Ziprasidone for Psychotic Disorders: A Meta-Analysis and Systematic Review of the Relationship Between Pharmacokinetics, Pharmacodynamics, and Clinical Profile

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ABSTRACT

Background: Among atypical antipsychotics, ziprasidone exhibits a unique clinical profile. However, prescription rates for this medication remain among the lowest of all atypical antipsychotics.

Objective: The present meta-analysis examined premature study discontinuation (PSD) and dose-response associated with ziprasidone. Furthermore, a systematic review of the clinical pharmacokinetic and pharmacodynamic properties and tolerability of ziprasidone was conducted to explain the meta-analytic findings.

Methods: A systematic search was performed in the electronic databases PubMed and EMBASE using the key words *ziprasidone, randomized, positron emission tomography, pharmacokinetic,* and *tolerability*. This search looked for open-label or blinded studies of oral ziprasidone use in patients with psychoses (schizophrenia-spectrum disorders and/or bipolar mania) published between January 1, 1992, and February 1, 2011. Comparisons with antipsychotics for which there were <3 studies in total were excluded. PSD (all causes) was used as a measure of overall effectiveness.

Results: Thirty-one studies were included in the final analysis. The rates of PSD were significantly higher with ziprasidone compared with olanzapine (inefficacy and all causes, $P < 0.001$) and risperidone (all causes, $P = 0.004$). In contrast, the rates of PSD due to inefficacy and adverse events were significantly lower with ziprasidone compared with quetiapine ($P = 0.03$) and haloperidol ($P = 0.03$), respectively. On dose-response analysis, the rate of all-cause PSD was significantly lower with combined 120–160 mg/d compared with placebo ($P = 0.001$). Low levels of hyperprolactinemia and weight gain/metabolic adverse events, and moderate extrapyramidal symptoms and corrected QT-interval prolongation were reported with ziprasidone use. Ziprasidone exposure was increased when the medication was administered with food, irrespective of fat content. Ziprasidone 120–160 mg/d was correlated with 60% to 80% occupancy in studies of D_2 binding with the administration of multiple doses. However, the same occupancy was achieved with single-dose administration at much lower doses (20–60 mg/d).

Conclusions: The findings from this meta-analysis and review suggest that ziprasidone 120–160 mg/d is a less effective treatment for psychotic disorders compared with olanzapine and risperidone, but that the low levels of hyperprolactinemia and weight gain/metabolic adverse events associated with ziprasidone may make it a useful option in patients in whom antipsychotics are poorly tolerated for these reasons. (*Clin Ther*. 2011;33:1853–1867) © 2011 Elsevier HS Journals, Inc. All rights reserved.

Key words: antipsychotic, meta-analysis, pharmacokinetic, premature study discontinuation, psychosis, schizophrenia, tolerability, ziprasidone.

INTRODUCTION

Ziprasidone is an atypical antipsychotic approved for use in the United States, Europe, and more recently Canada for the treatment of psychotic disorders.[1] Ziprasidone exhibits a unique pharmacokinetic, pharmacodynamic, and tolerability profile compared with the other atypical antipsychotics, including the lowest potential for drug–drug interactions due to the involvement of 2 competing metabolic pathways (aldehyde oxidase and cytochrome P450 [CYP] 3A4).[2] Its use has been associated with low weight gain/metabolic adverse events.[3] Ziprasidone binds with high affinity to dopamine (D)-2 receptors and has a similar

affinity for serotonergic receptors (eg, 5-HT$_{1A,2A}$), which would be expected to translate to high efficacy with low risks for extrapyramidal symptoms (EPS) and hyperprolactinemia.[4,5]

Based on these putative benefits, and due to evidence that risk–benefit ratio has a greater influence on the choice of antipsychotic than do demographic and illness-related variables,[6] one would expect ziprasidone to be often prescribed for psychotic disorders such as schizophrenia and bipolar mania. However, the prescription rates of ziprasidone in the United States remain among the lowest of all atypical antipsychotics.[7] On analysis of claims data from 7017 schizophrenia and 18,158 bipolar treatment episodes, more switches to other antipsychotics were prescribed in patients treated with ziprasidone than any of the other agents evaluated (olanzapine, risperidone, quetiapine, and typicals).[8,9]

The present meta-analysis and systematic review attempted to elucidate the gap between the unique profile of ziprasidone and its lack of prescription for psychotic disorders. Meta-analytic data from comparisons of the effectiveness (as measured by premature study discontinuation [PSD]) of ziprasidone and other antipsychotics are presented. Data on dose-response and tolerability (prolactin concentrations, EPS, corrected QT [QTc] interval, weight gain/metabolic events) of ziprasidone are presented. The pharmacokinetic and pharmacodynamic properties (D$_2$ binding) of ziprasidone in humans are discussed. Finally, insight is provided on which patients may be most suitable for ziprasidone therapy and on potential strategies to optimize treatment with this medication.

METHODS
Literature Search

A systematic search of the electronic databases PubMed and EMBASE was performed using the key words *ziprasidone, randomized, positron emission tomography, pharmacokinetic,* and *tolerability.* Studies of oral ziprasidone (open-label or blinded) in adult patients with psychoses (schizophrenia-spectrum disorders and/or bipolar mania) and published between January 1, 1992, and February 1, 2011, were included. Additional trials were identified by cross-referencing of articles and by searching for *ziprasidone* in the clinicaltrials.gov database.

Study Selection

For the meta-analysis of head-to-head trials, studies employing both fixed- and flexible-dose schedules were included. To improve the reliability and validity of the meta-analytic findings, comparisons with antipsychotics for which there were <3 studies in total were excluded (aripiprazole, amisulpride, iloperidone, clozapine, perphenazine, and chlorpromazine). For head-to-head studies in which multiple fixed doses of ziprasidone were administered, the data from studies of the standard clinical dosage (120–160 mg/d) were used. To provide an estimate of the effects of ziprasidone versus low-dose ziprasidone or versus placebo, the meta-analyses of dose-response and review of tolerability included only data from fixed-dose studies. Due to a lack of data, dose-response was not calculated using comparisons with 10 and 200 mg of ziprasidone. To decrease variability in the analysis of the effects of ziprasidone on QTc interval, only data from randomized studies specifically designed to measure this end point were included.[10] The analysis of EPS rates examined prescription rates of adjunct benztropine and β-blockers. Studies of the clinical pharmacokinetic and pharmacodynamic properties (D$_2$ binding) of ziprasidone were included to elucidate the findings from the meta-analyses and tolerability review.

Data Extraction and Quantitative Data Synthesis

Two of the authors (S.Z. and H.M.) independently reviewed and extracted the data. Using comprehensive meta-analysis,[11] risk ratios were calculated for dichotomous variables. First authors were contacted for missing data. The level of significance was set at $P < 0.05$.

Homogeneity of Effect-Size Estimates

To determine the homogeneity of risk ratios, the Q statistic for the risk ratios of the studies included in the meta-analysis was calculated. The level of significance for homogeneity estimates was set at $P < 0.1$. When studies were homogeneous, risk ratios were aggregated using fixed-effects models. When studies were found to be heterogeneous, risk ratios were aggregated using random-effects models. Relative to fixed-effects models, random-effects models take into account interstudy variance and allow for population-level inferences.[12]

RESULTS

Thirty-five articles fit the initial search criteria, 31 of which were included in the final analysis. One long-term study in chronically ill schizophrenic patients (ZEUS [Ziprasidone Extended Use in Schizophrenia][13]) was excluded from the dose-response meta-analysis to minimize