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REVIEW

# Using Oral Ziprasidone Effectively: the Food Effect and Dose-Response

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## ABSTRACT

Ziprasidone is a newer "atypical" or "second-generation" antipsychotic. Oral ziprasidone (ziprasidone hydrochloride) has been approved by the US Food and Drug Administration (FDA) for the treatment of schizophrenia, and acute manic or mixed episodes associated with bipolar disorder (with or without psychotic features). Comparisons with other second-generation antipsychotics in meta-analyses reveal similar efficacy to that observed for quetiapine or aripiprazole, but inferior efficacy to that of olanzapine or risperidone in the treatment of schizophrenia. However, the rate of dose titration and the dose achieved may have an important bearing on ziprasidone's efficacy profile, with a target dose range of 120-160 mg/day being associated with optimal symptom control and greater persistence with treatment. In addition, enhancing ziprasidone's effectiveness requires ensuring that ziprasidone is administered with a 500 kcal meal; otherwise, absorption of oral ziprasidone is substantially reduced and cannot be compensated for by increasing the prescribed dose. Regarding tolerability, ziprasidone has important advantages in that it is not associated with clinically significant weight gain or adverse changes in cholesterol, triglycerides, or glycemic control, and patients may experience moderate improvement in these measures when switching to ziprasidone from a different antipsychotic. Ziprasidone also lacks significant persistent effects on prolactin levels, is not anticholinergic, and only infrequently causes extrapyramidal side effects or postural hypotension; however, it can be associated with somnolence. Ziprasidone may prolong the electrocardiogram (ECG) QT interval but this does not appear to pose a substantial clinical problem. Provided that an adequate dose of ziprasidone is prescribed, and administered with a 500 kcal meal, ziprasidone can be effectively used to control symptoms without the long-term liabilities of metabolic side effects.

**Keywords:** bipolar disorder; dosing; food; schizophrenia; ziprasidone

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## INTRODUCTION

Ziprasidone hydrochloride, an oral second-generation antipsychotic, was approved by the US Food and Drug Administration (FDA) in February 2001 for the treatment of schizophrenia, and for the treatment of acute manic or mixed episodes associated with bipolar disorder (with or without psychotic features) in August 2004.

Ziprasidone is promoted as a better-tolerated alternative to other antipsychotic medications. Among the key advantages for ziprasidone are a benign extrapyramidal side effect profile, little or no effect on prolactin, no significant weight gain, and no adverse changes in glucose metabolism or blood lipid levels.[1] Initial concerns about ziprasidone's propensity to cause prolongation of the electrocardiogram (ECG) QT interval have not persisted as no clinically relevant problems have emerged over time. According to the product label,[2] ziprasidone should be avoided in patients with some types of cardiac disease and with uncontrolled electrolyte disturbance, and that the use of ziprasidone with other drugs that prolong the QT interval should be avoided. However, under most clinical circumstances, ziprasidone may be safely used without ECG monitoring.[3]

In an older meta-analysis exploring the efficacy of the second-generation antipsychotics in comparison with first-generation antipsychotics,[4] effect sizes for clozapine, amisulpride, risperidone, and olanzapine were found to be significantly greater than those for first-generation antipsychotics. However, there were no significant differences in the effect sizes of aripiprazole, quetiapine, remoxipride, sertindole, or ziprasidone in comparison with the first-generation antipsychotics. This is consistent with a more recently conducted meta-analysis that included 78 studies[5] and found ziprasidone less efficacious than olanzapine or risperidone, but similar in efficacy to quetiapine or aripiprazole.

