In recent years, several guidelines and algorithms have appeared to help clinicians address the issues of best practice in the management of psychiatric disorders. As the standard of care has moved from the use of first-generation antipsychotic medications to the use of atypical antipsychotics in the treatment of schizophrenia and bipolar disorder, clinicians are faced with the challenge of when to change medications in patients and which medications to choose. And, with the widespread use of atypical antipsychotics has come an increased concern with the evaluation, treatment, and possible prevention of metabolic syndrome and other complications associated with antipsychotic pharmacotherapy.

What is the standard of care in treating schizophrenia and bipolar disorders? How can clinicians optimize outcomes in treating serious mental illness across the lifetime of the patient? What should guide the clinician in choosing a therapeutic agent? And, if complications arise, how can the clinician move confidently from one agent to another? This article presents a summary of the recent literature on treatment response and recommended interventions in individuals who present with psychotic illness, paying particular attention to strategies that optimize treatment and outcomes in the stable phase. It addresses the clinical issues that bear on the selection of antipsychotic agents and examines the process of switching from one antipsychotic to another. With the introduction of second-generation antipsychotic agents has come a change in the concept of stability and a redefinition of the goals for the stable phase of illness. This article reviews the process of assessment of ongoing treatment, considering what goals are appropriate, and when to revise treatment goals. Finally, this article examines new assessment tools and collaborative treatment models. ([Adv Stud Med. 2005;5(3C):S216-S229])

Schizophrenia and bipolar disorders are lifelong illnesses that can have devastating effects on the social, occupational, and interpersonal lives of patients and families. These disorders are associated with high rates of suicide, serious medical problems, and enormous economic burden to patients, families, and to society as a whole. Treatment across the life cycle involves pharmacotherapy and a coordinated program of psychological interventions, family education and support, and social and vocational rehabilitation.

In recent years, several guidelines have been developed for the treatment of schizophrenia and bipolar disorder to provide clinicians with recommendations on treatment based on empirical data and on expert knowledge. Among these guidelines are the American Psychiatric Association’s (APA) practice guidelines for the treatment of patients with schizophrenia and bipolar disorder; the Expert Consensus Guideline Series; the Schizophrenia Patient Outcomes Research Team treatment recommendations; the Texas Medication Algorithm Project; and other guidelines. The guidelines differ in scientific rigor, comprehensiveness, and clinical applicability, but taken...
together, they provide guidance to the clinician based on available evidence and expert opinion in those areas where scientific evidence is limited.10

**TREATMENT MODELS**

The guidelines for the treatment of disorders such as schizophrenia and bipolar disorder address the course of illness, models of vulnerability and coping, and dimensions of outcome. Although there are less data available on the treatment of bipolar disorders, many of the same principles apply. Guidelines emphasize the following goals of treatment: to reduce or eliminate symptoms; to maximize the quality of life and adaptive functioning of the patient; and to promote and maintain recovery from the long-term effects of illness as much as possible. To achieve these goals, the psychiatrist must create a supportive therapeutic alliance with the patient to learn not only about the patient’s symptoms and concerns but also about his or her goals and hopes, thus developing a collaborative treatment plan, and to maximize the likelihood of adherence to medication.1 For an optimal outcome, the psychiatrist must identify targets of treatment, use outcome measures to clarify progress, and be prepared to reassess the treatment plan as the patient’s situation changes or as new therapeutic tools become available.

**MODEL OF ILLNESS AND OUTCOME MEASURES**

A useful conceptualization of maintenance treatment of schizophrenia is based on a model of vulnerability, stress, and coping,11-13 which posits a multifactorial predisposition leading to an increased risk of symptomatology. Interaction between neurocognitive processes (such as deficits in information processing or executive functioning) and environmental stressors (such as high expressed emotion in the family or untoward events at key developmental milestones) can lead the patient from a subsyndromal state toward manifestation of illness. Biological, psychological, and social protective factors, such as antipsychotic medication, good coping strategies, and a calm and structured environment, may moderate the emergence of clinical symptoms. This biopsychosocial model supports an approach to treatment that integrates pharmacologic treatment with evidence-based psychosocial interventions (such as family psychoeducation, social skills training, and cognitive behavior therapy).

The biopsychosocial model also points toward several areas that should be considered in assessments of treatment efficacy and outcome.14 These areas include clinical dimensions, such as positive and negative symptoms, depression and anxiety, and side effects of medication; rehabilitative dimensions, such as social, vocational, and interpersonal functioning; “humanitarian” issues, such as quality of life and satisfaction with treatment; and issues relating to the public welfare, such as safety and cost of treatment.

**COURSE OF ILLNESS**

The treatment plan will vary according to the needs of the patient at a particular time within the longitudinal course of illness. Over a lifetime, psychotic illness waxes and wanes and generally follows an unsteady and often unpredictable pattern.15 The course of an episode has been divided into the acute phase, the stabilization phase, and the stable phase.1 Treatment planning reflects these divisions. Although there is evidence that early treatment may reduce morbidity and allow a better quality of life for patients and families, many patients do not receive adequate psychiatric help until 12 to 24 months after their symptoms first appear.16-18 Therefore, the subsyndromal or prodromal stage has become the focus of early intervention programs that are studying the impact of psychoeducation, cognitive behavior therapy, and antipsychotic medication.

