Ziprasidone in the Treatment of Affective Disorders: A Review

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Ziprasidone was the fifth atypical antipsychotic approved by Food and Drug Administration (FDA) for use in bipolar mania and mixed episodes. This atypical antipsychotic has a unique profile, as it acts primarily through serotonergic and dopaminergic receptor antagonism, but also exerts effects as an inhibitor of norepinephrine reuptake. Moreover, one of the advantages of ziprasidone is its safety profile as it is not associated with clinically significant metabolic side effects and little or no effect on prolactin level or anticholinergic side effects. Most of the studies evaluating ziprasidone's efficacy and safety are short-term double-blind, placebo-controlled studies in acute mania and mixed episodes. In two of them, ziprasidone was associated to significant improvement in the primary measures assessed. However, an add-on study, lithium plus ziprasidone showed similar results than lithium monotherapy, although there was a significant advantage for the combination within the first week. In a more recent trial, ziprasidone was compared with placebo and haloperidol as monotherapies, again beating placebo. In that trial, ziprasidone appeared to be safer and better tolerated, although less likely efficacious than haloperidol. Particularly, subjects treated with ziprasidone were less likely to switch to depression. Despite the well-studied efficacy of ziprasidone in the first weeks of treatment, there are no controlled trials that evaluate the role and efficacy of ziprasidone in long-term treatment of bipolar disorder (BD). Overall, in the open-label extension studies, there was a global improvement at all visits compared with baseline scores. Furthermore, ziprasidone appears to offer some antidepressant effect in patients with major depressive episode and resistant to treatment, as demonstrated in add-on open-label studies with ziprasidone plus selective serotonin reuptake inhibitor (SSRI).

Introduction

Atypical antipsychotics are commonly used in the treatment of bipolar disorder (BD) [1,2]. In particular, for the treatment of acute mania, most of the guidelines recommend monotherapy with a mood stabilizer or an atypical antipsychotic drug as first-line treatment [3,4]. Ziprasidone was the fifth atypical antipsychotic that became available in 2001 for use in the acute treatment for schizophrenia and schizoaffective disorder in the United States. In August 2004, ziprasidone received additional Food and Drug Administration (FDA) approval for use in bipolar mania, including acute manic and mixed episodes. It acts primarily through serotonergic and dopaminergic receptor antagonism, and exerts effects

as an inhibitor of norepinephrine reuptake. Data from placebo-controlled trials demonstrated that ziprasidone provides significant improvement in both manic and depressive symptoms, with limited motor side effects. In addition, ziprasidone has important advantages due to its safety profile as it is not associated with clinically significant metabolic side effects and little or no effect on prolactin level or anticholinergic side effects [5–7].

Introduction to the Compound

Chemistry

Ziprasidone (5-[2-[4-(1,2-benzisothiazol-3-yl)piperazin-1-yl]ethyl]-6-chloroindolin-2-one hydrochloride

Figure 1 Chemical structure of ziprasidone.

hydrate) is a benzisothiazolyl piperazine compound that was developed from the chemically related antipsychotic tiospirone (see Fig. 1). Capsules contain a monohydrochloride, monohydrate salt of ziprasidone, while the injectable formulation is a lyophilized form of ziprasidone mesylate trihydrate.

Pharmacodynamics

Ziprasidone pharmacological profile is unique characterized by high-affinity antagonism 5HT_{2A}, 5HT_{2C}, 5HT_{1D}, and D₂ receptors. Ziprasidone affinity for 5-HT_{2A} receptors is approximately 1000 fold higher than for D₂ receptors, which has been associated with a lower risk of extrapyramidal symptoms (EPS) [8]. Specifically, 5-HT_{2A} receptor antagonism results in subsequent downregulation of these receptors, which is believed to mediate antidepressant activity. Ziprasidone has two other interesting pharmacologic characteristics. First, it is an agonist at the 5-HT_{1A} receptor, which is believed to occur pre- and postsynaptically [9]. This agonist activity on 5-HT_{1A} confer ziprasidone affective and anxiolytic properties as well as might improve hostility and cognition. Ziprasidone possesses modest activity at α_1 adrenergic and histamine H₁ receptors, which are associated with its modest orthostatic effects, sedation, and weight gain, respectively. Finally, ziprasidone has low activity on muscarinic1 receptors which provides a low incidence of anticholinergic side effects [9,10].

