Journal of Central Nervous System Disease

Libertas Academica
FREEDOM TO RESEARCH

OPEN ACCESS
Full open access to this and thousands of other papers at http://www.la-press.com.

REVIEW

Ziprasidone Hydrocloride: What Role in the Management of Schizophrenia?

Chiara Mattei[1,2], Maria Paola Rapagnani[1,3] and Stephen M. Stahl[1,4]

[1]Department of Psychiatry, University of California San Diego, CA, USA. [2]Department of Psychiatry, University of Genoa, Genoa, Italy. [3]Department of Medicine and Public Health, Section of Psychiatry and Clinical Psychology, University of Verona, Verona, Italy. [4]Department of Psychiatry, University of Cambridge, Cambridge, UK.
Corresponding author email: smstahl@neiglobal.com

Abstract:
Background: Since schizophrenia is considered one of the top ten causes of disease-related disability in the world, the development of second-generation (atypical) antipsychotics (SGAs) has increased the hopes of psychiatrists. SGAs, however, cannot be considered a unique pharmacological class since each SGA has many complex pharmacologic actions, only some of which are shared with other SGAs. Even though manyantipsychotics have similar efficacy on average, prescribers may be able to achieve better than average results by considering differences in selecting a specific drug for a specific patient. Clinicians know that each patient is unique. In order to achieve best outcomes for the individual patient, the better therapy is the therapy tailored for the single patient.
Objectives: With this article, we provide information on a relatively new antipsychotic ziprasidone released in 2001 by Pfizer for the treatment of schizophrenia. Compared with other first line atypical antipsychotics ziprasidone has a unique profile due to potent interaction with serotonergic receptors and lesser action upon α1 adrenergic, H1 and M1 antagonist activities. This paper describes the development of ziprasidone, its unique properties and its metabolically-friendly profile including its receptor binding affinities, pharmacokinetics, CNS activity results of clinical efficacy and relevant clinical trials. Safety, efficacy and patient preference are also examined. The available literature on ziprasidone of the last five years is reviewed.

Keywords: ziprasidone, schizophrenia, second generation antipsychotic, safety, efficacy

Journal of Central Nervous System Disease 2011:3 1–16

doi: 10.4137/JCNSD.S4138

This article is available from http://www.la-press.com.

© the author(s), publisher and licensee Libertas Academica Ltd.

This is an open access article. Unrestricted non-commercial use is permitted provided the original work is properly cited.

Introduction

Schizophrenia is a highly complex disorder characterized by positive symptoms (hallucinations, delusions, speech disturbance) and negative symptoms (social withdrawal, apathy, loss of emotional response) accompanied by marked impairments in social and cognitive function. The degree of suffering and disability is considerable with 80%–90% not working and in the 15–44 year old group, schizophrenia is considered one of the top ten causes of disease-related disability in the world.[1–3]

The introduction of the atypical antipsychotics (also called second generation antipsychotics or SGAs) has changed the way we treat patients with schizophrenia. Despite a resurgence of interest in classical first generation antipsychotics due to their lower cost and comparable efficacy, atypical antipsychotics are now the preferred first-line treatments for schizophrenia by most clinicians, owing to their ability to manage effectively the positive and negative symptoms of schizophrenia with minimized EPS (extrapyramidal symptoms) and reduced risk of tardive dyskinesia. However, even as use of second generation atypical agents increases, many psychiatrists still ponder the distinctions among the various atypical agents asking if these drugs are interchangeable and how differently they target the various symptoms associated with schizophrenia. In the absence of a critical mass of comparative data, the most relevant hypotheses for providing answers to these questions may be found through consideration of the psychopharmacologic binding properties as well as clinical trials results of individual atypical antipsychotic agents. Here we review these features of the atypical second generation antipsychotic ziprasidone.

Ziprasidone hydrochloride, a newer "atypical" or "second-generation" antipsychotic with many noteworthy receptor binding properties that contribute to its unique clinical profile, was approved by the US Food and Drug Administration (FDA) in 2001.[4] It was first approved for the treatment of schizophrenia, and subsequently for acute mania or mixed states and then as adjunctive maintenance treatment of bipolar disorder when added to lithium or valproate-treated patients. Finally an intramuscular preparation was approved for acute agitation in schizophrenia as well.[5]

Mechanism of Action

Ziprasidone is an atypical antipsychotic possessing a multireceptor-binding profile unique from that of any other antipsychotic agent in its class; the receptor-binding profile of ziprasidone may explain its performance in clinical studies and psychiatric practice. Ziprasidone, similar to most other SGAs, is a full antagonist of D2 dopamine receptors as well as 5HT2A (serotonin, 5HT, 5-hydroxytryptamine) receptors. All 5-HT2A/D2 antagonists share the same clinically ambitious goals: to quiet hyperactive dopamine neurons that mediate psychosis in the mesolimbic pathway, and to preserve physiologic function in dopamine neurons that regulate extrapyramidal movement and prolactin secretion respectively in the nigrostriatal and tuberoinfundibular pathway.

Ziprasidone has one of the highest 5-HT2A/D2 receptor affinity ratios and this has been correlated with a lower propensity for EPS and may also signify activity against the negative symptoms of schizophrenia and explain its proven antipsychotic effects and its possible antidepressant/anxiolytic effects. That said, SGAs are also a heterogeneous group of agents and beyond 5HT2A/D2 antagonism, ziprasidone acts at multiple serotonin receptors (not just 5-HT2A but also 5-HT1A partial agonism, 5-HT2C and 5-HT1D antagonism), has a unique blockade of monoamine transporters (5HT reuptake and NE reuptake) and lacks potent alpha1, muscarinic cholinergic M1 and histamine H1 antagonism. (see Table 1). Potent 5HT1A partial agonist and 5HT2C antagonist actions may predict not only potential cognitive and affective actions of ziprasidone but also potential antidepressant and anxiolytic properties, due to the theoretical increases in dopamine and norepinephrine in prefrontal cortex. However, these properties have not been proven in controlled clinical trials. The 5HT2C antagonist actions of ziprasidone may also explain its activating actions when given in subtherapeutic doses. Ziprasidone's affinity for the 5-HT2C receptor is 10 times more potent than its affinity for the D2 receptor. Thus, low doses (eg, 40 mg/day) block 5-HT2C receptors but have little D2 receptor antagonism. On average, sufficient antagonism of D2 receptors for antipsychotic efficacy does not occur with ziprasidone until the dose

Table 1. Receptors' Clinical Profile.

Receptor type	Potential clinical implications of receptor activity
D2 antagonism	Positive symptom efficacy, EPS, endocrine effects
5-HT2A antagonism	Negative symptom efficacy, reduce EPS
5-HT2C antagonism	Sleep improvement, improved cognition, weight gain; activation, agitation
5-HT1A partial agonism	Short term: increased likelihood of agitation Long-term: antidepressant and anxiolytic activity
Alpha1-adrenergic antagonism	Postural hypotension
M1-muscarinic antagonism	Anticholinergic side effects (eg, cognitive impairment)
H1-histaminergic antagonism	Sedation, weight gain

Note: Stahl SM, *J Clin Psych,* 2003; Schmidt AW, *Eur J Pharmacol*, 2001.

reaches 120–160 mg/day. The differences in relative engagement of serotonin and dopamine receptors at different doses may explain why early "activation" with ziprasidone is associated with lower doses (because blockade of 5-HT2C receptors can cause the release of dopamine in the brain) and then abates at higher doses (eg, 120 mg/day) when that effect is mitigated by D2 receptor antagonism. For this reason, ziprasidone's activating actions may actually be diminished by increasing its dose, possibly due to recruiting substantial D2 antagonism.[5–8]

As far as adverse effects are concerned, the low H1 receptor antagonism of ziprasidone predicts generally low amounts of sedation; low affinity for alpha 1-adrenoreceptors suggests that ziprasidone is less likely to induce orthostatic hypotension and sedation; no significant affinity for muscarinic cholinergic receptors predicts a low propensity for anticholinergic side effects such as dry mouth, blurred vision, constipation, tachycardia and cognitive dysfunction.[9] The mechanism whereby some atypical antipsychotics mediate weight gain and dyslipidemia is unknown, but ziprasidone is among the agents (also including aripiprazole and lurasidone) least likely to have these side effects and has the reputation for being a more "metabolically friendly" drug.[10]

Pharmacokinetic Profile, Metabolism and Dosing

Ziprasidone exhibits linear and predictable pharmacokinetics and has low potential for drug interactions; it is extensively metabolized after oral administration with only a small amount excreted unchanged in the urine (<1%) or feces (<4%), is highly protein bound (>99%) and its half life is about 6–7 hours reaching the steady-state plasma levels within 1–3 days. Age, gender, clinically significant cirrhosis (Child-Pugh A or B) and mild-to-moderate renal impairment have been shown to have no effects on the pharmacokinetic profile of ziprasidone.[11]

Ziprasidone's oral bioavailability is 60% if taken without food: a meal equal to or greater than 500 kcal, irrespective of fat content, (eg, turkey sandwich and a piece of fruit) is required for optimal and reproducible bioavailability (100%) of the administered dose.[12,13] The reason for this does not appear to be the fat content of the meal, but the bulk of the food, since keeping ziprasidone in the stomach for a longer period of time is what appears to be important as there is less absorption lower in the gastrointestinal tract. This factor of requiring food for optimal absorption is a major issue in attaining a consistent clinical effect, since the amount of drug absorbed drops significantly if a patient stabilized on dosing with food then takes a dose without food.

