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Olanzapine

Updated: January 26, 2014.

OVERVIEW

Introduction

Olanzapine is an atypical antipsychotic that is used currently in the treatment of schizophrenia and bipolar illness. Olanzapine is not infrequently associated with serum aminotransferase elevations during therapy and there have been rare instances of clinically apparent acute liver injury linked to its use.

Background

Olanzapine (oh lan' za peen) is a thienobenzodiazepine derivative which appears to act as a dopamine (D1-4) and serotonic (5-HT2A/2C and 5-HT6) receptor antagonist. Olanzapine was approved for use in schizophrenia in the United States in 1996 and continues to be used for this indication. Olanzapine is also used in mood disturbances of bipolar I disorder and in combination with other agents for treatment of resistant depression in adults. Olanzapine is available as tablets of 2.5, 5, 7.5, 10, 15 and 20 mg generically and under the brand name Zyprexa; formulations for parenteral use and orally disintegrating tablets are also available, as are fixed combinations with antidepressants such as fluoxetine (Symbyax and generics). A typical dose regimen is 5 to 20 mg daily, starting with a low dose and increasing cautiously. Common side effects include sedation, increased appetite, weight gain, constipation, orthostatic hypotension, dizziness, dry mouth, weakness and akathisia (restlessness).

Hepatotoxicity

Liver test abnormalities have been reported to occur in 10% to 50% of patients on long term therapy with olanzapine. These abnormalities are usually mild, asymptomatic and transient, and can reverse even with continuation of medication. In addition, instances of more marked elevations in serum aminotransferase levels and clinically apparent hepatitis with jaundice have been reported in patients taking olanzapine. The pattern of serum enzyme elevations has ranged from hepatocellular to mixed and even cholestatic. Allergic manifestations (rash, fever, eosinophilia) and autoimmune markers are uncommon. The time to onset of liver injury with olanzapine therapy has varied widely, from a few weeks to a year after starting. In all cases, the injury has resolved rapidly with drug discontinuation. Cases with a long latency and accompanied by significant weight gain may represent nonalcoholic fatty liver disease, rather than olanzapine hepatotoxicity.

Mechanism of Injury

The mechanism by which olanzapine causes serum aminotransferase elevations is not known. Some instances of ALT elevations occurring on olanzapine therapy may be due to nonalcoholic fatty liver disease caused by weight gain that occurs in at least one-quarter of treated patients generally during the first 1 to 2 years of therapy.

Weight gain averages 1 kg/month and can be extreme (20 to 30 kg). Olanzapine has extensive hepatic metabolism, partially via the cytochrome P450 system, and some cases of clinically apparent hepatotoxicity may be due to production of a toxic intermediate of metabolism.

Outcome and Management

The serum aminotransferase elevations that occur on olanzapine therapy are usually self-limited and rarely require dose modification or discontinuation of therapy. No instances of acute liver failure, chronic liver disease or vanishing bile duct syndrome have been attributed to olanzapine. Switching to other atypical antipsychotics is occasionally, but not always associated with recurrence of hepatic injury.

Drug Class: Antipsychotic Agents, Atypicals

CASE REPORT

Case 1. Acute liver injury due to olanzapine.

[Modified from: Domínguez-Jiménez JL, Puente-Gutiérrez JJ, Pelado-García EM, Cuesta-Cubillas D, García-Moreno AM. Liver toxicity due to olanzapine. Rev Esp Enferm Dig 2012; 104: 617-8. PubMed Citation]

A 47 year old patient with a history of paranoid schizophrenia developed jaundice 11 months after starting olanzapine (10 mg daily). She had a vague history of alcoholic liver disease. Laboratory test results showed a total bilirubin of 7.5 mg/dL, ALT 173 U/L and alkaline phosphatase of 178 U/L (Table). Olanzapine was stopped and haloperidol started in its place. Tests for viral hepatitis and autoantibodies were negative. Within 2 weeks, serum bilirubin levels had fallen and all test results returned to normal when she was seen 3 months later.