In addition to the heterogeneity in efficacy and tolerability among the different oral antipsychotics, there is also substantial individual heterogeneity regarding overall effectiveness of a specific regimen for an individual patient.[6] Thus for an individual patient, suitability for ziprasidone is a compromise between efficacy, adverse effects, the individual patient's history of previous drug treatment and its results, the patient's family history of diabetes, the patient's preferences, and drug cost. Enhancing the effectiveness of ziprasidone is further dependent on two additional considerations: administration with food and titration of the dose to a therapeutic amount. This review will summarize the available data regarding these issues. Details regarding the clinical trials of ziprasidone, including a comprehensive review of efficacy and safety, can be found elsewhere.[1]

## PHARMACOKINETICS AND THE FOOD ISSUE

The mean half-life of ziprasidone is 7 hours and steady-state concentrations are achieved within 1-3 days of dosing.[2] Time to peak serum concentration is 6-8 hours and the bioavailability of a 20 mg dose under fed conditions is approximately 60%.[2] However, when ziprasidone is administered under fasting conditions, the bioavailability of ziprasidone is substantially less. In an early study that tested the hypothesis of whether a high-fat meal impacted absorption of ziprasidone, eight healthy male volunteers participated in an open, randomized, crossover protocol.[7] Ziprasidone 20 mg was administered under fasting conditions and after a standard high-fat breakfast. Serial blood samples were obtained over 36 hours. The area under the serum concentration versus time curve (AUC,

a measure of exposure to a medication) for the fasting state was about half that for the fed state. In another study, ziprasidone absorption was assessed in eight healthy men administered oral ziprasidone (20, 40, and 80 mg) after an 8-hour fast or immediately following a standard high-fat breakfast.[8] The AUC was greater in fed than in fasting states at each dose (20 mg, +48%; 40 mg, +87%; 80 mg, +101%). The issue of whether the fat content contributed to the differential absorption was examined in another randomized crossover study in 14 healthy subjects (six men, eight women).[8] Subjects received ziprasidone (40 mg) under three conditions: fasting, with a high-fat meal (60% fat), and with a moderate-fat meal (30% fat). The AUC and the maximum serum ziprasidone concentration under fed conditions increased by 104% and 84% (60% fat meal) and 79% and 98% (30% fat meal), respectively, relative to the fasting state. Because there was no clear difference in ziprasidone bioavailability between the fed groups, it appears that meal fat content is not a major determinant of bioavailability.

The product label notes that bioavailability is reduced by as much as 50% when ziprasidone is not taken with food;[2] however, this is likely to be an underestimate when treating actual patients within the target dose range of ziprasidone 120-160 mg/day. Essentially, doubling an oral dose of 40-80 mg in order to administer ziprasidone in the fasting state in an attempt to compensate for the food effect will not double the serum drug concentration. This is because under fasting conditions increases in the AUC and maximum serum drug concentration are less than dose proportional; however, under fed conditions they are dose proportional with less pharmacokinetic variability.[8] The only extant report of the food effect with ziprasidone in actual patients consisted of 15 completers who received a dose of ziprasidone 80 mg twice a day for at least 2 weeks.[9] Diagnoses included schizophrenia, schizoaffective disorder, bipolar disorder, or psychotic disorder not otherwise specified. Patients took ziprasidone under six meal conditions in randomized sequences (fasted, low calorie/low fat, low calorie/high fat, medium calorie/high fat, high calorie/low fat, and high calorie/high fat). Serial blood samples were obtained over the 12 hours after administration of the dose. The highest ziprasidone exposures were observed with high-calorie (1000 kcal) and medium-calorie (500 kcal) meals, which were nearly twice those observed under fasting conditions. Low-calorie meals (250 kcal) were associated with exposures that were approximately 60%-90% lower than those of medium-calorie and high-calorie meals, and approached exposures seen under fasting conditions. As with the study with normal volunteers,[8] fat content of the meal had no significant effect on ziprasidone absorption. The ziprasidone exposures observed with medium-calorie and high-calorie meals had less variability than those with low-calorie meals and under fasting conditions. Thus, among patients receiving 160 mg/day of ziprasidone, it is imperative that this medication is taken with food, and that a meal equal to or greater than 500 kcal, irrespective of fat content, is required for optimal and reproducible bioavailability of the administered dose. A simple snack would be inadequate, as demonstrated in Table 1 (see also Vreeland et al.[10] and http://caloriecount.about.com), which includes different foods and their caloric counts.

