Atypical Antipsychotics: Sedation Versus Efficacy

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Many patients with schizophrenia or bipolar disorder experience disturbances in their sleep-wake cycle, which may be a result of the disorder itself, of pharmacotherapy, or of a comorbid sleep disorder. These sleep disruptions can seriously impair patients' functioning as well as their quality of life. Therefore, accurate assessment of sleep problems is essential to appropriately treat patients and promote symptomatic remission. Sedating antipsychotics may ameliorate sleep disturbances, as well as agitation or other behavioral emergencies; however, these agents may also sedate patients to the point of dissatisfaction with the medication and/or impaired functioning, which may, in turn, increase treatment noncompliance and nonadherence. Using short-term adjunctive medications, such as benzodiazepines or hypnotic agents, with a nonsedating antipsychotic to alleviate sleep disturbances is a reasonable treatment option for patients with schizophrenia or bipolar disorder. Overall, the pharmacokinetics and pharmacodynamics of atypical antipsychotics are important factors to consider in the risk-benefit analysis, as are dosing strategies and individual patient factors, and clinicians must decide which agents are most appropriate for which patients.

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SLEEP DISTURBANCES IN PATIENTS WITH SCHIZOPHRENIA AND BIPOLAR DISORDER

Patients with schizophrenia or bipolar disorder commonly experience sleep disturbances.[1–4] These disruptions can seriously impair patients' functioning as well as their quality of life,[5,6] and any changes in patients' regular sleep-wake cycle may indicate an upcoming psychotic or syndromal relapse.[4,7,8]

Schizophrenia

According to the International Classification of Sleep Disorders,[1] insomnia and excessive sleepiness are common features of psychosis in patients with schizophrenia, and most psychotic patients experience some degree of sleep disruption when their illness is worsening. Monti and Monti[7] found that sleep-onset insomnia and maintenance insomnia are problematic for both never-medicated and previously medicated patients with schizophrenia. In patients with untreated schizophrenia, insomnia was found to be a prodromal symptom of psychotic relapse and decompensation.[4] Additionally, comorbid sleep disorders are also common in patients with schizophrenia, and sleep problems can also be exacerbated or induced by antipsychotic pharmacotherapy.[4]

Sleep architecture has been measured by electroencephalogram (EEG), electrooculogram (EOG), and electromyogram (EMG). Rapid eye movement (REM) sleep follows 4 stages of nonrapid eye movement (NREM): stage 1 sleep is the initial stage and has low-voltage waves (4–7 Hz) in the theta range, with slow eye movements; stage 2 sleep is characterized by sleep spindles (12–16 Hz) and K complexes (100 μV); stage 3 is the beginning of slow-wave sleep or deep sleep and transitions into stage 4 sleep with delta waves (0.5–3 Hz or slower and 75mV or greater); and stage 4 sleep is an intense slow-wave sleep of delta-wave activity over 50%.[3] REM sleep begins after a cycle of the first 4 stages of sleep and has low-voltage, mixed-frequency activity, much like that of stage 1 sleep, with heightened brain activity and short bursts of eye movements.[3] A meta-analysis[3] of sleep architecture studies in patients with schizophrenia found reduced duration of stage 4 sleep and reduced REM latency, although duration of REM sleep appeared to remain unchanged. Additionally, sleep-onset insomnia and mainte-

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TAKE-HOME POINTS

- Understand that sleep disruptions may be an inherent characteristic of schizophrenia or bipolar disorder symptomatology, or may result from antipsychotic treatment, poor sleep hygiene, or a comorbid psychiatric or sleep disorder
- Take a proactive approach in addressing sleep disturbances in the acute setting
- Be aware that treatment decisions have long-term implications
- Distinguish between the sedating side effects and the calming therapeutic effects of antipsychotic medications
- Use a short-term adjunctive treatment to target sleep disruption, if necessary
- Continually evaluate the risks and benefits of pharmacotherapy
- Select the most appropriate agents to optimize patients' outcomes

nance insomnia were associated, not with a particular phase of the illness or with treatment status, but rather with the illness itself.[3] A study[9] assessing delta-wave sleep deficits in patients with schizophrenia showed reduced visually scored delta sleep as well as reduced delta-wave counts but not REM counts, which indicates that delta-sleep deficits in this population may be related to the primary disorder of schizophrenia and not an iatrogenic disorder resulting from its treatment. Although these findings indicate a relationship between sleep disruptions and schizophrenia, future research is needed on areas of the central nervous system related to NREM and REM sleep in this disorder.[7]

Bipolar Disorder

At least 90% of patients with mood disorders experience a sleep disturbance at some point in their lives.[1] According to the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (DSM-IV),[10] criteria for a manic episode include a decreased need for sleep, that is, patients feel rested after sleeping for 3 hours or less, and criteria for a major depressive episode include insomnia or hypersomnia nearly every day for at least 2 weeks.

Sleep problems may either trigger or intensify mood states. Bauer et al.[8] found that sleep dysregulation in patients with bipolar disorder is often a warning sign of manic or depressive relapse and indicated that any change of more than 3 hours in patients' sleep-wake cycle may signal an impending mood change in the next 24 hours. A study[11] of 34 patients with bipolar disorder showed a significant relationship between sleep duration and manic symptomatology ($p = .01$); the shorter time the patients slept, the more intense their manic symptoms were the next day. Conversely, sleep loss has been shown to improve mood in people experiencing a depressive episode.[12] In a study[13] of 26 patients with either bipolar or unipolar depression, 25% remitted and 20% improved after sleep deprivation, thus illustrating the important effects of sleep and sleep duration on syndromal relapse and improvement.

ASSESSING SLEEP DISTURBANCES IN SCHIZOPHRENIA AND BIPOLAR DISORDER

Because sleep disturbances are often not the predominant complaint from patients with schizophrenia or bipolar disorder, clinicians may become preoccupied with the presenting symptoms of the illness; however, obtaining an in-depth sleep history is essential to identify the cause of the sleep disturbance.[5,14] Clinicians should have a 24-hour perspective of patients' habits and sleep patterns, including assessing behaviors and cognitive activities associated with sleep (sleep hygiene), sleep latency, sleep duration and nighttime awakenings, daytime nap taking, specific sleep disturbances and symptoms, overall quality of sleep, and day-to-day variability in patients' sleep. Clinicians should also obtain a thorough history of patients' general medical and psychiatric conditions, functional impairments, cognitive function, mood, current medications, previous and current substance use (including the use of illicit substances, alcohol, and caffeine), and life circumstances, including active and chronic stressors and environmental factors that may affect their sleep hygiene. Asking patients a few screening questions at every visit can help clinicians ascertain the nature of the sleep disturbance and determine the most appropriate course of treatment (Table 1).