Key Points

Medication:	Olanzapine
Pattern:	Mixed (R=3.0)
Severity:	3+ (jaundice and hospitalization)
Recovery:	3 months
Other medications:	None mentioned

Laboratory Values

Time After Starting	Time After Stopping	ALT (U/L)	GGT (U/L)	Bilirubin (mg/dL)	Other
11 months	0	173	178	7.5	Admission
	2 weeks	775	181	2.7	
12 months	6 weeks	79	161	0.6	Haloperidol
14 months	14 weeks	9	80	0.4	
Normal Values		**<42**	**<130**	**<1.2**	

Comment

A brief case report with missing information but somewhat typical presentation of drug induced liver injury with a mixed hepatocellular-cholestatic pattern. Olanzapine is a common cause of transient serum aminotransferase elevations, but has rarely been implicated in cases of clinically apparent liver injury with jaundice.

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Olanzapine – Zyprexa®

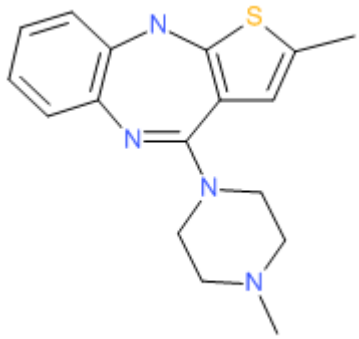
DRUG CLASS

Antipsychotic Agents

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NUMBER	MOLECULAR FORMULA	STRUCTURE
Olanzapine	132539-06-1	C17-H20-N4-S	

ANNOTATED BIBLIOGRAPHY

References updated: 26 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).

Larry D, Ripault MP. Hepatotoxicity of psychotropic drugs and drugs of abuse. In, Kaplowitz N, DeLeve LD, eds. Drug-induced liver disease. 3rd ed. Amsterdam: Elsevier, 2013, pp. 443-62.

(Review of hepatotoxicity of psychiatric agents mentions that olanzapine has rarely been implicated in causing clinically apparent hepatic toxicity).

Beasley CM, Tollefoson GD, Tran PV. Safety of olanzapine. J Clin Psychiatry 1997; 10: 7-13. PubMed PMID: 9265911.

(Retrospective analysis of registration trials of olanzapine as therapy of schizophrenia; weight gain of at least 7% in 40.5% of patients treated with olanzapine, 12.4% with haloperidol and 3.1% with placebo; ALT elevations occurred in 9.4% of olanzapine treated patients, usually within 1-2 weeks of starting and rising above 200 U/L in 2.1%; no cases of clinically apparent hepatitis).

McElroy SL, Frye M, Denicoff K, Altshuler L, Nolen W, Kupka R, Suppes T, et al. Olanzapine in treatment-resistant bipolar disorder. J Affect Disord 1998; 49: 119-22. PubMed PMID: 9609675.

(Open label study of olanzapine in 14 patients, no information on liver test abnormalities).

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, quetiapine +2.5, risperidone +1.7, loxapine +0.6, haloperidol +0.5, ziprasidone +0.3, molindone -0.1, and pimozide -2.7 kg).

Marcus EL, Vass A, Zislin J. Marked elevation of serum creatinine kinase associated with olanzapine therapy. Ann Pharmacother 1999; 33: 697-700. PubMed PMID: 10410183.

(39 year old man was found to have CPK 2252 U/L without symptoms 3 days after starting olanzapine [bilirubin not reported, AST 65 U/L], resolving within a week of stopping).

Conley RR, Meltzer HY. Adverse events related to olanzapine. J Clin Psychiatry 2000; 61 (Suppl 8): 26-29. PubMed PMID: 10811240.

(Review of side effects of olanzapine from large registration trials; weight gain averaged 2-3 kg, but was dose dependent and averaged 12 kg with high dose at one year; "Transient, non-dose-dependent, asymptomatic elevations in liver enzymes have also been noted in olanzapine-treated patients").

