



## Central Nervous System (CNS) Stimulants

Updated: August 12, 2021.

### OVERVIEW

Central nervous system stimulants used for attention deficit disorder, narcolepsy or excessive sleepiness include the amphetamines, methylphenidate, atomoxetine, modafinil, armodafinil, pitolisant and solriamfetol. Stimulants that are no longer used for medical conditions, but that are abused, include cocaine and ecstasy or methylenedioxymethamphetamine (MDMA). The individual agents discussed include the following:

The following links are to individual drug records.

- [Amphetamines](#) (including ecstasy or methylenedioxymethamphetamine)
- [Armodafinil](#)
- [Atomoxetine](#)
- [Cocaine](#)
- [Methylphenidate](#)
- [Modafinil](#)
- [Oxybate](#)
- [Pitolisant](#)
- [Solriamfetol](#)

### PRODUCT INFORMATION

#### REPRESENTATIVE TRADE NAMES

Armodafinil – Generic, Nuvigil®

Atomoxetine – Generic, Strattera®

Dextroamphetamine – Generic, Adderall®, Dexedrine®

Dextroamphetamine and Amphetamine – Generic, Adderall®

Lisdexamfetamine – Vyvanse®

Methamphetamine – Generic, Desoxyn®

Modafinil – Generic, Provigil®

Oxybate – Xyrem®

Pitolisant – Wakix®

Solriamfetol – Sunosi®

## COMPLETE LABELING [Dextroamphetamine]

Product labeling at DailyMed, National Library of Medicine, NIH

**CHEMICAL FORMULAS AND STRUCTURES**

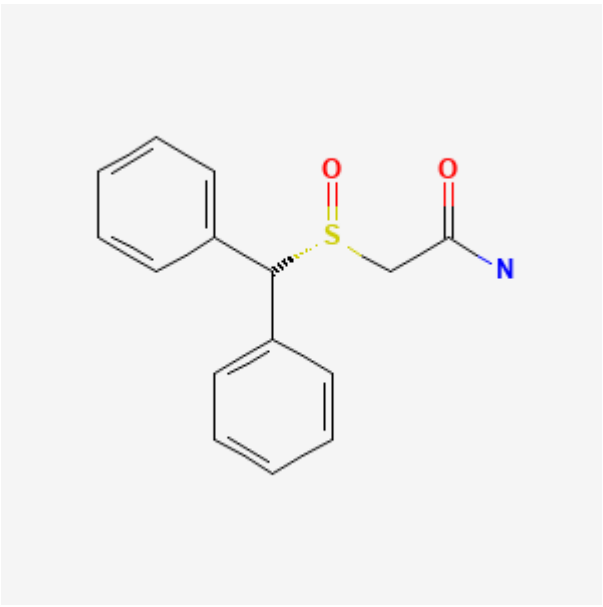
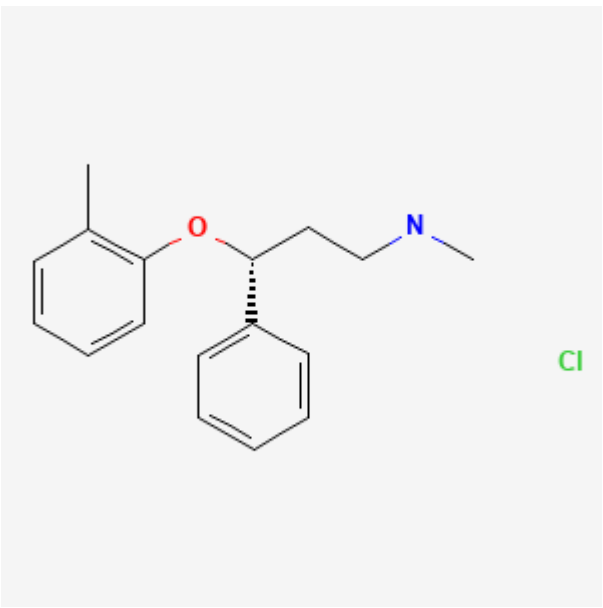
DRUG	CAS REGISTRY NUMBER	MOLECULAR FORMULA	STRUCTURE
Armodafinil	112111-43-0	C <sub>15</sub> H <sub>15</sub> N-O <sub>2</sub> S	 <p>The chemical structure of Armodafinil is shown. It features a central chiral carbon atom bonded to a phenyl ring (top-left), a propylsulfonamide group (top-right, with a dashed bond to the sulfur atom), and another phenyl ring (bottom). The propylsulfonamide group consists of a sulfur atom double-bonded to an oxygen atom, and a propyl chain ending in a primary amide group.</p>
Atomoxetine	83015-26-3	C <sub>17</sub> H <sub>21</sub> N-O	 <p>The chemical structure of Atomoxetine is shown. It features a central chiral carbon atom bonded to a 3-methoxyphenyl group (top-left, with a dashed bond to the oxygen atom), a phenyl ring (bottom), and a propyl chain ending in a secondary amine group (top-right, with a dashed bond to the nitrogen atom). A green 'Cl' is present to the right of the structure, indicating the presence of a chloride counterion.</p>

