Switching Antipsychotic Medications

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Compared with conventional antipsychotics, the so-called "atypical" antipsychotics promise improved side effect profiles and better control of the symptoms of schizophrenia. Therefore, most patients currently taking conventional antipsychotics could potentially benefit from a switch to an atypical antipsychotic. Often, the key issue in deciding whether to switch is the presence of countervailing factors that mitigate against the change. This paper discusses the indications and contraindications for switching antipsychotics, plus issues that require consideration before a switch is made. Also, the advantages and disadvantages of various switching techniques are discussed, with a particular focus on the newer antipsychotic olanzapine. *(J Clin Psychiatry 1997;58[suppl 10]:63–72)*

Over the last few years, there have been major advances in psychopharmacologic options for patients with schizophrenia and other chronic psychotic disorders. Many patients treated with "atypical" antipsychotic agents (e.g., clozapine, risperidone, and olanzapine) have achieved much greater control of their symptoms than during their previous treatment with conventional antipsychotics. Over the next few years, many other patients will be switched from conventional to these and other emerging atypical antipsychotics. However, at this time, there has been little research on crucial issues concerning selection of patients for treatment with atypical antipsychotics. In addition, knowledge about crossover techniques is lagging behind the urgent clinical needs of our patients. This paper addresses clinical issues of patient selection and the process of starting treatment with atypical antipsychotics. Some of the material presented here, e.g., patient selection issues and signs of antipsychotic withdrawal, pertain to starting treatment with any new antipsychotic. Other information is more specific to the newly introduced atypical antipsychotic olanzapine. Olanzapine became available in late 1996 and there is a particular need to understand how to start treatment with this agent. Information on changing from conventional oral antipsychotic therapy to risperidone, clozapine, or depot medications is provided elsewhere.[1–6]

The following discussion considers outpatients and inpatients separately since the clinical challenges differ with the treatment setting.

SWITCHING OUTPATIENTS

Indications for Outpatients

The literature contains little information on the selection of outpatients currently on maintenance therapy with a conventional antipsychotic who would benefit from a switch to an atypical antipsychotic. The indications for such a switch, presented in Table 1, include persistent positive symptoms,[7] persistent negative symptoms,[8] relapse despite compliance,[9,10] persistent extrapyramidal symptoms (EPS),[11,12] tardive dyskinesia,[13,14] and hyperprolactinemia.[15] Table 1 presents these indications along with how they are perceived and reported by patients and their families. Switching treatments is undertaken under the premise (and with the hope) that a newer medication will lead to improvement in at least one of these areas. Given the broad scope of these indications and the limitations of conventional antipsychotics, it is very easy to find indications to change medications. In practice, then, the decision to change is often more influenced by the presence or absence of contraindications and countervailing clinical factors that mitigate against changing medications.[5]

Contraindications and Countervailing Clinical Factors for Outpatients

Relative contraindications. The greatest clinical concern in changing antipsychotic medications for "stable" outpatients is the potential risk of exacerbation of psy-

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Table 1. Indications for Switching Antipsychotics From the Perspective of the Clinician, the Patient, and the Family*

Clinician's Perspective	Patient's Perspective	Family's Perspective
Persistent positive symptoms	Distress from positive symptoms Secondary anxiety and depression from positive symptoms	Disruptiveness and agitation
Persistent negative symptoms	Inability to meet life's goals	Emotional and financial burden of caretaker role
Relapse despite compliance	Inability to function independently in the community	Dealing with multiple crises and setbacks
Persistent EPS[a] and/or tardive dyskinesia	Dysphoria or distress from EPS Annoyance from increased complexity of regimen and side effects from the addition of anticholinergic medications	Heartbreak of seeing their relative or partner burdened by akinesia or tardive diskinesia
Hyperprolactinemia (galactorrhea and amenorrhea in women, gynecomastia and impotence in men)	Disruption of self-image and self-esteem because of disturbances in reproductive function	Disappointment or frustration on the part of the sexual partner

