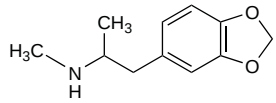
## Methylenedioxymethamfetamine ⊗

MDMA; Methylenedioxymethamphetamine; 3,4-Methylenedioxymethamphetamine; Metilendioximetanfetamina. *N*,α-Dimethyl-1,3-benzodioxole-5-ethanamine.

$C_{11}H_{15}NO_2$ = 193.2.

*CAS — 42542-10-9.*



NOTE. The following terms have been used as 'street names' (see p.vi) or slang names for various forms of methylenedioxymethamfetamine:
007s; 69s; Adam; Adam MTX; Anastasia; Apples; Baby slits; Bacalao; Batmans; B-bombs; Bean; Beans; Bens; Benzedrine; Bermuda triangles; Bibs; Bicho; Bickies; Bikkies; Biphetamine; Biscuits; Blue kisses; Blue lips; Blue nile; Booty juice; Bomber; Brownies; Burgers; Candies; Candy; Care bears; Cat in the hats; Charity; Chocolate chips; Chrystal methadrine; Clarity; Cloud nine; Clovers; Cowies; Cristal; Crowns; Dancing Shoes; Dead road; Debs; Decadence; Deccadence; Dennis the Menaces; Dex; Dexedrine; Diamonds; Diamond Whites; Disco biscuit; Disco biscuits; Doctor; Dollars; Dolls; Dolphins; Doobies; Dove; Doves; Drivers; E; EA1475; Eazy; Eazy E; E-ball; Ebeneezer; E-bomb; E-bombs; Eccies; Ecstacy; Ecstasy; Ecstasy Tablets; Eddie Bo; Egg Rolls; Egyptians; Ekies; Elaine; Elephants; Em; Empathy; Essence; Eve; Ex; Exiticity; Extasy; Fantasia; Fantasy; Fastin; Fizzle; Flipper; Flipping; Four leaf clover; Fuckstasy; Gaggler; Gary Ableths; Garys; Go; Googs; Green triangles; Greenies; Grey biscuits; Gum; Gurners; Gurns; GWM; Hamburger; Hamburgers; Happy drug; Happy pill; Herbal bliss; Hug drug; Hug-Drug; Huggers; Hydro; Hype; Iboga; Ice; Igloo; Illies; Jack and jills; Jellies; Jerry Garcias; Jiggas; Jills; Junnov; Khat; Kiks; Kleenex; Letter biscuits; Light meth; Lollies; Long lasting lollies; Louie Vuitton; Love-Bug; Love doctor; Love Doves; Love drug; Love drug of the '80s; Love drug of the '90s; Love Medicine; Love pill; Love potion #9; Lovers' special; Lover's speed; Lucky charmz; "M"; M25; Madman; Malcolm; Mandy; MAO; MDM; MDMA; Mercedes; Meth amps; Methedrine; Mini beans; Mitsibushis; Mitsies; Mitsu's; Mitsubishi; Mitsubishis; M&M; M&Ms; Mellow drug of America; Molly; Mollys; Monoamine oxidase; Morning shot; New Yorkers; Nineteen; Number 9; Orange bandits; Orbit; Pasti; Pillage; Pills; Pilules d'Amour; Pingers; Pink Calis; Pink panthers; Pink studs; Playboy bunnies; Playboys; Pollutants; Pressies; Rave energy; Red devils; Rhubarb & Custards; Rib; Ritual spirit; Road Runner; Roca; Roker's Barnet; Rolexes; Roll; Rolling; Rolls Royce; Running; Scooby snacks; Scum; Shabu; Skates; Slammin'; Slamming; Slits; Slows; Smartees; Smurfs; Speed for lovers; Spivias; Stars; Strawberry shortcake; Supermans; Swadger; Swans; Sweeties; Sweets; Tablets; Tabs; Tacha; Tachas; Tangos; Tens; The love drug; Thizz; Tom and Jerries; Triple crowns; Triple rolexes; Triple stacks; Tutus; Tweety Birds; Ultimate Xphoria; U.S.P.; Vitamin E; Vitamin X; Vowels; Wafers; Wee Boys; West Coast turnarounds; Wheels; Whiffledust; White diamonds; White dove; White doves; Whiz bombs; Wigits; Wingers; X; X-ing; X-Men; X-Men 2; X-Pills; XTC; Yips; Yokes; Yuppie psychedelic.

