the use of sleep-inducing drugs have been well known throughout medical history. Similarly, sleep disturbances induced by ill-timed use of beverages such as alcohol and coffee, as well as by the desired or undesired effects of recreational drugs, are common knowledge. Drugs are also associated with parasomnias, a category of sleep behavioral disorders in which abnormal events, such as sleepwalking, occur during sleep.

In contrast to the therapy of sleep disorders, little attention was paid to the adverse effects of therapeutic drugs on sleep until the introduction of barbiturates as hypnotics. The long-term use of hypnotics as a cause of drug-induced insomnia was recognized in 1970s. Reports of sleep disturbances associated with other therapeutic drugs also started to appear in the 1970s and 1980s. Nightmares were observed with the initiation or withdrawal of tricyclic antidepressants and with the use of neuroleptic drugs (Strayhorn and Nash 1978). Although levodopa was introduced in the 1960s, reports of levodopa-induced sleep disruptions did not appear until several years later (Sharf et al 1978).

Sleep may be disturbed as a sequel of other drug-induced adverse drug reactions. For example, patients with movement disorders may have difficulty sleeping and patients on diuretics may have to get up frequently at night to urinate. This article describes sleep disorders associated with the use of therapeutic drugs. The information is based on a review of the literature and on reports of adverse reactions received by pharmaceutical manufacturers. The causal relationship is not proven by the usual scientific criteria, but the list of drugs should be considered during investigation of patients with sleep disorders. The International Classification of Sleep Disorders ICSD-3 mentions “sleep disorders resulting from a drug or substance” under the following categories: (1) central sleep apnea; (2) sleep-related hypoventilation; (3) hypersomnia; (4) parasomnia; and (5) sleep-related movement disorders (American Academy of Sleep Medicine 2014). “Drug or substance” can be a prescription medication, recreational drug, caffeine, alcohol, or food item or exposure to an environmental toxin. A practical classification of drug-induced sleep disorders, reflecting the manner in which they are reported in the literature, is shown in Table 1. This article is focused on sleep disorders associated with therapeutic use of drugs, and other substances, such as recreational drugs, are not included.

Table 1. Classification of Drug-Induced Sleep Disorders
Excessive sleepiness
- daytime sleepiness
Insomnia due to drugs or other substances
Rebound and withdrawal insomnia
Drug-induced sleep-related breathing disorders
- snoring
- sleep apnea
Drug-induced sleep-related movement disorders
- excessive movements of limbs, restless legs syndrome
- myoclonus
Drug-induced parasomnias: sleep behavioral disorders
- rapid eye movement sleep behavior disorder
- vivid dreams and nightmares
- sleepwalking
- sleep-eating
- sleep paralysis
- enuresis
- bruxism

Clinical manifestations

Presentation and course
Clinical features of sleep disorders induced by drugs are similar to those due to other causes. Temporal association with the use of drugs known to cause sleep disturbances is an important feature. Some of the clinical manifestations of various sleep disorders shown in Table 1 may be linked. For example, sleep apnea may manifest as insomnia.

Most people experience vivid dreams and nightmares at some time during their lives. These may be associated with sleep disturbances and psychiatric disorders or may be reported as isolated events. Vivid dreams are often associated with insomnia, which appears to be paradoxical. The explanation for this lies in the fact that waking appears to be necessary if the dreams are to be remembered.

Prognosis and complications
The prognosis for recovery from drug-induced sleep disorders is good if the responsible medication is identified and discontinued.

Biological basis
Etiology and pathogenesis
Etiology should be considered according to the type of disturbance.

Central disorder of hypersomnolence. The term "excessive sleepiness" should be differentiated from somnolence, which literally means sleepiness, because the term signifies abnormal drowsiness in a medical context. ICSD-3 refers to this group of sleep disorders as those in which "the primary complaint is daytime sleepiness not caused by disturbed nocturnal sleep or misaligned circadian rhythms." Drug or substance abuse is considered as a cause when it is responsible for extended periods of sleepiness. The term "hypersomnolence" is rarely used in pharmacovigilance, either in clinical trials or postmarketing surveillance. However, the more frequently used terms "sleepiness" and "drowsiness" often overlap and are used interchangeably in various reports. Falling asleep suddenly during the day ("sleep attack") has also been described as an adverse reaction to some drugs and should be differentiated from narcolepsy. According to ICSD-3 criteria, narcolepsy type 1 is characterized by excessive daytime sleepiness, cataplexy, rapid eye movement sleep phenomena such as sleep paralysis, and hypnagogic hallucinations.

Drowsiness. Drug-induced drowsiness or sleepiness is usually a self-reported event, and its effect on performance is
difficult to assess. Bayesian methods have been used to estimate sensitivity to drug-induced sleepiness (Fiedler et al 2010). Drugs that produce drowsiness are listed in Table 2.