**THE ACUTE PHASE**

In the acute phase, the goals of treatment are “to prevent harm, control disturbed behavior, reduce the severity of psychosis and associated symptoms (e.g., agitation, aggression, negative symptoms, and affective symptoms), determine and address the factors that led to the occurrence of the acute episode, effect a rapid return to the best level of functioning, develop an alliance with the patient and family, formulate short- and long-term treatment plans, and connect the patient with appropriate aftercare in the community.”11 Treatment with antipsychotic medication is fundamental to achieving these aims. Atypical antipsychotics available in the United States at this time include aripiprazole, clozapine, olanzapine, quetiapine, risperidone, and ziprasidone. Because of concerns about agranulocytosis, clozapine is not recommended as a first-line therapy and is treated separately from the other medications in all guidelines and treatment recommendations. The practice guide-
lines of the APA divide antipsychotic medication into 4 groups:

- Group 1, first-generation agents: chlorpromazine, fluphenazine, and haloperidol;
- Group 2: risperidone, olanzapine, quetiapine, ziprasidone, aripiprazole;
- Group 3: clozapine; and
- Group 4: long-acting injectable antipsychotic agents.

The APA guidelines suggest that group 2 is the “default” treatment for most patients needing treatment for an acute psychotic episode and support the choice of clozapine for persistent suicidal ideation or behavior, persistent hostility and aggressive behavior, or for patients with tardive dyskinesia. Although some meta-analyses suggest that the choice of atypical over first-generation antipsychotics is unsettled, there is growing consensus about the use of atypical antipsychotics as first-line drugs in the treatment of first-episode psychosis, in addition to in the treatment for recurrent psychosis. The British National Institute for Clinical Excellence recommended to the English and Welsh National Health Services that atypical antipsychotics should be considered alongside first-generation antipsychotics as one of the first-choice options to treat people with newly diagnosed schizophrenia. The Texas Medication Algorithm Project recommends using atypical antipsychotics for first-episode patients or those patients never before treated with atypical antipsychotics, and recently revised their recommendations to include aripiprazole and ziprasidone among those first-line agents.

**TREATMENT IN THE STABILIZATION AND STABLE PHASES**

The APA defines these goals of treatment in the stabilization phase, between acute illness and stability: “to reduce stress on the patient and provide support to minimize the likelihood of relapse, enhance the patient’s adaptation to life in the community, facilitate continued reduction in symptoms and consolidation of remission, and promote the process of recovery.” The primary aim in the stable phase is to prevent relapse. Relapse prevention, once achieved, permits the patient to focus on maintaining or improving his or her level of functioning and quality of life and ensure that increases in symptoms or relapses are effectively treated and clinical monitoring for adverse treatment effects continues. These goals include establishing effective control of positive symptoms, such as delusions and hallucinations, self-injury and suicidal or homicidal ideation, and aggressive or violent behavior. Additional concerns include the mitigation of negative symptoms, depression, anxiety, and disorganized thoughts and the attenuation of social withdrawal. It is essential to identify and address complications, such as poor medication adherence or comorbid substance abuse, both of which are common barriers to recovery. Other psychosocial issues, such as homelessness, social and occupational functioning, and involvement with the criminal justice system, must be addressed.

**THE WHOLE PATIENT AND THE RECOVERY MODEL**

Stability is often defined as the absence of relapse. Used as such, the concept of stability does not tell us anything about most of the other essential features of outcome. In particular, although a patient may not show an acute exacerbation of the illness, they may continue to experience symptom breakthrough, impairment in relationships, and side effects from medications. This phase generally marks a period of ongoing engagement in pharmacologic treatment and psychosocial programs that support activities of daily living. In the past, these were reasonable maintenance goals in the treatment of chronic psychiatric illness. However, this view is a long way from recovery. The recovery model has emerged in the context of second-generation antipsychotic medications as an organizing principle in thinking about aims of treatment. Recovery should not be misunderstood as cure because cure is not a realistic expectation at this time. Instead, the recovery model aims not only to prevent relapse and control symptoms but to look at the patient’s hopes and goals and to attempt to reintegrate the patient into as full a life as possible. Recovery is not linear nor is it a function of medication alone. It is a process involving medication evaluations and re-evaluation, psychosocial interventions, rehabilitation, and psychological therapy to address patients’ needs as those needs change. We do not know how to predict which patients will recover, or how much they will recover, over how long a time. However, we do know that if expectations are low, there will be little incentive to try innovative therapies that may offer possible benefits. Therefore, the assessment of the “stable” patient should address a variety of domains:

- Are there persistent positive symptoms? How do they impact the patient’s level of functioning? Do they help (eg, voices may be welcome compan-
ions) or do they hurt (as when paranoia causes social withdrawal)?

- Are there cognitive problems? Might they be caused by positive symptoms, sedation, anticholinergic effects, or drug-drug interactions in polypharmacy?
- Are there persistent negative symptoms? Might they be caused by positive symptoms, extrapyramidal symptoms (EPS), such as akinesia, sedation, or social withdrawal, in response to stigma?
- Are there persistent affective symptoms? Are they caused by depression, EPS, or demoralization?
- Are there persistent problems with side effects of medication? What are the consequences of those side effects for the patient's health and self-image?
- How do these symptoms and side effects affect the patient's quality of life? Does the patient have close relationships? How does the patient spend his or her time? What goals does the patient care about? What concerns do the patient and family have regarding the risks and benefits of changes in medication?22

The psychiatrist who treats a patient with these questions in mind will regularly review the current treatment plan not only in terms of recurrence of symptoms but also in terms of quality of life for patients and families. In seeking to optimize patient outcomes, the psychiatrist will consider the patient's level of function across many domains.

