A Review of Pharmacologic Strategies for Switching to Atypical Antipsychotics

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Background: In daily clinical practice, frequent switching of antipsychotic medications is widespread. There are various reasons for switching, including a partial or complete lack of efficacy, adverse side effects, and partial or noncompliance with medication. Patients switched from conventional drugs to oral atypical antipsychotic drugs have been shown to benefit from significant improvements in clinical response and tolerability. This review examines the strategies for switching patients from conventional antipsychotic drugs to both oral and long-acting formulations of atypical antipsychotic drugs that are the recommended treatment in the majority of patients with schizophrenia.

Data Sources and Study Selection: An electronic literature search of relevant studies using MEDLINE (January 1994–June 2004) was performed using the search terms *antipsychotic*, *atypical*, *conventional*, *schizophrenia*, and *switching*. English-language articles, references from bibliographies of reviews, original research articles, and other articles of interest were reviewed.

Data Extraction and Synthesis: Data quality was determined by publication in the peer-reviewed literature and the most important information identified. Data from clinical trials suggest that switching to an atypical antipsychotic drug is beneficial for the patient with schizophrenia.

Conclusions: If initiated appropriately, switching to atypical antipsychotic medications should not compromise patient functioning; indeed, individualized strategies have been shown to provide continuous treatment efficacy. Switching to atypical antipsychotic therapy should, therefore, be employed as a pharmacologic strategy to maximize patient outcomes.

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In the treatment of schizophrenia, many patients are often switched between antipsychotic therapies. One study carried out under conditions of routine clinical care indicated that patients may receive up to 7 different antipsychotics within a 1-year period (mean number of antipsychotics was 2.1).[1] In addition to frequent switching from one drug to another, many patients remain on multiple antipsychotics. How much of this is rational polypharmacy, and how much is due to concern on the part of the clinician of a worsening of symptoms following cessation of the initial treatment, is not clear. Indeed, many clinicians begin the process of switching antipsychotics with the intention of discontinuing the original drug, but ultimately continue with multiple drugs.[2]

Atypical drugs are the recommended first-line treatment in many patients with schizophrenia.[3] Several studies have reported that the atypical antipsychotics have superior efficacy and improved adverse event profiles compared with the older typical antipsychotics.[4–9] Although metabolic side effects are of increasing concern with some atypical drugs,[10] patients are likely to derive most benefit when switched from a conventional to an atypical antipsychotic. Several novel atypical antipsychotics are now available, and although practical guidelines for switching to these newer atypical antipsychotic drugs are not yet available, increasing clinical experience can provide some guidance. This article, therefore, highlights the factors that prompt switching a patient to an atypical antipsychotic drug. The available evidence for the clinical benefits of switching to oral or long-acting injectable atypical antipsychotics in terms of 3 key factors—efficacy, tolerability, and compliance—are also briefly reviewed. On the basis of available clinical data, several strategies for switching to an atypical antipsychotic drug are then examined.

METHOD

An electronic literature search of relevant studies using MEDLINE (January 1994–June 2004) was performed using the search terms *antipsychotic*, *atypical*, *conventional*, *schizophrenia*, and *switching*. English-language articles, references from bibliographies of reviews, original research articles, and other articles of interest were reviewed. Data quality was determined by publication in the peer-reviewed literature and the most important information identified.

FACTORS THAT CONTRIBUTE TO SWITCHING TO ATYPICAL ANTIPSYCHOTIC DRUGS

Several factors contribute to the rationale for switching to an alternative antipsychotic drug, including a partial or total lack of efficacy for the treatment of positive or negative symptoms or the occurrence of adverse effects such as movement disorders, weight gain, somnolence, endocrine side effects, sexual side effects, or metabolic dysfunction. A retrospective survey[11] carried out among 60 patients with schizophrenia identified some of the main reasons underlying medication switching. Insufficient compliance was the cause in 26.7% of cases, lack of efficacy (although "lack of efficacy" is often secondary to partial compliance) in 66.7% of cases, and complexity of treatment in 10% of cases.[11] Patient and family choice may also play a part in medication switching in schizophrenia, particularly if these individuals are informed of new treatment options.

