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Initiate the antipsychotic at a reasonable, not overly high dose, then use a nonantipsychotic to help control insomnia, anxiety, and agitation

on PSYCHOTICS

Manage, don't accept adverse 'calming' effect

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Sedation is a frequent side effect of antipsychotics, especially at relatively high doses. Antipsychotics' sedative effects can reduce agitation in acute psychosis and promote sleep in insomnia, but long-term sedation may:

- interfere with schizophrenia patients' efforts to go to work or school or engage in normal socialization
- prevent improvement from psychosocial training, psychiatric rehabilitation, and other treatments.

This article discusses how to manage acute psychosis without oversedation and ways to address persistent sedation and chronic insomnia with less-sedating antipsychotics or adjunctive medications.

Neurobiology or psychopharmacology?

Many patients experience only mild, transient somnolence at the beginning of antipsychotic treatment, and most develop some tolerance to the sedating effects with continued administration. Others may have persistent daytime sedation that interferes with normal functioning.

Sedation is especially common in elderly patients receiving antipsychotics. Compared with younger patients, older patients receiving the same doses of the same medications become more heavily sedated for longer periods of time. The resulting sedation can impair arousal levels during the day and increase the risk of falls.

continued



Sedation

Clinical Point

Choose the initial antipsychotic for its effectiveness, rather than relying on its side effects to control disease manifestations

Table 1
Antipsychotics' potency, dosages, and sedative properties

Medication	Relative potency (mg)*	Common dosage (mg/d)	Sedation
First-generation antipsychotics			
Chlorpromazine	100.0	300 to 600	Moderate
Fluphenazine	1.0 to 2.0	4 to 20	Mild
Haloperidol	2.0	5 to 20	Mild
Second-generation antipsychotics			
Aripiprazole	7.5	15 to 30	Mild
Clozapine	50.0	250 to 500	Marked
Olanzapine	4.0	15 to 30	Moderate
Quetiapine	80.0	300 to 800	Moderate
Risperidone	1.0	2 to 6	Mild
Ziprasidone	20.0	80 to 160	Mild

* Approximate dose equivalent to 100 mg of chlorpromazine

Source: Data from reference 9.

Sedation can occur with first-generation antipsychotics (FGAs) and second-generation antipsychotics (SGAs), but it is seen more commonly and tends to be more severe with low-potency FGAs than with SGAs. Clinical challenges come with:

- distinguishing between sedation and negative symptoms of schizophrenia such as avolition, amotivation, withdrawal, and anhedonia
- determining whether an individual's cognitive impairment is related to the antipsychotic's sedative properties.

Because the treatments are different, it is important to try to distinguish negative symptoms and/or cognitive impairment related to schizophrenia's neurobiology from sedation related to the antipsychotic. Ask patients if they nap during the day or just lie around, and if they want to do things but can't:

- If they want to do things but feel too tired, this likely is sedation caused by the antipsychotic. Treatment might be a dose reduction.
- If they are not interested in doing things, the likely cause is negative symptoms. Treatment might be a medication such as a selective serotonin reuptake inhibitor.
- If they want to do things but cannot organize themselves to be able to do them, this likely is cognitive impairment. Treatment might be cognitive training or remediation.

Efficacy and sedation

Antipsychotics are thought to exert their effect by antagonism of postsynaptic dopamine D2 and serotonin 5HT2A receptors and possibly other receptors in the brain. Four SGAs—risperidone, olanzapine, quetiapine, and ziprasidone—act as dopamine D2 and 5HT2A antagonists. Aripiprazole is a dopamine D2 partial agonist, serotonin 5HT1A partial agonist, and serotonin 5HT2A antagonist.¹ Efficacy data comparing SGAs with each other and with FGAs vary, but all 5 of these SGAs have been shown to be effective antipsychotics.²⁻⁴ They also generally cause less sedation than FGAs.