**THE STABLE PHASE: PHARMACOLOGIC TREATMENT**

Importantly, the prevention of relapse almost always requires that the patient accept long-term pharmacologic treatment.23 Unfortunately, in practice, medication nonadherence is the biggest limitation, with postdischarge nonadherence rates as high as 90% in the first year,24-27 which in turn results in higher rates of psychiatric and medical hospitalization and greater overall cost.28,29 Although improved compliance with atypical antipsychotics has yet to be convincingly demonstrated,30-31 if adherence is to increase, the medications used must be effective, safe, and free of significant side effects.32 Traditional antipsychotic drugs are associated with high rates of extrapyramidal side effects and tardive dyskinesia, which occurs in approximately 5% of patients after 1 year of antipsychotic treatment.33 Further, traditional antipsychotic drugs do not address negative symptoms or ameliorate the depression that often accompanies chronic psychotic illness. Atypical antipsychotics offer the possibility of medication effective in more domains and with more tolerable side effects. Do new-generation antipsychotics show greater efficacy in the prevention of relapse?

"In seeking to optimize patient outcomes, the psychiatrist will consider the patient's level of function across many domains."

**PREVENTION OF RELAPSE: THE PRIMARY GOAL**

Thus far, there are only a small number of long-term studies of the effectiveness of atypical antipsychotics on relapse in the literature. A combined analysis of large controlled trials found that risperidone was superior to haloperidol for the control of positive symptoms, such as hallucinations and delusions.34 Based on this finding, Csernansky et al compared risperidone with haloperidol in a 1-year trial studying relapse rates in patients with schizophrenia and schizoaffective disorder.35 In a double-blind study at 40 sites, they randomly assigned 397 stable adult outpatients with chronic schizophrenia or schizoaffective disorder to receive treatment with flexible doses of risperidone or haloperidol for a minimum of 1 year. Patients in the risperidone group were treated for a median of 364 days at a mean dose of 4.9 mg per day; those patients in the haloperidol group were treated for a median of 238 days at a mean dose of 11.7 mg per day. At the end of the study, 25.4% of patients in the risperidone group had relapsed, significantly lower than the 39.9% of relapse in the group treated with haloperidol. Survival curve estimates of the risk of relapse showed an even more robust difference between the risperidone group and the haloperidol group (34% vs 60%; \( P \) < .001). In addition, significant differences between risperidone- and haloperidol-treated subjects were seen in total scores on the Positive and Negative Syndrome Scale (PANSS) and in 4 of 5 factor scores at the last study rating. In the risperidone group, improvements from baseline to 1 year or to last study rating were seen in total scores and in positive symptoms, negative symptoms, disorganized thoughts, and in anxiety-depression; in the haloperidol group, symptoms were not improved over
baseline. In both groups, a large number of patients discontinued treatment for reasons other than relapse, 44.1% in the risperidone group and 52.7% in the haloperidol group. Adverse events were experienced by almost 90% of patients in both groups. Approximately 20% of patients treated with haloperidol experienced somnolence, agitation, and hyperkinesia, whereas risperidone-treated patients experienced a mean increase in body weight of 2.3 kg or 5.0 lbs.

In 2003, Leucht et al published a meta-analysis of studies of atypical antipsychotics in relapse prevention in schizophrenia. Restricting their analysis to trials with a minimum duration of 6 months, they looked at 6 randomized controlled trials comparing new-generation antipsychotic drugs with placebo and at 11 trials comparing atypical antipsychotics with conventional antipsychotic agents. They examined relapse, overall treatment failure, and drop-out rates caused by adverse events in studies involving more than 3,000 patients using the antipsychotics amisulpride, clozapine, olanzapine, risperidone, sertindole, ziprasidone, and zotepine. Considered as a group, the new antipsychotics were statistically significantly superior to placebo in relapse rates and treatment failure. No significant difference was found with respect to adverse events. However, the drop-out rate was high across all studies: 43% of patients treated with new antipsychotics compared to 72% of patients treated with placebo left the studies early because of relapse, inefficacy of treatment, adverse events, or loss to follow-up.

In the comparison of first- versus second-generation antipsychotics, 10 of 11 studies used haloperidol as the comparator. Considered as a group, raw relapse rates for the new antipsychotics were statistically significantly superior to conventional antipsychotics (risk difference, 0.08), particularly when relapse rates estimated from survival curves were analyzed. However, taken individually, only risperidone showed a significantly lower raw relapse rate compared to conventional antipsychotics and olanzapine showed a lower relapse rate calculated from survival curves. Treatment failure was significantly less for risperidone and olanzapine individually compared to conventional antipsychotics and, when the results across all drugs were pooled, the atypical antipsychotics were significantly superior. Approximately 49% of 1,314 patients treated with new antipsychotics compared to 66% of 669 patients treated with conventional antipsychotics left the studies early because of an undesirable outcome. In individual and pooled results, there was no significant superiority of new antipsychotics compared to conventional antipsychotics in the number of dropouts because of adverse events.

The authors point out that there are limitations to a meta-analysis, which cannot distinguish among differences in study design, and that in this study the results for individual new drugs were pooled in an exploratory way because of the small number of relevant trials. In the studies using placebo as comparator, only a few of the newer antipsychotics were tested, and patients were for the most part in the continuation rather than maintenance phase of treatment. In studies comparing atypical versus conventional drugs in the prevention of relapse, the magnitude of the advantage for atypical drugs was modest. Additionally, most studies used doses of haloperidol greater than 5 mg/day, exceeding the dose used by many clinicians for control of psychosis and high enough to lead to extrapyramidal side effects in most patients. Clearly more long-term studies of relapse need to be done, involving each of the atypical antipsychotic drugs. Nonetheless, these studies thus far lend support to the superiority of atypical antipsychotic medication in relapse prevention, in addition to in tolerability and symptom suppression.