*Assumes that the patient is receiving therapeutic doses of a conventional antipsychotic and that the persistent symptoms cannot be attributed to compliance problems and/or substance abuse problems; see text for further discussion. Abbreviation: EPS = extrapyramidal symptoms.
[a]Assumes that the patient is receiving treatment with optimal doses of a conventional antipsychotic and unsuccessfully attempted treatment with antiparkinson or antiakathisia agents.

chotic symptoms during the crossover process. Therefore, the contraindications described below relate mostly to the risk of relapse. In our opinion, the following patients should not be switched electively to another antipsychotic until the complicating clinical situation has been successfully addressed*:

- Patients for whom any exacerbation of psychotic symptoms in the near future would present an unacceptable risk of danger to themselves or to others.
- Patients who have recently recovered from an acute psychotic episode and remain on the same medication successfully used to treat that episode. Such patients probably should not be electively switched to another agent until they have been stable for approximately 3 to 6 months after recovery from a major relapse.
- Patients recently noncompliant to oral medications who are now compliant with a depot antipsychotic. Unless they are in a situation in which there is steady and reliable supervision of oral medications, such patients should not be electively switched to any oral agent until they have been compliant with the depot regimen for at least 1 year.

Additional clinical concerns. The following issues and concerns should be considered and addressed prior to changing antipsychotics:

- There are times when the target symptoms may be more easily resolved by a more straightforward medication adjustment, such as altering the dosage of the current regimen. For example, if a patient is experiencing persistent flare-ups of positive symptoms when treated with low-dose haloperidol decanoate (e.g., 100 mg i.m. per month), the first step should be to increase the dose of haloperidol decanoate to a target of 200 mg per month. Or, if there are persistent EPS, clinicians should first try adding benztropine or propranolol (for akathisia).
- It is unlikely that switching antipsychotics will solve active substance abuse problems. Patients with active substance abuse problems need psychosocial interventions targeting the specific issues facing the dual diagnosis patient. Overemphasis on a psychopharmacologic solution may be a distraction from psychosocial interventions or may create false expectations that the new treatment by itself will cure the substance abuse problem. Also, because many dual diagnosis patients will stop their oral medications during episodes of street drug or alcohol use, switching a dual diagnosis patient who is actively using street drugs or alcohol from a depot therapy regimen would be of particular concern.
- Special consideration must be given to the proper timing of a switch. Patients who anticipate the occurrence of a major life stressor, such as a move, a new job, or final examinations, should not be switched until these stressors have passed. The switch should be made only when no significant life stressors are anticipated.[5]

Barriers to Switching Outpatients

The most obvious barrier to switching an outpatient to an atypical antipsychotic is cost. These agents are considerably more expensive than the conventional antipsychotics. Most patients with schizophrenia cannot afford medications and rely on third-party payers. Since the cost issue is well known, it will not be discussed any further here. A less obvious barrier to switching medications during maintenance treatment is the limited time available from mental health staff. Changing medications during the maintenance phase requires a greater commitment of time

*Because there is little research literature or established practice guidelines in the area of patient selection for atypical antipsychotics, these recommendations are based on the authors' clinical experiences.

from the treating clinician or treatment team. For psychiatrists working with treatment teams in busy outpatient mental health services, the time required for patients whose medications are being switched is much greater than that required for patients whose old prescription is simply renewed. Furthermore, the follow-up period after switching requires increased monitoring and may overtax staff, especially when the mental health clinicians have a fixed number of outpatients. Finally, treatment of patients who were formerly nonfunctional because of negative symptoms may lead to sufficient improvement to require rehabilitation.[16–18] This need will increase the demand placed on rehabilitation services and may further stress an already overburdened service system.

STARTING (OR SWITCHING) INPATIENTS

Indications for Inpatients

The characteristics of the ideal candidate for starting (or switching to) an atypical antipsychotic as an inpatient are very similar to those discussed above for outpatients. An atypical antipsychotic is indicated for those patients who are admitted to the hospital because they are refractory to their current treatment despite compliance during an adequate trial of conventional antipsychotics (e.g., a 6-month trial of depot treatment) or for those inpatients who do not respond to or cannot tolerate a trial of a conventional antipsychotic. Another important indication for switching while the patient is hospitalized is a request for a new medication from the outpatient service.

