ABSTRACT

Clinical trials of antipsychotic medications frequently fail to generate all of the information needed for clinical decision making. Trial methods are frequently lacking, primarily because it is difficult to identify appropriate efficacy targets in an illness as complex as schizophrenia. In addition to symptom response, other outcomes are important, such as effects on cognition, mood, anxiety, and freedom from burdensome medical and neurologic side effects. Standard rating scales, such as the Positive and Negative Syndrome Scale (PANSS), are not indicative of the severity of the disease; for example, a classification of “mild” on most PANSS items is calibrated for ongoing debilitating symptoms.

The essential question of how best to use clinical trial information in clinical practice remains a matter of individual physician judgment and individual patient status. Another vexing issue is how to generalize from short-term trials to other types of settings and clinical situations. For example, physicians must decide whether and how to switch patients to different antipsychotics. A key consideration is whether an individual patient is willing to tolerate extensive symptoms and side effects in order to maximize long-term efficacy.

The integration of basic science theory and clinical observation is one of the cornerstones of the practice of medicine. However, we can only observe inasmuch as our measures and our instruments are accurate and precise. That is the intent, but not always the accomplishment, of the controlled clinical trial. Clinical trials of antipsychotics for the treatment of schizophrenia illustrate the gap between clinical measures and scientific understanding. Going back one half of a century, the first controlled clinical trial represented a breakthrough in scientific thought—it featured a random-assignment placebo-controlled design with quantitative measurements of an outcome measure of psychosis, and measured its relationship to dose escalation over time. More than 50 years later, clinical trial designs of antipsychotics follow this early model, with data arranged in terms of average response to treatment across groups of patients. Although pharmaceuticals have advanced tremendously over the past 5 decades, the instruments used to assess their effectiveness remain relatively unchanged.

When assessing short-term efficacy of a medication, it is important to consider phase of illness as well as absolute level of symptoms in order to accurately measure therapeutic response. One would expect an acutely ill patient to have mostly responded to acute antipsychotic treatment over 4 weeks, whereas in a chronically ill patient, 4 weeks represents only the beginning of the anticipated response. Another consideration is the likelihood of achieving a therapeutic response, which is typically measured across groups, with the results reported as mean reduction in symptom response rate. Yet an individual response rate can be quite different from the group mean. There are no clinical predictors of individual response, yet clinicians need to take individual variations into consideration as...
Newest Atypical vs Conventional Antipsychotics

Efficacy of the earlier atypical antipsychotics (olanzapine, quetiapine, and risperidone) has been widely reported in the medical literature. One of the pivotal studies influential in introducing atypical antipsychotic agents to the therapeutic armamentarium for schizophrenia was an early study by Kane and colleagues showing that over 6 weeks, clozapine achieved response in 30% of treatment-resistant patients, compared with 4% of patients taking chlorpromazine. Clozapine produced significantly greater improvement on the Brief Psychiatric Rating Scale, Clinical Global Impression Scale, and Nurses' Observation Scale for Inpatient Psychiatric Rating Scale, and Clinical Global Impression Evaluation. This study showed us that total blockade of the dopamine D2 receptor is not necessary to achieve therapeutic effect, as clozapine's D2 receptor agonist activity is mild compared with that of chlorpromazine. This understanding of the efficacy of partial D2 receptor agonists has led to the development of the atypical medications we have come to rely on within our clinical practice today—medications that generally have improved efficacy, yet have reduced the extrapyramidal side effects associated with substantial D2 receptor blockade.