Patients with acute exacerbation of psychosis often have insomnia and frequently report paranoia that "something" will happen to them while they sleep. When treating agitated patients, many clinicians consider calming effects and true antipsychotic effects to be one in the same, which is not correct. All available antipsychotics are, on average, equally effective in treating acute psychotic symptoms but vary considerably in the amount of sedation they produce. Studies of short-acting injectable SGAs, such as ziprasidone and aripiprazole, have shown that agitation and acute symptoms can be controlled without significant sedation.^{5,6}

Antipsychotic effects are not immediate and historically were thought to occur

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Table 2

Antipsychotics' sedative effects by the numbers: Equilibrium dissociation constants at brain receptors*

	Receptors		
	Dopamine D2	Serotonin 5-HT2A	Histamine H1
FGA			
Haloperidol	2.60	61.00	260.0
SGAs			
Aripiprazole	0.34	3.40	61.00
Clozapine	210.00	2.60	3.10
Olanzapine	20.00	1.50	0.10
Risperidone	3.80	0.15	5.20
Quetiapine	770.00	31.00	19.00
Ziprasidone	2.60	0.12	4.60

* Lower numbers are equivalent to higher receptor binding affinity. Each antipsychotic's sedative effect is determined by histamine H1 affinity and the amount of drug that reaches H1 receptors in the CNS—which in turn is affected by the agent's dosage and dopamine D2 receptor affinity.

FGA: first-generation antipsychotic; SGAs: second-generation antipsychotics

Source: References 1,14,15

over several weeks. Recent meta-analyses suggest, however, that some antipsychotic effects are evident within the first week of treatment.^{7,8} To avoid overmedication, therefore, it's important to separate calming effects from antipsychotic effects.

Recommendations. Choose the initial antipsychotic based on its effectiveness in treating the underlying disease, rather than relying on side effects—such as sedation—to control disease manifestations. Without sedation, patients are better able to engage in therapy; participate in family, social, school, and work activities; and increase their chances of recovery.

Initiate the antipsychotic at or titrate to a reasonable, not overly high dose—such as:

- olanzapine, 10 to 20 mg/d
- risperidone, 3 to 6 mg/d
- ziprasidone, 100 to 140 mg/d
- quetiapine, 400 to 600 mg/d
- aripiprazole, 15 mg/d.

Continue the patient on that dose, and use a nonantipsychotic such as a benzodiazepine to help control insomnia, anxiety, and agitation. Two to 4 weeks is generally adequate, but some patients may need the adjunctive therapy for several months. If you initiate a more sedating antipsychotic acutely, switching to a less sedating agent when the patient is stable and the illness

is in remission may support adherence and improve outcomes.

Dosages and sedation. Not all FGAs have the same sedative effect, nor do all SGAs (Table 1, page 40).⁹ In general, the high-milligram, low-potency FGAs—such as chlorpromazine—produce more sedation than the low-milligram, high-potency FGAs—such as haloperidol and fluphenazine.⁹ This principle tends to hold true for the SGAs as well. For example, the high-potency, low-dose SGA risperidone is less sedating than the lower-potency, high-dose SGAs quetiapine and clozapine.

Dose does not always determine sedation, however. Olanzapine, which is commonly dosed at 15 to 30 mg/d, is more sedating than ziprasidone, for which the usual range is 80 to 160 mg/d.^{3,10-12}

Mechanism and sedation

The mechanisms of antipsychotics' therapeutic and sedative properties appear to be different.¹³ The degree of sedation shows little relationship with the various antipsychotics' potency at the dopamine D2 receptor, which suggests that dopamine D2 receptor antagonism is not involved in causing sedation.

Instead, the degree of sedation may be associated with each antipsychotic's affinity

Clinical Point

The combination of H1 affinity and the amount of drug reaching the histamine H1 receptors determines the sedative effect



Sedation

Clinical Point

Patients with sleep disturbances may feel more rested after awakening because SGAs have potential to improve sleep quality

Table 3

Normal sleep architecture, which can be disordered in schizophrenia

Nonrapid eye movement (NREM) sleep	
Stage 1	Drowsiness; represents transition between waking and sleeping
Stage 2	Sleep deepens
Stages 3 and 4	Deepest levels of NREM sleep; subjects are most difficult to arouse (slow-wave or delta sleep)
Rapid eye movement (REM) sleep	
Vivid dreams; pulse and respiration rates are higher and more variable than during NREM sleep	
During the second half of the night, slow-wave sleep decreases compared with the first half of the night, but REM periods become more frequent and prolonged.	

for the histamine H1 receptor, which is highly variable (Table 2, page 43).^{1,14,15} In general:

- agents that are more potent histamine H1 antagonists—such as olanzapine and clozapine¹⁴—produce more sedation
- agents that are weaker H1 antagonists—such as risperidone, ziprasidone, and aripiprazole—produce less sedation.