**Table 2. Drugs That May Have Excessive Drowsiness as a Side Effect**

**Anticonvulsants**
- phenobarbital
- phenytoin
- valproic acid

Antidepressants: tricyclic

Antiemetic drugs
- hyoscine
- prochlorperazine
- perphenazine

Antihistaminics

Antihypertensive drugs
- methyldopa
- reserpine
- beta blockers

Antiparkinsonian drugs
- dopamine agonists
  - pramipexole
  - ropinirole

Antipsychotic drugs
- clozapine
- haloperidol

Beta blockers
- propranolol
- labetalol
- timolol
- metoprolol

Swine flu vaccine

**Insomnia due to drugs or substances.** ICSD-3 defines insomnia as “a repeated difficulty in sleep initiation, duration, consolidation, or quality that occurs despite adequate opportunity and circumstances for sleep, and results in some form of daytime impairment.” This is a difficult symptom to evaluate. The term "rebound insomnia," not included in ICSD-3, is used in the literature to describe sleep disturbance characterized by an increase in wakefulness above the previous baseline level after the withdrawal of sedative-hypnotic drugs. It is not synonymous with "withdrawal insomnia," which implies drug dependence and is usually seen with long-term use of hypnotics. Other hypnotic drugs, such as chloral hydrate, can also lead to withdrawal problems. Withdrawal from sedative or hypnotic drugs is defined as a temporary increase in the severity of insomnia after stopping treatment. If insomnia is worse than it was before the treatment started, the term "recoil" or "overshoot insomnia" is used rather than "rebound insomnia."

Patients with preexisting insomnia are at greater risk for developing aggravation of this symptom as an adverse effect of drugs. Drugs and substances associated with insomnia are listed in Table 3, and further details are given under various drugs along with other sleep disorders.

**Table 3. Drugs and Substances Associated with Insomnia**

Alcohol

Antidepressants
- selective serotonin reuptake inhibitors (SSRIs): fluoxetine
- MAO inhibitors
- stimulant tricyclics
Antiepileptic drugs
  • phenytoin
Antihistaminics
Antimalarials
  • mefloquine
  • chloroquine
Antineoplastics
  • daunorubicin
  • interferon alfa
  • medroxyprogesterone
Antiobesity drugs targeting monoamine systems
Antiparkinsonian drugs: dopaminergic
  • amantadine
  • levodopa
Anxiolytic drugs: buspirone
Bismuth, chronic toxicity
Bronchodilators
  • albuterol
  • ipratropium bromide
  • metaproterenol
  • salmeterol
  • terbutaline
  • theophylline
Cardiovascular drugs
  • antidiuretic: acetazolamide
  • antiarrhythmic drug: lorcainide, quinidine
  • antihypertensives
    - beta-blockers
    - clonidine
    - methylldopa
    - reserpine
  • calcium channel blockers: flunarizine
Cholesterol lowering drugs
  • lovastatin*
Cholinesterase inhibitors
  • donepezil
CNS stimulants
  • amphetamine
  • caffeine
  • ephedrine
  • methylphenidate
  • nicotine
Drug withdrawal: opioids
Endocrine preparations
  • adrenocorticotropic hormones
  • corticosteroids
  • oral contraceptives
  • progesterone
  • thyroid preparations
Hypnotics or sedatives
  • benzodiazepines
  • zaleplon
  • zolpidem
Vivid dreams and nightmares. Drugs affecting the neurotransmitters norepinephrine, serotonin, and dopamine are associated with patient reports of nightmares, and agents affecting immunological response to infectious disease are likely to induce nightmares in some patients. Opioids are well known to be associated with vivid dreams and nightmares (Okamoto et al 2013). Ketamine, a non-opiate analgesic/anesthetic agent, is used for management of chronic pain, and it occasionally causes vivid dreams or nightmares, which can be prevented by gradual dose titration. Drugs that have been reported to be associated with these phenomena are listed in Table 4.

