



Ziprasidone

Updated: January 1, 2014.

OVERVIEW

Introduction

Ziprasidone is an atypical antipsychotic used in the treatment of schizophrenia and bipolar disorder. Use of ziprasidone has not been consistently associated with serum enzyme elevations and has yet to be linked to instances of clinically apparent acute liver injury.

Background

Ziprasidone (zi pras' i done) is a benzisothiazolyl piperazine-type atypical antipsychotic that appears to act as a dopamine type 2 (D2) and serotonin (5-HT₂) receptor antagonist. It also has moderate activity against α -adrenergic and histamine receptors. Ziprasidone is indicated for the therapy of schizophrenia and as either monotherapy or adjunctive therapy for acute manic episodes and maintenance therapy for manic and mixed episodes in bipolar disorder. Ziprasidone was approved for use in the United States in 2001 and is widely used. Ziprasidone is available as capsules of 20, 40, 60 and 80 mg generically and under the brand name Geodon. It is also available as an oral suspension and as a solution for intramuscular injection. The typical initial dose is 20 mg twice daily, which can be increased to a maximum of 100 mg twice daily. Common side effects include somnolence, dizziness, restlessness, fatigue, headache, nausea, dyspepsia, anorexia, dry mouth and blurred vision. Weight gain is uncommon and extrapyramidal symptoms occur in about 5% of patients.

Hepatotoxicity

Liver test abnormalities have been reported in patients taking ziprasidone, but they have not been well characterized in the literature and the frequency of elevations appears to be similar to placebo therapy. Several instances of hypersensitivity reactions have been reported in patients taking ziprasidone, arising within 1 to 4 weeks of starting therapy and with rapid recurrence on reexposure in at least one case. In several instances, the hypersensitivity reaction qualified as DRESS syndrome with an accompanying liver injury either in the form of moderate serum enzymes or a mixed hepatitis with jaundice. In all instances, the symptoms, signs and laboratory abnormalities resolved rapidly with stopping ziprasidone. Thus, on rare occasions, ziprasidone can cause acute hypersensitivity reactions that can be accompanied by hepatitis, but the liver injury is usually mild and self-limited.

Mechanism of Injury

Ziprasidone is largely excreted unchanged in the urine and its hepatic metabolism is minimal, perhaps accounting for why hepatotoxicity is rare. The liver injury caused by ziprasidone is likely due to hypersensitivity

and is idiosyncratic in nature. Ziprasidone is less likely to cause weight gain than other atypical antipsychotics and has not been linked to cases of steatosis.

Outcome and Management

The hypersensitivity reactions to ziprasidone are likely to recur with reexposure and rechallenge should be avoided. Ziprasidone has not been reported to cause acute liver failure, chronic hepatitis or vanishing bile duct syndrome in the published literature. Persons with hypersensitivity to ziprasidone are likely to tolerate other atypical antipsychotic medications, but prospective monitoring is warranted if other such agents are used.

Drug Class: [Antipsychotic Agents](#), Atypicals

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Ziprasidone – Generic, Geodon®

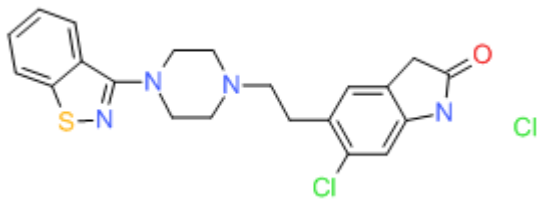
DRUG CLASS

Antipsychotic Agents

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NUMBER	MOLECULAR FORMULA	STRUCTURE
Ziprasidone	122883-93-6	C ₂₁ -H ₂₁ -Cl-N ₄ -O-S	 The chemical structure of ziprasidone is shown. It consists of a benzothiazole ring system connected via a nitrogen atom to a piperazine ring. The piperazine ring is further connected to a benzimidazole ring system, which has a chlorine atom at the 6-position and a carbonyl group at the 2-position. A separate chlorine atom is shown to the right of the structure.

ANNOTATED BIBLIOGRAPHY

References updated: 01 January 2014

Meyer JM. Pharmacotherapy of psychosis and mania. In, Brunton LL, Chabner BA, Knollman BC, eds. Goodman & Gilman's the pharmacological basis of therapeutics. 12th ed. New York: McGraw-Hill, 2011, pp. 417-56. (*Textbook*

of pharmacology and therapeutics).