### Profile

Methylenedioxymethamfetamine is a phenylethylamine compound structurally related to amfetamine and mescaline and is an analogue of tenamfetamine (p.2164). It is subject to abuse. Its toxicity is similar to that of dexamfetamine (see Abuse, below and under Dexamfetamine, p.2153) and may be treated similarly.

**Abuse.** Methylenedioxymethamfetamine may be ingested as tablets, capsules, or inhaled as a powder. It is often mixed with a combination of adulterants such as other amfetamines, caffeine, ephedrine, and pseudoephedrine.[1]

The toxicity associated with abuse of methylenedioxymethamfetamine has been the subject of a number of discussions.[2-7] Acute effects can be severe and symptoms have included cardiac arrhythmias, fulminant hyperthermia, convulsions, disseminated intravascular coagulation, rhabdomyolysis, and acute renal failure; fatalities may occur. Repeated use may cause hepatic damage. Psychiatric effects reported include psychosis[8-10] and depression.[9-11] Damage to central serotonergic nerves has been implicated[8-12] and hence there is some concern regarding the long-term effects of methylenedioxymethamfetamine abuse.[13,14] Hyponatraemia, inappropriate antidiuretic hormone secretion, and cerebral oedema have also been reported;[15-20] the severity may be increased by excessive fluid intake that is frequently advocated to prevent dehydration and hyperthermia.[18-22] Urinary retention has also been reported.[23]

Concern has been expressed regarding abuse during *pregnancy.* Twelve congenital malformations, including 2 cases of congenital heart disease, have been noted among 78 liveborn infants whose mothers had taken methylenedioxymethamfetamine, often with other drugs of abuse, during their pregnancies.[24]

For reviews of the properties of other phenylethylamine compounds, see under Tenamfetamine, p.2164.


1. Smith KM, *et al.* Club drugs: methylenedioxymethamphetamine, flunitrazepam, ketamine hydrochloride, and γ-hydroxybutyrate. *Am J Health-Syst Pharm* 2002; **59:** 1067–76.
2. Henry JA. Ecstasy and the dance of death. *BMJ* 1992; **305:** 5–6.
3. Henry JA, *et al.* Toxicity and deaths from 3,4-methylenedioxymethamphetamine ("ecstasy"). *Lancet* 1992; **340:** 384–7.
4. O'Connor B. Hazards associated with the recreational drug 'ecstasy'. *Br J Hosp Med* 1994; **52:** 507–14.
5. McCann UD, *et al.* Adverse reactions with 3,4-methylenedioxymethamphetamine (MDMA; 'Ecstasy'). *Drug Safety* 1996; **15:** 107–115.
6. Hall AP. Ecstasy and the anaesthetist. *Br J Anaesth* 1997; **79:** 697–8.
7. Schwartz RH, Miller NS. MDMA (ecstasy) and the rave: a review. *Pediatrics* 1997; **100:** 705–8.
8. McGuire P, Fahy T. Chronic paranoid psychosis after misuse of MDMA ("ecstasy"). *BMJ* 1991; **302:** 697.
9. Winstock AR. Chronic paranoid psychosis after misuse of MDMA. *BMJ* 1991; **302**: 1150–1.
10. Schifano F. Chronic atypical psychosis associated with MDMA ("ecstasy") abuse. *Lancet* 1991; **338:** 1335.
11. Benazzi F, Mazzoli M. Psychiatric illness associated with "ecstasy". *Lancet* 1991; **338:** 1520.
12. McCann UD, *et al.* Positron emission tomographic evidence of toxic effect of MDMA ("Ecstasy") on brain serotonin neurons in human beings. *Lancet* 1998; **352:** 1433–7.
13. Green AR, Goodwin GM. Ecstasy and neurodegeneration. *BMJ* 1996; **312:** 1493–4.
14. Bolla KI, *et al.* Memory impairment in abstinent MDMA ("Ecstasy") users. *Neurology* 1998; **51:** 1532–7.
15. Maxwell DL, *et al.* Hyponatraemia and catatonic stupor after taking "ecstasy". *BMJ* 1993; **307:** 1399.
16. Kessel B. Hyponatraemia after ingestion of "ecstasy". *BMJ* 1994; **308:** 414.
17. Satchell SC, Connaughton M. Inappropriate antidiuretic hormone secretion and extreme rises in serum creatinine kinase following MDMA ingestion. *Br J Hosp Med* 1994; **51:** 495.
18. Holden R, Jackson MA. Near-fatal hyponatraemic coma due to vasopressin over-secretion after ecstasy (3,4-MDMA). *Lancet* 1996; **347:** 1052.
19. Matthai SM, *et al.* Cerebral oedema after ingestion of MDMA (ecstasy) and unrestricted intake of water. *BMJ* 1996; **312:** 1359.
20. Parr MJA, *et al.* Hyponatraemia and death after ecstasy ingestion. *Med J Aust* 1997; **166:** 136–7.
21. Cook TM. Cerebral oedema after MDMA ('ecstasy') and unrestricted water intake. *BMJ* 1996; **313:** 689.
22. Henry JA, *et al.* Low-dose MDMA ("ecstasy") induces vasopressin secretion. *Lancet* 1998; **351:** 1784.
23. Bryden AA, *et al.* Urinary retention with misuse of 'ecstasy'. *BMJ* 1995; **310:** 504.
24. McElhatton PR, *et al.* Congenital anomalies after prenatal ecstasy exposure. *Lancet* 1999; **354:** 1441–2.