Table 4. Drugs Associated with Vivid Dreams and Nightmares

Analgesics
- nonsteroidal antiinflammatory drugs: naproxen
- non-opiate analgesics: ketamine
- opioids
Antianxiety agent: bupropion
Antibiotics
- erythromycin
- fluoroquinolone
  - fleroxacin
  - ciprofloxacin
- Antivirals
  - efavirenz for treatment of HIV (Kenedi and Goforth 2011)
  - ganciclovir
Antidepressants:
- Selective serotonin reuptake inhibitors
  - fluoxetine
  - paroxetine (Kobayashi and Yamauchi 2012)
  - venlafaxine
- Tricyclic antidepressants
- Monoamine-oxidase inhibitors
Antiepileptics: valproic acid
Antiparkinsonian drugs
- amantadine
- cabergoline
- levodopa
- selegiline
Antipsychotics
- chlorpromazine
- thiothixene
Cardiovascular drugs
- ACE-inhibitor: captopril
- Beta-blockers: bisoprolol
- Calcium channel blocker: verapamil
- Candesartan (Pemzek): angiotensin II receptor blocker for hypertension
- Digoxin
- Ivabradine for treatment of coronary heart disease (Lappegard and Nordmo 2011)
- Statins: atorvastatin for lowering cholesterol
Corticosteroids, high dose
CNS stimulants
- amphetamine
- methylphenidate
- phenmetrazine
Drugs for Alzheimer disease
- Donepezil, cholinesterase inhibitors
- Galantamine (Corbo et al 2013)
- Memantine
Hypnotics and sedatives
  • Barbiturates, short-acting
  • Benzodiazepines: nitrazepam
  • Ketamine
Miscellaneous drugs
  • Alpha-agonists
  • Flutamide
  • Oxybutynin
  • Procarbazine
  • Rauwolfia alkaloids
  • Varenicline for smoking cessation
Withdrawal of drugs
  • Alcohol withdrawal
  • Benzodiazepine withdrawal
  • Hypnotic withdrawal

Sleepwalking. Sleepwalking occurs out of deep NREM of sleep and apparently represents a disorder of arousal. It can be considered to be 1 form of parasomnia. Subjects with epilepsy and those with a past or family history of sleepwalking are more liable to manifest this as an adverse reaction to drugs. Sleepwalking has been reported in association with the use of the drugs listed in Table 5.

Table 5. Drugs Associated with Sleepwalking
Antipsychotic and psychotropic agents
  • Lithium and neuroleptics
  • Olanzapine, an atypical antipsychotic agent
Sedatives and hypnotics
  • Chloral hydrate derivatives
  • Benzodiazepines
  • Zolpidem, an imidazopyridine hypnotic agent (Perez-Diaz et al 2010)
Antidepressants
  • Paroxetine, a selective serotonin reuptake inhibitor for the treatment of depression and anxiety
  • Reboxetine
Miscellaneous drugs
  • Bupropion, a noradrenergic and dopaminergic drug, used for smoking cessation
  • Topiramate (Mathew et al 2012)

Drug-induced disorders of breathing during sleep. Snoring is known to increase after intake of alcohol or sedative hypnotics in the evening before going to bed. Snoring alone, in the absence of sleep apnea, has not been proven to disrupt sleep or have a serious adverse effect on health. Obstructive sleep apnea, which is a risk factor for cardiovascular diseases and cognitive decline, is a cause for concern. Obstructive sleep apnea associated with methylenedioxymethamphetamine, a serotonin neurotoxin, suggests that dysfunction of the brain serotonin system may be involved in the pathophysiology (McCann et al 2009). Drugs that have been reported to be associated with obstructive sleep apnea are listed in Table 6.

Table 6. Drugs Reported to be Associated with Obstructive Sleep Apnea
  • Alcohol
  • Anesthetics
  • Antihypertensives
  • Growth hormone
  • Narcotics, eg, opioids
  • Recreational drugs, eg, methylenedioxymethamphetamine
  • Nitrous oxide inhalation
• Sedative-hypnotics
• Testosterone
• Benzodiazepines
• Neuroleptics

Sleep apnea has been reported in patients receiving methadone as opiate replacement therapy, and prescription of benzodiazepine is not recommended in such situations. Sedative-hypnotics, anesthetics, and analgesics alter sleep architecture, which likely contributes to abnormal postoperative sleep architecture with exacerbation of obstructive sleep apnea and postoperative complications (McEntire et al 2014). Main drugs involved in case reports of drug-induced sleep apnea in the French pharmacovigilance database are benzodiazepines, neuroleptics, and opioids (Linselle et al 2015).

Sleep paralysis. Sleep paralysis is the transient inability to move or speak during the onset of sleep, or on wakening. It may occur as a manifestation of narcolepsy and is often associated with mental disorder. Isolated sleep paralysis during awakening from sleep may occur in the absence of other clinical features of narcolepsy. It is more common in users of anxiolytic medications.

Drug-induced enuresis. Enuresis has been associated with several drugs, as shown in Table 7. The enuretic event is a predominantly nonrapid eye movement sleep phenomenon.