**OTHER GOALS OF TREATMENT**

In addition to the prevention of relapse, other major goals of treatment in the stable phase of psychosis include the improvement of cognitive impairment, the prevention or amelioration of negative symptoms, and the reintegration of the patient into as full a life as possible. It is in these domains that the atypical antipsychotics offer greater hope than traditional antipsychotics. We will examine each of these domains individually.

**NEUROCOGNITIVE FUNCTION**

Cognitive impairment is an important determinant of functional outcome in schizophrenia and bipolar disorder, and research is beginning to examine the effects of newer antipsychotic drugs on cognitive measures. Keefe et al, in a meta-analysis of 15 studies published between 1990 and April 1998 (of which all but one concerned clozapine or risperidone), concluded that newer antipsychotics are significantly more effective than conventional antipsychotics at improving cognitive function. In particular, verbal fluency, digit symbol substitution, fine
motor function, and executive function showed most improvement, whereas there was modest improvement in attention subprocesses and little improvement in learning and memory. Subsequent reviews have confirmed an improvement in verbal fluency and psychomotor speed on clozapine, an improvement in working memory on risperidone, and general cognitive improvements in patients taking olanzapine and risperidone compared with haloperidol. These early studies were characterized by methodological problems and varying outcome measures that make generalizations difficult. Nonetheless, in a review of antipsychotic drug treatment in 2001, Barnes and Joyce concluded that the new antipsychotics, as a group, are superior to conventional drugs with respect to cognitive function and suggested that each of the atypical antipsychotics may have a distinct effect on cognitive function, which further research could illuminate.

Subsequent studies have added support to the possible benefits of the atypical antipsychotics on cognitive function. An open-label test in which patients were switched to olanzapine showed a statistically significant improvement in 3 cognitive domains: immediate recall, category fluency, and time on Trail A and B making tasks. Harvey et al showed improvement in global cognition in 6-week switch studies to ziprasidone from conventional antipsychotics olanzapine and risperidone. Although no study has shown that the atypical antipsychotics actually normalize cognitive function, future research may better define and understand the areas of cognitive function affected by specific atypical antipsychotic medications. At that point, it may be possible to tailor drug regimens best suited to individual patients’ needs. It is also important to recognize that 2 common side effects of antipsychotic medications—anticholinergic side effects and sedation—can also cause or exacerbate cognitive dysfunction in schizophrenia.

**Negative Symptoms**

Negative symptoms may represent a core feature of schizophrenia and also may be secondary to paranoia, medication side effects, depression, anxiety, or environmental deprivation. Negative symptoms are already seen in some prodromal states, and their prevalence in first-episode schizophrenia is reportedly between 4% and 10%. They are more prominent in males than females, and are more prominent with duration of illness. Treatment depends first on evaluating and addressing those secondary causes that may contribute to the appearance of negative symptoms. Although there are as yet no treatments of proven efficacy for primary negative symptoms, the results of short-term studies indicate that atypical antipsychotic drugs are more effective than haloperidol for the treatment of emotional blunting and social withdrawal. Amisulpride, quetiapine, olanzapine, risperidone, ziprasidone, and aripiprazole have all been reported to have efficacy against negative symptoms. Expert consensus guidelines consistently recommend the use of atypical antipsychotics for patients with predominantly negative symptoms or for those patients with a combination of positive and negative symptoms. In addition to pharmacologic therapies, several studies have shown a large aggregated effect of cognitive behavior therapy over supportive therapy for reducing negative symptoms, and one study of family psychoeducation reported an improvement in negative symptoms.

**Quality of Life**

Research indicates that positive symptoms show a low correspondence with functional impairments among patients with schizophrenia; instead, it is the cognitive impairment and negative symptoms that correlate with functional impairment and consequent quality of life. In one recent study, switching to an atypical antipsychotic resulted in significant improvement for most patients in positive symptoms, general psychopathology, and quality of life. Clozapine has been associated with significant improvement in social and occupational functioning. Because thus far there is limited evidence to support the efficacy of medications in improving functional status, the major interventions remain psychosocial and rehabilitative. Supported employment, including individualized job development, rapid placement in competitive employment, ongoing job supports, and integrated vocational and mental health services, has been found effective in helping patients achieve competitive employment, although studies have found that these patients experience difficulty in retaining these jobs because of cognitive impairments and other illness-related factors. Social skills training has also been found helpful in addressing difficulties in socialization and daily living skills. Self-help groups and advocacy organizations have also been found to be effective in increasing patients’ social networks and quality of life.
SWITCHING ANTIPSYCHOTICS: INDICATIONS AND RATIONALE

