Expert Canadian consensus suggestions on the rational, clinical use of ziprasidone in the treatment of schizophrenia and related psychotic disorders

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Abstract: Many atypical antipsychotic medications are becoming available for clinical use. Ziprasidone is a recent addition to this group and is expected to become available for clinical use in Canada in 2005. Ziprasidone has some significant differences compared with other atypicals currently available in Canada. Clinicians need to understand the benefits and risks associated with each of the antipsychotic medications available for the treatment of schizophrenia and related psychotic disorders to ensure their most appropriate utilization. At the suggestion of Professor Stan Kutcher (chair) and as part of an ongoing commitment to provide independent education pertaining to the utility of new psychotropic compounds to health professionals, a panel of Canadian experts in the treatment of schizophrenia spectrum disorders was convened to provide consensus suggestions for the appropriate clinical use of ziprasidone. The consultations regarding the development of these recommendations were organized by Brainworks International (BWI) with arms-length funding from Pfizer Canada. This paper describes the experts' consensus views on the efficacy and safety of ziprasidone, their suggestions on which patients may be suitable for ziprasidone treatment, and how to initiate treatment (including how to switch from other antipsychotic medications), manage side effects, and monitor patients in long-term therapy. These suggestions are those of the authors only and are not endorsed by or necessarily reflect the opinions of BWI or Pfizer Canada.

Keywords: schizophrenia, treatment, ziprasidone, consensus, schizoaffective, atypical antipsychotic, psychosis

Introduction

Schizophrenia and related psychotic disorders, such as schizoaffective disorder, schizophreniform disorder, and psychotic disorder not otherwise specified (NOS), are serious brain disorders characterized by disturbances in cognition, perception, behavior, mood, and functioning, which collectively affect approximately one percent of the population (Eaton 1985; Bhalla 2004; Brannon 2004). The onset of these disorders is typically in late adolescence or early adulthood (Haefner and an der Heiden 1997), and the longitudinal course often involves relapses, deterioration in functioning, and chronicity. These disorders can be associated with significant comorbidity, including substance abuse, depression, and suicide (Cassano et al 1998). As a result, schizophrenia and related psychotic disorders impose tremendous burden on the individuals affected, their families (Thompson and Doll 1982), and society (Murray and Lopez 1996; Goeree 1999). Treatment includes pharmacological and

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psychosocial interventions; antipsychotic medication is necessary but is not sufficient as a treatment strategy. Clinical outcomes can only be optimized by ensuring that antipsychotic medications are rationally and appropriately used, within the context of best available rehabilitation interventions.

The discovery in 1952 of the antipsychotic properties of chlorpromazine and the subsequent development of numerous other conventional antipsychotics represented a major advance in the treatment of psychotic disorders. Although these medications have similarly good efficacy in treating positive psychotic symptoms such as delusions and hallucinations, their efficacy in treating negative symptoms (eg, anhedonia, avolition, and alogia) and cognitive impairment is typically unsatisfactory. Furthermore, these medications are associated with significant adverse effects, particularly extrapyramidal symptoms (EPS) (eg, parkinsonism, dyskinesia, and akathisia). Side effects such as EPS, sedation, weight gain, and sexual dysfunction, are an important determinant of poor adherence to medication (Fleischhacker et al 1994; Weiden et al 2004) which, in turn, is associated with relapse and poorer outcome (Verdoux et al 2000). The development of antipsychotic medications that are more effective, safer, and better tolerated has therefore remained an important goal.

Since the introduction of clozapine (considered the prototype of the atypical antipsychotics) three other atypical antipsychotics – risperidone, olanzapine, and quetiapine – have become available in Canada. Two additional agents – ziprasidone and aripiprazole – are available in the USA, and ziprasidone is likely to become available on the market in Canada in 2005. All of the atypical antipsychotics have demonstrated efficacy in the treatment of schizophrenia but have somewhat different pharmacokinetics, pharmacodynamics, and side effect profiles. When a new medication is introduced into the market, it is important for clinicians to be provided with clinically relevant information based on available evidence and independent of pharmaceutical company detailing, to ensure the most appropriate use of the new compound and thereby optimize treatment outcome. One way in which to fulfil this need for information is to convene a panel of experts familiar with a given new compound and use their expertise to create clinically meaningful suggestions for its use.

This paper is the result of a consensus meeting attended by Canadian experts in schizophrenia spectrum disorders. The goal of the meeting and of this paper was to create a set of practical, clinically relevant suggestions for clinicians on the appropriate use of ziprasidone for the treatment of schizophrenia and related psychotic disorders (schizoaffective disorder, schizophreniform disorder, and psychotic disorder NOS).

Method

At the request of Brainworks International (an independent company dedicated to mental health associated clinical research and education for health professionals), Pfizer Canada agreed to fund a meeting of a Canadian group of experts in the treatment of schizophrenia and related psychotic disorders. Fourteen invitees were selected by Professor Stan Kutcher (chair) for their regionally or nationally recognized authority in the field of schizophrenia spectrum disorders. Their clinical expertize, research experience with ziprasidone, publications in treatment research, and involvement in the development of regional or national guidelines on schizophrenia and related psychotic disorders were factors in their selection. Additionally, a pharmacist and a cardiologist were invited to give their expert perspectives on particular topics. These two specialists and eight of the schizophrenia experts accepted their invitations. Prior to the meeting, all ten experts were asked to prepare written and oral presentations on a topic chosen by the chair.

The consensus meeting took place on November 3rd, 2003, in Halifax, Nova Scotia. An independent medical writer recorded the proceedings. Three observers from the meeting sponsor attended but did not participate in the presentations. Seven presentations were made that collectively encompassed the safety and efficacy of ziprasidone and suggestions for its practical clinical use. Each presentation was followed by group discussion. The schizophrenia experts were then divided into two subgroups, and each subgroup was charged with identifying practical clinically relevant suggestions for clinicians addressing the following: when to consider the use of ziprasidone; how to initiate ziprasidone treatment (including switching from another antipsychotic medication and how to use injectable ziprasidone); and important aspects of monitoring of ongoing treatment with ziprasidone. The subgroups presented their suggestions for discussion and a group consensus was reached. Three further presentations reviewed receptor affinity research, advantages and disadvantages of all available atypical antipsychotics, and a cardiology perspective on ziprasidone's prolongation of the QTc

interval. The meeting closed after a final group discussion on the implications of this information for clinicians.

The independent medical writer drafted a consensus statement based on the proceedings of the meeting and available literature on ziprasidone. The draft statement was circulated to all attendees for their comments. Revisions were made accordingly and revised drafts were recirculated to give attendees opportunities to make changes to the manuscript. Submission of the manuscript for publication followed written confirmation by each of the authors as to their agreement with all of the information found in the paper.

Practical summary of atypical antipsychotic drugs

Although individual patient responses are varied, both conventional and atypical antipsychotics are reasonably effective at controlling the positive symptoms of schizophrenia (including delusions, hallucinations, thought disorder, and behavioral dysinhibition). Selected atypicals (ie, risperidone and olanzapine) have shown a small advantage (effect size ≈ 0.2) over conventional agents in treating negative symptoms (Geddes et al 2000; Rosenheck et al 2003), while findings from research on mood and cognition have been inconsistent (Meltzer and McGurk 1999; Harvey and Keefe 2001; Rosenheck et al 2003). The atypical agents are considerably less likely than conventional agents to cause EPS (Wright and O'Flaherty 2003) and, with the exception of risperidone, also less likely to cause hyperprolactinemia (and its sequelae, which can include amenhorrhea, galactorrhea, menorrhagia, and sexual dysfunction). However, these advantages may be somewhat offset by the propensities of the atypical antipsychotics to cause a metabolic syndrome characterized by substantial weight gain, elevations in glucose and lipid plasma levels, increased risk of type II diabetes (Lebovitz 2003), and possibly cardiovascular disease (Allison et al 1999). Clozapine and olanzapine are particularly associated with a high risk of substantial weight gain and increases in serum triglyceride levels (Allison et al 1999; Osser et al 1999; Atmaca et al 2003; Kelly et al 2003). Quetiapine and risperidone appears to be less problematic than clozapine and olanzapine in this respect (Allison et al 1999; Atmaca et al 2003), but risperidone is more prone to cause problems related to sexual functioning, EPS, and hyperprolactinemia (Simpson and Lindenmayer 1997; Mullen et al 2001).

Pharmacology

Pharmacodynamics of ziprasidone

Most of the efficacy of antipsychotic agents in improving positive symptoms can be attributed to blockade of dopaminergic D_2 receptors in the mesolimbic and mesocortical systems. To varying extents, antipsychotic agents also antagonize D_2 receptors in the nigrostriatal pathway and tuberoinfundibular pathways, which can result in EPS and hyperprolactinemia, respectively. The mechanisms underlying the lower propensity of atypical antipsychotics to cause these particular adverse events are not fully understood and may differ for different atypicals (Kapur 1996; Reynolds et al 1997). The original postulate stated that it was due to atypicals' strong antagonism of 5-HT_2 receptors (Meltzer et al 1989). More recently, it has been proposed that atypicals spend less time blocking D_2 receptors than conventional agents, and thereby give way more readily to dopamine (Kapur and Seeman 2001). In this respect, however, there are differences among the atypicals. Clozapine and quetiapine bind relatively loosely to D_2 receptors, whereas risperidone and olanzapine bind more tightly. Atypicals' affinities for 5-HT receptors are nevertheless implicated in bringing about moderately improved negative symptom relief, enhanced modulation of mood, and cognitive improvement. Other side effects common to atypicals such as anticholinergic effects (eg, blurred vision, constipation, urinary retention, and confusion), metabolic effects (eg, weight gain), and postural hypotension are attributed to their antagonism of muscarinic (M_1), histaminic (H_1), and alpha adrenergic (α_1) receptors, respectively. Differences among the various atypicals in the strengths with which they antagonize these receptors result in differences in their propensities to cause these various side effects.

Ziprasidone demonstrates in vitro binding affinities for D_2 and 5-HT_{2A} receptors similar to those of risperidone and stronger than those of olanzapine, clozapine, and quetiapine (Goodnick 2001). Ziprasidone's in vitro 5-HT_{2A}/D_2 receptor binding ratio (approximately 8:1) exceeds that of risperidone, olanzapine, quetiapine, and aripiprazole (Tandon et al 1997; Stahl and Shayegan 2003). In human brain tissue, ziprasidone exhibits strong antagonism of 5-HT_{2C} and 5-HT_{1D}, receptors. Uniquely, it also has strong agonist activity at 5-HT_{1A} receptors (Seeger et al 1995) and moderately inhibits synaptic reuptake of serotonin and norepinephrine (Zorn et al 1995). This suggests that

ziprasidone may have moderate antidepressant effects. Its agonism of 5-HT_{1A} receptors has also been hypothesized to prevent insulin resistance (Goodnick 2001). Like quetiapine and olanzapine, ziprasidone has lower affinity for α_1 receptors than risperidone and clozapine, suggesting a lower propensity to cause postural hypotension. Ziprasidone's low antagonistic activity at H_1 receptors and its very weak antagonistic activity at M_1 receptors are both lower than risperidone, olanzapine, quetiapine, and clozapine (Schmidt et al 1998), suggesting reduced likelihood of causing anticholinergic and metabolic side effects.

