Switching Antipsychotics: Why, When, and How?

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This article summarizes the reasons for switching an antipsychotic and explains when it becomes necessary to switch, as well as how the switch is best accomplished.

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At the end of this article, readers should be able to:
1. Describe the reasons for switching an antipsychotic.
2. Assess the optimum time to switch.
3. Recognize the best ways to switch.

The need to switch from one antipsychotic drug to another is a frequent challenge in the long-term management of patients with schizophrenia and related psychotic disorders, even when an antipsychotic that is effective for managing acute symptoms is continued during maintenance treatment. For instance, antipsychotic discontinuation rates ranged from 64% (for olanzapine) to 82% (for quetiapine) in the first phase of the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study, despite evidence indicating clinical improvement.1

Although low treatment adherence contributes to the high rates of antipsychotic switching observed in clinical practice, there are specific instances in which deliberately switching from one antipsychotic drug to another is warranted. When switching occurs, the clinical effects (both positive and negative) are uncertain, thus posing considerable challenges to practitioners. Familiarity with common indications (and contraindications) for switching antipsychotics, strategies for selecting and switching medications, and important psychosocial considerations can help patients attain optimal therapeutic outcomes while minimizing the risk of adverse events—including relapse.

Indications for antipsychotic switching
Indications for switching antipsychotic drugs in patients with schizophrenia or bipolar disorder12-14

Reasons for switching antipsychotics fall into 3 broad categories. The first two—inadequate therapeutic response and intolerable adverse effects (Table 1)—were the most common reasons for antipsychotic discontinuation in the CATIE phase 1 study.1 A third common indication is patient and/or caregiver request. Less commonly, switching may be prompted by the need to minimize medication costs (by switching to a less expensive antipsychotic or the generic form of the same drug) or to simplify dosing (by switching to an antipsychotic taken only once daily).

Suboptimal therapeutic response. Despite advances in antipsychotic treatments, some patients respond poorly to a given agent, even when fully adherent. Patients who have a positive response to pharmacotherapy may still be left with persisting symptoms that are associated with poor clinical outcomes and impaired functioning.

For patients who achieve no (or only minimal) clinical benefit, or who have residual impairing symptoms, switching antipsychotics is often indicated. This may be especially so when:
• Clinical factors associated with poor response to treatment have been ruled out (eg, misdiagnosis, comorbidities, poor medication adherence, inadequate dosage or duration of treatment)
• Optimization of antipsychotic dose and/or taking a medication for a long time has not resulted in added benefit
• Further dose increases or combination pharmacotherapy is contraindicated, is not likely to be effective, or is otherwise not feasible
• A patient acutely relapses despite good medication adherence

Thus, before making the decision to switch, great care must be taken to ensure that treatment with the pre-switch antipsychotic was optimized in terms of adherence, treatment duration, and dose. Poor antipsychotic tolerability. Adverse effects are common during short- and long-term treatment with antipsychotics, some of which can be severe or persistent. When adverse effects are clearly attributable to the antipsychotic drug and outweigh clinical benefit or threaten adherence, they become treatment-limiting. Under these circumstances, watchful waiting is typically not practicable,
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and a therapeutic antipsychotic switch may be indicated. Switching may be especially indicated when:

• The antipsychotic dose cannot be lowered because of unacceptable risk of clinical worsening
• A treatment-limiting adverse effect is unlikely to diminish at lower doses
• Specific treatments (such as an anticholinergic medication for managing antipsychotic-induced extrapyramidal effects) for a treatment-limiting adverse effect do not exist, are ineffective, or are contraindicated
• Antipsychotic treatment has resulted in clinically significant increases in glucose or lipid levels, and the patient is unwilling or incapable of adhering to dietary or medical interventions (or dietary or medical intervention is ineffective)

When intolerable adverse effects occur as a result of drug-drug interactions, it is often necessary to reduce the dosage of—or discontinue altogether—the complicating medication. If the complicating medication is medically necessary, no reasonable alternatives to it exist, and lowering the dosage of the antipsychotic or complicating medication is ineffective or should not be attempted, an antipsychotic switch may be indicated. Any proposed changes in a patient’s medication regimen should be discussed with all treatment providers.

Patient and/or caregiver request. Occasionally, patients and/or caregivers will request a switch in antipsychotic drug treatment. These requests can be made on the basis of any of the reasons discussed above. However, such requests can also be prompted by misinformation, misattribution of negative outcomes to medications, ambivalence about drug treatment in general, underappreciation of illness severity, or an incomplete understanding of what antipsychotic treatment alone can accomplish. As much detail as possible about the reasons for requesting a drug switch should be ascertained, especially if the patient has had a positive response to the current medication.

