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## Drugs Inducing Insomnia as an Adverse Effect

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### 1. Introduction

Insomnia is a symptom, not a stand-alone disease. By definition, insomnia is "difficulty initiating or maintaining sleep, or both" or the perception of poor quality sleep (APA, 1994). As an adverse effect of medicines, it has been documented for several drugs. This chapter describes some drugs whose safety profile includes insomnia. In doing so, it discusses the mechanisms through which drug-induced insomnia occurs, the risk factors associated with its occurrence, and ends with some guidance on strategies to prevent and manage drug-induced insomnia.

### 2. How drugs induce insomnia

There are several mechanisms involved in the induction of insomnia by drugs. Some drugs affects sleep negatively when being used, while others affect sleep and lead to insomnia when they are withdrawn. Drugs belonging to the first category include anticonvulsants, some antidepressants, steroids and central nervous stimulant drugs such amphetamine and caffeine. With regard to caffeine, the mechanism by which caffeine is able to promote wakefulness and insomnia has not been fully elucidated (Lieberman, 1992). However, it seems that, at the levels reached during normal consumption, caffeine exerts its action through antagonism of central adenosine receptors; thereby, it reduces physiologic sleepiness and enhances vigilance (Benington et al., 1993; Walsh et al., 1990; Rosenthal et al., 1991; Bonnet and Arand, 1994; Lorist et al., 1994). In contrast to caffeine, methamphetamine and methylphenidate produce wakefulness by increasing dopaminergic and noradrenergic neurotransmission (Gillman and Goodman, 1985). With regard to withdrawal, it may occur in 40% to 100% of patients treated chronically with benzodiazepines, and can persist for days or weeks following discontinuation. Withdrawal symptoms include dizziness, confusion, and depression (Lader et al., 2009).

Another feature of discontinuation of drugs is rebound insomnia, which is an increase in insomnia symptoms beyond their baseline level. Rebound is thought to be associated primarily with short-acting benzodiazepines. Patients who demonstrate rebound insomnia tend to have worse baseline sleep and higher medication doses than patients without rebound (Merlotti et al., 1991; Roehrs et al., 1986; Hajak et al., 1998; Griffiths and Weerts, 1997). While insomnia can also result from chronic use of hypnotics such as benzodiazepines and other sedatives, the following classes of drugs can cause insomnia when withdrawn: central nervous depressants such as alcohol, certain antidepressants, and

barbiturates, opioids both legal and illicit such as cocaine, heroin, marijuana; as well as monoamine oxidase inhibitors and phencyclidine.

Moreover, it is known that adrenal dysfunction can cause catecholamine secretion that may lead to sympathetic activation and insomnia. Similarly, excessive glucocorticoid levels also cause insomnia (Attarian, 2004). Furthermore, an indirect effect through neurologic and psychiatric effects such as headaches, irritability, anxiety and agitation may also lead to insomnia. This is the case for commonly prescribed hypnotics that cause irritability and many psychoactive drugs that induce abnormal movements during sleep (Zammit et al., 1999; Breslau et al., 1996). Drugs which suppress rapid eye movement (REM), commonly result in REM rebound nightmares on withdrawal, as in the case of opioid analgesics. While such drugs are being taken, the relative lack of REM sleep may lead to underestimation of the severity of sleep apnea. Drugs which suppress slow-wave sleep (SWS) commonly leave the patient unrested, as seen with corticosteroids.

Parasomnias, defined as unusual behaviours during sleep such as sleepwalking, sleep-talking, teeth grinding, bedwetting, sleep starts, sleep terrors, and confusion awakenings are sleep disturbances associated and leading to drug-induced insomnia. Sleepwalking may occur in over 15% of healthy children and 3% of adults, typically take place during short wave sleep. Several medications which increase this stage of sleep may induce sleepwalking: lithium, thioridazine, and amitriptyline. Drugs that suppress REM sleep increase the likelihood of some parasomnias: tricyclic antidepressants, for example, and triazolam. Nightmares, reported at least occasionally by 40-50% of adults, are known to be associated with REM sleep (Novak and Shapiro, 1997).

