U.S. National Library of Medicine
National Center for Biotechnology Information

**NLM Citation:** LiverTox: Clinical and Research Information on Drug-Induced Liver Injury [Internet]. Bethesda (MD): National Institute of Diabetes and Digestive and Kidney Diseases; 2012-. Sertraline. [Updated 2013 Dec 23].
**Bookshelf URL:** https://www.ncbi.nlm.nih.gov/books/


# Sertraline

Updated: December 23, 2013.

# OVERVIEW

## Introduction

Sertraline is a selective serotonin reuptake inhibitor (SSRI) used in the therapy of depression, anxiety disorders and obsessive-compulsive disorder. Sertraline therapy can be associated with transient asymptomatic elevations in serum aminotransferase levels and has been linked to rare instances of clinically apparent acute liver injury.

## Background

Sertraline (ser' tra leen) is a selective serotonin reuptake inhibitor (SSRI) that acts by blocking the reuptake of serotonin in CNS synaptic clefts, thus increasing serotonin levels in the brain which is associated with its psychiatric effects. Sertraline was approved for use in the United States in 1991, and it remains in wide use, with almost 40 million prescriptions being filled yearly. Indications for sertraline include major depression, obsessive-compulsive disorder, panic disorder, and major anxiety disorders including social anxiety, post-trauma stress and generalized anxiety disorder. Sertraline is also used for headache, premenstrual dysphoric disorder, diabetic neuropathy and premature ejaculation. Sertraline is available as tablets of 25, 50 and 100 mg and as an oral suspension in multiple generic forms and under the brand name of Zoloft. The recommended dosage for depression in adults is 50 or 100 mg once daily, increasing the dosage by 25 or 50 mg increments to a maximum of 200 mg. Common side effects are drowsiness, dyspepsia, nausea, headache, increased sweating, increased appetite, weight gain and sexual dysfunction.

## Hepatotoxicity

Liver test abnormalities have been reported to occur in up to 1% of patients on sertraline, but elevations are usually modest and infrequently require dose modification or discontinuation. Rare instances of acute, clinically apparent episodes of liver injury with marked liver enzyme elevations with or without jaundice have been reported in patients on sertraline. The onset of injury is usually within 2 to 24 weeks and the pattern of serum enzyme elevations has varied from hepatocellular to mixed and cholestatic. Autoimmune (autoantibodies) and immunoallergic features (rash, fever, eosinophilia) are uncommon. Actue liver failure due to sertraline has been described but is very rare.

## Mechanism of Injury

The mechanism by which sertraline causes liver injury is not known. Sertraline is metabolized at least in part by the liver, mainly via the cytochrome P450 system and PYP 2D6 and 2B6 which can cause drug-drug interactions. The hepatotoxicity of sertraline may be mediated by toxic intermediates of its metabolism.

## Outcome and Management

The serum aminotransferase elevations that occur on sertraline therapy are usually self-limited and do not require dose modification or discontinuation of therapy. Rare instances of acute liver failure have been attributed to sertraline therapy. Rechallenge usually results in recurrence of liver injury and should be avoided. Persons with intolerance to sertraline may have similar reactions to other SSRIs and careful monitoring is warranted if other such agents are used.

Drug Class: Antidepressant Agents

Other Drugs in the Subclass, SNRIs/SSRIs: Citalopram, Escitalopram, Duloxetine, Fluoxetine, Fluvoxamine, Levomilnacipran, Paroxetine, Venlafaxine, Vilazodone, Vortioxetine

# CASE REPORT

## Case 1. Acute liver injury due to sertraline.

[Modified from: Hautekeete ML, Colle I, van Vlierberghe H, Elewaut A. Symptomatic liver injury probably related to sertraline. Gastroenterol Clin Biol 1998; 22: 364-5. PubMed Citation]

