

# Optimizing Pharmacotherapy to Maximize Outcome in Schizophrenia

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## The Evolution of Antipsychotic Agents: A Mechanisms-Based Review

Although abundant evidence shows that dysfunction in multiple neurotransmitter systems (including the serotonergic and the glutamatergic systems) contributes to the pathogenesis of schizophrenia, alterations in dopaminergic systems are the best-documented neurochemical dysfunctions associated with this illness, according to Anissa Abi-Dargham, M.D. The modern dopamine hypothesis of schizophrenia proposes that positive symptoms of psychosis in patients with schizophrenia arise from a condition of up-regulated dopaminergic neuronal activity in subcortical pathways, whereas negative symptoms and cognitive impairment result from a dopamine deficit in the cortical dopamine (DA) pathways.<sup>1,2</sup> Traditional support for this hypothesis derives from the fact that typical antipsychotic agents, whose main property is the antagonism of D<sub>2</sub> dopamine receptors, suppress positive symptoms but do not significantly improve and may even worsen negative symptoms.<sup>2</sup> The D<sub>2</sub>-antagonist activity of the typical antipsychotics also leads to extrapyramidal dysfunction (arising from the high blockade of dopamine receptors in the striatum), disinhibition of prolactin release, and subsequent hyperprolactinemia (caused by the blockade of dopamine receptors in the pituitary).<sup>1</sup> Additional support for the hypothesis comes from the fact that dopamine agonists can induce psychotic states, and acute exposure to amphetamines causes emergence or worsening of positive symptoms in patients with schizophrenia.<sup>3</sup>

However, direct testing of the dopamine hypothesis of schizophrenia was

not possible until the relatively recent advent of in vivo neuroreceptor imaging studies. Initial studies have confirmed that schizophrenia is associated with increased dopamine transmission after acute amphetamine challenge, providing the first direct evidence supporting the hypothesis of dysregulation of central dopamine transmission in patients with schizophrenia.<sup>3-5</sup> Furthermore, investigators have found that dopamine occupies a greater proportion of striatal D<sub>2</sub> receptors in patients with schizophrenia during episodes of illness than in matched control subjects. Increased dopamine stimulation of D<sub>2</sub> receptors in these patients predicted a better and faster response to antipsychotic treatment.<sup>6</sup>

In addition to these studies, which have supported the role of dopaminergic hyperactivity in patients with schizophrenia, indirect evidence has emerged of mesocortical dopaminergic hypoactivity in patients with schizophrenia, indicating that these patients have increased D<sub>1</sub> receptor availability in the dorsolateral prefrontal cortex. It is hypothesized that this increased D<sub>1</sub> receptor availability represents a compensatory up-regulation secondary to sustained deficiency in mesocortical dopamine function.<sup>7</sup>

Presuming that the dopamine hypothesis of schizophrenia is true, Dr. Abi-Dargham noted, treatment with a D<sub>2</sub> partial agonist, such as aripiprazole, would appear to have advantages over treatment with a full D<sub>2</sub> antagonist, such as a typical antipsychotic. As a partial agonist, aripiprazole displays properties of an agonist in animal models of dopaminergic hypoactivity and

properties of an antagonist in animal models of dopaminergic hyperactivity.<sup>8</sup> Thus, in the regions of the brain involved in dopaminergic overactivation, aripiprazole is thought to act as an antagonist to improve positive symptoms, whereas in the mesocortical regions of the brain in which there is a dopamine deficit, aripiprazole is thought to serve as an agonist to diminish negative symptoms and to improve cognition. However, it should be noted that DA transmission in the cortex is mediated primarily by D<sub>1</sub>, rather than D<sub>2</sub>, receptors. Thus, a D<sub>1</sub> partial agonist might be more effective than a D<sub>2</sub> partial agonist at improving cognition in patients with schizophrenia. In addition to the beneficial effects of partial D<sub>2</sub> agonism on the positive and negative symptoms of schizophrenia, aripiprazole lacks the adverse effects of the typical antipsychotics, including extrapyramidal symptoms (EPS).<sup>9</sup> Aripiprazole demonstrates minimal EPS when given at 15 or 30 mg daily,<sup>9</sup> doses that lead to greater than 80% occupancy of striatal D<sub>2</sub> dopamine receptors and sometimes to even greater than 90% occupancy.<sup>10</sup> Investigators have speculated that this is the result of the partial agonist effect of aripiprazole at the D<sub>2</sub> receptor.<sup>10</sup>

Farde et al.<sup>11</sup> previously noted that patients receiving antipsychotic treatment who experienced EPS tended to have higher D<sub>2</sub> occupancies than did patients with no EPS.

Similarly, administering aripiprazole does not result in the elevated prolactin levels seen with the typical antipsychotics; instead, a 57% decrease in prolactin level occurs.<sup>9</sup> This also can be attributed to the partial agonist effect of aripiprazole at the D<sub>2</sub> receptor as opposed to the full D<sub>2</sub> antagonism of the typical antipsychotics. Rather than fully blocking D<sub>2</sub> receptors in the pituitary and thereby disinhibiting prolactin release, aripiprazole may act as an agonist and may inhibit prolactin level elevation.

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## Optimizing the Long-Term Effectiveness of Antipsychotic Therapy

As the management of schizophrenia continues to evolve, so do the needs of patients with this disorder and of their families, noted Stephen R. Marder, M.D. No longer is it sufficient to prevent relapse and to maintain the patient in the community; rather, patients strive to recover functions lost because of their illness. Patients and family members want to be partners in developing a management plan.