Drugs which predispose to nightmares include beta-blockers, especially those that more easily penetrate into the brain, like propranolol. Stimulant drugs which disrupt night-time sleep include theophylline and sympathomimetic bronchodilators such as ephedrine. Drugs which may worsen sleep apnea include alcohol, opioid analgesics, and anaesthetic drugs. Among the cardiovascular drugs, some antihypertensive drugs are particularly important in their effects on sleep, generally a decrease in the duration of REM sleep, but it is unclear how significant these effects are for patients. REM sleep is decreased by blockers of beta-adrenoreceptors like pindolol, stimulants of alpha adrenoreceptors like clonidine and guanfacine, serotonin stimulators like ritanserin and ketanserin, and methyl dopa. Only reserpine increases REM sleep. Beta-blockers like propranolol in particular increase wakefulness by causing insomnia and nightmares, and by suppressing REM sleep. However, the frequency of these effects may be low, especially with types of beta-blockers that do not readily penetrate to the brain, like atenolol (Novak and Shapiro, 1997; Roehrs et al., 2000; Roth and Roehrs, 2003).

Other drugs produce insomnia by interfering with melatonin. Melatonin has the ability to influence the timing of the circadian sleep-wake cycle (Sack et al., 2000), has sedative effects possibly via direct inhibition of the suprachiasmatic nucleus via a feedback loop (Dubocovitch, 1995). It is suggested that melatonin promotes sleep in humans, presumably by inhibiting circadian wakefulness mechanisms and affecting the activity of brain networks compatible with sleep induction (Cajochen et al., 2003; Wyatt et al., 2000; Liu et al., 1997; Shochat et al., 1997; Gorfine et al., 2006). However, numerous studies have shown decreased melatonin levels in the elderly relative to subjects aged less than 30 years (Sharma et al.,

1989; Zhou et al., 2003) because of the decline in the number of pinealocytes, and/or neuronal degeneration and resultant circadian desynchrony (Kripke et al., 1998). Yet, melatonin deficiency may be induced by a variety of medications commonly used by the elderly, including beta-blockers and non-steroidal anti-inflammatory drugs (Gorfine et al., 2006; Liu et al., 1997).

**Examples of classes of drugs inducing insomnia and their mechanisms of action**

Through melatonin

- Beta-blockers
- Non-steroidal anti-inflammatory drugs

Through interfering with REM

- Beta-blockers
- Tricyclic antidepressants: eg.
- Stimulant drugs : eg. Theophylline
- Serotonin stimulators: eg. ritanserin

Through interfering with slow-wave sleep

- Corticosteroids

Through increasing dopaminergic and noradrenergic neurotransmission

- methamphetamine
- methylphenidate

Through withdrawal

- Benzodiazepines
- Barbiturates
- Opioids such as cocaine, heroin, marijuana

Through direct action by antagonism of central adenosine receptors

- Caffeine

Box 1. Mechanisms involved in drug induction of insomnia

### 3. Risk factors of drug-induced insomnia

From the mechanisms of action described above, it appears that several factors would contribute to the occurrence of insomnia as a result of using a particular drug or withdrawing it. Reports of sleep disturbances associated with therapeutic drugs appeared 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).

Factors related to a particular drug include the chemical structure of the drug that dictates its activities, its pharmacological mechanisms of action, and the dosage used in a particular patient (Lancel, 1999; Mendelson et al., 1983; Olsen and Tobin, 1990). As shown below some drugs induce insomnia only when a certain level of dosage is reached. Factors related to an individual patient include race, lower socioeconomic status, and unemployment as well as age, sex, use of medications and comorbidities.