Pharmacokinetics of ziprasidone

Two formulations of ziprasidone are currently available in the USA: an intramuscular (IM) formulation (ziprasidone mesylate) indicated for rapid control of acute agitation in patients with schizophrenia; and an oral formulation (ziprasidone hydrochloride) indicated for both acute and long-term management of schizophrenia. Time to maximum serum concentration for oral ziprasidone is 6–8 hours, and steady-state concentrations are achieved after 2–3 days (Wilner et al 2000). IM ziprasidone attains peak concentration within approximately 30 minutes (Miceli et al 1998). Ziprasidone is extensively metabolized, with less than 1% and 4% being excreted unchanged in urine and faeces, respectively (Prakash et al 1997). In vitro studies (Prakash et al 2000; Kamel et al 2002) and quantitative excretion data analysis in short-term studies of healthy volunteers (Prakash et al 1997; Miceli, Anziano, et al 2000; Miceli, Smith, et al 2000) suggest that ziprasidone is metabolized by the liver, approximately two-thirds mediated by aldehyde oxidase and one-third mediated by cytochrome P450 isoform 3A4. Its metabolites are inactive. The involvement of two alternate pathways in ziprasidone metabolism reduces the potential for pharmacokinetic interactions between ziprasidone and other drugs (Beedham et al 2003). The mean elimination half-life of oral ziprasidone is approximately 7 hours (range: 3–10 hours), and that of IM ziprasidone is 2–4 hours. With the exception of quetiapine (mean elimination half-life of 2–3 hours), these are shorter than those of the other atypical agents: clozapine 12 hours; risperidone (and its active metabolites) 20 hours; quetiapine 2–3 hours; olanzapine 30 hours; and aripiprazole (and its active metabolites) 94 hours (Keck and McElroy 2002; Winans 2003).

Efficacy of ziprasidone

The efficacy of IM ziprasidone in achieving rapid control of acute psychotic agitation has been evaluated in patients with schizophrenia, schizoaffective disorder, and to a lesser extent, other psychotic disorders. The efficacy of oral ziprasidone has been evaluated as a treatment for patients with schizophrenia and, to a lesser extent, patients with schizoaffective disorder in the following domains: treatment of acute psychotic exacerbation; switching from a current antipsychotic to ziprasidone; and maintenance treatment and relapse prevention.

Rapid control of psychotic agitation

Rapid control of agitation with IM ziprasidone has been demonstrated in two 24-hour, randomized, double-blind, fixed-dose studies in inpatients with acute agitation associated with schizophrenia or another psychotic disorder. (Approximately 50% of patients had a primary diagnosis of schizophrenia, and 30% had a primary diagnosis of schizoaffective disorder.) The first study (Lesem et al 2001) compared 10 mg of IM ziprasidone (n = 63) with 2 mg of IM ziprasidone (n = 54). The second study (Daniel et al 2001) compared 20 mg (n = 41) and 2 mg doses (n = 38). In both studies, efficacy assessments were conducted with the Behavioral Activity Rating Scale (BARS; Swift et al 2002) just before the first injection and at 15, 30, 45, 60, 90, and 120 minutes after the first injection, and at hourly intervals thereafter until the next dose or until the study end point (at 4.0 hours) if no further injections were given. Relative to the 2 mg group, the 10 mg group showed significantly greater improvement at 15 and 60 minutes after the first injection ($p < 0.05$ in both cases) and at all subsequent time points ($p < 0.001$ for the 1.5–3.5 hour time points and $p < 0.01$ for the 4.0 hour time point). The 20 mg group showed significantly greater improvement at 30 minutes ($p < 0.01$) and at all subsequent time points ($p < 0.001$ in each case) relative to the 2 mg group. Both the 10 mg and 20 mg groups also yielded a significantly higher percentage of responders (≥ 2 point BARS decrease) 2.0 hours after the first injection ($p < 0.001$). At 4.0 hours post-injection, the 20 mg group additionally yielded significantly greater improvements over the 2 mg group on the Clinical Global Impression of Severity Scale (CGI-S; Guy 1976a), which was used to rate agitation rather than overall illness ($p < 0.01$) and on the Positive and Negative Syndrome Scale (PANSS; Kay et al 1987) agitation items score ($p < 0.05$). A cross-study analysis of the 10 mg

and 20 mg groups indicated that the efficacy of ziprasidone was dose-related (Reeves et al 1998).

Two open-label, randomized, haloperidol-controlled studies with inpatients with acute psychotic agitation also support IM ziprasidone's efficacy in the rapid control of agitation. In a flexible-dose study (Brook et al 2000), patients were given either 5–20 mg (maximum 80 mg/day; n = 90) of IM ziprasidone or 2.5–10 mg of IM haloperidol (maximum 40 mg/day; n = 42) every 4–6 hours for up to 3 days. Ziprasidone (mean [SD] dose 25.3 [18] mg/day) yielded significantly greater reductions than haloperidol (mean [SD] dose 8.7 [8] mg/day) in the total score of the Brief Psychiatric Rating Scale (BPRS; Woerner et al 1988) score and on its agitation items score ($p < 0.05$ in both cases), and on the CGI-S scale ($p < 0.01$). In a randomized, fixed-dose study with similar inpatients (Brook et al 2001), initial 10 mg or 20 mg doses of IM ziprasidone followed with further doses as required (maximum of 40 mg/day for 3 days; n = 417) were compared with initial 2.5 mg or 5 mg doses of IM haloperidol followed with further doses as required (maximum 10 mg/day; n = 133). Ziprasidone yielded significantly greater improvements on the BPRS total score and the Covi Anxiety Scale (Lipman 2001) than haloperidol at the end of the IM phase ($p < 0.01$ in both cases), although the two drugs were not differentiable on the CGI-S, number of injections required, or number of days of injections.

Efficacy of oral ziprasidone in treating acute psychotic exacerbation

The efficacy of oral ziprasidone over placebo in treating acute exacerbations in cases of schizophrenia or schizoaffective disorder has been demonstrated in a number of 4- and 6-week randomized, double-blind studies (Keck et al 1998, 2001; Daniel et al 1999). In one of these studies (Daniel et al 1999), 80 mg (n = 106) and 160 mg (n = 104) daily doses of ziprasidone were significantly better than placebo (n = 92) in treating both positive and negative symptoms, according to improvement scores at 6 weeks on the PANSS total, BPRS total, BPRS core items, CGI-S, and PANSS negative subscale scores ($p < 0.05$ and $p < 0.001$ in all cases for the 80 mg and 160 mg groups, respectively). The 160 mg/day dose was also significantly better than placebo in treating symptoms of depression in patients with clinically significant depressive symptoms at baseline (n > 50 for each treatment group) according to total scores on the Montgomery-Asberg Depression Rating Scale (MADRS; Montgomery and Asberg 1979; $p < 0.05$).

The efficacy of oral ziprasidone in treating cases of acute psychotic exacerbation has also been compared with other antipsychotic medications, and found to be generally similar in efficacy. A randomized, open-label, blinded-assessment, sequential IM/oral comparison of ziprasidone (10 mg or 20 mg IM initially with additional IM doses to 40 mg/day for ≤ 3 days then oral 40 mg bid [twice a day] for 1 day and oral 40–80 mg/day thereafter; n = 429) to haloperidol (2.5 mg or 5 mg IM initially with additional IM doses to 10 mg/day for ≤ 3 days then oral 5 mg bid for 1 day and oral 5–20 mg/day thereafter; n = 138) for the treatment of inpatients with acute schizophrenia or schizoaffective disorder indicated that ziprasidone's control of symptoms was sustained through the transition from IM to oral formulations as effectively as that of haloperidol (Brook et al 2001). In a 6-week, placebo-controlled, double-blind study (Anonymous 2000), inpatients with schizophrenia or schizoaffective disorder were randomized to either a fixed dose of ziprasidone (40, 120, or 200 mg/day; n = 86, 76, and 82, respectively), 15 mg/day of haloperidol (n = 82) or placebo (n = 91). Ziprasidone (at each of the 3 doses) and haloperidol yielded statistically greater improvements relative to placebo in BPRS total scores, PANSS total scores and CGI-S scores ($p < 0.05$ and $p < 0.001$ in all cases for ziprasidone and haloperidol, respectively) although only haloperidol and the 200 mg/day dose of ziprasidone were superior to placebo on the PANSS negative symptoms subscale ($p < 0.01$ and $p < 0.05$, respectively). Additionally, MADRS scores of all four groups were significantly more improved than those of the placebo group ($p < 0.01$ for 120 mg/day ziprasidone and $p < 0.05$ in the other groups). In an 8-week double-blind, flexible-dose study (Addington et al 2002) with similar patients, ziprasidone (40–80 mg bid; n = 149) was found to be as effective as risperidone (3–5 mg bid; n = 147) on the BPRS, PANSS, MADRS, and Global Assessment of Functioning (APA 1987) scales. The mean daily dose was 114.2 mg for ziprasidone and 7.4 mg for risperidone. Additionally, in similar 6-week, randomized, flexible-dose, double-blind study (Simpson et al 2001), ziprasidone (40–80 mg bid; n = 136) was found to be as effective as olanzapine (5–15 mg/day; n = 133) on the BPRS, CGI-S, PANSS, and Calgary Depression Scale for Schizophrenia (Addington et al 1992). Ziprasidone was titrated rapidly from 40 mg bid on days 1 and 2, to 80 mg bid for days 3–7, before flexible dosing was allowed. The mean daily dose was 130 mg/day for ziprasidone and 11 mg for olanzapine.

Efficacy of ziprasidone in maintenance treatment and relapse prevention

The efficacy of oral ziprasidone in the maintenance treatment of stable patients with schizophrenia has been examined in a number of longer-term studies. A 28-week, randomized, double-blind, flexible-dose study (Hirsch et al 2002) showed that ziprasidone (80–160 mg/day; n = 148) was as effective as haloperidol (5–15 mg/day; n = 153) in improving positive symptoms, symptoms of depression, and scores on the Quality of Life Scale (Heinrichs et al 1984) in stable outpatients with schizophrenia who required antipsychotic medication. (Inclusion criteria included a score of ≥ 10 on the negative subscale of the PANSS.) Respectively, only 45% and 42% of the ziprasidone and haloperidol patients completed all 28 weeks of treatment. However, among non-protocol violators who completed at least 14 days of therapy and at least one post-baseline efficacy assessment (74% and 76% of all ziprasidone and haloperidol patients, respectively), discontinuation rates due to insufficient clinical response were the same (18%) for the two groups, while discontinuations due to side effects were more common for haloperidol than ziprasidone patients (18% and 8%, respectively). The study also found that ziprasidone was significantly better than haloperidol at yielding responders on the negative symptoms subscale of the PANSS (defined as ≥ 20% reduction in score) at the study end point ($p < 0.05$). However, ziprasidone patients' mean change score from baseline to study end point (with last observation carried forward (LOCF)) on this subscale was not significantly different from that of haloperidol patients (mean decreases of 3.6 and 3.0, respectively).

