

Rationale and strategies for switching antipsychotics

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Switching a patient from one antipsychotic drug to another can be compared to changing horses in midstream; both are associated with risks and uncertainties but may be required under a variety of circumstances. The difference, however, is that the need for switching drugs, unlike that for switching horses, can generally be foreseen in the form of lapses in compliance or efficacy or the onset of unacceptable adverse effects. Consequently, protocols and guidelines can be developed in advance for minimizing the risks and maximizing the success of treatment.

Determining an appropriate switching strategy will not only minimize risk and maximize efficacy but, by affecting these two outcomes, reduce health care resource utilization. This article reviews some of the reasons for switching drugs and discusses various strategies that can be used in different situations. The perspective used is that of the patient, since drug efficacy and adverse effects are the primary factors that affect patient compliance and generally determine the need for a change in medications. Although the indications and strategies for switching medications may differ between outpatients and inpatients, the main focus here is outpatients, since minimizing relapses and maintaining a patient in the community (i.e., reducing the rate of rehospi-

Abstract: Reasons for switching patients to different antipsychotic drugs and strategies for doing so are reviewed.

Atypical antipsychotics have better adverse-effect profiles than conventional agents and may have subtle advantages in terms of efficacy. Patients who do not respond satisfactorily to one atypical antipsychotic agent may do so to another. Thus, many patients taking antipsychotic agents may benefit from a switch to another drug. However, the transition from one agent to another is itself associated with risks and uncertainties. Several switching strategies have been proposed that involve the abrupt or gradual cessation of the old drug combined with the abrupt or gradual initiation of the new drug. There are few data to suggest that one strategy is superior to another. A clinical appraisal of the conditions

under which switching of drugs should occur and a careful evaluation of the appropriate strategy can help minimize the risks of switching. Planning and follow-up should include the patient, the patient's family, and social-support personnel. Guidelines for switching drugs and managing patients during the transition are being developed.

When switching patients from one antipsychotic to another, good clinical judgment and a conservative approach can be used to balance the risk of clinical exacerbation with that of increased adverse effects.

Index terms: Antipsychotic agents; Drugs; Protocols; Toxicity

Am J Health-Syst Pharm. 2002; 59(Suppl 8):S22-6

talization) provide economic benefits to the health care system¹ in addition to health benefits for the patient.

Indications for switching medications

The main reasons for switching medications are a lack of efficacy and the presence of adverse effects. Primary lack of efficacy may be due to inadequate dosages, the development of tolerance to the medication, or patient variability in responses. Secondary lack of efficacy results from noncompliance with the drug regimen, which

may occur for a variety of reasons, including adverse effects the patient finds intolerable and patient lack of insight into the disease process.

Recent studies evaluating patients' perceptions of and satisfaction with medications reinforce the importance of patients' complaints. In a survey of schizophrenic patients, Buis² found that weight gain was among the top three things that patients disliked most about their medications. A much larger study conducted in the United Kingdom solicited information from more than 2200 patients on a range of

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Based on the proceedings of a symposium held December 3, 2001, during the ASHP Midyear Clinical Meeting, New Orleans, LA, and supported by an unrestricted educational grant from Janssen. Dr. Ganguli received an honorarium for participating in the symposium.

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issues related to medications.³ When the patients were asked to describe the five worst things about taking antipsychotic drugs, the primary complaint was weight gain. Subjective adverse effects, such as sedation, lethargy, and lack of motivation, were considered to be more important than objective adverse effects, such as tremors and shaking, which have long been considered by physicians to be the most important adverse effects of these drugs. These findings highlight the potential differences between what physicians and patients consider to be acceptable consequences of taking a medication.