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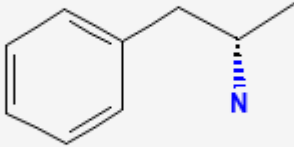
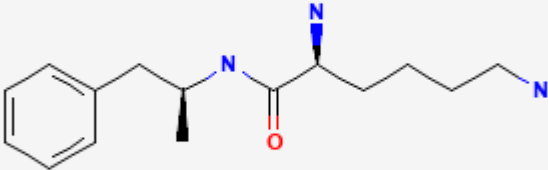
DRUG	CAS REGISTRY NUMBER	MOLECULAR FORMULA	STRUCTURE
Dextroamphetamine	51-64-9	C <sub>9</sub> -H <sub>13</sub> -N	 <p>The chemical structure of Dextroamphetamine is shown. It consists of a benzene ring attached to a two-carbon chain. The second carbon of this chain is bonded to a methyl group and a nitrogen atom. The nitrogen atom is highlighted in blue and has a dashed bond to the carbon, indicating its stereochemistry.</p>
Lisdexamfetamine	608137-32-2	C <sub>15</sub> -H <sub>25</sub> -N <sub>3</sub> -O	 <p>The chemical structure of Lisdexamfetamine is shown. It features a benzene ring attached to a two-carbon chain. The second carbon of this chain is bonded to a methyl group (represented by a wedge) and a nitrogen atom. This nitrogen atom is part of a secondary amide group, which is further bonded to a carbonyl group (C=O, with the oxygen in red). The carbonyl carbon is bonded to a nitrogen atom (highlighted in blue) which is part of a propylamine chain (N-CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>-N). The nitrogen at the end of this chain is also highlighted in blue.</p>

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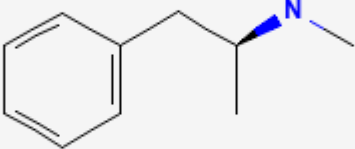
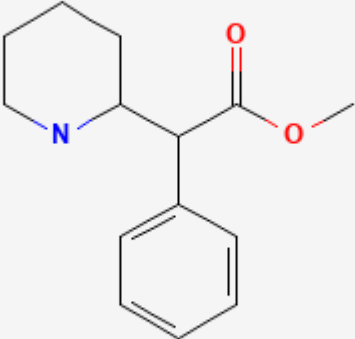
DRUG	CAS REGISTRY NUMBER	MOLECULAR FORMULA	STRUCTURE
Methamphetamine	537-46-2	C10-H15-N	 <p>The chemical structure of Methamphetamine is shown. It consists of a benzene ring attached to a two-carbon chain. The second carbon of this chain is also bonded to a methyl group and a nitrogen atom, which is further bonded to another methyl group. The nitrogen atom is highlighted in blue.</p>
Methylphenidate	113-45-1	C14-H19-N-O2	 <p>The chemical structure of Methylphenidate is shown. It features a piperidine ring (a six-membered ring with one nitrogen atom) attached to a central carbon atom. This central carbon is also bonded to a phenyl ring and a methyl ester group (a carbonyl group bonded to a methoxy group). The nitrogen atom in the piperidine ring and the oxygen atoms in the ester group are highlighted in blue and red, respectively.</p>