The goals of long-term schizophrenia treatment are 3-fold: to prevent relapse, to promote recovery, and to improve the health of this patient population, whose life expectancy is 20% shorter than that of the general population.<sup>1</sup>

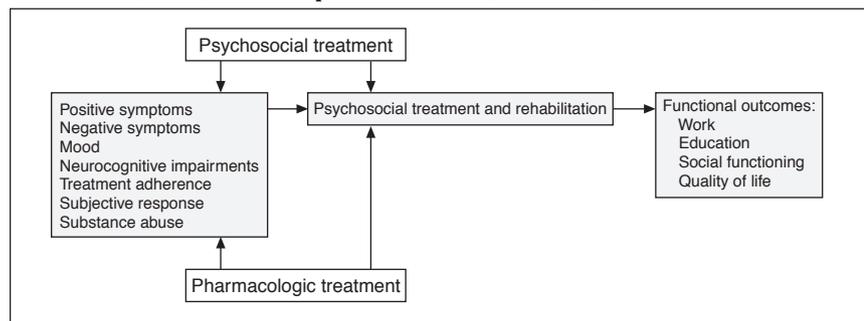
### Prevention of Relapse

To prevent relapse, effective therapies, taken as directed, are essential. First- and second-generation antipsychotic agents have been evaluated on their ability to prevent relapses and on their tolerability for the acute and chronic treatment of schizophrenia. Noncompliance has emerged as a significant barrier to successful treatment.

**Efficacy.** Although all approved antipsychotic agents similarly reduce relapse rates, second-generation agents may be more effective than first-generation agents as chronic maintenance therapy for schizophrenia. In a long-term evaluation of stable patients,<sup>2</sup> 70% of those treated with halo-

peridol and 80% of those treated with risperidone were relapse free at 6 months. A meta-analysis by Leucht and colleagues<sup>3</sup> demonstrated a small, but statistically significant, advantage for second-generation antipsychotics in preventing relapse.

**Compliance.** Given that only 58% of patients remain on antipsychotics for up to 2 years after initiation,<sup>4</sup> clinicians should find drugs that patients are willing to take. Patients perceive considerable differences in drug tolerability; some patients complain bitterly about antipsychotic-induced weight gain, whereas others accept it. If drug-related distress is significant, consideration should be given to switching to

**Figure 1. Model for Success: Combining Pharmacologic and Psychosocial Interventions to Facilitate Improvements in Functional Outcome**

another agent<sup>5</sup> because substantial differences exist in the tendency of antipsychotics to cause weight gain.<sup>6</sup>

In a comparative trial using patient-completed and physician-administered rating instruments, subjects treated with risperidone reported feeling better than those treated with haloperidol, suggesting that second-generation agents may be better tolerated than first-generation agents.<sup>7</sup> Similarly, during long-term trials comparing risperidone<sup>4</sup> or aripiprazole with haloperidol, a significantly greater proportion of haloperidol-treated subjects discontinued the ineffective or intolerable therapy than subjects treated with the newer agents.<sup>8</sup>

Because forgetfulness and taking medications incorrectly are the usual causes of noncompliance, adherence to treatment may be improved by switching from daily oral medication to a long-acting depot injection, as suggested by Davis et al.<sup>9</sup> In surveying the literature, Davis et al.<sup>9</sup> found that subjects managed with depot injections had lower relapse rates than those on oral antipsychotic therapy.

### Promotion of Recovery

For a successful outcome, the road to recovery must include psychosocial intervention along with pharmacologic therapy. Antipsychotics may prevent psychotic relapses, but they do not improve social relationships or help patients find jobs. However, the maintenance of stability through pharmacologic therapy facilitates participation

in psychosocial programs and rehabilitation and can lead to improved functional outcomes (Figure 1).

Second-generation antipsychotics may have a greater influence on the success of psychosocial programs than do first-generation agents. Bond and associates<sup>10</sup> found that patients taking second-generation antipsychotics had higher enrollment rates in vocational rehabilitation, higher employment rates, and higher earnings than subjects taking first-generation agents. Similarly, Rosenheck and colleagues<sup>11</sup> reported that patients taking clozapine were more likely than those taking haloperidol to participate in higher levels of psychosocial programs.

Effective psychosocial treatments include illness education, family interventions that provide education and support, assertive community treatment, skills training, supported employment, and cognitive behavior-oriented psychotherapy.<sup>12</sup> Although psychosocial programs are underused, when they are involved, major milestones in recovery can be realized, as evident in the supported employment initiatives through which work fosters community integration and improves self-esteem.

### Improvement in Health

Persons with schizophrenia have a 1.6 to 2.6 times higher mortality rate, a 1.5 to 2 times higher prevalence of diabetes and obesity, and a 2 times greater risk for dying of cardiovascular disease than those without schizophre-

**Table 1. American Diabetes Association Consensus on Antipsychotic Drugs: Metabolic Abnormalities of Second-Generation Antipsychotics<sup>a</sup>**

Drug	Weight Gain	Risk for Diabetes	Worsening Lipid Profile
Clozapine	+++	+	+
Olanzapine	+++	+	+
Risperidone	++	+/-	+/-
Quetiapine	++	+/-	+/-
Aripiprazole <sup>b</sup>	+/-	-	-
Ziprasidone <sup>b</sup>	+/-	-	-

<sup>a</sup>Adapted with permission from the American Diabetes Association.<sup>13</sup>  
<sup>b</sup>Newer drugs with limited long-term data.  
 Symbols: + indicates increased effect; - indicates no effect.

nia.<sup>1</sup> Compounding this problem is the adverse metabolic profile (weight gain, increased lipid levels, risk for diabetes) associated, to varying degrees, with second-generation antipsychotic agents (Table 1).<sup>13</sup> In clinical trials, clozapine- and olanzapine-treated patients had the greatest weight gain and the highest occurrence of hyperglycemia and dyslipidemia; aripiprazole- and ziprasidone-treated patients had the lowest or no weight gain, hyperglycemia, or dyslipidemia; and risperidone- and quetiapine-treated patients were somewhere in between.<sup>13</sup> The American Diabetes Association has developed guidelines for monitoring blood pressure, weight, and lipid and glucose levels of patients on the initiation of antipsychotics and at least yearly thereafter.<sup>13</sup> Guidelines from the Mount Sinai Consensus Conference also suggest monitoring for prolactin level elevation, neurologic adverse effects, and eye changes.<sup>14</sup>

### Conclusion

Improving the general health of patients with schizophrenia through preventive and therapeutic measures and monitoring their metabolic profiles constitutes the third of 3 steps essential for optimizing the long-term effectiveness of antipsychotic therapy. Consideration must be given to selecting an agent that will not adversely affect the patient's concomitant metabolic ill-

nesses, such as diabetes or obesity, and with which the patient will remain compliant to prevent relapses. In addition, Dr. Marder concluded, attention must be given to maximizing the use of psychosocial intervention, which, in conjunction with antipsychotics, offers the highest probability for success.