Table 7. Drugs Reported to be Associated with Enuresis

<table>
<thead>
<tr>
<th>Category</th>
<th>Drugs</th>
</tr>
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<tbody>
<tr>
<td>Alprazolam</td>
<td></td>
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<tr>
<td>Antipsychotics</td>
<td>clozapine, risperidone</td>
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<tr>
<td>Chemotherapy</td>
<td></td>
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<tr>
<td>Selective serotonin reuptake inhibitors</td>
<td>Monji et al 2004</td>
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<tr>
<td>Pimozide</td>
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<tr>
<td>Urapidil</td>
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<td>Valproic acid</td>
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Drug-induced sleep bruxism. Bruxism (grinding movements of the jaws) is considered to be a form of focal tardive dystonia and can occur during sleep; in which case it is referred to as sleep bruxism. Sleep bruxism has been reported with antidopaminergic agents such as antipsychotic drugs. Studies of the effects of dopamine agonists such as levodopa and of antagonists such as antipsychotics indicate a central role of dopamine in the pathogenesis of drug-induced bruxism and other mechanisms involving different neurotransmitters are emerging (Falsi et al 2014). For example, antihistaminergic drugs may induce bruxism as a result of their disinhibitory effect on the serotonergic system.

Sleep bruxism has been reported with use of selective serotonin reuptake inhibitors. In one study, incidence of antidepressant-induced bruxism was 14%, and the prevalence of bruxism was significantly higher in the antidepressant-group (24.3%) than in the control group (15.3%) with paroxetine, venlafaxine, and duloxetine as most frequently involved drugs (Uca et al 2015). Bruxism is an also an adverse effect of drug abuse, eg, ecstasy.

Drug-induced sleep-related eating disorders. There are several case reports of sleep-related eating disorders in association with use of zolpidem, with recovery following discontinuation of the drug (Najjar 2007). Most of the published cases involve females, but a male on zolpidem was reported to exhibit an unexpected and bizarre eating behavior during somnambulistic state (Dang et al 2009). Zolpidem-induced sleep-related eating disorder has been reported in a patient with restless legs syndrome (Yun and Ji 2010). Drug-induced sleep-related eating disorders should be considered when evaluating patients with nocturnal sleep-related eating disorders.

Drug-induced rapid eye movement sleep behavior disorder. REM sleep behavior disorder occurs mainly in patients with neurodegenerative diseases, particularly Parkinson disease, and can be drug-induced or occur on drug withdrawal (Gugger and Wagner 2007). Antidepressants are among the drugs associated with this disorder. REM sleep behavior disorder was reported in 4 patients with Parkinson disease after start of mirtazapine therapy and resolved after discontinuation of the drug (Onofri et al 2003). A retrospective study of idiopathic REM sleep behavior disorder
implied direct or indirect correlations with medication use, although causal relationship could not be demonstrated (Teman et al 2009).

**Drug-induced restless legs syndrome.** Restless legs syndrome, often associated with periodic limb movement disorder in sleep, is recognized as a primary disorder, but exacerbation of this disorder and secondary forms may be caused by psychotropic medications such as antidepressants and antipsychotics (Cohrs et al 2008). Antidepressant use is more strongly associated with restless legs syndrome in men than in women (Baughman et al 2009). Some drugs used to treat restless legs syndrome, particularly dopaminergic drugs, may aggravate symptoms (augmentation).

Drug-induced sleep-related leg cramps. These have been reported as adverse reactions to treatment with diuretics, vincristine, beta2 agonists, sodium oxybate, donepezil, oxcarbazepine, statins, and cholinesterase inhibitors.

For drugs to have a disturbing effect on sleep mechanism, access to the tissues of the brain is required. Important factors are lipid solubility of the drug and the ability of the drug to cross the blood-brain barrier. The background disease affecting a person may play a role in the pathomechanism of drug-induced sleep disorder. The occurrence of sleepwalking, sleep-related eating disorder, and rapid eye movement sleep behavior-like disorder among the psychiatric population are likely due to interaction of mental illnesses, sleep disturbances, and psychotropic medications (Lam et al 2008). Sleep-related adverse effects of drugs can be considered according to therapeutic categories, and rebound insomnia is considered to be a special entity for the discussion of pathomechanism.

**Antidepressants.** Sleep disturbances are generally more prevalent among patients with depression. These disturbances may improve with antidepressant treatment, but there may also be adverse effects due to antidepressant drugs. Some antidepressants adversely affect the physiological structure of sleep, whereas others restore it. Most antidepressants cause REM sleep reduction, generally with increased serotonin function (Aszalos 2006). Intense and prolonged dreams often accompany abrupt withdrawal from antidepressant drugs as a manifestation of REM sleep rebound after drug-induced REM sleep deprivation (Costa e Silva 2006). Investigations suggest patterns of NREM disturbances associated with depression and antidepressants, which may result in a disturbance of the stability of NREM sleep that may predispose to 1 or more parasomnias (Kierlin and Littner 2011).

Tricyclic antidepressants promote sleep in patients with insomnia due to depression and are likely to cause drowsiness. Tricyclic antidepressants also disturb REM sleep and are likely to cause nightmares.