Ziprasidone is metabolized by 2 major pathways: aldehyde oxidase and cytochrome P450 enzymes. About two thirds of ziprasidone metabolism is mediated by aldehyde oxidase, which has no known clinically relevant inhibitors or inducers. Approximately one third of ziprasidone's metabolism is mediated via CYP450-catalyzed oxidation through CYP3A4. Neither CYP450 3A4 nor CYP450 2D6 inhibitors significantly affect ziprasidone plasma levels. Moreover, there is little potential to affect metabolism of drugs cleared by CYP450 enzymes. As ziprasidone, unlike clozapine and olanzapine, is not metabolized by CYP1A2, cigarette smoking (a CYP1A2 inducer) is unlikely to influence ziprasidone pharmacokinetics.[14]

According to the manufacturer (Pfizer) ziprasidone dosing in schizophrenia should be administered at initial oral dose of 20 mg twice a day; however, starting at 40 mg twice a day or 60 mg twice a day (this is considered the minimum effective dose)

may be better tolerated in many patients, and then titrated to 80 mg twice a day in many patients. The best efficacy in schizophrenia and bipolar disorder is at doses >120 mg/day, but patients are often inadequately dosed in clinical practice.[15]

Doses of 20–40 mg twice a day are not only too low for antipsychotic efficacy, but often activating and not well tolerated, perhaps due to potent 5HT2C antagonist properties. Paradoxically, such activation is often reduced by increasing the dose to 60–80 twice a day, perhaps due to increasing amounts of dopamine 2 receptor antagonism.

Even if some patients seem to respond better to doses >160 mg/day and up to 320 mg/day in two divided doses (ie, 80–160 mg twice a day) an increase to a dose greater than 80 mg twice daily is not generally recommended by the manufacturer as the safety of doses above 100 mg twice a daily have not been systematically evaluated in regulatory trials.[12]

Nevertheless, doses higher than 160 mg/day are often used in hospital settings and with severe patients but doses higher than 160 mg/day are considered off label as they are not approved doses by the FDA or other regulatory agencies.[16]

Rapid up-titration of ziprasidone to the optimal daily dose of 120–160 mg/day by day three of treatment is needed for optimum antipsychotic efficacy.[17] Some authors reported success with once-daily ziprasidone usually at bedtime, but only when taking consistently with food and only in individuals taking doses <160 mg/day.

For the intramuscular formulation (IM), recommended dose is 10–20 mg given as required; doses of 10 mg may be administered every 2 hours: doses of 20 mg may be administered every 4 hours; maximum daily dose is 40 mg intramuscularly; the intramuscular form should not be administered for more than 3 consecutive days. IM formulation can reduce agitation in 15 minutes. Ziprasidone intramuscular can be given short-term, both to initiate dosing with oral ziprasidone or another oral antipsychotic and to treat breakthrough agitation in patients maintained on oral antipsychotics.[12]

Clinical Trials in Acutely Ill Patients

Ziprasidone versus placebo

Ziprasidone was approved for schizophrenia on the basis of the results of four randomized, placebo controlled trials lasting 4 or 6 weeks in which fixed doses ranging from 40 to 200 mg daily were studied in 1060 inpatients with schizophrenia. Data supported the idea that the effect of ziprasidone is profoundly dose-dependent and pooled analysis of the four placebo-controlled comparator trials found optimal dosing to be 120 mg/day or more. At these doses ziprasidone is significantly more effective than placebo in improving the overall scores and had significantly more responders than placebo. At doses of less than 80 mg per day most trials have failed to find any consistent superiority over placebo. A study comparing ziprasidone 40 or 120 mg/day and placebo found 120 mg/day to be significantly more effective than placebo in improving the overall, depressive and anergia scores, and had significantly more responders than placebo.[18] Daniel et al compared 80 mg/day and 160 mg/day of ziprasidone with placebo finding ziprasidone at 160 mg/day reduces depressive symptoms in those schizophrenic patients with clinically significant depression at baseline (as defined by a score on the Montgomery-Asberg Depression Scale of >14).[19]

Ziprasidone versus SGA

To evaluate the efficacy of ziprasidone in the treatment of acute schizophrenia we have considered 4 randomized controlled trials with an SGA active comparator and two studies with conventional antipsychotic comparator (see Table 2). They are presented in chronological order. The first two RCTs compared ziprasidone with an SGA appeared in 2004. One was an 8-week double blind trial in 296 patients with acute exacerbations of schizophrenia or schizoaffective disorder of ziprasidone and risperidone. Equivalence was demonstrated in Positive and Negative Syndrome Scale (PANSS) total scores, Clinical Global Impression Severity (CGI-S) scores, PANSS negative subscale scores, Brief Psychiatric Rating Scale (BPRS) total and core item scores, and PANSS total and CGI-I responder rates. Both agents were well tolerated. Risperidone exhibited a significantly higher Movement Disorder Burden (MDB) score ($P < 0.05$) and higher incidence of prolactin elevation and clinically relevant weight gain. As the author pointed out, study dosing may have been high for some risperidone-treated patients (mean dose = 7.4 mg/day) and

Table 2. Acute-phase trials for ziprasidone.

Authors	Zipr. dose (mg/day)	Comparator	n	Duration	Efficacy of ziprasidone
Keck et al[18]	40 and 120	Placebo	139	4 w.	120 mg superior overall
Daniel et al[19]	80 and 120	Placebo	302	6 w.	Both dose superior overall, positive and negative
Goff et al[24]	4, 10, 40, and 160	Haloperidol (15 mg)	90	4 w.	160 mg equal
Addington et al[20]	80–160	Risperidone (3 to 5 mg)	296	8 w.	Equal
Simpson et al[21]	40, 60 and 80	Olanzapine (5, 10 or 15 mg)	269	6 w.	Equally effective
Zimbroff et al[22]	80–120–160	Aripiprazolo (10–15–30 mg)	253	4 w.	Both treatments were effective
Grootens et al[29]	80–120–160	Olanzapine (10–15–20 mg)	73	8 w.	Comparable reductions from baseline in the primary outcome variable PANSS total
Kahn et al[25]	40–160	Haloperidol (1–4 mg/day)	489	48 w.	Lower risks for any cause Discontinuation

low for some ziprasidone-treated patients (mean dose = 114.2 mg/day).[20]

In the second study patients were assigned to ziprasidone or olanzapine (n = 136 and 133, respectively) for 6 weeks; ziprasidone and olanzapine demonstrated comparable antipsychotic efficacy but this study limited the olanzapine dose to 15 mg/day which is below the upper limit of 20 mg/day in olanzapine's label. Differences favoring ziprasidone were observed in metabolic parameters.[21] The conclusions from these two studies are essentially equivalent efficacy when ziprasidone is compared with risperidone and olanzapine.