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example, in most clinical trials, data from the last observation are carried forward, analyzed, and used as the end-of-study results. Regardless of whether subjects complete the full term of the trial, their efficacy and safety results are analyzed with the data collected at the conclusion of the study. Therefore, differences cannot be determined between patients who finish the study and those who do not finish it.

Nowhere is the impact greater than in the evaluation of time-dependent adverse effects. In particular, last-observation-carried-forward (LOCF) methods seriously underestimate the impact of adverse effects that progress over time. This shortcoming of LOCF will underestimate the true differences in time-dependent side effects between antipsychotic medications, especially as the side effect differences widen over time. The importance of this time factor is illustrated in a study by McQuade et al.<sup>1</sup> that compared the time course of weight differences between patients randomly assigned to aripiprazole or olanzapine over 6 months of treatment. In subjects remaining on therapy until week 26, a mean weight loss of 1.37 kg was reported with aripiprazole compared with a mean weight gain of 4.23 kg with olanzapine (Figure 2). These weight differences favoring aripiprazole would not be as apparent with LOCF methods, because the weight changes in early dropouts would have been carried forward and averaged into those of patients who stayed on these medications over the full 26 weeks.

Several issues are associated with the use of LOCF analyses. Differences in efficacy between comparative groups may be underestimated or overestimated. Differences and prevalence of adverse effects between comparative groups may be underestimated. Tabulated endpoint values may be incorrect.

To minimize the influence of LOCF on the interpretation of clinical trial results, data from observed cases should be reviewed to predict how pa-

## What Is Effectiveness With Antipsychotic Medications?

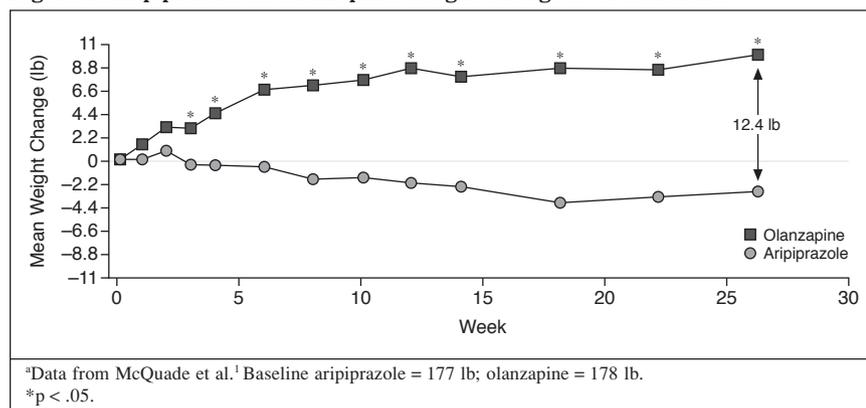
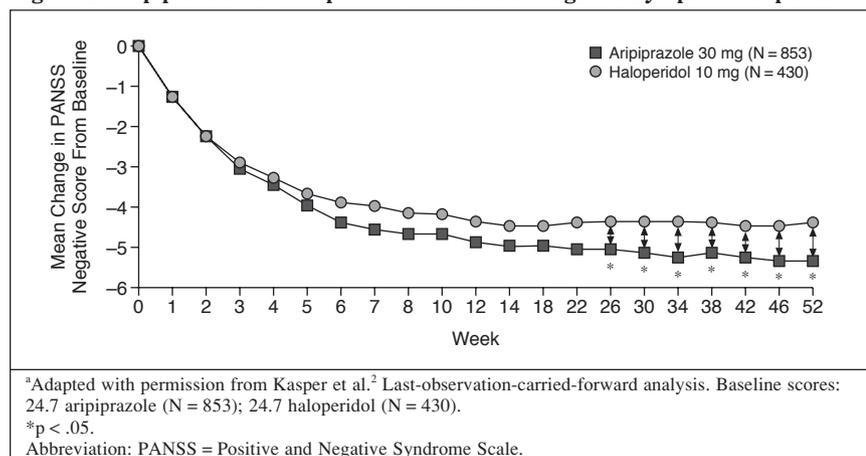
Effectiveness is the usefulness of a medication under conditions of actual clinical practice, stated Peter J. Weiden, M.D. On the other hand, efficacy denotes how well a medication works as established through rigorous and controlled clinical investigation, such as the trials required for drug approval. Effectiveness is relevant only after efficacy has been established, but both measures expand our understanding of the usefulness of a given therapy within the context of other available treatments.

The story of clozapine is a wonderful illustration of the difference between efficacy and effectiveness. To this day, clozapine has the best efficacy of all the antipsychotics. From an effectiveness perspective, it has not

had a large impact on public health because drug-associated adverse effects limit its use in clinical practice. There also is another side to the effectiveness story of clozapine. Clozapine was a “tipping point” in the theory of mechanism of action for it disproved the widely held belief that extrapyramidal symptoms were a necessary consequence of antipsychotic efficacy. The success of clozapine changed the course of drug development and ultimately resulted in the 5 post-clozapine atypical antipsychotics that, unlike clozapine, can be and are widely used as first-line therapy.