**Interactions.** A psychotic reaction has been reported in a patient who took methylenedioxymethamfetamine while receiving therapy with *citalopram.*[1]

A patient receiving *phenelzine* and lithium therapy experienced a serotonin syndrome (p.416) after ingesting methylenedioxymethamfetamine.[2] Symptoms included markedly increased muscle tension, tremulousness, abnormal posturing, limited pain response, tachycardia, hypertension, hyperthermia, increased white blood cell count, increased creatine phosphokinase concentration, respiratory acidosis, metabolic acidosis, delirium, and agitation. Within 15 minutes of methylenedioxymethamfetamine ingestion the patient was comatose; within 5 hours the patient was alert with a normal muscle tone. An interaction between phenelzine and methylenedioxymethamfetamine was suggested as the cause of the serotonin syndrome.

A fatal serotonergic reaction to methylenedioxymethamfetamine possibly due to an interaction with *ritonavir* has been described.[3] A prolonged and exaggerated effect from a small dose of methylenedioxymethamfetamine has been reported[4] in another patient also receiving ritonavir. Although this patient was also receiving saquinavir, the authors postulated that the mechanism may be ritonavir-induced inhibition of the cytochrome P450 isoenzyme CYP2D6.


1. Lauerma H, *et al.* Interaction of serotonin reuptake inhibitor and 3,4-methylenedioxymethamphetamine? *Biol Psychiatry* 1998; **43:** 923–8.
2. Kaskey GB. Possible interaction between an MAOI and "ecstasy". *Am J Psychiatry* 1992; **149:** 411–12.
3. Henry JA, Hill IR. Fatal interaction between ritonavir and MDMA. *Lancet* 1998; **352:** 1751–2.
4. Harrington RD, *et al.* Life-threatening interactions between HIV-1 protease inhibitors and the illicit drugs MDMA and γ-hydroxybutyrate. *Arch Intern Med* 1999; **159:** 2221–4.


## Methylphenidate Hydrochloride *(BANM, rINNM)* ⊗

Hidrocloruro de metilfenidato; Methyl Phenidate Hydrochloride; Méthylphénidate, chlorhydrate de; Methylphenidati hydrochloridum; Metilfenidat Hidroklorür. Methyl α-phenyl-2-piperidylacetate hydrochloride.

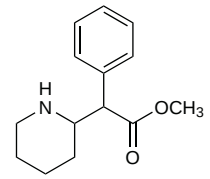
Метилфенидата Гидрохлорид

$C_{14}H_{19}NO_2$,HCl = 269.8.

*CAS — 113-45-1 (methylphenidate); 298-59-9 (methylphenidate hydrochloride).*

*ATC — N06BA04.*

*ATC Vet — QN06BA04.*



*(methylphenidate)*

NOTE. The following terms have been used as 'street names' (see p.vi) or slang names for various forms of methylphenidate:
Rities; Vitamin R; West coast.

**Pharmacopoeias.** In *Chin., Swiss,* and *US.*

**USP 31** (Methylphenidate Hydrochloride). A white, odourless, fine crystalline powder. Freely soluble in water and in methyl alcohol; soluble in alcohol; slightly soluble in acetone and in chloroform. Solutions are acid to litmus.