Screening tools, such as the Pittsburgh Sleep Quality Index (PSQI),[15] the Insomnia Severity Index (ISI),[16] and the Women's Health Initiative Insomnia Rating Scale (WHIIRS),[17] are available to assess insomnia in patients with schizophrenia or bipolar disorder (Appendix 1), although these tools were originally developed to assess primary insomnia as opposed to sleep disturbances in psychiatric illnesses. These tools do not necessarily have to be used in routine clinical scenarios, but clinicians should be aware of them and be familiar with their language. The PSQI is a self-rated questionnaire that assesses sleep quality and sleep disturbances over the past month. Seven component scores are generated for the patient based on subjective sleep quality, sleep latency, sleep duration,

Table 1. Screening Questions to Assess Patients' Sleep Disturbances

Do you go to bed at the same time every night or does your bedtime vary?
How long does it take you to fall asleep?
How many times do you wake up during the night?
Once you wake up, can you go back to sleep?
What time do you wake up in the morning?
Do you use caffeine, alcohol, or illicit substances?

habitual sleep efficiency, sleep disturbances, the use of sleep medication, and daytime dysfunction. From these 7 scores, 1 global score (0–21) designates the patient as a good or a poor sleeper. In an 18-month assessment[15] of clinimetric properties, a global PSQI score of greater than 5 indicated poor sleep quality and differentiated between good (N = 52) and poor (N = 116) sleepers with 89.6% diagnostic sensitivity and 86.5% specificity ($p < .001$). Buysse et al.[15] concluded that the PSQI was a consistent and valid instrument for assessing sleep disturbances in both psychiatric and research settings.

The ISI is a self-report questionnaire of 7 items, each scored from 0 to 4, that provide information about sleep satisfaction, perceived severity of initial as well as maintenance insomnia and early morning awakenings, levels of impairment and distress/worry caused by sleep problems, and perceived noticeability of one's sleep problems to others. The ISI yields a global score from 0 to 28, with any score of 15 or greater indicating moderate to severe insomnia. A study[16] examined the internal consistency and concurrent validity of the ISI by comparing patients' global scores with their respective sleep diaries and polysomnography results, as well as with those scores obtained from significant others and clinicians. Bastien et al.[16] found this self-report measure to have adequate internal consistency and to be a clinically effective tool in evaluating patients' perceived insomnia or sleep difficulties.

The WHIIRS is an easy-to-administer, 5-item self-report questionnaire that assesses sleep latency, maintenance insomnia, early morning awakening, and sleep quality over the past month. The items are scored from 0 to 4 and total a global score from 0 to 20, with higher scores indicating greater insomnia. An epidemiologic study[17] of almost 66,300 postmenopausal women found the reliability of the WHIIRS to be 0.786. A test-retest reliability sample of 2887 women found the correlation for same-day retests to be 0.96, whereas tests and retests separated by more than 1 year had a reliability of 0.66. Overall, Levine et al.[17] concluded that the WHIIRS questionnaire may provide clinically meaningful results.

Other, more time-consuming assessment measures include polysomnography, which is the combination of the EEG, EOG, and EMG,[3] or the Multiple Sleep Latency Test (MSLT).[5] These tools may be used to accurately diagnose serious sleep disorders (e.g., sleep apnea, periodic limb movement disorder, and narcolepsy) but should not be routinely used to screen patients who complain of sleep disturbances or insomnia.[5]

ADVANTAGES AND DISADVANTAGES OF SEDATING ATYPICAL ANTIPSYCHOTICS

Prescribing sedating atypical antipsychotics in patients with schizophrenia or bipolar disorder can be advantageous in the acute management of syndromal or psychotic relapse. Sedating agents will ameliorate insomnia and regulate patients' sleep-wake cycle, which is an important therapeutic goal over the course of treatment. Other benefits of using sedating antipsychotics during the acute phase of treatment include resolving behavioral emergencies and managing agitation and restlessness.

Most patients develop a tolerance to the sedating effects of these agents after the acute phase, and the initial sedation therefore poses no long-term problems. However, a substantial minority of patients continue to experience persistent sedation or somnolence, which impacts on quality of life. Patients may complain of impairments in their normal functioning in vocational, academic, social, and recreational activities, which can cause dissatisfaction with the medication. Although patients may not be able to accurately describe their symptom as persistent sedation, they may complain that they have no energy, that they constantly feel tired, or that they cannot think clearly. Patients' families may also indicate that patients do not want to get out of bed or participate in any activities, which may increase the burden on the caregiver. Additionally, persistent sedation can contribute to weight gain and other metabolic risk factors, which may add to patients' overall dissatisfaction with the medication and contribute to long-term health risks.[18,19] Patients with sedation may also suffer from impaired cognitive and motor performance,[20–24] resulting in increased risk for injurious accidents (e.g., car accidents)[25] and causing patients further dissatisfaction due to interference in their daily lives. Patients who are dissatisfied with their medication may discontinue the treatment or may become nonadherent, for example, by decreasing their dosage of medication with or without alerting their physician, which can lead to suboptimal medication efficacy. Sedating atypical antipsychotics may also contribute to the perceived stigma of taking medications.

Sedation may also increase the risk of falls as a result of patients not paying attention to where they are going. Another factor that increases the risk of falls is α_1-receptor blockade of antipsychotics, which can induce orthostasis,[20–22,26] resulting in dizziness.[27] Clinicians should be aware of orthostasis in at-risk populations, such as the elderly, those with low blood pressure, and those who are dehydrated, and titrate the dosage accordingly. Extrapyramidal symptoms (EPS), by impairing patients' gait, can also increase the risk of falls. In a study[27] of 2005 elderly patients taking antipsychotics, similar hazard ratios were

reported for typical agents (1.35), risperidone (1.32), and olanzapine (1.74). Thus, despite the decrease in EPS with atypical antipsychotics compared with conventional antipsychotics, atypical agents were not associated with fewer falls.[27]

PHARMACOKINETICS AND PHARMACODYNAMICS OF ATYPICAL ANTIPSYCHOTICS

Understanding the differences in the pharmacokinetic and pharmacodynamic profiles of atypical antipsychotics is essential to prescribing the appropriate medication for each individual patient. For example, knowing the half-life and peak plasma concentration levels of each medication, as well as the neurotransmitter systems involved in atypical antipsychotic mechanisms of action, can help clinicians formulate a comprehensive risk-benefit analysis to determine not only the best treatment choice but also an appropriate dosing strategy. For example, some agents require dose titration to reach a therapeutic level, while others do not. Pharmacokinetics can influence the speed of titration, which may affect the speed of onset of efficacy.

Pharmacokinetics

Aripiprazole[20] has a mean elimination half-life of 75 hours, and steady-state concentrations are achieved within 14 days of administration. Because of this long half-life, changes in dose may not have an immediate therapeutic effect, and patients should expect to wait a few days. Elimination of aripiprazole is primarily through hepatic metabolism, acting at the cytochrome P450 (CYP450) enzymes CYP2D6 and CYP3A4, and shows no effect on the metabolization of other agents with these enzymes. Oral aripiprazole[20] is well absorbed after dosing, reaching peak plasma concentrations in 3 to 5 hours, and has a bioavailability of 87%. The co-administration of food may or may not affect these levels. Intramuscular aripiprazole[20] reaches peak plasma concentrations at a median of 1 to 3 hours, and the mean maximum concentration is approximately 19% higher than that achieved with the oral formulation. The absolute bioavailability of the intramuscular formulation is 100%.

Clozapine[24] has average steady-state peak plasma concentration of 319 ng/mL (range, 102–771 ng/mL) following a dose of 100 mg b.i.d., which occurs at 2.5 hours (range, 1–6 hours), and food does not appear to affect this bioavailability. The mean elimination half-life of clozapine after a 75-mg dose averages 8 hours (range, 4–12 hours), and the mean elimination half-life after a 100-mg b.i.d. dose is 12 hours (range, 4–66 hours). Clozapine is a substrate for the CYP450 enzymes (1A2, 2D6, and 3A4, specifically), and caution should be used when administering other agents that inhibit or induce these enzymes.

