

The role of ziprasidone in adjunctive use with lithium or valproate in maintenance treatment of bipolar disorder

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Objectives: This article addresses the clinical role for ziprasidone used adjunctively with a mood stabilizer in maintenance treatment of bipolar disorder. This review also addresses the strengths and limitations of design features in adjunctive studies of second-generation antipsychotic drugs added to mood stabilizers.

Methods: The principal study relevant to this review enrolled subjects who were ≥ 18 years of age, experiencing a recent or current manic or mixed bipolar I episode, with at least moderately severe current manic symptoms. To meet criteria for randomization to 6 months maintenance treatment, patients had to have failed a short course of treatment with either lithium or valproate and achieved benefit with added ziprasidone for 8 consecutive weeks.

Results: Time to intervention for a new mood episode as well as time to discontinuation for any reason was significantly longer with adjunctive ziprasidone treatment than with monotherapy treatment with mood stabilizer. Three dosages of ziprasidone augmentation were studied. Patients treated with 120 mg/day had better efficacy and overall outcomes than did patients who received 80 or 160 mg/day of ziprasidone.

Conclusions: Good evidence exists that adjunctive ziprasidone will likely provide greater overall efficacy coupled with good tolerability for at least a 6-month period than a strategy of continued monotherapy with a mood stabilizer. Changes in open phases of maintenance studies to reduce study enrichment, in study endpoints, and in statistical approaches to analysis of data are warranted.

Keywords: bipolar disorder, mania, maintenance, prophylaxis, ziprasidone, mood stabilizer

This review addresses the effectiveness and pragmatic clinical role for ziprasidone used adjunctively with a mood stabilizer (MS, lithium or valproate) in maintenance treatment of bipolar disorder. The review also addresses the strengths and limitations of the unique design features in adjunctive studies of second-generation antipsychotic (SGA) drugs added to mood stabilizers. Since the turn of the millennium, four studies in bipolar disorder of antipsychotic + mood stabilizer vs mood stabilizer monotherapy relapse prevention have been completed. Each study required predefined evidence of a syndromal episode at the time of enrollment, or within the prior several months. Three required that patients prospectively treated with lithium or valproate for 2 weeks have failed to benefit manic, or in one study, manic or depressive symptomatology.¹⁻³ Each required a period of treatment with the SGA of interest added openly to continued MS, resulting in a portion of enrolled subjects meeting criteria for remission who then constituted the sample for the randomized, blinded maintenance trial. The data sets were all principally analyzed with Wilcoxon or log-rank life table methods.⁴ No studies have looked at the effectiveness of SGAs compared to MS when used in the context of

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other medications required to manage bipolar patients, which would be of interest since bipolar disorder patients take a median of 3 medications for optimal outcomes.⁵ Studies and guidelines indicate that combination regimens have become standard care in the treatment of the majority of patients with bipolar disorder.^{6–10}

The ziprasidone adjunctive maintenance study, along with two quetiapine studies, are the first to address concerns by the US Food and Drug Administration (FDA) that earlier maintenance trials conducted for purposes of a new indication have had insufficient symptomatic stabilization during an open phase to yield reliable and pragmatically useful data on relapse prevention. The ziprasidone study is the first to limit the use of adjunctive medication to MS for the last 4 weeks of the required period of stabilization to the drug of research interest.

Synopsis of important features of the study design

Subjects were ≥ 18 years of age, experiencing a recent or current manic or mixed bipolar I episode, with current symptom severity per the Mania Rating Scale of ≥ 14 , including having scores ≥ 2 on ≥ 4 items. Subjects were outpatients, except that patients hospitalized at the screening visit could be enrolled if sufficiently stable for outpatient management within approximately 5 days. Lorazepam at ≤ 2 mg/day for anxiety or insomnia for ≤ 4 days a week, or a similar drug was permitted. Subjects were excluded who had ≥ 8 mood episodes over the previous 12 months, mental retardation, organic brain syndrome, substance-induced psychotic disorder or behavioral disturbance within 2 months of screening, substance abuse/dependence, treatment resistance to ≥ 2 other antipsychotic medications, were treatment resistant or intolerant to ziprasidone, or were at risk of harm to themselves or others. These criteria were established to reduce heterogeneity but also to allow most persons with manic bipolar I syndromal symptomatology into the study, thereby improving generalizability of results. Consented subjects first received either lithium or valproate at a therapeutic serum concentration (lithium 0.6–1.2 mEq/L or valproate 50–125 $\mu\text{g/mL}$) for ≥ 2 weeks, as selected by the study psychiatrist. Those still meeting inclusion criteria were then entered into the open phase of the study for up to 16 weeks during which ziprasidone was added at one of three dosages: 80, 120, or 160 mg/day to the MS regimen. Subjects whose Clinical Global Impressions-Improvement scale (CGI-I) scores were ≤ 3 for 8 consecutive weeks, with allowance for a CGI-I score ≥ 4 at no more than one visit