Contraindications to switching medications

Just as some of the indications for switching medications are clearly defined, certain factors may contraindicate a switch.⁴ These factors include recent recovery from a psychotic episode. Patients should not be switched from a medication that is successfully controlling recovery from a psychotic state unless they have been stable for three to six months. A change is also contraindicated if unacceptable risk to the patient or others may result from an exacerbation of symptoms. Switching medications carries the risk of an exacerbation of symptoms that may or may not depend on the type of switching strategy employed. Another factor is a history of non-compliance, especially with oral medications. Patients who are currently compliant with a depot formulation but who have a history of noncompliance with oral formulations should not be switched unless regular supervision can be provided to ensure full compliance during and for several months after the switch. For example, it might be prudent to arrange for an intensive case manager to keep close track of the patient's compliance and clinical response before initiating the switch. If such supervision cannot be worked out or the patient refuses to accept it, and

current medications are associated with stable remission, attempting a switch of medications is inadvisable.

In patients for whom switching is contraindicated, alternative strategies may be used to try to resolve the factors leading to the need for a switch. Increasing or reducing the dosage can sometimes improve efficacy or limit adverse effects. Adding a drug to alleviate adverse effects may sometimes provide relief, especially in patients who demonstrate good compliance. However, polypharmacy should generally be avoided for several reasons, including possible drug interactions, greater complexity of dosage regimens, and increased costs.

Strategies

Once it has been determined that there is a need for a change in medications and the absence of contraindications has been confirmed, it is important to ensure that all parties are committed to the change and understand the procedures and potential consequences. Education regarding the switch should be provided to the patient, the patient's family, and social-support personnel.⁴ It is important to emphasize that the quality of the response of the individual patient

cannot be predicted in advance and that, while switching medications is expected to result in improvement, there may be no improvement or even worsening of symptoms.

Three basic strategies may be used for switching medications: abrupt switching (abrupt cessation of the current drug, with abrupt introduction of the new one at the expected therapeutic dosage), gradual switching (slow downward adjustment of the dosage of the current medication, with slow upward adjustment of the dosage of the new drug), and overlapping switching (abrupt introduction of the new medication overlapping with the current medication, followed by downward adjustment of the dosage of the current medication). The main advantages and disadvantages of these approaches are summarized in Table 1.

Although there is no single correct or recommended method of switching medications, specific conditions may predispose health care providers to prefer one method over another. For example, although abrupt switching is less likely to result in medication errors, it may be more likely to induce a relapse or withdrawal reactions due to the sudden drop in plasma drug levels. In patients who are taking depot an-

Table 1.

Advantages and Disadvantages of Three Methods of Switching Antipsychotic Medications^{4,a}

Method ^b	Advantage(s)	Disadvantage(s)
Abrupt switching	Less likelihood of medication errors Rapid Appropriate for switching from depot formulations (long half-lives)	Greater chance of flare-ups and withdrawal reactions Supervision may be required Not recommended for patients receiving clozapine
Gradual switching	May provide relief from extrapyramidal symptoms	Possibility of a subtherapeutic dosage if tapering is too rapid
Overlapping switching	Most effective strategy in preventing relapse Appropriate for recently stabilized patients Crossover can be used to test compliance in patients receiving depot agents	Increased possibility of continued polypharmacy Potential for drug-related adverse effects

^aAdapted from reference 4, with permission.

^bAbrupt switching = abrupt cessation of the current drug, with abrupt introduction of the new one at the expected therapeutic dosage; gradual switching = slow downward adjustment of the dosage of the current medication, with slow upward adjustment of the dosage of the new drug; overlapping switching = abrupt introduction of the new medication overlapping with the current medication, followed by downward adjustment of the dosage of the current medication.

tipsychotics, the long plasma half-life provides extended efficacy and a natural taper while the new drug is being introduced.

In contrast, when clozapine is the current drug, slow withdrawal is required to avoid withdrawal symptoms due to rebound from its anticholinergic and antiadrenergic effects. Since clozapine is generally used as a second-, third-, or fourth-line agent in refractory patients, switching from clozapine may be required only infrequently. The development of agranulocytosis in a patient taking clozapine requires immediate cessation of the medication. In such cases, rebound withdrawal phenomena should be expected and steps taken to mitigate them.