Although dosage and affinity for histamine H1 receptors play important roles in the sedative effect of a medication, what ultimately determines sedative effect is the combination of histamine H1 affinity and the amount of drug reaching the histamine H1 receptors in the CNS.

For example, the SGA quetiapine—which has moderate affinity for histamine H1 receptors¹⁴—also has relatively low affinity for dopamine D2 receptors. Higher dosages of quetiapine are therefore required to produce antipsychotic effects compared with other SGAs—such as risperidone, ziprasidone, and aripiprazole—that have higher affinities for the dopamine D2 receptors.

Because of higher dosing, higher amounts of quetiapine are assumed to be reaching the histamine H1 receptors in the CNS. This is why quetiapine causes more sedation in clinical use than does risperidone, even though risperidone has greater affinity for the histamine H1 receptor.

Sleep patterns in mental illness

Sleep disturbances—including changes in sleep patterns, insomnia, and excessive sleeping—occur frequently in patients with psychiatric disorders. The sleep process itself (Table 3) is disrupted in patients with schizophrenia.

A study that examined sleep patterns in 40 patients with schizophrenia found longer sleep latency, more frequent arousals, and increased periods of wakefulness after sleep onset compared with controls without a psychiatric disorder. Ratings of sleep efficiency—ratio of sleep time to time in bed—were:

- 95% in the control group
- 78% in antipsychotic-naïve patients with schizophrenia
- 72% in patients with chronic schizophrenia.¹⁵

A study of sleep in 19 patients with schizophrenia and 13 nonpsychiatric controls¹⁶ found individuals with schizophrenia had:

- increased duration of stage 1 sleep
- decreased duration of stages 3 and 4 (slow-wave) sleep
- 83% total sleep efficiency, compared with 95% in nonpsychiatric controls.

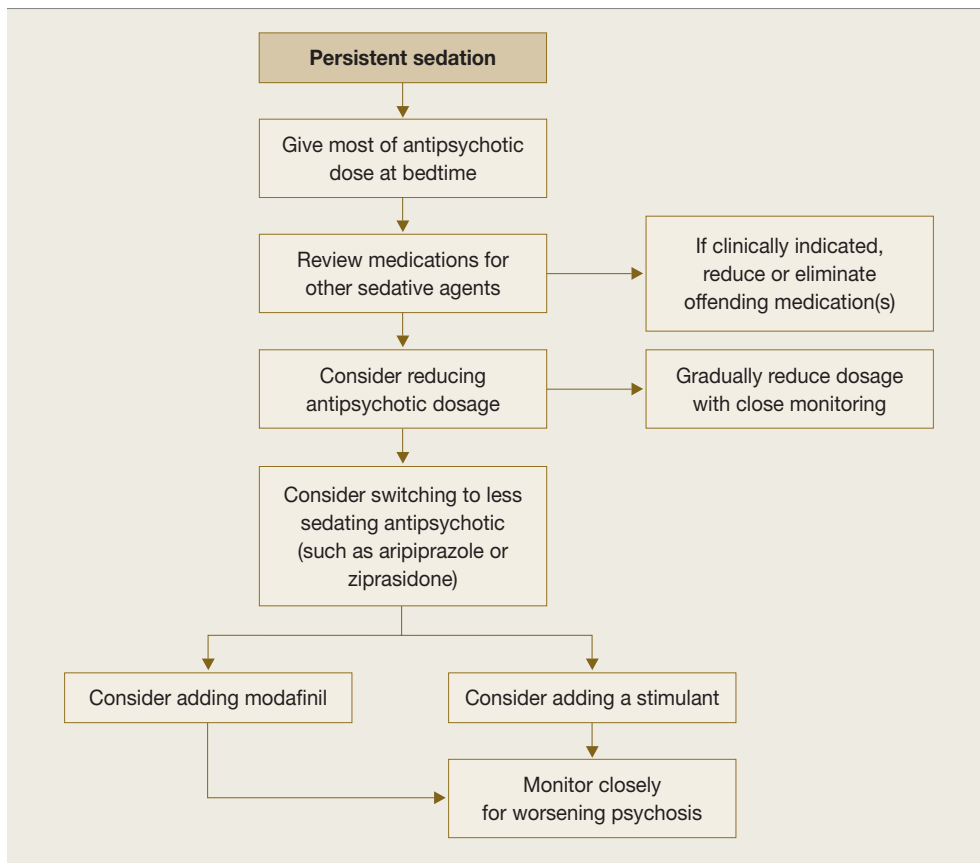
Because of these differences in sleep patterns, patients with schizophrenia often experience inadequate sleep.