Monoamine oxidase inhibitors have also been shown to suppress REM sleep in patients with depression, even eliminating REM sleep in some patients. This class of antidepressants also appears to reduce total sleep time and may decrease sleep efficiency.

Serotonin/norepinephrine reuptake inhibitors and selective serotonin-reuptake inhibitors can derange sleep architecture and decrease restorative sleep (Holshoe 2009). Selective serotonin reuptake inhibitors are more likely to cause insomnia. Fluoxetine significantly reduces sleep efficiency as well as REM time. The mechanism responsible for this is not known, but it may be due to a general increase in central arousal.

**Antiemetic drugs.** Most antiemetic drugs penetrate the blood-brain barrier and produce sleepiness by their action on the dopaminergic, histaminergic, or cholinergic systems. Hyoscine is a short-acting but powerful anticholinergic agent that reduces REM sleep but increases light (stage 2) sleep. REM sleep is increased on withdrawal of the drug. Domperidone is an exception because it acts on the chemoreceptor trigger zone outside the blood-brain barrier and is unlikely to cause sleepiness.

**Antiepileptic drugs.** The older antiepileptic drugs are associated with a variety of sleep disturbances including marked reduction in REM sleep and insomnia. Newer antiepileptic drugs have less of these disturbances. In a cross-sectional analysis of veterans attending an epilepsy clinic, 40% reported insomnia, which was significantly associated with post-traumatic seizure etiology and lamotrigine, whereas levetiracetam treatment was associated with lower odds for insomnia (Lopez et al 2013).

**Antihistaminics.** Histamine, as a neurotransmitter, takes part in the regulation of sleep. Therefore, sleep is affected by antihistaminics. The older antihistaminics such as triprolidine cause daytime sleepiness. The newer H1-antagonists, such as terfenadine, either do not penetrate the blood-brain barrier or enter the brain slowly, and they do not induce sleep, except in high doses. Among H2-antagonists, cimetidine increases the duration of slow wave sleep but ranitidine
Antiobesity drugs. Insomnia is the most common adverse effect with drugs targeting monoamine systems. These drugs include sibutramine, bupropion, and tesofensine, and they have some positive effects on mood and anxiety with added therapeutic benefits in obese patients (Nathan et al 2011).

Antiparkinsonian drugs. The primary pathologies involved in Parkinson disease appear to be the greatest contributors to the development of daytime sleepiness, but dopamine agonists may exacerbate sleepiness in a small subset of patients (Rye 2006). Parkinson disease patients treated with dopaminergic agents have frequent abnormal sleep patterns and hallucinations. Dopaminergic drugs have a biphasic influence on sleep (ie, they can cause both insomnia and excessive sleepiness). The exact mechanism of this paradoxical effect is not known. Lower doses of these drugs may downregulate dopaminergic input to the reticular activating system. For example, small doses of levodopa appear to improve sleep, although higher doses cause insomnia. Different dopaminergic receptor types or changes in receptor sensitivity may explain these phenomena.

There are case reports of sudden episodes of daytime sleepiness in patients taking ropinirole or pramipexole (motor vehicle accidents have resulted from some patients falling asleep when driving), and daytime sleepiness ceased when the drugs were discontinued. All dopamine agonists have the potential to produce sleep attacks during the day. Isolated cases have also been reported with bromocriptine, lisuride, pergolide, or piribedil. Excessive daytime sleepiness has been reported in patients treated by use of pramipexole, cabergoline, and levodopa as monotherapy with no significant differences between the 3 drugs. Important predictive factors are high doses, older age, and advanced disease. Sedation is considered to be rather a class effect of dopamine agonists. A study has shown that switching from pramipexole or ropinirole to piribedil maintains the same therapeutic motor effect but reduces daytime sleepiness to a clinically relevant degree in patients with excessive daytime sleepiness (Eggert et al 2014). Higher prevalence of sleepiness in patients with Parkinson disease, as compared with those suffering from other neurologic diseases, is related to the stage of the disease and medications, but the causes of variability in sedation levels in patients with Parkinson disease are mostly unknown. The possibility that individual susceptibility to a specific antiparkinsonian drug may play a role in the genesis of sleepiness should be kept in mind.

Antipsychotic drugs. Antipsychotics have been classified as high somnolence (clozapine), moderate somnolence (olanzapine, perphenazine, quetiapine, risperidone, ziprasidone), and low somnolence (aripiprazole, asenapine, haloperidol, lurasidone, paliperidone, cariprazine), but other factors such as dose and condition of the patient also influence the frequency and degree of somnolence (Fang et al 2016). The mechanisms of antipsychotic-induced somnolence are multifactorial, although the blockade of histamine 1 receptors and alpha 1 receptors may play a major role.

