Introduction

Ziprasidone in Schizophrenia: From Acute Treatment to Long-Term Management

John M. Kane, M.D.

Schizophrenia is a highly complex, chronic, often lifelong, mental illness that severely compromises social, intellectual, and occupational functioning. About 1% of the population will develop schizophrenia, and annually more than 2 million Americans suffer from the disorder.[1] People with schizophrenia on average live 15 fewer years than individuals in the general population, dying prematurely of natural (e.g., cardiovascular and respiratory diseases) as well as unnatural causes (primarily suicide).[2]

One of the challenges of treating this disorder is its relapsing/remitting nature, which requires pharmacotherapy that can rapidly improve symptoms. Also, its complex presentation, including varying individual degrees of positive, negative, and affective symptoms and cognitive impairment, demands effectiveness across symptom domains.

Atypical antipsychotics are now widely considered first-line treatment agents for schizophrenia and other psychotic disorders. These agents are at least as effective in controlling psychotic symptoms as are older, conventional agents, and indeed may possess superior efficacy against negative symptoms. Moreover, they offer a lower movement disorder burden than do conventional drugs, a critical clinical advantage, and arguably better overall tolerability. However, the enthusiasm generated by the advent of atypical antipsychotics has been diminished by weight gain, glucose metabolism disturbances, and serum lipid elevations reported in recent years with some of these agents. Furthermore, no atypical antipsychotic has been available for intramuscular (IM) injection, an important unmet need in the management of agitated psychotic patients.

Management of schizophrenia and schizoaffective disorder represents a continuum of care. Ideally, antipsychotic therapy will rapidly control acute psychotic episodes; improve positive, negative, and affective symptoms and cognitive function; prevent relapse; and offer a tolerability profile that facilitates patient adherence and positive overall health outcomes. With these criteria in mind, the articles that compose this supplement to *The Journal of Clinical Psychiatry* examine ziprasidone, the first and currently only atypical antipsychotic available in both oral and IM formulations.

Stephen M. Stahl, M.D., Ph.D., and coauthor Darius K. Shayegan, B.S., begin the exploration by applying the receptor-binding properties of ziprasidone to real-world psychiatric practice and showing through clinical trial data that the agent's clinical activity is consistent with its receptor profile. As with other atypical agents, ziprasidone is a serotonin-2A (5-HT_{2A})/dopamine-2 (D_2) antagonist. Dr. Stahl and Mr. Shayegan note that ziprasidone has the highest $5\text{-HT}_{2A}/D_2$ receptor affinity ratio among first-line atypical antipsychotic agents, which is correlated with a lower propensity for extrapyramidal symptoms as well as with activity against the negative symptoms of schizophrenia. The drug's potent interaction with 5-HT_{2C}, 5-HT_{1D}, and 5-HT_{1A} receptors predicts heightened relief of negative symptoms, enhanced modulation of mood, improvement of cognitive symptoms, and reduced motor dysfunction. The authors further note that ziprasidone's moderate affinity for 5-HT and norepinephrine reuptake sites are predictive of antidepressant/anxiolytic activity, and its low affinity for α_1-adrenergic, histamine H_1, and muscarinic M_1 receptors is predictive of a relatively low incidence of orthostatic hypotension, sedation, cognitive disturbance, weight gain, or dysregulation of prolactin levels.

Shlomo Brook, M.D., discusses the prospects of moving beyond the use of IM conventional antipsychotic agents in the emergency treatment of acutely agitated psychotic patients who cannot take oral medication.

Although atypical antipsychotics are now widely acknowledged as the first-line treatment for schizophrenia, their use in acutely agitated psychotic patients has been considerably limited by the lack of an IM formulation. Dr. Brook examines the efficacy and tolerability of IM ziprasidone. Agitation is reduced in as quickly as 15

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minutes postadministration with IM ziprasidone, with sustained improvement for ≥ 4 hours. Intramuscular ziprasidone has also been shown to be more effective than haloperidol in improving overall symptom severity, and it has been shown to sustain symptom control through transition from IM to oral formulations. Dr. Brook notes that the improved side-effect profile of ziprasidone over conventional antipsychotics has a positive effect on patient satisfaction and thus may improve compliance with long-term therapy.

Myriad factors affect choices surrounding antipsychotic therapy, from rapid alleviation of symptoms in exacerbations of schizophrenia to ineffective symptom treatment or tolerability problems in the stable patient. In the third article of this supplement, I assess the clinical utility of ziprasidone by reviewing data from short-term, placebo-controlled and active comparator clinical trials. In placebo-controlled trials of 4 to 6 weeks' duration, ziprasidone produced significant improvements in overall psychopathology and negative symptoms in as little as 1 week. In active comparator trials lasting 4 to 8 weeks, ziprasidone's efficacy was comparable to that of haloperidol, olanzapine, and risperidone. Patients who were switched to ziprasidone from conventional antipsychotics, olanzapine, or risperidone because of suboptimal efficacy or tolerability showed symptom improvement in 6-week open-label studies. The short-term study data indicate that ziprasidone offers important tolerability advantages, for example, a lower movement disorder burden than risperidone, a lower liability for weight gain than risperidone or olanzapine, and, in a comparison with olanzapine, an absence of significant deleterious effects on serum lipid levels or glucose metabolism. The available clinical data support rapid titration to ≥ 120 mg/day for optimal efficacy in patients with acute exacerbation of schizophrenia.