Several studies suggest there are ethnic and racial differences in sleep disturbances. Studies exploring associations between disturbed sleep and health-related quality of life (HR-QOL) have examined the role of comorbid conditions, gender, and race/ethnicity (Krystal, 2007; Baldwin et al., 2004; Katz and McHorney, 2002; Chowdhury et al., 2008). As with studies of sleep disturbances, the majority of HR-QOL research focused on differences between African American and Caucasian participants. Elderly African Americans with mild sleep apnea had significantly poorer physical and mental HRQOL than African Americans without it (Redline et al., 1997; Stepnowsky et al., 2000). African American, Hispanic, and other minority participants had both worse quality of sleep and poorer well-being than Caucasian participants (Jean-Louis et al., 2000). However, when sex, education, age, marital status, and healthcare coverage were controlled for, Caucasians were more likely to report not getting enough sleep than African Americans and Hispanics; when mood, medication use, socioeconomic status and perceived health were controlled for, Caucasians reported more restless sleep than African Americans (Kutner et al., 2004).

With regard to age, as explained above, the extent of melatonin suppression may be more profound in the elderly than in younger subjects. In addition to medications, a variety of primary conditions, such as chronic pain, myocardial infarction, and ischemic stroke are strongly associated with decreased melatonin levels in the elderly as animal studies have shown decreased levels of the Mel1a receptor with aging (Garfinkel et al., 1995; Murphy et al., 1996; Van den Heuven et al., 1997; Richardson and Tate, 2000). The elderly constitutes a group of individuals who are known as more susceptible to actions of drugs such as antidepressants, antihistaminic drugs, certain antipsychotics, and amphetamines (Fick et al., 2003). Furthermore, people who are elderly have a higher incidence of general medical conditions and are more likely to be taking medications that cause sleep disruption. Sleep studies objectively confirm the disturbed sleep of asthmatics. They are often woken with coughing, wheezing, and breathlessness. Similar problems apply to patients with chronic obstructive pulmonary disease (COPD or emphysema). Besides direct drug effects on their sleep, asthmatics suffer many other factors affecting sleep, such as gastroesophageal reflux, which can be aggravated by theophylline. Theophylline also has a central nervous system stimulatory effect that can disturb sleep, particularly in patients newly taking this drug.

With regard to commonly used medications, the following medicines are reported to promote chronic insomnia. These include selective serotonin reuptake inhibitors, lamotrigine, phenytoin, atorvastatin and oral contraceptives. Other risk factors of insomnia include the patient's health status, susceptibility, and co-morbidity (Balter and Uhlenhuth, 1992; Sharpley and Cowen, 1995; Espiritu, 2008; Saddichha, 2010).

With regard to comorbidities, the incidence of insomnia in hypertensive Japanese patients under antihypertensive therapy has been reported as 0.77/100 person-years; the factors contributing to insomnia onset were  $\alpha$  blockers (OR, 2.38; 95% confidence interval [CI], 1.14-4.98),  $\beta$  blockers (OR, 1.54; 95% CI, 0.99-2.39), and calcium channel blockers (OR, 0.62; 95% CI, 0.43-0.90) compared with angiotensin-converting enzyme inhibitors; female sex (OR, 1.76; 95% CI, 1.27-2.44); complication of gastric/duodenal disorders (OR, 2.35; 95% CI, 1.14-4.86) or musculoskeletal system/connective tissue disorders (OR, 2.43; 95% CI, 1.23-4.79); and concomitant antihypertensive therapy (Tanabe et al., 2011). In patients suffering from myasthenia gravis, the prevalence of insomnia was 39.1% (Qui et al., 2010). Lastly, sleep disturbance is one of the most common complaints reported in 74-96% of patients suffering from Parkinson's disease. Insomnia is associated with increased morbidity and mortality caused by cardiovascular disease and psychiatric disorders and has other major public health and social consequences, such as accidents and absenteeism (Roth and Roehrs, 2003).

**Risk factors associated with drug-induced insomnia**

- Age
- Race and ethnicity
- Sex
- Medication use and drug interactions
- Comorbidities

Box 2. Risk factors for drug induced insomnia

#### 4. Specific classes of drugs reported to cause insomnia

The following list is not comprehensive or exhaustive; it is purely presented for illustration purposes.