Beta blockers. Sleep disruption and excessive daytime sleepiness caused by beta blockers depend on the lipid solubility of the drugs. Propranolol, which is the most lipid-soluble drug of this group, is most liable to cause sleep disruption, and atenolol, the least lipid-soluble drug, is the least likely to cause sleep disruption.

Calcium channel blockers. The exact pathomechanism of flunarizine-induced insomnia is not known, but it may be related to interference with the dopaminergic system.

Cholesterol-lowering drugs. The proposed pathomechanism is related to the differential penetration of these agents across the blood-brain barrier, a property related to lipophilicity. Simvastatin, 1 drug of this class, has been reported to produce less sleep disturbances, indicating that lipophilicity alone is not responsible for these side effects.

CNS-stimulant drugs. Wake-promoting drugs such as modafinil are used therapeutically for the treatment of narcolepsy and have been shown to increase extracellular dopamine. Dopamine transporters are necessary for the specific wake-promoting action of modafinil, as experimental animals with deletions of dopamine transporter gene are nonresponsive to modafinil but hypersensitive to the wake-promoting effects of caffeine (Wisor et al 2001).

CNS-stimulating drugs may lead to disruption of sleep and subsequent excessive daytime sleepiness. At high levels of arousal, caffeine in moderate doses may induce overarousal, leading to prolonged wakefulness and impaired sleep. In clinical trials, insomnia has been reported to be increased in children with attention-deficit hyperactivity disorder who are receiving the CNS stimulant methylphenidate as compared to children in the placebo group. A randomized, double-blind, crossover trial showed that children receiving twice-daily atomoxetine had shorter sleep-onset latencies relative
to thrice-daily methylphenidate, based on objective actigraphy and polysomnography data (Sangal et al 2006). Although both medications decreased nighttime awakenings, the decrease was greater for methylphenidate. In a double-blind, placebo-controlled study of controlled-release methylphenidate in adults with attention-deficit hyperactivity disorder, insomnia was reported in 22% of those receiving the drug as compared to 8% in the placebo group (Jain et al 2007).

Nicotine administered as a transdermal patch in nonsmokers can cause disruption of the sleep architecture by increased catecholamine release as a result of stimulation of the central nicotinic cholinergic pathways.

**Hypnotic drugs.** Excessive sleepiness may be an extension of the effect of hypnotic drugs, either due to excess dosage or an idiosyncratic response of the patient. Excessive daytime sleepiness may be due to the disruption of the sleep wake cycle. In 2007, the FDA requested that all manufacturers of sedative-hypnotic drug products should strengthen their product labeling to include stronger language concerning potential risks. These risks include complex sleep-related behaviors like sleep-driving, defined as driving when not fully awake after ingestion of a sedative-hypnotic product, with no memory of the event. The focus of the revised labeling includes the following 13 medications (U.S. Food and Drug Administration 2007):

- Estazolam
- Eszopiclone
- Ethchlorvynol
- Flurazepam hydrochloride
- Pentobarbital and carbromal combination
- Quazepam
- Ramelteon
- Secobarbital
- Butabarbital sodium
- Temazepam
- Triazolam
- Zaleplon
- Zolpidem

**Pathomechanism of rebound insomnia.** This is not well understood. Psychosocial factors and behavioral problems may play a role in development of rebound insomnia. Knockout studies, together with genetic studies in mouse models, have shown that withdrawal from zolpidem is influenced by a chromosome 11 locus, which points to the Gabrg2 gene, a GABA receptor subtype gene, as a promising candidate to underlie phenotypic differences in sedative-hypnotic physiological dependence and associated withdrawal episodes (Hood et al 2006).

It is generally believed that rebound insomnia is related to rapid elimination of benzodiazepines, which results in a CNS deficiency of inhibitor mechanisms. Hypnotics suppress REM sleep movements, subsequently causing a compensatory excess of REM sleep after withdrawal.

Benzodiazepines are known to facilitate GABA receptor function, which is a major inhibitory system in the CNS, and withdrawal symptoms can be regarded as that of GABA deficiency. It may be presumed that during the period of drug administration, the production of endogenous benzodiazepine is suppressed by exogenous diazepam. This concept is compatible with a lack of rebound effect with long-acting benzodiazepines (slow elimination) or gradual reduction of the dose of short-acting benzodiazepine, which attenuates the rebound effect.

A randomized placebo-controlled study has investigated the likelihood of primary insomniacs experiencing rebound insomnia and a withdrawal syndrome on repeated placebo substitutions over 12 months of nightly use of zolpidem, which is a nonbenzodiazepine hypnotic but binds to GABA(A) receptors at the same location as benzodiazepine (Roehrs et al 2012). No clinically significant manifestations of withdrawal or differences in rebound insomnia rates between the placebo group and zolpidem group were observed on the discontinuation nights over the 12 months of nightly use. It was concluded that chronic nightly hypnotic use at therapeutic doses for primary insomnia does not lead to rebound insomnia or withdrawal symptoms.