Two double-blind, flexible-dose extension studies in which patients with schizophrenia or schizoaffective disorder were continued on ziprasidone or another atypical agent – olanzapine (Simpson et al 2002) or risperidone (Addington et al 2003) – after receiving these medications in short-term acute exacerbation studies (Simpson et al 2001; Addington et al 2002), provide further data on the efficacy of ziprasidone in maintenance treatment. When interpreting the results of these extension studies, however, it should be noted that they pertain only to patients who completed their initial study with a satisfactory clinical response, and agreed to participate in the extension study. Thus, these results should not be assumed to be generalizable to the wider group of patients who were started on treatment in the initial study. Given the design of these studies, they are only able to provide upper limits on positive outcome rates and lower limits on adverse event rates. Furthermore, to meaningfully compare the efficacy of different medications in an extension study, the rates and reasons for discontinuations for each medication need to be reasonably similar to one another during the preceding short-term study as well as during the extension study. With these caveats in mind, these studies indicate that in patients who already tolerated and responded satisfactorily to their respective medication over a 6- or 8-week period, ziprasidone (80–160 mg/day) was similarly effective as a long-term maintenance treatment as both olanzapine (5–15 mg/day, over 20 weeks) and risperidone (3–5 mg bid, over 44 weeks), respectively. Measures included the BPRS, PANSS, CGI-S scale, and a clinician-rated depression scale.

Results obtained by Kane et al (2003) in a 28-week, randomized, double-blind study in which ziprasidone (80–160 mg/day; n = 271) was compared with a higher dosage range of olanzapine (10–20 mg; n = 277) in inpatients and outpatients with schizophrenia suggested that olanzapine had superior efficacy according to LOCF PANSS total scores ($p < 0.001$), PANSS positive and negative subscale scores ($p < 0.001$ and $p < 0.01$, respectively), and CGI-S scores ($p < 0.001$). Patients for whom treatment with olanzapine or ziprasidone was withdrawn in the preceding 6 months due to problematic adverse events or to lack of efficacy were precluded from enrolment in the study. Discontinuation rates due to lack of efficacy were significantly higher for ziprasidone (13.7%) than for olanzapine (7.2%; $p < 0.05$), while discontinuation rates due to adverse events were comparable (15.1% and 11.6%, respectively). It is possible that the titration schedule for ziprasidone (20 mg bid for 3 days, 40 mg bid, and incremental dose increases at weekly intervals) was not sufficiently rapid to achieve optimal efficacy or to minimize the occurrence of aggravated psychosis, which accounted for 29% of its discontinuations due to adverse events.

A 1-year, randomized, double-blind, placebo-controlled study (Arato et al 2002) of inpatients with stable, chronic schizophrenia demonstrated that daily doses of 40 mg (n = 72), 80 mg (n = 68), and 160 mg/day (n = 67) of ziprasidone significantly reduced the rate of relapse over one year from a placebo (n = 71) rate of 61% to rates of 38% ($p < 0.01$), 31% ($p < 0.001$), and 34% ($p < 0.01$), respectively.

Switching patients from another antipsychotic medication to ziprasidone

Three 6-week, open-label, blinded rater studies (Weiden, Simpson, et al 2003) have been conducted to examine

whether differences exist in patient outcomes among three methods of switching stable but symptomatic outpatients with schizophrenia or schizoaffective disorder from treatment with their current antipsychotic drug to treatment with ziprasidone. Prior to having their medication switched, 108 patients were taking a conventional antipsychotic, 104 were taking olanzapine, and 58 were taking risperidone. Each patient was randomized to one of the following three switching strategies: (1) initiation of ziprasidone treatment with immediate discontinuation of patients' current antipsychotic; (2) initiation of ziprasidone treatment together with administration of the current antipsychotic for one week at 50% of its original dose, followed by discontinuation of the current antipsychotic after day 7; and (3) initiation of ziprasidone treatment together with administration of the current antipsychotic, the dose of which was tapered over one week (100% of original dose for days 1, 2, and 3 and 50% for days 4 through 7). All groups were started on 80 mg/day of ziprasidone for 2 days followed by flexible dosing (40–160 mg/day). Efficacy measures included the BPRS, PANSS, and CGI-S scales.

No significant differences in outcome were observed among the different switching strategies on any measure, including rates of discontinuation. Data were therefore pooled across switching strategies and the influence of the prior medication on outcome was considered. Mean (and SD) daily doses of ziprasidone for patients previously on conventional antipsychotics, olanzapine, or risperidone were respectively 91 (26), 90 (23), and 92 (24) mg/day. Total discontinuation rates for these three groups were respectively 28%, 21%, and 21%; the respective rates of discontinuations deemed to be due to either adverse events or inadequate clinical response were 14.8%, 10.6%, and 10.3%. The groups switched from conventional antipsychotics, and the groups switched from olanzapine both showed significantly improved scores on both the positive and negative subscales and the total score of the PANSS at the study end point ($p < 0.01$ and in all cases respectively for the two groups; LOCF). Patients switched from risperidone also showed significantly improved scores on the negative subscale and the total score of the PANSS ($p < 0.01$ in both cases), and their scores on the positive subscale indicated a trend of improvement that approached statistical significance ($p = 0.08$). These improvements in PANSS total scores and subscale scores reached statistical significance for patients switched from risperidone and from olanzapine earlier (at or before week 2) than for patients switched from conventional antipsychotics (for whom the differences first reached significance at week 3). This study was not appropriately designed to compare the efficacy of ziprasidone to other antipsychotic agents, however. It was limited by an open-label design, a sample selected for suboptimal clinical response to their original medication, opportunities for bias including regression to the mean, rater bias, and other methodological factors may have contributed to the observed improvements in patients' symptoms. Nevertheless, it does demonstrate that several switching methods can be used when changing antipsychotic therapy to ziprasidone in suboptimally responding patients.

Efficacy of ziprasidone with regard to cognitive performance

A recently published report (Harvey et al 2004) indicates that Weiden, Simpson, et al (2003) outpatients who were switched from conventional antipsychotics (n = 108), olanzapine (n = 104), or risperidone (n = 58) to ziprasidone (40–160 mg/day) showed improvements in performance on various cognitive functioning tests. Statistically significant but modest improvements were observed on each of three verbal learning and memory tasks (the Rey Auditory Verbal Learning Test; Spreen and Strauss 1998) in all three groups, although performance on a computerized spatial learning/memory task did not change. Scores on each of two tests of attention/vigilance (the Trailmaking Test A; Spreen and Strauss 1998) and Digit Span Distraction Test (DSDT; Oltmanns and Neale 1975) improved significantly in patients switched from conventional antipsychotics, and did not change in patients switched from olanzapine. Patients switched from risperidone improved significantly only on the DSDT task. Statistically significant improvements were observed on one but not both tasks of executive functioning (the Trailmaking Test B; Spreen and Strauss 1998 and (Wisconsin Card Sorting Test; Heaton et al 1993) in patients switched from either risperidone or conventional antipsychotics; patients switched from olanzapine did not improve on either task. Scores on one but not both tests of verbal fluency ("category" and "letter" conditions; Spreen and Strauss 1998) improved significantly in each of the patient groups. Improvements in all of the tasks could be attributable to patient selection bias, changes in patient expectations and motivation levels, and/or practice effects, however, and need to be replicated in prospective, double-blind studies. Nevertheless, the results indicate that patients requiring a change in antipsychotic therapy are unlikely to exhibit worsening cognitive performance and may exhibit improvements following a switch to ziprasidone.

Safety and tolerability of ziprasidone

Considerable attention has been paid to the finding that ziprasidone, like several other antipsychotics (thioridazine, chlorpromazine, pimozide, and haloperidol), increases the duration of the cardiac QT interval. The QT interval is the time from the beginning of the QRS complex to the end of the T wave in an electrocardiogram (ECG). The QTc interval is the QT interval corrected for heart rate. (Values quoted in this paper were calculated using Bazett's correction formula.) Normal QTc intervals are <430 ms for males and <450 ms for females (Anonymous 2002). Within individuals, mean variability in QTc interval duration over a 24-hour period has been reported as 76 ms (SD = 19 ms, range = 38–108 ms; n = 20 males; Morganroth et al 1991). Prolongation of the QTc interval has been associated with the potentially lethal paroxysmal ventricular cardiac arrhythmia torsades de pointes, which can cause recurrent syncope, ventricular fibrillation, and sudden death. Clinically a QTc interval of >450 ms is considered to be of concern (Vieweg 2002), although a precise QTc interval at which the risk of torsades de pointes is greatest has not been clearly established. The vast majority of reported cases of torsades de pointes are seen in individuals with measured QTc intervals of ≥500 ms and therefore prolongation to ≥500 ms provides a clinically meaningful measure for the purposes of assessing QTc risk.

In clinical development studies, 2/3095 (0.06%) of patients receiving ziprasidone were found to have a QTc interval >500 ms, compared with 1/440 (0.23%) of patients receiving placebo (Romano 2000). Across several short-term (4–6 week), double-blind, placebo- or haloperidol-controlled studies of ziprasidone (Keck et al 1998, 2001; Daniel et al 1999), doses of 80–160 mg/day were associated with mean QTc interval increases of 5–10 ms, whereas small (< 3 ms) decreases were observed in placebo- and haloperidol reference groups. QTc increases of >30 ms were observed in 13.7% of ziprasidone patients compared with 8.0% of placebo patients. For QTc increases >60 ms, the respective rates were 1.1% and 0.7%. However, given that post-baseline ECG measurements were not targeted at the time of peak drug exposure in these studies, the change in QTc interval may have been underestimated.

In consultation with the Food and Drugs Administration (FDA), a randomized, open-label study (Harrigan et al 2004) was conducted to measure the effects of ziprasidone (20–80 mg bid; n = 31), risperidone (1–8 mg bid; n = 25), olanzapine (5–20 mg/day; n = 24), quetiapine (25–375 mg bid; n = 27), thioridazine (25–150 mg bid; n = 30), and haloperidol (2–15 mg/day; n = 27) on the QTc interval at maximum serum concentration after dosing. Participants were volunteer patients who were hospitalized for chronic schizophrenia. Serial ECGs (approximately 30 per patient) were recorded under fasting conditions and at the time of estimated peak serum concentration for each study drug. Patients took their randomly allocated antipsychotic alone and also in the presence of a metabolic inhibitor to measure the potential impact of P450 drug interactions on the serum concentrations of the antipsychotic and on QTc prolongation. A mean prolongation of QTc interval was found for each antipsychotic agent tested, including haloperidol, for which a dose-prolongation relationship was detected. No patient had a QTc interval ≥500 ms. The QTc prolongation effect of ziprasidone, at 20 ms, was approximately 10 ms larger than the prolongation effects of haloperidol, quetiapine, risperidone, and olanzapine, and approximately 10 ms smaller than the effect of thioridazine. Ziprasidone demonstrated no further QTc prolongation in the presence of metabolic inhibition (ketoconazole, 200 mg bid). A subsequent dose escalation study (Miceli et al 2003) with 26 patients with schizophrenia or schizoaffective disorder demonstrated that escalation of ziprasidone from the maximum recommended clinical dose (160 mg/day) to twice this dose (320 mg/day) produced only a marginal additional mean increase in QTc prolongation. ECGs were collected at baseline (drug-free condition) and at 5, 6 (estimated time of maximum serum concentration), and 7 hours post-dose on three steady-state drug administration days (each day being the fourth consecutive day at a particular dose). Relative to baseline, mean QTc interval increases at doses of 40, 160, and 320 mg/day were respectively 4.5, 19.5, and 22.5 ms. A further study (Miceli et al 2002) has shown that IM ziprasidone (20 mg then 30 mg injections, 4 hours apart; n = 31) and IM haloperidol (7.5 mg then 10 mg injections, 4 hours apart; n = 27) cause comparable mean increases to QTc intervals at maximum observed serum/plasma concentrations for each injection (respectively, 4.6 ms, and 12.8 ms for injections 1 and 2 of ziprasidone, and 6.0 ms and 14.7 ms for injections 1 and 2 of haloperidol). No patient had a change from baseline QTc ≥75 ms, and no patient had a QTc interval ≥500 ms at any time.