Daniel DG, Zimbhoff DL, Potkin SG, Reeves KR, Harrigan EP, Lakshminarayanan M. 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: 491-505. PubMed PMID: 10192829.

(Controlled trial of ziprasidone in two doses [n=210] vs placebo [n=92] for 6 weeks; “Changes in liver enzymes were notably rare.” Three of 210 patients had ALT above 3 times ULN, but these were judged to be unrelated to drug therapy; further characterization not given).

Allison DB, Mentore JL, Heo M, Chandler LP, Cappelleri JC, Infante MC, Weiden PJ. Antipsychotic-induced weight gain: a comprehensive research synthesis. *Am J Psychiatry* 1999; 156: 1686-96. PubMed PMID: 10553730.

(Systematic review of 81 articles on weight change with antipsychotics, using change after 10 weeks to compare agents: clozapine +5.7, olanzapine +4.2, chlorpromazine +4.2, risperidone +1.7, loxapine +0.6, haloperidol +0.5, ziprasidone +0.3, molindone -0.1, and pimozide -2.7 kilograms).

Balestrieri M, Vampini C, Bellantuono C. Efficacy and safety of novel antipsychotics: a critical review. *Hum Psychopharmacol* 2000; 15: 499-512. PubMed PMID: 12404619.

(Review on efficacy and safety of antipsychotics; 3 of 702 patients on ziprasidone discontinued therapy because of liver test abnormalities).

Ziprasidone (Geodon) for schizophrenia. *Med Lett Drugs Ther* 2001; 43: 51-2. PubMed PMID: 11402259.

(Brief review of efficacy and safety of ziprasidone shortly after its approval in the United States; side effects include somnolence, extrapyramidal symptoms, and transient prolactin elevations; no mention of ALT elevations or hepatotoxicity).

Arato M, O'Connor R, Meltzer HY; ZEUS Study Group. 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: 207-15. PubMed PMID: 12177583.

(Controlled trial of placebo vs ziprasidone in 3 doses in 294 patients; laboratory abnormalities reported in similar proportion of ziprasidone as placebo treated subjects, but details of ALT levels not provided).

Caley CF, Cooper CK. Ziprasidone: the fifth atypical antipsychotic. *Ann Pharmacother* 2002; 36: 839-51. PubMed PMID: 11978164.

(Review of structure, pharmacology, kinetics, metabolism, efficacy and side effects of ziprasidone; no mention of effects on ALT levels or liver injury).

Choice of an antipsychotic. *Med Lett Drugs Ther* 2003; 45: 102-4. PubMed PMID: 14679353.

(Common side effects of ziprasidone are insomnia, anxiety, headache, nausea, constipation and lightheadedness; unlike clozapine, olanzapine, risperidone and quetiapine, it has little or no effect on weight; no mention of hepatic side effects).

Prior TI, Baker GB. Interactions between the cytochrome P450 system and the second-generation antipsychotics. *J Psychiatry Neurosci* 2003; 28: 99-112. PubMed PMID: 1267017.

(Review of the interactions of the atypical antipsychotics with the P450 system; clozapine metabolized by CYP 1A2 and 3A4 and possibly 2C9 and 2D6; risperidone by CYP 2D6 and possibly 3A4; olanzapine by CYP 1A2 and possibly 2D6; quetiapine and ziprasidone by CYP 3A4).

Tsai CF, Tsai SJ, Hwang JP. Ziprasidone-induced hypersensitivity syndrome in an aged schizophrenia patient. *Int J Geriatr Psychiatry* 2005; 20: 797-9. PubMed PMID: 16035110.

(69 year old Chinese woman developed skin rash and fever 11 days after starting ziprasidone followed by jaundice [bilirubin 4.4 mg/dL, ALT 72 U/L, Alk P 398 U/L, eosinophils 5%], with resolution of all abnormalities within 3 weeks of stopping).

Rettenbacher MA, Baumgartner S, Eder-Ischia U, Edlinger M, Graziadei I, Hofer A, Huber R, et al. Association between antipsychotic-induced elevation of liver enzymes and weight gain: a prospective study. *J Clin Psychopharmacol* 2006; 26: 500-3. PubMed PMID: 16974192.