Contraindications to antipsychotic switching

As we have seen, there are advantages to antipsychotic switching for some patients. There are also risks involved, but very few absolute contraindications. Absent a compelling reason to proceed otherwise, switching is generally ill-advised for the following types of patients:

• Those who have recently recovered from an acute psychotic episode and are taking an antipsychotic drug that was clearly beneficial during acute-phase treatment
• Those who are currently stable on long-acting injectable antipsychotics but have a history of clinical instability before using long-acting injectable agents resulting from poor adherence to oral antipsychotics
• Those who are presently stable with a clear positive response to antipsychotic treatment but have a history of violence, self-harm, severe symptoms, or profound self-neglect during acute psychotic episodes

The risk of clinical symptom exacerbation with a new antipsychotic drug may outweigh achievable benefit for these patients. Absent a compelling reason for switching, stable patients who require long-acting injectable antipsychotics to maintain clinical stability should continue on their long-acting injectable therapy. Ideally, patients who can be maintained on oral antipsychotics should be clinically stable for at least 3 to 6 months after resolution of acute-phase symptoms before a switch to an oral antipsychotic is considered, although this is not always possible.

Procedures for antipsychotic switching

Before switching antipsychotics, the specific indication(s) should be clearly identified, and both provider and patient should agree on a specific set of target goals to be achieved by the switch. Myths or unrealistic expectations tied to switching medications should be empathically ascertained and clarified. An assessment of patient readiness for a full therapeutic trial of the post-switch antipsychotic is important. At minimum, the patient and caregivers must be willing to switch medication and comply with more frequent patient visits during the early post-switch period. Other considerations are summarized in Table 2. Attention to these details will help ensure that the reasons for switching and switch objectives are realistic and agreed on; potential complications of switching are anticipated; plans for managing likely complications are in place should they occur; and patients, caregivers, and the treatment team are active participants in the entire switch process. Medication selection. Post-switch medication selection for routine indications will ultimately be determined by the complex interplay between clinical evidence, unique patient characteristics, the clinical pharmacology of the antipsychotic drugs themselves, and patient and provider preferences. Important factors to consider are summarized in Table 2.

Evidence supports switching to clozapine for treatment-resistant schizophrenia and for patients with schizophrenia who are at high risk for suicide. There is also support for switching to a long-acting
injectable antipsychotic for patients with treatment-responsive schizophrenia who are clinically unstable because of poor adherence.4

Beyond these specific indications, there are few direct studies that support the utility of antipsychotic switching for improving efficacy. With the exception of clozapine for treatment-resistant schizophrenia, there appears to be considerable overlap in the effectiveness of most antipsychotics, although some studies have documented improved outcome after switching from a typical neuroleptic to an atypical antipsychotic.5,6 The effects of switching from an atypical antipsychotic to a typical neuroleptic have not been extensively investigated.

On the other hand, the adverse-effect profiles of individual antipsychotics vary considerably and are generally easier to predict—an especially important factor when switching to improve antipsychotic tolerability. Patients who have previously discontinued antipsychotics because of treatment-limiting adverse effects are not likely to adhere to treatment with a new antipsychotic if they experience the same effects. A rational strategy in this circumstance would be to replace a poorly tolerated medication with one that has a lower risk of causing the adverse effect(s) under consideration. Indeed, evidence supports this strategy to reduce extrapyramidal adverse effects, hyperprolactinemia, weight gain, and related dysmetabolic effects.5,7,8 Selection of an appropriate switch strategy: factors to consider13-14

Options for antipsychotic switching. Once a post-switch antipsychotic has been selected, there are several switching options. Each of these options has particular advantages and disadvantages, depending on the clinical situation, patient characteristics, and the specific antipsychotics involved (Table 3). In general, options for switching between oral antipsychotics include:

• Abrupt discontinuation of pre-switch antipsychotic with immediate initiation of a new antipsychotic at clinically effective dosages
• Cross-tapering: gradual tapering (25% to 50% reduction in milligrams per day every 4 or 5 half-lives) of pre-switch antipsychotic with gradual initiation and dose titration of the new antipsychotic; pre-switch antipsychotic is then discontinued when the new antipsychotic is within its clinically effective dosage range
• Overlap and discontinuation: continuing the pre-switch antipsychotic at full therapeutic dosage while initiating and titrating the new antipsychotic; once the new antipsychotic is at a clinically effective dosage, the pre-switch antipsychotic is then tapered and eventually discontinued

No one switch option is uniformly superior to another when switching between oral antipsychotics. Therefore, the decision about which option to adopt must be made on an individual basis. Illness severity, relapse history (including history of suicidal, violent, or other dangerous behaviors), tolerance of previous antipsychotic switches, current level of clinical stability, level of insight, and psychosocial support are all important factors.

