



## Methylphenidate

Updated: February 3, 2020.

### OVERVIEW

#### Introduction

Methylphenidate is a central nervous system stimulant used for the therapy of attention deficit disorder and narcolepsy. Methylphenidate has been linked to a low rate of serum aminotransferase elevations during therapy and to rare instances of acute, clinically apparent liver injury, generally after its intravenous abuse.

#### Background

Methylphenidate (meth" il fen' i date) is a piperidine derivative that is structurally related to amphetamine which acts as a central nervous system (CNS) sympathomimetic stimulant, probably by causing release of norepinephrine at CNS nerve terminals promoting neurotransmission. Methylphenidate may also affect dopaminergic neurotransmission. Therapy with methylphenidate has been shown to increase cognitive abilities and improve psychological functioning and performance in children and adults with suspected attention deficit disorders. It has a paradoxical calming action in children with hyperactivity. Methylphenidate is also used in the therapy of narcolepsy. Methylphenidate was approved for use in the United States for attention deficit disorder in adults in 1955, and its indications were subsequently broadened to include children above the age of 6 and adolescents with attention deficit disorder. Methylphenidate is available in multiple forms for oral administration including capsules, tablets, oral solutions and as extended release and long acting forms in concentrations varying from 2.5 to 54 mg in generic forms and under several brand names including Ritalin, Concerta, Jornay and Quillivant. A transdermal formulation is also available under the brand name Daytrana. The usual initial dose of standard oral methylphenidate in adults is 10 mg two times daily, and average maintenance dosage is 40 to 60 mg daily in 2 or 3 divided doses. The dosage in children varies by formulation. Methylphenidate is a controlled substance (Schedule II) and has abuse potential. Common side effects include headache, insomnia, irritability, palpitations, tachycardia, nasal stuffiness, decreased appetite, nausea, cough and rash. Uncommon, but potentially severe adverse events include psychotic symptoms, cardiovascular events, abuse and dependence and, with long term therapy in children, reduced adult height.

#### Hepatotoxicity

In prelicensure clinical trials, methylphenidate was not associated with serum aminotransferase elevations or instances of hepatic injury, but reports of enzyme elevations were received by the sponsor and appeared in publications after it was marketed. The elevations were transient, mild-to-moderate in severity and rarely associated with jaundice or symptoms. In addition, there have been several case reports of marked serum enzyme elevations with jaundice and clinically apparent acute liver injury attributed to methylphenidate given intravenously. These cases occurred largely after illicit intravenous use of methylphenidate and frequently in

patients with underlying chronic hepatitis C. The onset was generally soon after initiation of therapy. The pattern of liver enzyme elevations was hepatocellular and the clinical phenotype typical of acute hepatic necrosis with rapid onset and rapid recovery. Immunoallergic features were uncommon. A single case associated with low levels of autoantibodies has been published. Some cases have been severe and at least one fatality after intravenous abuse has been reported. Recurrence upon rechallenge was documented in one instance (Case 1).

Likelihood score: C[H] (probable cause of clinically apparent liver injury when given in high doses)

## Mechanism of Injury

The mechanism by which methylphenidate might cause liver injury is unknown, but the injury occurring after intravenous use is likely due to direct toxicity. Methylphenidate is extensively metabolized in the liver and has many drug-drug interactions.

## Outcome and Management

The liver injury due to oral methylphenidate is usually self-limited and resolves rapidly. Injury from intravenous use can be severe and fatalities have been reported. There have been no instances of chronic liver injury or vanishing bile duct syndrome associated with either oral or intravenous methylphenidate. Cross reactivity with other amphetamine related chemicals has not been demonstrated. However, recurrence of injury with reexposure has been demonstrated.

Central nervous system stimulants used for attention deficit disorder, narcolepsy or excessive sleepiness include methylphenidate, atomoxetine, modafinil, armodafinil and the amphetamines. Stimulants that are no longer used for medical conditions, but that are abused, include cocaine and ecstasy or methylenedioxymetamphetamine. Non-stimulants used for attention deficit disorder include the antihypertensive alpha-2 agonists, clonidine and guanfacine.