#### Limitations of Assessment Tools

Methodologies used in efficacy studies may skew study results. For

**Figure 2. Aripiprazole vs. Olanzapine: Weight Change Over 6 Months<sup>a</sup>****Figure 3. Aripiprazole vs. Haloperidol: Differential Negative Symptom Response<sup>a</sup>**

questions as: *What is the likelihood that my patient will respond in a similar fashion? What will my patient look like 6 months from now if he takes one drug rather than the other?*

In translating efficacy to effectiveness, clinicians must recognize what a broader range of symptom efficacy means for their patients. When Kasper et al.<sup>2</sup> evaluated the differential negative symptom response in their study comparing aripiprazole with haloperidol, they made an interesting discovery. After 6 months, responses in the haloperidol-treated group leveled off and remained flat until the end of the study, whereas patients randomly assigned to aripiprazole continued to improve, albeit slowly, for the entire 12 months. From an efficacy point of view, one might argue that these differences in the overall pattern of symptom response are not impressive. However, from an effectiveness perspective, the finding that the negative symptom response of aripiprazole becomes differentiated from that of haloperidol at 6 months is truly remarkable and has profound prognostic and educational implications (Figure 3).<sup>2</sup> What this tells us is that the slope of change is different between an atypical antipsychotic and a conventional antipsychotic. This finding translates into the ability to tell patients and their families that negative symptoms continue to improve (heal) over time and that, if this does not occur, additional options exist before they have to resort to clozapine.

### Benefit of Switching Therapy

Open-label switching trials represent an effectiveness, "real-world" orientation that is possible only after efficacy is established. An example of such a switching study is the one undertaken by Weiden et al.<sup>3</sup> in which 3 groups of stable but symptomatic outpatients (total N = 270) were switched to ziprasidone. One question was whether the specific preswitch antipsychotic (conventional, olanzapine, or risperidone) made a difference in

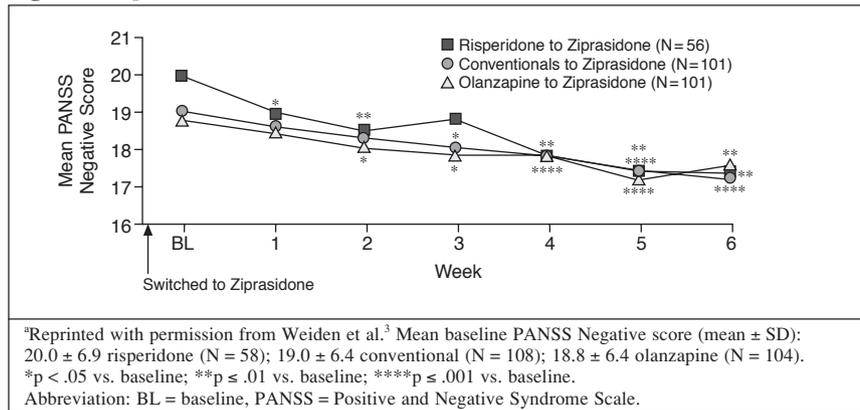
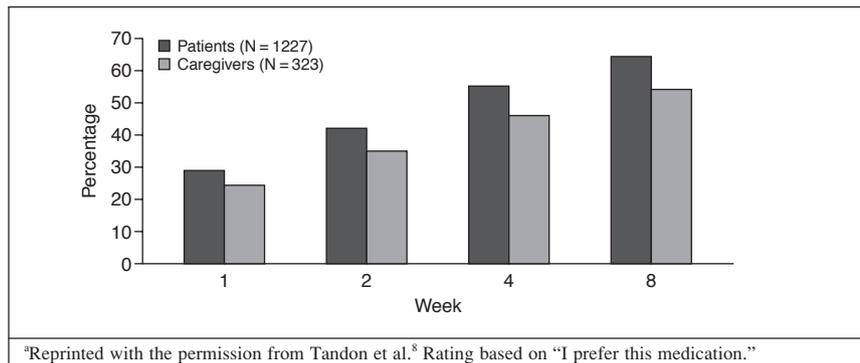
tients would fare for the duration of the study. If multiple efficacy scales are reported, it may be helpful to evaluate the results of the Clinical Global Impressions scale, a means of measuring the degree of improvement and the severity of illness.

Unfortunately, most published studies of antipsychotics have not reported efficacy and tolerability results in both LOCF and observed cases/completers analyses. Dr. Weiden cited observed case data whenever available and strongly encourages authors of future publications to include observed cases analyses.

### Translating Efficacy to Effectiveness for Usual-Care Patients

The efficacy of antipsychotics is well established. Applying results from

a research setting to community practice requires thorough evaluation of their applicability to patients receiving usual care. This is not easily accomplished because most drug studies are efficacy studies, leaving the reader to interpret the results with effectiveness in mind. An example is the 52-week study by Kasper et al.<sup>2</sup> comparing aripiprazole 30 mg with haloperidol 10 mg in acutely ill patients. In the course of the evaluation, 43% of patients randomly assigned to aripiprazole and 30% of the haloperidol group completed the study. The former group demonstrated maintenance of response and relapse protection (trend level) superior to those of the group on haloperidol. Although this is a post hoc efficacy study, it could be reevaluated as an effectiveness study through such

**Figure 4. Ziprasidone Switch Studies<sup>a</sup>****Figure 5. Percentage of Patients and Caregivers Rating Preference of Medication as Much Better<sup>a</sup>**

outcome. The results (Figure 4) show that significant benefits occurred from switching to ziprasidone for symptomatic outpatients regardless of whether their prior medication was a conventional or a (non-clozapine) atypical antipsychotic.<sup>3</sup> The point of this switch study is not that ziprasidone is better than the other medications (in fact, investigators in switching studies go out of their way to choose patients who are not doing well on their current regimen) but that ziprasidone is *different*. The same pattern of differential efficacy is supported by other switch studies of olanzapine, quetiapine, and aripiprazole, suggesting that the variations in results are on an individual level.<sup>4-7</sup>