Clinical guidelines identify several different reasons for switching from a conventional antipsychotic drug to an atypical antipsychotic drug. These include the occurrence of persistent psychotic symptoms, extrapyramidal symptoms (EPS),[12] or patient relapse despite compliance with medication.[12] However, since compliance is difficult to measure accurately,[13] the cause of relapse may not be entirely attributable to lack of therapeutic effect. Recommendations also propose that patients who have relapsed or who have experienced an unsatisfactory response to a conventional antipsychotic should be considered suitable for a treatment switch to an atypical antipsychotic drug.[3,12] Furthermore, patients who are currently achieving adequate symptom control, but who are experiencing unacceptable side effects, should also be switched to atypical antipsychotics.[3,12] Switching may, therefore, be an appropriate option for patients with either acute psychosis or stable disease. Current protocols recommend that patients not be switched from a medication that is successfully controlling recovery from a psychotic state until they have been stable for 3 to 6 months,[14] unless they are experiencing side effects that are of clinical concern.

Patients who have compliance issues may also be suitable candidates for switching to an atypical antipsychotic drug. High rates of noncompliance or partial compliance with antipsychotics have been demonstrated in patients with schizophrenia,[15] which can lead to recurrence or exacerbations of existing symptoms and, ultimately, to increased rates of relapse and hospitalization.[16–18] Furthermore, 1 study[19] demonstrated that, in addition to being more common, relapses were more severe and disruptive and were associated with increased recovery time in patients who were noncompliant compared with those who were compliant. The issue of partial compliance is particularly pertinent to young and first-episode patients, since it has been shown that, with each relapse, the likelihood of a patient's symptoms returning to premorbid levels decreases.[20,21] Patients with early-episode schizophrenia are also more vulnerable to partial compliance, since they and their caregivers often do not appreciate that the schizophrenia requires long-term maintenance treatment. Thus, patients experiencing problems with compliance may particularly benefit from changes in treatment strategies, such as increased psychosocial support and/or switching to long-acting injectable antipsychotics, for example, since these drugs have been shown to provide sustained delivery of the prescribed antipsychotic.[22]

EVIDENCE OF CLINICAL BENEFITS FOR A SWITCH TO AN ORAL ATYPICAL ANTIPSYCHOTIC

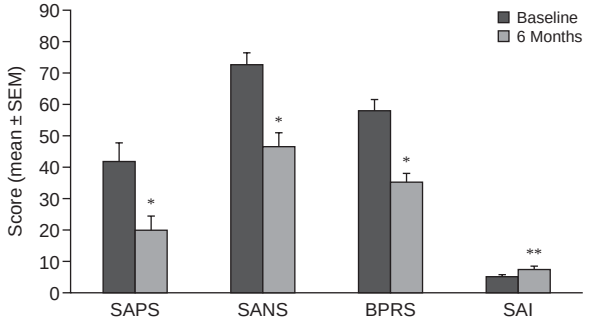
Symptom Control and Tolerability

Switching from conventional to oral atypical antipsychotics has been shown to provide both symptom improvement[23,24] and long-term benefits in terms of cognition, patient functioning, and insight.[25–29] Indeed, such switches have been associated with significant improvements in clinical response in long-term treatment.[4,30] This section presents an overview of the clinical experience gained in switching patients from various antipsychotic drugs to atypical oral antipsychotic medication.

One longitudinal naturalistic study[31] examined 43 stable outpatients who were switched to oral atypical antipsychotic medication (risperidone, clozapine, or olanzapine) because they were experiencing suboptimal response or side effects with conventional antipsychotic medication. The inclusion criteria for the study stated that patients had to be receiving a single conventional antipsychotic treatment prior to the trial, and patients were monitored for 2 years before and 2 years after the switch to atypical medication. At the end of the study, patients demonstrated significant improvements in positive symptoms, general psychopathology, and quality of life compared with the 2-year prestudy period.[31] In a separate naturalistic study,[26] which examined 22 patients diagnosed with schizophrenia with a mean duration of illness of approximately 13 years, patients also experienced improvements in symptoms after switching their medication from haloperidol to clozapine, risperidone, or olanzapine. At the study endpoint after 6 months of treatment with the atypical antipsychotics, patients showed an improvement in global functioning, a reduction in positive and negative symptoms, and, interestingly, an increase in their insight (Figure 1).[26]