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 antipsychotic agents; transient elevations in ALT in 9.4% of olanzapine treated patients, but no clinical symptoms or jaundice reported).

Gerber JE, Cawthon B. Overdose and death with olanzapine: two case reports. Am J Forensic Med Pathol 2000; 21: 249-51. PubMed PMID: 10990286.

(Two patients found dead after olanzapine overdose with high serum levels; no evidence of hepatic toxicity mentioned).

Cadario B. Olanzapine (Zyprexa): suspected serious reactions. CMAJ. 2000; 163: 85-6, 89-90. PubMed PMID: 10920744.

(Among 153 adverse event reports due to olanzapine, there were 22 deaths but none attributed to liver injury; 9 cases of ALT elevation, only 2 above twice normal and one with jaundice [bilirubin not given, ALT 527 U/L, alkaline phosphatase 211 U/L] after 5 months of treatment, without further details or follow up information).

Raz A, Bergman R, Eilam O, Yungerman T, Hayek T. A case report of olanzapine-induced hypersensitivity syndrome. Am J Med Sci 2001; 321: 156-8. PubMed PMID: 11217818.

(34 year old man developed rash, fever, and eosinophilia 2 months after starting olanzapine [bilirubin 1.1 mg/dL, ALT 518 U/L, Alk P 68 U/L], resolving upon stopping olanzapine, but with confounding history of amoxicillin exposure; tolerated risperidone in follow up).

Dumortier G, Cabaret W, Stamatiadis L, Saba G, Benadhira R, Rocamora JF, Aubriot-Delmas B, et al. [Hepatic tolerance of atypical antipsychotic drugs]. Encephale 2002; 28: 542-51. PubMed PMID: 12506267.

(Review of reports of liver injury due to atypical antipsychotics).

Mouradian-Stamatiadis L, Dumortier G, Januel D, Delmas BA, Cabaret W. Liver function tests during treatment with antipsychotic drugs: a case series of 23 patients. Prog Neuropsychopharmacol Biol Psychiatry 2002; 26: 1409-11. PubMed PMID: 12502031.

(23 hospitalized patients on atypical antipsychotics, 6 had ALT or AST elevations by day 14, ALT 48-158 U/L, 2 on risperidone, 2 olanzapine and one amisulpride; 1 on risperidone required discontinuation).

Kelly DL, Conley RR, Richardson CM, Tamminga CA, Carpenter WT Jr. Adverse effects and laboratory parameters of high-dose olanzapine vs. clozapine in treatment-resistant schizophrenia. Ann Clin Psychiatry 2003; 15: 181-6. PubMed PMID: 14971863.

(Crossover study of 8 weeks of olanzapine vs clozapine in 13 patients; ALT elevations occurred in 66% of clozapine, but no olanzapine treated patient; weight gain was greater with olanzapine [~3.4 kg] than clozapine [~1.4 kg]).

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

(Despite a similar chemical structure to clozapine, olanzapine does not appear to cause agranulocytosis; weight gain is common and can be marked; "Increases in hepatic transaminase activity have been reported").

Gonzalez-Heydrich J, Raches D, Wilens TE, Leichtner A, Mezzacappa E. Retrospective study of hepatic enzyme elevations in children treated with olanzapine, divalproex, and their combination. J Am Acad Child Adolesc Psychiatry 2003; 42: 1227-33. PubMed PMID: 14560173.

(52 children receiving olanzapine and/or valproate; ALT elevations occurred in all 12 on combination, 59% on olanzapine alone and 26% on valproate alone; only 2 had ALT >3 times ULN, one with pancreatitis and one with steatohepatitis, resolving with stopping olanzapine).

Haberfellner EM, Honsig T. Nonalcoholic steatohepatitis: a possible side effect of atypical antipsychotics. J Clin Psychiatry 2003; 64: 851. PubMed PMID: 12934993.