An armamentarium of antipsychotic drugs provides an additional benefit to patients with schizophrenia. Cumulative improvements in response, as-

suming differential efficacy, are more likely when serial trials of antipsychotic medications are prescribed. Having the option of trying different medications has proven beneficial to patients' well-being, as was demonstrated in the Broad Effectiveness Trial With Aripiprazole study.<sup>8</sup> In this trial emulating real-world clinical practice, conducted by community practitioners, patients initiating antipsychotic therapy or those for whom a change in antipsychotic medication was warranted were randomly assigned in a 4:1 ratio to aripiprazole or to the investigator's selected antipsychotic for 8 weeks. Most patients were considered for a medication change due to poor positive or negative symptom control, weight gain, or somnolence. In addition to improvement in overall patient well-being with aripiprazole irrespective of prior therapy, study find-

ings included high completion rates (65% for aripiprazole), good response rates (70% for aripiprazole), and high medication preference rates.<sup>8</sup> Figure 5 shows that, by the end of the treatment trial, about two thirds of the patients and over one half of their caregivers preferred aripiprazole to their prior medication.<sup>8</sup> This finding suggests that, from the perspective of subjective response, motivated patients who were experiencing difficulties with their prior antipsychotic medication were likely to feel that the effort of switching to aripiprazole was worthwhile. One important finding is that the reported preference takes time to develop and goes up linearly over the course of 8 weeks' exposure. From an effectiveness perspective, this finding supports, but does not prove, the notion that the atypical antipsychotics are not interchangeable. From the perspective of the patient and family, there is a good chance that further subjective improvements occur when switching across the class of atypical antipsychotics.

## Summary

The efficacy of antipsychotic therapy must be established before its effectiveness can be analyzed, stated Dr. Weiden. Effectiveness is better understood as a mind-set rather than as a research tool. It adds context and perspective to help match treatment choices to the needs of the individual patient.

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## Management of Patients With Treatment-Resistant Schizophrenia

Despite recent advances in schizophrenia management, a significant proportion of patients remain treatment resistant, stated John M. Kane, M.D. Although the prevalence of treatment resistance is difficult to determine given the lack of agreement in defining the term, it is estimated that 20% to 45% of patients with schizophrenia of more than 2 years' duration are only partially responsive to antipsychotic medication.<sup>1,2</sup>

Several studies have documented greater treatment resistance to haloperidol than to the atypical antipsychotics risperidone, olanzapine, and quetiapine. Specifically, haloperidol is associated with a higher number of treatment discontinuations because of lack of efficacy and a larger proportion of patients who do not meet 20% improvement criteria.<sup>3–7</sup>

Treatment resistance or failure of another type also can be determined by examining relapse rates for patients on existing therapy. Leucht et al.<sup>8</sup> conducted a meta-analysis of 1-year studies determining relapse rates of atypical and typical antipsychotic agents. They found that typical neuroleptics resulted in an average 1-year relapse rate of 23% in contrast to 15% for atypical treatment; this difference was found to be highly statistically significant ( $p < .00001$ ).<sup>8</sup>

In a 14-week double-blind study, Lindenmayer et al.<sup>9</sup> showed that the atypical antipsychotics clozapine, olanzapine, and risperidone were associated with significant improvements

in 3 of 5 syndromal domains (positive, cognitive, and depression/anxiety) of schizophrenia compared with haloperidol. These findings confirm that atypical agents show improvement of an expanded spectrum of symptoms in patients with treatment-resistant schizophrenia. Differences between atypical and traditional antipsychotics may be attributed to the differences in receptor-binding profiles of these 2 classes of drugs and may warrant greater study.

### Clozapine: The Criterion Standard in Treatment-Resistant Schizophrenia

Clozapine has demonstrated significant efficacy in patients with treatment-resistant schizophrenia and therefore is considered the criterion standard treatment in this subgroup. In a 6-week double-blind trial of 268 patients meeting criteria for treatment resistance, clozapine was significantly more effective than chlorpromazine (response rates of 30% and 4%, respectively).<sup>10</sup> This study led to the U.S. Food and Drug Administration's approval of clozapine for patients with treatment-resistant schizophrenia.

More recent studies have established the superiority of clozapine over haloperidol<sup>11</sup> and risperidone<sup>12</sup> in randomized double-blind trials. In a study by Bitter et al.,<sup>13</sup> the efficacy of clozapine was found to be similar to that of olanzapine in patients with treatment-resistant and treatment-tolerant schizophrenia. However, in this study, cloza-

pine was administered at a mean final dose of approximately 200 mg/day, which is much lower than the doses routinely used in the United States.

Unfortunately, clozapine has been associated with potentially fatal agranulocytosis in approximately 0.5% to 1% of patients.<sup>14</sup> For this reason, clozapine should be used as second- or third-tier therapy if lack of efficacy resulted in treatment resistance or drug withdrawal with the previous choice of antipsychotic agent.

### Newer Atypical Antipsychotics

Newer atypical antipsychotics may be beneficial for patients with treatment-resistant schizophrenia and may have the added advantage of relatively benign adverse effects. A recent study by Kane et al.<sup>15</sup> compared the effect of aripiprazole with that of the traditional neuroleptic perphenazine for patients with treatment-refractory schizophrenia. Perphenazine was chosen because it is a typical agent that has been found efficacious for the treatment of patients with schizophrenia, it is relatively well tolerated (low incidence of extrapyramidal side effects), and it currently is not widely used, thereby ensuring a low probability that patients had received previous perphenazine therapy. The study design included a 6-week treatment period with open-label risperidone or olanzapine to ascertain that only patients with treatment-resistant schizophrenia were enrolled in the subsequent phases of the study. Patients were randomly assigned to double-blind aripiprazole or perphenazine treatment for 6 weeks. Both drugs were equally efficacious in the treatment of patients with refractory schizophrenia. Additionally, aripiprazole showed a trend toward significance ( $p = .052$ ) in quality-of-life response compared with perphenazine at 6 weeks.<sup>15</sup>

In double-blind parallel-group trials and open-label switching studies,<sup>16–18</sup> ziprasidone resulted in significant improvement in patients with treatment-refractory schizophrenia. Ziprasidone also demonstrated favorable

tolerability, including a low liability for weight gain.

