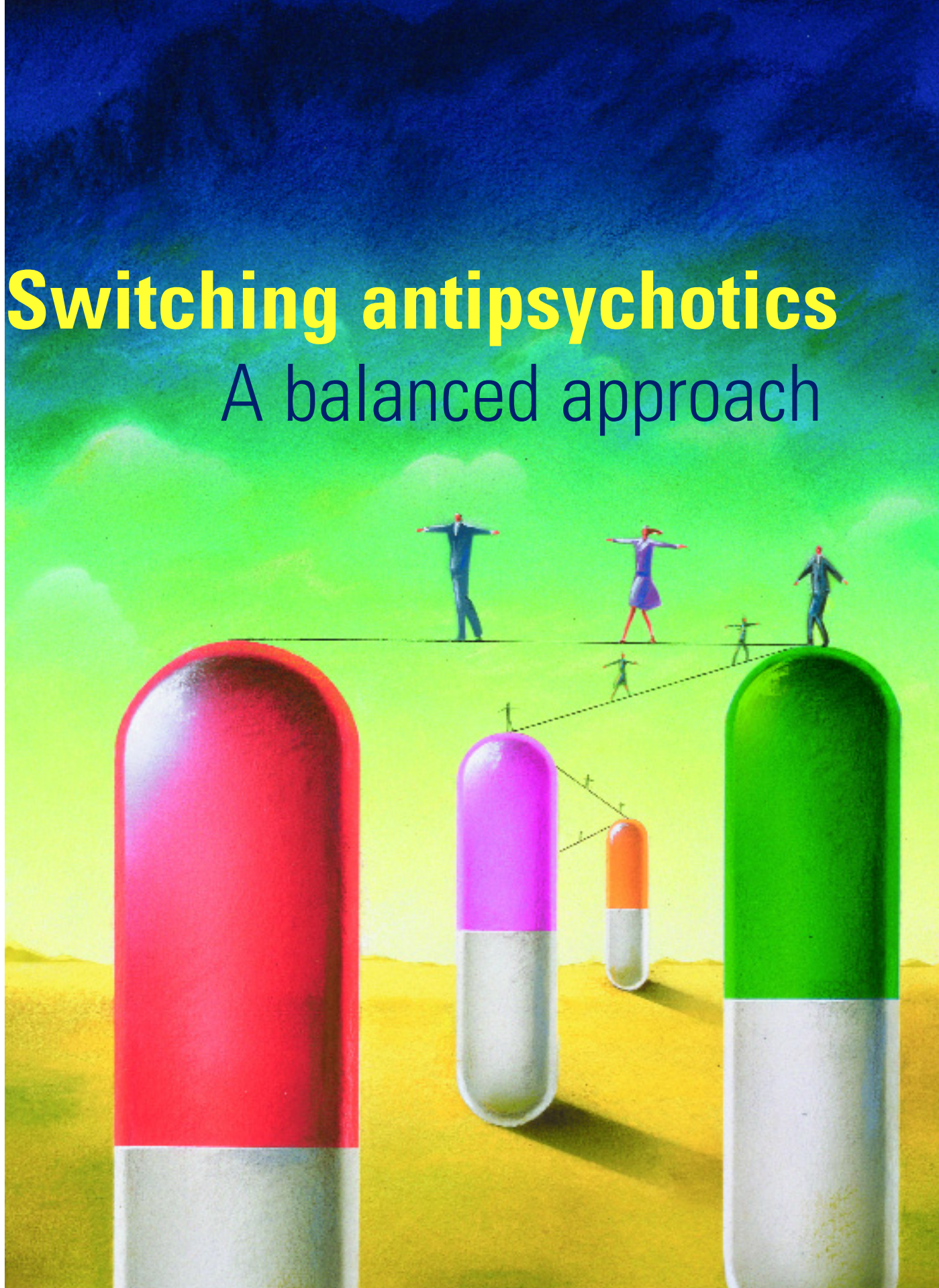


Switching antipsychotics

A balanced approach



to ease the transition

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With no standards or guidelines,
you're working without a net.
Here's evidence you need to
hone your clinical judgment
and help patients switch safely.

W

hen switching antipsychotics for patients with schizophrenia, you can ease this potentially perilous passage by choosing the right time to switch and preventing psychotic relapse. This article describes four keys to a smooth transition:

- assess response and side effects with the existing medication
- weigh the pros and cons of switching, with input from the patient or caregiver
- select a replacement with characteristics that could improve patient function
- choose a switching strategy while considering safety and efficacy data.