Pharmacokinetics and Metabolism

Orally administrated ziprasidone absorption is limited, and the duration and extent of absorption is greatest when it was administered after eating, which is a relevant issue in clinical practice. The mean $t_{1/2}$ for ziprasidone is 6.6 h (range: 4–7 h) being the time to steady-state plasma concentration is approximately 1–2 days. At steady-state, and at doses within the therapeutic range (40–160 mg/day), ziprasidone exhibits dose proportional,

linear changes in exposure. It is highly protein bound (>99%), but there are no protein-binding displacement interactions reported with other drugs as warfarin or propranolol. In humans, a small proportion of the ziprasidone is eliminated unchanged in the urine and feces [9]. Ziprasidone is metabolized into at least 12 different metabolites: S-methyl-dihydroziprasidone (M9) is the major metabolite formatted through the noncytochrome P450 enzyme aldehyde oxidase. It is considered to potentially contribute to the clinical activity of drug. Three other metabolites are generated through CYP3A4 and the known inhibitors of the CYP3A4 isoenzyme (ketoconazole) appear in increasing ziprasidone concentrations. On the other hand, carbamazepine, a known inducer of CYP3A4 increased ziprasidone clearance by 35%, which is also relevant given the potential use of this combination in clinical practice. Older patients and patients with hepatic dysfunction have experienced higher mean serum ziprasidone concentration than younger subjects and patients without liver impairment, respectively [7].

The bioavailability of intramuscular (IM) ziprasidone is 100%. Peak plasma concentrations of ziprasidone 20 mg IM are comparable with those achieved with 80 mg oral given twice daily. These plasma concentrations occur 1 h postdose or earlier with single doses and the half-life elimination is 2.5 h. IM administration of ziprasidone is not expected to affect metabolic pathways [7]. However, ziprasidone IM is approved by the FDA for the treatment of acute agitation in patients with schizophrenia but not in patients with BD up to date [11].

Clinical Efficacy

Adult Population

Ziprasidone in Acute Mania and Mixed Episodes

(a) Short-term, randomized controlled trials: Monotherapy. There are three main know short-term, randomized controlled trials, to evaluate efficacy and safety of ziprasidone monotherapy in acute mania and mixed episodes. Keck et al. [6] conducted the first double-blind, randomized placebo controlled trial during 3-weeks. Bipolar I patients in a current manic or mixed episode were randomized to receive ziprasidone (80–160 mg/day, $n = 140$) or placebo ($n = 70$) following 1-week washout period. Primary efficacy analyses were assessed from baseline to endpoint in mean Mania Rating Scale (MRS) derived from the Schedule for Affective Disorders and Schizophrenia, change version (SADS-C), and Clinical Global Impression severity scale (CGI-S). The median duration of treatment for patients assigned to receive ziprasidone was 20 days. Of the 140 patients, 87 (62%) completed ≥ 14 days in randomized treatment. The

median duration of treatment was 15 days for placebo-treated patients, of whom 36 of 70 (51%) completed ≥ 14 days. Ziprasidone-treated patients demonstrated a significant reduction in mean score of 12.4 ± 12.0 points in the 11-item MRS whereas placebo-treated patients experienced a decrease of 7.8 ± 12.9 ($F = 9.20$, $df = 1$, 164 , $P < 0.005$) from baseline to endpoint. Patients in the manic and mixed subsets had comparable improvement in MRS scores at endpoint (mania, mean: -13.1 , SD: 12.8 , and mixed, mean: -11.2 , SD: 10.6 , respectively). A significant difference between the ziprasidone and placebo groups in mean change in the MRS was evident by the second day of treatment and was maintained throughout the 21-day trial.