The third study of ziprasidone with an SGA appeared in (2007) and compared ziprasidone and aripiprazole over a 4-week course of treatment (n = 125 and 128 respectively), in acutely ill patients with a primary diagnosis of schizophrenia or schizoaffective disorder. Both treatments were effective in improving global illness severity and overall psychopathology. Both agents were well tolerated, with safety profiles that were consistent with prior reports. Somnolence occurred more frequently in the ziprasidone group than in the aripiprazole group (26.4% vs. 13.3%), whereas dyspepsia and nausea were more frequent in the aripiprazole than in the ziprasidone group. Differences were seen in the onset of drug action favoring ziprasidone.[22]

A recent paper compares the efficacy and tolerability of ziprasidone (n = 39) and olanzapine (n = 35) in patients with recent-onset schizophrenia (8). The results of this study indicate that ziprasidone and olanzapine have comparable efficacy, resulting in remission rates of around 40% within 8 weeks but differ in their side effect profile. However, there is a risk of a type II error because of the small number of patients in this study.[23]

Ziprasidone versus haloperidol

Despite the relatively small sample size, high drop-out rate, and brief duration of the trial, one RCT comparing ziprasidone (n = 73) and haloperidol (n = 15) found that ziprasidone 160 mg/day is as effective as haloperidol 15 mg/day in improving overall psychopathology and positive symptoms in patients with an acute exacerbation of schizophrenia or schizoaffective disorder. Furthermore, ziprasidone 160 mg/day seems to have a lower potential to induce EPS than haloperidol.[24]

More recently an interesting open-label randomized, 1-year clinical trial (EUFEST) comparing haloperidol versus second-generation antipsychotic drugs (ziprasidone, amisulpride, olanzapine, quetiapine) proved, as expected, that treatment discontinuation over 12 months was significantly greater in patients given a low dose of haloperidol than in those assigned to treatment with second-generation antipsychotic drugs. Furthermore the weight change from baseline was lowest with ziprasidone compared with other SGA.[17,25]

Long Term Efficacy in Chronic Schizophrenia and Maintenance Studies

Once an acute episode of schizophrenia is effectively managed, the treatment goal is to prevent recurrence or relapse. Hence, long-term studies are very relevant to actual clinical practice. Individuals must be able to stay on a medication with maintained benefits and tolerable side effects in order to sustain the benefits shown in acute studies.[26]

Ziprasidone versus placebo

In one long term maintenance study chronic patients were randomized to ziprasidone or placebo. Compared with placebo the probability of relapse at one year was lower in all three ziprasidone groups. Of the patients who remained on treatment for at last 6 months, only 9% relapsed on ziprasidone compared with 42% on placebo. All the three doses of ziprasidone were significantly superior to placebo on Positive and Negative Syndrome Scale (PANSS).[27]

Ziprasidone versus SGA

There have been several additional studies with conflicting results using active comparators. A 6-month double- blind for continuation/extension study for patients who had responded to olanzapine (n = 71) or ziprasidone (n = 57) in a previous 6-week acute comparison study continued willing patients up to 6 months. At 6 months, the mean ziprasidone dose was 135.2 mg/day and the mean olanzapine dose was 12.6 mg/day. Dose of olanzapine was lower than that commonly used in clinical practice. At 6 months, the groups did not significantly differ on efficacy outcome measures of BPRS, CGI-S, PANSS, and Calgary Depression Scale for Schizophrenia (CDSS), or on study discontinuation rates.[26]

In contrast, in a similar 28 week randomized, double-blind multi center study the olanzapine-treated patients showed significantly more improvement than the ziprasidone-treated patients.[28] In another 44-week, double-blind, continuation study comparing ziprasidone and risperidone in a long term treatment of schizophrenia, both ziprasidone and risperidone were effective as continuation and maintenance treatments in patients recovering from acute exacerbations of schizophrenia or schizoaffective disorder. Risperidone had greater adverse effects on weight gain, EPS measures, and prolactin than ziprasidone. Ziprasidone may be associated with

Table 3. Long term trial for ziprasidone.

Authors	Zipr. dose (mg/day)	Comparator	n	Duration	Efficacy of ziprasidone
Hirsch et al[34]	80	Haloperidol (5 mg)	301	28 w.	Equivalent efficacy
Harvey et al[35]	102	Haloperidol (11,5 mg)	186	196 w.	Higher efficacy
Arato et al[27]	40–80–160	Placebo	278	48 w.	Low probability of relapse than placebo
Breier et al[28]	80–160	Olanzapine (10–20 mg)	548	28 w.	Less effective than olanzapine
Simpson et al[39]	80–120–160	Olanzapine (5–10–15 mg)	269	24 w.	Comparable long term efficacy
Liebermann et al[30]	40–160	Olanz 7,5–30 Queti 200–800 Risp 1,5–6	1493	72 w.	Time of discontinuation longer in the olanzapine group
Stroup et al[31]	40–160	Olanz 7,5–30 Queti 200–800 Risp 1,5–6	444	24 w.	Risp et olanz were more effective than quet and ziprasidone
Addington et al[29]	80 to 160	Risperidone (6 to 10 mg)	139	44 w.	Similar efficacy
Potkin[36] Stahl et al[1]	80–120	Haloperidol (5–20 mg)	599	196 w.	Improvement in remission, negative symptoms and quality of life

beneficial effects on depressive symptoms associated with schizophrenia in patients undergoing long-term treatment, based on a post hoc analysis.[29]

The Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE), a large, double-blind study funded by the US National Institute of Mental Health (NIMH), compared "real-world" effectiveness of antipsychotic drugs in patients with schizophrenia at 57 sites in the United States. In the first part of the CATIE study, (Phase I) the enrolled patients were randomized to flexible doses of different antipsychotics (olanzapine, quetiapine, risperidone, ziprasidone or perphenazine—notably, aripiprazole was not included). Ziprasidone was added after the study was already initiated as an additional arm, and consequently fewer individuals were randomized to receive it (n = 185; 40–160 mg/day). The principal outcome measure was the length of time patients stayed on their assigned medication until a maximum of 18 months. The discontinuation rate for ziprasidone was 79%, compared to 64% for olanzapine, 74% for risperidone, 75% for perphenazine, and 82% for quetiapine. NNT (Number Needed to Treat) for all-cause discontinuation comparing the best-performing medication (olanzapine) with ziprasidone was 7.[30]

In the second part of the CATIE study called the Phase II "tolerability" pathway because the patients who did not tolerate their initially assigned medication, including 444 subjects who discontinued phase I for any reason, were randomly reassigned to a double-blind treatment where they could receive a different new antipsychotic (olanzapine, quetiapine, risperidone, ziprasidone). The study's main aim was to determine if there were differences between these four treatments in effectiveness measured by discontinuation for any reasons. At the end of the study results demonstrated that patients stayed on their medication significantly longer if they were receiving olanzapine (median 6.3 months) or risperidone (7.0 months), compared with quetiapine (4.0 months) or ziprasidone (2.8 months) even though ziprasidone was associated with modest improvement in weight and lipid parameters.[31] The doses of antipsychotics used in the phase I and II CATIE studies may have affected the results because the dose ranges for quetiapine, risperidone and ziprasidone may not have been optimal.[32]

Recently, in an open-label multicenter clinical trial, 293 patients were randomized to 12 weeks treatment with either ziprasidone 80–160 mg/day or with one of the comparator drugs (olanzapine, risperidone, quetiapine). Ziprasidone treatment patients showed significant improvements in the mean PANSS total score, negative symptom score and positive symptom score. Moreover, as already showed by precedent studies the authors confirm a favorable effect of ziprasidone on weight loss.[33]

Ziprasidone versus Haloperidol

One double-blind study compared ziprasidone with haloperidol in 301 stable outpatients over 28 weeks finding equivalent efficacy with modal doses. More ziprasidone treatment patients were negative symptom responders. Despite the low dose of haloperidol, ziprasidone had clear advantages in all evaluations of movement disorders. No significant laboratory or cardiovascular changes were observed.[34]

Three recent reports based upon a very long term randomized comparison of ziprasidone and haloperidol showed that in a specific subgroup of patients with schizophrenia, clinically responsive, adherent, and willing to remain in treatment for extended periods of time, functional benefits are detectable and somewhat greater in patients treated with the atypical antipsychotic medication ziprasidone than with the conventional antipsychotic medication haloperidol.[35] Also, in this same 196 week double blind study, Potkin et al report that haloperidol seems to reach a plateau of efficacy after about 40 weeks and that patients who have not achieved remission by then are unilikely to do so during the next three years. In contrast, ziprasidone in this study was associated with gradual and sustained improvement in remission rate and quality of life during the three year extension treatment period.[36] These results have been confirmed by another post hoc analysis based on Potkin study: the analysis supports the efficacy of ziprasidone for sustained negative symptom remission and adequate psychosocial functioning status in the maintenance phase.[1]