Oral olanzapine[21] is well absorbed after administration and reaches peak plasma concentration about 6 hours after dosing, which is not affected by the co-administration of food. The half-life ranges from 21 to 54 hours, and plasma clearance ranges from 12 to 47 L/h, although these calculations may vary according to age, gender, and smoking status. Intramuscular olanzapine[21] is rapidly absorbed, reaching peak plasma concentrations in 15 to 45 minutes; although this rate is much faster than that for oral olanzapine, the half-life remains similar. Both formulations are primarily metabolized via direct glucuronidation and CYP450 enzyme–mediated oxidation, possibly involving the CYP1A2 and CYP2D6 enzymes according to in vitro studies, with a minor metabolic pathway in vivo through the CYP2D6 enzyme.

Quetiapine[22] is rapidly absorbed after administration and reaches peak plasma concentrations in approximately 1.5 hours. The relative bioavailability of quetiapine is 100% and is moderately affected when administered with food. The mean terminal half-life is 6 hours, and steady-state concentrations are expected to be reached within 2 days of dosing. Quetiapine is highly metabolized by the CYP3A4 isoenzyme in the liver. Because it does not inhibit or induce CYP450 enzymes, it is unlikely to interfere with other agents that are metabolized by this system.

Risperidone[23] is well absorbed and reaches mean peak plasma concentrations at approximately 1 hour. The absolute bioavailability is 70% and relative bioavailability is 94%, and neither is affected by the ingestion of food. Risperidone is converted to an active metabolite (9-hydroxyrisperidone) by the CYP2D6 isoenzyme and steady-state concentrations are achieved in approximately 5 days. Because risperidone weakly binds to and is predominantly metabolized by the CYP2D6 enzyme, it is not likely to interfere with drugs metabolized by this enzyme.

Oral ziprasidone[26] reaches peak plasma concentration in 6 to 8 hours, and the bioavailability of a 20-mg dose is about 60%. When taken with food, absorption of this agent increases up to 2-fold. Oral ziprasidone has a half-life of approximately 7 hours, and steady-state concentrations are usually achieved within 1 to 3 days of initial dosing. Ziprasidone is metabolized in the liver by aldehyde oxidase and CYP3A4 enzymes and is unlikely to interfere with medications that are metabolized by CYP450 enzymes. Intramuscular ziprasidone[26] reaches peak serum concentration at approximately 1 hour and has a mean half-life of 2 to 5 hours.

Pharmacodynamics

Atypical antipsychotics act at several neurotransmitter sites, including dopaminergic, serotonergic, adrenergic, histaminergic, and cholinergic muscarinic receptors (Table 2).[20–22,26,28] Receptor activity has various associated side effects, such as somnolence and weight gain with histaminic action, cognitive impairment with cholinergic muscarinic action, and orthostatic hypotension with adrenergic action.

Table 2. Relative Binding Affinity of Atypical Antipsychotics to Specific Neuroreceptors[a]

	Antipsychotic					
Receptor	Aripiprazole[b] (K_i, nM)	Clozapine[c] (K_i, nM)	Olanzapine[d] (K_i, nM)	Quetiapine[e] (IC_{50}, nM)	Risperidone[c] (K_i, nM)	Ziprasidone[f] (K_i, nM)
D_1	...	...	11	1268	...	...
D_2	0.34	256	...	329	6.5	4.8
D_3	0.8	...	...	...	...	7.2
D_4	44	...	31	...	...	...
5-HT_{1A}	1.7	104.8	...	717	427.5	3.4
5-HT_{2A}	3.4	5.4	4	148	0.17	0.4
5-HT_{2C}	15	17	11	...	35	1.3
α_1	57	1.64	19	94	5	10
H_1	61	1.2	7	30	15	47
M_1	> 1000[g]	...	73	> 5000	...	> 1 μM[g]

[a]Ellipses indicate data not presented.
[b]Data from Otsuka America Pharmaceutical, Inc.[20]
[c]Data from Kroeze et al.[28]
[d]Data from Eli Lilly and Company.[21]
[e]Data from AstraZeneca Pharmaceuticals, LP.[22]
[f]Data from Pfizer, Inc.[26]
[g]IC_{50}.
Abbreviations: 5-HT = serotonin, α = adrenergic, D = dopamine, H = histamine, IC_{50} = concentration that inhibits 50%, M = muscarine, nM = nanomolar.

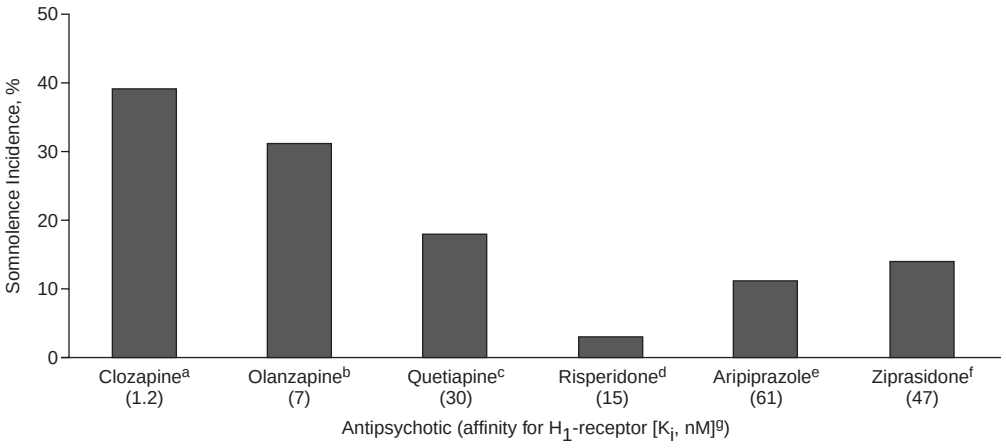
According to labeling information, aripiprazole[20] has a high affinity for dopamine D_2 and D_3 receptors and serotonin 5-HT_{1A} and 5-HT_{2A} receptors; a moderate affinity for dopamine D_4 receptors, serotonin 5-HT_{2C} receptors, α_1-adrenergic receptors, and histamine H_1-receptors; and almost no affinity for cholinergic muscarinic receptors. Clozapine[24] has a high affinity for dopamine D_4 receptors and acts as an antagonist at adrenergic, cholinergic, histaminergic, and serotonergic receptors. Olanzapine[21] has a high affinity for serotonin 5-HT_{2A} and 5-HT_{2C} receptors; dopamine D_1, D_2, D_3, and D_4 receptors; histamine H_1 receptors; and α_1-adrenergic receptors and has a moderate affinity for muscarinic M_1 receptors. Quetiapine[22] is an antagonist at serotonin 5-HT_{1A} and 5-HT_{2A} receptors, dopamine D_1 and D_2 receptors, histamine H_1 receptors, and α-adrenergic receptors, but has no appreciable affinity for cholinergic muscarinic receptors. Risperidone[23] has a high affinity for serotonin 5-HT_{2A} receptors, dopamine D_2 receptors, α-adrenergic receptors, and histamine H_1 receptors; has a low to moderate affinity for serotonin 5-HT_{1A} and 5-HT_{1C} receptors; has a weak affinity for dopamine D_1 receptors; and has no affinity for cholinergic muscarinic receptors. Ziprasidone[26] has a high antagonist activity at dopamine D_2 and D_3 receptors, serotonin 5-HT_{1A}, 5-HT_{2A}, and 5-HT_{2C} receptors, and α_1-adrenergic receptors; has a moderate affinity for histamine H_1 receptors; and has no appreciable affinity for cholinergic muscarinic receptors.