were entered into the randomized, blinded maintenance phase. The study design required systematic tapering of ziprasidone by 20 mg twice per day every 2 days for subjects randomized to lithium or valproate plus placebo. The study was conducted at 98 centers internationally, with 584 subjects entering and receiving treatment in the open phase and 127 randomized to ziprasidone plus MS compared with 113 to placebo plus MS in the maintenance phase, yielding an open stabilization phase completion rate of 41.1%. For subjects randomized to lithium or valproate plus placebo, ziprasidone was systematically tapered off by 20 mg twice per day every 2 days. Eighty-four of the 127 ziprasidone plus MS subjects (66.1%) completed the 6-month randomized phase compared with 54 (48.2%) in the placebo plus MS group, which comprised 112 who received treatment, yielding an overall randomized phase completion rate of 57.7%. Additional details of inclusion/exclusion criteria, interventions and analytical methodologies are provided in the primary publication of the study results.³

Efficacy and effectiveness

The primary efficacy endpoint, time to intervention for a mood episode, was statistically significantly longer for ziprasidone plus MS than MS plus placebo ($P = 0.0104$). Intervention for a mood episode was required by 19.7% of subjects receiving ziprasidone, compared with 32.4% of subjects receiving placebo. The median time to intervention for a mood episode was longer for ziprasidone plus MS than MS alone (43.0 days vs 26.5 days) among subjects who required an intervention for a mood episode ($n = 61$). Time to discontinuation for any reason also significantly favored the adjunctive group ziprasidone (P value = 0.0047). These findings were driven by ziprasidone plus mood stabilizer preventing manic/mixed more than depressive recurrence.

Among the subset of 106 lithium-treated subjects, the proportion of subjects who required intervention for a mood episode for ziprasidone plus lithium was 21.1% compared with 44.9% ($P = 0.0024$) for placebo plus lithium. In contrast, among the 133 valproate-treated subjects, 18.6% of ziprasidone plus valproate subjects required an intervention compared with 22.6% ($P = 0.4863$) of placebo plus valproate subjects.

Post hoc analyses for time to intervention for episodes by dose group of ziprasidone indicated that the 120 mg/day group was both more efficacious and associated with greater persistence with treatment than either the 80 or 160 mg/day groups. Rates of intervention for a mood episode for 80 mg, 120 mg, and 160 mg daily dosage groups were 23.3%, 10%,

and 25.9%, compared with 32.4% for the placebo plus MS group. Only the 120 mg/day group was superior to placebo ($P=0.004$). Similarly, for discontinuation for any reason, the rates for 80 mg, 120 mg and 160 mg/day respectively were 41.7%, 20%, and 37% and for the placebo plus MS group, 51.4%. Only the 120 mg/day group was significantly superior to placebo ($P=0.001$).

Tolerability

For adverse events that occurred at $>5\%$ in either randomized treatment group, excluding weight change and prolactin levels, tremor was the only adverse event that occurred at a higher incidence in the ziprasidone plus MS treatment group (6.3% vs 3.6%). Rates for serious adverse events and for adverse events leading to discontinuation did not differ significantly between the two treatment groups.

Weight change was minimal during the open stabilization phase. Increase in weight $\geq 7\%$ occurred in 5.5% of subjects; rates for a $\geq 7\%$ decrease in weight were 3.2%. Similarly, over the 24 weeks of double-blind treatment, mean weight changes in the ziprasidone plus MS group were -0.8 kg (SD = 4.8) and $+0.5$ kg (SD = 4.9) in the placebo plus MS group, and the rate of at least 7% weight gain was 5.6% in completers for both groups.