If the potential for relapse is high, overlapping switching appears to be the safest strategy, since the first drug is not fully withdrawn until there is a sufficient plasma concentration of the second drug to ensure a continuing therapeutic effect. Although this strategy may minimize relapses, an increase in the number of drugs a patient is taking carries the risk of drug interactions and increased adverse effects.

Regardless of the strategy used, the transition period should be closely monitored by the health care provider, the patient's family, and any other members of the support network. Monitoring includes evaluation for symptoms associated with withdrawal of the current agent (Table 2), favorable or unfavorable responses to the new medication, and treatment-emergent adverse effects. The prescribing physician must also be available to see the patient

promptly if needed. As part of the monitoring, social services and education should be provided to the patient's family to enable it to support the patient and cope with any problems that may arise.

Switching to novel antipsychotics

Study results. Although clinical data on switching antipsychotic medications are limited, several studies have evaluated the efficacy and safety of different switching strategies. Kinon et al.⁵ compared four strategies in switching patients to olanzapine from either conventional antipsychotic drugs or risperidone. Patients were randomized to either an abrupt drug withdrawal or a tapered withdrawal. Within each of these groups, patients were randomized to receive either immediate initiation of olanzapine 10 mg/day or an increasing dosage of olanzapine over a period of three weeks (placebo during the first week and olanzapine 5 mg/day during the second week and 10 mg/day during the third week).

Comparable clinical outcomes were obtained for all groups, although the most favorable transition strategy was the one in which olanzapine was started immediately and the patient's current medication tapered off. In this group there was significantly greater improvement in both the Clinical Global Impression (CGI) scale and the Patient's Global Impression (PGI) scale during the first week of treatment than in the other groups ($p < 0.05$). Pairwise comparison demonstrated a highly significant difference after the first week in both PGI and CGI scores, favoring

abrupt initiation plus gradual discontinuation compared with abrupt discontinuation plus gradual initiation ($p < 0.005$). All differences between groups disappeared by the third week. Several differences were observed in the rates of certain adverse effects, which could have explained the differences in CGI and PGI scores. Patients who were abruptly withdrawn from their current drug and given an increasing olanzapine dosage had a significantly higher frequency of adverse effects related to poor sleep patterns—a not wholly unexpected result, considering that these patients received no drug during the first week of the study (abrupt discontinuation with concomitant placebo). Patients undergoing both abrupt drug discontinuation and abrupt olanzapine initiation had a significantly higher rate of drowsiness. Consequently, it may be concluded that all the switching strategies had similar outcomes, with the only differences being related to adverse effects that are likely to diminish after the period of withdrawal and transition.

Weiden et al.⁶ observed a similar lack of difference in efficacy among three switching strategies in an open-label study that moved patients from conventional antipsychotic drugs to ziprasidone. Patients whose medication needed to be changed because of limited efficacy or unacceptable adverse effects were randomized to receive ziprasidone 80 mg/day; this dosage could subsequently be adjusted (by 40–160 mg/day) concomitantly with either an abrupt discontinuation of the current drug; 50% reduction of the current drug for seven days, with subsequent cessation; or continuation of the current drug for three days, followed by cessation on day 8. Although no differences were observed among the three groups, the transition to ziprasidone was accompanied by significant improvements from baseline in mean total Positive and Negative Syndrome Scale (PANSS) scores and

Table 2.

Common Withdrawal Symptoms Resulting from Discontinuation of Antipsychotic and Anticholinergic Medications during Switching

Symptom	Usual Timing
Anticholinergic withdrawal	First few days
Rebound akathisia	First few days
Rebound dystonia	First few days
Rebound parkinsonism	First week
Withdrawal dyskinesia	One to four weeks

positive and negative subscale scores, significant improvements in cognitive functions, lower extrapyramidal symptom (EPS) scores, and reductions in use of anticholinergic medications. This study suggests the value of switching to an atypical antipsychotic from conventional agents, regardless of the transition strategy used.