Based on the above studies, a conceptual model for the exposure to ziprasidone under fasting and fed states by oral dose can be constructed (Figure 1). The lines representing the fasting and fed states are simplified and do not include the potential variability observed among persons receiving ziprasidone. However, from the data, variability would be expected to be

**Table 1.** Common foods and caloric counts, all of which alone are less than 500 kcal, and each alone would be inadequate to ensure optimal absorption of ziprasidone.

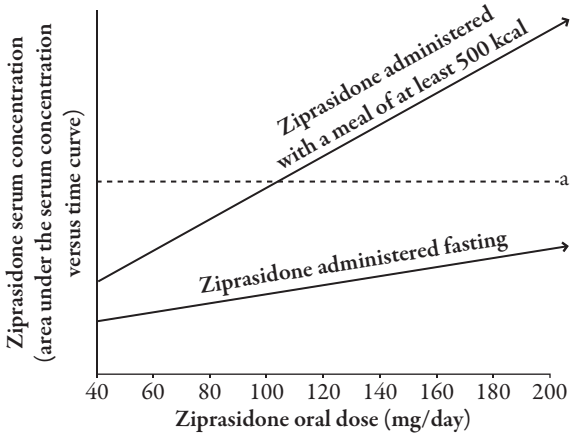
| Item | Approximate kcal value |
|---|---|
| 1 large bagel | 350 |
| 1 doughnut | 120 |
| 1 cup of cornflakes cereal | 100 |
| Small fast food french fries | 230 |
| Ham and cheese sandwich | 350 |
| Hamburger, with bun, plain | 270 |
| Hotdog, with bun, plain | 240 |
| Egg sandwich in English muffin | 300 |
| Danish fruit pastry | 335 |
| 1 egg, boiled | 70 |
| 2 snack cakes with crème filling | 250 |
| 1 slice pizza | 350 |
| 20 potato chips | 200 |
| 1 orange | 80 |
| 1 banana | 90 |
| 1 apple | 80 |

Abstracted from http://caloriecount.about.com and Vreeland B, Toto AM, Sakowitz M. Solutions for Wellness. 3rd edition. Indianapolis, IN: Eli Lilly and Co; 2008.[10]

greater in the fasting state, with levels achieved being more predictable in the fed state. It is possible that adequate serum concentrations of ziprasidone can never be achieved for patients receiving ziprasidone while fasting, no matter how high the oral dose. Further studies examining the bioavailability of ziprasidone among actual patients, comparing the fasting versus the fed state, for several fixed doses of ziprasidone, including doses above 80 mg twice a day, would be desirable.

As a caveat, observational studies of oral ziprasidone under noncontrolled conditions may be inadequate in evaluating medication effectiveness. It remains unclear in those circumstances whether or not patients have been adherent to instructions to take ziprasidone with food. This is not usually a problem in double-blind controlled clinical trials, particularly among inpatients, where the delivery of ziprasidone can be scheduled together with a meal. For clinical trials of this type, the study protocol usually makes explicit that ziprasidone be administered to patients in the nonfasting state. Although compliance to this rule cannot always be guaranteed, individual study reports and meta-analyses of randomized controlled trials should be interpreted assuming that ziprasidone was administered under optimal conditions.

**Figure 1.** Conceptual model of exposure to ziprasidone under fasting versus fed states, by oral dose. a=possible serum concentration threshold necessary to optimize antipsychotic efficacy.