The mean ziprasidone dose was 81.3 ± 24.5 mg on day 1, 147.1 ± 30.2 mg on day 2, 139.1 ± 29.4 mg/day during days 8–14, and 130.1 ± 34.5 mg/day during days 15–21. Significantly more ziprasidone-treated patients than placebo-treated subjects were classified as responders (50% vs. 35%; $P < 0.005$). At endpoint, the mean CGI-S scale scores were reduced by 1.3 ± 1.5 for ziprasidone group and by 0.9 ± 1.6 for placebo group ($P < 0.01$). At the CGI-improvement (CGI-I) scale scores were 2.9 ± 1.4 for the ziprasidone group and 3.5 ± 1.7 ($P < 0.001$) for placebo group. Ziprasidone-treated patients showed lower scores on the PANSS than placebo ($P < 0.001$). The mean global assessment of functioning (GAF) scores were higher for the ziprasidone than placebo group (15.3 ± 18.7 vs. 8.3 ± 18.7 , $P < 0.005$) at endpoint. A significant between-group difference in improvement in GAF scores was evident by day 7. In this study, the ziprasidone and placebo-treated patients displayed a comparable requirement for supplementary benzodiazepine medication, as measured by both mean daily and cumulative doses. However, if the effects of ziprasidone in improving manic symptoms had been largely due to the use of benzodiazepines, the placebo-treated patients would have experienced similar results.

Another study carried out by Potkin et al. [12] confirmed the previous results reported by Keck et al. [6]. They conducted a similarly designed 21-day trial, where 206 manic or mixed bipolar inpatients were randomized to receive ziprasidone (80–160 mg/day) or placebo following 10 days washout period. Efficacy was assessed with the SADS-C (which contains the MRS), PANSS, CGI-S scale, CGI-I scale, GAF, Hamilton Depression Rating Scale (HAM-D), and the Montgomery Asberg Depression Rating Scale (MADRS). The median duration of treatment for patients assigned to receive ziprasidone was 20.0 days. Around the 70% of patients randomized to ziprasidone and the 60% of patients receiving placebo completed more than 14 days of treatment. As in previous reports, a significant difference on the MRS scale

between ziprasidone and placebo was noted by day 2 and was maintained from day 7 to the end of study (-11.1 vs. -5.6 , $P < 0.01$). Among patients receiving ziprasidone, the mean daily dose was 86.7 mg on day 2, 107.6 mg on day 4, 120.5 mg on day 7, 125.5 mg from days 8–14, and 126.5 mg from days 14–21. The responder rate at study endpoint was almost 50% in the ziprasidone group versus one third percent in the placebo ($P < 0.05$). Ziprasidone group showed greater improvement in CGI-S and CGI-I scales than placebo group ($P < 0.001$). Mean improvements were significantly greater for the ziprasidone group than for the placebo on Manic Syndrome ($P \leq 0.01$) and Behavior and Ideation Subscale Scores ($P \leq 0.001$). In PANSS total and positive subscale scores significantly greater mean improvements were observed with ziprasidone than placebo ($P < 0.01$). The global functioning, as measured by GAF, was twice greater for the ziprasidone as for the placebo ($P < 0.001$). As demonstrated in the Keck study [6], the ziprasidone and placebo-treated patients displayed a comparable requirement for supplementary benzodiazepine medication.

(b) Add-on therapy to lithium. The third study evaluates the efficacy of ziprasidone as an adjunct treatment to lithium. In this 3-week placebo-controlled add-on trial, 205 bipolar I inpatients with MRS score ≥ 14 were randomized in two groups, one receiving ziprasidone (80–160 mg/day) plus lithium, and the other placebo plus lithium (to maintain serum levels of 0.8 to 1.2 mEq/L). The primary efficacy variables were changes of MRS and CGI-S from baseline to day 4, 14, and day 21. Secondary efficacy measures were assessed by Manic Syndrome and Behaviour and Ideation scales, HAM-D, CGI-I and PANSS Total, PANSS Positive and Negative Subscales. The primary efficacy variables did not achieve statistical significance at the endpoint (week 3). Ziprasidone dosage was 80 mg on day 1, 160 mg on day 2, and adjusted from days 3–21 within the range of 80–160 mg/day. From baseline to day 4, improvement was significantly greater in the MRS ($P < 0.05$), PANSS total ($P < 0.01$), Positive Subscales ($P < 0.05$), Negative Subscales ($P < 0.01$), CGI-I ($P < 0.01$), and HAM-D ($P < 0.05$). By day 14, improvements in primary and secondary efficacy variables were comparable in the two groups. Ziprasidone induced greater reduction in PANSS total ($P < 0.05$), PANSS positive subscales ($P < 0.05$), and PANSS negative subscale ($P < 0.05$) than placebo at day 21. In summary, the findings obtained in this study are not conclusive but can be seen as modestly supportive of the efficacy of ziprasidone in mania, as there was a clear signal of improvement in overall psychopathology, as seen in PANSS scores [13].