Results of a meta-analysis examining the efficacy of olanzapine, quetiapine, and risperidone vs first-generation antipsychotics in the acute treatment of schizophrenia and schizophrenia-like psychoses indicated that the average response across these agents was equal to or slightly better compared with older conventional antipsychotics. Not included in this meta-analysis are the newest agents approved as first-line antipsychotics in the United States, namely, ziprasidone and aripiprazole. Therefore, the efficacy and dose-response characteristics of these 2 antipsychotics will be discussed in greater detail. The results of acute 4- to 6-week trials of ziprasidone show that its overall positive symptom efficacy is similar to haloperidol and olanzapine. In acute studies of aripiprazole, we see similar results, with the overall positive symptom efficacy of aripiprazole being comparable to haloperidol and risperidone as measured by the Positive and Negative Syndrome Scale (PANSS). In terms of average efficacy across groups of patients in acute-phase trials, the efficacy across the “first-line” (non-clozapine) atypical antipsychotics is more similar than it is different.

The next question relates to acute-phase dosing. Again, the focus will be on ziprasidone and aripiprazole. When it comes to dosing and regimen characteristics, there are significant differences between ziprasidone and aripiprazole. Ziprasidone has a substantial dose-response relationship. Although labeled for daily doses between 40 and 160 mg, a daily dose of 80 mg is a more appropriate starting dose for acute-phase patients. A 6-week acute dose-finding study showed that although both the 80-mg daily and 160-mg daily doses were more effective than placebo, there is a striking visual contrast between the magnitude of the response, which favored 160 mg over 80 mg. Other dosing issues concerning ziprasidone are that it has a short half-life and thus is labeled for twice-daily dosing, and has an absorption profile such that it should be taken with meals. Aripiprazole, on the other hand, is labeled for dosing between 10 mg and 30 mg per day. However, for the acutely ill patient, aripiprazole seems best dosed between 15 mg and 30 mg per day. Of interest is that, at least when considering efficacy in groups of patients, there is no difference in magnitude in symptom response between 15-mg and 30-mg doses. Therefore, aripiprazole seems to have a different dose-response pattern than other first-line antipsychotics. It also has a long half-life and can therefore be taken once daily, without regard to meals. A starting dose of 15 mg is the same as a therapeutic target dose.

In addition to total PANSS measures, measures of negative symptoms are an important clinical consideration. Of note is the fact that “mild” schizophrenia, as defined by the PANSS scale, belies the seriousness of the condition. A patient with mild negative symptoms is capable of only marginal social interaction and is, in fact, seriously debilitating, again pointing to the inadequacies of our current measurement tools. Because negative symptoms are similar to behaviors exhibited in Parkinson's disease, the assumption is that the symptoms are the result of low dopamine function. Therefore, the extent of dopamine receptor blockade may be a key clinical consideration when choosing medication for such patients. The clinician should be mindful of negative symptom outcomes in the clinical data, in addition to total PANSS scores. Many studies in schizophrenia are short term, due to the complexity of the disease and issues relating to long-term treat-
ment compliance. However, short-term analysis, particularly of negative symptoms, is another substantial limitation in our approach to investigating schizophrenia. Reduction of negative symptoms over the long term is a more relevant indicator of a patient's overall recovery compared with acute relief of these symptoms.

Given this inherent drawback in short-term study design, the clinical evidence reported in one such study indicates that aripiprazole dosed at 20 or 30 mg daily is significantly better than placebo for reduction of negative symptoms, as measured by the PANSS negative scale, with substantial improvements reported as early as week 1 of therapy. In a separate study arm, risperidone was also found to be superior to placebo for reduction of negative symptoms, but the difference did not reach statistical significance until week 2 of therapy. Clinically, it is also important to recognize that positive symptoms, such as hallucinations, may prompt fear and withdrawal in a patient, thus falsely presenting as negative symptoms. Drug-induced extrapyramidal symptoms may also present as negative symptoms, an additional factor worthy of clinical consideration during patient assessment. A much better way to evaluate the efficacy of drugs on negative symptoms is with long-term trials. In a double-blind, 1-year study of acutely ill patients, patients were randomized to either 10 mg per day of haloperidol or 30 mg per day of aripiprazole. In this study, the negative-symptom response of both medications was similar during the acute period; at 6 months, however, there was a better negative-symptom response in patients taking aripiprazole compared with haloperidol. The differences in negative-symptom efficacy between atypical and older antipsychotics are subtle, and there is a lag time between acute positive-symptom response and negative-symptom improvement.