Switching

It is common in clinical practice to switch from an initial antipsychotic to another due to inefficacy or

poor tolerability. It is estimated that switching because of suboptimal antipsychotic efficacy or tolerability occurs in 30%–50% of patients a year in outpatient clinics.[37] Since ziprasidone arrived after many other antipsychotics were already on the market, many patients who receive ziprasidone will be switched from previous treatment. The most recent studies found that patients switched from olanzapine or risperidone (Simpson, 2008), olanzapine, risperidone and haloperidol (Alptekin, 2009) and aripiprazole (Kim, 2010) demonstrated significant improvement in metabolic parameters and in all movement disorder assessments. An open label but randomized six-week study in patients only partially responsive to olanzapine (n = 104), risperidone (n = 58) and a conventional agent (n = 108) studied switching to ziprasidone. In each case the switch was both well tolerated and resulted in improvement on all the symptom measures.[38]

These data support the use of ziprasidone (or aripiprazole) as a first switch treatment option in patients with metabolic abnormalities.[37,39,40] Furthermore, the study by Alptekin et al found that patients switched from haloperidol, risperidone or olanzapine to ziprasidone experienced statistically significant improvements from baseline in positive and negative symptoms, and global functioning.[41] Converting patients from one antipsychotic to another requires great care to avoid withdrawal symptoms, rebound psychosis, or aggravation of side effects.[42]

Based on the literature review, the proper strategy for "switching" to any antipsychotic, let alone ziprasidone, remains undefined. In the Alptekin study the preferred switch strategy was immediate discontinuation but in a recent study by Stip (2010) the authors provide some evidence for the potential advantages of the slow taper approach in maximizing efficacy at the early part of the switch but the differences did not remain significant at endpoint.[43]

Generally it is rarely a good idea to precipitously stop one antipsychotic and start the other at full dose; rather, it is frequently prudent to "cross-titrate" by reducing the dose of the first drug while building up the dose of the other over a few days to a few weeks. In particular, when switching from a sedating antipsychotic to a non sedating one such as ziprasidone, one can even consider adding a benzodiazepine first and then start the up-titration of the ziprasidone (nonsedating agent) while maintaining the full dose of the sedating agent. Once the ziprasidone is at a therapeutic dose, the benzodiazepine can be maintained and the sedating agent can be tapered. When the patient is stable the benzodiazepine can be tapered or stopped.[42] Given the frequency and importance of antipsychotic switching in patients with schizophrenia, there is a need for additional data to further elucidate the reasons for switching in an individual patient and the implementation of switching strategies that meet the individual needs and expectations of patients.[37]

Treatment of Resistant Schizophrenia

Unfortunately a significant proportion of patients with schizophrenia experience only partial remission (30%–40%) and monotherapy with the currently available compounds proves to be insufficient to control the illness. Almost 50% of patients receive more than one simultaneous antipsychotic agent (ie, antipsychotic polypharmacy) even if guideline-oriented pharmacotherapy of schizophrenia strongly emphasizes antipsychotic monotherapy as the gold standard in schizophrenia and polypharmacy results with low levels of evidence.[44]

Clozapine is considered the treatment of choice for patients with schizophrenia resistant to antipsychotic drug treatment. In the study by Kane et al (1988), together with subsequent studies, clozapine demonstrated superior efficacy and reduced risk of extrapyramidal symptoms (EPS) compared to conventional antipsychotics in treatment-resistant schizophrenia.[45] Approximately 20% to 35% of patients with schizophrenia who receive an adequate trial fail to respond to prescribed antipsychotics, so there is a great need for agents to treat patients with schizophrenia who fail to respond to other antipsychotics, especially if the patient cannot take clozapine or refuses clozapine.

Some studies demonstrate the efficacy of ziprasidone in treatment-resistant or treatment-intolerant patients with schizophrenia. Recently, one head-to-head trial comparing the combination of clozapine with risperidone (CR) versus clozapine with ziprasidone (CZ), differed with a marked prolactin increase

in the CR group and a statistically significant QTc elongation in the CZ group[46,47] Many other studies and anecdotal reports also report coadministration of ziprasidone with clozapine. In some cases, ziprasidone has been added to clozapine in attempts to reduce metabolic side effects as well as to optimize antipsychotic efficacy. Kuwilsky et al found that in treatment resistant schizophrenia the combinations of clozapine with ziprasidone or risperidone exhibit long-term efficacy, but the level of evidence is limited because sample size was small.[47]

The MOZART (Monitoring Oral Ziprasidone As Rescue Therapy) trial involved antipsychotic-resistant and/or intolerant patients with schizophrenia and is a double blind randomized controlled trial that evaluated ziprasidone as an alternative to clozapine in treatment-refractory schizophrenia patients. Even if the inclusion criteria of this trial used a weak definition of treatment resistance (no serum levels, short term treatment, side effects) this trial indicates that both ziprasidone and clozapine, having comparable general safety and tolerability, may be regarded as valuable options for the short-term treatment of "difficult-to-treat" schizophrenia patients with a history of multiple resistance and/or intolerance to antipsychotics. However, at the current state of art, clozapine remains the first line treatment in treatment resistant schizophrenia.

In two comparative trials in treatment-resistant patients, ziprasidone showed comparable efficacy to chlorpromazine on positive symptoms, greater efficacy against negative symptoms and well-tolerated over 1 year. Moreover, ziprasidone was better with respect to prolactin levels and weight gain.[45,48]

Special Symptoms

Cognition

The importance of cognitive impairment in schizophrenia is considerable because cognitive impairments are the main determinant of functional impairment in the illness and they may be more closely linked to functional outcome than are other symptoms.[49] Ziprasidone's interaction on 5HT2C and 5HT1A receptors may contribute to potential efficacy in cognitive as well as affective symptoms in some patients. In addition, ziprasidone appears to improve cognitive function anecdotally in some chronic schizophrenic patients.[50–52] However, one of the most recent studies looked at the short term neurocognitive effects of treatment with ziprasidone versus olanzapine in a double blind randomized controlled trial and found that cognition appeared enhanced after treatment, but was not significantly different between treatment groups, either for the verbal memory measures, or for the neurocognitive composite score. Furthermore, cognitive enhancement did not correlate with clinical improvement. This was the first study to compare the effects of a short term treatment of olanzapine versus ziprasidone on cognitive functioning in recent onset schizophrenia.[53]

Negative symptoms

Negative symptoms are an important component of schizophrenia and their severity is linked closely to social and vocational disability as well as to poor long-term functional outcomes. It is not yet clear the apparent benefit of atypical antipsychotics in treating these symptoms.[1] The improvement in negative symptoms of schizophrenia with ziprasidone was equivalent to that with amisulpride in primary endpoint (assessed using mean change from baseline in PANSS negative symptom subscale scores in the evaluable population) in a 12-week multicenter European double-blind study of 123 patients randomized to flexible doses of ziprasidone 80–160 mg/day or amisulpride 100–200 mg/day study.[54]

As already described by Hirsch et al there was a significantly higher percentage of negative symptom responders (improvement in PANSS-negative symptom subscale of ≥20% in evaluable patients at endpoint, LOCF) in the ziprasidone group compared to the haloperidol group in another study.[34]

A recent post hoc exploratory analysis of negative symptoms and psychosocial function in patients with schizophrenia confirms the superiority of ziprasidone on haloperidol in negative symptoms remission and instrumental role functioning during an extended double-blind follow-up period of up of 196 weeks.[1]

Depression

Bearing in mind the interactions at 5HT1A and 5HT1D receptors as well as effects on blocking reuptake of serotonin and norepinephrine transporters

(especially at high doses), in schizophrenic patients with clinically relevant levels of depression, ziprasidone 160 mg/day was associated with a significant improvement at 6 weeks and in another study ziprasidone 120 mg/day was associated with a significant improvement at 4 weeks.[14]

Kinon et al (2006) employed a depression scale for individuals with schizophrenia as a primary outcome measure. Authors randomized 394 patients with schizophrenia or schizoaffective disorder and moderate depressive symptoms to 24-week treatment with either ziprasidone (80, 120, or 160 mg/day) or olanzapine (10, 15, or 20 mg/day), and used the Calgary Depression Scale for Schizophrenia (CDSS) as the primary outcome measure. For up to 8 weeks, patients treated with olanzapine or ziprasidone had significant improvements on CDSS but at 24 weeks the olanzapine group was superior to the ziprasidone group on CDSS improvement.[55]

In contrast, Simpson et al compared the effects of ziprasidone, 80–160 mg/day, and olanzapine, 5–15 mg/day, and reported that patients in both treatment groups improved on the CDSS, with no significant difference between them at 6 weeks or at 6 months for those who qualified for the extension study.[21]

Intramuscular Formulation

Since ziprasidone was the first atypical antipsychotic to be approved for use in the US in both an oral and intra-muscular (IM) formulation, there are many studies that show that the IM form may be considered a possible alternative treatment as listed in Table 4. The results of these studies are all consistent with the evidence that IM ziprasidone has less risk of extrapyramidal symptoms (EPS) compared to haloperidol and does not cause sedation, confusion or ataxia created by the use of benzodiazepine. Furthermore IM ziprasidone seems to be as effective as haloperidol in agitated patients and is associated with sustained improvement in symptoms and is well tolerated.