In general, greater urgency for switching antipsychotics favors abrupt discontinuation or a very rapid cross-taper (over a period of only a few days). For example, abrupt discontinuation is often preferred when acute, severe adverse effects from the pre-switch antipsychotic occur, such as agranulocytosis with clozapine. Here the risks of rapid switching are clearly outweighed by the severity of the adverse effect.

On the other hand, when the risks associated with acute relapse are the most important clinical factor—or when the urgency of switching is lower (eg, in outpatient settings)—slower cross-tapering (over 4 to 8 weeks) or overlap and discontinuation may be more favorable. Slow tapering of the pre-switch antipsychotic may also be preferred for patients who have a history of poorly tolerating abrupt switching or if the pre-switch antipsychotic has potent anticholinergic properties or sedating effects. Overlap and discontinuation may be a very good option for patients who require an antipsychotic switch but are not yet fully stabilized with the pre-switch antipsychotic or for those who are prone to severe psychotic symptoms or dangerous behaviors if they are under-medicated during a medication switch. Additional guidance for switching between oral antipsychotics is provided in Table 3.

Long-acting injectable antipsychotics: special considerations. Switching from an oral to long-acting injectable antipsychotic is often easy to carry out in most clinical settings. Regardless of agent, the first step is to establish good tolerability of the oral form of the long-acting agent. This can be accomplished by establishing the absence of treatment-limiting adverse effects on therapeutic doses of the oral form of the long-acting antipsychotic. Alternatively, patients who can tolerate 2 oral daily doses of risperidone (1 mg) or paliperidone (3 mg) will likely tolerate the long-acting injectable form of these drugs.

The oral pre-switch antipsychotic should be continued for at least the first 3 weeks at therapeutic

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Table 3

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<thead>
<tr>
<th>Switching Options</th>
<th>Description</th>
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<td>Abrupt discontinuation</td>
<td>Immediate initiation of a new antipsychotic</td>
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<tr>
<td>Cross-tapering</td>
<td>Gradual tapering of the pre-switch antipsychotic</td>
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<tr>
<td>Overlap and discontinuation</td>
<td>Continuation of the pre-switch antipsychotic at full dosage</td>
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Switching from oral antipsychotics other than olanzapine to long-acting injectable olanzapine, however, has not been systematically investigated, and patients should be closely monitored for postinjection sedation, neurological effects, and/or delirium after each olanzapine long-acting injection. For long-acting typical neuroleptics (haloperidol or fluphenazine), the oral antipsychotic can be maintained for 5 days following the first injection of long-acting antipsychotic. Afterward, the oral dose can be tapered and discontinued.\footnote{11}

As discussed earlier, switching patients who are stable on a long-acting injectable antipsychotic to an oral antipsychotic is generally discouraged, unless there is a compelling need to do so. When it is necessary to switch from a long-acting injectable to an oral antipsychotic, the new oral antipsychotic can usually be started immediately, without need for additional doses of the long-acting pre-switch antipsychotic. An additional scheduled injection may be needed, however, if the initiation of the new oral antipsychotic and the next scheduled long-acting injection closely correspond in time, particularly for patients who are highly prone to relapse during gaps in treatment or if the new oral antipsychotic must be initiated at subtherapeutic doses and requires slower titration to its target dose.

**Post-switch follow-up.** Careful patient monitoring and follow-up are required during and after antipsychotic switching. This is generally easier to do when the switch occurs in an inpatient setting. Outpatients who undergo an antipsychotic switch will generally require more frequent visits and/or follow-up contact (including by telephone or through an intensive case manager, as appropriate) during the first several weeks of post-switch follow-up. Once clinical stability and good overall tolerability with the new antipsychotic have been established, the frequency of follow-up visits can be reduced.

Progress toward achieving the goals of the switch should be evaluated at every follow-up encounter. Ideally, the initial target symptoms, adverse effects, and other factors identified and documented during the pre-switch period will be improved, thus providing evidence that the specific objectives of the antipsychotic switch have been attained.