According to data on file with Pfizer, the manufacturer of ziprasidone, there have been no confirmed reports of torsades de pointes and no indications of increased cardiovascular risk during clinical development trials of

ziprasidone (> 2700 patient-years of ziprasidone treatment) nor during post-marketing surveillance to date (> 500 000 patients having received ziprasidone). These are selected populations however; patients with identified risk factors for cardiac arrhythmia would have been excluded.

In summary, the evidence thus far suggests that the QTc prolongation effect of ziprasidone is moderate, and that when ziprasidone is appropriately prescribed, it does not demonstrate clinically significant QTc effects. However, clinicians should be aware of the risk factors for prolongation of the QTc interval and should carry out a thorough assessment of patient and family medical history before deciding whether the benefits of ziprasidone treatment outweigh the risks. (See *Addressing the risk of QTc prolongation* below for further information.)

Adverse events associated with IM ziprasidone

Results from two 24-hour, double-blind, fixed-dose IM ziprasidone studies (2 mg versus 20 mg, Daniel et al 2001; 2 mg versus 10 mg, Lesem et al 2001), a 3-day, randomized, open-label, flexible-dose, haloperidol-controlled IM ziprasidone study (10 mg initial injection, then 5–20 mg injections every 4–6 hours, as needed, mean daily dose ≈ 23 mg/day; Brook et al 2000), and a similar haloperidol-controlled study (10 or 20 mg of IM ziprasidone initially, then additional injections ≤ 40 mg/day as needed, mean daily dose ≈ 26 mg/day; Brook et al 2001) that included a sequential 6-week oral treatment phase, indicate that IM ziprasidone is safe and well tolerated. In the two 24-hour studies, common adverse events related to IM ziprasidone treatment (reported in ≥ 10% of patients in any of the ziprasidone groups) included headache, injection site pain, nausea, and somnolence. Discontinuations due to ziprasidone-related adverse events were uncommon (1.1% of all patients receiving 2 mg injections and 0.6% of all patients receiving higher doses). In the two haloperidol-controlled studies, EPS occurred significantly less frequently in ziprasidone patients than in haloperidol patients ($p < 0.001$ in both studies) during IM treatment. No adverse events were reported to be statistically significantly more common to IM ziprasidone treatment than to IM haloperidol treatment in either study. The Brook et al (2000) study which, of the two studies, reported more details of laboratory abnormalities arising during IM treatment, reported that total rates for laboratory abnormalities were similar (14% and 13% respectively), as were mean changes in QTc intervals (< 3 ms for each group). The most common laboratory abnormality for both IM ziprasidone and IM haloperidol was elevated random glucose (> 1.2 × upper limit of normal) and this occurred at the same frequency (10%) in both groups. The report stated that there was no evidence of hematologic or hepatic toxicity.

Adverse events associated with oral ziprasidone

Evidence from 4- to 6-week randomized, double-blind, placebo-controlled studies (Keck et al 1998, 2001; Daniel et al 1999) and from 6- to 8-week randomized, double-blind studies comparing ziprasidone to haloperidol, risperidone, and olanzapine, respectively (data on file, Pfizer 2003; Anonymous 2000; Simpson et al 2001; Addington et al 2002), indicate that oral ziprasidone is safe and well tolerated and is not associated with adverse metabolic effects. The total rate of treatment-related adverse events and the rate of discontinuations due to such events in ziprasidone patients (approximate rates 80% and 4%, respectively) in these studies were similar to those of the placebo, haloperidol, risperidone, and olanzapine patients. The most prevalent adverse event that was statistically more common in ziprasidone patients than in placebo patients was somnolence (approximate rates respectively 14% and 7%; $p < 0.05$). Compared with the rates of the majority of specific adverse events in patients receiving haloperidol, risperidone, or olanzapine (including somnolence, EPS, akathisia, and weight gain) rates were significantly lower or not significantly different in patients receiving ziprasidone. Insomnia was an exception, being significantly more common in ziprasidone patients than risperidone patients (approximate rates respectively 25% and 12%; $p < 0.01$; Addington et al 2002), but this result was not obtained in the other studies. Total rates and rates of specific laboratory abnormalities in ziprasidone patients were significantly lower than or not significantly different from those in control patients in these studies.

Three 6-week, open-label, blinded rater studies in which patients experiencing suboptimal efficacy or tolerability were switched to ziprasidone from conventional antipsychotics (n = 108), olanzapine (n = 104), or risperidone (n = 58) observed improvements in several measures of physical health. Patients switched from olanzapine or risperidone experienced statistically significant reductions in body weight, BMI, triglycerides, and total cholesterol. Patients switched from conventional antipsychotics or risperidone experienced statistically significant reductions in prolactin levels and EPS. No clinically significant changes

Table 1 Frequency over one year of discontinuations, laboratory (lab) abnormalities, and treatment-related adverse events (AE) in patients treated with ziprasidone or placebo

	Ziprasidone 40 mg/day		Ziprasidone 80 mg/day		Ziprasidone 160 mg/day		Placebo	
	n	%	n	%	n	%	n	%
Reason for discontinuation								
Sample size	72		68		67		71	
Total discontinued	42	58	39	57	37	55	61	86
Lab abnormality	0	0	1	1	2	3	1	1
AE	7	10	7	10	5	7	11	15
Relapse	27	38	21	31	23	34	43	61
Other	8	11	10	15	7	10	6	8
Median duration of treatment	200 days		149 days		271 days		72 days	
Any lab abnormality at any time[a]	14	20[b]	18	26[c]	15	21[d]	13	18[e]
Any AE at any time	52	72	50	74	47	70	54	76
Percentage rates of particular AEs occurring in ≥ 10% of patients in any treatment group								
Insomnia	28		28		45		31	
Agitation	13		12		10		18	
Anxiety	11		10		13		17	
Akathisia	10		9		12		6	
Depression	8		6		10		6	
Headache	4		7		10		6	

[a] All participants who underwent lab tests at baseline and within 6 days of the last treatment day.
[b] n = 70, [c] n = 70, [d] n = 71, [e] n = 74.

in ECG were observed in any patients and none exhibited a QTc interval ≥ 500 ms.

A 1-year, double-blind, study (Arato et al 2002) in inpatients with stable, chronic schizophrenia reported the rates of adverse events associated with daily doses of 40 mg (n = 72), 80 mg (n = 68), and 160 mg/day (n = 67) of ziprasidone, and placebo treatment (n = 71). Questionnaires screening for particular adverse events were not used. All adverse events were either observed by the investigators or voluntarily reported by subjects, which may have led to underestimation of the actual frequency of adverse events. The total rates of all laboratory abnormalities and of all other adverse events were similar across the four groups, as were the rates of discontinuation due to treatment-related events. Table 1 summarizes these results, and provides the frequencies of the most common adverse events (events experienced at rates ≥ 10% in one or more groups); namely, insomnia, agitation, anxiety, akathisia, depression, and headache.

Among the less frequent adverse events, the following were experienced at moderate rates (< 10% in all four groups but > 5% in one or more ziprasidone groups): diarrhoea, hypertension, weight loss, rash, vomiting, EPS, asthenia, tooth disorder, respiratory tract infection, bronchitis, pharyngitis, tremor, accidental injury, infection, and flu syndrome. All remaining events occurred at low rates in all the ziprasidone groups (≤ 3% for the first three events listed, and ≤ 4% for the rest): tachycardia, increased salivation, dry mouth, somnolence, dyskinesia, dyspepsia, and nausea. Of all the reported adverse events, only asthenia was statistically more frequent ($p < 0.05$) in any ziprasidone group (the 160 mg/day group, in which the rate was 9%) compared with the placebo group (in which the rate was 0%). Serious adverse events that were classed as treatment-related were experienced by one placebo patient and four patients on ziprasidone (40 mg/day). One ziprasidone patient experienced EPS, asthenia, dehydration, and hypotension on day 6; another had a recurrence of acute dystonia on day 13; a third ziprasidone patient had vomiting and cardiac insufficiency on day 2; and the fourth had a grand mal seizure also on day 2.

Most of the laboratory abnormalities were isolated reports in single patients. Changes in blood pressure and pulse rate and changes in hematological, renal, liver, and hormonal measures were all clinically insignificant and no more frequent in ziprasidone patients than in placebo patients. Median serum prolactin levels decreased in all treatment groups (1–4.25 ng/mL). No opthalmological abnormalities were observed. No clinically significant ECG abnormalities and QTc interval changes were observed in the ziprasidone groups. No patient had a QTc interval > 500 ms.

Ziprasidone and placebo patients were indistinguishable in terms of changes (small mean improvements) from baseline scores on the Simpson-Angus Scale (a measure of EPS; Simpson and Angus 1970), the Barnes Akathisia Scale (Barnes 1989), and the Abnormal Involuntary Movements Scale (Guy 1976b). Rates of concomitant use of anti-cholinergic medication at some time during the study were 17%, 13%, 19%, and 13% for the 40, 80, and 160 mg/day ziprasidone groups, and the placebo group, respectively (nonsignificant differences). Beta-blocker use was negligible in all groups.

In a 28-week, flexible dose, double-blind study (Hirsch et al 2002), rates of the majority of specific adverse events were similar or lower in patients receiving ziprasidone (80–160 mg/day; n = 148) compared with patients receiving haloperidol (5–15 mg/day; n = 153). The percentages of patients who experienced at least one adverse event in the two groups were 77% and 85%, respectively. Insomnia was a common adverse event in both groups (16% and 18%, respectively). Akathisia was significantly less common ($p < 0.01$) in ziprasidone patients (5%) than in haloperidol patients (16%). Body weight changes were small and similar in the two groups. Few adverse events were serious enough to result in discontinuation. Laboratory abnormalities were experienced at similar rates in ziprasidone and haloperidol patients (38% and 34%, respectively). Mild postural hypotension was experienced by one ziprasidone patient. Otherwise, QTc interval, blood pressure, pulse rate, liver function, and hematologic assessments revealed no clinically significant treatment effects in either group.

Two double-blind, flexible-dose extension studies comparing ziprasidone to olanzapine (Simpson et al 2002) and ziprasidone to risperidone (Addington et al 2003) and a randomized, double-blind 28-week study comparing ziprasidone with olanzapine (Kane et al 2003) provide additional information on the relative long-term safety and tolerability of ziprasidone. While caution is needed when interpreting the two extension studies, because patients whose medication was ineffective and/or intolerable in the preceding short-term phase did not participate in the extension phase, the longer-term data obtained indicates that the rates of most of the more common (mild or moderate) adverse events experienced by patients receiving ziprasidone, olanzapine, or risperidone were not significantly different. Adverse effect frequencies and laboratory abnormalities that emerged between ziprasidone and olanzapine in these longer-term studies, which were statistically significant, are shown in Table 2. The table also includes differences between ziprasidone and risperidone that were likely to have been statistically significant but for which significance values were not provided in the original report.

Summary of safety and efficacy of ziprasidone

Evidence to date demonstrates the efficacy of ziprasidone in the management of acute psychotic agitation, in the treatment of acute exacerbations and in maintenance treatment and relapse prevention in patients with schizophrenia or schizoaffective disorder. Its efficacy is superior to that of placebo, and comparable to that of risperidone and haloperidol. Its efficacy compared with olanzapine remains to be clarified, and may depend on the dosing range permitted for each drug, and the rate of titration of ziprasidone.