### Adverse Effects, Treatment, and Precautions

As for Dexamfetamine Sulfate, p.2153. Hypersensitivity reactions have been reported. Skin reactions have included exfoliative dermatitis and erythema multiforme. Purpura, thrombocytopenia, and leucopenia have occurred. Blood counts should be monitored periodically during prolonged therapy.

◊ References.


1. Ahmann PA, *et al.* Placebo-controlled evaluation of Ritalin side effects. *Pediatrics* 1993; **91:** 1101–6.
2. Efron D, *et al.* Side effects of methylphenidate and dexamphetamine in children with attention deficit hyperactivity disorder: a double-blind, crossover trial. *Pediatrics* 1997; **100:** 662–6.
3. Rappley MD. Safety issues in the use of methylphenidate: an American perspective. *Drug Safety* 1997; **17:** 143–8.
4. Klein-Schwartz W. Abuse and toxicity of methylphenidate. *Curr Opin Pediatr* 2002; **14:** 219–23.
5. Leonard BE, *et al.* Methylphenidate: a review of its neuropharmacological, neuropsychological and adverse clinical effects. *Hum Psychopharmacol* 2004; **19:** 151–80.


**Abuse.** Reports of adverse effects after the abuse of methylphenidate by injecting solutions of crushed tablets.[1-3] Intravenous abuse of methylphenidate with pentazocine has also been reported.[4,5] In addition, there are also reports of intranasal methylphenidate abuse,[6-8] including fatalities.[8]

See also Effects on the Liver, below.


1. Wolf J, *et al.* Eosinophilic syndrome with methylphenidate abuse. *Ann Intern Med* 1978; **89:** 224–5.
2. Gunby P. Methylphenidate abuse produces retinopathy. *JAMA* 1979; **241:** 546.
3. Parran TV, Jasinski DR. Intravenous methylphenidate abuse: prototype for prescription drug abuse. *Arch Intern Med* 1991; **151:** 781–3.
4. Debooy VD, *et al.* Intravenous pentazocine and methylphenidate abuse during pregnancy: maternal lifestyle and infant outcome. *Am J Dis Child* 1993; **147:** 1062–5.
5. Carter HS, Watson WA. IV pentazocine/methylphenidate abuse—the clinical toxicity of another Ts and blues combination. *J Toxicol Clin Toxicol* 1994; **32:** 541–7.
6. Jaffe SL. Intranasal abuse of prescribed methylphenidate by an alcohol and drug abusing adolescent with ADHD. *J Am Acad Child Adolesc Psychiatry* 1991; **30:** 773–5.
7. Garland EJ. Intranasal abuse of prescribed methylphenidate. *J Am Acad Child Adolesc Psychiatry* 1998; **37:** 573–4.
8. Massello W, Carpenter DA. A fatality due to the intranasal abuse of methylphenidate (Ritalin ). *J Forensic Sci* 1999; **44:** 220–1.


**Breast feeding.** No adverse effects were noted[1] in a 6-month-old breast-fed infant whose 26-year-old mother had been taking methylphenidate 40 mg twice daily for about 5 weeks. Despite the relatively high milk-to-plasma ratio of 2.7 the relative infant dose was low, at 0.2% of the maternal dose. Nonetheless the authors recommended caution when giving methylphenidate to breast-feeding mothers. Licensed product information also recommends that methylphenidate should be used with caution or avoided during breast feeding.


1. Hackett LP, *et al.* Methylphenidate and breast-feeding. *Ann Pharmacother* 2006; **40:** 1890–1.


**Effects on the cardiovascular system.** For mention of the adverse cardiovascular effects of stimulants, see under Dexamfetamine Sulfate, p.2153.

**Effects on growth.** Concern has been expressed about the effects of central stimulants such as methylphenidate on growth rate when used to treat hyperactivity in children. One study showed that methylphenidate produced decreases in weight percentiles after 1 year of therapy and progressive decrement in height percentiles that became significant after 2 years of use.[1] However, another suggested that moderate doses might have a lower risk for long-term height suppression than dexamfetamine.[2] There has also been a study which showed that, even when methylphenidate had an adverse effect on growth rate during active treatment, final height was not compromised and that a compensatory rebound of growth appeared to occur on stopping stimulant treatment.[3]

See also under Dexamfetamine Sulfate, p.2153.


1. Mattes JA, Gittelman R. Growth of hyperactive children on maintenance regimen of methylphenidate. *Arch Gen Psychiatry* 1983; **40:** 317–21.