Levels of fasting glucose, total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and triglycerides did not change significantly in either randomized treatment group. Prolactin levels were elevated in 12.3% of ziprasidone plus MS subjects compared with 6% of placebo plus MS subjects. During the open phase, mean QT interval values at baseline and week 16 were 383.2 ms (range, 295.3–476.3) and 390.3 ms (range, 308.0–473.0). In no subject was the QTc interval ≥ 500 ms. At week 24 of the randomized phase, QTc interval did not differ between the 2 treatment groups (ziprasidone plus MS: 386.2 ms vs placebo plus MS: 378.8 ms, with no values ≥ 500 ms in either group).

Critical appraisal and recommendations for adjunctive ziprasidone use in maintenance treatment of bipolar disorder

For bipolar I patients who continue to experience inadequate control of manic or mixed symptomatology with lithium or valproate therapy, this study yields evidence that addition of ziprasidone will be likely to provide greater overall efficacy and effectiveness for at least a 6-month period than a strategy of continued monotherapy with MS. Although not powered

to test separately the benefit of adjunctive ziprasidone with lithium and valproate, the results indicate that adjunctive benefit is substantially greater with lithium than with valproate, consequent to worse performance for monotherapy lithium than monotherapy valproate. The study has suggestive indications that dosing of ziprasidone at 120 mg/day is both more efficacious, and as well tolerated, than either lower (80 mg/day) or higher (160 mg/day) regimens. Of note, two flexible dose studies of ziprasidone in monotherapy use reported that end-of-treatment mean dosages for ziprasidone were just over 120 mg/day.^{11,12}

The study provides strong evidence that the adjunctive use of ziprasidone with either lithium or valproate in maintenance treatment of adults is well tolerated. In contrast with consistent evidence of weight gain, worsening of lipid profiles, and of glucose dysregulation with monotherapy or adjunctive use of olanzapine^{4,13} or quetiapine,^{1,2} ziprasidone did not appear to worsen any of these parameters either during the open or randomized phases of the study. Thus, pooling the results of the two recent adjunctive (added to lithium or valproate) quetiapine studies, quetiapine plus mood stabilizer yielded at least 7% weight gain in 23.6% of subjects during the open stabilization phase and 9.4% during the randomized phase. The analogous rates with ziprasidone plus mood stabilizer in the current study were 5.5% and 5.6%.

Early acute phase studies raised concerns that ziprasidone might pose risks for cardiac dysrhythmias.³ The adjunctive maintenance study reviewed here, which of course has the advantage of yielding relatively long-term data (the mean time in study combining both the open phase and the randomized was over 200 days in both treatment groups), does not indicate any increase in risk for such adverse effects. To date, adjunctive maintenance studies in bipolar disorder with other second-generation antipsychotic drugs have not been published.

The study design has several important strengths that improve confidence in the results. The design of the trial, although intended to yield an enriched sample of nonresponders to lithium or valproate as monotherapy for a bipolar I manic or mixed episode, provided a more generalizable sample than other published adjunctive regimen trials in bipolar disorder that utilize failure of response in an open phase to select randomized phase subjects.¹³ The study design required systematic tapering of ziprasidone by 20 mg twice per day every 2 days for subjects randomized to lithium or valproate plus placebo. This step, plus that of requiring an extended period of symptomatic and functional stability, likely contributed to the high rate of randomized phase completion

of the 24-week study both in the ziprasidone plus MS group and the placebo plus MS group. The rate of randomized study completion (57.7%) is higher in the ziprasidone adjunctive study than any other published adjunctive, blinded, randomized trial in bipolar disorder published in this decade. For example, pooling the results of the two recent adjunctive (added to lithium or valproate) quetiapine studies, quetiapine plus mood stabilizer yielded a rate of randomized phase study completion of 39.2%. Additionally, visual inspection of the survival curves in the respective published adjunctive studies suggests that high early rates of relapse associated with withdrawal of the adjunctive medication at the end of the open phase was less a factor in the ziprasidone study, consequent to its design features.