RISKS AND BENEFITS OF SWITCHING

The two most compelling reasons to switch antipsychotics are enhanced clinical response and improved tolerability. Others may include lower medication cost, less-frequent monitoring, fewer drug interactions, or easier administration (such as once-daily versus twice-daily dosing).

The greatest risk in a relatively stable patient



Table 1

Sample response criteria to evaluate an antipsychotic switch

Improved functioning

- Able to be discharged from inpatient care
- Transition from nursing home to group home
- Able to hold a job or tolerate longer work periods
- Improvement in self-care

Decreased symptoms

- Hallucinations less frequent and bothersome
- Delusions held less tenaciously or interfere less often with thinking
- Less withdrawn or isolative
- Initiates social contact
- Interacts appropriately with others

Improved tolerability

- Tardive dyskinesia reduced
- Anticholinergic or beta-blocking agents no longer needed
- Weight gain subsides
- Patient reports feeling more energetic

is for psychotic symptoms to re-emerge. Be very careful when switching patients who:

- might harm themselves or others if their psychosis re-emerges during the switch
- were recently stabilized after an acute psychotic episode and have been maintained for less than 6 months on the medication that controlled their symptoms
- cannot adhere to oral medications and are being maintained on long-acting depot formulations.¹

Other factors to consider include:

- the need for more-frequent patient visits during the transition to monitor for adverse effects
- the patient's willingness to switch
- influence of external stressors—such as recent bereavement—or aspects of the

patient's workplace or living environment that may interfere with adherence to a new regimen

- medication cost and coverage by third-party payers.

Establishing specific response criteria for each patient (*Table 1*) will help you know when to continue or terminate a switch.

INADEQUATE RESPONSE

Because antipsychotics do not eliminate all positive and negative symptoms, an adequate response is considered a reasonable therapeutic goal. Many patients with schizophrenia respond adequately to traditional or atypical antipsychotics, but approximately one-third do not.²

What is an "adequate" response? No advisory groups or consensus panels have defined this term or set standards for when to switch. Therefore, psychiatrists must evaluate a patient's response to an antipsychotic by using clinical judgment and patient/caregiver input. To gather the information you need, it is important to:

- identify target symptoms at baseline
- regularly monitor symptom severity, frequency, and intrusion on activities of daily living and quality of life.

Quantitative measures. In research, response is measured as a percent reduction in scores on standard assessments such as the Positive and Negative Syndrome Scales (PANSS). Using the PANSS, however, is too time-consuming for clinical practice.

The Brief Psychiatric Rating Scale (BPRS) is simpler than PANSS and can be administered more quickly but is less specific for negative symptoms. Even so, using the BPRS can help quantify baseline symptoms and monitor clinical response. It is useful to complete a BPRS rating prior to a switch and at subsequent visits during the transition. A >20% reduction in the total score is considered an adequate response.

Qualitative measures. Rating scales do not mea-

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Table 2

Treatment-limiting antipsychotic side effects and options for switching

Treatment-limiting factor	Atypical antipsychotic options
Akathisia/activation	Clozapine, olanzapine, quetiapine
Hyperprolactinemia	Any atypical antipsychotic except risperidone
Insomnia	Olanzapine, quetiapine
Orthostatic hypotension	Ziprasidone
Pre-existing cardiac dysfunction	Aripiprazole, olanzapine, quetiapine, risperidone
Pre-existing diabetes	Aripiprazole, quetiapine, ziprasidone
Sedation	Aripiprazole, risperidone, ziprasidone
Excessive weight gain	Aripiprazole, quetiapine, risperidone, ziprasidone

sure patients' and families' subjective feelings. One patient may view a 50% decrease in psychotic symptoms as extremely favorable and another as unacceptable. Switching therefore may be reasonable for one patient but not for another with a similar clinical response.

Underdosing contributes to inadequate response, so assess whether an antipsychotic has been given a sufficient trial. For example, 400 to 800 mg/d of quetiapine is considered a therapeutic dosage, assuming adequate tolerability, but some clinicians stop increasing the dosage below that range. Similarly, the usual antipsychotic trial continues at least 3 to 4 weeks at a therapeutic dosage.

TREATMENT-LIMITING EFFECTS

Antipsychotic side effects that justify switching may be treatment-limiting or simply bothersome. For example, switching is necessary for antipsychotic-induced QTc prolongation in a patient with a history of cardiac dysrhythmias and reasonable for excessive daytime sedation in a patient who is working or attending school.

