Switching Antipsychotic Therapy: What to Expect and Clinical Strategies for Improving Therapeutic Outcomes

Tim J. Lambert, B.Sc., M.B.B.S., Ph.D., F.R.A.N.Z.C.P.

When a patient taking an antipsychotic is not experiencing symptomatic remission, or is experiencing adverse effects (AEs) that are intolerable or damaging to his or her physical health, a change in medication may be the best path to a good outcome. However, many clinicians are reluctant to switch medications in all but the clearest cases of failure. This reluctance is intensified by the occurrence of AEs caused by transitioning patients too rapidly between agents with different receptor-binding profiles. Emergent antipsychotic-switching syndromes include the "withdrawal triad," comprised of cholinergic rebound, supersensitivity psychosis, and emergent withdrawal dyskinesias (and other motor syndromes). More recently, another element has been observed consistent with an activation syndrome. This activation syndrome may occur as a consequence of switching from highly sedative agents or as a consequence of initial prodopaminergic drive. All of these effects can be minimized by careful planning of gradual switch procedures and judicious use of adjunctive medications.

(J Clin Psychiatry 2007;68[suppl 6]:10–13)

A medication switch may be motivated by lack of efficacy, especially when considering multidimensional outcomes, patient relapse, or treatment intolerance and adverse effects (AEs) associated with the current medication.[1] A medication regimen involving an antipsychotic that still fails to reduce positive symptoms after an adequate 4- to 6-month trial[1] is clearly ineffective, but inadequate responses in other key treatment domains, including persistence of moderate-to-severe negative symptoms, primary or secondary cognitive deficits, and neuroleptic-associated affective disorder, also constitute grounds for a switch because these variables have a significant impact upon patient function and have been linked to poorer long-term (distal) outcomes.

Patient relapse may also prompt a switch to a new antipsychotic. Medication nonadherence, however, is a frequent contributor to relapse and should be investigated when a patient presents with inadequate treatment outcome or relapse. The possibility that the patient is engaging in substance abuse or has serious psychosocial difficulties should also be assessed prior to changing the medication because a switch may not be necessary if these other issues can be addressed.

Adverse effects that cause the patient significant distress or have negative implications for patient health in the short- or long-term may also motivate a switch. In these cases, careful consideration is fundamental in balancing the potential benefits of a switch with the possibility that the switch will result in relapse rather than improvement. Ideally, the decision whether or not to switch will be made with the full and informed participation of the patient as well as the caregiver.

SWITCHING ANTIPSYCHOTICS

Many switches fail not for lack of medication efficacy, but because the switch has been poorly planned. Often, switches are executed too quickly, increasing the risk of AEs, and the target dose of the new medication is too low to be effective at treating the disorder. Adverse effects that occur during the switch are frequently attributed to the new medication, but are, in fact, often symptoms of withdrawal from the old agent or are triggered by pharmacologic differences between the old agent and the new one. Patients should be forewarned that, although the new medication may be more effective (or more tolerable) than the old, it will take time before the new drug's benefits are fully experienced, and there may be points during the cross-titration when the patient may actually feel worse.[2]

Switching strategies include the abrupt switch, the taper switch, and the cross-taper switch. These techniques can also be combined into a hybrid switch (Figure 1). Abrupt