Common problems that arise during the early post-switch period include increased psychotic symptoms, anxiety, agitation, insomnia, and extrapyramidal effects. These may represent adverse effects of the new medication, rebound effects due to withdrawal of the pre-switch antipsychotic, or general anxiety about switching antipsychotics. Depending on their severity, these clinical signs and symptoms can be managed in a variety of ways:

- **Watchful waiting:** if symptoms are mild and are expected to improve and there is good psychosocial support in place
- **Slowly tapering (or restarting) the pre-switch antipsychotic:** to reduce rebound effects or to manage withdrawal dyskinesias or psychotic symptom exacerbations
- **Adding an anticholinergic medication:** to manage extrapyramidal effects or to treat agitation, restlessness, and anxiety related to anticholinergic rebound
- **Adding a benzodiazepine:** to temporarily manage anxiety, restlessness, or insomnia
- **Adding a nonbenzodiazepine sleep medication:** to manage insomnia
- **Dividing the dose of new antipsychotic:** to limit concentration-dependent adverse effects

Concomitant medications that serve as adjuncts to antipsychotic treatment are increasingly common for managing nonpsychotic symptoms of schizophrenia (eg, antidepressants, benzodiazepines, mood stabilizers) or adverse effects from the pre-switch antipsychotic (eg, anticholinergics). In general, these adjuncts should not be discontinued until the transition to a new antipsychotic has been successful. The need for these adjunctive treatments should be continuously reevaluated, and if no clear benefit can be established (or if adverse-effect burden from these medications outweighs their clinical benefit), they should be discontinued.

**Conclusion**

Switching antipsychotics is a common occurrence in clinical practice. Occasionally, situations are encountered in which the risk-benefit assessment clearly favors switching antipsychotics, such as when a given medication is clearly ineffective or when severe adverse effects arise. Other situations are far less straightforward—for example, patients with schizophrenia experience partial (but suboptimal) symptom control or develop nonmedically serious but distressing adverse effects or adverse effects that present potentially serious long-term neurological (eg, tardive dyskinesia) or general medical (eg, new-onset diabetes, severe cardiovascular morbidity, early mortality) risk.
Although these patients may also benefit from switching antipsychotics, this still represents a major therapeutic change that carries the risk of clinical worsening. On the basis of controlled evidence, switching from metabolically higher-risk antipsychotics to lower-risk agents in patients who experience clinically significant weight gain, hyperglycemia, or atherogenic dyslipidemia with their current antipsychotic is an option worth considering if other management options are ineffective or not feasible. Regardless of the reasons for switching, specific and agreed-on target objectives; judicious selection of post-switch antipsychotics and switch strategies; careful follow-up and evaluation of progress toward achieving the goals of switching during the post-switch period; and close communication with the patient, caregivers, and treatment team members during every phase of the switch process will help minimize risk and optimize clinical outcome.

Note: This article was originally published as a CME in the March 2013 issue of *Psychiatric Times*. Portions of it may have since been updated.

### Table 1: Indications for switching antipsychotic drugs in patients with schizophrenia or bipolar disorder

- Post-treatment response
- Acute illness phase: despite good treatment adherence
- Persisting and impairing positive or negative symptoms
- Persisting and impairing mood symptoms or cognitive impairment
- Life-threatening movements in pharmacological treatment
- Fatigue or clinical instability due to poor adherence vs. other treatment options
- Excessive pain or on indication for switch in drug:
  - Antipsychotic activity: antipsychotic therapy
  - On indication for switch in dosing
- Prolonged symptoms of exacerbation
- Affective or behavioral effects
- Cognitive effects leading to difficulties in social or occupational functioning
- Amelioration of general medical conditions that are antipsychotic drug
- Increased anxiety or stress: increased anxiety levels

### Table 2: Procedures for switching antipsychotics

- Confirming the indication for switch
- Initial assessment of current antipsychotic
- Selection of appropriate post-switch antipsychotics
- Identification of potential side effects
- Identification of potential benefits
- Selection of appropriate switch strategy
- Post-switch follow-up
- Monitoring and adjustment of dosing

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Ralph Aquila, MD, (peer/content reviewer) has disclosed that he participates in speaker bureau programs for Novartis, Sunovion, Lilly, and he serves as a consultant for Novartis.

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17. Weiden PJ. Switching antipsychotics: an updated review with a focus on quetiapine. *J*