Ziprasidone's side effect profile may prove to be safer and more acceptable to patients compared with other antipsychotic agents. Ziprasidone does not appear to cause the metabolic syndrome (weight gain and elevations in glucose, insulin, cholesterol, and lipid levels) associated to varying degrees with other atypical antipsychotic medications. It also appears to be less likely than haloperidol and risperidone to cause EPS and hyperprolactinemia. Ziprasidone has been found to lengthen the cardiac QTc interval. As yet there is insufficient long-term data to determine the relative risks of ziprasidone versus other antipsychotic medications in causing life-threatening cardiac arrhythmia. Clinicians should be aware of the risk factors for prolongation of the QTc interval and should obtain a patient and family medical history before deciding whether a trial with ziprasidone treatment is appropriate (see below).

Recommendations for the practical, clinical use of ziprasidone

Addressing the risk of QTc prolongation

Measuring an individual patient's mean baseline and mean post-baseline QTc intervals is not a clinically useful method of monitoring or managing the QTc prolongation effects of ziprasidone or other antipsychotic agents. An individual's QTc interval varies considerably over the course of a day, which means that mean measurements will have large standard errors and will therefore be unreliable for

Table 2 Safety/tolerability differences emerging in three longer-term studies (28–44 weeks) comparing ziprasidone to olanzapine or to risperidone

	Safety/tolerability results that favored ziprasidone (40–80 mg bid) over:		
	Olanzapine 5–15 mg bid	**Olanzapine 10–20 mg bid**	**Risperidone 3–5 mg bid**
	6-month, blinded extension for completers of a 6-week, randomized, double-blind study (Simpson et al 2002[a])	28-week, randomized, double-blind study (Kane et al 2003)	44-week, blinded extension for completers of 8-week, randomized, double-blind study (Addington et al 2003[b])
Overall rates of laboratory abnormalities	(no significant differences)	NR	Zip 57% Risp 96% Group difference $p < 0.001$
Weight	Zip ≈ –3 lbs $p < 0.001$ Olanz ≈ +10 lbs $p < 0.001$ Group difference $p < 0.001$	Zip –2.5 lbs (p not given) Olanz +6.7 lbs (p not given) Group difference $p < 0.001$	Zip ≈ +1 lb Risp ≈ +8 lbs (p not given)
Body mass index change	Zip no change ns Olanz mean gain $p < 0.001$ Group difference $p < 0.001$	NR	NR
Insulin	Zip +1 µ/mL ns Olanz +2 µ/mL $p < 0.01$ Group difference ns	NR	NR
Glucose	Zip +2 mg/dL ns Olanz +5 mg/dL $p < 0.05$ Group difference ns	Zip 0 mg/dL ns Olanz +5 mg/dL (p not given) Group difference $p < 0.001$	NR
Prolactin	NR	(no significant differences)	Zip –8 ng/mL Risp +26 ng/mL (p not given)
Total cholesterol	Zip –1 mg/dL ns Olanz +13 mg/dL $p < 0.05$ Group difference ns	Zip –12 mg/dL (p not given) Olanz +3 mg/dL (p not given) Group difference $p < 0.001$	NR
HDL cholesterol	NR	Zip +1 mg/dL (p not given) Olanz –3 mg/dL (p not given) Group difference $p < 0.001$	NR
LDL cholesterol	Zip +9 mg/dL ns Olanz +17 mg/dL $p < 0.05$ Group difference ns	Zip –10 mg/dL (p not given) Olanz +2 mg/dL (p not given) Group difference: $p < 0.01$	NR
Triglycerides	NR	Zip –20 mg/dL (p not given) Olanz +32 mg/dL (p not given) Group difference $p < 0.001$	NR
Hepatic enzymes	Zip no change in AST level Olanz increased AST $p < 0.001$ Group difference $p < 0.05$ Zip no change in ALT level Olanz increased ALT $p < 0.01$ Group difference $p < 0.01$	NR	NR
Rates of specific adverse effects	Zip vs olanz: Weight gain 0% vs 17% $p < 0.01$	Zip vs olanz: Weight gain 2% vs 13% $p < 0.001$ Increased appetite 3% vs 7% $p < 0.05$	Zip < risp: Increased salivation (≈ 5 times lower) Akathisia (≈ 3 times lower)(actual rates and p not given)

Table 2 *continued*

	Safety/tolerability results that favored ziprasidone (40–80 mg bid) over:		
	Olanzapine 5–15 mg bid	**Olanzapine 10–20 mg bid**	**Risperidone 3–5 mg bid**
Abnormal movements	Baseline to end point: Zip AIMS –0.3 (p not given) Olanz AIMS –0.8 (p not given) Group difference $p < 0.05$ (no significant group differences on BAS or ESRS scores)	Largest changes from baseline Zip: AIMS +0.5 (p not given) Olanz: AIMS +0.2 (p not given) Group difference $p = 0.01$ Zip: BAS +0.3 (p not given) Olanz: BAS +0.2 (p not given) Group difference $p < 0.05$ Zip: SAS +0.6 (p not given) Olanz: SAS –0.0 (p not given) Group difference $p < 0.001$	(No significant group differences on AIMS, BAS, MDBS, or SAS)
Rates of specific adverse effects	Zip vs olanz: EPS 11% vs 4% $p < 0.05$ Tremor 8% vs 3% $p < 0.05$	Zip vs olanz: Insomnia 22% vs 7% $p < 0.001$ Vomiting 9% vs 4% $p < 0.05$ Anorexia 3% vs 0% $p < 0.05$ Dystonia 0% vs 2% $p < 0.05$ Hypotension 0% vs 2% $p < 0.05$ Aggravated psychosis[c] 4% vs 1% $p < 0.05$	Zip > risp: Insomnia (≈ 3 times higher)(actual rates and p not given)

[a] Changes from start of 6-week phase (Simpson et al 2001) to end of extension phase (last observation carried forward, unless otherwise stated).
[b] Changes from start of 8-week phase (Addington et al 2002) to end of extension phase (last observation carried forward, unless otherwise stated).
[c] Cases of aggravated psychosis that led to discontinuation of treatment.
Abbreviations: AIMS, Abnormal Involuntery Movements Scale; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BAS, Barnes Akathisia Scale; EPS, extrapyramidal symptoms; ESRS, Extrapyramidal Symptom Rating Scale; HDL, high-density lipoprotein; LDL, low-density lipoprotein; MDBS, Movement Disorder Burden Scale; NR, not reported; ns, not significant; olanz, olanzapine; risp, risperidone; SAS, Simpson-Angus Scale; zip, ziprasidone.

comparison. Furthermore, group studies indicate that the extent of QTc prolongation does not appear to be linearly related to the potential for cardiac arrhythmia problems (Morganroth 1993).

As when any new antipsychotic medication is being considered, the patient should receive medically needed physical assessments, laboratory tests, and other evaluations according to standards of good clinical practice (CPA 1998; APA 2004). In addition to obtaining the patient's medical history, the clinician should establish whether there is a family history of syncope or sudden unexplained death, as these may indicate congenital long QT syndrome.

Clinicians should be aware of the FDA guidelines on the use of ziprasidone. Table 3 provides a list of risk factors for QTc prolongation that have implications for the use of ziprasidone. The table also provides possible actions regarding decisions concerning ziprasidone treatment.

Additional risk factors for QTc interval prolongation have been identified; these include the female sex as well as endocrine/metabolic abnormalities, such as obesity, diabetes, and thyroid abnormalities (Rautaharju et al 1992; Carella et al 1996; Brown et al 2001; Vieweg 2002). Clinicians should use their own judgment in weighing the potential benefits and risks of ziprasidone in these cases, and operate within their personal comfort zone. In the opinion of the authors, these additional risk factors are not themselves compelling reasons to rule out ziprasidone treatment. If clinicians opt to obtain an ECG, a QTc interval >450 ms would be a contraindication for treatment with any drug that prolongs the QTc interval.

When to consider a trial with ziprasidone

Given the current clinical data available, the authors suggest that ziprasidone be considered as a first-line antipsychotic medication in both the acute and long-term maintenance treatment of people with schizophrenia, schizoaffective disorder, or schizophreniform disorder. At this time, due to a lack of information, it would be premature to suggest using ziprasidone in treatment-resistant patients, those patients stabilized on clozapine, or in elderly patients with complex medical problems. As discussed above, patients with risk factors for QTc prolongation listed in Table 3 should not be prescribed ziprasidone.

According to Canadian Clinical Practice Guidelines (CPA 1998), patients should have regular reassessments of their symptoms, treatment regime (including psychosocial aspects as well as dosing and side effects of medications), and functional recovery. In stable patients, these

Table 3 Risk factors for QTc interval prolongation and implications regarding the use of ziprasidone

Risk factor	Suggestion
Diagnosed or suspected congenital long QT syndrome	Ziprasidone treatment should be avoided
Personal or family history of syncope	Ziprasidone treatment should be avoided
Family history of sudden unexplained death	Ziprasidone treatment should be avoided
Cardiac disease, with a history of cardiac arrhythmias, myocardial ischemia, or congestive heart failure	Ziprasidone treatment should be avoided
Bradycardia	Ziprasidone treatment should be avoided
Central nervous system lesions (eg, stroke, infection, trauma, Parkinson's disease)	Ziprasidone treatment should be avoided
Interaction with other drugs that can prolong the QTc interval (see Table 4)	Ziprasidone should not be used if exposure to other drugs that prolong the QTc interval can not be avoided
Electrolyte imbalance (hypokalemia or hypomagnesemia)	Ziprasidone should not be used unless the electrolyte imbalance is corrected
Use of diuretics, kidney disease	Patients at risk of electrolyte imbalances should have baseline measurements and regular monitoring of potassium and magnesium levels

reassessments should be approximately every 6 months. Should patient recovery be less than optimal, consideration can be given to changing antipsychotic medication. Ziprasidone may be considered for treatment optimization in patients who have responded to another antipsychotic medication but who either have clinically relevant residual symptoms or clinically significant side effects, eg, problematic weight gain or other problematic metabolic symptoms. In addition to its use as a first-line oral treatment or as an optimizing agent, IM ziprasidone can be used in patients presenting with psychosis-related acute agitation in emergency room settings.

Dosing: initiating and switching

Whenever ziprasidone is prescribed, steps must be taken to ensure that patients are not exposed to other prescription drugs or over-the-counter medications known to prolong the QTc interval. Table 4 provides a list of common medications with QTc prolongation action. A more complete up-to-date list of all such agents is available at http://www.qtdrugs.org.

Initiating oral ziprasidone treatment in patients naive to antipsychotic drugs

It is important to the future adherence of medication that patients' first experiences of antipsychotic medication is agreeable (ie, minimal experiences of unpleasant side effects). Patients with first-episode psychosis (FEP) tend to be more sensitive to the therapeutic effects and adverse effects of antipsychotic medication. Although there are limited data relevant to initiating ziprasidone treatment in drug-naive patients to date, the following suggestions are made for the initiation of ziprasidone therapy in drug-naive patients, based on the group consensus:

- 20 mg bid on day 1;
- 40 mg bid for days 2–5;
- Maintain at 40 mg in the morning; titrate the evening dose up to the minimum effective therapeutic dose, leaving enough time between dose increments to evaluate symptom response (approximately 6–10 days);
- Adjust timing and balance of the morning and evening doses in response to problems with somnolence/insomnia;
- Total daily dose should not usually exceed 120 mg in FEP patients. Doses above 120 mg/day (up to the maximum total daily dose of 160 mg) should only be considered in FEP patients in the presence of an initial but suboptimal response and in the absence of significant side effects;
- Concurrent anticholinergic treatment is *not* usually necessary.