Histamine H_1-receptor antagonism. Of the neurotransmitter systems affected by antipsychotics, blockade of the histamine H_1 receptor is most associated with sedation, somnolence, and weight gain.[28–30] Histamine H_1-receptor antagonism is linked with changes in sleep architecture, specifically a reduction in REM sleep and induced sedation and drowsiness, resulting in a reduction in cognitive function, impairments in performances that require attention, and an increased risk of accidents.[29,31,32] Similarly, histamine H_1-receptor antagonism has also been shown to decrease wakefulness and increase slow-wave sleep.[33] Further, functional and behavioral studies have implicated histamine receptors in regulating circadian and other rhythmic functions as well as patients' sleep-wake cycle.[34–37]

Olanzapine[21] and clozapine[24] are the most potent histamine H_1-receptor antagonists, whereas quetiapine,[22] risperidone,[23] aripiprazole,[20] and ziprasidone[26] have weaker affinity for the histamine H_1 receptor (Figure 1). Somnolence rates vary, with some correspondence to histamine affinity. According to labeling information, the histamine H_1-receptor antagonism of olanzapine,[21] quetiapine,[22] and ziprasidone[26] may account for the somnolence associated with these medications.

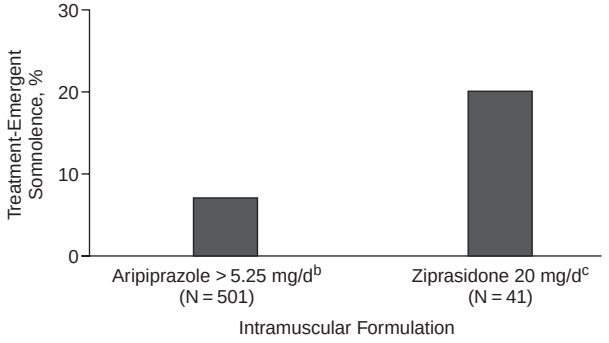
Discrepancies exist between evidence-based and clinical practices when using atypical antipsychotics regarding sedation secondary to histamine H_1-receptor affinity. Much of the pharmacodynamic data[28] comes from animal studies and does not consider clinical dosing, adjunctive medications such as benzodiazepines, and individual variability. For example, olanzapine is dosed in 5-mg intervals while ziprasidone is dosed in 20-mg intervals, a difference that may change the sedative effect of each agent. Additionally, although quetiapine has a moderate affinity for the histamine H_1-receptors, its affinity for this receptor is much higher than its affinity for any other receptors, and because this medication is commonly prescribed at higher milligram dosages than other atypical antipsychotics, it is frequently associated with sedation.[38] For intramuscular formulations, discrepancies can also be seen between the low-sedating agents aripiprazole and ziprasidone. Both of

Figure 1. Somnolence Incidence and H_1-Receptor Affinity of Atypical Antipsychotics



[a]Data from Novartis Pharmaceuticals Corporation.[24]
[b]Data from Eli Lilly and Company.[21]
[c]Data from AstraZeneca Pharmaceuticals, LP.[22] This value is IC_{50}.
[d]Data from Janssen, LP.[23]
[e]Data from Otsuka America Pharmaceutical, Inc.[20]
[f]Data from Pfizer, Inc.[26]
[g]Data from Kroeze et al.[28]

Figure 2. Treatment-Emergent Somnolence With Low-Sedating Intramuscular Aripiprazole and Intramuscular Ziprasidone[a]



[a]Treatment-emergent somnolence occurring in more than 1% of patients.
[b]Data from Otsuka America Pharmaceutical, Inc.[20]
[c]Data from Pfizer, Inc.[26]

these medications have a moderate histamine H_1-receptor affinity, yet the rates of somnolence differ considerably (Figure 2).[20,26] Although these specific rates are for treatment of acute agitation in patients with schizophrenia or bipolar disorder, this discrepancy may be due to the clinical administration of each agent; ziprasidone is often prescribed at higher milligram doses than aripiprazole, making this antipsychotic appear more sedating. Therefore, when treating patients with atypical antipsychotics, clinicians should examine the receptor affinities but should also consider dosing and other variables.

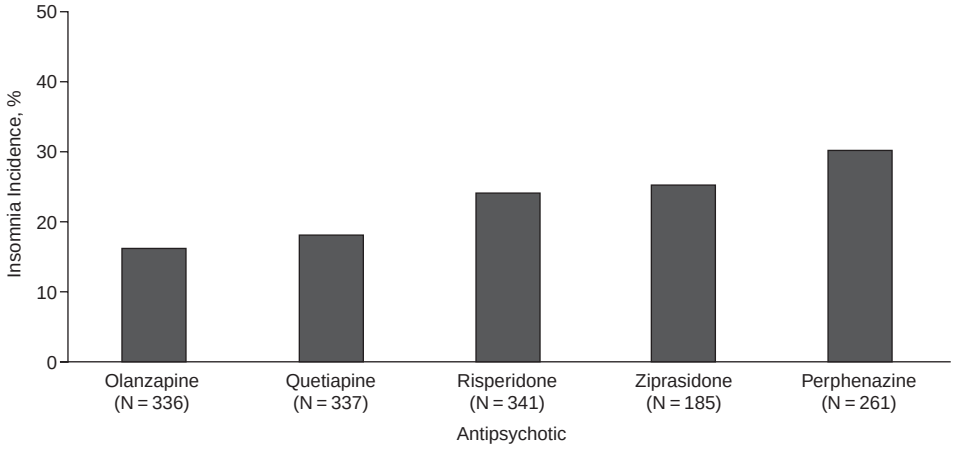
CATIE TRIAL RESULTS ON DISCONTINUATION, INSOMNIA, AND HYPERSOMNIA/SLEEPINESS

The Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE)[39] were funded by the National Institute of Mental Health with the goal of comparing the efficacy, safety, and tolerability of the atypical antipsychotics olanzapine, quetiapine, risperidone, and ziprasidone with the typical antipsychotic perphenazine. Ziprasidone was not included in the study until approximately 40% of patients were already enrolled, when it received approval by the U.S. Food and Drug Administration. This research predated the availability of aripiprazole and paliperidone.

The study[39] included 1493 patients diagnosed with schizophrenia according to the DSM-IV[10] criteria whose ages ranged from 18 to 65 years. Patients were excluded if they had schizoaffective disorder, mental retardation, or other cognitive disorders; had only 1 episode of schizophrenia; had experienced adverse reactions to any of the antipsychotics included in the study; had a history of treatment resistance; were pregnant or breast-feeding; or had a severe medical illness. All antipsychotic capsules were identical in appearance, and the mean modal dosages per day were 20.1 mg of olanzapine, 543.4 mg of quetiapine, 3.9 mg of risperidone, 112.8 mg of ziprasidone, and 20.8 mg of perphenazine.