Whereas all of the atypical antipsychotics have been reported to be equally or more efficacious compared with traditional therapies, side effects vary from drug to drug. As discussed by Dr Roth (pages S776-S781), each agent has a distinct receptor profile that triggers fairly predictable side effects. Clinical observations of side effects associated with individual atypical drugs are presented in Figure 1. Low extrapyramidal effects, particularly with drugs such as haloperidol, may actually be the result of concomitant use of anti-Parkinson's medications, such as benztropine. Aripiprazole and ziprasidone use is clinically associated with few extrapyramidal side effects without

**Figure 1. A Clinical Opinion: Summary of Side-Effect and Safety Concerns with Atypical Antipsychotics**

<table>
<thead>
<tr>
<th></th>
<th>Clz</th>
<th>Ris</th>
<th>Olz</th>
<th>Qtp</th>
<th>Zip</th>
<th>Ari</th>
</tr>
</thead>
<tbody>
<tr>
<td>Orthostasis</td>
<td>+++</td>
<td>++</td>
<td>+0</td>
<td>++</td>
<td>0/+</td>
<td>0/+</td>
</tr>
<tr>
<td>Somnolence</td>
<td>+++</td>
<td>+0</td>
<td>+/++</td>
<td>++</td>
<td>+/0</td>
<td>0</td>
</tr>
<tr>
<td>EPS</td>
<td>0</td>
<td>+/+++</td>
<td>0/+</td>
<td>0</td>
<td>0/0</td>
<td>0/0</td>
</tr>
<tr>
<td>Prolactin</td>
<td>0</td>
<td>++</td>
<td>0/+</td>
<td>0/+</td>
<td>0/+</td>
<td>0</td>
</tr>
<tr>
<td>QTc prolongation</td>
<td>No clinical relevance to date</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>W eight gain</td>
<td>+++</td>
<td>++</td>
<td>+++</td>
<td>++</td>
<td>-/+</td>
<td>-/+</td>
</tr>
<tr>
<td>Lipids</td>
<td>++</td>
<td>+</td>
<td>++</td>
<td>+</td>
<td>0/-</td>
<td>0/-</td>
</tr>
<tr>
<td>Glucose intolerance</td>
<td>Cause and effect not clearly established; may be related to weight gain</td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

Symbols indicated relative degree of concern; 0 = no concern; +++ = strong/severe concern. Clz = clozapine; Ris = risperidone; Olz = olanzapine; Qtp = quetiapine; Zip = ziprasidone; Ari = aripiprazole; EPS = extrapyramidal symptoms.


**Figure 2. Clinically Significant (≥7%) Weight Gain During Antipsychotic Treatment**

Data for aripiprazole, ziprasidone, risperidone, quetiapine, and olanzapine from US labels.
concomitant benztrapine, and is also observed to be weight-neutral in most patients (Figure 2). Based on the overall data from short- and long-term trials, aripiprazole has a favorable metabolic profile, with no adverse effects on the plasma lipid levels compared with haloperidol and risperidone. Its cardiovascular profile is also favorable, with no significant QTc prolongation reported. Dopamine agonists, even partial agonists such as aripiprazole, can cause insomnia and are also associated with nausea and vomiting during the first 2 to 3 weeks. Initiating therapy at lower doses and advising patients about the potential for nausea may be helpful to minimize these effects.

Switching Antipsychotic Medications

Although most of the therapeutic data relates to the treatment of acutely ill patients, treatment of stable outpatients raises additional questions. If we assume that we cannot cure schizophrenia and that most of our patients may be stabilized but may not achieve complete remission, a major existential question surrounds the possibility of switching medications. Will a medication switch render more improvement? At what point are symptoms acceptable or not acceptable? What are the therapeutic goals, and can a different medication help to achieve them better? These are questions that can only be answered through extensive work and assessment with individual patients and their families. A summary of indications for switching antipsychotics from the perspective of the clinician, patient, and family is presented in Table 1.