Agitation is a common problem in drug-naive patients receiving low doses of ziprasidone. See section on the management of side effects for suggestions on how this problem can be managed.

Use of IM ziprasidone treatment in cases of acute exacerbation of agitation

Injectable ziprasidone may be used when necessary in the treatment of acute psychosis.

- A starting dose of 20 mg IM (10 mg IM in drug-naive patients) is suggested.
- The maximum dose should be 40 mg/24 hours for ≤ 3 days.
- Concomitant benzodiazepines can be used.
- Prophylactic anticholinergic medications are not usually necessary.

Switching to ziprasidone from current treatment with another atypical antipsychotic agent

Data from current studies (Weiden, Simpson, et al 2003) showed no difference in outcome between different switching strategies. It is suggested that a cross-over strategy be used (ie, the current drug is gradually decreased while ziprasidone is begun and titrated upward). Duration of a typical cross-over period would be in the order of 1–2 weeks, but this needs to be individualized and based on patient tolerance and on the patient setting (inpatient or outpatient). Patients should not be maintained on intermediate doses of both medications.

Available data suggest a starting dose of ziprasidone of 80 mg/day (given as 40 mg bid) for the first two days, followed by flexible dosing**.** Most patients requiring maintenance treatment respond at doses in the range 80–160 mg/day. Most patients requiring treatment of an acute exacerbation respond at doses in the range 120–160 mg/day. There is some evidence that rapid titration to doses in the range 120–160 mg/day results in earlier improvements in symptoms in cases of acute exacerbation as well as better prevention of relapse in patients requiring maintenance treatment compared with doses ≤ 80 mg/day (Murray et al 2003). To date, there is little evidence of greater improvement in symptom control using doses above 160 mg/day (Anonymous 2000; Davis and Chen 2004).

Switching to ziprasidone from current treatment with a conventional antipsychotic agent

For patients being switched from an oral conventional antipsychotic, a cross-over strategy is similarly suggested, as described above. (Suggested dosing of ziprasidone is also as described above for patients being switched from another atypical agent.) If the patient was previously taking anticholinergic medication, this anticholinergic medication should be continued at the same dose for 2 weeks after discontinuation of the conventional antipsychotic to reduce

Table 4 Drugs with generally accepted QTc interval prolongation action, organized by class of drug

Usage/Class of drug	Drug names
Alpha1-blocker	Alfuzosin
ADHD	Atomoxetine, methylphenidate
Antianginal	Bepridil[a]
Antiarrhythmic	Amiodarone, disopyramide, dofetilide, flecainide, ibutilide, procainamide, quinidine, sotalol
Sympathomimetic (asthma)	Salmeterol
Antibiotic	Azithromycin, clarithromycin, erythromycin, fluconazole, gatifloxacin, grepafloxacin, ketoconazole, levofloxacin, moxifloxacin, sparfloxacin, telithromycin
Anticancer	Arsenic trioxide, tamoxifen
Anticonvulsant	Felbamate, fosphenytoin
Antidepressant	Venlafaxine
Antiemetic	Ondansetron
Antifungal	Voriconazole
Antihistamine	Astemizole,[a] terfenadine[a]
Antihypertensive	Isradipine, moexipril/hydrochlorothiazide, nicardipine
Antiinfective	Pentamidine
Antimalarial	Chloroquine, halofantrine
Antimania	Lithium
Antinausea	Dolasetron, domperidone, droperidol, granisetron
Antipsychotic	Chlorpromazine, clozapine, haloperidol, mesoridazine, pimozide, quetiapine, risperidone, thioridazine
Antiviral	Amantadine, foscarnet
Appetite suppressant	Fenfluramine, phentermine, sibutramine
Bronchodilator	Salbuterol, ephedrine, levalbuterol, metaproterenol, terbutaline
Catecholamine	Dobutamine, epinephrine, isoproterenol
Decongestant	Ephedrine, phenylephrine, phenylpropanolamine, pseudoephedrine
Diuretic	Indapamide
Dopaminergic (Parkinson's)	Amantadine
Endocrine	Octreotide
Gastrointestinal stimulant	Cisapride,[a] erythromycin
Immunosuppressant	Tacrolimus
Muscle relaxant	Tizanidine
Opiate agonist	Levomethadyl, methadone
Sedative	Chloral hydrate, droperidol[a]
Uterine relaxant	Ritodrine
Vasoconstrictor	Epinephrine, midodrine, norepinephrine, phenylephrine
Vasodilator	Vardenafil
Other	Cocaine

A more complete up-to-date list of all such agents is available at www.qtdrugs.org.
[a] These medications are no longer available in Canada but may still be available elsewhere.

the risk of withdrawal dyskinesia. Over the next 2–4 weeks, the anticholinergic medication should be gradually tapered and discontinued.

Before being switched to ziprasidone, patients taking depot conventional antipsychotics given intramuscularly should be reassessed with a focus on the reasons for the use of long-acting medication. If nonadherence to oral medication is considered likely, the patient should not be switched to ziprasidone at this time. Patients taking depot conventional antipsychotics and an oral anticholinergic medication who are assessed as suitable candidates for a trial with oral ziprasidone need to be continued on their anticholinergic medication for at least 12 weeks following the cessation of the conventional antipsychotic. The anticholinergic drug should not be stopped abruptly as withdrawal has been documented.

Management of side effects of ziprasidone

Sleep disturbance

Somnolence during the day can be managed by splitting the bid dosing into a lower dose in the morning and a higher dose in the evening. Conversely, insomnia at night can be managed by splitting the dosing into a higher dose in the morning and a lower dose in the evening and/or by adjusting the timing of the evening dose.

Agitation/akathisia during initiation of ziprasidone in patients naive to antipsychotic medication

Agitation needs to be differentiated from akathisia. Agitation is a common problem when drug-naive patients are receiving low doses of ziprasidone. If the symptoms are due to agitation, suggested treatment is an increased dose of ziprasidone and/or short-term use of benzodiazepines, not treatment with beta-blockers. Agitation usually settles within 2–3 days of an increase in dose of ziprasidone. In situations in which the symptomatology is unclear, small doses of medium-acting benzodiazepines (such as clonazepam) can be considered.

Important aspects of monitoring of ongoing treatment with ziprasidone

As part of the management of patients with schizophrenia and related psychotic disorders, all should receive good medical care, including yearly physical medical examinations and 6-monthly assessment of symptoms, functioning, and side effects. Table 5 provides a summary of features to assess at baseline and at subsequent assessments, in order to evaluate ziprasidone treatment. Long-term monitoring should be individualized according to patient history and the baseline assessment. No special long-term monitoring is required for patients on ziprasidone except for those who were experiencing medical problems prior to ziprasidone treatment. For example, a patient with elevated glucose and lipid plasma levels related to a previous

Table 5 Patient characteristics to assess at baseline and at 6-monthly follow-up assessments

Target symptoms	
Positive symptoms	Hallucinations, delusions, behavioral abnormalities, disorganization
Negative symptoms	Social isolation, reduced motivation, reduced speech, reduced pleasure
Mood	Low mood, suicidal thoughts
Cognition	Memory problems, attention deficits, concentration difficulties
Target aspects of daily life	
Personal care	Poor hygiene (washing, bathing, grooming), appearance, clothing
Social	Most of day alone, little interaction with friends/family
Housing	Frequent moves, living on the street
Nutrition	Poor diet, frequently missing meals, excessive consumption of high-fat fast foods
Vocational	Difficulties finding and/or keeping up with job/school
Organizational/social	Difficulty connecting with community supports
Overall	Recurring need for hospitalization
Quality of life	As perceived by informants, as perceived by patient
Target side effects	
Movements	Akathisia, parkinsonism, tardive dyskinesia, tremor
Cardiovascular	Hypotension
Endocrine[a]	Gynecomastia, galactorrhea, oligomenhorrhea, amenhorrhea
Metabolic[a]	Weight gain, lipid elevation, glucose intolerance/diabetes
Sexual functioning	Loss of libido, impotence
Emotional/Cognitive	Flattened affect, difficulties with concentration and memory
Sleep	Sedation, insomnia

[a] Monitor *if* these were problems prior to treatment with ziprasidone.

antipsychotic medication should be periodically monitored to see if these problems are reversing. A patient with kidney disease should be monitored to assess whether potassium and magnesium levels are within the normal range.

Nonadherence to antipsychotic medication

The biggest challenge to the effectiveness of antipsychotic medication in prevention of relapse may not be efficacy (Marder and May 1986; Wyatt 1991) but high rates of nonadherence (Fenton et al 1997). Patients prescribed medications for treatment of schizophrenia report a median nonadherence rate of 55% (range 24%–88%) within two years (Young et al 1986; Fenton et al 1997). Forty percent stop within one year and about 75% do so within two years. In cases of FEP, poor medication adherence ranges from 33% to 44%, with more than half (53%) interrupting their medication at least once within two years (Verdoux et al 2000). The likelihood of relapse after treatment of FEP is at least sixfold higher if the patient stops antipsychotic medication (Robinson et al 1999). A significantly more episodic course and higher rates of readmission to hospital are also reported for FEP patients with poor medication adherence (Verdoux et al 2000).

Some of the correlates of nonadherence can be considered unintentional (eg, due to intolerable side effects from medications, or unwieldy medication regimens). However, a substantial proportion of patients intentionally stop taking medication because of lack of insight about the nature of their illness, refusal to acknowledge the possibility of relapse, or other health-related belief systems. Poor therapeutic alliance, lower occupational status, alcohol abuse/dependence, the initial intensity of delusions, suspiciousness, and persecution are also predictive of nonadherence to medication in FEP (Verdoux et al 2000; Perkins 2002). Poor adherence to medication early in treatment also predicts poor adherence in the longer term (Lacro et al 2002). Focus groups conducted with patients, families, and clinical staff suggest the role of the following additional factors related to nonadherence: peer pressure, "feeling different", misattribution of symptoms to side effects of medications, and cultural attitudes, particularly among young patients. Designing interventions to improve adherence to medication very early in the course of illness is crucial to preventing relapse. Availability of medications whose side effects are more tolerable to patients would aid such endeavors.

To promote adherence to medication, clinicians should fully explore patients' views about their illness and patients' attitudes and behaviors regarding their medications (Zygmunt et al 2002). Identifying patients' goals and aspirations and relating them to treatment outcomes has been found to increase treatment adherence (Kemp et al 1998). Patients should be offered group educational sessions to provide information on the nature of their illness and its treatment, and to discuss strategies to resolve common problems with treatment adherence. Patients should be encouraged to report side effects and clinicians should be responsive in trying to diminish or eliminate side effects. When appropriate, family members should also be offered education to foster their involvement in helping patients adhere to their treatment regimes, and to provide family members with advice and support in coping with patients' illnesses (Dixon and Lehman 1995; Dixon et al 2000; Addington et al 2001). Further information regarding factors affecting adherence to antipsychotic medications can be found in the American Psychiatric Association treatment guidelines on schizophrenia (APA 2004).