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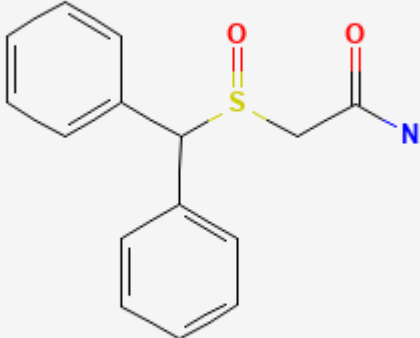
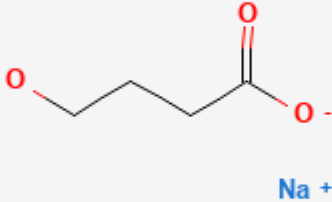
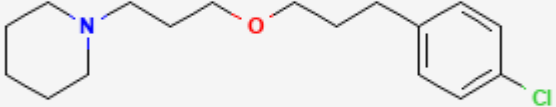
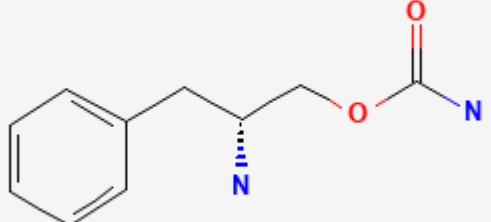
DRUG	CAS REGISTRY NUMBER	MOLECULAR FORMULA	STRUCTURE
Modafinil	68693-11-8	C <sub>15</sub> H <sub>15</sub> N-O <sub>2</sub> S	 <p>The chemical structure of Modafinil is shown. It consists of a central carbon atom bonded to two phenyl rings, a sulfur atom, and a nitrogen atom. The sulfur atom is double-bonded to an oxygen atom, and the nitrogen atom is double-bonded to another oxygen atom. The sulfur atom is also bonded to a methylene group, which is in turn bonded to the nitrogen atom.</p>
Sodium Oxybate	502-85-2	C <sub>4</sub> H <sub>7</sub> -Na-O <sub>3</sub>	 <p>The chemical structure of Sodium Oxybate is shown. It consists of a four-carbon chain with a carboxylate group at one end and an ether oxygen at the other. The carboxylate group is shown as a carbonyl group bonded to an oxygen atom with a negative charge. The sodium ion (Na<sup>+</sup>) is shown as a counterion.</p>

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DRUG	CAS REGISTRY NUMBER	MOLECULAR FORMULA	STRUCTURE
Pitolisant	362665-56-3	C <sub>17</sub> -H <sub>26</sub> -Cl-N-O	
Solriamfetol	178429-62-4	C <sub>10</sub> -H <sub>14</sub> -N <sub>2</sub> -O <sub>2</sub>	

## ANNOTATED BIBLIOGRAPHY

References updated: 12 August 2021

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 psychotropic agents does not discuss modafinil and armodafinil).

Westfall TC, Macarthur H, Westfall DP. Narcolepsy and sleep/wake imbalance. 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. 207.

(Textbook of pharmacology and therapeutics).