Another hypothesis is that rebound insomnia is related to tolerance and decreased receptor density. The point against this hypothesis is that tolerance is related to the duration of administration, which does not alter the intensity of rebound insomnia. Another explanation is that less sleep is needed following the discontinuation of hypnotics once the
The patient has reached sleep satiation (i.e., after the sleep need, induced by hypnotics, has been satisfied). Observations support this hypothesis, which show that subjects with insomnia who receive hypnotics show reduced daytime sleepiness.

**Pathomechanism of drug-induced sleep apnea.** Several drugs affect respiration during sleep producing obstructive sleep apnea and nocturnal oxygen desaturation. Sleep in normal persons predisposes to hypoventilation, but reflex muscular dilatation of the pharynx occurs to prevent narrowing and increase respiratory effort. This reflex is depressed by some drugs leading to pharyngeal narrowing and obstructive sleep apnea. Benzodiazepines have a depressant effect on upper airway muscles and, given as preanesthetics to patients with sleep apnea, can lead to severe airway obstruction even when awake.

The prevalence of sleep apnea among hypertensives is high, and sleep apnea can also lead to daytime hypertension. However, the role of antihypertensive drugs in breathing during sleep has not been studied adequately.

Drugs may induce sleep apnea indirectly by producing an adverse effect that is a known risk factor for developing sleep apnea. For example, drugs that produce weight gain may indirectly contribute to sleep apnea.

**Epidemiology**

Sleep disorders are common, but there are no epidemiological studies to determine the percentage of these caused by drugs. Some examples with specific drugs are:

**Monoamine oxidase inhibitors.** Isocarboxazid-associated insomnia has been reported in patients treated with this drug for atypical depression. Moclobemide, a reversible monoamine oxidase inhibitor, is also associated with insomnia.

**Lorcainide.** This antiarrhythmic agent is associated with sleep disturbances (difficulty in falling asleep, nightmares, and vivid dreams).

**Flunarizine.** This is a calcium channel blocker used for the treatment of migraine and has been reported to be associated with insomnia.

**Pramipexole.** In clinical trials, somnolence has been reported in early Parkinson disease patients treated with pramipexole, a synthetic dopamine agonist.

**Prevention**

Observance of generally accepted methods of sleep hygiene reduces the probability of development of drug-induced sleep disorders.

The important preventive measure is avoidance of the use of drugs known to produce disturbances of sleep. Long-term use of sedative-hypnotic drugs should be avoided. Although most withdrawal reactions have been reported with long-acting benzodiazepines, rebound insomnia occurs with greater frequency and severity with short-acting agents. Benzodiazepine therapy should be stopped as early as possible with tapering after moderate dose, prolonged-use therapy, or both.

CNS depressants should be avoided in infants less than 1 year of age, as they may cause sudden death in apnea-prone infants.

**Differential diagnosis**

There are no characteristic clinical features of sleep disorders associated with drugs. The diagnosis is based on history of drug use and findings of sleep laboratory examinations to document the disturbances related to drug use. Drug-induced sleep disorders need to be differentiated from the disorders known to occur as a manifestation of diseases being treated with drugs. Discontinuation of the suspected drug with resulting improvement may help in the diagnosis.

It is important to differentiate common types of insomnia from drug-induced insomnia and pathological sleep because medications commonly used for insomnia, such as benzodiazepines, may aggravate pathological sleep.

Patients with advanced Parkinson disease have sleep disturbances that need to be differentiated from those induced by dopaminergic agents. Sleep attacks induced by drugs need to be differentiated from narcolepsy. Sleep disturbances
are a feature of delirium, which is often drug-induced. The sleep-wake cycle is disrupted in delirium, leading to drowsiness during the day and insomnia at night. During sleep, there may be nightmares that might merge into hallucinations.

**Diagnostic workup**

The first (and most important) step is elucidation of a complete drug history. In drug-induced drowsiness, blood levels of a suspected drug should be accurately measured. For example, in an elderly patient with phenytoin toxicity who presented with drowsiness and gait disturbance, free phenytoin level was calculated to be 27 ng/dL (normal 10-20 ng/dL) after taking his albumin level into account, whereas total serum phenytoin level was reported to be normal (Imam et al 2014). Phenytoin was discontinued with resolution of symptoms.