An open, naturalistic, 14-week study[32] demonstrated significant improvements in the Clinical Global Impressions (CGI) scale, negative symptoms, and Positive and Negative Syndrome Scale (PANSS) total scores in 25 stable patients with schizophrenia or schizoaffective disorders following a switch from their conventional long-acting antipsychotic medication (> 6 months' treatment duration) to olanzapine. Results from an international, multicenter, double-blind study[6] in patients who did not

Figure 1. Effect of Switch to Oral Atypical Drugs (olanzapine, clozapine, and risperidone) From Haloperidol on SAPS, SANS, BPRS, and SAI Patient Scores[a,b]



[a]Adapted from Aguglia et al.[26]
[b]The SAPS, SANS, and BPRS scores were significantly reduced after the switch to oral atypical antipsychotic drugs, while an increase in the level of insight was observed, reflecting an increase in disease awareness, therapy compliance, and identification of psychotic symptoms.
Abbreviations: BPRS = Brief Psychiatric Rating Scale, SAI = Schedule for Assessing the Three Components of Insight, SANS = Scale for the Assessment of Negative Symptoms, SAPS = Scale for the Assessment of Positive Symptoms.
Symbols: * = $p < .001$, ** = $p < .05$.

respond to 1 month of fluphenazine and were switched to quetiapine or haloperidol, found that patients taking quetiapine demonstrated significantly greater reductions in PANSS total score ($p = .043$). Furthermore, a post hoc subanalysis[33] of this trial also found that quetiapine was associated with greater improvements in CGI scores compared with haloperidol ($p = .023$). Quetiapine was also well tolerated, with a greater reduction in EPS and fewer treatment-emergent EPS-related adverse events when compared with haloperidol.[5]

In a double-blind prospective study,[5] 397 stable patients with chronic schizophrenia and a duration of illness of approximately 16 years were assigned to receive either haloperidol or risperidone treatment for 1 year, having switched from an unspecified antipsychotic therapy. At the end of the 1-year trial, patients receiving treatment with risperidone showed significantly greater improvements in the status of their illness than those receiving treatment with haloperidol.[5] The improvements seen with risperidone included a lower risk of relapse, improvement in overall symptoms, and an amelioration of movement disorders. In contrast, patients receiving haloperidol demonstrated a worsening of both their symptoms and movement disorders.[5]

A large single-blinded, naturalistic, prospective study[30] evaluated 150 patients with schizophrenia or schizoaffective disorder who were switched from oral conventional antipsychotics to risperidone (N = 50), olanzapine (N = 50), or quetiapine (N = 50) and monitored for a period of 2 to 6 years. Patients were considered for a switch in medication due to inadequate symptom control or side effects. A large proportion (85%) of patients benefited from the switch to atypical antipsychotics (defined as stabilization and satisfaction with treatment).[30] The atypical antipsychotics were significantly better tolerated and had positive effects on treatment adherence, psychosocial functioning, and quality of life.

Two studies[23,24] have recently been published describing the benefits of switching to aripiprazole or ziprasidone from other antipsychotic drugs in patients with schizophrenia or schizoaffective disorder. In a 6-week, randomized, open-label trial,[24] patients with persistent symptoms or troublesome side effects taking a stable oral monotherapy regimen (± 25% of the recommended daily dose) of conventional antipsychotic drugs (N = 108), olanzapine (N = 104), or risperidone (N = 58), were found to benefit from a switch to ziprasidone. Significant improvements in total PANSS scores ($p < .05$) and negative symptoms ($p < .005$) were observed compared to baseline. Movement disorders were infrequent after a switch to ziprasidone in the total patient group, while patients switched from olanzapine, and to a lesser degree risperidone, experienced a reduction in weight (–3.9 kg, $p < .001$ and –1.9 kg, $p < .05$, respectively).[24] In an open-label study,[23] patients who received a stabilized dose of oral conventional (haloperidol or thioridazine) or oral atypical (risperidone or olanzapine) drug for at least 1 month were switched to aripiprazole for 8 weeks. Symptoms, as measured by PANSS total, positive, and negative score assessments, improved in all patients, although these changes did not reach significance.[23] No deterioration in EPS was observed, although a small decrease in weight was observed over the study period (–1.3 kg to –1.7 kg; no significance values given).[23]