Discontinuation of treatment for any reason (e.g., efficacy failure, side effect intolerability, and patient or physician decision) was the primary outcome measurement of the CATIE study.[39] By 18 months of follow-up, 74% of patients had discontinued the study medication. Overall

Figure 3. CATIE Reported Adverse Events: Rates of Insomnia[a,b]



[a]Data from Lieberman et al.[39]
[b]p < .001; p values for percentages are from a Poisson regression accounting for differential exposure times and adjusting for whether the patient had had an exacerbation in the preceding 3 months.
Abbreviation: CATIE = Clinical Antipsychotic Trials of Intervention Effectiveness.

time to treatment discontinuation for any cause was significantly longer with olanzapine than with quetiapine ($p < .001$), risperidone ($p = .002$), ziprasidone ($p = .028$), and perphenazine ($p = .021$); however, the differences between olanzapine and ziprasidone, and olanzapine and perphenazine, were not significant after adjusting for multiple comparisons (required p value ≤ .013 and ≤ .017, respectively).

The overall time to treatment discontinuation for lack of efficacy was also significantly longer with olanzapine than with quetiapine ($p < .001$), risperidone ($p < .001$), ziprasidone ($p = .026$), and perphenazine ($p < .001$). Again, differences between olanzapine and ziprasidone were not significant after adjusting for multiple comparisons (required p value ≤ .013). Treatment discontinuation as a result of intolerable side effects significantly differed between antipsychotics ($p = .04$), with risperidone having the lowest rate at 10% and olanzapine having the highest rate at 18%. The most intolerable side effects resulting in antipsychotic discontinuation were weight gain (ranging from 1% with perphenazine to 9% with olanzapine), EPS (ranging from 2% with olanzapine to 8% with perphenazine), and sedation (ranging from 0% with ziprasidone to 3% with quetiapine and perphenazine). Although these side effects were the most intolerable, the most frequently reported adverse events in this study were insomnia and hypersomnia/sleepiness. Olanzapine and quetiapine had slightly lower rates of insomnia than risperidone, ziprasidone, and perphenazine (Figure 3), and rates of hypersomnia or sleepiness were similar across all antipsychotics (Figure 4). However, patients were allowed to take concomitant medications in the CATIE study,[39] many of which had sedative properties, and this could have minimized differences in the relative rates of sedation of the various antipsychotics.

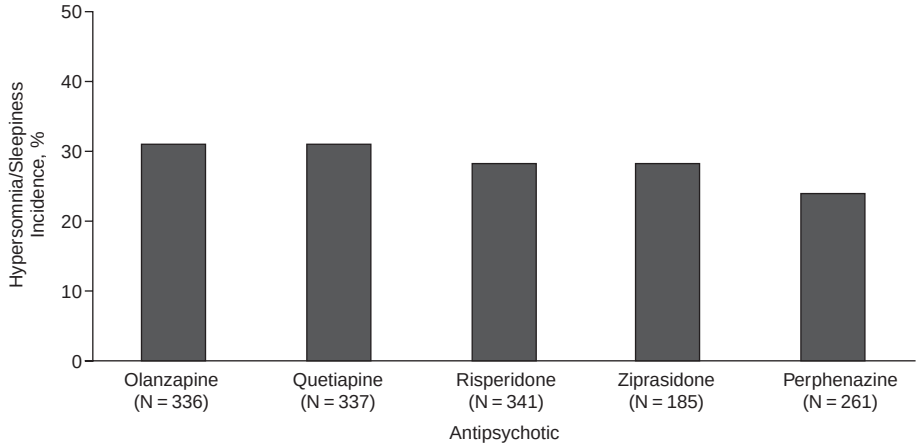
The CATIE study[39] demonstrated the high rates of discontinuation and medication switches that occur with antipsychotics. Because insomnia is a common symptom of this illness, antipsychotics may mitigate insomnia or may induce hypersomnia depending on the sedative potential of the medication. Therefore, it is essential that clinicians ascertain their patients' sleep disturbances at first assessment and conduct a risk-benefit analysis when prescribing antipsychotics to determine the most appropriate medication that will have the least intolerable adverse effects.

ACUTE TREATMENT

Clinicians may commonly encounter hyperarousal, disruption in the sleep-wake cycle, increased psychomotor activity, agitation, and mood dysregulation in patients with schizophrenia who are experiencing an acute relapse. When making drug selection decisions in the acute setting, clinicians must take into account the goals of treatment of the acute psychotic relapse as well as long-term goals of maintenance therapy to effectively stabilize patients and optimize outcomes.

Case report 1. A 26-year-old man with schizophrenia, Mr. A, was brought to the emergency department by his parents because of worsening symptoms over the past 10 days, which include pacing most of the night, talking to himself, and being reluctant to leave his bedroom. During the psychiatric evaluation, Mr. A exhibits hypervigilance, persecutory delusions, and auditory hallucinations; he continues pacing in the hallway, although he is not aggressive or threatening;

Figure 4. CATIE Reported Adverse Events: Rates of Hypersomnia/Sleepiness[a,b]



[a]Data from Lieberman et al.[39]
[b]p = .18; p values for percentages are from a Poisson regression accounting for differential exposure times and adjusting for whether the patient had had an exacerbation in the preceding 3 months.
Abbreviation: CATIE = Clinical Antipsychotic Trials of Intervention Effectiveness.

and his urine toxicology screen is negative. The attending psychiatrist's assessment is that Mr. A is experiencing an acute psychotic exacerbation of schizophrenia.

Short-term goals in the clinical management of the acute stage of relapse in schizophrenia include ensuring the safety of the patient and of the hospital staff members, controlling the patient's agitation, ameliorating the patient's anxiety, initiating appropriate and specific treatment for the dominant psychotic symptoms, and regulating the patient's disrupted sleep-wake cycle. To accomplish these goals, clinicians can implement several pharmacotherapeutic strategies that will help the patient attain remission and effectively transition the patient into maintenance therapy. If the patient is not currently taking an antipsychotic and one must be selected, clinicians should differentiate between the sedating effects and the therapeutic effects of these agents. Sedation may be a desirable effect to calm the patient and to reduce anxiety, but sedation is not essential to the therapeutic value of the antipsychotic agent, as most atypical antipsychotics reduce hostility and excitement through mechanisms other than sedation.[40] If a sedating antipsychotic is used, the patient may experience an immediate improvement in sleep and a gradual improvement in the underlying psychopathology. Unfortunately, using sedating atypical antipsychotics may also result in persistent daytime sedation if the patient does not develop tolerance to the sedating effects; additionally, these agents are more likely to be associated with weight gain compared with less sedating atypical antipsychotics.[39]

If a nonsedating atypical antipsychotic is used, the patient will experience a gradual improvement in sleep as the underlying psychopathology improves. One solution to accelerating the patient's sleep improvement is to initially augment with a benzodiazepine or a hypnotic agent. Benzodiazepines can be used to augment the patient's current antipsychotic for effective short-term alleviation of the patient's agitation, anxiety, and insomnia.[3] A review[41] of 11 trials (N = 701) found that combination treatment with a benzodiazepine and an antipsychotic was superior to monotherapy with either agent in emergency settings. Therefore, clinicians could implement this treatment in an acute setting, for the few days that the patient is in the hospital, but adjunctive benzodiazepines should not be considered a long-term intervention. A benzodiazepine could be kept at the patient's home for use in the event of a one-night sleep disruption. A short-term alternative to benzodiazepines, if motor activity is not marked, is a hypnotic agent to help the patient sleep at night for the first week or two. When the sleep patterns and the underlying psychopathology improve, the hypnotic should be withdrawn, and the patient transitioned to maintenance treatment.