Transition from IM to oral ziprasidone has been well tolerated, with maintenance of symptom control. Changes in QTc interval associated with ziprasidone are comparable to those seen with haloperidol. Thus, injectable ziprasidone was found to be more

Table 4. Trials with IM ziprasidone.

Authors	Zipr. dose (mg/day)	Comparator dose (mg/day)	n	Duration	Efficacy
Brook et al[72]	Ziprasidone IM 5–60 mg up to 3d. than oral 80–200 mg	Haloperidol IM 2,5–10 mg up to 3 days than oral 10–80 mg	Zipr (n = 90) Halo(n = 42)	1 w.	Reduction in BPRS total, BPRS agitation and CGI-S
Daniel et al[74]	Ziprasidone IM 2 mg	Ziprasidone IM 20 mg	Zipr 2 mg (n = 38) Zipr 20 mg (n = 41)	24 h	20 mg dose reduced symptom of acute agitation. Both doses well tolerated
Lesem et al[76]	Ziprasidone IM 2 mg	Ziprasidone IM 10 mg	Zipr 2 mg (n = 51) Zipr 10 mg (n = 63)	24 h	10 mg dose more effective in reducting agitation
Daniel et al[72]	Ziprasidone IM 5–10–20 mg up to 3 days than oral	Haloperidol IM 10–20 mg up to 3 days than oral	Zipr (n = 206) Halo(n = 100)	1 w.	Equivalent efficacy Low burden of movement disorders
Brook et al[73]	Ziprasidone IM 10–20 mg up to 3 days than oral 80–160 mg	Haloperidol IM 2,5–5 mg up to 3 days than oral 5–20 mg	Zipr (n = 429) Halo (n = 138)	6 w.	Ziprasidone offers Important efficacy and tolerability
Preval et al[77]	Ziprasidone IM 20 mg	Various doses conventional antipsychotic	Zipr (n = 110) Halo (n = 9)	2 h	Ziprasidone effective for severe agitation; may reduce time in restrain
Kohen et al[78]	Ziprasidone IM 20 mg	Haloperidol w/wth lorazepam	Zipr (n = 15) Halo (n = 20)	2 h	Simialrly effective in elderly

Abbreviations: *BPRS, brief psychiatric rating scale; CGI-S, clinical global impressions-severity scale.

efficacious at higher rather than lower doses, and to be superior to conventional short-acting medications (Table 4).

Safety

General profile

Patients with schizophrenia are approximately twice as likely to die as a result of cardiovascular disease as the rest of the population (59–63). Atypical antipsychotics can lead to cardiometabolic risk, from weight gain and obesity to hypertriglyceridemia, dyslipidemia and diabetes (59–63). The best practices are to monitor these parameters in anyone taking atypical antipsychotics. Since the pharmacologic properties of ziprasidone are different from the other SGAs it appears to have comparable efficacy compared to other atypical and conventional antipychotics with lower metabolic side effects.

The most common reported adverse events with ziprasidone are somnolence, headache, nausea, dyspepsia, dizziness, akathisia, and extrapyramidal symptoms.[56] Minor side effects such as headache and dry mouth were seen to be increased at 160 mg/day compared with 80 mg/day; serious side effects, such akathisia, agitation EPS and metabolic changes were not observed with any greater incidence.[11]

Extrapyramidal side effects

Ziprasidone, like the other second-generation antipsychotics, at therapeutic doses, does not have a high incidence of prolactin elevation nor of extrapyramidal symptoms. However, the results of a recent systematic review and meta-analysis of head to head comparisons where the primary outcome was ‘‘use of antiparkinson medication” showed that ziprasidone needed more use of antiparkinson medication than olanzapine and quetiapine. No significant differences were found with amisulpride and clozapine (although the data on the ziprasidone-clozapine comparison were very limited).[57] On the other hand, as seen in pooled data from Pfizer’s trials, ziprasidone seems to have less propensity to cause extrapyramidal side effects than haloperidol.[4] Furthermore, in the CATIE schizophrenia trial the authors compared the incidence of treatment-emergent parkinsonism, dystonia, akathisia and tardive dyskinesia associated with second-generation antipsychotics and perphenazine. Regarding ziprasidone treatments they found there were only eight cases of acute dystonia reported during the study and three were receiving ziprasidone (two discontinued). Moreover, analyses of incidence of discontinuation for parkinsonism suggested there was a lower rate of discontinuation for quetiapine and ziprasidone.[58] In this long term trial the proportion of patients with severe EPS and/or related adverse events was not significantly different between patients receiving ziprasidone and those receiving olanzapine, risperidone, quetiapine, or in phase 1 of the trial, perphenazine.[59]

In general, therefore, ziprasidone has a low incidence of EPS but some patients do have EPS on ziprasidone. Low EPS incidence enhances the tolerability of ziprasidone for many patients, and this can improve compliance compared to agents that have a higher incidence of EPS. Furthermore, EPS are associated with worsened negative and cognitive symptoms, and thus preventing EPS may itself be associated with better efficacy if the patients are able to take ziprasidone long term.[1]

Metabolic effects

In very recent head-to-head comparisons of metabolic side effects of second-generation antipsychotics (amisulpride, aripiprazole, clozapine, olanzapine, quetiapine, risperidone, sertindole, ziprasidone, zotepine) in randomized controlled trials, weight change was chosen as the primary outcome, glucose and cholesterol changes as secondary outcomes. These studies found that ziprasidone (together with aripiprazole) was associated with lower weight gain, less elevation of glucose, and with the least effects on the lipid status).[30,60]

The first phase of CATIE trials also found that those receiving ziprasidone lost a mean of 0.1 kg/month compared with weight gain for the other SGAs. In the second phase of the same studies 42% of the patients treated with ziprasidone lost over the 7% of their body weight.[26] Therefore when ziprasidone is given to patients with obesity and dyslipidemia associated with prior treatment with another atypical antipsychotic, many experience weight loss and decrease in fasting triglycerides.[13] One of the correlates of weight gain can be changes in lipid levels and various studies of short duration and longer duration, including

CATIE phases 1 and 2a duration have documented improvement in significant reductions in nonfasting total plasma cholesterol and triglycerides in patients treated with ziprasidone.[61–63] Since the CATIE trial did not include either aripiprazole or the newly approved lurasidone, it is not possible to make comparisons of ziprasidone with other agents that may also have metabolically friendly profiles.

Patients with schizophrenia and other psychotic disorders exhibit an elevated risk for developing glucose intolerance or diabetes mellitus.[59–61,63] Although antipsychotics as a class are all labeled as having risk for developing weight gain, dyslipidemia, glucose intolerance or diabetes mellitus, this risk seems to be lower for ziprasidone and aripiprazole and possibly for lurasidone compared to other SGAs.[61,64] Since metabolic side effects are especially important as they have significant long-term consequences, such as cardiovascular disease (CVD) patients need to be informed about the differences in efficacy and side effects of the different SGAs.