2. Greenhill LL, *et al.* Prolactin, growth hormone and growth responses in boys with attention deficit disorder and hyperactivity treated with methylphenidate. *J Am Acad Child Psychiatry* 1984; **23:** 58–67.
3. Klein RG, Mannuzza S. Hyperactive boys almost grown up III: methylphenidate effects on ultimate height. *Arch Gen Psychiatry* 1988; **45:** 1131–4.

**Effects on the liver.** Hepatotoxicity with raised liver enzyme values in a 67-year-old woman was associated with the use of methylphenidate hydrochloride 30 mg daily by mouth.[1] Methylphenidate-induced hepatocellular injury was reported in a 19-year-old woman who developed jaundice, fever, and malaise after intravenous abuse of methylphenidate hydrochloride tablets.[2]

1. Goodman CR. Hepatotoxicity due to methylphenidate hydrochloride. *N Y State J Med* 1972; **72:** 2339–40.
2. Mehta H, *et al.* Hepatic dysfunction due to intravenous abuse of methylphenidate hydrochloride. *J Clin Gastroenterol* 1984; **6:** 149–51.

**Effects on the skin.** A fixed drug eruption of the scrotum has been reported in 2 children treated with methylphenidate for attention deficit disorder.[1]

1. Cohen HA, *et al.* Fixed drug eruption of the scrotum due to methylphenidate. *Ann Pharmacother* 1992; **26:** 1378–9.

**Tourette's syndrome.** For a discussion on whether central stimulants provoke Tourette's syndrome, see Dexamfetamine Sulfate, p.2153.

## Interactions

As for Dexamfetamine Sulfate, p.2153.

**Anticoagulants.** For the effect of methylphenidate on *ethyl biscoumacetate*, see Central Stimulants under the Interactions of Warfarin, p.1430.

**Antidepressants.** For the effect of methylphenidate on *tricyclic antidepressants*, see under Amitriptyline, p.379.

**Antiepileptics.** Methylphenidate blood concentrations decreased, and symptoms of attention deficit hyperactivity disorder worsened, in a 13-year-old girl after starting therapy with *carbamazepine*.[1]

For the effect of methylphenidate on antiepileptics, see under Phenytoin, p.500.

1. Schaller JL, *et al.* Carbamazepine and methylphenidate in ADHD. *J Am Acad Child Adolesc Psychiatry* 1999; **38:** 112–13.

## Pharmacokinetics

Methylphenidate is readily absorbed from the gastrointestinal tract. The presence of food in the stomach accelerates the rate of absorption but not the total amount absorbed. Peak plasma concentrations are reached about 2 hours after oral doses; methylphenidate undergoes extensive first-pass metabolism. Protein binding is low. It is excreted as metabolites mainly in the urine with small amounts appearing in the faeces; less than 1% appears in the urine as unchanged methylphenidate. The major metabolite is ritalinic acid (2-phenyl-2-piperidyl acetic acid). The plasma elimination half-life is about 2 hours. Methylphenidate is distributed into breast milk.

◊ References.

1. Aoyama T, *et al.* Nonlinear kinetics of threo-methylphenidate enantiomers in a patient with narcolepsy and in healthy volunteers. *Eur J Clin Pharmacol* 1993; **44;** 79–84.
2. Aoyama T, *et al.* Pharmacokinetics and pharmacodynamics of (+)-threo-methylphenidate enantiomer in patients with hypersomnia. *Clin Pharmacol Ther* 1994; **55:** 270–6.
3. Shader RI, *et al.* Population pharmacokinetics of methylphenidate in children with attention-deficit hyperactivity disorder. *J Clin Pharmacol* 1999; **39:** 775–785.
4. Kimko HC, *et al.* Pharmacokinetics and clinical effectiveness of methylphenidate. *Clin Pharmacokinet* 1999; **37:** 457–70.
5. Modi NB, *et al.* Single- and multiple-dose pharmacokinetics of an oral once-a-day osmotic controlled-release OROS (methylphenidate HCl) formulation. *J Clin Pharmacol* 2000; **40:** 379–88.
6. Teo SK, *et al.* A single-dose, two-way crossover, bioequivalence study of dexmethylphenidate HCl with and without food in healthy subjects. *J Clin Pharmacol* 2004; **44:** 173–8.
7. Quinn D, *et al.* Single-dose pharmacokinetics of multilayer-release methylphenidate and immediate-release methylphenidate in children with attention-deficit/hyperactivity disorder. *J Clin Pharmacol* 2007; **47:** 760–6.