Nina R. Schooler, Ph.D., next discusses the ability of ziprasidone to maintain symptom control long term. Although atypical antispychotics have gained acceptance and offer tolerability advantages over conventional antipsychotics in the treatment of schizophrenia or schizoaffective disorder, there are differences among the atypicals that may affect compliance with therapy. In clinical trials lasting up to 52 weeks, ziprasidone was associated with a reduced risk of relapse, improvement in negative symptoms, and sustained positive symptom control. The long-term efficacy of ziprasidone was comparable to that of other atypical antipsychotic agents, and was superior to that of haloperidol in terms of the proportion of negative-symptom responders. Ziprasidone was also associated with significant sustained improvement in negative symptoms in patients switched from other atypical or conventional antipsychotic agents. Dr. Schooler notes that the clinical implication of this finding is substantial since the persistence of negative symptoms during the course of schizophrenic illnesses has been shown to have a deleterious impact on outcome. She also notes that in long-term treatment, ziprasidone has demonstrated a tolerability profile similar to that of placebo. In a 1-year trial, small mean reductions in body weight, reductions in median prolactin levels, and small mean improvements in movement disorder scores were seen in both groups. In 6 months of double-blind treatment, ziprasidone was associated with favorable/neutral effects on weight and fasting insulin levels, plasma glucose levels, and serum lipid levels, whereas olanzapine was associated with significant weight gain and adverse changes in these metabolic parameters. Ziprasidone has also been associated with less weight gain, less prolactin elevation, and a lower movement disorder burden than risperidone.

Cognitive impairment is a primary debilitating effect of schizophrenia that can dramatically affect a patient's ability to acquire and maintain the necessary skills for adequate functioning. Philip D. Harvey, Ph.D., reviews ziprasidone's effect on cognitive function. Existing data show that atypical antipsychotics are associated with greater improvements in cognitive function than are conventional agents. Dr. Harvey reports on recent data from three 6-week switch studies in which suboptimal antipsychotic therapy was replaced with ziprasidone 40 to 160 mg/day and from a longer continuation trial (6 months) comparing ziprasidone with olanzapine. Collectively, these study results suggest that ziprasidone is associated with improvements in an array of cognitive domains in patients with schizophrenia. Overall, patients who received ziprasidone demonstrated significant improvements in multiple cognitive domains, such as episodic memory, attention/vigilance, executive function, and visuomotor speed, which are key to functional outcome.

Data from the continuation study show that ziprasidone appears to be as effective as olanzapine at enhancing cognition in clinically unstable patients with schizophrenia. During the 6-week phase of the comparative trial, both ziprasidone (40 to 80 mg b.i.d.) and olanzapine (5 to 15 mg b.i.d.) were associated with significantly improved measures of verbal memory, vigilance, motor speed, and executive function; after 6 months, both groups continued to show improvements in attention/vigilance, learning/memory, executive function, and verbal fluency, with observed benefits being more pronounced in those receiving ziprasidone.

Dr. Harvey further discusses how path analysis of pooled data from switching studies suggests that improvement in the Positive and Negative Syndrome Scale (PANSS) cognitive subscale directly affected changes in the PANSS anxiety-depression cluster and a PANSS "prosocial" subscale composed of items related to social engagement. This interrelationship among improvements in cognitive function, affective symptoms, and social engagement, notes Dr. Harvey, warrants future investigation.

The supplement concludes with a discussion of ziprasidone's tolerability profile by David G. Daniel, M.D. Dr. Daniel draws upon data from pharmacokinetic and clinical trials of ziprasidone versus placebo or active comparators to assess the safety and tolerability of both the IM and oral formulations. Adverse events most commonly associated with ziprasidone in clinical trials include somnolence, insomnia, gastrointestinal disturbances, akathisia, dizziness, and headache, of which, most were reported as being of mild to moderate intensity. As with other atypicals, the incidence of movement disorder–related adverse events with ziprasidone has been low.

A tolerability advantage that separates ziprasidone from several other atypical agents, including olanzapine, risperidone, and clozapine, is its weight-neutral profile. Aside from the well-documented association of overweight with conditions such as cardiovascular disease, type 2 diabetes, and respiratory problems, antipsychotic-induced weight gain negatively affects compliance with drug therapy and, consequently, long-term medical outcomes.

Ziprasidone's tolerability profile is further enhanced by a lack of deleterious effects on plasma lipid levels and glucose levels. The relationship between cardiovascular disease and increased levels of low-density lipoprotein (LDL) cholesterol and triglycerides, as well as increases in weight, is well established. Olanzapine and risperidone can elevate cholesterol and triglyceride levels, and ziprasidone's observed minimal effects on total and LDL cholesterol and triglyceride levels may be a consideration for patients with cardiovascular risk factors.

The modest increases in QTc associated with ziprasidone have been well characterized. Experience to date has not shown any increased risk of clinical events attributable to QT prolongation. Ziprasidone's labeling defines limited populations in which the agent is contraindicated. Dr. Daniel emphasizes that the risk-benefit analysis of drug treatment options must consider the individual patient and further notes that for many patients with schizophrenia and schizoaffective disorder, ziprasidone is a welcome option.

Antipsychotic medication is the cornerstone of the short- and long-term treatment of patients with schizophrenia. Symptom control, prevention of relapse, and long-term health consequences are the primary criteria for the selection of an optimal antipsychotic for individual patients with schizophrenia. The clinical data presented here by expert clinicians and investigators provide a firm basis for the selection of the atypical antipsychotic ziprasidone across the continuum of care—from treating the patient with acute psychotic agitation to the prevention of relapse in the stable patient with schizophrenia or schizoaffective disorder.

Drug names: haloperidol (Haldol and others), olanzapine (Zyprexa), risperidone (Risperdal), ziprasidone (Geodon).

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