



Quetiapine

Updated: May 15, 2018.

OVERVIEW

Introduction

Quetiapine is an atypical antipsychotic used in the treatment of schizophrenia and bipolar disorder. Use of quetiapine has been associated with serum aminotransferase elevations and in rare instances with clinically apparent acute liver injury.

Background

Quetiapine (kwe tye' a peen) is an atypical antipsychotic and dibenzodiazepine derivative which appears to act as a dopamine (D1-4) and serotonin (5-HT₂) receptor antagonist. It also may have activity against histamine and alpha adrenergic receptors. Quetiapine is indicated for the treatment of schizophrenia and as either monotherapy or adjunctive therapy for acute manic episodes or as maintenance therapy in bipolar I disorder. It is also used in treatment of depressive episodes associated with bipolar I or II disorder and for major depressive disorders in combination with antidepressants. Quetiapine was approved for use in the United States in 1997 and is still widely used. Quetiapine is available as tablets of 25, 50, 100, 200, 300 and 400 mg under the brand name Seroquel. Typical doses vary from 300 to 800 mg daily given in two divided doses. Extended release forms are also available for once daily dosing. Common side effects include dizziness, sedation, somnolence, dry mouth, constipation, weakness, postural hypotension, increased appetite and weight gain. Rare, but potentially severe adverse events include neuroleptic malignant syndrome, tardive dyskinesia, severe dyslipidemia, diabetes, weight gain, hypotension, bone marrow suppression and cataracts.

Hepatotoxicity

Liver test abnormalities may occur in up to 30% of patients on long term therapy with quetiapine, but elevations are uncommonly above 3 times the upper limit of normal. The aminotransferase abnormalities are usually mild, asymptomatic and transient, reversing even with continuation of medication. Instances of clinically apparent acute liver injury have been reported due to quetiapine, but they are rare. The onset of jaundice is within 1 to 4 weeks of starting the drug, and the pattern of serum enzyme elevations is typically hepatocellular. Signs of immunoallergic manifestations (fever, rash and eosinophilia) are rare, as are autoantibodies. Most cases are mild to moderate in severity and self-limited in course. Instances of acute liver failure have been reported but not vanishing bile duct syndrome or chronic liver injury.

Likelihood score: B (likely but rare cause of clinically apparent liver injury).

Mechanism of Injury

The mechanism by which quetiapine causes serum aminotransferase elevations is not known, but is likely due to production of a toxic intermediate by its metabolism. Quetiapine is extensively metabolized by the liver via sulfoxidation and oxidation, partially via CYP 3A4. Some instances of serum aminotransferase elevations occurring on quetiapine 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.

Outcome and Management

The serum aminotransferase elevations that occur on quetiapine therapy are usually self-limited and usually do not require dose modification or discontinuation of therapy. Cases of clinically apparent liver injury are usually mild to moderate in severity and self-limited course. Rare instances of acute liver failure due to quetiapine have been reported, but it has not been implicated in cases of chronic liver disease or vanishing bile duct syndrome. Patients with quetiapine induced liver injury may have cross sensitivity to other atypical antipsychotics (risperidone) but may tolerate others.

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

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Quetiapine – Seroquel®

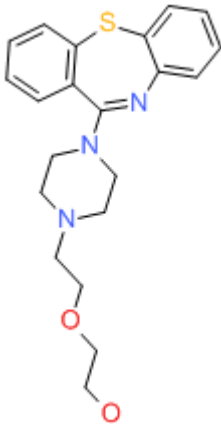
DRUG CLASS

Antipsychotic Agents

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NUMBER	MOLECULAR FORMULA	STRUCTURE
Quetiapine	111974-69-7	C ₂₁ -H ₂₅ -N ₃ -O ₂ -S	 <p>The chemical structure of Quetiapine is shown. It features a central benzothiazine ring system. One of the benzene rings in the benzothiazine core is substituted with a piperazine ring. The piperazine ring is further substituted with a propyl chain that ends in an ether linkage (-O-CH₂-CH₂-O-).</p>

ANNOTATED BIBLIOGRAPHY

References updated: 15 May 2018

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).

Quetiapine for schizophrenia. Med Lett Drugs Ther 1997; 39: 117-8. PubMed PMID: 9422044.

(Brief review of efficacy and safety of quetiapine shortly after its approval in the US; common side effects include somnolence, dizziness, constipation, postural hypotension, dry mouth and weight gain; "increases in serum aminotransferase activity have occurred in some patients").

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).

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 quetiapine; "Mild, transient, reversible and asymptomatic elevations in the liver enzymes were seen in a small number of patients").

Garver DL. Review of quetiapine side effects. J Clin Psychiatry 2000; 61 (Suppl 8): 31-3. PubMed PMID: 10811241.

(Discussion of side effects [weight gain, sedation, extrapyramidal syndrome] of quetiapine based upon known profile of neuroreceptor blockade).

Mullen J, Jobson MD, Sweitzer D. A comparison of the relative safety, efficacy, and tolerability of quetiapine and risperidone in outpatients with schizophrenia and other psychotic disorders: the quetiapine experience with safety and tolerability (QUEST) study. Clin Ther 2001; 23: 1839-54. PubMed PMID: 11768836.