Given the potential benefits to patients in tolerability, symptom control, cognitive functioning, and quality of life, there are compelling reasons to consider switching patients from a traditional antipsychotic to an atypical, and to consider switching among atypicals to obtain the best possible outcome. The decision to switch a patient is always an individualized assessment of potential benefit and risk. Relatively compelling factors to consider in switching from traditional to atypical antipsychotics include persistent positive symptoms, persistent negative symptoms, relapse despite compliance, persistent EPS and/or tardive dyskinesia, and symptoms of hyperprolactinemia, such as galactorrhea and amenorrhea, in women and gynecomastia in men. Relatively strong tolerability factors to consider for switching among atypical antipsychotics include problems, such as lack of adequate response, and side effects from some of the newer medications, such as obesity, dyslipidemia, residual EPS, or the development of metabolic syndrome. In addition, switching may be indicated for issues related to the patient’s quality of life. Patients who once had hopes for close relationships and work satisfaction may have narrowed their social and occupational spheres enormously. Although it is important not to raise expectations unrealistically, it is equally important to consider whether newer drugs may offer a patient a greater chance at a fuller and more satisfying life. Quality-of-life issues should be approached respectfully and cautiously with modest expectations, but they are important considerations to raise with patients and families, along with discussions about the control of symptoms. Patients and families may have anxieties about any change in medication, fearing that relapse could occur or that any change, good or bad, will be destabilizing. And, indeed, change is destabilizing. Potential risks and benefits of switching should be discussed with patients, families, and with all members of the treatment team, such as case managers and clinic staff, thus all involved can develop realistic expectations and be alert to the changes that may ensue. Patients and families need reassurance that there will be adequate supervision by psychiatrists and others involved in the patients’ care, not only to manage symptom changes but also to address the patient’s feelings about the changes that occur.

How should clinicians approach the decision to switch? Weiden et al has written extensively on this topic and recommends the following general rules:

- **First, allow an appropriate time frame for assessing symptom response.** For an acute episode, 3 to 6 weeks is probably adequate; for chronic but stable outpatients who are being switched for elective reasons, allow at least 3 months.

- **Second, be aware of the complexity of assessing positive symptoms.** Effects of monotherapy can only be confidently assessed after 4 to 6 weeks because until that time the prior antipsychotic may exert some activity, even if blood levels are negligible. An early improvement may be followed by worsening at 4 to 6 weeks, leading to disappointment of patients and families. Alternatively, patients may appear to worsen but actually improve, if they begin to disclose symptoms that they had hidden in the past, thus it is important to ask how long the symptoms have been present.

- **Third, be cautious in expecting change in negative symptoms.** Improvements may be partial and limited and too subtle to be detected on standard assessment scales. Families and patients should have modest expectations, and any change should be considered a success.

- **Fourth, be aware of changes in affective symptoms.** Although there is good reason to think that newer antipsychotics will reduce the burden of depressive symptoms in schizophrenia, postpsychotic depression is still a risk, particularly if the patient has a past history of depression combined with a recent history of positive symptom improvements. In such cases, aggressive management is called for, including increasing the level of psychosocial support and monitoring, and adding antidepressant medication.

- **Fifth, pay attention to changes in side effects.** Patients switching from a typical to atypical medication can be expected to experience a reversal of persistent tremor, rigidity, akinesia, or akathisia and may no longer need an anticholinergic agent. Because amenorrhea and galactorrhea will normalize over 3 to 6 months as prolactin normalizes, it is important to prepare patients for the need to use birth-control measures if they have not been using them. Changes in tardive dyskinesia cannot be predicted, but must be assessed at 6 months after switching and yearly thereafter. Atypical antipsychotics, although less likely to
cause tardive dyskinesia than traditional drugs, are not entirely without risk, thus it is still necessary to obtain informed consent and monitor for tardive dyskinesia on a regular basis.57

**Contraindications to Switching**

Important contraindications to switching relate primarily to the risk of relapse, but they also include other concerns. Elective switching in patients in the maintenance phase is contraindicated if an exacerbation of psychotic symptoms in the near future would represent an unacceptable risk of danger to the patient or others; if the patient is within 3 to 6 months of recovery from an acute episode and remains on the medication successfully used to treat that episode; and if noncompliance with oral medication is a problem, but compliance is good with depot medications.56 Furthermore, if target symptoms can be altered more simply by changing the dose of current medication, that should be tried first. Expert consensus guidelines recommend maximizing the dose of one atypical antipsychotic before switching to another, except when switching from a typical antipsychotic because of concerns about side effects and tardive dyskinesia at higher doses.62 Finally, switching should be attempted when the patient’s psychosocial situation is as stable as possible. If there is active substance abuse, psychosocial instability, or significant life stressors such as a change in housing or job, it will be difficult to evaluate the effects of a new drug.

Switching medications usually requires more frequent monitoring by psychiatrists and clinic staff, additional costs of medication and increased visits, and potentially increased demands on rehabilitation services. However, cost concerns may be offset by decreased hospitalization days and ultimately greater stability.58,59

**Switching Antipsychotics: How to Do It**

Several studies have examined the process of switching from one antipsychotic to another.50,52,60-63 The optimal switching strategy would minimize relapse of psychotic symptoms because of inadequate doses of antipsychotic medication, avoid drug discontinuation syndromes, and limit the potential for drug-drug interactions characterized by sedation, confusion, and other cognitive problems, and difficulties with motor coordination that may occur when one drug is being tapered at the same time another is being added.62

**Switching Studies**

In a study of patients switching from clozapine to olanzapine, Tolleson et al abruptly discontinued clozapine (mean dose 324 mg/day) in 106 subjects, randomly assigning them to receive double-blind placebo or olanzapine 10 mg for 3 to 5 days, and then continuing all subjects in an open-label olanzapine trial for an additional 9 weeks.61 Statistically significantly more placebo-treated than olanzapine-treated patients (24.5% vs 7.5%) experienced a discontinuation-associated increase of at least one psychotic sign or symptom, most commonly delusions, hallucinations, hostility, agitation, and/or paranoia. These symptoms were reflected in worsening PANSS subscale scores in general psychopathology (most affected), negative symptoms, and positive symptoms (least affected). Furthermore, the Montgomery-Asberg Depression Rating Scale indicated a substantial disturbance in mood ($P < .001$) in those patients assigned to the placebo group. Patients who experienced relapse or clinically significant discontinuation symptoms were entered into a crossover arm of the trial, thus they received clozapine and olanzapine for a period up to 28 days. Given the symptoms that emerged with abrupt clozapine discontinuation, the authors conclude that it is safest to gradually taper clozapine before discontinuation and to substitute an alternative antipsychotic agent simultaneously, with a period of overlap, even though problems associated with immediate olanzapine monotherapy were few.