(Prospective study of 67 patients started on atypical antipsychotics [6 on ziprasidone]; ALT elevations were more frequent in 14 patients who gained >7% of body weight than in 53 who did not [50% vs 19%], and mean changes in ALT, AST and GGT were greater in those who gained weight; all abnormalities were transient, asymptomatic and not associated with bilirubin elevations).

Wright TM, Vandenberg AM. Risperidone- and quetiapine-induced cholestasis. *Ann Pharmacother* 2007; 41: 1518-23. PubMed PMID: 17666578.

(30 year old man developed jaundice on risperidone and lithium for 8 years [bilirubin 4.7 mg/dL, ALT 99 U/L, Alk P 267 U/L], resolving with change of risperidone to ziprasidone, but recurrent jaundice 1 year later 3 weeks after starting quetiapine, having tolerated olanzapine).

Akkaya C, Sarandol A, Aydogan K, Kirli S. Urticaria and angio-oedema due to ziprasidone. *J Psychopharmacol* 2007; 21: 550-2. PubMed PMID: 17446198.

(36 year old Turkish woman developed urticaria and facial edema 4 weeks after starting ziprasidone with normal liver tests and no fever, resolving within 3 days of stopping).

Chalasani N, Fontana RJ, Bonkovsky HL, Watkins PB, Davern T, Serrano J, Yang H, Rochon J; Drug Induced Liver Injury Network (DILIN). Causes, clinical features, and outcomes from a prospective study of drug-induced liver injury in the United States. *Gastroenterology* 2008; 135: 1924-34. PubMed PMID: 18955056.

(Among 300 cases of drug induced liver disease in the US collected between 2004 and 2008; several antidepressants [duloxetine, sertaline, fluoxetine, amitryptilline], but none of the atypical antipsychotic agents were implicated).

Torrent C, Amann B, Sanchez-Moreno J, Colom F, Feinares M, Comes M, Rosa AR, et al. Weight gain in bipolar disorder: pharmacological treatment as a contributing factor. *Acta Psychiatr Scand* 2008; 118: 4-18. PubMed PMID: 18498432.

(Review of frequency of weight gain in patients treated for bipolar disorders, most weight gain occurred with clozapine and olanzapine, but some weight gain also with quetiapine, risperidone, lithium, valproate and gabapentin; not with aripiprazole, ziprasidone, carbamazepine or lamotrigine).

Parsons B, Allison DB, Loebel A, Williams K, Giller E, Romano S, Siu C. Weight effects associated with antipsychotics: a comprehensive database analysis. *Schizophr Res* 2009; 110: 103-10. PubMed PMID: 19321312.

(Analysis of weight gain in 21 placebo controlled trials [~3300 patients]; average monthly weight gain in pounds was +0.1 with placebo, +0.8 olanzapine, +0.6 risperidone, -0.3 ziprasidone. A 5% increase in weight occurred after one year in 13% of placebo, 39% haloperidol, 20% ziprasidone, 45% risperidone and 60% olanzapine treated subjects).

Sacchetti E, Galluzzo A, Valsecchi P, Romeo F, Gorini B, Warrington L; on behalf of the INITIATE Study Group. Ziprasidone vs clozapine in schizophrenia patients refractory to multiple antipsychotic treatments: The MOZART study. *Schizophr Res* 2009; 113: 112-21. PubMed PMID: 19269791.

(Controlled trial of clozapine [300 mg] vs ziprasidone [80-160 mg] daily for 18 weeks; similar efficacy; weight gain +0.8 kg with clozapine vs -2.6 kg with ziprasidone; "no detrimental effects for either drug were observed with regard to liver functions...").

Díaz-Marsá M, Sánchez S, Rico-Villademoros F; for the ZIP-IIG-79 Study Group. Effectiveness and tolerability of oral ziprasidone in psychiatric inpatients with an acute exacerbation of schizophrenia or schizoaffective

disorder: a multicenter, prospective, and naturalistic study. *J Clin Psychiatry* 2009; 70: 4: 509-17. PubMed PMID: 19358789.

(Open label study in 196 inpatients given ziprasidone; no mention of ALT levels or hepatotoxicity).

Addington DE, Labelle A, Kulkarni J, Johnson G, Loebel A, Mandel FS. 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: 46-54. PubMed PMID: 19175979.