Switching medications at the time of relapse and rehospitalization has several advantages over switching during outpatient treatment. Since the chief risk of switching antipsychotics among stable outpatients is relapse, this risk is no longer relevant if the new medication is started when the patient has already relapsed. Also, since relapse usually is associated with increased monitoring and supervision of treatment, introducing the new agent at this time is easier because the additional monitoring needed during the crossover is already in place. Thus, some of the problems of switching will be minimized if the patient is crossed over at the time of relapse in an inpatient setting.

Contraindications and Countervailing Clinical Factors for Inpatients

Contraindications. In our opinion, the following inpatients should not be electively switched to another antipsychotic:

- Patients with a history of excellent response to their previous antipsychotic medication.
- Patients who refuse the recommendation to switch. Refusal, though an obvious reason, may not be apparent to family members, who may need an explanation for the decision not to try an atypical antipsychotic.
- Patients who absolutely need a short-acting intramuscular route of antipsychotic medication. At present, none of the atypical antipsychotic agents are available as a short-acting intramuscular injection. Many clinicians supplement an oral antipsychotic with intramuscular lorazepam for acute agitation[19]; in such a situation, the lack of a short-acting intramuscular preparation of atypical antipsychotics is not a problem.
- Patients whose psychosis requires immediate stabilization because they present a danger to themselves or others. For such patients, the need for a medication regimen that works as quickly as possible must take priority. For example, a patient with a history of violent behavior on an inpatient ward who is known to respond quickly to a combination of haloperidol and lorazepam should be restarted on that regimen upon admission. For this patient, resolution of the immediate psychosis overshadows long-term outcome issues. Often, the psychopharmacologic history is of paramount importance. Starting the patient described above on an atypical antipsychotic would be very sensible if the history indicates that the past violent behavior did not respond quickly to conventional antipsychotics.
- Patients who will definitely need depot medication for compliance reasons after discharge.

Countervailing clinical factors. The following issues and concerns, although not necessarily contraindications for switching, require consideration before the decision is made to switch antipsychotic agents in an inpatient setting:

- The patient was started on an intramuscular form of a conventional antipsychotic at the time of admission. Agitated patients being admitted through an emergency service are frequently started on intramuscular forms of conventional antipsychotics, often combined with the short-acting benzodiazepine lorazepam. A common question for clinicians is whether or not to switch to an atypical antipsychotic after patients are admitted from the emergency room and have already been started on a conventional antipsychotic.
- It may be somewhat more difficult to start atypical antipsychotics in patients who, because of acute symptoms, temporarily refuse oral antipsychotics during the beginning of their hospitalization. For those patients, clinicians would have to decide between maintaining continuity of the acute regimen or switching to an atypical in the midst of an acute treatment.

Barriers to Starting Inpatients

While *in theory* an inpatient hospitalization may be an ideal time to start a new treatment, *in reality* this opportunity is often lost. In many cases, the physician does not know the patient well and will have to glean information

from outpatient sources. The lack of available information from the outpatient source may be a major limitation to switching medication at the time of hospitalization. The flow of information between outpatient and inpatient settings is notoriously poor and may not be sufficient for the hospital staff to ascertain that a change in treatment would be acceptable to or adequately supported by the patient's outpatient system. Also, there may not be enough time to initiate and monitor the switch if a patient is hospitalized for only a brief period. The physician will be faced with the trade-off between controlling and stabilizing the psychosis rapidly and changing the patient to a different medication that may offer greater benefits in the long run. Finally, there may be a question as to whether the outpatient setting is willing and able to prescribe and monitor the newer antipsychotic after discharge.

PSYCHOEDUCATION

Translating Indications Into Patient and Family Concerns

Adequate and effective psychoeducation must be provided to patients and their families before a medication switch is made. It is important to keep in mind that patients and families do not think of their problems in terms of the clinical language used by physicians. Rather, patients are concerned with the day-to-day consequences of their symptoms and their effects on their relationships, jobs, and ability to function. Patients are worried about how medications help, or limit, their ability to meet life's goals. They are also concerned that they will be stigmatized by appearing "medicated." Families may be distressed about the risk of violence or disruptive behavior in the home, or they may become heartbroken when they see their loved one appear lifeless, either as a direct result of the illness or as a consequence of the medication. To discuss new treatment options in ways that are meaningful to the patient, physicians must express symptoms and side effects as they relate to the concerns and frustrations of patients and families (see Table 1). The left-hand column of Table 1 shows common problems that are standard clinical indications for switching antipsychotics. The middle and right columns list parallel examples of how patients and families experience and report these problems.