Adherence to treatment with ziprasidone

The relatively low incidence of EPS and the low risk for weight gain associated with ziprasidone may make ziprasidone more acceptable at the outset and as treatment continues for many patients. As discussed above, when ziprasidone is prescribed to FEP patients, clinicians should pay particular attention to quickly addressing agitation and sleep disturbances (insomnia, somnolence) to which drug-naive patients are especially susceptible, to avoid early abandonment of ziprasidone treatment.

Conclusion

Ziprasidone is an effective acute and long-term maintenance treatment option for patients with schizophrenia, schizoaffective disorder, and schizophreniform disorder. It is safe when used with patients who do not have risk factors for QTc prolongation. Ziprasidone is less likely than haloperidol to cause EPS and hyperprolactinemia. Ziprasidone does not appear to cause the metabolic syndrome (weight gain and elevations in glucose, insulin, cholesterol, and lipid levels) associated to varying extents with other atypical antipsychotics. It also appears to be less likely than risperidone to cause hyperprolactinemia. Common adverse events associated with ziprasidone

treatment include agitation and sleep disturbances. It is well tolerated if these problems are managed appropriately (as described above). Ziprasidone can be considered for patients currently receiving other antipsychotic medication if their response to their current medication is suboptimal and/or they are experiencing problematic side effects. It can also be considered for FEP patients.

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References

Addington D, Addington J, Maticka-Tyndale E, et al. 1992. Reliability and validity of a depression rating scale for schizophrenics. *Schizophr Res*, 6:201–8.

Addington D, Pantelis C, Benattia I. 2002. Ziprasidone vs risperidone in schizophrenia: results of an 8-week, multicenter, double-blind trial. Poster presented at 42nd Annual New Clinical Drug Evaluation Unit (NCDEU) Meeting. 2002 Jun 10–13; Boca Raton, FL, USA. Abstract accessed 18 Feb 2004. URL: http://www.nimh.nih.gov/ncdeu/abstracts2002/ncdeu3047.cfm.

Addington D, Pantelis C, Dineen M, et al. 2003. Ziprasidone vs risperidone in schizophrenia: 52 weeks' comparative data. Abstract of poster in: Program and Abstracts from the American Psychiatric Association 156th Annual Meeting. 2003 May 17–22; San Francisco, CA, USA.

Addington J, Addington D, Jones B. 2001. Family intervention in an early psychosis program. *Psychiatr Rehabil Skills*, 5:272–86.

Allison DB, Mentore JL, Heo M, et al. 1999. Antipsychotic-induced weight gain: a comprehensive research synthesis. *Am J Psychiatry*, 156: 1686–96.

Anonymous. 2000. Briefing Document for ZELDOX® CAPSULES (Ziprasidone HCl). FDA Psychopharmacological Drug Advisory Committee, 2000. Accessed 15 Feb 2004. URL: http://www.fda.gov/ohrms/dockets/ac/00/backgrd/3619b1a.pdf.

Anonymous. 2002. The clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for non-antiarrythmic drugs. Preliminary discussion paper. FDA/Health Canada. Accessed 10 Jan 2003. URL: http://www.hc-sc.gc.ca/hpfb-dgpsa/tpd-dpt/qt_conceptpaper_e.html.

[APA] American Psychiatric Association. 1987. Diagnostic and statistical manual of mental disorders. 3rd ed. Washington: APA.

[APA] American Psychiatric Association. 2004. Practice guideline for the treatment of patients with schizophrenia. 2nd ed. *Am J Psychiatry*, 161(Suppl):1–56.

Arato M, O'Connor R, Meltzer H. 2002. A 1-year, double-blind, placebo-controlled trial of ziprasidone 40, 80 and 160 mg/day in chronic schizophrenia: the Ziprasidone Extended Use in Schizophrenia (ZEUS) Study. *Int Clin Psychopharmacol*, 17:207–15.

Atmaca M, Kuloglu M, Tezcan E. 2003. Serum leptin and triglyceride levels in patients with atypical antipsychotics. *J Clin Psychiatry*, 64:598–604.

Barnes TR. 1989. A rating scale for drug-induced akathisia. *Br J Psychiatry*, 154:672–6.

Beedham C, Miceli J, Obach R. 2003. Ziprasidone metabolism, aldehyde oxidase, and clinical implications. *J Clin Psychopharmacol*, 23: 229–32.

Bhalla R. 2004. Schizophreniform disorder. Accessed 30 Mar 2004. URL: http://www.emedicine.com/MED/topic3350.htm.

Brannon G. 2004. Schizoaffective disorder. Accessed 30 Mar 2004. URL: http://www.emedicine.com/med/topic3514.htm.

Brook S, Lucey J, Gunn K. 2000. Intramuscular ziprasidone compared with intramuscular haloperidol in the treatment of acute psychosis. *J Clin Psychiatry*, 61:933–41.

Brook S, Walden J, Benattia I. 2001. Ziprasidone versus haloperidol in sequential IM/oral treatment of acute schizophrenia. Poster presented at the American College of Neuropsychopharmacology (ACNP) 40th Annual Meeting. 2001 Dec 9–13; Waikoloa, HI, USA.

Brown DW, Giles WH, Greenlund KJ, et al. 2001. Impaired fasting glucose, diabetes mellitus, and cardiovascular disease risk factors are associated with prolonged QTc duration. Results from the Third National Health and Nutrition Examination Survey. *J Cardiovasc Risk*, 8:227–33.

[CPA] Canadian Psychiatric Association, Canadian Alliance for Research on Schizophrenia. 1998. Canadian clinical practice guidelines for the treatment of schizophrenia. *Can J Psychiatry*, 43(Suppl 2):19.

Carella MJ, Mantz SL, Rovner DR, et al. 1996. Obesity, adiposity, and lengthening of the QT interval: improvement after weight loss. *Int J Obes Relat Metab Disord*, 20:938–42.

Cassano G, Pini S, Saettoni M, et al. 1998. Occurrence and clinical correlates of psychiatric comorbidity in patients with psychotic disorders. *J Clin Psychiatry*, 59:60–8.

Daniel D, Potkin S, Reeves K. 2001. Intramuscular (IM) ziprasidone 20 mg is effective in reducing acute agitation associated with psychosis: a double-blind, randomized trial. *Psychopharmacology*, 155:128–34.

Daniel D, Zimbroff D, Potkin S. 1999. Ziprasidone 80 mg/day and 160 mg/day in the acute exacerbation of schizophrenia and schizoaffective disorder: a 6-week placebo-controlled trial. *Neuropsychopharmacol*, 20:490–505.

Davis JM, Chen N. 2004. Dose response and dose equivalence of antipsychotics. *J Clin Psychopharmacol*, 24:192–208.

Dixon L, Adams C, Lucksted A. 2000. Update on family psychoeducation for schizophrenia. *Schizophr Bull*, 26:5–20.

Dixon LB, Lehman AF. 1995. Family interventions for schizophrenia. *Schizophr Bull*, 21:631–43.

Eaton WW. 1985. Epidemiology of schizophrenia. *Epidemiol Rev*, 7: 105–26.

Fenton WS, Blyler CR, Heinssen RK. 1997. Determinants of medication compliance in schizophrenia: empirical and clinical findings. *Schizophr Bull*, 23:637–51.

Fleischhacker WW, Meise U, Gunther V, et al. 1994. Compliance with antipsychotic drug treatment: influence of side effects. *Acta Psychiatr Scand*, 89:11–15.

Geddes J, Freemantle N, Harrison P, et al. 2000. Atypical antipsychotics in the treatment of schizophrenia: systematic overview and meta-regression analysis. *BMJ*, 321:1371–6.

Goeree R, O'Brien BJ, Goering P, et al. 1999. The economic burden of schizophrenia in Canada. *Can J Psychiatry*, 44:464–72.

Goodnick PJ. 2001. Ziprasidone: profile on safety. *Expert Opin Pharmacother*, 2:1655–62.

Guy W. 1976a. CGI. In Guy W (ed). ECDEU Assessment manual for psychopharmacology. Revised ed. (Publication ADM 76-338). Washington: US Department of Health, Education, and Welfare. p 218–22.

Guy W. 1976b. AIMS. In Guy W (ed). ECDEU Assessment manual for psychopharmacology. Revised ed. (Publication ADM 76-338). Washington: US Department of Health, Education, and Welfare. p 534–5.

Haefner H, an der Heiden W. 1997. Epidemiology of schizophrenia. *Can J Psychiatry*, 42:139–51.

Harrigan EP, Miceli JJ, Anziano R, et al. 2004. A randomized evaluation of the effects of six antipsychotic agents on QTc, in the absence and presence of metabolic inhibition. *J Clin Psychopharmacol*, 24:62–9.

Harvey PD, Keefe RSE. 2001. Studies of cognitive change in patients with schizophrenia following novel antipsychotic treatment. *Am J Psychiatry*, 158:176–84.

Harvey PD, Meltzer H, Simpson GM, et al. 2004. Improvement in cognitive function following a switch to ziprasidone from conventional antipsychotics, olanzapine, or risperidone in outpatients with schizophrenia. *Schizophr Res*, 66:101–13.

Heaton RK, Chelune CJ, Talley JL, et al. 1993. Wisconsin Card Sorting Test Manual-Revised and Expanded. Odessa: Psychological Assessment Resources.

Heinrichs DW, Hanlon TE, Carpenter WT. 1984. The Quality of Life Scale: an instrument for rating schizophrenic deficit syndrome. *Schizophr Bull*, 10:388–98.

Hirsch S, Kissling W, Baeuml J. 2002. A 28-week comparison of ziprasidone and haloperidol in outpatients with stable schizophrenia. *J Clin Psychiatry*, 63:516–22.

Kamel A, Prakash C, Obach S. 2002. Determination of the enzymes involved in the reductive cleavage of ziprasidone to dihydroziprasidone and the formation of S-methyldihydroziprasidone using human in vitro systems and electrospray ionisation tandem mass spectrometry (ESI/MS/MS). Presentation at the 50th American Society for Mass Spectrometry (ASMS) Conference. 2002 Jun 2–6; Orlando, FL, USA.

Kane JM, Berg PH, Thakore J, et al. 2003. Olanzapine versus ziprasidone: results of the 28-week double-blind study in patients with schizophrenia. Poster presentation at the International Congress on Schizophrenia Research (ICOSR) Meeting. 2003 Mar 29–Apr 2; Colorado Springs, CO, USA.

Kapur S. 1996. 5-HT_2 antagonism and EPS benefits: is there a causal connection? *Psychopharmacology*, 124:35–9.

Kapur S, Seeman P. 2001. Does fast dissociation from the dopamine D-sub-2 receptor explain the action of atypical antipsychotics? A new hypothesis. *Am J Psychiatry*, 158:360–9.

Kay SR, Fiszbein A, Opler LA. 1987. The positive and negative syndrome scale (PANSS) for schizophrenia. *Schizophr Bull*, 13:261–76.

Keck P, Buffenstein A, Ferguson J. 1998. Ziprasidone 40 and 120 mg/day in the acute exacerbation of schizophrenia and schizoaffective disorder: a 4-week placebo-controlled trial. *Psychopharmacology*, 140:173–84.

Keck P, Reeves K, Harrigan E. 2001. Ziprasidone in the short-term treatment of patients with schizoaffective disorder: results from two double-blind, placebo-controlled, multicenter studies. *J Clin Psychopharmacol*, 21:27–35.