Another study that utilized an abrupt switching strategy was conducted by Goldstein and Cantillon⁷. Quetiapine was abruptly initiated at a dosage of 400 mg/day in patients being switched from either haloperidol (5–30 mg/day) or risperidone (4–10 mg/day). Somnolence was the main adverse effect reported in these patients, and when quetiapine was subsequently withdrawn abruptly after at least 16 days, the main adverse effects associated with withdrawal were vomiting and insomnia.

Development of guidelines. None of the studies on switching have identified one strategy that is clearly superior to the others in terms of efficacy or safety. However, guidelines for switching patients to different antipsychotics are needed to reinforce the basic clinical principles that should be considered before switching. These guidelines should also serve to remind health care providers to take into account individual drug characteristics, such as mechanism of action, pharmacokinetics, pharmacodynamics, and adverse effects. Clinical guidelines are being developed for risperidone and will be for other atypical agents.

As with any medication change, before switching to risperidone a sound clinical evaluation is needed to make sure that such a move is indicated and that there are no contraindications. In addition, collaboration and commitment should be obtained from the patient and family or other caregivers, both to provide support and help maintain compliance. An educated decision should involve the health care provider, the patient, and the family so that all par-

Figure 1. Trade-offs between different rates of adjustment of antipsychotic drug therapy.

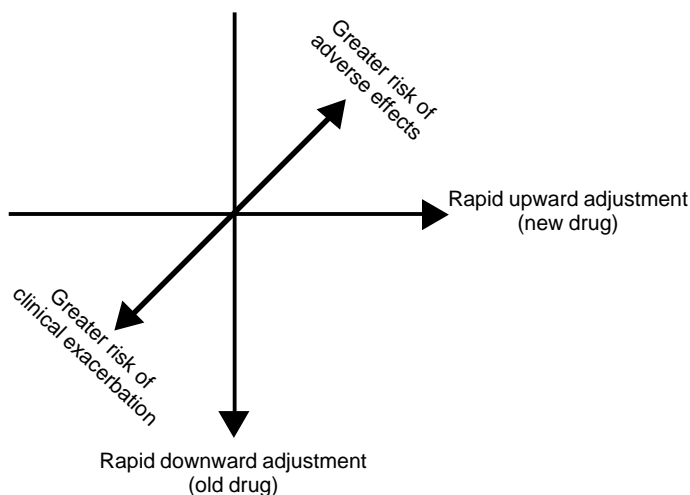


Figure 2. Example of transition from haloperidol to risperidone in an inpatient.

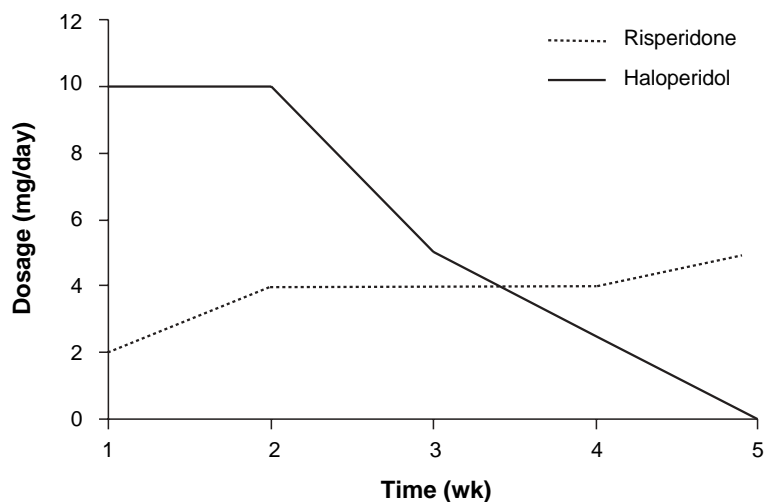


Figure 3. Example of transition from haloperidol to risperidone in an outpatient.