MAINTENANCE TREATMENT

After effectively stabilizing the patient during an acute phase of relapse, clinicians should transition the patient into maintenance therapy via the patient's current antipsychotic. Long-term treatment goals for the management of schizophrenia include maintaining the therapeutic effect of the chosen antipsychotic and minimizing the side effect burden, as well as monitoring for substance abuse, stressors that may trigger relapse, treatment adherence, and the emergence of comorbid disorders.

Case report 2. Mr. B, a 25-year-old male patient diagnosed with schizophrenia, has shown adequate response to his medication and has been recently discharged from his third hospitalization in the past 4 years. Mr. B is employed part-time in a sporting goods store as part of a supportive employment program and appears to be functioning well overall. However, his rehabilitation counselor has communicated to the psychiatric team that Mr. B may be overmedicated and has been sleeping during the day and has difficulty participating in rehabilitation activities because of sleepiness and a lack of energy, which Mr. B has also complained about in his follow-up visits.

When confronted with patients who are achieving a response with the current medication but are also experiencing adverse events, clinicians should evaluate the medication in a risk-benefit analysis to decide if the therapeutic effects of the medication outweigh the side effects. In Mr. B's case, somnolence and fatigue may resolve with tolerance and do not warrant switching his medication; however, clinicians are sometimes faced with a dilemma when adverse events are severe and negatively affect patients' overall quality of life to the point of being intolerable; such situations may warrant switching medications. However, several strategies can be used to manage daytime somnolence in the maintenance setting before drastic interventions, such as switching the patient's medication, are necessary. For example, clinicians can eliminate all other sedating agents that the patient is taking, switch the time of dosing of the medication to late evening or bedtime so that the maximum sedation (C_{max}) occurs at night,[23] check the patient for thyroid dysfunction, and make sure that the patient is not taking over-the-counter medications or illicit substances that may be causing the somnolence and fatigue. Additionally, patients should be educated about the benefits of good sleep hygiene, such as having the same bedtime every night. Clinicians should also assess patients for concomitant depressive symptoms, which may be an early sign of psychotic relapse, and treat the patient accordingly.

If the patient still experiences these side effects, clinicians may need to consider a slow and cautious reduction in the current dosage of the medication.[23] As a last-resort intervention, clinicians may switch the patient to a less-sedating agent, such as risperidone, ziprasidone, or aripiprazole.[42,43] If somnolence and fatigue continue to persist, clinicians may prescribe alerting agents like modafinil, bupropion, or stimulants, although the use of these medications is controversial.[44] For patients with bipolar disorder, the concern with using these agents is that they may precipitate rapid cycling by inducing a manic episode. However, one study[45] found no evidence of stimulant-induced manic switching, and adjunctive stimulants were well-tolerated in this population. Thus, the researchers concluded that augmenting stimulants may be a reasonable option for treating medication-induced sedation, although more studies are needed to establish this strategy as a legitimate pharmacotherapeutic intervention. Additionally, having the patient ingest the natural alerting agent caffeine, such as by drinking coffee, may also be helpful in ameliorating the sedating effects of atypical antipsychotics.

CONCLUSION

In conclusion, clinicians should routinely assess their patients with schizophrenia or bipolar disorder for disruptions in their sleep-wake cycle. These disturbances may be prodromal symptoms of psychotic or syndromal relapse, and addressing them early may prevent symptomatic exacerbation in those patients. Using sedating atypical antipsychotics can adequately treat sleep disturbances in these patients; however, long-term treatment with these agents may result in more disadvantages than advantages. Instead, clinicians can use short-term adjunctive medications, such as benzodiazepines or hypnotics, with a nonsedating antipsychotic to help bring about remission, and then taper off the augmenting agent. In this way, patients can benefit from the full therapeutic effects of the antipsychotic without experiencing long-term sedation and somnolence. However, clinicians should always conduct a risk-benefit analysis and decide which medication is appropriate for each individual patient. Sedating atypical antipsychotics may be the best choice for some patients, whereas nonsedating agents may be ideal for others.

REVIEW QUESTION

In addition to histamine H_1-receptor affinity, what factors do you consider when selecting medications to treat your patients with schizophrenia or bipolar disorder who experience sleep dysregulation?

Drug names: aripiprazole (Abilify), bupropion (Wellbutrin and others), clozapine (Clozaril, FazaClo, and others), haloperidol (Haldol and others), modafinil (Provigil), olanzapine (Zyprexa), paliperidone (Invega), quetiapine (Seroquel), risperidone (Risperdal), ziprasidone (Geodon).

Disclosure of off-label usage: The authors have determined that, to the best of their knowledge, no investigational information about pharmaceutical agents that is outside U.S. Food and Drug Administration–approved labeling has been presented in this article.

REFERENCES

1. American Academy of Sleep Medicine. International Classification of Sleep Disorders, Revised: Diagnostic and Coding Manual. Chicago, Ill: American Academy of Sleep

