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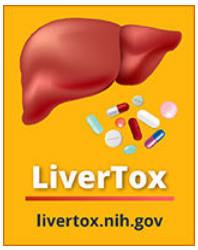


Mirtazapine

Updated: February 26, 2020.

OVERVIEW

Introduction

Mirtazapine is a tetracyclic antidepressant with a somewhat unique mechanism of action. Mirtazapine 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

Mirtazapine (mir taz' a peen) is a tetracyclic derivative with a somewhat unique antidepressant activity in comparison to the selective serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants. Its mechanism of action is not well defined, but it is a potent antagonist of serotonin 5-HT2 and 5-HT3 receptors and appears to enhance central noradrenergic and serotonergic (5-HT1A) activity with less activity against peripheral receptors. Mirtazapine was approved for use in moderate and severe depression in the United States in 1996 and remains in wide use, with more than 6 million prescriptions being filled yearly. The major indication for mirtazapine therapy is major depressive disorder. Mirtazapine is available as regular and oral disintegrating tablets of 7.5, 15, 30 and 45 mg in multiple generic forms and under the brand name Remeron. The recommended dosage in adults is 15 mg once daily at bedtime, which can be increased to a maximum of 45 mg daily. Common side effects are drowsiness, fatigue, blurred vision, dry mouth, increased appetite and weight gain. Rare, but potentially severe adverse events include suicidal thoughts and behavior, activation of mania, seizures, serotonin syndrome and hypersensitivity reactions including Stevens Johnson Syndrome.

Hepatotoxicity

Liver test abnormalities have been reported to occur in up to 10% of patients on mirtazapine, but elevations are usually modest and rarely 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 mirtazapine. The onset of injury has varied greatly from several months to several years. The pattern of serum enzyme elevations is usually hepatocellular, but mixed forms have also been described. Autoimmune (autoantibodies) and immunoallergic features (rash, fever, eosinophilia) are uncommon.

Likelihood score: C (probable rare cause of clinically apparent liver disease).

Mechanism of Injury

The mechanism by which mirtazapine causes liver injury is not known. Mirtazapine is extensively metabolized by the liver, mainly via the cytochrome P450 system, predominantly CYP 3A4, and is susceptible to multiple

drug-drug interactions with agents that induce or inhibit CYP activity. The metabolic intermediates of mirtazapine may be toxic which could account for its hepatoxicity. In other instances, serum enzyme elevations might be due to nonalcoholic steatohepatitis triggered by weight gain caused by mirtazapine therapy.

Outcome and Management

The serum aminotransferase elevations that occur on mirtazapine therapy are usually self-limited and do not require dose modification or discontinuation of therapy. Rare instances of acute liver failure and chronic hepatitis have been attributed to mirtazapine therapy. Persons with intolerance to mirtazapine may have similar reactions to other antidepressants and careful monitoring is warranted if other such agents are used.

Drug Class: Antidepressant Agents

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Mirtazapine – Generic, Remeron®

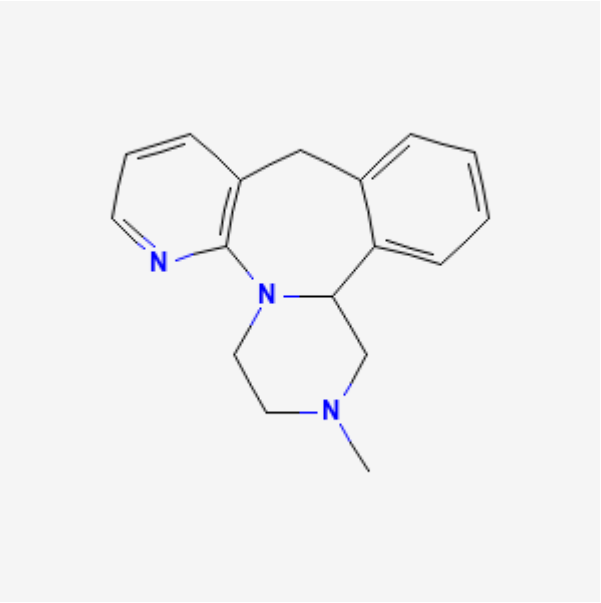
DRUG CLASS

Antidepressant Agents

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NUMBER	MOLECULAR FORMULA	STRUCTURE
Mirtazapine	61337-67-5	C17-H19-N3	

ANNOTATED BIBLIOGRAPHY

References updated 20 February 2020

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; no mention of mirtazapine).