Establishing a Consensus During Psychoeducation

A person with schizophrenia is often treated by an extended network of mental health care professionals, or may be supported by a network of concerned family or friends. The impact of switching antipsychotic medications can reverberate through these networks. Possible effects within the patient's network range from providing short-term support during the crossover period to readjusting long-term rehabilitation goals should the person respond to the new medication. Therefore, it is a good idea to discuss the pros and cons of the medication changes *in advance* with anyone directly involved in the patient's mental health care or social support network. Potential concerns of anyone in the patient's network are discovered before the crossover and can be worked out before the crossover is started. This step may seem cumbersome and time-consuming in the short-run, but, in the long run, it saves time and improves the chances of a successful crossover. Case managers and family members are more likely to support medication changes if they know about them beforehand and the decision to change medications becomes a *collaborative* one.

Short-Term Crossover Issues

Crossover to a new treatment can lead to a number of problems in the short term. Patients must be made to understand that their symptoms may flare-up as the treatment is changed, and there may be a transient increase in side effects ensuing from withdrawal of the previous treatment. Clinicians need to discuss these issues with patients and their families to ensure realistic expectations for the new treatment and to avoid disappointment. Clinicians need to walk a fine line here, on the one hand giving a sense of hope that changing medication might be helpful, while on the other hand not promising too much or guaranteeing success. It is important that the physician discuss the expected outcome of new antipsychotic treatment with the patient before making the switch. As patients begin to improve, they may have hope for a cure and then later have to deal with the realization and ensuing disappointment that they still are not cured. Physicians will maintain more credibility by predicting the limitations of treatment *before* the switch than by trying to explain these limitations *after* the patient has been disappointed from such unrealistic expectations of the new medication.

Patients or families may also have unrealistic expectations regarding the time frame in which benefits from the new medication will occur. These, in turn, may lead to disappointment and premature abandonment of any antipsychotic medication. It can be helpful to predict these issues and to obtain a commitment from the patient (and family) to be fastidious about the medication regimen, to promptly report any side effects or flare-ups that may occur, and to persist with treatment at therapeutic doses for at least several months before making any final evaluations on the medication's effectiveness. For patients who "occasionally" use street drugs or alcohol (despite admonitions), the physician could try to get a commitment from the patient to temporarily refrain from using street drugs or alcohol during the crossover period.

For outpatients who are switched for elective reasons, the treatment trial with the newer medication should be at least 6 weeks and preferably last 3 months. However, 3 months feels like a long time for outpatients who are in distress and want to feel better right away. Physicians need to be especially supportive and encouraging during this period.

Table 2. Advantages and Disadvantages of Various Crossover and Crosstaper Options*

Crossover Method	Advantages	Disadvantages
Abrupt discontinuation of the previous antipsychotic and starting the new antipsychotic	Most straightforward Medication errors less likely than with other approaches Appropriate for inpatient settings where patients are supervised and fast crossovers are needed Appropriate for patients on maintenance depot therapy because of long half-life of depot route	Chance of symptom flare-up during crossover may be greater than with other methods Increased chance of withdrawal reactions (eg, withdrawal dyskinesia) associated with withdrawal of previous antipsychotic Not recommended for clozapine patients
Adding a new antipsychotic and immediately tapering the previous antipsychotic	Starts crossover process when olanzapine is initiated Appropriate when relief from EPS is needed	If taper is too quick, there is the possibility that both medications are given at subtherapeutic doses
Adding a new antipsychotic and delaying the taper of the previous antipsychotic	Probably the safest method when consequences of crossover relapse are the greatest concern May be appropriate when switching patients who have only recently been stabilized (< 3 months) from an acute psychotic episode May be appropriate to use the crossover time as a test period to ascertain oral compliance for patients on depot antipsychotics	Greater possibility of ongoing polypharmacy should taper not be finished (eg, patient is discharged on combination antipsychotics and the crossover is never finished by the outpatient clinician)

*EPS = extrapyramidal symptoms.