The precise mechanism by which ziprasidone absorption is affected by food is not known.[9] At present, there are no other alternatives other than administration with a meal. It may be possible to monitor plasma levels of ziprasidone in selected cases.[11]

## EFFICACY AND DOSE-RESPONSE

The product label[2] states that the efficacy of ziprasidone in treating schizophrenia was demonstrated in a dose range of 40-200 mg/day, administered twice a day in short-term clinical trials, and that there were inconsistent trends toward dose-response within the range of

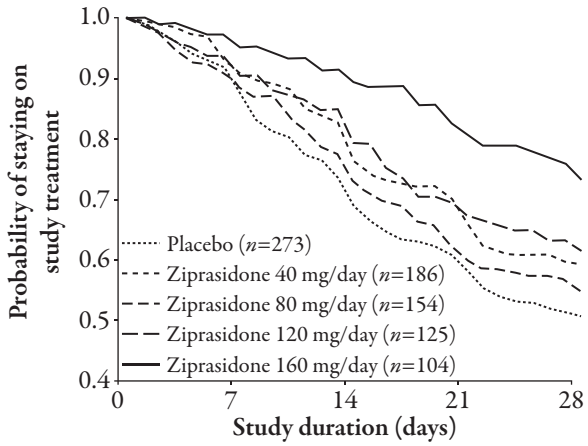
40-160 mg/day. Per label, an increase to a dose greater than 160 mg/day is not generally recommended, and "no additional benefit" was evidenced for doses above 40 mg/day for the maintenance treatment for schizophrenia. Moreover, the recommended titration for ziprasidone for schizophrenia (start at 40 mg/day and adjust at intervals of not less than 2 days) differs from that for bipolar mania (start at 80 mg/day and increase to 120 or 160 mg/day the next day). However, by combining all available information regarding ziprasidone dosing it becomes clear that enhancing effectiveness requires dosing to the range of 120-160 mg/day. Additional studies suggest that a low initial prescribed dose may result in a higher rate of discontinuation, as discussed below.

Observational studies have demonstrated that ziprasidone is currently being prescribed at higher doses compared to when ziprasidone first became commercially available. This has been demonstrated among outpatients where the initial prescription mean daily and overall mean daily doses of ziprasidone in patients with schizophrenia significantly increased across Medicaid and Commercial populations, with similar trends observed for patients with bipolar disorder.[12] For example, the first (May 2001) and last (December 2005) observed 3-month mean daily doses for ziprasidone were 112 mg/day and 138 mg/day for patients with schizophrenia, and 93 mg/day and 113 mg/day for those with bipolar disorder in the Medicaid cohort.[11] Increases in ziprasidone mean daily dose have also been observed among inpatients in state-operated psychiatric facilities.[13-15] It is possible that these increases have occurred because once clinicians obtained more experience with prescribing ziprasidone they found higher doses to be more effective. In a study evaluating the relationship between the maximum dose of ziprasidone and time to discontinuation in the treatment of schizophrenia/schizoaffective disorder and bipolar disorder in clinical practice, patients receiving ziprasidone 120-160 mg/day experienced a statistically significant lower discontinuation rate compared with those receiving lower doses.[16]

The starting dose may be important in increasing the likelihood of continued treatment with ziprasidone. In a report of 1096 adult Medicaid recipients diagnosed with schizophrenia or schizoaffective disorder, a start with a high dose (120-160 mg/day) was associated with a 20% lower risk of discontinuation than with a low dose (20-60 mg/day).[17] Similarly among 1058 patients who were commercially insured there was a significantly lower risk for discontinuation of therapy when patients were started on ziprasidone 120-160 mg/day, compared with 40-80 mg/day.[18]

However, complicating the interpretability of observational studies is that ziprasidone should be administered with a meal. Thus, a post-hoc analysis was conducted that pooled together the data from available prospective double-blind randomized fixed-dose studies of ziprasidone.[19] The principal advantage of doing this rather than relying only on observational studies is that there is greater assurance that ziprasidone was administered with food, as specified in the study designs. A potential disadvantage of using randomized clinical trial data is that generalizability may be limited because the participants may differ substantially from patients receiving treatment in the "real world", as will be discussed later. Nonetheless, this analysis was consistent with the observational studies and found that higher doses of ziprasidone (120-160 mg/day) were associated with significantly lower all-cause discontinuation rates (Figure 2). These were primarily driven by lower rates of discontinuation due to lack of efficacy. These results are consistent with the observed