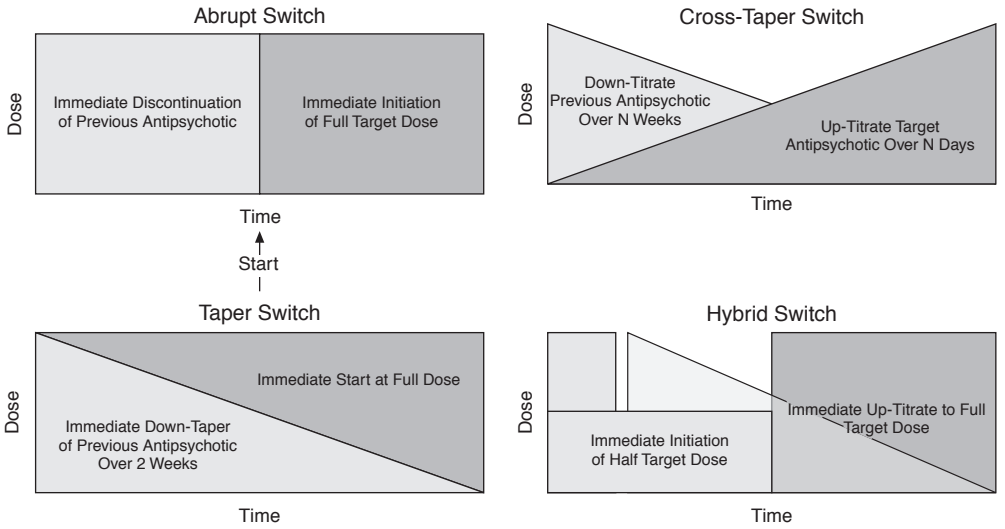
From the Department of Psychological Medicine, University of Sydney, Sydney, Australia.

This article was derived from the curriculum roundtable "The Art and Science of Switching Antipsychotic Medications," which was held January 21, 2006, in Atlanta, Ga., and supported by an educational grant from Bristol-Myers Squibb Company and Otsuka America Pharmaceutical, Inc.

Dr. Lambert is a consultant for Bristol-Myers Squibb and Janssen; is a member of the speakers/advisory boards for Janssen, Eli Lilly, Bristol-Myers Squibb, and Mayne Pharma; and has received other financial or material support from Janssen.

Corresponding author and reprints: Tim J. Lambert, B.Sc., M.B.B.S., Ph.D., F.R.A.N.Z.C.P., Chair, Department of Psychological Medicine, University of Sydney, and Head, Schizophrenia Treatment and Outcomes Research Brain and Mind Research Institute, 100 Mallet St., Camperdown, NSW 2050, Australia (e-mail: tlambert@med.usyd.edu.au).

Figure 1. Four Common Methods of Switching Antipsychotics[a]



[a]Of these switching strategies, the cross-taper is practiced in most circumstances.

switches are preferred when the patient is suffering from a serious AE, but this type of switch carries a high risk of withdrawal reactions and should only be conducted under conditions in which the patient can be closely monitored. A gradual cross-taper switch, in which the patient is tapered off the old medication before having the new medication titrated up, is associated with a low risk of withdrawal symptoms and drug-drug interactions. However, a gradual switch is associated with a higher risk of relapse than other methods because of the amount of time the patient spends at subtherapeutic doses. A cross-taper switch, during which the old medication is tapered down while the new medication is titrated up, is the safest way to prevent relapse, but interactions between the 2 drugs are possible.[1] Most experts recommend the cross-taper switching strategy.

In order to maximize the patient's chance of success with the new treatment regimen, the clinician must choose not only the appropriate dosage of the new drug, but also plan the best approach to weaning the patient off the old medication while titrating the new medication upward. Target doses can be generated through dose equivalency tables; however, there is considerable variety among and even within some equivalency tables, which complicates dose selection.[3] Doses that are too high can result in AEs, but doses that are too low risk patient relapse. A comprehensive review of dose-response studies of antipsychotics found no difference in efficacy between higher and more moderate doses for any commonly used conventional or atypical antipsychotic, and although common wisdom and many guidelines hold that lower doses are required for maintenance therapy, there is little evidence to support this.[4]

It is common practice to start the patient on a low dose of a new antipsychotic and titrate upward. Titration that is too rapid increases the risk of AEs, but, conversely, titration that is too slow increases the risk of relapse if the patient spends too much time at too low a dose. At roughly equal rates, the patient must be tapered off the old medication while being titrated onto the new medication. If the patient's original antipsychotic dose was high, dose reduction to an average dose prior to initiation of cross-titration may reduce the duration of the cross-titration period relative to maintaining the original dose strength. This method also seems to be associated with more successful switches than a long, slow titration from the peak dose of the original compound, possibly because patients are more likely to become nonadherent during prolonged switching protocols. Additionally, the treating physician has a more hands-on approach to supervising this dose prereduction before the switching occurs.