These studies illustrate that given their superior adverse-effect profiles, newer atypical antipsychotics may be as beneficial in patients with treatment-resistant schizophrenia as typical agents and should be considered before switching a patient's treatment to a traditional neuroleptic. Finally, if a response is not seen with these agents, clozapine should be considered. Although this approach in the management of patients with treatment-resistant schizophrenia may be effective, there are concerns about how many atypical antipsychotics should be tried before making the switch to a traditional neuroleptic or clozapine.

### Polypharmacy Concerns

Physicians sometimes prescribe a concurrent antipsychotic or mood stabilizer for patients with treatment-resistant schizophrenia with the hope of enhancing or speeding up treatment results. However, extreme caution must be exercised in polypharmacy because evidence is lacking regarding its benefits, and few randomized controlled trials support such practice. Additionally, it is possible to inadvertently prescribe a higher than necessary total dose, which could result in an increased number of acute adverse effects and would lead to increased risk for nonadherence. Other concerns with polypharmacy include drug-drug interactions and difficulty determining the specific effects of each drug.<sup>19</sup> Patients with treatment-resistant schizophrenia should continue to be managed using single antipsychotics while the efficacy of some newer antipsychotics and, ultimately, clozapine is evaluated.

### Summary

Treatment-resistant schizophrenia remains a significant management challenge. The atypical antipsychotic clozapine has established benefits but remains problematic for long-term therapy. The newer atypical antipsychotics aripiprazole and ziprasidone

also may provide benefit to some patients resistant to previous therapy and should be considered before switching to traditional antipsychotics, concluded Dr. Kane.

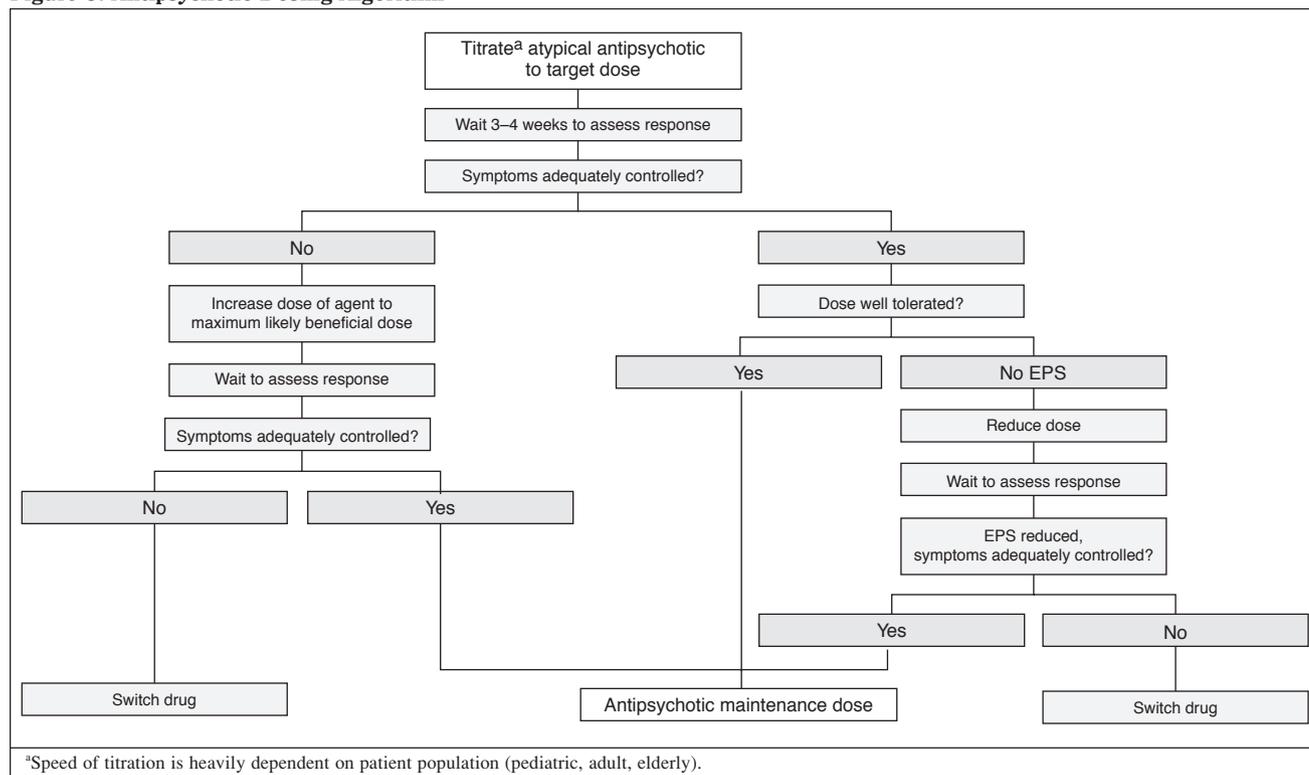
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## Optimizing Effectiveness of Atypical Antipsychotics Across Patient Groups

As stated by Rajiv Tandon, M.D., the 1950s saw the arrival of the first effective agents for treating patients with psychosis. However, with these first-generation neuroleptics, antipsychotic effects and extrapyramidal side effects (EPS) were commonly seen in the same dose range, and, for many years, the accepted wisdom was that EPS were unavoidable. Second-generation atypical antipsychotics have

changed this thinking. These drugs are termed *atypical* because they provide an equivalent antipsychotic effect with a low propensity to induce EPS. As a result, atypical antipsychotics provide a broader spectrum of efficacy than traditional neuroleptics and a substantially lower risk for tardive dyskinesia (TD),<sup>1</sup> and they have been increasingly used to treat patients with various psychoses and other psychiatric conditions.

Figure 6. Antipsychotic Dosing Algorithm<sup>a</sup>

Atypical antipsychotics have diverse receptor-binding profiles that produce different efficacy and adverse effect profiles<sup>1</sup>; therefore, patients do not respond in the same manner to different atypical agents. Target symptoms and patient characteristics (such as age, race, and sex) are the major elements that impact drug selection and influence dosing strategies.