Medicine; 2001. Available at: http://www.absm.org/PDF/ICSD.pdf. Accessed June 27, 2007
2. Costa e Silva JA. Sleep disorders in psychiatry. Metabolism 2006;55(suppl 2):S40–S44
3. Monti J, Monti D. Sleep disturbance in schizophrenia. Int Rev Psychiatry 2005;17:247–253
4. Benson K. Sleep in schizophrenia: impairments, correlates, and treatment. Psychiatr Clin North Am 2006;29: 1033–1045
5. Chesson A Jr, Hartse K, Anderson WM, et al, for the Standards of Practice Committee of the American Academy of Sleep Medicine. Practice parameters for the evaluation of chronic insomnia: an American Academy of Sleep Medicine report. Sleep 2000;23:237–241
6. Hofstetter J, Lysaker P, Mayeda A. Quality of sleep in patients with schizophrenia is associated with quality of life and coping. BMC Psychiatry 2005;5:13 Available at: http://www.biomedcentral.com/1471-244X/5/13. Accessed Aug 28, 2007
7. Monti J, Monti D. Sleep in schizophrenia patients and the effects of antipsychotic drugs. Sleep Med Rev 2004;8: 133–148
8. Bauer M, Grof P, Rasgon N, et al. Temporal relationship between sleep and mood in patients with bipolar disorder. Bipolar Disord 2006;8:160–167
9. Keshavan MS, Reynolds CF, Miewald MJ, et al. Delta sleep deficits in schizophrenia: evidence from automated analyses of sleep data. Arch Gen Psychiatry 1998;55:443–448
10. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition. Washington, DC: American Psychiatric Association; 1994
11. Barbini B, Bertelli S, Colombo C, et al. Sleep loss, a possible factor in augmenting manic episode. Psychiatry Res 1996;65:121–125
12. Demet E, Chicz-Demet A, Fallon J, et al. Sleep deprivation in depressive illness and Parkinson's disease. Prog Neuropsychopharmacol Biol Psychiatry 1999;23:753–784
13. Larsen J, Lindberg M, Skovgaard B. Sleep deprivation as treatment for endogenous depression. Acta Psychiatr Scand 1976;54:167–173
14. Hoyt BD. Sleep in patients with neurologic and psychiatric disorders. Prim Care 2005;32:535–548
15. Buysse DJ, Reynolds CF 3rd, Monk TH, et al. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. Psychiatry Res 1989;28: 193–213
16. Bastien C, Vallieres A, Morin C. Validation of the Insomnia Severity Index as an outcome measure for insomnia research. Sleep Med 2001;2:297–307
17. Levine D, Kripke D, Kaplan R, et al. Reliability and validity of the Women's Health Initiative Insomnia Rating Scale. Psychol Assess 2003;15:137–148
18. Collaborative Working Group on Clinical Trial Evaluations. Adverse effects of the atypical antipsychotics. J Clin Psychiatry 1998;59(suppl 12):17–22
19. Wetterling T. Bodyweight gain with atypical antipsychotics: a comparative review. Drug Saf 2001;24:59–79
20. Abilify [package insert]. Tokyo, Japan: Otsuka America Pharmaceutical, Inc; 2006. Available at: http://www.otsuka.com/documents/AbilifyFullPI.pdf. Accessed June 6, 2007
21. Zyprexa [package insert]. Indianapolis, Ind: Eli Lilly and Company; 2006. Available at: http://pi.lilly.com/us/zyprexa-pi.pdf. Accessed April 17, 2007
22. Seroquel [package insert]. Wilmington, Del: AstraZeneca Pharmaceuticals; 2006. Available at: http://www.astrazeneca-us.com/pi/seroquel.pdf. Accessed Jan 31, 2007
23. Risperdal [package insert]. Titusville, NJ: Janssen, L.P.; 2007. Available at: http://www.janssen.com/active/janus/en_US/assets/common/company/pi/risperdal.pdf. Accessed June 25, 2007
24. Clozaril [package insert]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; 2005. Available at: http://www.pharma.us.novartis.com/product/pi/pdf/Clozaril.pdf. Accessed June 25, 2007
25. Ramaekers J. Behavioural toxicity of medicinal drugs: practical consequences, incidence, management and avoidance. Drug Saf 1998;18:189–208
26. Geodon [package insert]. New York, NY: Pfizer, Inc; 2007. Available at: http://www.pfizer.com/pfizer/download/uspi_geodon.pdf. Accessed June 6, 2007
27. Hien le TT, Cumming RG, Cameron ID, et al. Atypical antipsychotic medications and risk of falls in residents of aged care facilities. J Am Geriatr Soc 2005;53:1290–1295
28. Kroeze WK, Hufeisen SJ, Popadak BA, et al. H1-histamine receptor affinity predicts short-term weight gain for typical and atypical antipsychotic drugs. Neuropsychopharmacology 2003;28:519–526
29. Richelson E. Receptor pharmacology of neuroleptics: relation to clinical effects. J Clin Psychiatry 1999;60 (suppl 10):5–14
30. Gardner DM, Baldessarini RJ, Waraich P. Modern antipsychotic drugs: a critical overview. CMAJ 2005;172: 1703–1711
31. Howard ME, Desai AV, Grunstein RR, et al. Sleepiness, sleep-disordered breathing, and accident risk factors in commercial vehicle drivers. Am J Respir Crit Care Med 2004;170:1014–1021
32. Nicholson AN, Pascoe PA, Turner C, et al. Sedation and histamine H1-receptor antagonism studies in man with the enantiomers of chlorpheniramine and dimethindene. Br J Pharmacol 1991;104:270–276
33. Monti JM. Pharmacology of the histaminergic system. In: Kales A, ed. Pharmacology of Sleep. The Handbook of Experimental Pharmacology, vol 116. New York, NY: Springer; 1995
34. Monti JM. Involvement of histamine in the control of the waking state. Life Sci 1993;53:1331–1338
35. Onodera K, Yamatodani A, Watanabe T, et al. Neuropharmacology of the histaminergic neuron system in the brain and its relationship with behavioral disorders. Prog Neurobiol 1994;42:685–702
36. Tuomisto L. Involvement of histamine in circadian and other rhythms. In: Watanabe T, Wada H, eds. Histaminergic Neurons: Morphology and Function. Boca Raton, Fla: CRC Press, Inc.; 1991:283–286
37. Inoue I, Yanai K, Kitamura D, et al. Impaired locomotor activity and exploratory behavior in mice lacking histamine H1 receptors. Proc Natl Acad Sci U S A 1996;93: 13316–13320
38. Buckley PF. Receptor-binding profiles of antipscyhotics: clinical strategies when switching between agents. J Clin Psychiatry 2007;68(suppl 6):5–9
39. Lieberman JA, Stroup TS, McEvoy JP, et al. Effectiveness of antipsychotic drugs in patients with chronic schizophrenia.

N Engl J Med 2005;353:1209–1223
40. McEvoy J. Assessment of the acutely agitated patient with psychosis. Presented at the 158th annual meeting of the American Psychiatric Association; May 21–26, 2005; Atlanta, Ga
41. Yildiz A, Sachs GS, Turgay A. Pharmacological management of agitation in emergency settings. Emerg Med J 2003;20:339–346
42. Expert Consensus Guideline Series: Treatment of Schizophrenia 1999. J Clin Psychiatry 1999;60(suppl 11):1–80
43. Sullivan G, Bienroth M, Jones M, et al. Practical prescribing with aripiprazole in schizophrenia: consensus recommendations of a UK multidisciplinary panel. Curr Med Res Opin 2007;23:1733–1744
44. Miller DD. Atypical antipsychotics: sleep, sedation, and efficacy. Prim Care Companion J Clin Psychiatry 2004;6(suppl 2):3–7
45. Carlson PJ, Merlock MC, Suppes T. Adjunctive stimulant use in patients with bipolar disorder: treatment of residual depression and sedation. Bipolar Disord 2004;6:416–420

Questions and Answers

Question: If an adjunctive benzodiazepine or hypnotic agent is added for the short-term alleviation of agitation, how long should clinicians continue the treatment?

Dr. Sharif: Every patient is different and may need varying therapeutic strategies to achieve clinical improvement. However, a useful guiding principle is to use these adjunctive medications for as short of a time as is clinically warranted. Thus, if a benzodiazepine is added to the patient's current antipsychotic and has effectively calmed the patient's agitation or decreased motor activity, the benzodiazepine should be tapered over the next 2 days and should be stopped by the third or the fourth day. This is the general method when treating inpatients whose average hospitalization is 5 to 7 days. Hypnotic drugs may be used somewhat longer, especially if the patient experiences sleep-wake cycle disruptions. However, when administering adjunctive hypnotics, clinicians should keep in mind that antipsychotics may also improve the patient's sleep hygiene as the psychotic episode resolves, and hypnotics may not be necessary to continue in the patient's long-term treatment.

Question: Can clinicians initiate first-time treatment with combination pharmacotherapy to reduce sedation as well as extrapyramidal side effects, such as by using olanzapine and aripiprazole?