**Figure 2.** All-cause discontinuation Kaplan-Meier survival curves, by treatment, in fixed-dose, short-term randomized clinical trials of ziprasidone in patients with schizophrenia.[19] Cox proportional hazard analysis $P$=0.0468, 0.031, and <0.0001, for ziprasidone 40 mg/day, 120 mg/day, or 160 mg/day, respectively, versus placebo. *Reprinted from Citrome L, Yang R, Glue P, Karayal ON. 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. Schizophrenia Res. 2009;111:39-45. Copyright 2009, with permission from Elsevier.*




changes in psychopathology as directly measured by the Brief Psychiatric Rating Scale (BPRS),[19] as well as a prior meta-analysis that aimed to establish dose-response curves and near-maximal effective dose for several antipsychotics.[20] These results are also consistent with positron emission tomography studies that indicate ziprasidone doses of approximately 120 mg/day are required to achieve the $D_2$ receptor blockade associated with reduction of psychotic symptoms.[21,22]

Thus, the optimal dose of ziprasidone as reflected by rates of discontinuation appears to be at least 120 mg/day. For schizophrenia, this is substantially different from guidance contained in product labeling, which includes statements such as "no additional benefit was evidenced for doses above 20 mg b.i.d." for maintenance treatment.[2] Fixed-dose controlled clinical trials are required to further elucidate the dose-response relationship for ziprasidone at labeled doses and beyond. It is important to be aware that dosing established in premarketing pivotal studies does not necessarily reflect the clinical realities when treating patients who are commonly found in public psychiatric settings. Registration studies may be designed without the benefit of complete knowledge of dose-response relationships, and implemented in study subjects who may differ from the patients who will generally receive these medications in the "real world". Examples of these differences include disease severity, chronicity, and the presence of comorbid psychiatric and medical conditions. Moreover, study design for registration protocols may err on the side of caution when selecting doses or the timing of titration to maximum dose, with the unintentional consequence of sacrificing efficacy.[23]

## CONSIDERATIONS WHEN SWITCHING TO ORAL ZIPRASIDONE

Switching antipsychotic treatment to ziprasidone has been assessed in several studies. Reports of three open-label switch studies that enrolled outpatients experiencing suboptimal efficacy or tolerability with their current antipsychotic found that specific benefits depended on the preswitch antipsychotic.[24,25] For example, the largest mean weight loss was observed for patients switched from olanzapine, followed by those switched from risperidone, and that those switched from first-generation antipsychotics had a nonsignificant increase in body weight.[24] Also reported were decreases in prolactin levels among those switched from risperidone and improvement in extrapyramidal symptoms among those switched from first-generation antipsychotics or risperidone.[24]

The three most frequently reported adverse events associated with ziprasidone were insomnia (reported in 21%-42% of patients), somnolence (14%-26%), and anxiety (19%-21%).[24] Transient nausea can also occur. Insomnia was most common in the patients switched from olanzapine. Adverse events were generally mild to moderate in severity. Discontinuations due to adverse events were relatively few (11%, 6%, and 9% after switching from first-generation antipsychotics, olanzapine, and risperidone, respectively).[24] Concomitant lorazepam was frequently used and was administered to 26.9% of patients switched from conventional antipsychotics, 39.4% of patients switched from olanzapine, and 22.4% of those switched from risperidone, compared with baseline usage rates of 12.0%, 18.3%, and 13.8%, respectively.[25] The rate of use of lorazepam was highest during the first week of the switch and by the end of the study at week 6, most patients who once received lorazepam were no longer taking it (5.6% of patients switched from conventional antipsychotics, 8.7% of patients switched from olanzapine, and 10.3% of patients switched from risperidone were still receiving adjunctive lorazepam).

The Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) schizophrenia study also informs us about switching. Phase 2 of CATIE included a "ziprasidone pathway" component, in which patients were re-randomized to receive double-blind ziprasidone, olanzapine, risperidone, or quetiapine.[26] Patients could not be randomized to the same medication they were receiving in phase 1.[27] About half of those in the ziprasidone pathway had discontinued phase 1 because of inefficacy. Although the ziprasidone pathway failed to demonstrate the superiority of ziprasidone in all-cause discontinuation, ziprasidone presented the most favorable weight and metabolic profile and an advantage for ziprasidone in terms of discontinuation because of weight or metabolic effects. Of 61 patients who gained over 7% of their body weight in phase 1, 42% of ziprasidone-treated patients, 20% of risperidone-treated patients, 7% of quetiapine-treated patients, and 0% of olanzapine-treated patients lost over 7% of their body weight during phase 2. This yields clinically significant effect sizes.[28]

General issues regarding switching include: the need to maintain a therapeutic dose of one medication at all times, the possibility of withdrawal effects from discontinuing the original antipsychotic, possibility of additive side effects while the two antipsychotics are taken concurrently, and the risk of medication error due to a complicated treatment regimen.[29] There is also the possibility that ziprasidone will not adequately control an individual patient's psychotic symptoms. Thus, switches offer both opportunity and risk, and the choice should be made using the principles of evidence-based medicine, namely incorporating into the medical decision-making process the best available research evidence regarding efficacy and safety, together with individualized patient assessment and patient preference.[30,31]

## INTRAMUSCULAR ZIPRASIDONE AND TRANSITION TO ORAL ZIPRASIDONE

A quantitative review of the efficacy and safety of the available rapid-acting intramuscular formulations of the second-generation antipsychotics, including ziprasidone, can be found elsewhere.[32] As with the oral formulation of ziprasidone, there appears to be a dose-response in terms of efficacy, with a 20 mg injection resulting in a larger percentage of responders than a 10 mg injection, based on reductions in agitation.[32] Three multicenter open-label randomized controlled studies have been published

that explore the transition from intramuscular ziprasidone to oral ziprasidone, compared with that for intramuscular and oral formulations of haloperidol.[33-35] Transition from intramuscular ziprasidone to the oral formulation occurred within 3 days and was generally well tolerated.[35] Advantages were observed for ziprasidone versus haloperidol in one study in terms of rate of discontinuations in patients assigned to haloperidol (19%) compared with those assigned to ziprasidone (8.9%), and for concomitant treatment with anxiolytics (required in 57.7% of patients in the ziprasidone group and 64.3% of patients in the haloperidol group).[33]

## CONCLUSIONS

Ziprasidone has been shown to be a clinically efficacious agent in the treatment of individuals with schizophrenia or who are experiencing a manic episode. Its major advantage over other second-generation antipsychotics is its more benign metabolic profile. The optimal dose range appears to be 120-160 mg/day for most patients. However, using ziprasidone effectively in the "real world" requires administration with a meal of at least 500 kcal (regardless of fat content). Dosing in the range of 120-160 mg/day in the absence of food will yield inadequate blood levels and result in diminished efficacy. Doubling the administered dose of ziprasidone will not compensate for the decreased bioavailability of ziprasidone without food. Patient education is required regarding this food effect, and the provision of concrete examples of what to eat can be useful. When administered in an inpatient setting, ziprasidone should be explicitly ordered to be given with a 500 kcal meal, even if mealtime is not necessarily when medication is routinely dispensed. Switching to ziprasidone from other antipsychotics can be done using a cross-tapering approach, with consideration given to prescribing lorazepam as needed for insomnia or anxiety when switching off a more sedating antipsychotic. Improvement in metabolic parameters can be expected. Given the above, starting or switching patients to ziprasidone may be a useful option, with consideration given to the varied tolerability and efficacy profiles of the different antipsychotics and the individual preferences of the patient.

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