A meta-analysis of 4 randomized, controlled trials explored methods of switching to various atypical antipsychotics (1 with aripiprazole, 1 with ziprasidone, and 2 with olanzapine).[5] Dosing discontinuation methods consisted of abrupt discontinuation and downward titration, and dosing initiation methods were immediate initiation at the target dose or titration up to the target dose over several weeks. The length of the titration periods varied between the studies. Results were analyzed according to the method of titration, not the original drug. In this analysis, method of drug discontinuation or initiation had no effect on study discontinuation and Positive and Negative Syndrome Scale total, negative, or positive scores. In addition, the theory that crossover switches may be associated with an increased incidence of AEs that are due to medication interactions was not upheld by this analysis.[5]

Unfortunately, the trials analyzed were not sufficiently vigilant in their patient monitoring to provide data

regarding withdrawal and activation syndromes that may occur during switching.[5] Although the meta-analysis did not support crossover switches as being safer, the heterogeneity of the trials included, as well as the consistently short nature of the crossovers utilized, make this conclusion far from definitive.[5] More research is needed to determine which methods of switching, lengths of taper, dosing schedules, and adjunctive medications are associated with successful transition to the new medication and the best patient outcomes.

Although there is as much art as science in the prescribing and administration of antipsychotics, many clinicians have reported benefit from using algorithmic or computer-assisted tools for switching. One such internationally available tool is the "Switching to Risperidone" CD-ROM.[6] This program guides clinicians step-by-step through a switch, adjusting for factors that clinicians should be aware of in order to minimize the chances of a switch failure. Such tools have the advantage of not only pointing out factors that are salient in the switch, including dose and class of medication, route, anticholinergic status, age, gender, ethnicity, and recent adherence, but also allow for embedded education regarding the clinical psychopharmacology of the switch process. Clinicians may also benefit from these approaches when they do not have experience with newer medications, are not clear about the pharmacologic aspects of the particular switch, are simply bemused by the complexity that some switches seem to demand, or have experienced switch failures due to withdrawal phenomena.

WITHDRAWAL SYMPTOMS

Withdrawal symptoms are a major barrier to successful switching. Adverse effects that arise during medication switches are often misattributed to the new medication, causing the clinician to abort what might otherwise have been a successful medication change. Alternatively, patients may be discouraged by withdrawal symptoms or medication interactions and either demand a return to the original medication or independently stop taking their medications. An informed clinician and a prepared patient are more likely to successfully avoid or weather these common effects.[2,3]

The "withdrawal triad" describes 3 syndromes relating to disruption of the cholinergic system (cholinergic rebound) and the dopamine system (supersensitivity psychosis and withdrawal-emergent extrapyramidal syndromes). The more commonly described signs and symptoms of antipsychotic withdrawal include rapid reemergence of psychotic symptoms, dyskinesia, nausea, vomiting, anorexia, diarrhea, rhinorrhea, diaphoresis, myalgia, paresthesia, anxiety, restlessness, vertigo, alternating feelings of warmth and chill, coldness, tremor, and gastrointestinal disturbances.[7] These symptoms often occur because neuronal receptors can be upregulated or downregulated in response to chronic therapy, and when the agent is withdrawn too quickly, neural circuits cannot immediately respond to the change in stimulation. These rebound AEs, many of which can be linked to the cholinergic, dopaminergic, and possibly serotonergic tracts, are most common when switching to drugs with different receptor-binding profiles; for example, switching from an agent with high intrinsic anticholinergic properties (e.g., thioridazine) to an agent with low anticholinergic properties (e.g., aripiprazole, risperidone, or ziprasidone).