Antipsychotic effects on sleep patterns.

Your choice of an antipsychotic also can affect the patient's sleep. In a study of sleep measures in patients with schizophrenia treated with risperidone or haloperidol, Yamashita et al¹⁷ reported a significant difference in the time each group spent in slow-wave sleep (27% with risperidone vs 20% with haloperidol). The authors suggested that risperidone might lengthen the amount of slow-wave sleep because of its higher affinity for serotonin 5-HT₂ receptors compared with haloperidol.

Salin-Pascual et al¹⁸ found that olanzapine improved total sleep time and sleep efficacy, reduced stage 1 sleep, and significantly enhanced stage 2 and slow-wave (delta) sleep.

Managing sedation in patients with schizophrenia



Serotonin 5-HT₂ receptors have been reported to be involved in controlling sleep quality.¹⁹ Similar to risperidone and olanzapine, the other SGAs also have a higher affinity than haloperidol for serotonin 5-HT₂ receptors (*Table 2, page 43*). Thus, although antipsychotics' sedative effects may adversely affect patients, SGAs may have the potential to improve sleep quality in individuals with schizophrenia. SGAs increase slow-wave sleep, and patients feel more rested after awakening.

Managing excessive sedation

Take steps to minimize bothersome sedation in patients taking antipsychotics (*Figure*). To reduce daytime sedation, instruct the patient to take all or most of the antipsychotic dose at bedtime. Also rule out medical conditions that can produce fatigue and sedation, such as hypothyroidism, obstructive sleep apnea (OSA), and restless legs syndrome.

Review the patient's medication list to determine if other potentially sedating medications can be reduced or eliminated. Psychotropics that can cause sedation include:

- antidepressants such as the tricyclics and mirtazapine
- mood stabilizers (particularly valproic acid, but also carbamazepine, lithium, and lamotrigine).

Also consider gradually reducing the patient's antipsychotic dose, and closely monitor for worsening of psychosis.

If sedation persists despite these interventions, consider switching the patient to a less sedating antipsychotic such as ziprasidone or aripiprazole. If these efforts also are ineffective, caffeine or off-label bupropion—75 to 100 mg once in the morning or up to twice daily—might help the patient feel more alert. Many patients taking antipsychotics drink several cups of coffee every morning to feel less sedated.

Clinical Point

Amphetamine-type stimulants could worsen psychosis, so their use in patients with persistent sedation is controversial



Sedation

Clinical Point

Caffeine might help the patient feel more alert; many patients taking antipsychotics drink several cups of coffee every morning

Table 4

Sedatives to treat insomnia in patients with schizophrenia

Medication	Common bedtime dose range*
Benzodiazepines	
Estazolam	1 to 2 mg
Flurazepam	15 to 30 mg
Temazepam	7.5 to 30 mg
Triazolam	0.125 to 0.25 mg
Benzodiazepine agonists	
Eszopiclone	2 to 3 mg
Zaleplon	5 to 10 mg
Zolpidem	5 to 10 mg
Zolpidem CR	6.25 to 12.5 mg
Melatonin receptor agonist	
Ramelteon	8 mg
H1 antihistamines	
Diphenhydramine	25 to 50 mg
Hydroxyzine	50 to 100 mg
Antidepressants	
Mirtazapine	15 to 30 mg
Trazodone	50 to 200 mg

* No dosage adjustment is required in this patient population

Stimulants. A consensus guideline on treating schizophrenia²⁰ recommends prescribing amphetamine-related stimulants for patients who are persistently sedated, but this practice is highly controversial. Many stimulants increase dopamine release in the CNS, which theoretically can worsen psychosis. A clinician could be held liable for the actions of patients medicated with stimulants.