(c) Double-dummy, ziprasidone with placebo, using haloperidol as an active control. A longer study of

12 weeks of duration has been conducted by Vieta et al. [14]. This is the first randomized study using an active control besides placebo arm, and with a 12-week maintenance phase postacute mania. This double-blind, double-dummy, multicenter study compared ziprasidone with placebo and haloperidol as an active control. Bipolar patients who had a diagnosis of bipolar I disorder, current manic, or mixed episode were randomized to receive ziprasidone (80–160 mg/day, $n = 178$), placebo ($n = 88$), or haloperidol ($n = 172$) following 1-week washout period. The primary efficacy variable was the change in the 11 items on MRS derived from the SADS-C from baseline to week 3. Secondary efficacy parameters were similar as those used in Potkin et al. [12]. These variables were assessed during acute mania/mixed (3 weeks) and in all study visits as continuing therapy for the management of BD (12 weeks). Study results, in concordance with previous reports, showed an earlier ziprasidone onset of action (as early as day 2), but greatly, the study highlights up to 88.1% of patients were in response maintenance from 3- to 12-week period with a significant superiority versus placebo ($P < 0.001$). Mean decreases in the MRS total score were 11.5 and 6.0 ($P < 0.01$) points for the ziprasidone and placebo-treated patients, respectively. At week 3, the ziprasidone group showed greater improvement in CGI-S than the placebo group ($P < 0.01$). Mean daily dosages through week 3 were 116 mg/day for ziprasidone and 16 mg/day for haloperidol. On the other hand, higher response was observed in haloperidol group up to 12-week period (96.3%) which could be explained by the high doses of haloperidol used, particularly in those patients enrolled in India. However, subjects treated with haloperidol were more likely than patients treated with ziprasidone to switch to depression over the first 3 weeks of treatment (4% vs. 2.6%, $P = 0.09$) and the 12 weeks (6.3% vs. 3.8%, $P = 0.05$). As haloperidol was much worse tolerated, the study results suggest that the investigators and clinicians may have substantially different perspectives related to benefit/risk ratio across cultures, an issue that has not been fully analyzed in the literature [14]. Table 1 summarizes the results of these four studies.

(d) Intramuscular ziprasidone. Although the ziprasidone IM has not been approved by FDA to treatment in BD, its efficacy and safety has been evaluated for the treatment of acute psychotic agitation in psychiatric patients. We describe some evidences about it.

Hospitalized: There are two 24-h, double-blind, multicenter studies comparing doses of ziprasidone IM, 2 or 10 mg and 2 or 20 mg in agitated psychotic patients. Both 10 mg IM and 20 mg IM were tolerated and showed efficacy as measured Behavioral Activity Rating Scale

(BARS) [15,16]. There are three open-label, multicenter studies comparing different doses of ziprasidone IM versus haloperidol, in acutely agitated psychotic patients without conclusive results. In the first study, ziprasidone IM showed significant improvement as measured by BPRS (agitation items) and CGI-S at the end administration period. However, at the endpoint analysis, ziprasidone showed superiority only on the CGI-S [17]. In the second larger and longer study, in schizophrenia and schizoaffective patients, ziprasidone IM only showed efficacy in the BPRS total at the end of the IM period, but not at the study endpoint. Finally, the third study with psychotic patients found similar results between ziprasidone IM and haloperidol in BPRS scores [18].

Emergency: A randomized, double-blind study compared ziprasidone versus droperidol and midazolam, in agitated patients. Despite a more rapid action in midazolam group, they required a higher doses frequency leading to a risk increment of respiratory depression [19]. An open-label, uncontrolled study in acute psychotic agitation patients (age >60 years) showed improvement in BPRS scores and BARS scores [20].