## Uses and Administration

Methylphenidate hydrochloride is a central stimulant and indirect-acting sympathomimetic with actions and uses similar to those of dexamfetamine (p.2154). It is used in the treatment of narcolepsy (p.2148) and as an adjunct to psychological, educational, and social measures in the treatment of hyperactivity disorders in children.

In the treatment of **narcolepsy** the usual oral dose is 20 to 30 mg daily in divided doses, normally 30 to 45 minutes before meals, but the effective dose may range from 10 to 60 mg daily.

In **hyperactivity disorders** in children aged 6 years and over, the usual initial dose is 5 mg once or twice daily by mouth, increased if necessary by 5 to 10 mg at weekly intervals to a maximum of 60 mg daily in divided doses. Methylphenidate may be given before breakfast and lunch. A later dose may be considered if the effect wears off in the evening causing rebound hyperactivity.

Methylphenidate hydrochloride is also available as modified-release preparations for the treatment of hyperactivity disorders. Some modified-release preparations also contain immediate-release methylphenidate within the formulation. Doses of modified-release preparations may vary according to the brand chosen. Recommended doses for one brand of modified-release tablets (*Concerta*: *Janssen-Cilag, UK*; *McNeil, USA*) are as follows:

- children and adolescents aged 6 to 17 years and not currently taking conventional methylphenidate should be started on 18 mg once daily in the morning
- the dose may then be increased at weekly intervals to a maximum of 54 mg once daily; the USA permits a maximum of 72 mg once daily in those aged 13 to 17 years
- the dose in patients already taking conventional methylphenidate should be based on their current dose although the initial dose should not exceed 54 mg once daily

Transdermal patches delivering amounts of methylphenidate ranging from 1.1 to 3.3 mg/hour are available for once-daily application in the treatment of hyperactivity disorders in children aged 6 to 12 years. Patients should be started on the lowest strength patch regardless of any previous methylphenidate use; thereafter, doses should be individually titrated for each patient according to response and increased at weekly intervals if necessary to a maximum of 3.3 mg/hour (at week 4). Patches should be applied to the hip area 2 hours before an effect is needed and removed after a maximum of 9 hours later.

Methylphenidate should be stopped if there is no improvement in symptoms after appropriate adjustments in dosage over one month. It also needs to be stopped from time to time in those who do respond, to assess the patient's condition. Treatment is not usually continued beyond puberty, however, in some patients drug therapy may be required into adulthood. In such cases doses are similar to those used in the treatment of narcolepsy.

A single isomer form of methylphenidate, dexmethylphenidate (p.2154) is also used for hyperactivity disorders.

◊ References.

1. Challman TD, Lipsky JJ. Methylphenidate: its pharmacology and uses. *Mayo Clin Proc* 2000; **75:** 711–21.

**Depression.** Stimulants are no longer recommended as sole treatment for depression (p.373), although they have been tried in augmenting the effect of standard antidepressants such as the SSRIs[1] in patients with refractory depressive disorders.

1. Stoll AL, *et al.* Methylphenidate augmentation of serotonin selective reuptake inhibitors: a case series. *J Clin Psychiatry* 1996; **57:** 72–6.

**Disturbed behaviour.** Disturbed behaviour can have a number of causes and is usually treated with an antipsychotic or benzodiazepine (see p.954). A review[1] of the published clinical trials between 1966 and June 2004 found that although methylphenidate was likely to improve memory, attention, concentration, and mental processing in patients with traumatic brain injury, its effect on behaviour remains to be determined; the most commonly used dosage was 300 micrograms/kg twice daily.

1. Siddall OM. Use of methylphenidate in traumatic brain injury. *Ann Pharmacother* 2005; **39:** 1309–13.

**Hyperactivity.** Methylphenidate is one of the main drugs used in hyperactivity, including attention deficit hyperactivity disorder (ADHD) (p.2148).

Small studies have indicated that different aspects of attention deficit disorders in children might respond to different doses of methylphenidate.[1-4] In addition to the morning and noon doses commonly used in hyperactivity disorders, studies[5,6] have shown improved clinical outcome with little adverse effect on sleep patterns if a third late afternoon dose is given.

