Drug-Induced Insomnia and Excessive Sleepiness

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KEYWORDS

• Drugs • Medication • Psychotropic • Nonpsychotropic • Sleep • Insomnia • Sedation • Sleepiness

KEY POINTS

- Undesirable side effects of insomnia and/or sleepiness may occur with many prescribed drugs, psychotropics as well as nonpsychotropics.
- These central nervous system (CNS) effects can be explained by the interactions of a drug with any of the numerous neurotransmitters and receptors that are involved in sleep and wakefulness.
- A close—sometimes bidirectional—relationship between disease and (disturbed) sleep/wakefulness is often present. Drug effects may increase the complexity of this interaction.
- Effects of disease and/or drugs on sleep and wakefulness may create a vicious circle, influencing health and quality of life.
- Direct and indirect effects of drugs on the disease as well as on sleep and wakefulness need to be weighed.

INTRODUCTION

Sleep and waking function are closely connected in a 24-hour rhythm. The central nervous system (CNS) structures involved in the promotion of the waking state include neurons containing serotonin (5-HT), norepinephrine (NE), dopamine (DA), acetylcholine (ACh), histamine (HA), orexin (OX), and glutamate (GLU). Selective activation of either DA receptor D_1 or DA receptor D_2; 5-HT, 5-HT_1, 5-HT_{2A}, 5-HT_{2C}, 5-HT_6, and 5-HT_7 receptors; NE α_1 receptor; HA H_1 receptor; ACh m_1 receptor; OX OX_1 and OX_2 receptors; or GLU AMPA, kainite, and *N*-methyl-D-aspartate receptors increases wake and reduces non–rapid eye movement (REM) and REM sleep.[1] Neurons that constitute the non-REM sleep–inducing system contain γ-aminobutyric acid (GABA) and galanin and inhibit cells involved in the promotion of wake. Somnogens, including adenosine, prostaglandin D_2, nitric oxide, and cytokines, also promote sleep, mainly non-REM sleep, in humans.[2] The REM sleep induction regions include predominantly glutamatergic neurons.[3]

Many drugs have the potential to disrupt sleep and waking function due to their pharmacologic effects at any of the numerous receptors and neurotransmitters involved in sleep-wake regulation. As such, insomnia and/or daytime sleepiness are common side effects of psychotropic as well as nonpsychotropic medication. The lipophilicity, which determines the easiness with which a drug crosses the blood-brain barrier (BBB), and the receptor binding profile determine its possible CNS effects.

Some general considerations have to be taken into account. First, there can be beneficial as well as adverse effects of drugs on sleep and wakefulness (**Table 1**). The effects may be desired when a drug is prescribed with the goal of creating sleep

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Table 1
Drug-induced adverse effects of insomnia or sleepiness with possible mechanism of action

Drug Class or Individual Drug	Induced Sleep-Wake Disturbance	Possible Mechanism of Action
ANTIDEPRESSANTS		
Sedating TCA (eg, amitriptyline and doxepin)	Sleepiness	Antagonism at NE α_1, HA H_1, and ACh receptors
Activating TCA	Insomnia	Inhibition of serotonin and NE reuptake
SSRI	Insomnia	Inhibition of serotonin and NE reuptake
SNRI	Insomnia	Inhibition of serotonin and NE reuptake
Bupropion	Insomnia	Inhibition of NE and DA reuptake
MAOI	Insomnia	Inhibition of MAO enzyme
Atypical sedating AD (eg, trazodone and mirtazapine)	Sleepiness	Antihistaminergic effect, 5-HT_2-receptor antagonism
ANTIPSYCHOTICS		
First generation	Mostly sleepiness, insomnia also reported	Antagonism at NE α_1, HA H_1, ACh, and DA receptors
Second generation, for example, clozapine, olanzapine, and quetiapine	Variable effects Sleepiness	DA-receptor and 5-HT-receptor antagonism; effects at other receptors vary for each agent
ANTIEPILEPTICS	Mostly sleepiness	Decreased neuronal excitation by variable mechanisms
ANTIPARKINSONIAN AGENTS		
DA replacement drugs	Low-dose sleepiness, high-dose insomnia	DA-receptor agonism
ANALGETICS		
NSAIDs		Prostaglandin synthesis inhibition
Opioids	Sleepiness	μ-Opioid and κ-opioid receptor agonism
Triptans	Sleepiness?	5-HT_1-receptor antagonism
ANTIHISTAMINES		
First generation	Sleepiness	Antagonism at HA H_1 receptor
Second generation	None to mild sleepiness	None to little BBB transport
CARDIOVASCULAR DRUGS		
β-Blocking agents	Insomnia	β receptor and 5-HT-receptor antagonism; melatonin suppression
β- and α_1-blocking agent	Insomnia, also sleepiness reported	β and 5-HT receptor antagonism; melatonin suppression; α_1-receptor antagonism
α_1 Antagonists		α_1-receptor antagonism
α_2 Agonist		α_2-receptor stimulation
ANGIOTENSIN-CONVERTING ENZYME INHIBITORS		Interfering dry cough
Angiotensin receptor blockers		?
Loop diuretics	Insomnia	Nocturia
CORTICOSTEROIDS	Insomnia, sleepiness also reported	Multiple effects on HPA axis; effects on cytokines
THEOPHYLLINE	Insomnia?	Adenosine antagonist