Long-Term Crossover Issues

After the switch is made and the short-term issues have been addressed, a number of long-term concerns need to be discussed as part of the psychoeducation process. Patients may find that they have traded one set of side effects for another, perhaps exchanging EPS for weight gain. Patients will have to learn to cope with any new effects and make an effort to keep the advantages and disadvantages of the new regimen in perspective. A successful switch may increase a patient's level of function, which in turn may lead to new challenges and stresses.[20,21] As a consequence, the patient may experience a return of symptoms and eventual disappointment in the limitations of the new medication. This eventual disappointment after patients are switched from conventional to atypical drugs is a long-term management problem that presents a significant challenge to patients and their clinicians.

ANTIPSYCHOTIC CROSSOVER TECHNIQUE

The Crossover Process

Once the decision has been made to switch antipsychotics and a specific agent has been chosen, treatment planning should focus on the technical aspects of making the crossover as safe and effective as possible. Complications may arise from any one of the following problems, which should be considered in the differential diagnosis of any increase in symptoms shortly after the crossover is started:

- Anxiety from changing medications causes symptom flare-up.
- Antipsychotic and anticholinergic withdrawal syndromes cause worsening of psychotic symptoms.[22]
- Medication errors during crossover result in under- or overmedication.
- The protective effects of the previous medication wear off before the newer one takes effect.[23]
- The newer medication is not as effective as the previous medication.[24]

Since there are virtually no published controlled clinical trials to determine the optimal means of crossing patients over from one antipsychotic agent to another, no single crossover technique has been recognized as the accepted protocol. However, because abrupt crossovers to risperidone have been reported to be unsatisfactory,[1] the current de facto standard of many clinicians for stable outpatients is to temporarily overlap ("crosstaper") the previous oral antipsychotic and the newer one.[23,25] An exception to the overlapping (crosstaper) is switching from depot therapy. Because of the long half-life of depot medications, the new antipsychotic can simply be added to the patient's regimen after the last injection of the depot agent. Abrupt crossovers are more routinely accepted as a reasonable approach for switching inpatients who can be monitored closely. It is too early to say whether the crossover experience with the newer antipsychotics (e.g., olanzapine or sertindole) will differ from that of risperidone. Table 2 outlines some of the advantages and disadvantages of different approaches to treatment crossover.

Management of Antipsychotic and Anticolinergic Withdrawal

There are few published observations concerning crossover to a new antipsychotic regimen. However, findings from studies on antipsychotic/anticholinergic withdrawal can be generalized to help us anticipate problems that may occur during crossover from one antipsychotic to another. Obviously, care must be taken in making such generalizations since the effect of adding an atypical agent following withdrawal of antipsychotic and anticholinergic treatment

Table 3. Common Withdrawal Syndromes During Antipsychotic or Anticholinergic Discontinuation

Category	Description	Usual Timing	Comments
Anticholinergic withdrawal	Symptoms include malaise, nausea, vomiting, and diarrhea	First few days	Occurs with low-potency conventional antipsychotics and clozapine More likely to happen with abrupt anticholinergic withdrawals
Rebound akathisia	Typical symptoms of akathisia but may be indistinguishable from psychosis or anxiety	First few days	Consider akathisia in differential diagnosis of behavioral changes soon after antipsychotic or anticholinergic withdrawal Addition of β-blocker or benzodiazepines might be helpful
Rebound dystonia	Acute dystonia precipitated by anticholinergic withdrawal	First few days	Restart anticholinergic, or in case of clozapine, add anticholinergic
Rebound parkinsonism	Parkinsonian symptoms of tremor, muscle rigidity, and akinesia	First week	Common when an anticholinergic agent is discontinued with the high-potency conventional antipsychotic May also occur from discontinuing low-potency antipsychotics
Withdrawal dyskinesia	Choreoathetoid movements that are indistinguishable from tardive dyskinesia	1 to 4 weeks	Dyskinesia is clinically indistinguishable from tardive dyskinesia Most are transient and abate within several months Should dyskinesia last > 3 months, change diagnosis to tardive dyskinesia