The ziprasidone study has several limitations that psychiatrists should consider in applying its results toward patients in standard clinical practice. The comparison was made in the maintenance treatment of adults with a manic or mixed episode of bipolar I disorder. The study therefore does not provide guidance on adjunctive use of ziprasidone in still symptomatic bipolar depressed patients, or patients younger than 18 years of age. Although no bipolar II patients were studied, in the opinion of the author, if a bipolar II patient treated with lithium or valproate presented with continuing hypomanic/manic symptomatology, the findings in this study provide some support that adjunctive addition of ziprasidone would be an evidence-based action.

A significant source of enrichment from other adjunctive study designs has revolved around subjects who experienced intolerable side effects or lack of efficacy, both of whom were excluded from randomization.^{2,4,10} In the ziprasidone adjunctive study, based on the low rates of adverse effects and the relatively high proportion of open phase treated patients who met the criteria for response and were randomized, even given the requirement for a sustained period of overall good clinical status, the enrichment favoring the ziprasidone group would appear to be minimal in this regard.

Implications of the ziprasidone adjunctive study for future study designs in maintenance treatment of bipolar disorder

Clinical trial designs for maintenance applications in bipolar disorder studies have largely repeated use of several design features that have limited generalizability of results and under-emphasized issues of safety and tolerability. The ziprasidone adjunctive design and several other recently published adjunctive studies in bipolar disorder provide a basis for

recommending approaches which will improve generalizability of results to real life settings, yield more effectiveness data, and facilitate public health and regulatory body actions in response to new study data. The aspects briefly addressed here are not mutually exclusive, but sufficiently distinct to treat individually: subject inclusion/exclusion criteria, open phase methods, duration of required improvement for randomization, endpoints and primary outcome measures in maintenance phase, duration of maintenance phase, and statistical approaches applied in analysis of data.

Subject inclusion/exclusion criteria

Studies will only be applicable to the types of illness states that are eligible for enrollment. In bipolar disorder, this essentially means deciding whether to require that the patient has current syndromal level illness, or that some recent episode will suffice. Studies that require only an episode within a 6-month period, for example, risk enrolling subjects without typically active illnesses, therefore weakening possibilities for identifying a bona fide efficacious intervention vs placebo.¹⁴⁻¹⁶ Requirement for a threshold level severity of manic and/or depressive symptomatology, as required in the ziprasidone study (manic symptomatology), can adequately assure severity of illness. Although from a clinical perspective enrollment of patients in all phases of bipolar illness might seem desirable, if a regimen of interest only has evidence of benefit for a certain component of the several major domains of bipolar disorder, it is reasonable to limit enrollment to patients with symptomatology in that domain or domains.

Open phase methods

To date, only one published maintenance study has utilized a design of allowing or requiring open phase treatment to include either of the treatments to which patients might be randomized in the maintenance phase.¹⁷ Such design allows a test of the question of whether continuation in maintenance of the regimen which was effective acutely is an effective strategy. One design strategy that would effectively reduce or eliminate enriching a randomized maintenance for one regimen would be to make the decision as to randomized group at the point of acute phase lead in treatment. One concern that has influenced lack of commitment to such a design is that the number of acute phase subjects would be expanded, since a lower proportion on a less effective regimen would become eligible for randomization, thereby increasing costs and duration of study. The ziprasidone study had one element of continuation of open phase treatment, in that randomized patients were continued on the same dosage of ziprasidone if

they became eligible for the maintenance phase. This feature allowed a meaningful secondary analysis of effectiveness of the respective dosages, thereby benefiting generalizability to address important clinician questions regarding optimal dosing strategies.

Duration of improvement required for randomization

The FDA has publically expressed expectations that a sustained period of open, acute phase improvement be required for eligibility for maintenance studies in bipolar disorder. One major basis for such concerns is that a brief, even point in time improvement will often be clinically meaningful, but will not establish that the patient has recovered from the clinical state at admission. Therefore, inclusion of such patients will lead to very early relapse in the randomized phase following discontinuation of the effective drug or regimen of the open phase. The 8 weeks of stabilization required in the ziprasidone study, carefully designed to also utilize the CGI-I score for randomization, appears to have been a successful strategy to address such concerns. Desirably, it also did not result in a low rate of open phase subjects meeting criteria for randomization. It also appears to have yielded a randomized sample that tested relapse prevention, rather than a substantial proportion of patients with re-exacerbation of an inadequately treated entering episode.