(4 month trial of quetiapine vs risperidone in 728 patients at 115 centers; no mention of ALT abnormalities or adverse events from liver injury).

Lieberman JA, Perkins DO. Quetiapine: a 5-year update. J Clin Psychiatry 2002; 63: Suppl 13: 3-4. Not in PubMed

(Editorial; quetiapine discovered in 1985 at AstraZeneca, approved in US for schizophrenia in 1997).

Nasrallah H, Tandon R. Efficacy, safety, and tolerability of quetiapine in patients with schizophrenia. J Clin Psychiatry 2002; 63: Suppl 13: 12-20. PubMed PMID: 12562142.

(Review of 9 clinical trials of quetiapine in patients with schizophrenia; ALT elevations occurred but were mild and reversible; ALT levels were >3 times ULN in 6% of quetiapine- vs 1% of placebo-recipients, usually within the first 3 weeks of treatment and without hepatitis or jaundice).

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

(Quetiapine, a second generation antipsychotic, is generally well tolerated; no mention of hepatic 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: 12670127.

(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).

El Hajj I, Sharara AI, Rockey DC. Subfulminant liver failure associated with quetiapine. *Eur J Gastroenterol Hepatol* 2004; 16: 1415-8. PubMed PMID: 15618854.

(58 year old woman developed jaundice 1 month after starting quetiapine [bilirubin 17.3 mg/dL, ALT 1245 U/L, Alk P 265 U/L, ANA 1:2560], progressing to liver failure and death within 21 days; autopsy showed massive necrosis).

Langman LJ, Kaliciak HA, Carlyle S. Fatal overdoses associated with quetiapine. *J Anal Toxicol* 2004; 28: 520-5. PubMed PMID: 15516308.

(Three cases of overdose with quetiapine, 39-56 year olds, found dead at home soon after overdose; respiratory arrest; no information on hepatic 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 started on atypical antipsychotics [9 on quetiapine]; ALT elevations were more frequent in 14 who gained >7% of body weight than in the 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 after being 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 1 year later developed recurrent jaundice 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 on 194 patients; ALT levels were >3 times ULN in 27% often in first month; among 48 receiving quetiapine, 27% had ALT elevations, 23% at 6 months, but they were modest and none had elevations greater than 3 fold).

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).

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, sertraline, fluoxetine, amitriptylline], but none of the atypical antipsychotic agents were implicated).

- Shpaner A, Li W, Ankoma-Sey V, Botero RC. Drug-induced liver injury: hepatotoxicity of quetiapine revisited. *Eur J Gastroenterol Hepatol* 2008; 20: 1106-9. PubMed PMID: 19047843.
- (21 year old man developed jaundice 10 days after starting quetiapine [bilirubin 14.7 mg/dL, ALT 2582 U/L, Alk P 167 U/L, ANA negative, prolonged INR], resolving completely with stopping).*
- 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).*
- 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; 1 each for quetiapine, nefazodone, fluoxetine and venlafaxine).*
- Naharci MI, Karadurmus N, Demir O, Bozoglu E, Ak M, Doruk H. Fatal hepatotoxicity in an elderly patient receiving low-dose quetiapine. *Am J Psychiatry* 2011; 168: 212-3. PubMed PMID: 21297052.
- (77 year old woman developed fatigue and jaundice 9 days after starting quetiapine [bilirubin 4.8 mg/dL, ALT 1565 U/L, Alk P 178 U/L, INR 4.1], with subsequent multiorgan failure and death, despite improvement in liver tests).*
- Al Mutairi F, Dwivedi G, Al Ameel T. Fulminant hepatic failure in association with quetiapine: a case report. *J Med Case Rep* 2012; 6: 418. PubMed PMID: 23234465.
- (59 year old woman developed weakness 3 weeks and jaundice 6 weeks after starting quetiapine [bilirubin 14.3 mg/dL, ALT 711 U/L, Alk P 196 U/L, INR 2.7], with signs of hepatic failure, but ultimate slow recovery after stopping).*
- Lin CH, Liu CM, Huang WL. Quetiapine-induced hepatocellular damage. *Psychosomatics* 2012; 53: 601-2. PubMed PMID: 23157997.
- (47 year old woman developed serum enzyme elevations within 3 weeks of starting quetiapine for schizophrenia [bilirubin 0.4 mg/dL, ALT 113 U/L, Alk P 547 U/L], having been normal shortly before and returning to normal within 2 weeks of decreasing the dose [from 400 to 300 mg daily] and recurring when high doses were restarted).*
- Sistanizad M, Peterson GM. Drug-induced liver injury in the Australian setting. *J Clin Pharm Ther* 2013; 38: 115-20. PubMed PMID: 23350857.
- (Among 17 cases of suspected drug induced liver injury seen at a single referral hospital in Tasmania over a 12 month period, one was attributed to quetiapine occurring in a 63 year old woman with a mixed pattern of liver injury [peak ALT 467 U/L, Alk P 265 U/L] and judged as only "possibly" due to the drug).*
- Greil W, Häberle A, Schuhmann T, Grohmann R, Baumann P. Age and adverse drug reactions from psychopharmacological treatment: data from the AMSP drug surveillance programme in Switzerland. *Swiss Med Wkly* 2013; 143: w13772. PubMed PMID: 23821346.
- (Among 39,728 patients treated with psychiatric medications in Swiss hospitals between 2001 and 2010 who were monitored in a drug surveillance program, rates of severe adverse events were similar in those above and below the age of 60 [1.6% vs 1.8%], although weight gain and ALT elevations were less frequent in the elderly [details not provided]).*