is not yet known. There is considerable disagreement in the literature regarding the nature of and interrelations between withdrawal problems. Nevertheless, review of published information on withdrawal of antipsychotic or anticholinergic drugs suggests that withdrawal problems can be categorized as (1) symptoms of anticholinergic withdrawal,[26–33] (2) rebound akathisia,[33–38] (3) rebound dystonia,[39–41] (4) rebound parkinsonism,[36–40,42–45] and (5) withdrawal dyskinesia.[29,46–53] These syndromes are described in Table 3. Clearly, there is a need to develop crossover techniques that will minimize or avoid these problems and enable patients to change their treatments without untoward effects.

Acute problems occurring during the first week of the crossover should be viewed as possible withdrawal reactions and, if appropriate, treated accordingly. Mild cases of anticholinergic rebound may pass after a few days and thus not require treatment. More severe cases should be treated by adding an anticholinergic or restarting the (anticholinergic) antipsychotic. Rebound akathisia and parkinsonism can often be prevented by continuing the patient's anticholinergic medication until a month after the crossover is fully completed, or by slowly tapering (not abruptly stopping) the anticholinergic. Rebound akathisia and parkinsonism should be treated with an appropriate anti-EPS agent. Withdrawal dyskinesia can occur later on and can be dealt with by reassurance or, if needed, by slowing the taper of or reinstituting the previous conventional antipsychotic.

Management of Symptom Exacerbation

The most important part of management during the crossover process for outpatients is increased monitoring. This could range from having the patient come in for extra visits to being available by telephone. If symptoms or side effects increase once the crossover is started, there should be an effort to continue the crossover process and complete the trial of the newer antipsychotic. Premature abandonment of the newer medication before a full trial is completed exposes patients to the risks of the switch without giving them the chance to reap the potential benefits. Management of symptoms occurring during crossover depends on the nature and the timing of the symptom. Situational anxiety from making a medication change can be treated psychologically with reassurance and pharmacologically with a benzodiazepine.

For flare-ups in psychotic symptoms that occur later in the switch, first consider whether the increase in symptoms is due to normal variations in the patient's symptoms. If so, watchful waiting is called for, along with encouraging the patient to avoid stressful situations. If there are breakthrough symptoms above and beyond baseline symptoms, options include adding a benzodiazepine, restarting or raising the dose of the previous medication, or increasing the dose of the newer antipsychotic. In these situations, the medication regimen should be checked to make sure that the patient is getting therapeutic doses of at least one of the antipsychotics. Finally, medication underdosing, medication noncompliance, and substance abuse should be considered when persistent psychotic symptoms extend beyond the crossover period.

Management of Noncompliance

It is well known that patients on conventional antipsychotics often have to contend with very distressing side effects related to EPS. The atypical antipsychotics are generally much better tolerated. Not surprisingly then, one of the most common goals of switching medications is to

improve compliance with an antipsychotic regimen. Paradoxically, however, one of the complications of switching medication can be to trigger noncompliance. Often, the noncompliance around the time of switching medications comes from the psychologic and pharmacologic disruptions inherent in the crossover process. Fortunately, these kinds of disruptions are quite predictable and amenable to intervention.

Medication errors. Medication errors are an underrecognized problem during crossover. Patients often do not fully understand medication instructions during this time. They can become confused or overwhelmed by what is asked of them. The likelihood of an error is greater for patients who have significant cognitive impairment from their schizophrenia. This is especially true when antipsychotic medications are overlapped during the crossover process, so that patients have to increase doses of the new antipsychotic while decreasing doses of their prior medication. It is important to carefully review the medication at each appointment, and it is helpful to have the patients bring their medications with them during their appointments so that you can review exactly what was taken.

Distress from early side effects. Some of the newer agents have their own set of side effects. It is important to educate patients on the temporary nature of some of these side effects. The EPS and anticholinergic withdrawal syndromes arising from withdrawing the previous antipsychotic or anticholinergic have already been mentioned; keep in mind that to the patient, these withdrawal problems feel like side effects from the newly started antipsychotic.