Drug Class: Drugs of Attention Deficit Disorder, CNS Stimulants, Clonidine, Guanfacine

## CASE REPORT

### Case 1. Acute hepatic necrosis after intravenous injection of methylphenidate.(1)

A 19 year old woman who had been abusing methylphenidate developed fatigue, fever and jaundice. She admitted to intravenous injection of methylphenidate tablets that had been dissolved in water. She had no history of liver disease or alcohol abuse. She was not taking other medications. On physical examination, she was jaundiced and had an enlarged, slightly tender liver. There were no peripheral manifestations of cirrhosis or chronic liver disease. Laboratory tests showed elevations in serum bilirubin (13 mg/dL) and AST (4,942 U/L), with minimal increase in alkaline phosphatase (100 U/L) (Table). Tests for hepatitis A and B were negative. Tests for hepatitis C were not available at the time of this report. A liver biopsy showed focal necrosis and portal inflammation with lymphocytes, plasma cells and eosinophils, typical of drug induced liver injury. Rechallenge with 4 injections of 20 mg of methylphenidate over two days led to rapid recurrence with a similar pattern of injury.

### Key Points

Medication:	Methylphenidate (by injection)
Pattern:	Hepatocellular (R=~100)

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Severity:	3+ (jaundice, hospitalization)
Latency:	Few days
Recovery:	Two weeks
Other medications:	None mentioned

## Laboratory Values

Days After Stopping	AST* (U/L)	Alk P* (U/L)	Bilirubin* (mg/dL)	Comments
Intravenous abuse of methylphenidate				
3	4942	100	13.0	Admission for jaundice
5	2300		14.5	
6	2090		16.0	Liver Biopsy
7	1900		17.0	
9	1650		17.2	
11	900		14.0	
14	250		11.0	
16	80		6.0	
18	25		2.5	
Rechallenge with four injections of 20 mg of methylphenidate				
0	15		0.5	Started rechallenge
0	450		2.5	Stopped rechallenge
1	900		4.0	
2	550		5.1	
3	100		5.2	
5	50		3.0	
7	20		1.0	Normal
<b>Normal</b>	<b>&lt;42</b>	<b>&lt;115</b>	<b>&lt;1.2</b>	

\* Values estimated from Figure 1.

## Comment

Abuse of methylphenidate and intravenous injections of dissolved tablets led to marked jaundice and serum enzyme elevations. Tests for hepatitis C were not available at the time of the report, but intravenous rechallenge led to recurrence with a similar pattern of injury. This degree of severity of liver injury has not been reported with oral methylphenidate which is a widely used medication with excellent tolerance. The pattern of injury associated with intravenous methylphenidate abuse is similar to that described with amphetamine, methylenedioxymetamphetamine and cocaine use, with acute hepatic necrosis (often with other organ damage) arising within 2 to 4 days of the exposure or overdose. Typical of methylphenidate, cocaine and amphetamine hepatotoxicity from intravenous exposure is both the rapidity of the rise and rapidity of the fall in serum aminotransferase levels. LDH levels can be similarly elevated, while alkaline phosphatase values are usually normal or near normal.

## PRODUCT INFORMATION

### REPRESENTATIVE TRADE NAMES

Methylphenidate – Generic, Concerta®, Ritalin®, Jornay PM®, Daytrana®

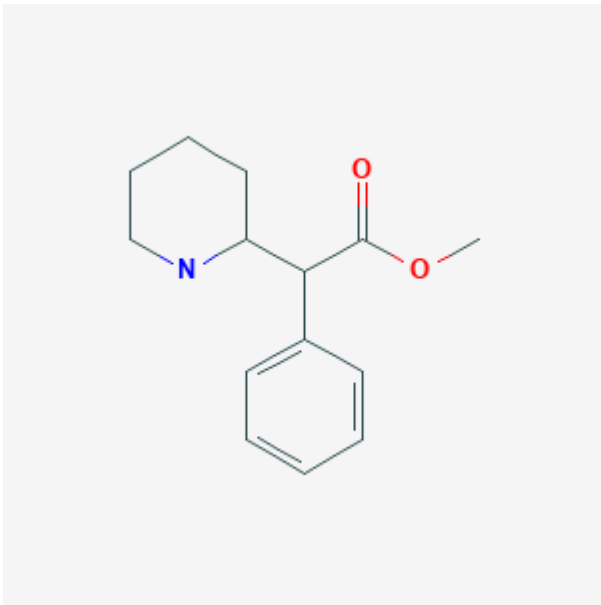
### DRUG CLASS

Central Nervous System Stimulants

### COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

## CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NUMBER	MOLECULAR FORMULA	STRUCTURE
Methylphenidate	113-45-1	C <sub>14</sub> H <sub>19</sub> N-O <sub>2</sub>	 <p>The chemical structure of Methylphenidate is shown. It consists of a piperidine ring (a six-membered ring with one nitrogen atom) attached to a central carbon atom. This central carbon atom is also bonded to a phenyl ring (a six-membered aromatic ring) and a methyl ester group (-COOCH<sub>3</sub>). The nitrogen atom in the piperidine ring is highlighted in blue, and the oxygen atoms in the ester group are highlighted in red.</p>

## CITED REFERENCE

1. Mehta H, Murray B, LoJudice TA. Hepatic dysfunction due to intravenous abuse of methylphenidate hydrochloride. *J Clin Gastroenterol.* 1984;6:149–51. PubMed PMID: 6715854.