A 44 year old woman with mild reactive depression was treated with sertraline (50 mg daily) and developed fatigue followed by pruritus and jaundice 4-5 weeks later. She was also on levothyroxine and birth control pills which she had been taking for several years. She drank little alcohol and had no previous history of liver disease or known exposures to hepatitis. On presentation, she was jaundiced but had no fever or rash. Laboratory tests showed elevations in serum bilirubin and enzyme levels (Table), which were reported to have been normal in the past. She was admitted for evaluation; sertraline and the oral contraceptives were discontinued. Tests for hepatitis A, B and C were negative. There were low titers of antinuclear antibody (ANA 1:40), but no smooth muscle or mitochondrial antibodies. Abdominal ultrasound showed no evidence of biliary obstruction. She began to improve without specific therapy; jaundice resolved within 1 month, pruritus within 2 months and laboratory tests were normal at 6 months after presentation. Oral contraceptives were restarted without further incident.

### Key Points

| | |
|---|---|
| Medication: | Sertraline |
| Pattern: | Initially mixed (R=2.5), later cholestatic (R=1.2) |
| Severity: | 3+ (jaundice, hospitalization) |
| Latency: | 1 month |
| Recovery: | 1-2 months symptomatically, 6 months biochemically |
| Other medications: | Birth control pills, levothyroxine |

### Laboratory Values

| Time After Starting | Time After Stopping | ALT* (U/L) | Alk P* (U/L) | Bilirubin* (mg/dL) | Other |
|---|---|---|---|---|---|
| Sertraline taken for 5 weeks | | | | | |
| 1 month | 0 | 300 | 333 | 4.2 | Sertraline stopped |
| | 1 week | 236 | 299 | 5.1 | Ultrasound normal |
| | 2 weeks | 116 | 311 | 3.3 | |
| 2 months | 4 weeks | 132 | 253 | 1.8 | |

*Table continued from previous page.*

| Time After Starting | Time After Stopping | ALT* (U/L) | Alk P* (U/L) | Bilirubin* (mg/dL) | Other |
|---|---|---|---|---|---|
| 3 months | 2 months | 84 | 173 | 0.8 | |
| 5 months | 4 months | 44 | Normal | 0.6 | |
| 7 months | 6 months | Normal | Normal | 0.6 | |
| **Normal Values** | | **<40** | **<115** | **<1.2** | |

*Converted from times the upper limit of normal to U/L using normals provided.

### Comment

More than 20 million prescriptions for sertraline are filled yearly in the United States, and therapy is typically long term. Nevertheless, cases of clinically apparent liver disease from sertraline are rare. This case was typical with an onset within 1 to 3 months of starting therapy and a somewhat prolonged course of cholestatic hepatitis, but with ultimate recovery. When patients develop acute liver injury from an SSRI, it is not clear whether another member of this group can be substituted. A structurally unrelated substitute along with careful monitoring is perhaps prudent if antidepressant therapy is considered necessary.

## PRODUCT INFORMATION

**REPRESENTATIVE TRADE NAMES**

Sertraline – Generic, Zoloft®

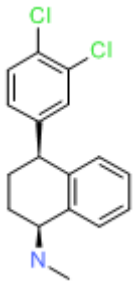
**DRUG CLASS**

Antidepressant Agents

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

## CHEMICAL FORMULA AND STRUCTURE

| DRUG | CAS REGISTRY NUMBER | MOLECULAR FORMULA | STRUCTURE |
|---|---|---|---|
| Sertraline | 79617-96-2 | C17-H17-C12-N |  |



## ANNOTATED BIBLIOGRAPHY

References updated: 23 December 2013

Zimmerman HJ. Antidepressants. In, Zimmerman HJ. Hepatotoxicity: the adverse effects of drugs and other chemicals on the liver. 2nd ed. Philadelphia: Lippincott, 1999, pp. 493-8.

*(Expert review of hepatotoxicity published in 1999; reports that one case of acute drug-induced liver injury attributed to sertraline has been published).*

Larrey 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 antidepressants mentions that clinically apparent liver injury from the SSRIs is rare and serratine has been implicated in only a few cases of severe hepatic injury).*

O'Donnell JM, Shelton RC. Pharmacotherapy of depression and anxiety disorders. In, Brunton LL, Chabner BA, Knollman BC, eds. Goodman & Gilman's the pharmacological basis of therapeutics. 12th ed. New York: McGraw-Hill, 2011, pp. 397-416.