##### 1. Amino-quinolones

Atovaquone plus proguanil, a combination that was used in the preventive and curative treatment of malaria has been reported to produce insomnia in 5.2% of patients (van Genderen et al., 2007).

##### 2. Anabolic steroids

It is well known that the abuse of anabolic steroids can cause the stimulation of the nervous system and this may result in euphoria or and insomnia (Papazisis et al., 2007; Kanayama et al., 2008).

##### 3. Anti-ADHD

Methylphenidate, a drug used to treat attention deficit hyperkinetic disorder (ADHD), was reported to produce insomnia in 19 of 62 patients who were included in an open label trial (Gucuyener et al., 2003).



#### 4. Anti-asthmatic drugs

Insomnia was one of the common side effects in 84 patients who completed a randomized trial of albuterol/salbutamol (Kissel et al., 2001). Insomnia was also reported in 1.75% of the 110 participants with COPD in a trial involving theophylline (Zhou et al., 2006).

#### 5. Antidepressants

In an open-label phase of a relapse prevention study, duloxetine (60 mg QD) was shown to be effective in the treatment of depression; among the 533 participants, insomnia was reported in over 10% of patients (Hudson et al., 2007).

#### 6. Antiepileptic drugs

Lamotrigine led to insomnia in 2 of 29 patients treated for refractory epilepsy (Garcia-Esciva et al., 2004). Levetiracetam led to insomnia in 105 (7.5%) of 1422 patients observed during studies (Ben-Menachem et al., 2003; Mula et al., 2004). Insomnia was reported in 9% of patients who were treated with a median dose of 300mg per day of topiramate (Giannokodimos S et al., 2005)

#### 7. Antihistamines

Insomnia has been reported in 30% taking loratadine plus pseudoephedrine versus 21% taking placebo (Berkowitz et al., 1989; Supiyaphun et al., 2002).

#### 8. Anti-muscarinic drugs

In a meta-analysis of 72 original randomized trials of antimuscarinic drugs, namely, oxybutynin, tolterodine, fesoterodine, propiverine, solifenacin, darifenacin, and trospium, adverse effects reported were, among others, insomnia and vertigo. The trials involved adults with overactive bladder using standard doses of medications (Paquette et al., 2011).

#### 9. Anti-obesity drugs

Insomnia was one of the most common adverse effect of monoamine system drugs such as sibutramine, bupropion, and tesofensine (Nathan et al., 2010).

#### 10. Antipsychotic drugs

Aripiprazole is known to produce fewer extrapyramidal effects, but in patients taking 15mg per day, insomnia in 42% of patients versus 18% in those taking the placebo (Shim et al., 2007; Carvajal et al., 2007).

In the 40-week extension of a clinical trial, insomnia was one of the common adverse effects seen in over 10% of patients treated with asenapine (McIntyre et al., 2010).

#### 11. Antiretroviral drugs

Efavirenz is known to produce neuropsychiatric effects including insomnia in up to 50% of patients (Kenedi and Goforth, 2011; Jena et al., 2009; Alavena et al., 2006). In a trial of single-pill fixed-dose regimen containing emtricitabine, tenofovir and efavirenz, four patients discontinued the trial because of insomnia (Airoldi et al., 2010). Insomnia has been reported in 5% to 16% patients on a regimen containing emtricitabine (Palacis et al., 2008).

## 12. Anti-tuberculosis agents

Of the 18 patients identified with neuropsychiatric problems in 18 French patients, six had insomnia (Fekih et al., 2011).

## 13. Benzimidazoles

Albendazole, in a clinical trial of 168 patients, led to insomnia in 2 patients that have been treated for 7 days due to heavy infestation (Sirivichayakul et al., 2003).