Cardiac

The most common worry about ziprasidone is the fear of QTc prolongation because lengthening of the QTc interval is associated with arhythmias and torsade de pointes (TdP), a serious and potentially fatal cardiac dysrhythmia with the risk of sudden cardiac death. In general, patients treated with antipsychotic drugs have a longer QTc interval than do controls., Moreover, all antipsychotic drugs can prolong the QT interval and for this reason, since patients are rarely drug-free at baseline for most clinical trials, the true extent of QT prolongation from the drug under study can be easily underestimated if the baseline medication also prolongs the QT interval.[65] Ziprasidone typically lengthens the QTc interval by around 10 ms greater than other atypical antipsychotics.[41]

Special studies were conducted by Pfizer Inc. who compared high dose of intramuscular ziprasidone (20 mg then 30 mg) with high dose IM haloperidol (7,5 mg then 10 mg); the effect of intramuscular ziprasidone on QTc prolongation was less than the prolongation seen with intramuscular haloperidol. Pfizer reported that ziprasidone's effect on the QTc interval did not seem very sensitive to oral dosage increase above 80 mg/day. Pfizer also reported that the number of sudden unexpected deaths in patients who had received oral ziprasidone is not significantly different from the findings with the placebo or active-drug comparator.[26] The concerns about dangerous QTc prolongation appear to be unjustified because ziprasidone does not cause dose dependent QTc prolongation, and few if any drugs have the potential to increase ziprasidone's plasma levels.[66–69]

It is not still clear if monitoring routinely the ECG parameters in patients treat with antipsychotics will decrease morbidity and mortality. Ziprasidone is contraindicated in patients with a known history of QTc prolongation, recent acute myocardial infarction and uncompensated heart failure and to be avoided if the patient is taking agents capable of significantly prolonging QTc interval (pimozide, thioridazine, selected antiarrhythmics, moxifloxacine and sparfloxacine) but EKGs are generally not recommended.[12] All that said, ziprasidone seems to be a very suitable first-line antipsychotic treatment for individuals with no known history of cardiac problems related to arrhythmia or QTc interval and without the need for EKG monitoring.[49]

Efficacy

Both short and long-term controlled clinical trials or in switch studies involving ziprasidone demonstrated improvement in positive and negative symptoms, cognitive domains, acute mania and the affective symptoms of schizophrenia or schizoaffective disorder. Ziprasidone's efficacy in clinical trials shows consistency with its unique pharmacological features. Ziprasidone is significantly effective in reducing symptoms in patients with acute schizophrenia but it is also effective in stable patients over the long term and for maintenance treatment.[5] Interrelated improvements in cognitive and affective symptoms have been correlated with enhanced social engagement in patients switched to ziprasidone from other antipsychotic agents because of side effects or inadequate response. Furthermore intramuscular ziprasidone may be a superior choice to conventional antipsychotics as an intramuscular treatment.

Moreover, clinical trials data indicate that ziprasidone has a lower liability for EPS than haloperidol,

a lower overall movement disorder burden and incidence of prolactin elevation than risperidone, significantly less weight gain, and more benign effects on lipid profile and glucose metabolism than several other SGAs.[63]

Patient Preference

Patients prefer antipsychotics with a low side effect burden, and sometimes value side effects over efficacy for psychosis. Most clinicians, however, prioritize efficacy for psychosis, and try to find the most efficacious agent that a patient can tolerate. This sometimes creates a lack of therapeutic alignment between patient and prescriber.

Ziprasidone is preferred by both patients and clinicians who are concerned about weight gain and dyslipidemia since this agent is probably the one with the lowest incidence of both. Ziprasidone is also preferred by patients who wish to avoid sedation as this agent is generally not sedating in many patients. However, the hassle of taking the drug twice a day plus having to take it with food is a problem for some patients, particularly those who may not have access to regular meals. Skipping a dose or taking a dose without food can result in highly variable drug levels, and thus fluctuating efficacy in some patients.

Thus, patients who are highly motivated and well organized and are higher functioning are perhaps those who prefer ziprasidone. Also, patients with current diabetes who must take an antipsychotic may prefer ziprasidone.

Place in Therapy

Although ziprasidone has the same relative efficacy in most head to head studies of schizophrenic patients compared to any other antipsychotic, it is often not used as first line therapy in first episode psychosis or in recurrent psychosis. Instead, ziprasidone is often seen as a switch agent for patients who fail to tolerate other antipsychotics, especially those associated with weight gain, dyslipidemia, or sedation. The overall use of ziprasidone is lower than several other antipsychotics, perhaps because of the perception that efficacy is not as robust in clinical practice as some other agents, and perhaps because of the perception that its QTc prolongation is dangerous. In reality, ziprasidone's efficacy can be made more consistent if dosed adequately, and if taken with food, and sometimes at doses higher than those usually recommended (>160 mg/day) and perhaps only once a day with food rather than twice a day. The QTc prolongation is now generally not considered to be dangerous and the "metabolically friendly" profile of low weight gain and dyslipidemia generally more important in defining ziprasidone's safety profile. Ziprasidone has the longest term study in schizophrenia of any SGA, which suggests that for those patients who initially respond to it and tolerate it, that remission of symptoms and improvement specifically of negative symptoms may be robust over a few years of treatment, and even better than the conventional antipsychotic haloperidol.

Since there is a large economic burden of schizophrenia due to cost associated with hospitalization, life long treatment and loss of productivity, in the present economic climate, judgment as to what is better will include consideration of financial costs of this illness.[70] Many FGAs are less expensive than SGAs, although several SGAs are now generic or will soon become so, with a corresponding reduction in medication cost. For patients who do not get adequate therapeutic benefit from a typical antipsychotic or a generic atypical antipsychotic or who cannot tolerate them, it is often proper to use a more expensive SGA. According to a recent study by McIntyre et al evaluating the projected health and economic impact of second-generation antipsychotic agents used for the treatment of patients with schizophrenia in Canada, ziprasidone treatment for example possesses cost and therapeutic advantages compared with olanzapine and quetiapine.[71]

Conclusion

The ultimate goal of treatment for schizophrenia is returning an individual to a productive life, ideally including independent living, social integration and participation in work or education. A number of agents are now available, providing new treatment options and producing heightened optimism for improved clinical outcomes. Judging by its receptor profile, ziprasidone offers a spectrum of activities predictive of efficacy and tolerability. Compared with other first-line atypical antipsychotics, ziprasidone has

more diverse serotonergic effects and a much lower burden of alpha 1-adrenergic, H1 and M1 antagonist activities. The clinical benefits predicted by this receptor-binding profile-good control of positive and negative symptoms, low incidence of EPS, weight gain and postural hypotension- have been observed in randomized clinical trials.[5]

Since ziprasidone with all the other atypical antipsychotics drugs are not miracle drugs and often fail to provide the early and robust responses that clinicians seek when faced with patients having severe and disabling symptoms, better agents for schizophrenia are still required.[52] The main advantage of ziprasidone is its low propensity to induce weight gain and associated metabolic problems such as cholesterol increase, which has been demonstrated, compared with olanzapine, quetiapine and risperidone.[3]

Determination of whether drugs like ziprasidone, each with its own unique receptor binding profile, can adequately address the range of symptoms characteristic of schizophrenia, and thereby help patients re-engage in meaningful social life, and especially to determine which unique individuals are best matched to any specific antipsychotic drug such as ziprasidone, requires both the scrutiny of controlled trials and the accumulated experience of individual clinicians.

Disclosure

This manuscript has been read and approved by all authors. This paper is unique and is not under consideration by any other publication and has not been published elsewhere. The authors confirm that they have permission to reproduce any copyrighted material. Stephen M. Stahl, is an adjunct professor of psychiatry at the University of California, San Diego School of Medicine and an honorary visiting senior fellow at the University of Cambridge, UK. Over the past 12 months (January 2009–January 2010) Dr. Stahl has served as a Consultant to Allergan, Astra Zeneca, BioMarin, BioVail, Boehringer Ingelheim, Bristol Myers-Squibb, Cenerex, Covance, Cypress Bioscience, Dainippon Sumitomo, Eisai, Eli Lilly, Forest, GlaxoSmith Kline, Labopharm, Lundbeck, Marinus, Meda Corp, Meiji, Merck, Novartis, Pfizer, Pfizer Canada, Pierre Fabre, PamLab, Prexa Pharmaceuticals, Propagate Pharma, Royalty Pharma, Sanofi, Schering Plough Corporation, Shire, SK Corporation, Soffinova, Solvay, Vanda and Wyeth.