Extrapyramidal symptoms (EPS) and hyperprolactinemia may limit a patient's tolerance of an antipsychotic. Patients who are especially sensitive to EPS may not tolerate high-potency agents such as haloperidol or even low to moderate dosages of risperidone. Others may not develop EPS while receiving haloperidol or higher dosages of risperidone.

Switching to an antipsychotic with relatively less histamine or alpha-adrenergic blockade may reduce problematic side effects such as sedation and orthostatic hypotension, respectively (*Table 2*).

Patients vary in how well they tolerate other side effects, such as weight gain. For example, a 10-lb weight gain may be acceptable to one patient and unacceptable to another. The decision to switch may be more obvious in a patient with diabetes, for whom substantial weight gain is unacceptable.

SWITCHING STRATEGIES

No method is universally accepted for switching from one antipsychotic to another. In clinical

Patients may view a 50% decrease in symptoms as very favorable or unacceptable

practice and research, three common methods (Figure) are used:

- immediately discontinuing drug A while starting drug B at full dosage
- slowly tapering drug A while starting drug B at full dosage
- slowly tapering drug A while slowly increasing drug B to full dosage.

Each method has advantages and disadvantages. Gradual cross-titration and tapering may reduce the risk of relapse but increase the risk of side effects. Elaborate regimens may confuse some patients—especially those with cognitive impairment—and increase the risk for adverse events and nonadherence.

Abruptly discontinuing an agent is less confusing and more convenient than gradual tapering, but patients may experience acute withdrawal (as with clozapine). Finally, no guidelines exist on how quickly to make the transition when one or both medications are cross-titrated and tapered. For inpatients receiving intense monitoring, a transition may be completed in 3 to 7 days, whereas outpatients may require 1 to 3 weeks.

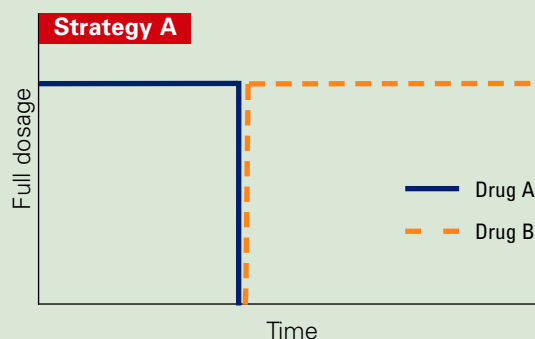
Recommendation. The evidence cited in the next section of this article suggests that any of the three methods can be used when switching antipsychotics, except clozapine. When switching from clozapine, extend the cross-taper period to help minimize or eliminate rebound psychosis and cholinergic symptoms.

SWITCHING FROM DEPOT TO ORAL AGENTS

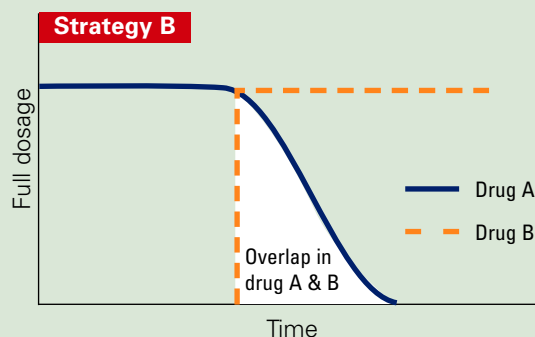
For patients switching from depot to oral antipsychotics, a 1-month cross-titration taper has been shown to be efficient and safe.

Godleski et al³ randomized 26 patients who had received IM depot antipsychotics (haloperidol or fluphenazine decanoate) for at least 3 years to either continue the IM depot antipsychotic or switch to olanzapine. Although the study was designed to assess the safety and efficacy of the switch, it also provided data on the transition method.

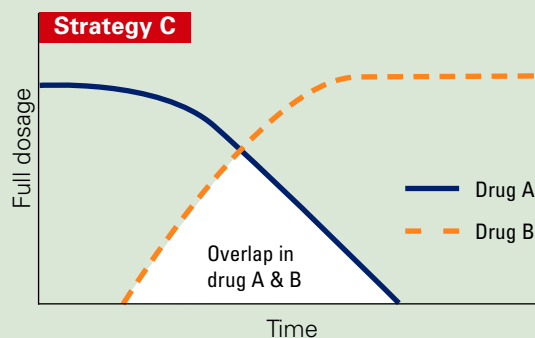
Figure
3 common antipsychotic switching strategies



Discontinue drug A immediately while simultaneously beginning drug B at full dosage



Slowly discontinue drug A while starting drug B at full dosage



Slowly discontinue drug A while slowly starting and increasing drug B to full dosage

continued



Subjects switching to olanzapine received their routine depot injection plus olanzapine, 10 mg/d for 1 month, followed by olanzapine monotherapy (5 to 20 mg/d) for 2 months. Those who continued IM depot therapy were maintained at a stable dose and dosing interval for 3 months. Safety and efficacy data were collected at baseline and monthly.