Another issue is early sedation. Sedation during the first weeks after crossover may be a problem with the newer antipsychotics and is most common with clozapine and olanzapine. Depending on the patient, the sedation may be a welcome benefit or a problem. If it is a problem, then the treatment for this kind of early sedation is usually to try to wait it out. Most of the time, this early sedation is self-limited and wanes several weeks after the crossover. However, it is important to warn patients about sedation and to reinforce the time-limited nature of the side effect. The case vignette below describes how patients can become disillusioned with olanzapine when misinterpreting sedation as a worsening of other symptoms.

> *Ms. A was switched to olanzapine because of persistent problems with motivation. After a week on olanzapine therapy, she reported that she wanted to discontinue the olanzapine because the sedation from olanzapine made her motivational problem worse. In fact, she was angry at her clinicians for suggesting that olanzapine might help her with this problem. She was reassured that this side effect was most likely temporary and was eventually persuaded to stay on olanzapine for a full 6-week trial. The sedation disappeared a few weeks later, and she went on to have a dramatic response to olanzapine. Six months later, Ms. A continues to improve and is appreciative that we convinced her to stay on the medication.*

Noncompliance from switching medication right after a change in treatment service. Sometimes, medication changes are a consequence of a change in doctors or treatment service. The new treatment team might have a different prescribing philosophy, or be more enthusiastic about the newer antipsychotics than the previous clinicians. However, you should be cautious about changing medications right away. First, you may need time to get to know the patient and the patient's treatment history. A more subtle issue can arise from unresolved transference feelings toward the previous doctor or treatment service. A medication regimen can be a tangible part of the therapeutic alliance with the prescribing physician. Patients may be very reluctant to change their medications because the medication represents the remains of their relationship with that clinician. When considering switching a patient's antipsychotic medication shortly after they have changed clinicians, it is a good idea to explore the meaning of the medication as it pertains to the patient's previous relationship with the prescribing doctor.

> *Ms. B had a history of repeated psychotic episodes until she was finally stabilized on thioridazine in the context of a weekly supportive therapy from a psychiatrist "who understood me better than any other doctor." Her therapist relocated, and she continued the combined psychopharmacologic and psychotherapeutic treatment with another doctor. Despite being stabilized, she had persistent positive and negative symptoms and seemed to be an ideal candidate to switch to an atypical antipsychotic. However, she reported that her prior therapist had "saved my life," and clearly connected the thioridazine prescriptions with that relationship. Therefore, although from a psychopharmacologic point of view it was appropriate to switch medications, the therapeutic alliance with the new doctor was not established. Accordingly, the switch was postponed for several months so the therapeutic relationship could be solidified before changing the antipsychotic medication.*

Crossover to Olanzapine

Because olanzapine has only recently become available, there is some uncertainty about the appropriate starting doses and target doses of this agent. Table 4 offers guidelines and prescribing options for patients who are being started on olanzapine. Further information about the dosing, metabolism, and side effects of olanzapine is provided elsewhere.[54–58]

Table 4. Possible Starting and Target Doses of Olanzapine and Their Advantages and Disadvantages*

Dose	Advantages	Disadvantages
Starting dose		
5 mg	For antipsychotics in general, titrating up from lower doses decreases risk of EPS Some clinicians are more comfortable with the prescribing principle of slower upward titration	Takes longer to reach therapeutic dose of 10 mg
10 mg	Straightforward: starting dose is therapeutic dose	May be more likely to cause initial sedation at the beginning of crossover than a starting dose of 5 mg
> 10 mg	Suitable for patients who might otherwise require higher doses of conventional antipsychotics (eg, an acutely ill, agitated, violent patient needing immediate sedation; or patients abruptly discontinuing clozapine or very high doses of conventional antipsychotics)	Generally not recommended. Starting doses > 10 mg are associated with greater likelihood of weight gain Doses > 10 mg/d are most appropriate after completion of an olanzapine trial at 10 mg/d
Target dose		
5 mg	May be a suitable lower target dose for the elderly or medically ill May be suitable for patients with *extreme* vulnerability to EPS (eg, patients with a history of NMS)	May be subtherapeutic for many patients
10 mg	Shown to be as effective as haloperidol for positive symptoms	Some patients may do better on doses > 10 mg/d
> 10 mg	May be more appropriate for patients being switched from clozapine; many clinicians recommend target olanzapine doses of ≥ 20 mg/d May be appropriate for patients who are partially responsive to lower olanzapine doses	Increased cost of medication. There may be some increased risk of EPS, especially when doses are > 15 mg/d Little information available on doses > 20 mg/d

*Abbreviations: EPS = extrapyramidal symptoms, NMS = neuroleptic malignant syndrome.