(Three men, ages 24 to 31 years with weight gain [24-26 kg] on olanzapine or risperidone for ~4 years had ALT elevations [47-91 U/L]; ultrasound showed evidence of fatty liver).

Kolpe M, Ravasia S. Effect of olanzapine on the liver transaminases. Can J Psychiatry. 2003; 48: 210. PubMed PMID: 12728748.

(Two women, ages 37 and 62 years, developed ALT elevations [237 and 179 U/L] after ~1 month of olanzapine therapy, resolving rapidly with discontinuation; no symptoms and bilirubin normal).

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 CYP1A2 and 3A4 and possibly 2C9 and 2D6; risperidone by CYP2D6 and possibly 3A4; olanzapine by CYP1A2 and possibly 2D6; quetiapine and ziprasidone by CYP3A4).

Jadallah KA, Limauro DL, Colatrella AM. Acute hepatocellular-cholestatic liver injury after olanzapine therapy. Ann Intern Med 2003; 138: 357-8. PubMed PMID: 12585842.

(78 year old woman developed fever, nausea and abdominal pain 13 days after starting olanzapine [bilirubin 1.3 rising to 9.1 mg/dL, ALT 204 to 965 U/L, Alk P 189 to 488 U/L], resolving within 4 weeks of stopping).

Tchernichovsky E, Sirota P. Hepatotoxicity, leucopenia and neutropenia associated with olanzapine therapy. Int J Psychiatry Clin Pract 2004; 8: 173-7. Not in PubMed

(37 year old woman with severe schizophrenia developed abnormal liver tests [bilirubin 1.5 mg/dL, ALT 102 U/L, Alk P 461 U/L] 19 days after starting olanzapine, which was not stopped until 11 weeks later when she had pancytopenia; recurrence on restarting olanzapine one year later [bilirubin 1.6 mg/dL, AST 110, Alk P 270 U/L, neutropenia and fever], resolving in several weeks of stopping).

Bender S, Grohmann R, Engel RR, Degner D, Dittmann-Balcar A, Ruther E. Severe adverse drug reactions in psychiatric inpatients treated with neuroleptics. Pharmacopsychiatry 2004; 37 (Suppl 1): S46-53. PubMed PMID: 15052514.

(Review of severe adverse drug reactions among 35,293 inpatients reported to AMSP; side effects were more common with atypicals [0.5-0.9%] than typical antipsychotics [0.02-0.2%]; increased liver enzymes was the most common adverse reaction to olanzapine, 4th in frequency to clozapine, 6th to haloperidol, 7th to risperidone; no mention of hepatitis or acute liver failure).

Pae CU, Lim HK, Kim TS, Kim JJ, Lee CU, Lee SJ, Lee C, et al. Naturalistic observation on the hepatic enzyme changes in patients treated with either risperidone or olanzapine alone. Int Clin Psychopharmacol 2005; 20: 173-6. PubMed PMID: 15812269.

(Retrospective analysis found ALT elevations more common among 145 patients on olanzapine [25%] than 298 on risperidone [13%] and particularly >3 times ULN [7.6% vs 2.8%]; no instances of jaundice or hepatitis).

Perlis RH, Baker RW, Zarate CA Jr, Brown EB, Schuh LM, Jamal HH, Tohen M. Olanzapine versus risperidone in the treatment of manic or mixed States in bipolar I disorder: a randomized, double-blind trial. J Clin Psychiatry 2006; 67: 1747-53. PubMed PMID: 17196055.

(3 week trial of olanzapine [n=165] vs risperidone [n=164] for bipolar illness; greater weight gain [16% vs 4%] and ALT elevations [by mean of 15.7 U/L vs 1 U/L] with olanzapine).

Green AI, Lieberman JA, Hamer RM, Glick ID, Gur RE, Kahn RS, McEvoy JP, et al.; HGDH Study Group. Olanzapine and haloperidol in first episode psychosis: two-year data. Schizophr Res 2006; 86: 234-43. PubMed PMID: 16887334.