Patients receiving olanzapine improved on several efficacy measures, although the clinical relevance was minimal. For example, their mean PANSS total score decreased 3.23 points. One patient—in the control group—was hospitalized. Those who received olanzapine preferred this agent to the IM depot formulations and chose to continue daily olanzapine therapy. Adverse events did not increase significantly while patients received IM depot injections plus olanzapine.

SWITCHING ORAL AGENTS

Clozapine. When risperidone entered the U.S. market in the 1990s, a number of patients who had been treated with clozapine were abruptly switched to risperidone. Many experienced acute symptom exacerbation,^{4,5} including some whose rebound psychosis was more severe than their original symptoms. Other adverse effects—including nausea, diarrhea, vomiting, headache, restlessness, and sweating—have been attributed to cholinergic rebound caused by abruptly discontinuing clozapine.

To minimize the potential for rebound psychosis and cholinergic symptoms, taper clozapine across a minimum of 1 to 2 weeks. When you need to discontinue clozapine immediately—such as for patients experiencing serious hematologic effects—adding an anticholinergic such as benztropine may minimize the cholinergic rebound.

Risperidone. No studies have formally assessed methods for switching patients to risperidone.

Olanzapine. When switching to olanzapine, a direct switch or cross-titration tapering appear to be viable options.

In one multicenter, open-label study,² 108 patients were randomly assigned to olanzapine, 10 mg/d, after abruptly discontinuing a previous antipsychotic (direct switch) or by cross-titration tapering in a 1:1 fashion. Patients in the cross-titration group started olanzapine and discontinued their original antipsychotics across 2 weeks. Olanzapine dosages were adjusted as needed from 5 to 20 mg/d.

At study entry, approximately 95% of subjects in the direct-switch group and 85% in the cross-titration taper group were taking at least one typ-

ical antipsychotic—usually haloperidol. A switch was considered successful if a patient completed the 6-week trial without psychotic symptom worsening or EPS.

The 92 (85%) subjects who completed the study comprised similar percentages from both groups. Their scores on the PANSS total and subscales and Clinical Global Impression (CGI)

scale also were similar.

The most common adverse events were somnolence, insomnia, and headache in the direct-switch group (all 11%), and somnolence (15%), headache (9%), insomnia (7%), and increased appetite (7%) in the cross-titration group. Differences in these percentages were not statistically significant.

EPS and akathisia improved significantly in both groups ($p < 0.01$) after switching to olanzapine. Thirteen (24%) patients in the direct-switch group and 17 (32%) in the cross-titration taper group required at least one dose of benztropine. Use of concomitant medications was similar.

Quetiapine can be abruptly discontinued with minimal risk of adverse events when initiating another antipsychotic.

Taper clozapine across at least 1 to 2 weeks to minimize potential for psychotic rebound

Cutler et al⁶ switched 50 stable patients who had been treated with risperidone, thioridazine, haloperidol, or haloperidol plus benztropine. The original antipsychotics were abruptly discontinued, and quetiapine was initiated in a dose-escalating fashion and then maintained at 300 mg/d for 12 days. After that, quetiapine was abruptly discontinued and patients were assessed for side effects, including EPS.

Most patients' BPRS or CGI-Severity of Illness scores did not change significantly. Two patients (4%) experienced psychotic relapse during the switch. The authors speculated that these relapses might have been related to subtherapeutic quetiapine dosing. Transient nausea and vomiting were reported after quetiapine was discontinued.

Ziprasidone. When switching from another antipsychotic to ziprasidone, all three strategies appear well tolerated and maintain symptom control.

Using randomized, open-label trials, Weiden et al⁷ investigated strategies for switching patients to ziprasidone from olanzapine, risperidone, and traditional antipsychotics. All participants were diagnosed with schizophrenia or schizoaffective disorder and had experienced partial or inadequate response or side effects with their original antipsychotics.