When considering a switch from a conventional to an atypical antipsychotic, the side effect profile of the atypical drug needs to be considered. In general, atypical antipsychotics have a reduced incidence of EPS compared with conventional drugs.[5] However, the incidence of other side effects differs according to the drug. For example, 1 study[34] has suggested that switching to clozapine or olanzapine is associated with a greater potential for glucose elevations than switching to risperidone. Recent evidence from a consensus document prepared by the American Diabetes and American Psychiatric Associations[10] has suggested that some atypical antipsychotic drugs, when compared with the conventional drugs, have an increased propensity to induce metabolic side effects such as diabetes and weight gain. The consensus group suggested that there may be differential liability between the atypical drugs and that this requires further investigation with prospectively designed studies.[10]

Medication Compliance Considerations

Compliance with medication is a challenge in achieving sustained, long-term treatment in patients with schizophre-

nia. As such, medication that can improve not only symptoms but also cognitive capacity would be valuable in improving long-term treatment outcomes in this population. Published data from a study[35] examining 110 outpatients with schizophrenia suggest that cognitive function may be the strongest single predictor of medication compliance, and another study[36] suggests that cognitive function is an important predictor of vocational outcome. Atypical antipsychotic drugs have been associated with positive effects on cognition,[37] although more work is required to elucidate this further. An additional benefit of using atypical antipsychotics is a moderate increase in the rate of patient compliance with medication[38] compared with conventional drugs. On the basis of the compliant fill rate method, the results from a 12-month study demonstrated higher adherence rates among patients treated with atypical antipsychotics compared with those treated with typical antipsychotics (54.9% vs. 50.1%, respectively).[38] Although 1 study[39] has reported that there are no differences in compliance rates between patients treated with conventional or atypical oral medications, another has concluded that compared with conventional antipsychotics, patients receiving atypical antipsychotics were significantly less likely to switch medication or to use concomitant anticholinergic and anxiolytic medications.[40] This finding is an important factor in long-term "outcome," as partial compliance has been associated with poorer patient functioning and a higher risk of relapse in patients with schizophrenia.[40]

The benefits following a switch from conventional to atypical antipsychotic drugs have been translated into reduced resource requirements and associated pharmacoeconomic benefits.[41,42] Indeed, 1 pharmacoeconomic study[42] has demonstrated a reduction in the overall cost of treatment when switching from conventional to atypical antipsychotic therapy, largely due to a 20% to 30% reduction in the number of days spent in hospital. In spite of higher acquisition costs, it is likely that overall treatment costs may be reduced due to significantly lower relapse and hospitalization rates following a switch from conventional to oral atypical antipsychotic treatment.[41] However, there is evidence that factors such as weight gain may need to be factored into this evaluation.[43]

The available evidence, therefore, suggests that switching from a conventional to an oral atypical antipsychotic may be clinically beneficial and potentially cost-saving and, thus, should be considered as a potential strategy to maximize outcomes for patients with schizophrenia.

EVIDENCE OF CLINICAL BENEFITS FOR A SWITCH TO A LONG-ACTING INJECTABLE ATYPICAL ANTIPSYCHOTIC

There are several well-recognized and established advantages to using a long-acting formulation of an antipsychotic drug, which have translated into positive benefits for the patients, their families, and also the treatment team. In order to receive treatment, the patient is required to attend an appointment with the treatment team; this provides the opportunity to strengthen the therapeutic alliance by increasing interaction between the patient and the treatment team. Moreover, this regular contact between patients and treatment teams provides the opportunity for more formal psychosocial support.

Patients and their caregivers appreciate that regular appointments with the treatment team to receive their medication afford a degree of control over the treatment regimen, and can reduce the burden and stigma associated with having to remember to carry medication and to take tablets regularly. Many patients have been shown to have positive attitudes toward long-acting medication.[44–46] However, some patients prefer oral atypical antipsychotics perhaps due to negative experiences with conventional depot drugs.[47] This is usually not, however, considered a major factor that influences physicians when selecting oral drugs.[48,49] For the physician and the patient's family, scheduled and regular contact means that they no longer have to "police" the patient's drug adherence, but they can still be assured that noncompliance is immediately identified. If a patient does become noncompliant, there is also some time advantage in allowing for the necessary intervention, since the antipsychotic medication is not cleared from the body as quickly as with oral formulations.[50] Thus, the opportunity for partial compliance is minimized, and the steps for intervention at an early stage can be initiated, subsequently reducing the risk of relapse. Importantly, the incidence of adverse events associated with medication or the occurrence of breakthrough symptoms can also be closely monitored. However, some physicians feel that the inability to stop medication immediately is a potential limitation to the use of long-acting drugs.[51] However, a recent expert consensus report on optimizing pharmacologic treatment in patients with psychiatric illness did not support this.[50] Even in neuroleptic malignant syndrome, assuming the condition was identified and treated, mortality rates in patients receiving long-acting drugs were not higher than those for patients who received oral medication.[52]