### What Are You Treating?

The nature of illness and its chronicity affect optimal atypical antipsychotic treatment. For example, in patients with bipolar disorder, among the mood stabilizers, lithium is effective for the treatment of acute mania, and, as maintenance treatment, divalproex is beneficial for the manic phase and lamotrigine for the depressive phase.<sup>2,3</sup> All atypical antipsychotics are effective in the treatment of acute mania and may be useful during the depressive phase and as maintenance treatment for bipolar disorder. In a randomized, placebo-controlled, double-blind

maintenance study, olanzapine significantly decreased the percentage of bipolar disorder patients with relapses, depression, or mania compared with placebo.<sup>4</sup> Although olanzapine is the only atypical antipsychotic approved for maintenance therapy, data are emerging for other atypical antipsychotics. In a 26-week, placebo-controlled, maintenance study of bipolar disorder patients, aripiprazole significantly decreased the percentage of relapses and the proportion of patients experiencing relapses compared with placebo.<sup>5</sup> A case series<sup>6</sup> reported that maintenance treatment with risperidone (1–3 mg/day), in combination with lithium, produced complete remission for up to 38 months.

### Who Are You Treating?

Patient characteristics, such as age, sex, and race, can also influence the effectiveness of atypical antipsychotics. Sensitivity to adverse effects, chronicity of illness, occurrence of comorbid conditions, pharmacokinetic

parameters, and risk for drug-drug interactions can be dependent on the patient's age.<sup>7</sup> Consequently, age is a critical factor for dosing, titration, tolerability, and drug choice.

**Pediatric population.** Growth and development in children can affect drug pharmacokinetics.<sup>8</sup> In addition, central nervous system development in young people affects antipsychotic efficacy. For example, children and adolescents have a greater density of striatal dopamine D<sub>2</sub> receptors than adults, which may increase the propensity for EPS.<sup>8</sup> In addition, adolescents are known to have a high propensity for dystonic reactions.

A major reason for noncompliance with atypical antipsychotics among pediatric patients is weight gain. Increased weight has a significant negative effect on the physical and the emotional development of children and adolescents.<sup>8</sup> For this reason, selecting an appropriate atypical antipsychotic is important. Clozapine and olanzapine are associated with the greatest weight

gain, risperidone and quetiapine with intermediate weight gain, and ziprasidone and aripiprazole, the newest atypical antipsychotics, with the lowest weight gain.<sup>9</sup>

**Elderly population.** Older patients are at an increased risk for EPS and have a higher propensity for TD, parkinsonian symptoms, and akathisia. EPS and TD can increase the likelihood and frequency of falls, which can have devastating consequences (e.g., hip fractures). Atypical antipsychotics have a lower propensity for EPS and are associated with notable cognitive benefit, mood advantage, and reduced risk for TD, offering an attractive treatment option for older patients.<sup>7</sup>

Weight gain caused by atypical antipsychotics is also an important adverse effect in the elderly.<sup>10</sup> Increased weight can lead to diabetes, hypertension, and elevated cholesterol levels, with significant consequences in older patients.

**Dosing.** Five elements can be considered for successful dosing of atypical antipsychotics (Figure 6):

1. **Initial target dose.** What is the initial target dose of medication at which one will wait for a response? It is important to know dose equivalents for the different atypicals. For example, quetiapine is prescribed at approximately 600 mg/day, whereas risperidone is prescribed at 5 mg/day for equivalent efficacy.

2. **Titration.** How rapidly should the target dose be achieved? Children and the elderly require slower titration to avert adverse effects such as sedation and orthostatic hypotension.

3. **Initial waiting period.** How long should one wait for a response before changing dose? Some national experts considered 3 to 6 weeks an adequate time for a trial of antipsychotics.<sup>11</sup>

4. **Highest dose.** What is the highest dose possible without incurring adverse effects? Experts recommend improving response by dose increases before switching to a different agent.<sup>11</sup>

5. **Total waiting period.** How long must one wait for favorable efficacy and tolerability before giving up and

switching from a drug? National experts indicate they would wait up to 10 weeks before making a major change to a treatment regimen.<sup>11</sup>

Clinical experience is extremely important in shaping dosing strategies, and clinical practitioners have played a critical role in redefining the target dose of many atypical antipsychotics. For example, the modal dose of risperidone has decreased over time from an approximate mean dose of 8 mg/day to 5 mg/day. In contrast, the modal dose of olanzapine has increased from an approximate mean dose of 10 mg/day to 19 mg/day.<sup>12</sup>

Comorbid medical and psychiatric conditions necessitate the prescribing of drugs that may affect atypical antipsychotic pharmacokinetics. Atypicals are eliminated primarily by hepatic metabolism through the cytochrome P450 (CYP) system. Inducers and inhibitors of CYP enzymes (e.g., selective serotonin reuptake inhibitors, smoking) can affect bioavailability, and drug doses should be adjusted accordingly.<sup>12</sup> Because atypicals are metabolized by different CYP isoenzymes, the bioavailability of each antipsychotic is affected differentially.<sup>1</sup>

### Summary

Target symptoms and patient characteristics dictate the selection and dosing strategies of atypical antipsychotics, which are the key factors in achieving optimal treatment outcome. Although atypical antipsychotics share clinical attributes, there are substantial differences among them, particularly with regard to their adverse effect profiles. Not all patients respond to these medications in the same way; therefore, Dr. Tandon emphasized, it is important to tailor antipsychotic treatment to a patient's individual need.