*(Textbook of pharmacology and therapeutics).*

Doogan DP. Toleration and safety of sertraline: experience worldwide. Int Clin Psychopharmacol 1991; 6 (Suppl 2): 47-56. PubMed PMID: 1806630.

*(Rates of drug discontinuation for serum enzyme elevations were 0.5% for 1902 patients on sertraline vs 0.6% of 500 on active comparators and 0.0% of 666 on placebo; no cases of clinically apparent liver injury).*

Menon RR, Howard R. Sertraline and liver toxicity in the elderly. Int J Geriatr Psychiatry 1994; 9: 332-4. Not in PubMed

*(Two cases of sertraline hepatotoxicity; 81 year old man had a rise in AST [36→98 U/L] and Alk P [78→452 U/L] without jaundice 3 weeks after starting sertraline, resolving within 2 months of stopping; 84 year old woman developed rise in ALT [1148 U/L] and Alk P [117→549 U/L], with subsequent multiorgan failure and death; few specific details given).*

Hautekeete ML, Colle I, van Vlierberghe H, Elewaut A. Symptomatic liver injury probably related to sertraline. Gastroenterol Clin Biol 1998; 22: 364-5. PubMed PMID: 9762229.

*(44 year old woman developed jaundice, fatigue and itching 4-5 weeks after starting sertraline [bilirubin 4.2 mg/dL, ALT 7.5 times ULN, Alk P 2.9 times ULN], resolving within few months of stopping).*

Mourilhe P, Stokes PE. Risks and benefits of selective serotonin reuptake inhibitors in the treatment of depression. Drug Saf 1998; 18: 57-82. PubMed PMID: 9466088.

*(Review of pharmacology, efficacy and safety of SSRIs; no mention of ALT elevations or hepatotoxicity).*

Grohmann R, Rüther E, Engel RR, Hippius H. Assessment of adverse drug reactions in psychiatric inpatients with the AMSP drug safety program: methods and first results for tricyclic antidepressants and SSRI. Pharmacopsychiatry 1999; 32: 21-8. PubMed PMID: 10071179.

*(Analysis of reporting of adverse events among inpatients in 29 German hospitals between 1993 to 1997; 896 severe adverse events among 48,564 patients [1.8%], both total and hepatic events were more common with tricyclics than SSRIs).*

Kim KY, Hwang W, Narendran R. Acute liver damage possibly related to sertraline and venlafaxine ingestion. Ann Pharmacother 1999; 33: 381-2. PubMed PMID: 10200868.

*(27 year old man took overdose of sertraline and cephalexin and had elevations of ALT to 1247 U/L, bilirubin 2.1 mg/dL; switched to venlafaxine, but 1 week later developed abdominal pain with bilirubin 1.6 mg/dL and ALT 814 U/L, improving on stopping but relapsing 3 days after restarting sertraline; recovered on stopping all SSRIs).*

Verrico MM, Nace DA, Towers AL. Fulminant chemical hepatitis possibly associated with donepezil and sertraline therapy. J Am Geriatr Soc 2000; 48: 1659-63. PubMed PMID: 11129758.

*(83 year old woman developed confusion and jaundice 4 months after starting sertraline and 10 days after starting donepezil [bilirubin 5.6 mg/dL, ALT 529 U/L and Alk P 369 U/L], resolving within 4 months of stopping both).*

Fartoux-Heymann L, Hézode C, Zafrani ES, Dhumeaux D, Mallat A. Acute fatal hepatitis related to sertraline. J Hepatol 2001; 35: 683-4. PubMed PMID: 11690719.

*(54 year old man with alcoholism developed jaundice within 2 weeks of starting sertraline [bilirubin 10.5 mg/dL, ALT 906 U/L, Alk P 121 U/L, eosinophilia and prothrombin activity of 30%], and progressed to liver failure and death within 10 days, autopsy showing extensive necrosis without fat or Mallory bodies).*

Galán Navarro JL. [Acute cholestatic hepatitis probably caused by sertraline]. Rev Esp Enferm Dig. 2001; 93: 822. PubMed PMID: 11995366.