Although until recently the availability of a long-acting atypical drug has been limited in some countries, including the United States, the available clinical data regarding the switch to a long-acting atypical drug are accumulating as experience with this drug increases. Long-acting risperidone is the first available long-acting atypical drug. Recently published data from 2 large clinical studies—a 12-week, double-blind, placebo-controlled study[53] and a 1-year open-label study[54]—have shown that long-acting risperidone is safe and effective in the treatment of patients with schizophrenia. These data suggest that there may be an opportunity for higher expectation of

treatment outcomes for patients above that simply conferred by symptomatic stability and beyond the traditional symptom stabilization. Further experience with this long-acting atypical antipsychotic will help clarify the clinical impact of this drug.

A number of subanalyses of the 1-year study have been reported. One subanalysis[55] demonstrated that clinically stable patients (N = 188) who were switched from depot conventional antipsychotics (mean ± SD duration of treatment = 766 ± 1175 days) to long-acting risperidone (25, 50, or 75 mg) experienced improvements in symptom scores compared with baseline ($p < .001$), and long-acting risperidone treatment was well tolerated. Patients were considered stable if they had received a stable dose of antipsychotic medication for at least 4 weeks prior to participation in the trial and were judged stable by the physician.[55] These benefits are further supported following a switch from long-acting conventional antipsychotics to long-acting risperidone observed in a separate 12-week study.[56] Similarly, clinically stable patients (N = 336) with schizophrenia have been shown to derive symptom improvements as measured by a 2.4-fold increase in the prevalence of favorable CGI severity ratings (1–3) ($p < .0001$) when switched from oral to long-acting risperidone.[57] Again, long-acting risperidone treatment was well tolerated in this patient population.[57] Subanalysis of the 1-year study has also demonstrated a reduction in the number of patients requiring hospitalization when treated with long-acting risperidone (38% to 12%, $p < .0001$).[58] Furthermore, elderly patients (aged > 65 years; average age = 70.9 years), who are more at risk of the side effects associated with conventional medications,[59] have been shown to experience well-tolerated treatment with long-acting risperidone.[60]

STRATEGIES FOR SWITCHING TO AN ATYPICAL ANTIPSYCHOTIC DRUG

Several strategies have been explored with regard to switching patients with schizophrenia to an atypical antipsychotic drug. However, before switching antipsychotic therapies, several factors and considerations may need to be taken into account. Patients may benefit from the treatment of any comorbid substance abuse prior to switching their antipsychotic therapy.[23] Provision of information concerning the delay between initiating the new antipsychotic drug and experiencing the clinical benefits of the new treatment may also be helpful.[23] Patients should also be made aware that, in some cases, they may experience a transient worsening of symptoms in this interim period, particularly in the case of symptoms such as insomnia and agitation.[16,41] It is important to remember that not all patients require a switch to a new antipsychotic medication; instead, they may benefit from a dose adjustment or the addition of another medication to resolve any problems. Furthermore, an appropriate trial length of treatment for the drug should elapse prior to any change in medication.[61] A suitable time frame is considered to be 4 to 6 weeks,[3,12] although longer periods may be appropriate in some cases.

Switch to an Oral Atypical Antipsychotic Drug

Switch from an oral antipsychotic drug. Overall, there are 4 types of strategies for switching to oral antipsychotics: (1) introduction of the new drug with titration to its therapeutic dose and gradual reduction of prior therapy, (2) simultaneous cessation of prior therapy and commencement of new drug, (3) introduction of the new drug with gradual titration to therapeutic dose and cessation of prior therapy, or (4) gradual cessation of prior therapy with initiation of the new drug at full dose. Each of these strategies has respective advantages and disadvantages,[14] and the chosen switching strategy should always consider the efficacy-to-safety benefit and be tailored to the individual patient.[61] Immediate cessation of the previous treatment and initiation of the new antipsychotic has been carried out successfully with several atypical drugs.[23,24,62–64] However, the success of this strategy in these instances may be partly due to the strong support system available in clinical trials and may not work as well in a "real world" situation, where there may be a less complete support network. In addition, cessation of existing therapy may be associated with withdrawal effects due to a sudden drop in plasma drug levels. These may include withdrawal dyskinesia and rebound cholinergic effects, which may be mistakenly associated with the new therapy introduced.[14]