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## Factors Having Impact on the Tolerability of Antipsychotic Agents

The atypical antipsychotics were launched in the 1990s. Compared with typical antipsychotics, they offered a greater therapeutic spectrum and caused fewer extrapyramidal side effects (EPS), which led to their rapid adoption (except clozapine) as the first-line treatment for patients with schizophrenia and mania, stated Henry A. Nasrallah, M.D. Recently, a new cluster of metabolic adverse effects

has emerged—hyperprolactinemia, obesity, the development of diabetes, and an atherogenic lipid profile—which is proving to be just as significant as EPS in terms of its impact on tolerability. However, there appears to be wide variation in the extent to which the various atypical agents are associated with these metabolic adverse effects. Given the equal efficacy of atypical antipsychotics at equivalent doses,<sup>1</sup> the choice of an agent for a given patient should be linked to its tolerability. This is critical because tolerability is a major factor in patient adherence and, ultimately, successful long-term remission of symptoms and relapse prevention. Dr. Nasrallah then provided an overview of those adverse effects.

### Extrapyramidal Side Effects

EPS, which include akinesia or hypokinesia, akathisia, dystonia, and tardive dyskinesia, are caused by the excessive antagonism of D<sub>2</sub> receptors in the nigrostriatal tract. The reduced propensity of atypical agents to cause EPS may be attributed to their transient binding properties to D<sub>2</sub> receptors, antagonism of 5-HT<sub>2</sub> receptors, or differential selectivity for receptors in the mesolimbic pathway. In placebo-controlled trials, risperidone, olanzapine, and ziprasidone are associated with dose-related increases in EPS, whereas quetiapine is not.<sup>2-5</sup> Aripiprazole is associated with an increased incidence of akathisia.<sup>6</sup> However, a long-term study shows that, at 52 weeks of treatment, the incidence of akathisia is equivalent to placebo levels.<sup>7</sup> Furthermore, switching treatment to aripiprazole from haloperidol or from other atypical antipsychotics results in a reduction in EPS.<sup>8</sup>

### Hyperprolactinemia

Hyperprolactinemia is the consequence of prolactin disinhibition after D<sub>2</sub> antagonism in the tuberoinfundibular pathway and is associated predominantly with the use of typical antipsychotics because of their lack of selectivity of D<sub>2</sub> antagonism. Risperi-

done causes a dose-related increase in prolactin secretion; olanzapine shows a slight increase at high doses, and quetiapine and ziprasidone have no effect.<sup>9</sup> In contrast, aripiprazole causes a decrease in prolactin secretion<sup>9</sup> by virtue of its partial agonist properties.<sup>10</sup> Clinical manifestations of hyperprolactinemia are attributed to the direct action of prolactin on its target tissues and to hypogonadism secondary to hyperprolactinemia. In women, these effects include amenorrhea, anovulation, and galactorrhea; in men, they include gynecomastia, hypospermia, and erectile and ejaculatory dysfunction. Loss of libido, a significant cause of treatment discontinuation, occurs in both sexes. Prolonged hyperprolactinemia may lead to increased risk for osteoporosis and cancer.<sup>11</sup>

### Obesity

Weight gain occurs to varying degrees across all dose ranges with most atypical antipsychotics.<sup>12</sup> Olanzapine is associated with the greatest weight gain, approximately 27 lb at 52 weeks; in the same period, patients gain an average of only 5 lb with risperidone and 4.8 lb with quetiapine.<sup>13-15</sup> Clozapine also is associated with significant weight gain—29 lb after 1 year.<sup>16,17</sup> Ziprasidone and aripiprazole have minimal impact on weight.<sup>4,6,18,19</sup> In addition to its well-established consequences of increased risk for diabetes, cardiovascular morbidity, and cancer, obesity has a major adverse impact on psychological well-being and self-esteem, one of the main factors associated with poor adherence to pharmacotherapy.

### Diabetes

Data on the association between the use of atypical agents and the development of diabetes, obtained from several retrospective cohort studies, have been summarized in a recent expert consensus statement.<sup>20</sup> The findings indicate that clozapine and olanzapine are associated with a clinically significant risk for diabetes, whereas aripiprazole and ziprasidone are not.<sup>20</sup> Data for risperi-

done and quetiapine in relation to diabetes are inconsistent.<sup>20</sup> The mechanism by which antipsychotic agents induce diabetes remains unknown. Reports of new-onset diabetes and diabetic ketoacidosis in the absence of significant weight gain suggest that additional mechanisms leading to insulin resistance may also play a role.

A controlled, large-scale, 5-year, prospective study (the Clinical Antipsychotic Trials of Intervention Effectiveness [CATIE] study) concluded in December 2004.<sup>21</sup> The results, to be released in 2005, should provide more definitive evidence for the association among the use of antipsychotics, the risk for diabetes, and the differential effect of individual agents.

### Dyslipidemia

Clozapine and olanzapine have also been shown to cause an atherogenic lipid profile—increased low-density lipoprotein cholesterol level, hypertriglyceridemia, and decreased high-density lipoprotein cholesterol level.<sup>20</sup> Risperidone and quetiapine produce inconsistent effects, whereas aripiprazole and ziprasidone produce little or no effect.<sup>20</sup>

### Conclusion

Persons with schizophrenia have an inherently increased risk for medical comorbidity, either directly as a result of their disease or indirectly as a result of the lifestyle imposed by their disease—smoking, poor diet, lack of exercise, and general self-neglect. With the emergence of obesity, diabetes, and dyslipidemia as serious metabolic adverse effects of some antipsychotics, it is imperative to prescribe an agent that will not impose additional health risks in susceptible patients. Dr. Nasrallah concluded that, given the therapeutic equivalence of antipsychotic agents and their varying adverse effect profiles, the main factor driving the decision-making process in the choice of an agent is the proper match between the patient's medical history and the adverse effect profile of the agent to be prescribed.

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**Drug names:** aripiprazole (Abilify), chlorpromazine (Thorazine, Sonazine, and others), clozapine (Clozaril, Fazaclon, and others), divalproex sodium (Depakote), haloperidol (Haldol and others), lamotrigine (Lamictal), lithium (Eskalith, Lithobid, and others), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal), ziprasidone (Geodon).

**Disclosure of off-label usage:** The chair has determined that, to the best of his knowledge, no investigational information about pharmaceutical agents has been presented in this article that is outside U.S. Food and Drug Administration–approved labeling.

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