# Antidepressant and Antipsychotic Drugs

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**KEYWORDS**

• Antidepressant drugs • Antipsychotic drugs
• Pharmacologic effects • Sleep-wake effects

The antidepressant and antipsychotic drugs are a set of agents with a wide range of different pharmacologic effects. Many of these pharmacologic effects have an impact on sleep-wake function. This can involve promoting sleep, promoting wakefulness, altering the amount or timing of sleep stages across the night, and increasing the likelihood of restless legs syndrome (RLS) and/or periodic movements of sleep, which can disturb sleep. Depending on the time of day of administration, the pharmacokinetics of the drug, the dose of the drug, and the context, some of these effects may be therapeutic and some may be adverse. For example, when administered at bedtime to a patient with sleep difficulty, the sleep-promoting effects of an antipsychotic medication can be therapeutic. If that medication is administered in the morning or if the combination of dosage and half-life of the medication result in next-day effects, however, the sleep promotion associated with this medication can be problematic. Some of the effects on sleep-wake function of these medications, such as altering the amount or timing of sleep stages, are of uncertain clinical significance but have long been of interest in terms of research that pursues whether or not these changes might be linked to therapeutic effects, such as antidepressant effects, sleep restoration, and improvement in negative symptoms in schizophrenia.

This article reviews the pharmacology and associated sleep-wake effects of the antidepressant and antipsychotic medications. It discusses factors relevant to these effects, such as pharmacokinetic properties, dosing, and therapeutic target. Comprehensive review of the clinical trials related to the use of these agents for the treatment of sleep-wake disorders are not covered in this article but are included in articles in Part II of this volume (**Table 1**).

## PHARMACOLOGIC MECHANISMS OF ANTIDEPRESSANTS AND ANTIPSYCHOTICS: EFFECTS ON SLEEP-WAKE FUNCTION

### *Promoting Sleep by Blocking the Activity of Wake-Promoting Neurotransmitters*

Sleep promotion occurs with antidepressants and antipsychotics that block receptors that mediate the wake-promoting effects of several neurotransmitters, including the serotonin (5-hydroxytryptamine [HT]) type 2 receptor (5-HT2), histamine (H1) receptors, muscarinic acetylcholine (Ach) receptors, norepinephrine receptors, and dopamine (DA) receptors.[1–6] These effects can potentially improve sleep at night but also have the potential to cause daytime sedation.

#### *5-HT2 antagonism*

The 5-HT system and its effects on sleep are complex. There is some evidence in both human and animal studies that suggests, however, that agents that selectively block 5-HT2 receptors improve the ability to stay asleep.[7–10] The inconsistency of findings in such studies has led to the hypothesis that the sleep-promoting effects of 5-HT2 antagonism may depend on the ratio of effects on 5-HT2A and 5-HT2C receptor subtypes as well as other factors. These data, however, along with the tendency of antidepressant and antipsychotic medications that have 5-HT2 antagonist effects to enhance sleep, have led to the general belief that 5-HT2 antagonism may be associated with sleep enhancement.

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**Table 1**
**Pharmacologic mechanisms of sleep-wake effects of antidepressants and antipsychotics**

| Mechanism | Sleep Promotion | Wake Promotion | REM Suppression | Increases SWS | Promotes RLS/PLMS |
|---|---|---|---|---|---|
| H1 antagonism | √ | | | | |
| Ach antagonism | √ | | √ | | |
| 5-HT2 antagonism | √ | | | √ | |
| $\alpha_1$-Antagonism | √ | | | | |
| $\alpha_2$-Antagonism | | √ | | | |
| D1/D2 antagonism | √ | | | | √ |
| 5-HT reuptake inhibition | | √ | √ | | √ |
| NE reuptake inhibition | | √ | | | |
| DA reuptake inhibition | | √ | | | |
| MAO inhibition | | √ | √ | | √ |
| 5-HT1A agonism | | √ | √ | | |

*Abbreviations:* NE, norepinephrine; SWS, slow-wave sleep.

### *Histamine antagonism*

Histamine is one of the most important wake-promoting neurotransmitter systems in the brain. It mediates its effects by binding to the H1 receptor.[1] Agents that increase histamine's release and binding to H1 receptors enhance wakefulness.[11]

Many antidepressant and antipsychotic agents block these H1 receptors and, thereby, promote sleep.[12,13] Although there is ample experience with agents with H1 antagonism, few data exist on the sleep-wake effects of medications with H1 antagonism effects and minimal effects on other receptor systems. As a result, understanding of the sleep-wake effects of H1 antagonism remains limited. Recent studies have been performed with doxepin at dosages from 1–6 mg where it seems to be a selective H1 antagonist (discussed later).[14,15] The data suggest that H1 antagonism may have its greatest sleep-enhancing effects at the end of the night. In these studies, differences between doxepin and placebo were greatest in hours 7 to 8 of the night despite achieving peak blood level 1.5 to 4 hours after dosing.[14,15] These data suggest that the sleep enhancement of H1 antagonism is dissociated from blood level and may be more related to time of day. Further evidence to support this conclusion and to suggest that the sleep-enhancing effects may be affected by activity level as well is that doxepin (1−6 mg) was not associated with sedation when assessed after waking; just 1 hour after the peak, sleep-enhancing effect was observed.[14,15]

### *$\alpha_1$-Adrenergic antagonism*

The wake-promoting effects of norepinephrine in the central nervous system are well established and believed to be mediated at least in part by $\alpha_1$ receptors.[1,16] This mechanism is believed to be responsible for some of the arousal achieved by stimulants, such as dextroamphetamine and methylphenidate.[16] On this basis, antidepressant and antipsychotic medications that block $\alpha_1$ receptors are believed to have sleep-enhancing effects.[17,18]

### *Dopamine antagonism*

Like norepinephrine, DA is also believed to be an important wake-promoting neurotransmitter.[1] There is evidence that some of the wake-promoting effects of the stimulants, dextroamphetamine and methylphenidate, are mediated through increasing dopaminergic activity at both D1 and D2 receptor subtypes.[16] Antipsychotic medications block these receptors and are believed to be associated with some degree of sleep-promoting effects as a result.[13]

### *Cholinergic antagonism*

Ach is one of the most important neurotransmitters mediating arousal.[19] For example, cholinergic neurons form the core of the brainstem reticular activating system.[20] Some of the arousal effects of Ach seem to be mediated via muscarinic cholinergic receptors, which are blocked by any antidepressant and antipsychotic medications, resulting in a decrease in arousal and promotion of sleep.[21]