A double-blind study[65] of 4 paradigms for switching from haloperidol to olanzapine found that a gradual tapering of haloperidol and introduction of full-dose olanzapine was the most efficacious and safe transition regimen as measured by CGI, PANSS, and EPS ratings and also the number of adverse events. In order to maximize patient outcomes during a medication switch, a tapering or crossover strategy may be more advisable.[11,14,65,66] However, recent open-label evaluations of the different strategies outlined above in patients who were switched to treatment with ziprasidone[24] or aripiprazole[23] from conventional or atypical drugs found no influence of the technique employed on the effectiveness or side effect profile observed. A strategy for switching from a conventional oral antipsychotic drug to an oral atypical antipsychotic drug is outlined in Table 1.[41]

Switch from a conventional long-acting antipsychotic drug. For patients switching from a long-acting conventional drug to an atypical oral drug, a 1-month, cross-titration taper has been shown to be efficient and safe,[61,67] and may be safer than switching patients using other approaches such as the introduction of the new drug with titration to its therapeutic dose and gradual reduction of

Table 1. Original "SWITCH" Strategy for Switching From an Oral Conventional Antipsychotic to an Oral Atypical Antipsychotic[a]

Strategy
Start oral atypical antipsychotic
Withdraw oral conventional antipsychotics slowly
Involve patient in rate of withdrawal
Titrate oral atypical antipsychotic to optimal dose
Challenge transient adverse effects
Halt oral conventional antipsychotics altogether

[a]Based on Masand and Berry.[41]

Table 2. Example of "SWITCH" Strategy Amended for Long-Acting Atypical Agents

Strategy
Start long-acting atypical antipsychotic, eg, long-acting risperidone at 25-mg dose
Withdraw oral antipsychotic supplementation after 3-week period, or as required
Involve the patient in treatment decisions
Titrate long-acting risperidone to optimal doses
Challenge transient adverse events
Hold regular appointments to monitor and offer support

prior therapy,[65] or introduction of the new drug with cessation of the other prior therapy.[68,69] In a recently published study by Godleski and colleagues,[67] patients who had been previously treated with haloperidol or fluphenazine decanoate for at least 3 years were switched to oral olanzapine or continued to receive their conventional antipsychotic depot injection. This study was primarily designed to investigate the efficacy and safety of switching between these 2 antipsychotic therapies, but it also provided information about the viability of the cross-titration strategy. At the beginning of the study, those patients who were to be switched received their next scheduled conventional depot injection with oral olanzapine for 1 month and were subsequently monitored on oral olanzapine monotherapy for 2 months.[67] This study demonstrated that patients who were switched to oral olanzapine experienced no more side effects during the transition phase than those who continued on their conventional depot monotherapy. Furthermore, patients who were switched experienced significant reductions in PANSS total score compared with those who continued to receive depot conventional medication.[67] Patients who were switched also indicated that they preferred the oral olanzapine therapy compared with the depot therapy.[67]

Switch to a Long-Acting Atypical Antipsychotic Drug

Long-acting risperidone contains an unmodified form of risperidone incorporated into microspheres (small biodegradable polymer beads), presented as an aqueous formulation.[70] Long-acting risperidone is delivered by intramuscular injection every 2 weeks.[71–73] Unlike conventional oil-based, long-acting antipsychotic formulations, which are often associated with pain and other adverse events at the injection site,[70,72] injection site pain with long-acting risperidone has been reported as mild, and to diminish from the first injection.[54]

Although no formal treatment guidelines exist for this new drug, several recent articles have been published[72] that outline the recommendations from consensus meeting discussions.[73] When switching a patient to treatment with long-acting risperidone, additional antipsychotic coverage should be provided during the first 3 weeks of treatment[70] due to the pharmacokinetic release profile of the microsphere injection.[70] Any dose adjustment of long-acting risperidone should be avoided until approximately 8 weeks (4 injections) after initiation of treatment. This is because steady-state levels of risperidone are not achieved until this time. A strategy for switching to along-acting atypical antipsychotic drug is outlined in Table 2.