He has served on speakers bureaus for Pfizer Inc; Wyeth Pharmaceuticals and Schering Plough Corporation and has received research and/or grant support from Astra Zeneca, Boehringer Ingelheim, Bristol Myers-Squibb, Cephalon, Dainippon, Eli Lilly, Forest, Lundbeck, Novartis, PamLabs, Pfizer, Pfizer Canada, Pharmasquire, Sanofi Aventis, Schering Plough, Shire and Wyeth.

Chiara Mattei and Maria Paola Rapagnani have no conflicts of interests.

References

1. Stahl SM, et al. A post hoc analysis of negative symptoms and psychosocial function in patients with schizophrenia: a 40-week randomized, double-blind study of ziprasidone versus haloperidol followed by a 3-year double-blind extension trial. *J Clin Psychopharmacol*. 2010;30(4):425–30.
2. Stone JM, et al. Review: the biological basis of antipsychotic response in schizophrenia. *J Psychopharmacol*. 2010;24(7):953–64.
3. Komossa K, et al. Ziprasidone versus other atypical antipsychotics for schizophrenia. *Cochrane Database Syst Rev*. 2009;4:CD006627.
4. Geodon Capsules and Injections for Intramuscular Use. USPI. LAB-0273-16.0. Revised 2009 Nov. Available from: http://media.pfizer.com/files/products/uspi_geodon.pdf.
5. Stahl SM, Shayegan DK. The psychopharmacology of ziprasidone: receptor-binding properties and real-world psychiatric practice. *J Clin Psychiatry*. 2003;64 Suppl 19:6–12.
6. HIGHLIGHTS A. A roadmap to key pharmacologic principles in using antipsychotics: application in clinical practice. *The Journal of Clinical Psychiatry* and p.-. CME ACTIVITY.
7. Weiden PJ. Switching in the era of atypical antipsychotics. An updated review. *Postgrad Med*. 2006;Spec No:27–44.
8. Stahl SM. *Stahl's Illustrated Antipsychotics*; 2009 Cambridge Univ Press, New York:168.
9. Stahl SM. Neurotransmission of cognition, part 2. Selective NRIs are smart drugs: exploiting regionally selective actions on both dopamine and norepinephrine to enhance cognition. *J Clin Psychiatry*. 2003;64(2):110–1.
10. Schwartz TL.e.a., *Ziprasidone in the Treatment of Bipolar Disorder*. 2010.
11. Ballas C, et al. Ziprasidone: a novel psychotropic with unique properties. *Expert Rev Neurother*. 2004;4(2):179–86.
12. Stahl S. *Stahl's Essential Psychopharmacology: The Prescriber's Guide.* 2009 Cambridge Univ Press, New york:645.
13. Gandelman K, et al. The impact of calories and fat content of meals on oral ziprasidone absorption: a randomized, open-label, crossover trial. *J Clin Psychiatry*. 2009;70(1):58–62.
14. Rajiv Tandon CB. Therapeutic benefits of ziprasidone: an update of clinical trials experience. In: *Advances in Preclinical and Clinical Psychiatry*, Escailier M, editor. Excerpta Medica; 2000.
15. Schwartz TL, Stahl S. Treatment strategies for dosing the second generation antipsychotics. *CNS Neuroscience and Therapeutics*. 2010, in press.
16. Citrome L, Jaffe A, Levine J. How dosing of ziprasidone in a state hospital system differs from product labeling. *J Clin Psychiatry*. 2009;70(7):975–82.
17. Fagiolini A, et al. Strategies for successful clinical management of schizophrenia with ziprasidone. *Expert Opin Pharmacother*. 2010;11(13):2199–220.
18. Keck P Jr, et al. Ziprasidone 40 and 120 mg/day in the acute exacerbation of schizophrenia and schizoaffective disorder: a 4-week placebo-controlled trial. *Psychopharmacology (Berl)*. 1998;140(2):173–84.
19. Daniel DG, et al. Ziprasidone 80 mg/day and 160 mg/day in the acute exacerbation of schizophrenia and schizoaffective disorder: a 6-week placebo-controlled trial. Ziprasidone Study Group. *Neuropsychopharmacology*. 1999;20(5):491–505.