A proper assessment of sleep disorders requires an overnight polysomnographic study that is usually done in a sleep laboratory. These studies document changes in sleep stages, number of arousals, sleep-related breathing disorders, and movements during sleep. This is not only important for the evaluation of sleep disorders, but also for investigation of the action of drugs on sleep. Activity monitoring by wrist actigraphs has proven its usefulness as an efficient method to assess the rest-activity cycle in sleep research. This technique is capable of measuring drug-induced changes in nocturnal and diurnal behavior.

**Management**

**Drug-induced insomnia.** Management usually involves discontinuation of the offending medication. Another possibility to consider is changing the time of administration of the suspected drug. For example, in case of insomnia associated with donepezil, the drug may be administered in the morning rather than in the evening. In situations where the responsible medication cannot be discontinued, drugs for management of insomnia may be considered, taking care to avoid drug interactions. Some examples of this approach are:

- Trazodone is effective in the treatment of antidepressant-associated insomnia.
- Low-dose quetiapine may be an alternative treatment for phenelzine-associated insomnia (Sokolski and Brown 2006).

**Antipsychotic-induced sleep disorders.** Drug-induced restless legs syndrome generally resolves when the dose is reduced or the drug is withdrawn. For management of periodic limb movement disorder in sleep in psychotic patients, switching the antipsychotic and additional use of a second line medication, such as an antiepileptic or a benzodiazepine, is recommended (Cohrs et al 2008). Increase in doses above 80 mg/d of lurasidone, an antipsychotic for schizophrenia, does not seem to increase efficacy and may be associated with a dose-related increase in sleepiness (Citrome 2011). To manage this side effect, the dose should be reduced to the usually recommended range between 40 and 80 mg/d.

Antipsychotic-induced somnolence is usually manifest at the start of therapy and few weeks should be allowed for tolerance to develop before decision to discontinue the antipsychotic and replace it with a low-risk one. Another measure would be to start with a low dose and titrate.

**Drug-induced sleep disturbances in Parkinson disease.** Currently available data are insufficient to provide effective guidelines for prevention and treatment of sleep events in patients taking dopamine agonists for Parkinson disease. Parkinson disease patients at risk of sleep attacks during the day can be managed by dose reduction of dopamine agonists and a change to alternative medications. Modafinil may be effective in reducing excessive daytime sleepiness in Parkinson disease patients who are treated with dopaminergic drugs. Deep brain stimulation of the subthalamic nucleus in patients with Parkinson disease may improve sleep quality through reduction of total medication intake, increased nocturnal mobility, and reduction of sleep fragmentation (Antonini et al 2004).

**Future prospects.** Drugs frequently cause sleep fragmentation either as a part of intended action or an adverse drug reaction. A better understanding of the sleep mechanisms may lead to development of drugs without the unintended side effects. One of the approaches is study of the circadian sleep patterns by EEG following drug exposure. Use of the Makarov model in the telemetered rat has shown that methylphenidate was 5-fold more potent an inducer of sleep fragmentation as compared to a new chemical entity (Diack et al 2011).
Special considerations

Anesthesia

Anesthetic agents, like other CNS depressants, decrease neural output to upper airway muscles to a greater extent than they depress the phrenic nerve activity. It is a common observation that normal persons develop upper airway obstruction during light general anesthesia if proper position of the head and neck is not maintained. Severe central apnea can develop following general anesthesia.

The use of opioids should be avoided in patients with preexisting sleep apnea syndrome, and special care is required during intubation and in the postanesthetic period. They should not be extubated until fully conscious.

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**References especially recommended by the author or editor for general reading.**

**ICD and OMIM codes**

**ICD codes**

ICD-9:
- Sleep disturbance, unspecified: 780.50
- Drug-induced sleep disorders: 292.85

ICD-10:
- Sleep disorder, unspecified: G47.9

**Profile**

**Age range of presentation**

- 0-01 month
- 01-23 months
- 02-05 years
- 06-12 years
- 13-18 years
- 19-44 years
- 45-64 years
- 65+ years

**Sex preponderance**
male=female

Family history
none

Heredity
heredity may be a factor

Population groups selectively affected
none selectively affected

Occupation groups selectively affected
none selectively affected

Differential diagnosis list
common insomnia
advanced Parkinson disease
narcolepsy
delirium
disorders known to occur as a manifestation of diseases being treated with drugs

Associated disorders
Daytime sleepiness
Nondrug-induced sleep disorders
Rebound insomnia
Sleep apnea
Sleep paralysis
Sleepwalking
Withdrawal insomnia

Other topics to consider
Central sleep apnea
Drug-induced neurologic disorders
Insomnia
Narcolepsy
Neuropharmacology
Nightmares
Obstructive sleep apnea
Sleep disorders
Sleep disorders associated with alcohol use and abuse
Sleep paralysis
Sleepwalking
Stimulant-dependent sleep disorder

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