(Controlled trial of ziprasidone vs risperidone in 139 patients for 8 weeks; less weight gain with ziprasidone; "One ziprasidone-treated patient had an elevation of liver enzymes and was discontinued from the study").

Kim SW, Shin IS, Kim JM, Bae KY, Yang SJ, Yoon JS. Effectiveness of switching from aripiprazole to ziprasidone in patients with schizophrenia. *Clin Neuropharmacol.* 2010; 33: 121-5. PubMed PMID: 20502130.

(Switching 19 patients with schizophrenia from aripiprazole to ziprasidone resulted in a decline in mean ALT levels [26 to 18 U/L], values becoming normal in 2 of 3 subjects with elevations on aripiprazole).

Reuben A, Koch DG, Lee WM; Acute Liver Failure Study Group. Drug-induced acute liver failure: results of a U.S. multicenter, prospective study. *Hepatology* 2010; 52: 2065-76. PubMed PMID: 20949552.

(Among 1198 patients with acute liver failure enrolled in a US prospective study between 1998 and 2007, 133 were attributed to drug induced liver injury, including 4 due to psychotropic agents; one each for quetiapine, nefazodone, fluoxetine and venlafaxine, but none for phenothiazines or ziprasidone).

Molleston JP, Fontana RJ, Lopez MJ, Kleiner DE, Gu J, Chalasani N; Drug-induced Liver Injury Network. Characteristics of idiosyncratic drug-induced liver injury in children: results from the DILIN prospective study. *J Pediatr Gastroenterol Nutr* 2011; 53: 182-9. PubMed PMID: 21788760.

(Among 30 children with suspected drug induced liver injury, half [n=15] were due to antimicrobials [minocycline 4, INH 3, azithromycin 3] and the rest largely due to CNS agents and anticonvulsants; one case was attributed to perphenazine, but none to ziprasidone).

Gordon JS, Neyman KM, Wells RD, Chen SC. Drug rash with eosinophilia and systemic symptoms (DRESS syndrome). *Cutis* 2012; 89: 180-2. PubMed PMID: 22611746.

(27 year old woman developed pharyngitis, facial swelling, rash and fever 2 weeks after starting ziprasidone [bilirubin 2.6 mg/dL, ALT 688 U/L, Alk P 812 U/L, eosinophils 19%], with recurrence 2 days after ziprasidone was restarted [bilirubin 11.5 mg/dL, ALT 2061 U/L], responding to high doses of prednisone and then tolerating risperidone).

Findling RL, Cavuş I, Pappadopulos E, Vanderburg DG, Schwartz JH, Gundapaneni BK, Delbello MP. Efficacy, long-term safety, and tolerability of ziprasidone in children and adolescents with bipolar disorder. *J Child Adolesc Psychopharmacol* 2013; 23: 545-57. PubMed PMID: 24111980.

(Controlled trial of ziprasidone vs placebo for 4 weeks with a 26 week open label extension study in 237 children or adolescents with bipolar disorder found no "clinically significant mean changes" in liver enzymes).

Drugs for psychiatric disorders. *Treat Guidel Med Lett* 2013; 11 (130): 53-64. PubMed PMID: 23715100.

(Concise summary of current therapies for psychiatric disorders, mentions that ziprasidone can cause prolongation of QT interval and extrapyramidal symptoms, but does not mention liver injury or ALT elevations).

Kim MS, Kim SW, Han TY, Son SJ, Lee JH, Kim EJ. Ziprasidone-induced hypersensitivity syndrome confirmed by reintroduction. *Int J Dermatol* 2014; 53: e267-8. PubMed PMID: 24117439.

(33 year old Korean woman developed rash and fever 3 weeks after starting ziprasidone and lithium, with resolution of stopping both and recurrence one day after restarting ziprasidone [ALT 141, atypical lymphocytes 12%], resolving within 2 weeks of stopping).

Mandrioli R, Protti M, Mercolini L. Evaluation of the pharmacokinetics, safety and clinical efficacy of ziprasidone for the treatment of schizophrenia and bipolar disorder. *Expert Opin Drug Metab Toxicol* 2015; 1: 149-74. PubMed PMID: 25483358.

(Review of the efficacy and safety of ziprasidone does not discuss ALT elevations or hepatotoxicity).