Björnsson ES, Bergmann OM, Björnsson HK, Kvaran RB, Olafsson S. Incidence, presentation and outcomes in patients with drug-induced liver injury in the general population of Iceland. *Gastroenterology* 2013; 144: 1419-25. PubMed PMID: 23419359.

(In a population based study of drug induced liver injury from Iceland, 96 cases were identified over a 2 year period, but none were attributed to quetiapine or other atypical antipsychotic agents).

Brown ES, Davila D, Nakamura A, Carmody TJ, Rush AJ, Lo A, Holmes T, et al. A randomized, double-blind, placebo-controlled trial of quetiapine in patients with bipolar disorder, mixed or depressed phase, and alcohol dependence. *Alcohol Clin Exp Res* 2014; 38: 2113-8. PubMed PMID: 24976394.

(Among 90 patients with bipolar disorder with depression and alcohol dependence who were treated with quetiapine or placebo for 12 weeks, alcohol use was similar in the two groups; ALT levels were not mentioned, but there were no liver related serious adverse events).

Hernández N, Bessone F, Sánchez A, di Pace M, Brahm J, Zapata R, A Chirino R, et al. Profile of idiosyncratic drug induced liver injury in Latin America. An analysis of published reports. *Ann Hepatol* 2014; 13: 231-9. PubMed PMID: 24552865.

(Systematic review of literature of drug induced liver injury in Latin American countries published from 1996 to 2012 identified 176 cases, none of which were attributed to quetiapine or other atypical antipsychotic medications).

Chalasani N, Bonkovsky HL, Fontana R, Lee W, Stolz A, Talwalkar J, Reddy KR, et al.; United States Drug Induced Liver Injury Network. Features and outcomes of 899 patients with drug-induced liver injury: The DILIN Prospective Study. *Gastroenterology* 2015; 148: 1340-52.e7. PubMed PMID: 25754159.

(Among 899 cases of drug induced liver injury enrolled in a US prospective study between 2004 and 2013, 3 of which were attributed to quetiapine).

Vatsalya V, Pandey A, Schwandt ML, Cave MC, Barve SS, Ramchandani VA, McClain CJ. Safety assessment of liver injury with quetiapine fumarate XR management in very heavy drinking alcohol-dependent patients. *Clin Drug Investig* 2016; 36: 935-44. PubMed PMID: 27503091.

(Among 218 adults with alcohol dependence treated with quetiapine or placebo for 12 weeks, there was a moderate increase in the likelihood of having ALT elevations in quetiapine treated subjects with and without preexisting elevations, although the differences [not provided] were judged to be "not clinically significant in that they required no medical management").

Morlán-Coarasa MJ, Arias-Loste MT, Ortiz-García de la Foz V, Martínez-García O, Alonso-Martín C, Crespo J, Romero-Gómez M, et al. Incidence of non-alcoholic fatty liver disease and metabolic dysfunction in first episode schizophrenia and related psychotic disorders: a 3-year prospective randomized interventional study. *Psychopharmacology (Berl)* 2016; 233: 3947-52. PubMed PMID: 27620899.

(Among 191 schizophrenic patients treated with an atypical antipsychotic agent for at least 3 years, surrogate markers for steatosis arose in 48 [25%], most of whom had a 7% increase in body weight [n=44: 92%], increase in triglycerides [54%], total cholesterol [52%], and waist circumference [68%]; changes in regard to fatty liver did not vary by specific antipsychotic agent [46 received quetiapine]).

Hayes JF, Marston L, Walters K, Geddes JR, King M, Osborn DP. Adverse renal, endocrine, hepatic, and metabolic events during maintenance mood stabilizer treatment for bipolar disorder. *PLoS Med* 2016; 13: e1002058. PubMed PMID: 27483368.

(Analysis of UK electronic health data on patients with bipolar disorder between 1995 and 2013, found greater than 15% weight gain to be higher with valproate [Hazard Ratio: HR=1.6], olanzapine [HR=1.8], quetiapine [HR=1.7] compared to lithium alone).

Das A, Guarda LA, Allen LG. Liver injury associated with quetiapine: an illustrative case report. J Clin Psychopharmacol 2017; 37: 623-5. PubMed PMID: 28786826.

(45 year old woman developed jaundice a year after starting and 3 weeks after increasing the dose of quetiapine [bilirubin 18.2 mg/dL, ALT 95 U/L, Alk P 267 U/L, INR 1.45], which improved on stopping, but documentation not provided).