*(57 year old woman developed jaundice and pruritus 8 weeks after starting sertraline [bilirubin 4.5 mg/dl, ALT 144 U/L, Alk P 1034 U/L], resolving within 6 months of stopping).*

Carvajal García-Pando A, García del Pozo J, Sánchez AS, Velasco MA, Rueda de Castro AM, Lucena MI. Hepatotoxicity associated with the new antidepressants. J Clin Psychiatry 2002; 63: 135-7. PubMed PMID: 11874214.

*(Analysis of cases of hepatotoxicity from antidepressants in Spanish Pharmacovigilance System from 1989-1999, identified 99 cases; among SSRIs, 26 were due to fluoxetine, 14 paroxetine, 6 fluvoxamine, 5 sertraline, 3 venlafaxine and 2 citalopram; among tricyclics, 16 were due to clomipramine 7 amitriptyline, 6 imipramine; among miscellaneous, 3 were due to nefazodone and 1 trazodone; but all had a similar incidence = 1-3 per 100,000 patient-years of exposure, except for nefazodone = 29 per 100,000).*

Lucena M, Carvajal A, Andrade R, Velasco A. Antidepressant-induced hepatotoxicity. Expert Opin Drug Saf 2003; 2: 249-62. PubMed PMID: 12904104.

*(Review of hepatotoxicity of antidepressants; antidepressant use has increased markedly between 1992 and 2002, accounting for 5% of cases of hepatotoxicity; SSRIs are less likely to cause injury than tricyclics and MAO inhibitors; range of presentations, typically self-limited and rapid recovery; no hallmarks of hypersensitivity).*

Persky S, Reinus JF. Sertraline hepatotoxicity: a case report and review of the literature on selective serotonin reuptake inhibitor hepatotoxicity. Dig Dis Sci 2003; 48: 939-44. PubMed PMID: 12772794.

*(23 year old woman developed fever and nausea during sertraline therapy [bilirubin 2.1 mg/dL, ALT ~850 U/L], resolving upon stopping and recurring [ALT~230 U/L] on restarting for 3 days).*

Spigset O, Hägg S, Bate A. Hepatic injury and pancreatitis during treatment with serotonin reuptake inhibitors: data from the World Health Organization (WHO) database of adverse drug reactions. Int Clin Psychopharmacol 2003; 18:157-61. PubMed PMID: 12702895.

*(Among 27,542 reports of hepatic injury in WHO database, 786 were related to SSRIs [3%], including citalopram 42, fluoxetine 222, fluvoxamine 54, paroxetine 191, sertraline 112, nefazodone 91 and venlafaxine 74; only nefazodone has an excess of hepatic reports in relationship to total reports).*

Degner D, Grohmann R, Kropp S, Rüther E, Bender S, Engel RR, Schmidt LG. Severe adverse drug reactions of antidepressants: results of the German multicenter drug surveillance program AMSP. Pharmacopsychiatry 2004; 37 Suppl 1: S39-45. PubMed PMID: 5052513.

*(Analysis of adverse drug reactions reported from 1993-2000 in 35 psychiatric hospitals; 0.7% of SSRI recipients had a severe adverse event; hepatic in 0.05%).*

Solomons K, Gooch S, Wong A. Toxicity with selective serotonin reuptake inhibitors. Am J Psychiatry 2005; 162: 1225. PubMed PMID: 15930079.

*(38 year old woman developed abdominal pain and ALT elevations [378 U/L] without jaundice 9 days after starting fluvoxamine; then had a positive rechallenge and recurrence with starting citalopram [ALT 379 within 4 days], and positive rechallenge with citalopram again 1 year later).*

Pinzani V, Peyriere H, Hillaire-Buys D, Pageaux GP, Blayac BP, Larrey D. Specific serotonin recapture inhibitor (SSRI) antidepressants: hepatoxicity assessment in a large cohort in France. J Hepatol 2006; 44: S256.