Kinon et al compared 4 different methods of switching partially remitted, clinically stable outpatients diagnosed with schizophrenia or schizoaffective disorder who were being treated with a conventional antipsychotic drug or risperidone.62 More than 200 patients were openly randomly assigned to abrupt or gradual discontinuation of their prior antipsychotic drug, and further randomly assigned in a double-blind fashion to immediate versus stepwise treatment with olanzapine. There were 4 treatment paradigms: abrupt discontinuation, immediate olanzapine initiation, 10 mg/day for 3 weeks;
abrupt discontinuation, stepwise initiation with week 1 on placebo, week 2 on olanzapine 5 mg/day, and week 3 on olanzapine 10 mg/day; gradual discontinuation, immediate olanzapine initiation, 10 mg/day for 3 weeks; and gradual discontinuation, stepwise initiation with week 1 on placebo, week 2 on olanzapine 5 mg/day, and week 3 on olanzapine 10 mg/day.

Patients were assessed using the Clinical Global Impressions (CGI) Improvement scale, Patient’s Global Impressions (PGI) Improvement scale, and PANSS. No significant difference was seen in discontinuation rates between the switching paradigms. The paradigm of gradual antipsychotic drug discontinuation combined with an initial full dose of olanzapine 10 mg/day demonstrated at week 1 a statistically significant greatest mean change in CGI and PGI improvement compared to the other paradigms. However, by week 3, there was no significant difference in improvement measures, and more than 90% of completing patients on all 4 switching paradigms were improved or clinically unchanged. No clinically significant differences between switching paradigms were seen in laboratory values or vital signs. Patients in the abrupt discontinuation and immediate treatment with 10 mg/day of olanzapine paradigm showed the most sedation, whereas those patients who experienced not only abrupt discontinuation but 1 week of placebo showed the most difficulty with sleep (P <.05 for both groups). However, overall, the study demonstrated that switching could be achieved without increased vulnerability to relapse or to occurrence of clinically burdensome antipsychotic drug withdrawal symptoms in the majority of patients.

Weiden et al examined the safety and tolerability of switching to ziprasidone using 3 distinct switching strategies, looking at 203 patients on 3 different medications before the switch. 50 Stable outpatients with persistent symptoms or troublesome side effects on conventional antipsychotic, olanzapine, or risperidone therapy were switched to an open-label 6-week flexible-dose trial of ziprasidone. In the crossover to ziprasidone, all groups were started on open-label oral ziprasidone at 40 mg twice daily for 2 days, followed by flexible dosing between 40 and 160 mg/day administered in divided twice-daily doses. Patients were randomly assigned to 1 of 3 schedules to discontinue their prior medication during the first week of ziprasidone therapy:
- Complete discontinuation of the previous antipsychotic the day before starting ziprasidone;
- Immediate dose reduction, with a 50% reduction in the dosage of the previous antipsychotic for the first week of ziprasidone, followed by discontinuation starting week 2;
- Delayed dose reduction, with a 50% reduction in the dosage of the previous antipsychotic on day 4 of ziprasidone, followed by discontinuation starting week 2.

All patients were on ziprasidone monotherapy after the first week of ziprasidone crossover. Baseline and outcome assessments included PANSS and CGI severity ratings. All 3 switching strategies were well tolerated for all 3 patient groups. There was no statistical difference across study groups in completion rates or in discontinuations because of inadequate response or adverse events. Among all patients in each of the 3 drug groups entering the study, there were no significant pairwise differences between any 2 switching strategies in outcome assessment of symptoms. The specific crossover technique used during the first week of ziprasidone therapy did not influence the outcome at 6 weeks in any of the medication groups. After 6 weeks on ziprasidone therapy, significant (P <.05) improvements were observed on all major symptom measures and almost all subscales for all switched subgroups.

Positive symptoms improved significantly for patients switched from conventional antipsychotics or olanzapine (P <.05), and negative symptoms improved significantly (P <.005) in all 3 switch groups. Tolerability of ziprasidone was good, with few patients discontinuing treatment. For patients switched from olanzapine, a significant reduction in mean body weight of -1.8 kg or -3.9 lb (P <.001) was observed after 6 weeks on ziprasidone. A lesser but still significant decrease in weight was seen in patients switched from risperidone (-0.9 kg or -1.9 lb; P <.05), but there was no significant weight change in patients switched from conventional antipsychotics. The authors conclude that stable but symptomatic outpatients being treated with a conventional antipsychotic, olanzapine, or risperidone may experience further improvement by switching to ziprasidone, but that there appears to be no difference in efficacy or tolerability between any of the 3 switching strategies. They caution that the 1-week overlap in this study is much shorter than is commonly used in clinical practice, and that consensus guidelines on switching indicate that the preferred switching method is to overlap the old and the new antipsychotic for several weeks. 5,4
Casey et al investigated the efficacy, safety, and tolerability of 3 dosing strategies for switching chronic, stable patients with schizophrenia from current oral antipsychotic monotherapy to once-daily oral aripiprazole monotherapy. Approximately 247 patients in this 8-week, open-label, out-patient study were randomized to 1 of the following strategies:

1) Immediate initiation of 30 mg/day aripiprazole with simultaneous immediate discontinuation of current antipsychotic;
2) Immediate initiation of 30 mg/day aripiprazole, while tapering off current antipsychotic over 2 weeks; or
3) Up-titrating aripiprazole to 30 mg/day over 2 weeks, while simultaneously tapering off current antipsychotic medication.