Larrey D, Ripault MP. Mirtazapine. Hepatotoxicity of psychotropic drugs and drugs of abuse. In, Kaplowitz N, DeLeve LD, eds. Drug-induced liver disease. 3rd ed. Amsterdam: Elsevier, 2013, pp. 452.

(Review of hepatotoxicity of antidepressants mentions that mirtazapine has been implicated in a small number of cases).

O'Donnell JM, Bies RR, Shelton RC. Drug therapy of depression and anxiety disorders. In, Brunton LL, Hilal-Dandan R, Knollman BC, eds. Goodman & Gilman's the pharmacological basis of therapeutics. 13th ed. New York: McGraw-Hill, 2018, pp. 267-78.

(Textbook of pharmacology and therapeutics).

Montgomery SA. Safety of mirtazapine: a review. Int Clin Psychopharmacol. 1995;10 Suppl 4:37–45.

(Summary of safety results from prelicensure trials; common side effects were drowsiness, dry mouth, increased appetite and weight gain; annual rate of serum enzyme elevations was 10% with mirtazapine, 12% with amitriptyline and 7% with placebo).

Marttila M, Jaaskelainen J, Jarvi R, Romanov M, Miettinen E, Sorri P, Ahlfors U, et al. A double-blind study comparing the efficacy and tolerability of mirtazapine and doxepin in patients with major depression. Eur Neuropsychopharm. 1995;15:441–6.

(In a controlled trial of doxepin vs mirtazapine in 163 patients with depression, there were no statistically significant changes in biochemical tests from baseline in either group and no instances of clinically apparent liver injury).

Fawcett J, Barkin RL. Review of the results from clinical studies on the efficacy, safety and tolerability of mirtazapine for the treatment of patients with major depression. J Affect Disord. 1998;51:267–85. PubMed PMID: 10333982.

(Review of chemical structure, pharmacology, mechanism of action, efficacy and safety of mirtazapine; side effects more common than with placebo include drowsiness, dry mouth, increased appetite, and weight gain; liver injury and ALT elevations were not mentioned).

Hui CK, Yuen MF, Wong WM, Lam SK, Lai CL. Mirtazapine-induced hepatotoxicity. J Clin Gastroenterol. 2002;35:270–1. PubMed PMID: 12192206.

(Two cases of mirtazapine hepatotoxicity; 54 year old woman developed jaundice 3 years after starting mirtazapine [bilirubin 28.7 mg/dL, ALT 316 U/L, Alk P 150 U/L, protime 27.8 sec], resolving slowly by 5 months after stopping; 49 year old woman developed jaundice 1 year after starting mirtazapine [bilirubin 8.2 mg/dL, ALT 550 U/L, Alk P 140 U/L, protime 18 sec], with worsening for 2 weeks [bilirubin 35.7 mg/dL], resolving slowly within 3 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 attributed to fluoxetine, 14 paroxetine, 6 fluvoxamine, 5 sertraline, 3 venlafaxine and 2 citalopram; among tricyclics, 16 clomipramine 7 amitriptyline, 6 imipramine; among miscellaneous, 3 nefazodone and 1 trazodone; but all similar in rate ~1-3 per 100,000 patient-years of exposure, except for nefazodone=29/100,000; mirtazapine not mentioned).

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; mirtazapine was not specifically mentioned).

Biswas PN, Wilton LV, Shakir SA. The pharmacovigilance of mirtazapine: results of a prescription event monitoring study on 13554 patients in England. J Psychopharmacol. 2003;17:121–6. PubMed PMID: 12680749.

(Analysis of prescription event monitoring in UK National Health Service between 1997-9 including 13,554 patients who received mirtazapine; 4.2% had adverse event, most common being drowsiness, malaise, dizziness, nausea, weight gain and headache; 12 reports of facial edema and 6 of allergy, but none of hepatitis or jaundice).

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: 15052513.

(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%).

Russo MW, Galanko JA, Shrestha R, Fried MW, Watkins P. Liver transplantation for acute liver failure from drug-induced liver injury in the United States. Liver Transpl. 2004;10:1018–23. PubMed PMID: 15390328.

(Among ~50,000 liver transplants done in the United States between 1990 and 2002, 270 [0.5%] were done for drug induced acute liver failure, only four being due to antidepressants: nefazodone [2], bupropion [1], and paroxetine [1]).

Andrade RJ, Lucena MI, Fernández MC, Pelaez G, Pachkoria K, García-Ruiz E, García-Muñoz B, et al; Spanish Group for the Study of Drug-Induced Liver Disease. Drug-induced liver injury: an analysis of 461 incidences submitted to the Spanish registry over a 10-year period. Gastroenterology. 2005;129:512–21. PubMed PMID: 16083708.