A planned switch should also account for the pharmacokinetics and pharmacodynamics of the medications involved. How quickly a drug is cleared from receptor binding sites (whether the drug has so-called fast on-off properties) also plays a role, as drugs that are cleared more quickly tend to be associated with more withdrawal effects. There also exists the possibility that drugs with very short half-lives may also contribute to difficulties with switching. When a patient is poorly adherent during a switch with a short half-life medication that is also weakly bound to central receptors, there may be rapid shifts in receptor occupancy that are likely to promote withdrawal reactions. These effects can generally be avoided or minimized by utilizing gradual cross-taper schedules and appropriate adjunctive medications.

Cholinergic Rebound

Cholinergic rebound (CR) occurs when either an antipsychotic with anticholinergic activity or an anticholinergic agent previously prescribed for extrapyramidal symptoms (EPS) is stopped too quickly, leaving the patient with rebound cholinergic hypersensitivity. Cholinergic rebound is characterized by nausea, vomiting, diaphoresis, restlessness, and insomnia.[7,8] These symptoms can be minimized by cross-titrating slowly, continuing any anticholinergic agents the patient may have been taking, or, if the patient is being titrated off a medication with anticholinergic effects, using an anticholinergic medication agent during the switching phase until the new antipsychotic is stabilized.[3] In its milder forms, CR may make the patient feel he or she has a mild flu; as a result, the patient may covertly become nonadherent because of ascribing this malaise to the new agent.

Dopamine Supersensitivity

Antipsychotic blockade of a dopamine receptor results in an upregulation of these same receptors.[9] When a dopamine antagonist is stopped or the dose is lowered, a patient may become hypersensitive to endogenous dopamine. This dopamine hypersensitivity may result in supersensitivity psychosis,[10] as a result of dopamine hyperactivity in the mesolimbic tract,[11] and rebound tardive dyskinesia (withdrawal-emergent dyskinesia), as a result of dopamine supersensitivity in the nigrostriatum.[7]

Supersensitivity psychosis presents like, and is often mistaken for, a relapse in schizophrenia.[11] The key difference in presentation is that supersensitivity psychosis generally appears soon after the change in dose (cessation or discontinuation), while true relapse usually takes longer to appear. In addition, patients suffering from supersensitivity psychosis are more likely to demonstrate other signs of dopamine supersensitivity, such as EPS and high plasma prolactin levels.[7] As with CR, the emergent symptoms are inappropriately ascribed to the new agent.

Withdrawal-emergent tardive dyskinesia[10] or other EPS, such as tremor, parkinsonism, akathisia, and emergent (tardive) dystonia, are also frequently misattributed to the new antipsychotic therapy. An increase in dose may alleviate symptoms, but a preferable approach is to plan a slow crossover switch that will give the receptors time to adapt.

Serotonin Rebound/Neuroleptic Malignant Syndrome–Like Syndromes

While there have been no systematic studies, there is some evidence to suggest that the abrupt discontinuation of serotonin 5-HT_{2A} antagonist antipsychotics can result in serotonin syndrome, a condition that more commonly occurs when a patient is taking multiple medications, resulting in an increase in serotonergic activity. Symptoms include agitation, diaphoresis, diarrhea, fever, hyperreflexia, incoordination, mental status change, myoclonus, shivering, and tremor.[12,13] A set of symptoms, similar to neuroleptic malignant syndrome and characterized by muscle rigidity and elevated body temperature, with the possible addition of diaphoresis, dysphagia, incontinence, mental status change, elevated or labile blood pressure, and elevated creatinine phosphokinase[14] has also been reported in patients whose antipsychotics were abruptly withdrawn.[15,16] The exact causes of this uncommon syndrome are not known, but dopaminergic and cholinergic involvement have both been hypothesized.[16]

Activation Syndromes

When patients are switched from a sedating medication to a less sedating agent, they may experience insomnia,[1] extreme pacing that may appear similar to pseudoakathisia, irritability, and anxiety because they have become accustomed to the sedating effects of the old medication. This might be described as rebound activation. However, there exists the possibility that the activation syndrome may be a phenomenon related to initial hyperdopaminergic drive with some of the newer atypical antipsychotics. The activation can be prevented or managed with the temporary use of benzodiazepines[3] or antihistamines and by utilizing a slow cross-taper approach.