Study endpoints

As noted earlier, single point in time endpoints, such as time to intervention for an episode, as employed in the ziprasidone study and many other maintenance trials in bipolar disorder, differ substantially from usual clinical care, in which psychiatrists are likely to continue treatment through exacerbations in symptomatic severity, even when meeting criteria for a depressive or mixed episode, generally by increasing frequency of visits and adjunctively modifying drug regimens.⁸ The ziprasidone design, despite principally utilizing such a single point in time endpoint, did succeed in maintaining a desirably large proportion of randomized in the randomized, blinded phase. One consequence of such desired persistence is that several of the features of Wilcoxon and log-rank analyses, eg, describing median time to development of a new episode, are generally inapplicable, since the proportions of subjects in at least one study arm will not reach as high as half of the sample. The application of logistic regression analyses and mixed effect repeat measure techniques, which take advantage of all time point assessments, provides a

well established and clinically relevant alternative to time to event analyses.

Duration of maintenance phase

Monotherapy maintenance trials have generally been planned for 12 to 18 months of randomized treatment. However, in all instances, the actual time in study, by all measures, has been substantially shorter than that. Even with little evidence that withdrawal phenomena impacted rates of new episodes in this trial, the majority of endpoints occurred within the first half of the 6-month period of maintenance. Most studies have reported completion rates below 30% even for the treatment arm with the best results. The ziprasidone study indicates that a 6-month randomized period will capture most outcome information needed to establish evidence for efficacy and safety of a regimen.

Statistical approaches

Kaplan–Meier survival analytic techniques which have been almost the sole analytic approach in not only adjunctive but also monotherapy studies in maintenance treatment of bipolar disorder do have utilities. They take into consideration time to a targeted outcome and can be conducted to improve sensitivity when most actions of interest occur early in a trial, or alternatively, late in the course of interventions. However, the assumption that all subjects will eventually have the endpoints taken as primary outcome measures is generally invalid. Further, except indirectly in survival analyses for discontinuation for any reason, it is difficult to identify and incorporate in an overall analysis the tolerability and adverse effects of a treatment. As is evident in the ziprasidone study, the desirable objective of retaining a high proportion of patients in a trial to study end can result in inability to report results as median time to event, both because, as noted earlier, some subjects will never have the event and the rates for the event may not reach the useful 50% median change from baseline. Finally, survival analyses do not deal adequately with missing data, which becomes critically important if over 15% of subjects enrolled do not complete a study. Mixed effects repeated measure techniques (MERM) are not a new technique, but with extensions of these techniques over the past decade their use has increased dramatically for longitudinal clinical trials.¹⁸ None of the maintenance studies in bipolar disorder published since 2000 has utilized MERM techniques. Because nonignorable missingness⁹ is highly likely in all monotherapy longitudinal trials in bipolar disorder, and with very low rates of subjects in all treatment arms completing these trials, MERM techniques offer

important clarifications over survival techniques. Hedeker and Gibbons¹⁹ provide a detailed overview of approaches to this issue, including assessment of the pattern of missingness. One particularly interesting analysis option allows a blending of survival and MERM analyses that models dropout and longitudinal trajectories in a “shared parameter” model that integrates information about dropout with the outcome trajectory prior to dropout. Another novel approach is a form of cluster analysis that identifies groups of patients with similar symptom trajectories over time. Such techniques would be relevant to a study with the design features and outcome characteristics of the ziprasidone study.

Conclusion

The adjunctive ziprasidone study in bipolar disorder provides pragmatic, reliable guidance to clinicians regarding why, when, and how to utilize such treatment in an overall therapeutic approach in management of bipolar disorders. The study has advantages of clear design, relatively high retention of subjects, clear outcomes in most areas of analysis, and also serves as a catalyst to consider limitations of current methodologies in maintenance trial design and alternative methods that can overcome such limitations.

Disclosure

The author reports no conflicts of interest.

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