Patients were assigned to one of three switching strategies:

- abruptly discontinue the initial antipsychotic
- decrease the initial antipsychotic's dosage by 50% for 1 week, then discontinue it
- gradually taper the initial antipsychotic, so that subjects received 100% for 3 days of ziprasidone treatment, 50% for the next 4 days, and none thereafter.

For all three strategies, ziprasidone was started at 80 mg/d for 2 days, with dosing adjusted as needed to 40 to 160 mg/d.

All three strategies were well-tolerated when switching to ziprasidone or aripiprazole

All patients' total score and positive and negative PANSS subscale scores improved significantly ($p < 0.01$) across 6 weeks, although these data represent symptom changes after switching

to ziprasidone. No efficacy or safety data were reported during switching. The authors concluded that patients could switch successfully to ziprasidone over a relatively short period using a variety of methods.

In another study, Stip⁸ switched 54 patients to ziprasidone from haloperidol. All received ziprasidone, 40 mg bid for 2 days and then 80 mg bid. Haloperidol was discontinued:

- immediately on day 1
- after the dosage was decreased by 50% for 7 days
- or after continuing the full dosage for 2 days, then taking 50% of the initial dosage for 5 days.

All patients maintained symptom control while switching, and 40 of 54 completed the trial. Among responders, BPRS and CGI scores improved significantly across 6 weeks, and EPS improved as expected.

Aripiprazole. Direct-switch and cross-titration tapering methods appear to be effective and well-tolerated when switching stable patients to aripiprazole.

In an 8-week, randomized, open-label trial, Casey et al⁹ switched 311 outpatients with schizophrenia or schizoaffective disorder to aripiprazole. The patients—who had been taking stable dosages of haloperidol, chlorpromazine, risperidone, or olanzapine for at least 1 month—were randomly assigned to three groups:

- **group 1** immediately discontinued the previous antipsychotic and started aripiprazole, 30 mg/d
- **group 2** started aripiprazole, 30 mg/d, and discontinued the previous antipsychotic across 2 weeks

continued



Switching antipsychotics

- **group 3** started aripiprazole (10 mg/d in week 1, 20 mg/d in week 2, and 30 mg/d in week 3) and tapered the previous antipsychotic (50% less in week 1, another 50% less in week 2, then discontinued).

Investigators assessed treatment efficacy using the PANSS and CGI at baseline and weeks 4 and 8. They questioned patients about adverse events at each follow-up visit.

Nearly three-fourths (72%) of patients completed the trial. Discontinuation rates were 31% in group 1, 34% in group 2, and 19% in group 3. Efficacy, safety, tolerability, and incidence of discontinuation because of worsening psychosis were comparable across groups.

Similar percentages of patients in each group reported one or more adverse event (89%, 89%, and 81% for groups 1, 2, and 3, respectively). Most adverse events were described as mild to moderate. Insomnia was reported most frequently. Other adverse effects that occurred in >10% of subjects included nausea, akathisia, anxiety, psychosis, headache (groups 2 and 3), somnolence, lightheadedness (groups 1 and 2) vomiting (group 2 only), agitation (group 3 only), and diarrhea (group 2 only).

Seven patients were hospitalized for serious adverse events—usually worsening psychosis.

Inadequate response and treatment-limiting side effects are the two most common reasons for switching antipsychotics. Successful switching requires balancing risks and benefits while working with the patient or caregiver. For safety, set goals and monitor for adherence and relapse.

BottomLine

Related resources

- Borison RL. Changing antipsychotic medication: guidelines on the transition to treatment with risperidone. The Consensus Study Group on Risperidone Dosing. *Clin Ther* 1996;18(4):592-607.

DRUG BRAND NAMES

Aripiprazole • Abilify
Benztropine • Cogentin
Chlorpromazine • Thorazine
Clozapine • Clozaril
Fluphenazine • Prolixin

Haloperidol • Haldol
Olanzapine • Zyprexa
Quetiapine • Seroquel
Risperidone • Risperdal
Ziprasidone • Geodon

DISCLOSURE

Dr. Winans is a consultant for Bristol-Myers Squibb Co. and is a speaker for Pfizer Inc., Abbott Laboratories, and Bristol-Myers Squibb Co.

Hospitalization rates were comparable among the three groups.

All groups improved slightly on the Barnes Akathisia Scale, Simpson Angus Rating Scale, and Abnormal Involuntary Movement Scale. Few patients in each group required benztropine (2%, 4%, and 7% for groups 1, 2 and 3, respectively).

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