Whether the activation syndrome extends the withdrawal triad to a tetrad will depend on further elucidation of its mechanism. Because many antipsychotics have rich pharmacologic profiles, withdrawal phenomena may develop as a result of cholinergic, dopaminergic, serotonergic, and other receptor dynamics, all interacting to potentially produce a state of "rich pharmacologic withdrawal" if not assiduously managed.

CONCLUSION

Successful switches require planning, time, and careful dosing. Counterintuitively, a patient's chances of achieving stable and successful monotherapy are maximized by an extended period of planned polypharmacy during which one medication is tapered down, a second titrated up, and adjunctive medications are used as clinically appropriate to ease the transition. Informing the patient and caregiver about not only the potential benefits of the switch, but also the unpleasant but temporary effects that may occur is a critical component in achieving the best possible therapeutic outcomes.

Drug names: aripiprazole (Abilify), olanzapine (Zyprexa), risperidone (Risperdal), ziprasidone (Geodon).

Disclosure of off-label usage: The author has determined that, to the best of his 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. Edlinger M, Baumgartner S, Eltanaihi-Furtmuller N, et al. Switching between second-generation antipsychotics: why and how? CNS Drugs 2005;19:27–42
2. Masand PS, Berry SL. Switching antipsychotic therapies. Ann Pharmacother 2000;34:200–207
3. Lambert TJ, Castle DJ. Pharmacological approaches to the management of schizophrenia. Med J Aust 2003;178(suppl 9):S57–S61
4. Davis JM, Chen N. Dose response and dose equivalence of antipsychotics. J Clin Psychopharmacol 2004;24:192–208
5. Remington G, Chue P, Stip E, et al. The crossover approach to switching antipsychotics: what is the evidence? Schizophr Res 2005;76:267–272
6. Lambert TC. Switching to Risperidone [CD-ROM]. Melbourne, Australia: Janssen-Cilag Medical Education Service; 1999
7. Borison RL. Changing antipsychotic medication: guidelines on the transition to treatment with risperidone. The Consensus Study Group on Risperidone Dosing. Clin Ther 1996;18:592–607
8. Luchins DJ, Freed WJ, Wyatt RJ. The role of cholinergic supersensitivity in the medical symptoms associated with withdrawal of antipsychotic drugs. Am J Psychiatry 1980;137:1395–1398
9. Burt DR, Creese I, Snyder SH. Antischizophrenic drugs: chronic treatment elevates dopamine receptor binding in brain. Science 1977;196: 326–328
10. Chouinard G, Jones BD, Annable L. Neuroleptic-induced supersensitivity psychosis. Am J Psychiatry 1978;135:1409–1410
11. Davis KL, Rosenberg GS. Is there a limbic system equivalent of tardive dyskinesia? Biol Psychiatry 1979;14:699–703
12. Zerjav-Lacombe S, Dewan V. Possible serotonin syndrome associated with clomipramine after withdrawal of clozapine. Ann Pharmacother 2001;35:180–182
13. Zesiewicz TA, Borra S, Hauser RA. Clozapine withdrawal symptoms in a Parkinson's disease patient. Mov Disord 2002;17:1365–1367
14. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition. Washington DC: American Psychiatric Association; 1994
15. Margetic B, Aukst-Margetic B. Neuroleptic malignant syndrome and clozapine withdrawal at the same time? Prog Neuropsychopharmacol Biol Psychiatry 2005;29:145–147
16. Amore M, Zazzeri N. Neuroleptic malignant syndrome after neuroleptic discontinuation. Prog Neuropsychopharmacol Biol Psychiatry 1995;19: 1323–1334