(Trial of olanzapine vs haloperidol for 2 years in 263 patients with psychosis; olanzapine more often led to weight gain [15.4 vs 7.5 kg] and ALT elevations [63% vs 29%], but no mention of clinically apparent liver injury).

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 [21 on olanzapine] started on atypical antipsychotics; ALT elevations were more frequent [and higher] in 14 patients who gained >7% of body weight than in 53 who did not [50% vs 19%]; all elevations were transient, asymptomatic and not associated with bilirubin elevations).

Ozcanli T, Erdogan A, Ozdemir S, Onen B, Ozmen M, Doksat K, Sonsuz A. Severe liver enzyme elevations after three years of olanzapine treatment: a case report and review of olanzapine associated hepatotoxicity. Prog Neuropsychopharmacol Biol Psychiatry 2006; 30: 1163-6. PubMed PMID: 16632162.

(44 year old woman with bipolar illness treated with olanzapine for 3 years developed anorexia and abdominal pain [normal bilirubin, ALT 710 U/L, GGT 56 U/L], resolving 3 weeks after stopping; ALT had been normal previously).

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

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

Atasoy N, Erdogan A, Yalug I, Ozturk U, Konuk N, Atik L, Ustundag Y. A review of liver function tests during treatment with atypical antipsychotic drugs: a chart review study. Prog Neuropsychopharmacol Biol Psychiatry 2007; 31: 1255-60. PubMed PMID: 17600607.

(Retrospective analysis of 194 patients receiving atypical antipsychotic agents; ALT >3 times normal occurred in 27% often in 1st month; among 33 receiving olanzapine, 30% had ALT elevation, 18% at 6 months, and 2 stopped drug for ALT elevations of 3 times "basal level").

Johnsen E, Jørgensen HA. Effectiveness of second generation antipsychotics: a systematic review of randomized trials. BMC Psychiatry 2008; 8: 31. PubMed PMID: 18439263.

(Systematic review of 16 reports of 10 randomized trials of antipsychotic agents; more weight gain with olanzapine, no mention of ALT elevations).

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).

Sikich L, Frazier JA, McClellan J, Findling RL, Vitiello B, Ritz L, Ambler D, et al. Double-blind comparison of first- and second-generation antipsychotics in early-onset schizophrenia and schizo-affective disorder: findings from the treatment of early-onset schizophrenia spectrum disorders (TEOSS) study. Am J Psychiatry 2008; 165: 1420-31. PubMed PMID: 18794207.

(Prospective trial of molindone [1st generation] vs olanzapine or risperidone [2nd generation antipsychotic agents] for schizophrenia in 199 youths found similar rates of efficacy [34-50%], but more weight gain [mean 6.1 kg] and ALT elevations with olanzapine).

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; severe antidepressants [duloxetine, sertaline, fluoxetine, amitryptilline], but none of the atypical antipsychotic agents, were implicated).

Kantrowitz JT, Citrome L. Olanzapine: review of safety 2008. Expert Opin Drug Saf 2008; 7: 761-9. PubMed PMID: 18983222.

(Review of side effects of olanzapine mentions that weight gain averages 1 kg/month at least for the first year and that ALT elevations occur in 2%).

Kane JM, Osuntokun O, Kryzhanovskaya LA, Xu W, Stauffer VL, Watson SB, Breier A. A 28-week, randomized, double-blind study of olanzapine versus aripiprazole in the treatment of schizophrenia. J Clin Psychiatry 2009; 70: 572-81. PubMed PMID: 19323965.

(Controlled trial of olanzapine [n=281] vs aripipazole [n=285] for 28 weeks at 60 centers; no mention of ALT values).

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).

Flanagan RJ. Fatal toxicity of drugs used in psychiatry. Hum Psychopharmacol 2008; 23 Suppl 1: 43-51. PubMed PMID: 18098225.