## ANNOTATED BIBLIOGRAPHY

References updated: 30 January 2020

Zimmerman HJ. Methylphenidate. *Miscellaneous drugs and diagnostic chemicals.* In, Zimmerman, HJ. *Hepatotoxicity: the adverse effects of drugs and other chemicals on the liver.* 2nd ed. Philadelphia: Lippincott, 1999, pp. 712.

*(Expert review of hepatotoxicity published in 1999; methylphenidate has been implicated in at least 3 instances of hepatic injury including two with positive rechallenge).*

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 methylphenidate has been implicated in hepatocellular injury).*

Westfall TC, Macarthur H, Westfall DP. Methylphenidate. Adrenergic agonists and antagonists. 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. 191-223.

*(Textbook of pharmacology and therapeutics).*

Goodman CR. Hepatotoxicity due to methylphenidate hydrochloride. N Y State J Med. 1972;72:2339-40. PubMed PMID: 4506888.

*(67 year old woman with depression developed mild elevations in ALT [56 U/L] and AST [72 U/L] without symptoms or jaundice 2 weeks after starting methylphenidate, and with rapid resolution on stopping and recurrence after 5 day rechallenge [bilirubin 0.6 mg/dL, ALT 145 U/L, AST 535 U/L, Alk P 18 U/L]).*

Mehta H, Murray B, LoIudice TA. Hepatic dysfunction due to intravenous abuse of methylphenidate hydrochloride. J Clin Gastroenterol. 1984;6:149-51. PubMed PMID: 6715854.

*(19 year old woman developed jaundice soon after starting injecting methylphenidate [bilirubin 13.0 mg/dL, AST 4,942 U/L, Alk P 100 U/L], resolving over next few weeks; upon challenge injection of methylphenidate [20 mg] AST rose to ~900 U/L and bilirubin to 5.2 mg/dL in 3-4 days: Case 1).*

Stecyk O, LoIudice TA, Demeter S, Jacobs J. Multiple organ failure resulting from intravenous abuse of methylphenidate hydrochloride. Ann Emerg Med. 1985;14:597-9. PubMed PMID: 3994088.

*(32 year old woman developed weakness, nausea and dyspnea 2 hours after injecting methylphenidate which she had been doing for ~5 months [bilirubin 1.4 mg/dL, ALT 2,560 U/L, Alk P 174 U/L, lactate 18 mEq/L, arterial pH 7.23, protime 23.7 sec and creatinine 4.0 mg/dL], requiring ICU care, but ultimate recovery over next few weeks).*

Hoover-Stevens S, Kovacevic-Ristanovic R. Management of narcolepsy in pregnancy. Clin Neuropharmacol. 2000;23:175-81. PubMed PMID: 11020119.

*(Review of the efficacy of medications for narcolepsy and their safety during pregnancy and breast feeding; there have been no studies on the safety of methylphenidate in pregnancy).*

Leonard BE, McCartan D, White J, King DJ. Methylphenidate: a review of its neuropharmacological, neuropsychological and adverse clinical effects. Hum Psychopharmacol. 2004;19:151-80. PubMed PMID: 15079851.

*(Review of mechanism of action, clinical efficacy and safety of methylphenidate; no mention of hepatotoxicity or serum ALT elevations).*

Lewis JJ, Iezzoni JC, Berg CL. Methylphenidate-induced autoimmune hepatitis. Dig Dis Sci. 2007;52:594-7. PubMed PMID: 17219064.

*(57 year old man developed marked enzyme elevations 4 years after liver transplantation for hepatitis C and 1 month after starting methylphenidate [bilirubin 2.7 rising to 4.1 mg/dL, ALT 338 U/L, ANA 1:80, IgG 1950 mg/dL], improving upon stopping methylphenidate and falling to baseline on prednisone therapy).*

Chalasanani 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, 3 cases were attributed to atomoxetine and one to methylphenidate, but none to cocaine or ecstasy).*

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.