Dr. Kane: Although these treatment methodologies may be used in clinical practice, there is insufficient evidence regarding these combinations to make clinical recommendations. Further, the goal of treatment is to use one medication to determine if that particular medication is appropriate for that individual patient. When using multiple medications at the same time, the therapeutic and adverse effects are difficult to attribute to a specific agent.

Question: What is the best route to control acute panic attacks or agitation in the hospital setting?

Dr. Sharif: If an acute panic attack occurs, benzodiazepines are effective and have a rapid onset of action, and therefore would be the most appropriate medication to use in this situation. For agitation, clinicians may use an antipsychotic as monotherapy or use an adjunctive benzodiazepine, especially if the antipsychotic is nonsedating.

Appendix 1.

Pittsburgh Sleep Quality Index (PSQI)[a]

The following questions relate to your usual sleep habits during the past month *only*. Your answers should indicate the most accurate reply for the majority of days and nights in the past month. Please answer all questions.

1. During the past month, when have you usually gone to bed at night?
   USUAL BED TIME _____
2. During the past month, how long (in minutes) has it usually taken you to fall asleep each night?
   NUMBER OF MINUTES _____
3. During the past month, when have you gotten up in the morning?
   USUAL GETTING UP TIME _____
4. During the past month, how many hours of *actual sleep* did you get at night? (This may be different than the number of hours you spend in bed.)
   HOURS OF SLEEP PER NIGHT _____

For the remaining questions, check the one best response. Please answer *all* questions.

5. During the past month, how often have you had trouble sleeping because you...
   (a) Cannot get to sleep within 30 minutes
   ❑ Not during the past month ❑ Less than once a week ❑ Once or twice a week ❑ Three or more times a week
   (b) Wake up in the middle of the night or early morning
   ❑ Not during the past month ❑ Less than once a week ❑ Once or twice a week ❑ Three or more times a week
   (c) Have to get up to use the bathroom
   ❑ Not during the past month ❑ Less than once a week ❑ Once or twice a week ❑ Three or more times a week
   (d) Cannot breathe comfortably
   ❑ Not during the past month ❑ Less than once a week ❑ Once or twice a week ❑ Three or more times a week
   (e) Cough or snore loudly
   ❑ Not during the past month ❑ Less than once a week ❑ Once or twice a week ❑ Three or more times a week
   (f) Feel too cold
   ❑ Not during the past month ❑ Less than once a week ❑ Once or twice a week ❑ Three or more times a week
   (g) Feel too hot
   ❑ Not during the past month ❑ Less than once a week ❑ Once or twice a week ❑ Three or more times a week
   (h) Had bad dreams
   ❑ Not during the past month ❑ Less than once a week ❑ Once or twice a week ❑ Three or more times a week
   (i) Have pain
   ❑ Not during the past month ❑ Less than once a week ❑ Once or twice a week ❑ Three or more times a week
   (j) Other reason(s), please describe _____
   How often during the past month have you had trouble sleeping because of this?
   ❑ Not during the past month ❑ Less than once a week ❑ Once or twice a week ❑ Three or more times a week
6. During the past month, how would you rate your sleep quality overall?
   ❑ Very good ❑ Fairly good ❑ Fairly bad ❑ Very bad
7. During the past month, how often have you taken medicine (prescribed or over-the-counter) to help you sleep?
   ❑ Not during the past month ❑ Less than once a week ❑ Once or twice a week ❑ Three or more times a week
8. During the past month, how often have you had trouble staying awake while driving, eating meals, or engaging in social activity?
   ❑ Not during the past month ❑ Less than once a week ❑ Once or twice a week ❑ Three or more times a week
9. During the past month, how much of a problem has it been for you to keep up enough enthusiasm to get things done?
   ❑ Not a problem ❑ Only a very slight problem ❑ Somewhat of a problem ❑ A very big problem
10. Do you have a bed partner or share a room?
    ❑ No bed partner or do not share a room ❑ Partner/roommate in other room ❑ Partner in same room but not same bed ❑ Partner in same bed
11. If you have a bed partner or share a room, ask him/her how often in the past month you have had...
    (a) Loud snoring
    ❑ Not during the past month ❑ Less than once a week ❑ Once or twice a week ❑ Three or more times a week
    (b) Long pauses between breaths while asleep
    ❑ Not during the past month ❑ Less than once a week ❑ Once or twice a week ❑ Three or more times a week
    (c) Legs twitching or jerking while you sleep
    ❑ Not during the past month ❑ Less than once a week ❑ Once or twice a week ❑ Three or more times a week
    (d) Episodes of disorientation or confusion during sleep
    ❑ Not during the past month ❑ Less than once a week ❑ Once or twice a week ❑ Three or more times a week
    (e) Other restlessness while you sleep, please describe _____
    ❑ Not during the past month ❑ Less than once a week ❑ Once or twice a week ❑ Three or more times a week

(continued)

Appendix 1 (continued).

Insomnia Severity Index (ISI)[b]

1. Please rate the current (i.e., last 2 weeks) SEVERITY of your insomnia problem(s).

	None	Mild	Moderate	Severe	Very
Difficulty staying awake	0	1	2	3	4
Difficulty staying asleep	0	1	2	3	4
Problem waking up too early	0	1	2	3	4

2. How SATISFIED/dissatisfied are you with your current sleep pattern?

Very Satisfied				Very Dissatisfied
0	1	2	3	4

3. To what extent do you consider your sleep problem to INTERFERE with your daily functioning (e.g., daytime fatigue, ability to function at work/daily chores, concentration, memory, mood, etc.)?

Not at All Interfering	A Little	Somewhat	Much	Very Much Interfering
0	1	2	3	4

4. How NOTICEABLE to others do you think your sleeping problem is in terms of impairing the quality of your life?

Not at All Noticeable	Barely	Somewhat	Much	Very Much Noticeable
0	1	2	3	4

5. How WORRIED/distressed are you about your current sleep problem?

Not at All	A Little	Somewhat	Much	Very Much
0	1	2	3	4

Guidelines for scoring/interpretation:

Add scores together for all seven items (1a + 1b + 1c + 2 + 3 + 4 + 5) = _____

Total score ranges from 0–28:
- 0–7 = No clinically significant insomnia
- 8–14 = Subthreshold insomnia
- 15–21 = Clinical insomnia (moderate severity)
- 22–28 = Clinical insomnia (severe)

Women's Health Initiative Insomnia Rating Scale (WHIIRS)[c]

These questions ask you about your sleep habits. Please mark *one* of the answers for each of the following questions. Pick the answer that best describes how often you experienced the situation in the *past 4 weeks.*

	No, not in past 4 weeks	Yes, less than once a week	Yes, 1 or 2 times a week	Yes, 3 or 4 times a week	Yes, 5 or more times a week
1. Did you have trouble falling asleep?	❑	❑	❑	❑	❑
2. Did you wake up several times at night?	❑	❑	❑	❑	❑
3. Did you wake up earlier than you planned to?	❑	❑	❑	❑	❑
4. Did you have trouble getting back to sleep after you woke up too early?	❑	❑	❑	❑	❑
	Very sound or restful	Sound or restful	Average quality	Restless	Very restless
5. Overall, was your typical night's sleep during the past 4 weeks:	❑	❑	❑	❑	❑

[a]Reprinted with permission from Buysse et al.[15]
[b]Reprinted with permission from Bastien et al.[16]
[c]Reprinted with permission from Levine et al.[17]