Switching From Clozapine*

Patients receiving clozapine are likely to have greater difficulties with crossover than patients receiving other agents.[22] No other atypical antipsychotic has been proved to be as effective as clozapine for treatment-refractory symptoms. Patients who are stable on clozapine should be electively withdrawn from this treatment only for good reasons.[23] Anecdotal reports suggest that patients withdrawn from clozapine may suffer more rapid relapse than would be expected following withdrawal from a typical neuroleptic.[25] Furthermore, despite a paucity of hard data, the clinical impression persists that the severity and frequency of withdrawal symptoms may be greater after discontinuation of clozapine than after discontinuation of typical antipsychotic treatments.[24] Finally, should the patient need to be restarted on clozapine, retitrating the clozapine regimen to therapeutic doses will take a long time.

Because the chemical structure of olanzapine is so similar to clozapine, the notion that olanzapine can replace clozapine has intuitive appeal. Unfortunately, early data and experience suggest that this will not be true for many patients. One study evaluated olanzapine against chlorpromazine with very ill, long-stay inpatients using a design that allowed the results to be directly comparable to the clozapine vs. chlorpromazine study.[59,60] The results suggest that olanzapine is not as effective as clozapine for this very ill population. Also, many experienced clinicians have noted unacceptably high relapse rates when clozapine is abruptly discontinued to start another antipsychotic such as olanzapine. For example, one experienced clinician found relapse rates as high as 80% within 4 weeks of stopping clozapine to start olanzapine (Levine R. Feb. 2, 1997. Written communication).

With these precautions in mind, the crossover from clozapine to olanzapine needs to be modified to reflect the increased risk. Of note is that there seems to be an informal consensus among expert clinicians on switching from clozapine to olanzapine. Whenever possible, clozapine should not be abruptly discontinued. Whenever possible, the new antipsychotic should be added to the clozapine regimen. Then, the clozapine regimen should be tapered very slowly. Many experts recommend a clozapine dosage reduction schedule of approximately 50 mg (range, 25–100) per week. Most experts recommend a target olanzapine dose of at least 20 mg per day. Whenever possible, the target dose of olanzapine should be fully in place before the clozapine is fully discontinued.

CONCLUSIONS

For many patients with schizophrenia, the atypical antipsychotics can offer remarkable benefits in terms of symptom relief or fewer side effects. However, the crossover process can be an obstacle to a successful change to

*This section covers elective crossover technique should a decision be made to switch from clozpine to olanzapine. However, most experts do not recommend switching clozapine responders to olanzapine.

this new treatment. To achieve the best results from a switch in antipsychotic medications, clinicians need to be comfortable with all aspects of the crossover procedure, including the risks and trade-offs involved in the various crossover options. Clinicians need to determine which patient is most likely to benefit from a medication change, to be able to communicate the plan in psychoeducation sessions, and to have the psychopharmacology skills to enact the crossover. Also, clinicians need to understand the ins and outs of the particular service system in which the switch takes place, especially when it involves transitions of care. In the short term, all of this requires greater effort on the part of the clinician. However, the extra time and effort invested in the crossover can be rewarding since the success of the switch often depends on these efforts. A crossover that results in relapse or premature cessation of the newer medication is at best demoralizing and can be a major setback to the patient, family, and clinician. In contrast, a successful crossover can lead to a life-changing response that can be a most gratifying experience.

Drug names: benztropine (Cogentin and others), chlorpromazine (Thorazine and others), clozapine (Clozaril), haloperidol (Haldol and others), lorazepam (Ativan and others), olanzapine (Zyprexa), propranolol (Inderal and others), risperidone (Risperdal), thioridazine (Mellaril).

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