*(Worldwide pharmacovigilance database contained 9036 hepatic adverse drug reactions in children, 2 agents used for attention deficit disorder were among the top 40 causes; methylphenidate [11th, 96 cases] and atomoxetine [14th, 64 cases]).*

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.

*(Among 313 cases of drug induced liver injury seen between 1997 and 2008 at a large hospital in Bangalore, India, one case was attributed to atomoxetine, none to methylphenidate).*

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 one attributed to cocaine and one to ecstasy but none to methylphenidate).*

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, 3 were attributed to atomoxetine and one to methylphenidate).*

Cantrell FL, Ogera P, Mallett P, McIntyre IM. Fatal oral methylphenidate intoxication with postmortem concentrations. *J Forensic Sci.* 2014;59:847–9. PubMed PMID: 24502813.

*(62 year old woman with chronic hepatitis C was found dead at home and autopsy showed high levels of methylphenidate consistent with drug overdose; liver histology showed chronic hepatitis and mild fatty change and no evidence of acute 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 methylphenidate)*

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, none of which were attributed methylphenidate).*

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. PMID: 25754159

*(Among 899 cases of drug induced liver injury enrolled in a US prospective study between 2004 and 2013, 12 [1.3%] were attributed to drugs used in transplant rejection, including 10 to azathioprine and 1 to tacrolimus, but none to mycophenolate).*

Newcorn JH, Nagy P, Childress AC, Frick G, Yan B, Pliszka S. Randomized, double-blind, placebo-controlled acute comparator trials of lisdexamfetamine and extended-release methylphenidate in adolescents with attention-deficit/hyperactivity disorder. *CNS Drugs*. 2017;31:999–1014. PubMed PMID: 28980198.

*(Among 1013 adolescents with attention deficit/hyperactivity disorder treated with methylphenidate or lisdexamfetamine or placebo for 6 or 8 weeks, both drugs improved symptoms more than placebo but both had higher and similar rates of adverse events; no mention of ALT elevations or hepatotoxicity or discontinuations for hepatic adverse events).*

Edvinsson D, Ekselius L. Long-term tolerability and safety of pharmacological treatment of adult attention-deficit/hyperactivity disorder: a 6-year prospective naturalistic study. *J Clin Psychopharmacol*. 2018;38:370–5. PubMed PMID: 29927781.

*(Among 112 adults with attention deficit disorder started on methylphenidate and followed for up to 6 years, half had discontinued treatment but no mention is made of ALT elevations, hepatotoxicity or drug discontinuations because of hepatic adverse events).*

Fekete S, Romanos M, Gerlach M. [Does methylphenidate cause liver damage? An analysis of ad hoc reports to the "Bundesinstitut für Arzneimittel und Medizinprodukte (BfArM)"]. *Z Kinder Jugendpsychiatr Psychother* 2018; 46: 342-8. German. PMID: 29237323

*(Have).*

Joshi G, DiSalvo M, Wozniak J, Ceranoglu TA, Yule A, Surman C, Fried R, et al. A prospective open-label trial of long-acting liquid methylphenidate for the treatment of attention deficit/hyperactivity disorder in intellectually capable adults with autism spectrum disorder. *World J Biol Psychiatry*. 2019.:1–17. PubMed PMID: 31607204.

*(Among 15 adults with attention deficit disorder treated with long acting methylphenidate, adverse events were frequent including headache [53%], insomnia [33%], anxiety [33%], and decreased appetite [27%]; no mention of ALT elevations or hepatotoxicity).*

Weiss MD, Childress AC, Donnelly GAE. Efficacy and safety of PRC-063, extended-release multilayer methylphenidate in adults with ADHD including 6-month open-label extension. *J Atten Disord*. 2020.:1087054719896853. PubMed PMID: 31916473.

*(Among 375 adults with attention deficit/hyperactivity disorder treated with 1 of 4 doses of extended release methylphenidate or placebo once daily for 6 months, adverse events included headache, insomnia, decreased appetite, dry mouth, and nausea, and there were “no clinically significant changes from baseline in laboratory findings”).*

Drugs for ADHD. *Med Lett Drugs Ther*. 2020;62(1590):9–15. PubMed PMID: 31999670.

*(Concise review of drugs for attention deficit/hyperactivity disorder mentions that methylphenidate and the CNS stimulants are the first line agents for school age children and adolescents and that adverse events can include decreased appetite, abdominal pain, headache and insomnia, but does not mention ALT elevations or hepatotoxicity).*