*(Abstract, not in PubMed; Analysis of French Pharmacovigilance data on SSRIs found 63 cases of hepatotoxicity from paroxetine, 45 fluoxetine, 30 citalopram, 18 sertraline, and 2 fluvoxamine).*

Sabaté M, Ibáñez L, Pérez E, Vidal X, Buti M, Xiol X, Mas A, et al. Risk of acute liver injury associated with the use of drugs: a multicentre population survey. Aliment Pharmacol Ther 2007; 25: 1401-9. PubMed PMID: 17539979.

*(Among 126 cases of drug induced liver injury seen in Spain between 1993-2000, 3 were attributed to paroxetine and 3 to fluoxetine, with a relative risk of injury to rate of use in the population of 3.0 and 1.8, respectively).*

DeSanty KP, Amabile CM. Antidepressant-induced liver injury. Ann Pharmacother 2007; 41: 1201-11.

*(Review of drug induced liver injury and reports of injury from MAO inhibitors, SSRIs, tricyclics and atypical agents).*

Collados Arroyo V, Plaza Aniorte J, Hallal H, Perez Cuadradob E. [Hepatotoxicity associated with sertraline]. Farm Hosp 2008; 32: 60-1. Not in PubMed. *(47 year old man developed fatigue one month after starting sertraline*

*[bilirubin 2.7 mg/dL, ALT 500 U/L, Alk P 377 U/L], resolving within 3 months 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 from 2004 to 2008, 6 were attributed to duloxetine, 3 atomoxetine, 2 fluoxetine, 2 bupropion, and 1 sertraline as single agents).*

Tabak F, Gunduz F, Tahan V, Tabak O, Ozaras R. Sertraline hepatotoxicity: report of a case and review of the literature. Dig Dis Sci. 2009; 54: 1589-91. PubMed PMID: 18958618.

*(17 year old boy developed jaundice 6 months after starting sertraline [bilirubin 2.1 mg/dL, ALT 1280 U/L, Alk P 483 U/L], resolving within 6 months of stopping).*

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, one was attributed to venlafaxine and one to fluoxetine but none to sertraline).*

Collados V, Hallal H, Andrade RJ. Sertraline hepatotoxicity: report of a case and review of the literature. Dig Dis Sci 2010; 55: 1806-7. PubMed PMID: 20411428.

*(Review of published cases of sertaline hepatotoxicity mentions 4 cases [bilirubin 2.6 to 10.5 mg/dL, ALT 144-906 U/L, Alk P 121-1034 U/L], one fatal and three resolving within 3 to 6 months).*

García-Aparicio J, Herrero-Herrero JI. [Toxic hepatitis following sequential treatment with cotrimoxazol, levofloxacin, doxycycline and sertraline in a patient with a respiratory infection]. Farm Hosp 2010; 34: 152-4. Spanish. PubMed PMID: 20471573.

*(65 year old woman developed jaundice several weeks after receiving several antibiotics and 15 days after starting sertraline [bilirubin 3.5 mg/dL, ALT 937 U/L, Alk P 373 U/L], resolving within 3 months of stopping sertraline).*

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. (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 amitriptyline, but sertraline was not PubMed PMID: 21788760.

*listed).*

Park SH, Ishino R. Liver injury associated with antidepressants. Curr Drug Saf 2013; 8: 207-23. PubMed PMID: 23914755.

*(Review of antidepressant-induced liver injury).*

Björnsson ES, Bergmann OM, Björnsson HK, Kvaran RB, Olafsson S. Incidence, presentation and outcomes in patients with drug-induced liver iInjury 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, none of which were attributed to sertraline even though it is ranked as one of the top 20 most prescribed medications in Iceland).*

Suen CF, Boyapati R, Simpson I, Dev A. Acute liver injury secondary to sertraline. BMJ Case Rep 2013; 2013. pii: bcr2013201022. PubMed PMID: 24072839.

*(26 year old pregnant woman developed nausea and dark urine 24 weeks after starting and 3 weeks after increasing the dose of sertraline [bilirubin 1.5 mg/dL, ALT 700 U/L, Alk P 113 U/L, INR normal], resolving within 80 days of stopping and subsequent normal delivery).*