Patients entered the study on a stable dose of haloperidol, thioridazine, risperidone, or olanzapine for at least 1 month before study entry. All had adequate clinical reason to consider a trial of an antipsychotic other than their current therapy. For patients in group 2 or 3, current antipsychotic medication was decreased by 50% during week 1, then decreased by another 50% during week 2, and totally discontinued at the start of week 3. Efficacy, using PANSS, CGI severity, and CGI improvement scores, was maintained with aripiprazole during the study in all 3 groups. The overall low incidence of adverse events was comparable across all groups, as were discontinuations caused by adverse events. Body weight was reduced in all groups between 1.3 and 1.7 kg over the 8-week study period, and plasma prolactin levels were reduced across all groups after the switch to aripiprazole. The authors conclude that any of the 3 strategies can be used safely for switching patients to aripiprazole from antipsychotic monotherapy, and that patients’ symptoms may continue to improve after switching to aripiprazole.

**Summary**

In summary, studies thus far have shown no distinct advantage for any particular strategy in switching from one antipsychotic to another. Clozapine represents a specific exception to this generalization because its discontinuation syndrome can be managed best by a gradual taper rather than abrupt cessation of the drug. Crossover times in the studies cited earlier in this section are shorter than those times normally used in clinical practice, and a more conservative approach of 1 to 2 weeks or longer is recommended by experts and by clinical experience to minimize abrupt transitions.

In switching for efficacy, it is difficult to predict which patients will do well with which new drug. Clozapine remains the gold standard, but has many problems associated with its use. Although there is no consensus on how many first-line atypicals to try before clozapine, several guidelines recommend a trial of at least 2 first-line atypicals. Of the first-line atypical antipsychotics, all are roughly equal in efficacy for positive symptoms. Data showing improvement from one medication to another in switch studies should be viewed with caution. Switch studies are open label, use patients who have not done well on prior medications, and provide increased contact and intervention for study subjects. Therefore, the benefits cannot be interpreted to show that the postswitch medication is better than the preswitch medication. Rather, the studies indicate that closely monitored switching represents a relatively low risk, particularly for patients whose level of function is suboptimal or whose current symptoms are persistent, and that there is reason for optimism that newer medications may offer patients a better outcome in control of positive symptoms, negative symptoms, or other outcome domains.

**Switching to Manage Side Effects**

It is much easier to predict the outcome of switching for side-effect problems, as the side-effect profiles of the atypical antipsychotics are well established. In the past, most side-effect switches were because of EPS. However, most side-effect switches between atypical antipsychotics now occur because of weight gain and sedation, in addition to more subtle residual EPS and a variety of less frequent concerns. In a review of side effects in 99 patients, akinesia, weight gain, anticholinergic problems, and sexual problems were each reported to cause moderate-to-severe distress by 30% to 40% of patients. Muscle rigidity and akathisia were each reported by approximately 20% of patients. The degree of benefit that switching affords will depend on the side-effect profile of the original medication compared to the side-effect profile of the new medication.

**Extrapyramidal Symptoms**

DeNayer et al looked at EPS reduction in more than 300 patients who were switched to quetiapine from olanzapine, risperidone, conventional antipsychotic, and haloperidol (dose <10 mg/day) monother-
apy. The degree of EPS reduction was statistically significant for all groups, but it was greatest in the haloperidol group, less in the conventional antipsychotic group, still less in the risperidone group, and least in the olanzapine group from baseline to week 12 of the study. A more recent study suggests that there may be continuing improvements in EPS with quetiapine over time, extending well beyond the improvements seen in the first 6 to 12 months.

**Weight Gain and Associated Problems**

Weight gain has become a major focus of concern in patients taking atypical antipsychotics. It contributes to poor self-image and to numerous medical problems, including elevated cholesterol and triglycerides, both independent risk factors for cardiovascular disease. Of greatest concern is the development of metabolic syndrome, a cluster of coronary heart disease risk factors with common insulin resistance, defined by abdominal obesity, hypertriglyceridemia, low high-density lipoprotein cholesterol, high blood pressure, and high fasting glucose. A comprehensive meta-analysis of estimated antipsychotic-induced weight change at 10 weeks showed that olanzapine and clozapine were associated with the greatest increases in weight (4.15 kg and 4.45 kg, respectively). Quetiapine and risperidone are associated with less weight gain, and aripiprazole and ziprasidone are weight neutral. In fact, aripiprazole and ziprasidone have been associated with weight loss when patients are switched from olanzapine and clozapine.