## 14. Complementary and alternative medicines (CAM)

Despite its voluntary recall of Pai You Guo in 2009, clinicians have noted its continued use among Brazilian-born women in Massachusetts. The majority of users (85%) reported at least one side effect, among them insomnia in 26% of respondents (Cohen et al., 2011).

## 15. Cholinesterase inhibitors

Donepezil and galantamine have been reported to have induced insomnia in some patients (Kavirajan and Schneider, 2007).

## 16. Cox-2 inhibitors

Celecoxib and rofecoxib, of the 142 reports received by the Australian Adverse Reactions Advisory Committee (ADRAC), 21 cases were about insomnia (ADRAC, 2003). This neuropsychiatric reaction seems to be a class effect.

## 17. Fluoroquinolones

Drugs of this group such as gatifloxacin, gemifloxacin, and moxifloxacin produce mild central nervous complications including insomnia (Sable and Murakawa, 2003; Sable and Murakawa, 2004). Other psychiatric effects include headaches, and agitation that occurred in 2-4% of patients (Saravolatz and Leggett, 2003). In double-masked, randomized, comparative trials of sparfloxacin (a 400-mg oral loading dose followed by 200 mg/d for 10 days) versus standard therapies (erythromycin, cefaclor, ofloxacin, clarithromycin, and ciprofloxacin), insomnia was reported in 4.3% of patients (Lipsky et al., 1999).

## 18. Human-murine monoclonal antibodies

Infliximab is used to treat refractory Crohn's disease; in one patient suffering from lupus erythematosus, insomnia was reported (Drosou et al., 2003).

## 19. Lipopeptide antibiotics

Daptomycin, a drug with bactericidal effects against Gram-positive bacteria has been reported to produce moderate neuropsychiatric effects such as headaches and insomnia (Gonzalez-Ruiz et al., 2011; FDA, 2003).

## 20. Metals

Antimony and arsenic: In observational studies, both antimony and arsenic caused insomnia in patients (Newlove et al., 2011; Takahashi, 2010). Insomnia was reported in 37.5% of people who were victims of chronic arsenic poisoning through drinking water in Mongolia (Guo et al., 2007).



### 21. Neuroleptics

The long-acting depot risperidone has a half-life of 3-6 days. Its most common adverse events include insomnia which is reported in 22.6% of patients (Louza et al., 2011). Insomnia was reported also as one of the common adverse effects of paliperidone in addition to extrapyramidal effects when used in patients with schizophrenia (Shim et al., 2008; Turkoz et al., 2011; Sliwa et al., 2011).

### 22. Norepinephrine re-uptake inhibitor (NRI)

Reboxetine-treated patients were more likely to experience constipation, difficulty urinating, and insomnia (Papakostas et al., 2008).

### 23. Opioid receptor agonists

Nalmefene, a drug used in order to promote abstinence in alcoholics, has been shown to induce insomnia in patients who received 20 micrograms per day (Anton et al., 2004).

### 24. Opioid analgesics

Insomnia has been reported as adverse event with dextromethorphan (Paul et al., 2004; Avis and Profile, 2005).

### 25. Selective serotonin reuptake inhibitor (SSRI)

Escitalopram, a selective serotonin reuptake inhibitor (SSRI) used in the treatment of major depressive disorder (MDD) and generalized anxiety disorder (GAD), has been reported to produce insomnia and decreased libido when used at 10 mg/day (Huska et al., 2007). In a large sample of 811 adult participants with depression in a part-randomised multicentre open-label study comparing escitalopram and nortriptyline, insomnia was reported in 36% of patients on escitalopram (Uher et al., 2009).

### 26. Smoking deterrent

In a review involving 120 studies (Mills et al., 2010), an increased risk of insomnia was associated with nicotine patch (OR 1.42, 95% CI, 1.21-1.66,  $P < 0.001$ )

### 27. Steroids

Insomnia has been reported in 27% of 103 patients treated for 8 days with more than 20mg/day of prednisone (Silverman et al., 1985; Aronson, 2010).