(Reports to a Spanish network found 461 cases of drug induced liver disease, antidepressants accounted for 23 cases [5%], but mirtazapine was not specifically mentioned).

Björnsson E, Olsson R. Suspected drug-induced liver fatalities reported to the WHO database. Dig Liver Dis. 2006;38:33–8. PubMed PMID: 16054882.

(Survey of drug induced liver fatalities reported to WHO database between 1968-2003 revealed 4690 reports; no antidepressant ranked among the top 21 agents that were linked to at least 50 cases each).

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; mirtazapine was not specifically mentioned).

DeSanty KP, Amabile CM. Antidepressant-induced liver injury. Ann Pharmacother. 2007;41:1201–11. PubMed PMID: 17609231.

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

Adetunji B, Basil B, Mathews M, Osinowo T. Mirtazapine-associated dose-dependent and asymptomatic elevation of hepatic enzymes. Ann Pharmacother. 2007;41:359.

(20 year old man developed asymptomatic rises in serum enzymes 3 months after starting mirtazapine [bilirubin 0.4 mg/dL, ALT 182 U/L, Alk P 131 U/L], resolving within 2 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, antidepressants accounted for 12 cases [4%]: duloxetine [6], bupropion [2], fluoxetine [2], amitriptyline [1], sertraline [1], but none were attributed to mirtazapine).

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, 3 of which were linked to antidepressants: one each for nefazodone, fluoxetine and venlafaxine).

Rodriguez-Pecci MS, Fuente-Aguado Jde L, Montero-Tinnirello J, Fernandez-Fernandez FJ. Med Clin (Barc). 2010;135:625–6. [Mirtazapine-associated hepatotoxicity]. Spanish. PubMed PMID: 19822332.

(63 year old man developed fatigue within 6 months of starting mirtazapine [bilirubin 0.4 mg/dL, ALT 96 U/L, Alk P 455 U/L, GGT 945 U/L], abnormalities resolving within 2 months of stopping).

Kang SG, Yoon BM, Park YM. Mirtazapine-induced hepatocellular-type liver injury. Ann Pharmacother. 2011;45:825–6. PubMed PMID: 21666084.

(19 year old man developed nausea and ALT elevations within 2 weeks of starting mirtazapine [bilirubin 0.7 mg/dL, peak ALT 358 U/L, Alk P 32 U/L], resolving within 2 weeks of stopping).

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 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, none of which were attributed to mirtazapine).

Montastruc F, Scotto S, Vaz IR, Guerra LN, Escudero A, Sáinz M, Falomir T, et al. Hepatotoxicity related to agomelatine and other new antidepressants: a case/noncase approach with information from the Portuguese, French, Spanish, and Italian pharmacovigilance systems. J Clin Psychopharmacol. 2014;34:327–30. PubMed PMID: 24561328.

(Among adverse event reports attributed to antidepressants submitted to 4 European pharmacovigilance databases, 3300 [10%] were for hepatotoxicity, rates being highest for agomelatine [14.6%], but also being high for mirtazapine in some databases, 2.0% to 11.8%]).

Voican CS, Corruble E, Naveau S, Perlemuter G. Antidepressant-induced liver injury: a review for clinicians. Am J Psychiatry. 2014;171:404–15. PubMed PMID: 24362450.

(Review of the hepatotoxicity of antidepressants mentions that aminotransferase elevations arise in 0.5-3.0% of patients being highest with MAO inhibitors and lower with SSRIs; mentions that all antidepressants have the potential to cause liver injury but risk is highest for nefazodone, imipramine, amitriptyline, duloxetine, bupropion, trazodone and agomelatine).

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.

(Among 176 reports of drug induced liver injury from Latin America published between 1996 and 2012, only one was due to an antidepressant [amitriptyline] and none to mirtazapine).

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, xx were attributed to antidepressants, but none to mirtazapine).

Gahr M, Zeiss R, Lang D, Connemann BJ, Hiemke C, Schönfeldt-Lecuona C. Drug-Induced Liver Injury Associated with antidepressive psychopharmacotherapy: an explorative assessment based on quantitative signal detection using different MedDRA terms. J Clin Pharmacol. 2016;56:769–78. PubMed PMID: 26470856.

(Using data on adverse drug reaction reports from the Uppsala Monitoring Center of WHO, there were higher relative hepatotoxicity reports for nefazodone, agomelatine, many tricyclics and mirtazapine).