Quetiapine and risperidone are associated with less weight gain, and aripiprazole and ziprasidone are weight neutral. In fact, aripiprazole and ziprasidone have been associated with weight loss when patients are switched from olanzapine and other antipsychotics. Following a switch to aripiprazole from olanzapine, patients showed a mean weight loss of 2 kg ($n = 169; P < .001$), whereas patients switching to aripiprazole from risperidone showed a mean weight loss of 0.6 kg ($n = 106; P < .077$). Patients switching from olanzapine to ziprasidone showed a mean weight loss of 1.5 kg after 6 weeks ($n = 104; P < .0001$), whereas those switching from risperidone to ziprasidone showed a weight change of approximately 0.5 kg ($n = 58; P < .05$). In a study of 185 patients followed over 58 weeks after switching to ziprasidone from olanzapine, risperidone, and conventional antipsychotics, substantial reductions in body weight and body mass index (BMI) were observed 6 weeks after switching from olanzapine and risperidone were progressive and sustained over 1 year. Substantial reductions in serum cholesterol and triglycerides were observed 6 weeks after switching to ziprasidone from all 3 preswitch antipsychotics were sustained over 1 year.

It is clear that the atypical antipsychotics have very different effects on weight, BMI, and lipid status, and that these metabolic parameters require monitoring over the course of treatment. Current recommendations (American Diabetes Association [ADA]/APA Consensus Statement, 2004) include obtaining baseline screening measures before the initiation of any antipsychotic medication, including:

- A personal and family history of obesity, diabetes, dyslipidemia, hypertension, or cardiovascular disease;
- Weight and height, thus a BMI can be calculated;
- Waist circumference;
- Blood pressure;
- Fasting plasma glucose; and
- Fasting lipid profile.

These assessments can determine if the patient is overweight (BMI 25–29.9) or obese (BMI >30), has prediabetes (ie, fasting plasma glucose of 100–125) or diabetes (fasting plasma glucose of >126 mg/dL), has hypertension (>140/90), or dyslipidemia. If any of these conditions are identified, appropriate treatment or referral should be initiated. Close collaboration with primary care physicians can expedite the screening and treatment process.

The patient’s weight should be reassessed at 4, 8, and 12 weeks after initiating or changing antipsychotic therapy, and quarterly thereafter. If a patient gains more than 5% of his or her initial weight at any time during therapy, clinicians should consider changing antipsychotics. Fasting plasma glucose, lipid levels, and blood pressure should also be assessed 3 months after starting an antipsychotic medication. After that, blood pressure and plasma glucose should be obtained annually or more frequently in those patients who have a higher baseline risk. For those patients with a normal lipid profile, repeat testing should be performed at 5-year intervals.

**Other Side Effects of Concern**

Decreases in serum prolactin have been reported in switches to aripiprazole from haloperidol, risperidone, and (to a much smaller degree) olanzapine. Sedation, a common complaint, is seen most often with clozapine, olanzapine, and quetiapine, and less with aripiprazole and ziprasidone. Other less common side effects that patients may experience with 1 atypical antipsychotic may be reduced with switching to another atypical.
FUTURE DIRECTIONS IN TREATMENT

EARLY INTERVENTION

There is increased interest in many countries in early recognition and intervention in the initial prodromal phase of illness to decrease the “duration of untreated psychosis.” Although the consequence of delayed treatment of psychosis is disruption in social, educational, and occupational development, the issue of to what degree early intervention programs can delay or prevent symptom expression is still an open question. In a recent study, ultra high-risk individuals who were administered a 6-month preventive intervention of low-dose risperidone and cognitive behavior therapy had a significantly lower transition rate to a first episode (9.7%) compared to those patients receiving a needs-based intervention (35.7%); however, this difference was not significant at 12 months. Several international research programs are attempting to define who is at risk, identify what predicts transition to psychosis, evaluate the timing and choice of interventions, and examine risk-benefit issues in the early treatment of psychosis.

MEDICAL CORMORBIDITIES

Recent epidemiologic and population studies have shown increased morbidity and mortality from medical illnesses in patients with serious and persistent mental illness. Individuals with major psychiatric disorders, such as schizophrenia or bipolar disorder, face an elevated mortality rate mostly because of higher rates of medical comorbidities, including obesity, diabetes mellitus, cardiovascular and pulmonary diseases, HIV infection, and cancer. The degree to which psychiatric factors may elevate medical comorbidity rates in these patients has not been well studied or described. The recent metabolic recommendations of the ADA/APA have sparked renewed interest in behavioral, biological, and psychosocial factors associated with schizophrenia and bipolar disorder that may contribute to comorbid medical illnesses.

PSYCHOSOCIAL TREATMENTS

Psychosocial treatments remain essential in the treatment of chronic psychosis and its comorbid conditions, such as homelessness, joblessness, social isolation, substance use, and involvement in the criminal justice system. However, in spite of evidence to support their efficacy, many patients have no access to these treatments. Economic arguments have been advanced to re-evaluate cost comparing the costs of inadequate treatment, including increased days of hospitalization, increased medical and psychiatric care needs, and other psychosocial consequences of poorly controlled psychosis, to the costs of treatment with newer antipsychotics and access to more robust psychosocial services. However, funding for mental healthcare and how to allocate limited resources is likely to remain an ongoing policy issue of great relevance to clinicians, patients, and their families.

BEST PRACTICE

In spite of the development of evidence-based guidelines and consensus recommendations, surveys have shown that psychiatrists’ adherence to guideline-based outpatient treatment is only approximately 50%. In community treatment centers, use of current guidelines was found to be limited by deficiencies in the medical record, nonstandardized progress notes, lack of computerized prescribing programs, and the structure of the guidelines. In inpatient care, decisions about which patients are switched to atypical antipsychotics depend strongly on factors such as institutional practices, in addition to previous disease course and healthcare use. If state-of-the-art treatment is to be widely used, clinicians must have access to treatment plans with outcome measures that are easy to use and facilitate comparisons among sequential trials of medications.

REFERENCES