Modafinil is a nonamphetamine CNS stimulant approved for use in disorders of excessive sleep such as narcolepsy, OSA, shift work sleep disorder, and fatigue related to multiple sclerosis. Its mechanism of action in promoting wakefulness in these disorders is not fully understood; it may activate histaminergic projections in the frontal cortex from the tuberomammillary nucleus, which plays a major role in maintaining wakefulness.²¹

Modafinil, 200 mg in the morning, has been reported to reduce total sleep time without adverse effects in 3 patients experiencing sedation associated with anti-

psychotics.²² A later double-blind, placebo-controlled trial by Sevy et al²³ found that modafinil and placebo were associated with similar, significant improvement in fatigue over time. Narendran²⁴ reported a case in which modafinil might have exacerbated psychosis in a patient with schizophrenia who was taking 200 mg qid.

Managing chronic insomnia

Schizophrenia patients with chronic insomnia usually require education about appropriate sleep habits, combined with additional treatments.

Sleep hygiene. Instruct patients to:

- Wake up at the same time every day, regardless of when they went to sleep.
- Maintain a consistent bedtime.
- Exercise regularly, preferably in the late afternoon but not within 2 to 4 hours of bedtime.
- Perform relaxing activities before bed.
- Keep the bedroom quiet and cool (extreme temperatures compromise sleep).
- Do not watch the clock at night.
- Avoid caffeine and nicotine for at least 6 hours before bedtime.
- Drink alcohol only in moderation, and avoid use for at least 4 hours before bedtime.
- Avoid napping; it may interfere with the ability to fall asleep at night.

Medications. The consensus guideline on treating schizophrenia²⁰ offers the option of switching the patient with chronic insomnia to one of the more sedating antipsychotics, such as olanzapine, quetiapine, or clozapine. Sedation alone should not be the reason to switch to clozapine, however.

You could consider adding a bedtime sedative to the patient's medications (*Table 4*). FDA-approved sedatives include non-benzodiazepines such as zolpidem, zolpidem extended-release, zaleplon, or eszopiclone, and the melatonin receptor agonist ramelteon. Although not approved as sedatives, some antidepressants such as trazodone or mirtazapine and antihistamines such as diphenhydramine and hydroxyzine

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are used to promote sleep. Benzodiazepines can be helpful but require caution when prescribed to patients with comorbid substance abuse disorders.

Sedatives have been studied extensively in general populations with insomnia but not in patients receiving antipsychotics. Combining antipsychotics and sedatives can produce daytime drowsiness and sedation.

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Related Resources

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Drug Brand Names

Aripiprazole • Abilify	Mirtazapine • Remeron
Bupropion • Wellbutrin	Modafinil • Provigil
Carbamazepine • Tegretol	Olanzapine • Zyprexa
Chlorpromazine • Thorazine	Quetiapine • Seroquel
Clozapine • Clozaril	Ramelteon • Rozerem
Diphenhydramine • Benadryl	Risperidone • Risperdal
Estazolam • ProSom	Temazepam • Restoril
Eszopiclone • Lunesta	Trazodone • Desyrel
Fluphenazine • Prolixin	Triazolam • Halcion
Flurazepam • Dalmane	Valproic acid • Depakote
Haloperidol • Haldol	Zaleplon • Sonata
Hydroxyzine • Vistaril, Atarax	Ziprasidone • Geodon
Lamotrigine • Lamictal	Zolpidem • Ambien, Ambien CR

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Clinical Point

When used to manage insomnia, adding sedatives to antipsychotic therapy can result in daytime drowsiness and sedation

Bottom Line

All antipsychotics are effective in reducing psychotic symptoms but vary in degree of sedation. For persistent sedation, consider nighttime dosing, rule out other sedating drugs or conditions, or switch antipsychotics. Consider adding a stimulant or modafinil, but monitor for worsening psychosis. For persistent insomnia, provide sleep hygiene education and consider adding a bedtime sedative.