The gravest clinical concern in changing antipsychotic medications for stable outpatients is that the patient will relapse during the crossover process. In the past few years, several open-label switching studies have been conducted that may assist clinicians who wish to switch medications (Table 2). Some have undertaken “cold-turkey” switching from one medication to another, and others have cross-tapered medications (Figure 3). Results from switch studies with aripiprazole, olanzapine, and other treatments suggest that the method used for switching is not a factor in clinical outcomes, as long as the patient is maintained on a therapeutic dose range of either the old or the new medication. Early side effects may occur with the initiation of a new medication—most frequently sedation with olanzapine and quetiapine and somnolence with ziprasidone or aripiprazole. Patients should be counseled about potential side effects and advised that these effects typically subside after several weeks of therapy. Adequate and effective psychoeducation regarding side effects and other relevant issues must be provided to patients and their families before a medication switch is made. Such discussions should be phrased in nonclinical terms that are meaningful to patients and families—in terms that address their concerns and frustrations about day-to-day activities.

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

<table>
<thead>
<tr>
<th>Clinician’s Perspective</th>
<th>Patient’s Perspective</th>
<th>Family’s Perspective</th>
</tr>
</thead>
<tbody>
<tr>
<td>Persistent positive symptoms</td>
<td>Distress from positive symptoms</td>
<td>Disruptiveness and agitation</td>
</tr>
<tr>
<td>Persistent negative symptoms</td>
<td>Secondary anxiety and depression from positive symptoms</td>
<td>Emotional and financial burden of caregiver role</td>
</tr>
<tr>
<td>Relapse despite compliance</td>
<td>Inability to meet life’s goals</td>
<td>Dealing with multiple crises and setbacks</td>
</tr>
<tr>
<td>Persistent EPS† and/or tardive dyskinesia</td>
<td>Inability to function independently in the community</td>
<td>Heartbreak of seeing their relative or partner burdened by akinesia or tardive dyskinesia</td>
</tr>
<tr>
<td>Hyperprolactinemia (galactorrhea and amenorrhea in women, gynecomastia and impotence in men)</td>
<td>Dysphoria or distress from EPS</td>
<td>Disappointment or frustration on the part of the sexual partner</td>
</tr>
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</table>

* Assumes that the patient is receiving therapeutic doses of a conventional antipsychotic and that the persistent symptoms cannot be attributed to compliance problems and/or substance abuse problems.
† Assumes that the patient is receiving treatment with optimal doses of a conventional antipsychotic and successfully attempted treatment with anti-Parkinson or antiakathisia agents.

EPS = extrapyramidal symptoms

An interesting finding across switching studies is that patients switched to one of the first-line atypical antipsychotics will improve regardless of whether their previous medication was a conventional or an atypical antipsychotic. This supports the notion that there is differential efficacy between atypical antipsychotics. However, caution is warranted—these findings may also be the result of investigator bias within the open-label study framework. Still, differential efficacy is consistent with the known differences among these atypical antipsychotics in terms of mechanisms of action as well as side effects.

**CONCLUSION**

It is important to recognize that mechanism of action and clinical observation are not separate pursuits but are inextricably linked. In recent years, major advances in psychopharmacologic options for patients with schizophrenia have developed, and many patients treated with the new atypical antipsychotics have realized improved symptom control. Important differences exist among schizophrenia therapies, giving patients new opportunities and choices. Switching from one antipsychotic to another may result in improved control of symptoms and offer still more options. With these opportunities for medication management bolstered by insights from clinical observation and psychosocial interventions, hopefully patients will experience less stigma and improved control of this lifelong disease.

**REFERENCES**

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