Friedrich ME, Akimova E, Huf W, Konstantinidis A, Papageorgiou K, Winkler D, Toto S, et al. Drug-induced liver injury during antidepressant treatment: results of AMSP, a drug surveillance program. Int J Neuropsychopharmacol. 2016;19:pyv126. pii. PubMed PMID: 26721950.

(Among 184,234 psychiatric inpatients from 80 hospitals, 149 cases [0.08%] of drug induced liver injury were reported including 39 attributed to mirtazapine among 43,902 patients exposed [0.09%], most cases being asymptomatic and anicteric).

Thomas E, Haboubi H, Williams N, Lloyd A, Ch'ng CL. Mirtazapine-induced steatosis. Int J Clin Pharmacol Ther. 2017;55:630–2. PubMed PMID: 28427497.

(48 year old woman developed lethargy, peripheral edema, and jaundice while on long term mirtazapine and had steatohepatitis on liver biopsy [bilirubin 11.6 mg/dL, ALT normal, Alk P 149 U/L], improving after stopping, BMI not reported and history of alcoholism in the past).

Chen VC, Lin CF, Hsieh YH, Liang HY, Huang KY, Chiu WC, Lee Y, McIntyre RS, et al. Hepatocellular carcinoma and antidepressants: a nationwide population-based study. Oncotarget. 2017;8:30464–70. PubMed PMID: 27783998.

(Among almost 50,000 cases of hepatocellular carcinoma registered in the Taiwan National Health Insurance Research Database, the rate of antidepressant use was lower than in approximately 250,000 matched controls from the database).

Bunchorntavakul C, Reddy KR. Drug hepatotoxicity: newer agents. Clin Liver Dis. 2017;21:115–34. PubMed PMID: 27842767.

(Review of hepatotoxicity of recently approved medications mentions that liver injury is rare in recently approved agents and only rare instances have been linked to antidepressant use, highest rates associated with duloxetine).

Ferrajolo C, Scavone C, Donati M, Bortolami O, Stoppa G, Motola D, Vannacci A, et al; DILI-IT Study Group. Antidepressant-induced acute liver injury: a case-control study in an Italian inpatient population. Drug Saf. 2018;41:95–102. PubMed PMID: 28770534.

(Among 179 cases of hospitalizations for unexplained acute liver injury enrolled in an Italian prospective study between 2010 and 2014, 17 had been exposed to antidepressants including citalopram [n=4], sertraline [n=3], amitriptyline [n=3] and paroxetine [n=2], and mirtazapine [n=1] and the combination of both trazodone and mirtazapine [n=1]).

Billioti de Gage S, Collin C, Le-Tri T, Pariente A, Bégaud B, Verdoux H, Dray-Spira R, et al. Antidepressants and hepatotoxicity: a cohort study among 5 million individuals registered in the French National Health Insurance Database. CNS Drugs. 2018;32:673–84. PubMed PMID: 29959758.

(Using the French National Health Insurance Database, 382 serious liver injuries were found in approximately 5 million persons initiating antidepressant therapy, rates being 32.8 per 100,000 with mirtazapine, 22.2 with venlafaxine, 19.2 for SSRIs and 12.6 with duloxetine).

Drugs for anxiety disorders. Med Lett Drugs Ther. 2019;61(1578):121–6. PubMed PMID: 31386647.

(Concise review of drugs for anxiety including SSRIs, SNRIs and benzodiazepines including mechanism of action, clinical efficacy, safety and costs; does not mention ALT elevations or hepatotoxicity).

Pladevall-Vila M, Pottegård A, Schink T, Reutfors J, Morros R, Poblador-Plou B, Timmer A, et al. Risk of acute liver injury in agomelatine and other antidepressant users in four European countries: a cohort and nested case-control study using automated health data sources. CNS Drugs. 2019;33:383–95. PubMed PMID: 30830574.

(Analysis of data sources from 4 European countries identified 3.2 million persons initiating antidepressant therapy among whom there was no increased risk for acute liver injury for agomelatine compared to citalopram, an SSRI with a low rate of hepatotoxicity).

Schwasinger-Schmidt TE, Macaluso M. Other antidepressants. Handb Exp Pharmacol. 2019;250:325–55. PubMed PMID: 30194544.

(Review of the pharmacology of antidepressants mentions that transient elevations in cholesterol and liver function tests can occur on mirtazapine therapy).

Drugs for depression. Med Lett Drugs Ther. 2020;62(1592):25–32.

(Concise review of the mechanism of action, clinical efficacy, safety and costs of drugs for depression; hepatotoxicity is mentioned only for nefazodone [now rarely used because of severe hepatotoxicity] and duloxetine [in heavy drinkers]).