Extension, Open-Label Studies

Despite the well-studied efficacy of ziprasidone in the first week of treatment by the trials mentioned above, there are not trials in the long-term treatment of BD. In the absence of controlled studies, little can be said on long-term efficacy. The extension studies and other open-label report suggest that ziprasidone is safe and well tolerated in long-term use, and there is no signal of worsening over time. Mean ziprasidone doses were between 90 to 130 mg/day. Three of these trials evaluate efficacy of ziprasidone in monotherapy [21–23] and one in adjunctive treatment with lithium [13]. In all of them, the efficacy is evaluated by changes in the MRS, CGI-I, and HAM-D scores through the time of the studies. MRS and CGI-S scores were significantly lower at all visits compared with baseline scores.

Ziprasidone in Treatment-Resistant Depression

The distinctive pharmacological profile of ziprasidone serotonergic plus norepinephrine reuptake inhibition makes it a promising additional drug to the armamentarium commonly used for different forms of depression including bipolar depression, psychotic depression, resistant unipolar depression [7]. Papakostas et al. [24], in an open-label 6-week study, of 20 patients with a major depressive episode resistant to selective serotonin reuptake inhibitor (SSRI) compared the efficacy of ziprasidone in addition to their SSRI. They observed

Table 1 Short-term trials with ziprasidone

Investigator	Diagnosis	Duration	Type of study	Monotherapy or adjunctive therapy	Doses (mg/day)	Findings	Primary efficacy	Secondary efficacy
Keck et al. 2003 [6]	Bipolar, acute mania	3-week	Double-blind, controlled, randomized	Monotherapy	160	Positive	Ziprasidone superior to placebo on MRS and CGI-S. More ziprasidone treated patients than placebo were classified as responders.	Significantly improved on GAF and PANSS total scores in the ziprasidone group compared to placebo.
Weisler et al. 2003 [13]	Inpatient bipolar, acute mania/mixed	3-week	Double-blind, add-on lithium, placebo-controlled, randomized	Adjunctive to lithium	80–160	Negative	Improvement was significantly greater on MRS at day 4 in the ziprasidone group, but no differences were found between the groups at day 21.	Ziprasidone induced greater reduction on PANSS scales than placebo at day 21. No differences between the groups were found at day-21 regarding CGI-I and HAM-D.
Potkin et al. 2005 [12]	Bipolar, acute mania/mixed	3-week	Double-blind, controlled, randomized	Monotherapy	80–160	Positive	Ziprasidone superior to placebo on MRS. 46% were identified as responders in the ziprasidone group versus 29% placebo.	Ziprasidone showed greater improvement on CGI-S, CGI-I, MSS, BHI, PANSS total, PANSS positive, and GAF than placebo.
Vieta 2008 [14]	Bipolar, acute mania/mixed	12-week	Double-dummy, placebo/haloperidol controlled, randomized	Monotherapy	80–160	Positive	Ziprasidone superior to placebo on MRS at 21 day and 12 weeks. Haloperidol was superior to ziprasidone on MRS at week-12.	Significantly improved on MSS, BHI, HAM-D, MADRS, PANSS scales, and GAF in the ziprasidone group compared to placebo.

MRS = Mania Rating Scale; MSS = Manic Syndrome scale; BIS = Behaviour and Ideation scales; CGI-S = Clinical Global Impression severity scale; CGI-I = Clinical Global Impression improvement scale; HAM-D = Hamilton Depression Rating Scale; PANSS total = Positive and Negative Syndrome scale; GAF = Global Assessment of Functioning.

that in the 50% of the sample there was $\geq 50\%$, a decrease in depressive symptoms as measured by 17-item HAM-D, with an overall proportion of responders of one quarter of the sample. Another recent open-label study, in treatment-resistant depression, reported greater clinical effect in the ziprasidone plus sertraline group than sertraline monotherapy, but these differences were not statistically significant [25]. In addition, at the moment a number of clinical trials in depressive bipolar I patients are ongoing. Three double-blind, multicenter, placebo controlled studies (6 weeks) are evaluating efficacy and safety of ziprasidone in bipolar I depression (NCT00282464; NCT00141271) and patients with mixed episodes (NCT00490542). There is also a double-blind, multicenter, placebo controlled study evaluating the efficacy and safety of flexible doses of oral ziprasidone as add-on, adjunctive therapy with lithium, valproate, or lamotrigine (NCT00483548). Furthermore, another open-label, 8-week, nonrandomized, flexible-dose trial (NCT00237666) evaluates the safety and efficacy of ziprasidone but in nonrapid-cycling bipolar II patients with major depression (<http://www.clinicalstudyresults.org>). All the trials of ziprasidone which are currently recruiting bipolar patients can be found in the: <http://www.clinicaltrials.gov>.