Keck PE, McElroy SL. 2002. Clinical pharmacodynamics and pharmacokinetics of antimanic and mood-stabilizing medications. *J Clin Psychiatry*, 63(Suppl 4):3–11.

Kelly DL, Kreyenbuhl J, Love RC. 2003. Six-month review of weight and metabolic parameters in patients receiving clozapine, risperidone, olanzapine, or quetiapine. *J Clin Psychiatry*, 64:1133–4.

Kemp R, Kirov G, Everitt B, et al. 1998. Randomised controlled trial of compliance therapy: 18-month follow-up. *Br J Psychiatry*, 172: 413–19.

Lacro JP, Dunn LB, Dolder CR. 2002. Prevalence of and risk factors for medication nonadherence in patients with schizophrenia: a comprehensive review of recent literature. *J Clin Psychiatry*, 63: 892–909.

Lebovitz HE. 2003. Metabolic consequences of atypical antipsychotic drugs. *Psychiatr Q*, 74:277–90.

Lesem M, Zajecka J, Swift R. 2001. Intramuscular ziprasidone, 2 mg versus 10 mg, in the short-term management of agitated psychotic patients. *J Clin Psychiatry*, 62:12–18.

Lipman RS. 2001. Covi Anxiety Scale. 1982. In Sajatovic M, Ramirez LF (eds). Rating scales in mental health. Hudson: Lexi-Comp. p 35–8.

Marder SR, May PR. 1986. Benefits and limitations of neuroleptics – and other forms of treatment – in schizophrenia. *Am J Psychother*, 40: 357–69.

Meltzer HY, Matsubara S, Lee JC. 1989. Classification of typical and atypical antipsychotic drugs on the basis of dopamine D1, D2 and serotonin 2 pK_i values. *J Pharmacol Exp Therap*, 251:238–46.

Meltzer HY, McGurk SR. 1999. The effects of clozapine, risperidone and olanzapine on cognitive function in schizophrenia. *Schizophr Bull*, 25:233–55.

Miceli J, Anziano R, Swift R, et al. 2002. IM ziprasidone and IM haloperidol show comparable QTc effects at C_{max}. Abstract of poster in: Program and Abstracts from the American Psychiatric Association 155th Annual Meeting. 2002 May 18–23; Philadelphia, PA, USA.

Miceli J, Shiovitz T, Swift R, et al. 2003. High-dose ziprasidone is associated with a marginal additional QTc increase. Abstract of poster in: Program and Abstracts from the American Psychiatric Association 156th Annual Meeting. 2003 May 17–22; San Francisco, CA, USA.

Miceli J, Wilner K, Folger C, et al. 1998. Pharmacokinetics of intramuscular ziprasidone in schizophrenic patients: population pharmacokinetic modelling. *Eur Neuropsychopharmacol*, 8:S215.

Miceli JJ, Anziano RJ, Robarge L, et al. 2000. The effect of carbamazepine on the steady-state pharmacokinetics of ziprasidone in healthy volunteers. *Br J Clin Pharmacol*, 49:65S–70S.

Miceli JJ, Smith M, Robarge L, et al. 2000. The effects of ketoconazole on ziprasidone pharmacokinetics-a placebo controlled crossover study in healthy volunteers. *Br J Clin Pharmacol*, 49:71S–76S.

Montgomery S, Asberg M. 1979. A new depression scale designed to be sensitive to change. *Br J Psychiatry*, 134:382–9.

Morganroth J. 1993. Relations of QTc prolongation on the electrocardiogram to torsades de pointes: definitions and mechanisms. *Am J Cardiol*, 72:10B–13B.

Morganroth J, Brozovich FV, McDonald JT, et al. 1991. Variability of the QT measurement in healthy men, with implications for selection of an abnormal QT value to predict drug toxicity and proarrhythmia. *Am J Cardiol*, 67:774–6.

Mullen B, Brar JS, Vagnucci AH, et al. 2001. Frequency of sexual dysfunctions in patients with schizophrenia on haloperidol, clozapine or risperidone. *Schizophr Res*, 48:155–8.

Murray CJL, Lopez AD. 1996. The global burden of disease. Cambridge, Mass: Harvard School of Public Health.

Murray S, Siu CO, Romano SJ. 2003. Optimal dosing of oral ziprasidone: analysis of clinical trial data. Abstract of poster in: Program and Abstracts from the 156th Annual meeting of the American Psychiatric Association. 2003 May 17–22; San Francisco, CA, USA.

Oltmanns TF, Neale JM. 1975. Schizophrenic performance when distractors are present: attentional deficit or differential task difficulty? *J Abnorm Psychol*, 84:205–9.

Osser DN, Najarian DM, Dufresne RL. 1999. Olanzapine increases weight and serum triglyceride levels. *J Clin Psychiatry*, 60:767–70.

Perkins DO. 2002. Predictors of noncompliance in patients with schizophrenia. *J Clin Psychiatry*, 63:1121–8.

Prakash C, Kamel A, Cui D, et al. 2000. Identification of the major human liver cytochrome P450 isoform(s) responsible for the formation of the primary metabolites of ziprasidone and prediction of possible drug interactions. *Br J Clin Pharmacol*, 49:35S–42S.

Prakash C, Kamel A, Gummerus J, et al. 1997. Metabolism and excretion of a new antipsychotic drug, ziprasidone, in humans. *Drug Metab Dispos*, 25:863–72.

Rautaharju PM, Zhou SH, Wong M, et al. 1992. Sex differences in the evolution of the electrocardiographic QT interval with age. *Can J Cardiol*, 8:690–6.

Reeves KR, Swift RH, Harrigan EP. 1998. Intramuscular ziprasidone 10 mg and 20 mg in patients with psychosis and acute agitation. Presentation at the 9th Congress of the Association of European Psychiatrists. 1998 Sep 20–24; Copenhagen, Denmark.

Reynolds LS, Braselton JP, Sprouse JS. 1997. Ziprasidone, unlike olanzapine, inhibits 5-HT neuronal activity by a 5-HT_{1A} mechanism. Presentation at the 27th Annual Meeting of the Society for Neuroscience. 1997 Oct 25–30; New Orleans, LA, USA. *Soc Neurosci Abstracts*, 23:1931.

Robinson DG, Woerner MG, Alvir J, et al 1999. Predictors of relapse following response from a first episode of schizophrenia or schizoaffective disorder. *Arch Gen Psychiatry*, 56:241–7.

Romano S. 2000. Cardiovascular safety profile of ziprasidone: review of clinical development data. Poster presented at the American College of Neuropsychopharmacology (ACNP) 39th Annual Meeting. 2000 Dec 10–14; San Juan, Puerto Rico, PR, USA.

Rosenheck R, Perlick D, Bingham S, et al. 2003. Effectiveness and cost of olanzapine and haloperidol in the treatment of schizophrenia. A randomized controlled trial. *J Am Med Assoc*, 290:2693–702.

Schmidt AW, Lebel LA, Johnson CG. 1998. The novel antipsychotic ziprasidone has a unique human receptor binding profile compared to other agents. Presentation at the 28th Annual Meeting of the Society for Neuroscience. 1998 Nov 7–12; Los Angeles, CA, USA. *Soc Neurosci Abstracts*, 24:2177.

Seeger TS, Seymour PA, Schmidt AW, et al. 1995. Ziprasidone (CP-88,059). A new antipsychotic with combined dopamine and serotonin receptor antagonist activity. *J Pharmacol Exp Therap*, 275:101–13.

Simpson G, Weiden P, Pigott T, et al. 2001. Ziprasidone vs olanzapine in schizophrenia. Abstract of poster in: Program and Abstracts from the American Psychiatric Association 154th Annual Meeting. 2001 May 5–10; New Orleans, LA, USA.

Simpson G, Weiden P, Pigott T, et al. 2002. Ziprasidone versus olanzapine in schizophrenia: 6-month continuation study. Abstract of poster in: Program and Abstracts from the American Psychiatric Association 155th Annual Meeting. 2002 May 18–23; Philadelphia, PA, USA.

Simpson GM, Angus JWS. 1970. A rating scale for extrapyramidal side effects. *Acta Psychiatr Scand*, 212:11–19.

Simpson GM, Lindenmayer JP. 1997. Extrapyramidal symptoms in patients treated with risperidone. *J Clin Psychopharmacol*, 17:194–201.

Spreen O, Strauss E. 1998. A compendium of neuropsychological tests and norms. 2nd ed. New York: Oxford Univ Pr.

Stahl SM, Shayegan DK. 2003. The psychopharmacology of ziprasidone: receptor-binding properties and real-world psychiatric practice. *J Clin Psychiatry*, 64(Suppl 19):6–12.

Swift RH, Harrigan EP, Cappelleri JC, et al. 2002. Validation of the behavioural activity rating scale (BARS): a novel measure of activity in agitated patients. *J Psychiatric Res*, 36:87–95.

Tandon R, Harrigan E, Zorn S. 1997. Ziprasidone: a novel antipsychotic with unique pharmacology and therapeutic potential. *J Serotonin Res*, 4:159–77.

Thompson Jr EH, Doll W. 1982. The burden of families coping with the mentally ill: an invisible crisis. *Fam Relations*, 31:379–88.

Verdoux H, Lengronne J, Liraud F, et al. 2000. Medication adherence in psychosis: predictors and impact on outcome. A 2-year follow-up of first-admitted subjects. *Acta Psychiatr Scand*, 102:203–10.

Vieweg WVR. 2002. Mechanisms and risks of electrocardiographic QT interval prolongation when using antipsychotic drugs. *J Clin Psychiatry*, 63(Suppl 9):18–24.

Weiden P, Simpson G, Potkin S. 2003. Effectiveness of switching to ziprasidone for stable but symptomatic outpatients with schizophrenia. *J Clin Psychiatry*, 64:580–8.

Weiden PJ, Daniel DG, Simpson G, et al. 2003. Improvement in indices of health status in outpatients with schizophrenia switched to ziprasidone. *J Clin Psychopharmacol*, 23:595–600.

Weiden PJ, Mackell JA, McDonnell DD. 2004. Obesity as a risk factor for antipsychotic noncompliance. *Schizophr Res*, 66:51–7.

Wilner KD, Tensfeldt TG, Baris B, et al. 2000. Single- and multiple-dose pharmacokinetics of ziprasidone in healthy young and elderly volunteers. *Br J Clin Pharmacol*, 49:15S–20S.

Winans E. 2003. Aripiprazole. *Am J Health Sys Pharm*, 60:2437–45.

Woerner MG, Mannuza S, Kane JM. 1988. Anchoring the BPRS: an aid to improved reliability. *Psychopharmacol Bull*, 24:112–17.

Wright P, O'Flaherty L. 2003. Antipsychotic drugs: atypical advantages and typical disadvantages. *Irish J Psychol Med*, 20:24–7.

Wyatt RJ. 1991. Neuroleptics and the natural course of schizophrenia. *Schizophr Bull*, 17:325–51.

Young JL, Zonana HV, Shepler L. 1986. Medication noncompliance in schizophrenia codification and update. *Bull Am Acad Psychiatry Law*, 14:105–22.

Zorn SH, Seeger TF, Seymour PA, et al. 1995. Ziprasidone (CP-88,059): preclinical pharmacology review. *Jpn J Neuropsychopharmacol*, 17:701–7.

Zygmunt A, Olfson M, Boyer CA, et al. 2002. Interventions to improve medication adherence in schizophrenia. *Am J Psychiatry*, 159: 1653–64.