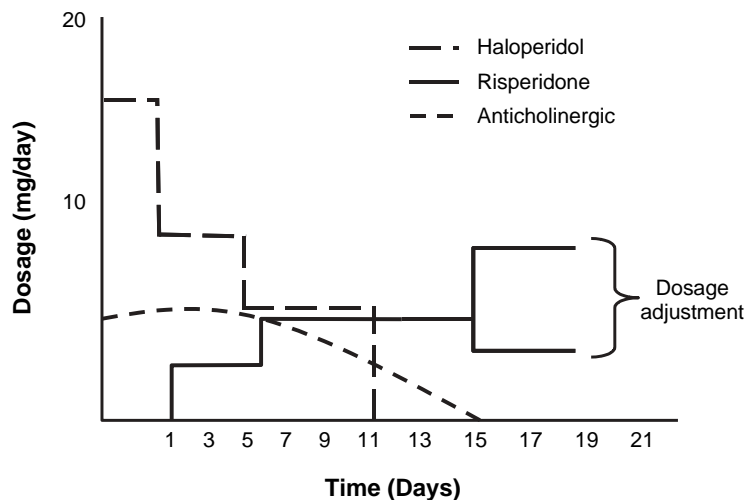


Table 3.

Strategy for Switching to Risperidone from Low-Dose Olanzapine

Time Frame (Weeks)	Olanzapine	Risperidone	Comments
1-2	Reduce to 5-10 mg/day	Initiate at 0.5-1 mg b.i.d.	Smaller initial dosage may enable faster adjustment
2-3	50% further reduction	Increase to 3-6 mg/day	Adjust on basis of patient's response
3-6	Discontinue	Stabilize at 4-6 mg/day	Avoid polypharmacy with early discontinuation if patient is stable

ties are aware of the goals and potential outcomes of switching drugs.

The physician and other health care providers involved in the transition should understand the clinical considerations that may be imposed by the choice of drug. These include drug interactions with other psychotropic medications (minimal with risperidone); the patient's age, since elderly patients will usually require lower dosages; and the presence of polypharmacy, so that an appropriate transition strategy can be determined for all medications. It is suggested that, in switching to risperidone, the first agent that should be stopped is the one that is being taken at the higher clozapine-equivalent dose. Once risperidone therapy is stabilized, the second agent can be decreased or stopped, with subsequent reevaluation of the risperidone dosage. In some cases, adverse effects can be managed by decreasing the dosage. For some adverse effects, such as insomnia and anxiety, benzodiazepines may be useful in the initial phase of the transition, but long-term polypharmacy should be avoided.

Clinical monitoring of the patient's health should be integrated into the strategy, starting with a baseline physical examination that includes blood pressure measurement, calculation of the body-mass index, and evaluation for tardive dyskinesia and EPSs. These variables should be monitored until the patient is stable on the new drug regimen and then at regularly scheduled intervals or as needed.

The exact strategy to be used with respect to the rate of adjustment of antipsychotics may depend in part on the patient's clinical condition and current medications; different adjustment rates have different potential tradeoffs (Figure 1). Two examples of switching to risperidone from haloperidol (in an inpatient and an outpatient) are illustrated in Figures 2 and 3. While both the inpatient and the outpatient had similar schedules for the initiation of risperidone, the tapering of haloperidol was more aggressive in the inpatient, since monitoring could be done more regularly.

Patients taking atypical as well as conventional antipsychotics may need to switch to risperidone. Table

3 presents a strategy for switching patients from olanzapine to risperidone. The exact time frame and dosage schedule may be modified on the basis of clinical conditions.

Conclusion

When switching patients from one antipsychotic to another, good clinical judgment and a conservative approach can be used to balance the risk of clinical exacerbation with that of increased adverse effects. Achieving this balance will not only help improve the patient's condition but will also reduce health care costs due to relapses, the necessity for antipsychotic polypharmacy, and concomitant treatment of adverse effects.

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