Pediatric Patients

(a) Short-Term, Open-Label Study: Monotherapy. An open-label study among youth subjects (median ages: 6–17 years) with 8 week of duration was carried by Bierderman et al. [26]. The primary measures used to assess outcome were the CGI-mania score ≤ 2 (much or very much improved) or a reduction in the young mania rating scale (YMRS) total score $\geq 30\%$. According by these criterions, 71% of subjects were classified as responders, although they continued to have residual symptoms of mania at endpoint (means YMRS score: 15.4). Patients on ziprasidone treatment showed reduction on depressive symptoms (50%) and attention-deficit hyperactivity disorder symptoms (33%). The mean dose of ziprasidone at study endpoint was 56.2 ± 34.4 mg/day (range: 20–120).

(b) Extension, Randomized Controlled Trial: Monotherapy. In a 6-month study, patients were in the range of 10–17 years old. The doses were fixed at the first 3 weeks and flexible until the end of the 6 months. They compare two groups, one with low doses (20–80 mg/day) and the other with high doses (40–160 mg/day). They also evaluate changes in the MRS and CGI-S score. Contrary to adult population, the higher decrease in MRS was achieved on the low-dose group [27].

Safety and Tolerability

Adverse Events

The safety profile of the atypical antipsychotics represents one of their most salient points of differentiation, especially given that long-term maintenance treatment is the norm. Ziprasidone possesses a side-effect profile quite different from other antipsychotics, especially with regard to EPS and metabolic effects. In two previous double-blind randomized, placebo controlled studies, the rates of discontinuation were 35–46% in the ziprasidone group. The main reasons reported for discontinuation of ziprasidone treatment were: lack of efficacy (33–42%), adverse events (8–15%), and other factors unrelated to the study drug (51%). Approximately 70% of the ziprasidone group reported adverse events. However, nearly all of the treatment-related adverse events were rated mild or moderate in severity, and no serious adverse events occurred. The most frequently adverse events reported in the ziprasidone group compared to placebo were somnolence (37.1% vs. 12.9%), headache (21.4% vs. 18.6%), dizziness (22.1% vs. 10%), hypertension (11.4% vs. 2.9%), nausea (11.4% vs. 10.0%), and akathisia (10.7% vs. 5.7%) [6,12]. Furthermore, patients on ziprasidone plus lithium treatment reported twice more adverse events than patients received on ziprasidone monotherapy [13].

Figure 2 shows the adverse events reported by $\geq 10\%$ of patients with bipolar I disorder.

Movement Disorders

The changes from baseline to endpoint on the Simpson-Angus Rating Scale (SAS), Barnes Akathisia Rating Scale (BAS), and Abnormal Involuntary Movements Scale (AIMS) did not significantly differ between the ziprasidone and placebo groups [6,12]. However, treatment-related EPS (benztropine or other antimuscarinics) were reported for 25% of patients treated with ziprasidone versus 6% of those treated with placebo [12]. Ziprasidone promotes also a better safety profile versus haloperidol, especially regarding the drug-related movement disorders (41% vs. 66.1% respectively) [14]. On the other hand, in add-on study, patients on lithium plus ziprasidone showed more movement disorders than ziprasidone monotherapy group [13]. Another open-label study that compares the rates of EPS caused by atypical antipsychotics (ziprasidone, olanzapine, aripiprazol, risperidone, and quetiapine) shows that half of the patients ($n = 8$) on ziprasidone-treatment (mean doses: 41.3 ± 21.7) experienced some EPS. The rates of EPS were similar among ziprasidone, olanzapine, and aripiprazol but lower than risperidone and quetiapine. In particular, in the

Figure 2 Adverse events reported by $\geq 10\%$ of patients with bipolar I disorder [6].

ziprasidone treatment group the most common EPS were tardive dyskinesia (1 patient), Parkinsonism (3 patients), and akathisia (3 patients) [2]. In addition, Weinstein *et al.* [28] reported two case reports where manic bipolar patients experienced acute dystonia (torticollis and jaw/mouth) in doses between 160 to 200 mg/day. Five cases of akathisia in female patients with BD (treated with 80–160 mg/day of ziprasidone) appeared to occur after a dose reduction [29]. There is one case report of tardive dyskinesia in a bipolar I patient with a previous history of this adverse event [30].