20. Addington DE, et al. Efficacy and tolerability of ziprasidone versus risperidone in patients with acute exacerbation of schizophrenia or schizoaffective disorder: an 8-week, double-blind, multicenter trial. *J Clin Psychiatry*. 2004;65(12):1624–33.
21. Simpson GM, et al. Randomized, controlled, double-blind multicenter comparison of the efficacy and tolerability of ziprasidone and olanzapine in acutely ill inpatients with schizophrenia or schizoaffective disorder. *Am J Psychiatry*. 2004;161(10):1837–47.
22. Zimbroff D, et al. Comparison of ziprasidone and aripiprazole in acutely ill patients with schizophrenia or schizoaffective disorder: a randomized, double-blind, 4-week study. *Int Clin Psychopharmacol*. 2007;22(6): 363–70.
23. Grootens KP, et al. Ziprasidone vs. olanzapine in recent-onset schizophrenia and schizoaffective disorder: results of an 8-week double-blind randomized controlled trial. *Schizophr Bull*. 2009.
24. Goff DC, et al. An exploratory haloperidol-controlled dose-finding study of ziprasidone in hospitalized patients with schizophrenia or schizoaffective disorder. *J Clin Psychopharmacol*. 1998;18(4):296–304.
25. Kahn RS, et al. Effectiveness of antipsychotic drugs in first-episode schizophrenia and schizophreniform disorder: an open randomised clinical trial. *Lancet*. 2008;371(9618):1085–97.
26. Greenberg WM, Citrome L. Ziprasidone for schizophrenia and bipolar disorder: a review of the clinical trials. *CNS Drug Rev*. 2007;13(2):137–77.
27. Arato M, O'Connor R, Meltzer HY. 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*. 2002;17(5):207–15.
28. Breier A, et al. Olanzapine versus ziprasidone: results of a 28-week double-blind study in patients with schizophrenia. *Am J Psychiatry*. 2005;162(10): 1879–87.
29. Addington DE, et al. A comparison of ziprasidone and risperidone in the long-term treatment of schizophrenia: a 44-week, double-blind, continuation study. *Can J Psychiatry*. 2009;54(1):46–54.
30. Lieberman JA, et al. Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. *N Engl J Med*. 2005;353(12):1209–23.
31. Stroup TS, et al. Effectiveness of olanzapine, quetiapine, risperidone, and ziprasidone in patients with chronic schizophrenia following discontinuation of a previous atypical antipsychotic. *Am J Psychiatry*. 2006;163(4): 611–22.
32. Citrome L, et al. Impact of real-world ziprasidone dosing on treatment discontinuation rates in patients with schizophrenia or bipolar disorder. *Schizophr Res*. 2009;115(2–3):115–20.
33. Lublin H, et al. Ziprasidone versus olanzapine, risperidone or quetiapine in patients with chronic schizophrenia: a 12-week open-label, multicentre clinical trial. *World J Biol Psychiatry*. 2009;10(4 Pt 3):710–8.
34. Hirsch SR, et al. A 28-week comparison of ziprasidone and haloperidol in outpatients with stable schizophrenia. *J Clin Psychiatry*. 2002;63(6): 516–23.
35. Harvey PD, et al. Reduction of functional disability with atypical antipsychotic treatment: a randomized long term comparison of ziprasidone and haloperidol. *Schizophr Res*. 2009;115(1):24–9.
36. Potkin SG, et al. Remission in schizophrenia: 196-week, double-blind treatment with ziprasidone vs. haloperidol. *Int J Neuropsychopharmacol*. 2009;12(9):1233–48.
37. Alptekin K, et al. Efficacy and tolerability of switching to ziprasidone from olanzapine, risperidone or haloperidol: an international, multicenter study. *Int Clin Psychopharmacol*. 2009;24(5):229–38.
38. Weiden PJ, et al. Effectiveness of switching to ziprasidone for stable but symptomatic outpatients with schizophrenia. *J Clin Psychiatry*. 2003;64(5):580–8.
39. Simpson GM, et al. Long-term improvement in efficacy and safety after switching to ziprasidone in stable outpatients with schizophrenia. *CNS Spectr*. 2008;13(10):898–905.
40. Kim SW, et al. Effectiveness of switching from aripiprazole to ziprasidone in patients with schizophrenia. *Clin Neuropharmacol*. 2010;33(3):121–5.
41. Schwartz TLS, Pappadopulos MS, Karayal E, Ziprasidone ON. *In the Treatment of Bipolar Disorders*. 2010, in press.
42. Stahl SM. *Stahl's essential psychopharmacology: neuroscientific basis and practical ....* 2008:1117. 3rd edition, Cambridge University Press, New York.
43. Stip E, et al. Switching from conventional antipsychotics to ziprasidone: a randomized, open-label comparison of regimen strategies. *Prog Neuropsychopharmacol Biol Psychiatry*. 2010;34(6):997–1000.
44. Zink M, Englisch S, Meyer-Lindenberg A. Polypharmacy in schizophrenia. *Curr Opin Psychiatry*. 2010;23(2):103–11.
45. Kane JM, et al. Efficacy and tolerability of ziprasidone in patients with treatment-resistant schizophrenia. *Int Clin Psychopharmacol*. 2006;21(1): 21–8.
46. Zink M, et al. Efficacy and tolerability of ziprasidone versus risperidone as augmentation in patients partially responsive to clozapine: a randomised controlled clinical trial. *J Psychopharmacol*. 2009;23(3):305–14.
47. Kuwilsky A, et al. Long-term efficacy and tolerability of clozapine combined with ziprasidone or risperidone. *Pharmacopsychiatry*. 2010.
48. Loebel AD, et al. Ziprasidone in treatment-resistant schizophrenia: a 52-week, open-label continuation study. *J Clin Psychiatry.* 2007;68(9): 1333–8.
49. Harvey PD, Bowie CR. Ziprasidone: efficacy, tolerability, and emerging data on wide-ranging effectiveness. *Expert Opin Pharmacother*. 2005;6(2): 337–46.
50. Harvey PD, et al. Improvement in cognitive function following a switch to ziprasidone from conventional antipsychotics, olanzapine, or risperidone in outpatients with schizophrenia. *Schizophr Res*. 2004;66(2–3):101–13.
51. Gibel A, Ritsner MS. Neurocognitive effects of ziprasidone and related factors in patients with chronic schizophrenia undergoing usual care: a 12-month, open-label, flexible-dose, naturalistic observational trial. *Clin Neuropharmacol*. 2008;31(4):204–20.
52. Keefe RS, Cognitive deficits in patients with schizophrenia: effects and treatment. *J Clin Psychiatry*. 2007;68 Suppl 14:8–13.
53. Van Veelen NM, et al. Short term neurocognitive effects of treatment with ziprasidone and olanzapine in recent onset schizophrenia. *Schizophr Res*. 2010;120(1–3):191–8.
54. Olie JP, et al. Ziprasidone and amisulpride effectively treat negative symptoms of schizophrenia: results of a 12-week, double-blind study. *Int Clin Psychopharmacol*. 2006;21(3):143–51.
55. Kinon BJ, et al. A 24-week randomized study of olanzapine versus ziprasidone in the treatment of schizophrenia or schizoaffective disorder in patients with prominent depressive symptoms. *J Clin Psychopharmacol*. 2006;26(2):157–62.
56. Miceli JJ, et al. Effects of high-dose ziprasidone and haloperidol on the QTc interval after intramuscular administration: a randomized, single-blind, parallel-group study in patients with schizophrenia or schizoaffective disorder. *Clin Ther*. 2010;32(3):472–91.
57. Citrome L, et al. Effect of ziprasidone dose on all-cause discontinuation rates in acute schizophrenia and schizoaffective disorder: a post-hoc analysis of 4 fixed-dose randomized clinical trials. *Schizophr Res*. 2009;111(1–3): 39–45.
58. Miller DD, et al. Extrapyramidal side-effects of antipsychotics in a randomised trial. *Br J Psychiatry*. 2008;193(4):279–88.
59. Swainston Harrison T, Scott LJ. Ziprasidone: a review of its use in schizophrenia and schizoaffective disorder. *CNS Drugs*. 2006;20(12): 1027–52.
60. Rummel-Kluge C, et al. Second-generation antipsychotic drugs and extrapyramidal side effects: a systematic review and meta-analysis of head-to-head comparisons. *Schizophr Bull*. 2010.
61. Meyer JM, et al. The Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) Schizophrenia Trial: clinical comparison of subgroups with and without the metabolic syndrome. *Schizophr Res*. 2005; 80(1):9–18.
62. Weiden PJ, et al. Long-term changes in weight and plasma lipids during maintenance treatment with ziprasidone. *Neuropsychopharmacology*. 2008;33(5):985–94.
63. McEvoy JP, et al. Prevalence of the metabolic syndrome in patients with schizophrenia: baseline results from the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) schizophrenia trial and comparison with national estimates from NHANES III. *Schizophr Res*. 2005;80(1):19–32.

64. Stahl SM, Mignon L, Meyer JM. *Which comes first: atypical antipsychotic treatment or cardiometabolic risk? Acta Psychiatr Scand*. 2009;119(3): 171–9.
65. Meyer MJ, Nasrallah HA. *Medical Illness and Schizophrenia.* 2009:455.
66. 1. Pfizer, C.I., Zeldox product monograph. 2008.
67. 1. Pfizer, F.P.D.A.C.B.d.f.Z.c.z.H.h.w.f.g.o.d.a.b.b.a.p.
68. Taylor D. Ziprasidone in the management of schizophrenia : the QT interval issue in context. *CNS Drugs*. 2003;17(6):423–30.
69. Levy WO, Robichaux-Keene NR, Nunez C. No significant QTc interval changes with high-dose ziprasidone: a case series. *J Psychiatr Pract*. 2004; 10(4):227–32.
70. Rice DP. The economic impact of schizophrenia. *J Clin Psychiatry*. 1999;60 Suppl 1:4–6; discussion 28–30.
71. McIntyre RS, et al. Comparison of the metabolic and economic consequences of long-term treatment of schizophrenia using ziprasidone, olanzapine, quetiapine and risperidone in Canada: a cost-effectiveness analysis. *J Eval Clin Pract*. 2010;16(4):744–55.
72. Brook S, Lucey JV, Gunn KP, Ziprasidone IM Study Group (2000) Intramuscular ziprasidone compared with intramuscular haloperidol in the treatment of acute psychosis. *J Clin Psychiatr*y 61:933–941.
73. Brook S, Walden J, Benattia I, Siu CO, Romano SJ (2005) Ziprasidone and haloperidol in the treatment of acute exacerbation of schizophrenia and schizoaffective disorder: Comparison of intramuscular and oral formulations in a 6-week, randomized, blinded-assessment study. *Psychopharmacology* 178:514– 523.
74. Daniel DG, Potkin SG, Reeves KR Swift RH, Harrigan EP (2001) Intramuscular (IM) ziprasidone 20 mg is effective in reducing acute agitation associated with psychosis: A double-blind, randomized trial. *Psychopharmacology* 155:128–134.
75. Daniel DG, Zimbroff DL, Swift RH, Harrigan EP (2004) The tolerability of intramuscular ziprasidone and haloperidol treatment and the transition to oral therapy. *Int Clin Psychopharmacol* 19:9–15.
76. Lesem MD, Zajecka JM, Swift RH, Reeves KR, Harrigan EP (2001) Intramuscular ziprasidone, 2 mg versus 10 mg, in the short-term management of agitated psychotic patients. *J Clin Psychiatry* 62:12–18.
77. Preval H, Klotz SG, Southard R, Francis A (2005) Rapid-acting IM ziprasidone in a psychiatric emergency service: A naturalistic study. *Gen Hosp Psychiatry* 27:140–144.
78. Kohen I, Preval H, Southard R,Francis A. Naturalistic study of intramuscular ziprasidone versus conventional agents in agitated elderly patients: retrospective findings from a psychiatric emergency service. *Am J Geriatr Pharmacother*. 2005;3(4):240–245.

Publish with Libertas Academica and every scientist working in your field can read your article

"I would like to say that this is the most author-friendly editing process I have experienced in over 150 publications. Thank you most sincerely."

"The communication between your staff and me has been terrific. Whenever progress is made with the manuscript, I receive notice. Quite honestly, I've never had such complete communication with a journal."

"LA is different, and hopefully represents a kind of scientific publication machinery that removes the hurdles from free flow of scientific thought."

Your paper will be:

- Available to your entire community free of charge
- Fairly and quickly peer reviewed
- Yours! You retain copyright

http://www.la-press.com