Switch from an oral antipsychotic drug. Patients switched from an oral antipsychotic drug can be initiated onto long-acting risperidone immediately. Patients should continue to receive their previous oral antipsychotic medication for the first 3 weeks after initiating the first dose of long-acting risperidone in order to ensure that adequate antipsychotic coverage is provided; following this period, oral antipsychotics should be tapered off over a period of time, dependent on the nature and dose of the previous oral antipsychotic.[46,73] Results from a recent 12-month, open study[74] of 336 symptomatically stable patients maintained on oral risperidone, who were subsequently switched to long-acting risperidone administered every 2 weeks, demonstrated a significant improvement in PANSS total scores, with the greatest improvement found for negative symptoms. The study also demonstrated several tolerability benefits of long-acting risperidone over oral risperidone, including progressive improvements from baseline ratings of EPS.[74] These results are encouraging and may indicate the potential for additional clinical improvement with long-acting treatments among patients who appear to be well treated on oral medications, although further controlled trials are needed to verify this.

Switch from a conventional long-acting antipsychotic drug. Patients who are switched from conventional long-acting antipsychotics to long-acting risperidone are unlikely to require oral supplementation in the initial stages. The long half-life of the previously administered conventional long-acting drug should provide sufficient antipsychotic coverage until therapeutic levels of long-acting risperidone are reached.[73] Initiation of long-acting risperidone can be carried out in one of 2 ways: either by administering long-acting risperidone 1 week prior to the next scheduled appointment, or by replacing the conventional long-acting antipsychotic at the next scheduled appointment.[72,75]

Table 3. Summary of Switching Strategies to Either an Oral or a Long-Acting Formulation of an Atypical Antipsychotic Drug[a]

Agent Switch	Suggested Switching Strategy
Switch to an oral atypical antipsychotic drug	Switch from an oral antipsychotic drug (4 potential strategies) Introduction of new drug with titration to therapeutic dose and gradual reduction of prior therapy Simultaneous cessation of prior therapy and commencement of new drug Introduction of new drug with titration to therapeutic dose and cessation of prior therapy Gradual cessation of prior drug with initiation of new drug at full dose Switch from a conventional long-acting antipsychotic drug 1-month, cross-titration taper
Switch to a long-acting atypical antipsychotic	Switch from an oral antipsychotic drug 3-week continuation with prior drug after initiation of the first dose of long-acting atypical antipsychotic; prior drug tapered off over a period of time, dependent on the nature and dose of the previous oral antipsychotic Switch from a conventional long-acting antipsychotic drug Cessation of prior drug and initiation of long-acting atypical antipsychotic either 1 week prior to the next scheduled appointment or at next scheduled appointment

[a]Based on Ganguli,[14] Casey et al,[23] Weiden et al,[24] Masand and Berry,[41] Winans,[61] Cutler et al,[62] Lee et al,[63] Kirov et al,[64] Kinon et al,[65] Peuskens,[66] Godleski et al,[67] Amery and Marder,[68] Taylor,[69] Eerdekens et al,[70] Risperdal Consta,[71] Marder et al,[72] Keith et al,[73] Lasser et al,[74] and Bloch et al.[75]

CONCLUSION

Antipsychotic medication switching is necessary for patients who achieve inadequate or suboptimal response of their psychotic symptoms, or who are dissatisfied with their treatment or experiencing intolerable side effects.

Ideally, patients should be switched to an atypical antipsychotic on the basis of the superior efficacy and decreased propensity of these drugs to induce movement disorders compared with conventional drugs. The possibility now exists that patients can be switched to either an oral or a long-acting formulation of an atypical antipsychotic, depending on the clinical profiles of the patients and their preferences. Strategies for switching to atypical antipsychotic agents are summarized in Table 3. The added benefits provided by long-acting formulations include more assured medication delivery and, therefore, improved treatment compliance.

In conclusion, antipsychotic medication switching, if carried out appropriately, should not compromise patient functioning, and individualized strategies have been shown to provide continuous treatment efficacy. Treatment switching should, therefore, not be limited by fear of adverse events; rather, it should be employed as a pharmacologic strategy to maximize outcomes for patients.

Drug names: aripiprazole (Abilify), clozapine (Clozaril, FazaClo, and others), fluphenazine (Prolixin and others), haloperidol (Haldol and others), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal), ziprasidone (Geodon).

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