In an investigation of glucocorticoid-induced side effects in 68 Japanese patients treated for autoimmune diseases with prednisolone, insomnia occurred in 50% of them. It lasted on average 6 days, ranging from 1 to 88 days (Nakajima et al., 2009).

In case series of children with such discrete conditions as asthma and nephrotic syndrome, up to 50% of those receiving oral glucocorticoids have had adverse behavioural and affective effects including elevated levels of depression and anxiety, as well as increases in insomnia (Estrada de la Riva, 1958; Bender et al., 1988; Hall et al., 2003).

## 5. Strategies to manage drug-induced insomnia

Given the mechanisms of action described above, prescribers and dispensers of drugs should alert and inform the patients of the possibility that the drug they will be taking may

lead to insomnia. For drugs that cause insomnia when withdrawn, the most common strategy has been to avoid abrupt withdrawal by tapering the dosing of the drug over several days (Lader et al., 2009).

For drugs that cause insomnia when being used, there are three strategies, namely, modification of dosage, discontinuation of drug, and switching to a different drug. When switching to a different drug, it is important to ensure that the insomnia as an adverse effect is not a “class-related effect” as shown above with regard to fluoroquinolones or cox-2 inhibitors. If so, a drug of a different class must be chosen or a drug that favourably enhances sleep should be considered as in case of salmeterol, a beta-adrenergic stimulator, that has been shown to improve quality of sleep. This medicine is recommended in asthmatics experiencing sleep disturbances (Lee et al., 2011; Nathan et al., 2006).

When insomnia occurs at a certain dosage level as in the case of prednisone, dosage reduction should be considered. This strategy is most relevant for the elderly. Generally, lower doses should be used in the elderly, although dose requirements may vary from person to person. Typically, starting doses for the elderly should be about one third to one half of the usual adult doses when a drug has a low therapeutic index or when another condition may be exacerbated by the drug (Kamal and Gammack, 2006).

With regard to preventing the occurrence of drug-induced insomnia, prescribers must be familiar with the drug and its potential adverse reactions. Drugs and initial dosage must be carefully selected for susceptible individuals such the elderly, those on cancer therapy, and children. Drugs which suppress slow-wave sleep (SWS) commonly leave the patient unrested; this might be counteracted by a sleeping medication that increases SWS, such as zopiclone. Clomipramine, a tricyclic antidepressant, may be used to suppress REM related nightmares. Both pharmacological and non-pharmacological treatment modalities should be explored in the management of drug-induced insomnia (Ellis et al., 2011; Foral et al., 2011).

## 6. Concluding remarks

Drug-induced insomnia is prevalent. It has been reported to occur to up to 50% of patients on specific drugs. While patients must be advised accordingly, precautions must be taken to avoid inducing insomnia through abrupt withdrawal of drugs, inappropriate dosing and irrational drug prescribing.

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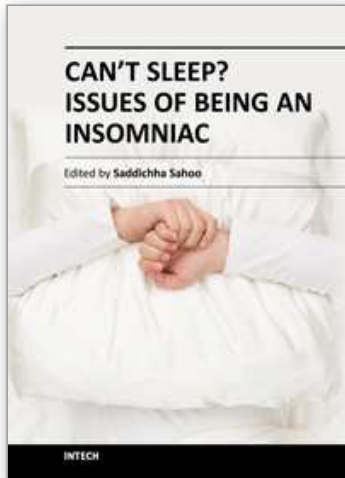


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### **Can't Sleep? Issues of Being an Insomniac**

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The word insomnia originates from the Latin "in" (no) and "somnus" (sleep). It is a disorder characterized by an inability to sleep or a complete lack of sleep. Various studies have noted insomnia to be quite a common condition, with symptoms present in about 33-50% of the adult population. This book provides a comprehensive state of the art review on the diagnosis and management of the current knowledge of insomnia and is divided into several sections, each detailing different issues related to this problem, including epidemiology, diagnosis, management, quality of life and psychopharmacology. In order to present a balanced medical view, this book was edited by a clinical psychiatrist.

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