(Deaths from fatal poisonings decreased in England and Wales between 1993-2004, antipsychotic overdose fatalities higher for phenothiazines than atypicals; deaths/million prescriptions being 29 for chlorpromazine, 15.5 thioridazine, 3.9 trifluoperazine, 13.3 olanzapine, 21 clozapine and 31.3 quetiapine).

Lui SY, Tso S, Lam M, Cheung EF. Possible olanzapine-induced hepatotoxicity in a young Chinese patient. Hong Kong Med J 2009; 15: 394-6. PubMed PMID: 19801701.

(17 year old man developed jaundice 8 days after starting olanzapine for schizophrenia [bilirubin 7.2 mg/dL, ALT 120 U/L, Alk P 250 rising to 440 U/L], resolving within 2 months of stopping).

Gómez Espín R, Sánchez Quiles I, Hallal H, Plaza J. [Acute hepatocellular lesion after successive exposure to clozapine and olanzapine in a patient with chronic hepatitis C infection]. Gastroenterol Hepatol 2010; 33: 150-2. Spanish. PubMed PMID: 19914745.

(35 year old man with chronic hepatitis C developed asymptomatic rise in ALT [188 to 721 U/L] and GGT [134 to 648 U/L] 2 months after starting clozapine, improving on stopping and recurring one month after starting olanzapine [ALT 166 to 714 U/L], resolving upon stopping again).

Devarbhavi H, Dierkhising R, Kremers WK, Sandeep MS, Karanth D, Adarsh CK. Single-center experience with drug-induced liver injury from India: causes, outcome, prognosis, and predictors of mortality. Am J Gastroenterol 2010; 105: 2396-404. PubMed PMID: 20648003.

(313 cases of drug induced liver injury were seen over a 12 year period at a large hospital in Bangalore, India; leading causes were antituberculosis agents [58%], anticonvulsants [11%], and NSAIDs [2%]; 17 cases [5%] were due to olanzapine).

McCormack PL. Olanzapine: in adolescents with schizophrenia or bipolar I disorder. CNS Drugs 2010; 24: 443-52. *(Review of indications, clinical efficacy and safety of olanzapine in adolescents;* 3-6 weeks of olanzapine therapy was associated with weight gain in 42% of adolescents and ALT elevations in 23%; average ALT increase was 20 U/L vs -3 U/L with placebo) PubMed PMID: 20369908.

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Ferrajolo C, Capuano A, Verhamme KM, Schuemie M, Rossi F, Stricker BH, Sturkenboom MC. Drug-induced hepatic injury in children: a case/non-case study of suspected adverse drug reactions in VigiBase. Br J Clin Pharmacol 2010; 70: 721-8. PubMed PMID: 21039766.

(World wide pharmacovigilance database contained 9036 hepatic adverse drug reactions in children, olanzapine ranked 16th with 62 reports [adjusted reporting odds ratio of 3.1], and clozapine ranked 38th wtih 36 cases [0.8]).

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, none were attributed to olanzapine or other atypical antipsychotic medications).

Manceaux P, Constant E, Zdanowicz N, Jacques D, Reynaert C. Management of marked liver enzyme increase during olanzapine treatment: a case report and review of the literature. Psychiatr Danub 2011; 23 Suppl 1: S15-7. PubMed PMID: 21894094.

(45 year old woman with intermittent mild elevations of ALT during therapy with olanzapine and clozapine [ALT 16-92 U/L, AST 16-46 U/L, GGT 26-269 U/L, bilirubin not given]).

Domínguez-Jiménez JL, Puente-Gutiérrez JJ, Pelado-García EM, Cuesta-Cubillas D, García-Moreno AM. Liver toxicity due to olanzapine. Rev Esp Enferm Dig 2012; 104: 617-8. PubMed PMID: 23368661.

(47 year old developed jaundice 11 months after starting olanzapine [bilirubin 7.5 mg/dL, ALT 173 U/L, Alk P 178 U/L], resolving within 3 months of stopping: Case 1).