- Randomized trial of modafinil for the treatment of pathological somnolence in narcolepsy. US Modafinil in Narcolepsy Multicenter Study Group. *Ann Neurol*. 1998;43:88–97. PubMed PMID: 9450772.
- (Controlled trial of modafinil [200 or 400 mg] vs placebo for 9 weeks; modafinil demonstrated an excellent safety profile for up to 40 weeks of open label treatment; “there were few clinically meaningful changes in laboratory values”).
- Randomized trial of modafinil as a treatment for the excessive daytime somnolence of narcolepsy. US Modafinil in Narcolepsy Multicenter Study Group. *Neurology*. 2000;54:1166–75. PubMed PMID: 10720292.
- (Controlled 9 week trial of two doses of modafinil [200 and 400 mg] vs placebo in 271 patients with narcolepsy: “There were no meaningful differences among treatment groups at week 9 in clinical laboratory test results”).
- Mitler MM, Harsh J, Hirshkowitz M, Guilleminault C. Long-term efficacy and safety of modafinil (PROVIGIL((R))) for the treatment of excessive daytime sleepiness associated with narcolepsy. *Sleep Med*. 2000;1:231–43. PubMed PMID: 10828434.
- (478 adults with narcolepsy were enrolled in two 40-week, open label extension studies using 200–400 mg of modafinil daily; common side effects were headache, nervousness, and nausea; clinically significant elevations in ALT occurred in 6 [1.5%] and total bilirubin in 1 patient, but no other details given).
- A new indication for gamma hydroxybutyrate (Xyrem) in narcolepsy. *Med Lett Drugs Ther*. 2006;48(1227):11–2. PubMed PMID: 16444137.
- (Concise review of narcolepsy and the mechanism of action, clinical efficacy, and adverse effects of oxybate, shortly after the broadening of its indications to include excessive daytime sleepiness in patients with narcolepsy; no mention of serum enzyme elevations or hepatotoxicity).
- 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, modafinil, or oxybate).
- 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. PubMed PMID: 25754159.
- (Among 899 cases of drug induced liver injury enrolled in a US prospective study between 2004 and 2013, one was attributed to methylphenidate, but none to amphetamines, modafinil, armodafinil, or oxybate).
- Kaplan S, Goehring EL Jr, Melamed-Gal S, Nguyen-Khoa BA, Knebel H, Jones JK. Modafinil and the risk of cardiovascular events: Findings from three US claims databases. *Pharmacoepidemiol Drug Saf*. 2018;27:1182–90. PubMed PMID: 30106194.
- (Analysis of 3 large US health care claims database systems [2006–2008] found no increased risk for myocardial infarction or cardiovascular hospitalization among modafinil users vs non-users).
- Solriamfetol (Sunosi) for excessive daytime sleepiness. *Med Lett Drugs Ther*. 2019;61(1579):132–4. PubMed PMID: 31581157.
- (Concise review of the mechanism of action, clinical efficacy, safety and cost of solriamfetol for excess sleepiness associated with narcolepsy and obstructive sleep apnea mentions adverse events of headache, nausea, anorexia, dry mouth, anxiety, and insomnia, but does not discuss ALT elevations or hepatotoxicity).
- Thorpy MJ. Recently approved and upcoming treatments for narcolepsy. *CNS Drugs*. 2020;34:9–27. PubMed PMID: 31953791.

(Review of the mechanism of action, pharmacology, drug-drug interactions, clinical efficacy and safety of newly approved medications for narcolepsy including pitolisant and solriamfetol; no mention of ALT elevations or hepatotoxicity).

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).

Nourbakhsh B, Revirajan N, Morris B, Cordano C, Creasman J, Manguinao M, Krysko K, et al. Safety and efficacy of amantadine, modafinil, and methylphenidate for fatigue in multiple sclerosis: a randomised, placebo-controlled, crossover, double-blind trial. *Lancet Neurol.* 2021;20:38–48. PubMed PMID: 33242419.

(In a placebo controlled, 4-period, crossover trial of amantadine, modafinil and methylphenidate for up to 6 weeks, none of the drugs were superior to placebo in improving fatigue, but all three were associated with more side effects than placebo; ALT elevations and hepatotoxicity were not mentioned).

Pitolisant (Wakix) for narcolepsy. *Med Lett Drugs Ther.* 2021;63(1617):19–21. PubMed PMID: 33647004.

(Concise review of the mechanism of action, and relative efficacy, safety and costs of pitolisant in relation to other medications for narcolepsy shortly after its approval for use in the US, mentions side effects of headache, insomnia, nausea and prolongation of the QTc interval).