ECG Parameters

No change in median values for systolic and diastolic blood pressure or pulse was seen with ziprasidone treatment. Regarding the ECG parameters, patients treated with ziprasidone experienced modestly greater QTc prolongation (mean <15 ms) but no patient had a QTc interval ≥ 500 ms. A prolonged QTc is generally considered a warning of the potential for torsades de pointes, a serious and potentially fatal cardiac dysrhythmia. In the studies requested by the FDA, Pfizer reported that the ziprasidone's effect on the QTc interval did not seem to be very sensitive to dosage increases above 80 mg/day in the short-term placebo controlled studies. In a comparison with other antipsychotics with groups of 20–30 patients each, ziprasidone (160 mg/day) increased the QTc interval by a mean 20.3 ms, compared with an increase of 11.6 ms for risperidone, 6.8 ms for olanzapine,

14.5 ms for quetiapine, 35.6 ms for thioridazine, and 4.7 ms for haloperidol. Although, there was not any significant clinical sequelae associated with it, it has recommended that clinicians who undertake treatment with ziprasidone should be aware of the potential risk, and should not prescribe ziprasidone to patients with a known history of QT prolongation or uncompensated heart failure [10].

Weight Gain and Laboratory Values

One of the most important advantages of ziprasidone is the relative absence of weight gain associated with its use and a lack of changes in laboratory values [6]. However, a study reports that 27% of ziprasidone-treated patients versus 36% of placebo-treated patients experienced an increase of tryglicerides and ketone urine [12].

Ziprasidone Induced Hypomania/Mania

It has been proposed that the mood-altering effects of the atypical antipsychotics derive from high 5-HT_{2A} receptor affinity, particularly as a function of the 5-HT_{2A}/D₂ occupancy ratio and an inhibitor of presynaptic uptake of serotonin and noradrenaline [31]. These latter mechanisms of action are similar to tricyclic-antidepressants which could explain a ziprasidone's possible propensity to induce mania in susceptible individuals. We performed a MEDLINE search of the literature from January 2003 to august 2007 using the terms ziprasidone, hypomania, and mania. Four case reports were found where bipolar

patients experienced hypomanic/manic symptoms after receiving ziprasidone treatment. In the three case reports, the dose of ziprasidone was initiated at 20 mg twice per day and the hypomanic symptoms starting on day 3, 4, or 7 [32,33]. However, the data are from a series of cases and might not be applicable to other patients.

Conclusions

Ziprasidone has a unique profile that makes it a very interesting compound for the treatment of mood disorders. It acts primarily through serotonergic and dopaminergic receptor antagonism, but also exerts effects as an inhibitor of norepinephrine reuptake. Moreover, one of the advantages of ziprasidone is its safety profile as it is associated with minimal rates of EPS and almost no effect on weight, glucose, lipid and prolactin levels. Ziprasidone has low potential for drug interactions which appear to be an other strong point. Short-term efficacy of ziprasidone monotherapy in acute mania has been established in three double blind, placebo-controlled trials. Ziprasidone was also efficacious in the treatment of all bipolar I patients with mania or mixed episodes. In combination with lithium, ziprasidone results in a more rapid improvement. Despite the efficacy measures between ziprasidone and haloperidol were similar, benefits to the ziprasidone treatment in terms of side effects and switch into depression were greater than haloperidol. Ziprasidone appears to reduce manic symptoms in extension studies either in monotherapy as in adjunctive therapy. In addition, the distinctive pharmacological profile makes it a promising additional drug to the medications commonly used for different forms of depression like SSRI.

Conflict of Interest

Eduard Vieta has acted as a consultant, received grants, or been hired as a speaker by the following companies: Almirall, AstraZeneca, Bial, Bristol-Myers-Squibb, Eli Lilly, GlaxoSmithKline, Janssen-Cilag, Lundbeck, Merck Sharp & Dohme, Novartis, Organon, Otsuka, Pfizer, Sanofi Aventis, Servier, and UCB.

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