Modified-release preparations with a slow onset of action have been developed to overcome the short duration of action of methylphenidate although they may be less effective than immediate-release preparations. A study,[7] using a regimen to simulate the prolonged steady plasma concentration profile obtained with the slow-onset, modified-release preparations, has suggested that unlike twice-daily treatment acute tolerance might develop with the use of modified-release preparations. However, a newer modified-release preparation has been reported to be as effective as an immediate-release preparation in short-term studies.[8,9] Transdermal patches containing methylphenidate released over 9 hours are available in the USA.[10]

UK guidelines for the use of methylphenidate in children and adolescents with ADHD are available.[11]

1. Sprague RL, Sleator EK. Methylphenidate in hyperkinetic children: differences in dose effects on learning and social behavior. *Science* 1977; **198:** 1274–6.
2. Tannock R, *et al.* Dose-response effects of methylphenidate on academic performance and overt behavior in hyperactive children. *Pediatrics* 1989; **84:** 648–57.
3. Sebrechts MM, *et al.* Components of attention, methylphenidate dosage, and blood levels in children with attention deficit disorder. *Pediatrics* 1986; **77:** 222–8.
4. Barkley RA, *et al.* Attention deficit disorder with and without hyperactivity: clinical response to three dose levels of methylphenidate. *Pediatrics* 1991; **87:** 519–31.
5. Kent JD, *et al.* Effects of late-afternoon methylphenidate administration on behavior and sleep in attention-deficit hyperactivity disorders. *Pediatrics* 1995; **96:** 320–5.
6. Stein MA, *et al.* Methylphenidate dosing: twice daily versus three times daily. *Pediatrics* 1996; **98:** 748–56.
7. Swanson J, *et al.* Acute tolerance to methylphenidate in the treatment of attention deficit hyperactivity disorder in children. *Clin Pharmacol Ther* 1999; **66:** 295–305.
8. Pelham WE, *et al.* Once-a-day Concerta methylphenidate versus three-times-daily methylphenidate in laboratory and natural settings. Abstract: *Pediatrics* 2001; **107:** 1417. Full version: http://pediatrics.aappublications.org/cgi/content/full/107/6/e105 (accessed 15/04/04)
9. Wolraich ML, *et al.* Randomized, controlled trial of OROS methylphenidate once a day in children with attention-deficit/hyperactivity disorder. *Pediatrics* 2001; **108:** 883–92.
10. Anderson VR, Scott LJ. Methylphenidate transdermal system: in attention-deficit hyperactivity disorder in children. *Drugs* 2006; **66:** 1117–26.
11. NICE. Methylphenidate, atomoxetine and dexamfetamine for attention deficit hyperactivity disorder (ADHD) in children and adolescents: review of Technology Appraisal 13 (Technology Appraisal 98, issued March 2006). Available at: http://www.nice.org.uk/nicemedia/pdf/TA098guidance.pdf (accessed 11/08/08)

## Preparations

***USP 31:*** Methylphenidate Hydrochloride Extended-release Tablets; Methylphenidate Hydrochloride Tablets.

**Proprietary Preparations** (details are given in Part 3)

***Arg.:*** Concerta; Methylin; Ritalina; Rubifen; ***Austral.:*** Attenta; Concerta; Lorentin†; Ritalin; ***Austria:*** Concerta; Ritalin; ***Belg.:*** Concerta; Rilatine; ***Braz.:*** Concerta; Ritalina; ***Canad.:*** Concerta; Riphenidate†; Ritalin; ***Chile:*** Aradix; Concerta; Elem†; Nebapul; Ritalin; Ritrocel; ***Cz.:*** Ritalin; ***Denm.:*** Equasym; Motiron; Ritalin; ***Fin.:*** Concerta; ***Fr.:*** Concerta; Ritaline; ***Ger.:*** Concerta; Equasym; Medikinet; Ritalin; ***Gr.:*** Concerta; Ritaline; ***Hong Kong:*** Concerta; Ritalin; ***Hung.:*** Ritalin; ***Indon.:*** Concerta; Ritalin; ***Irl.:*** Concerta; Equasym; Ritalin; ***Israel:*** Concerta; Metadate; Ritalin; ***Malaysia:*** Concerta; Ritalin; Rubifen; ***Mex.:*** Concerta; Ritalin; Tradea; ***Neth.:*** Concerta; Equasym; Ritalin; Rubifen†; Tifinidat; ***Norw.:*** Concerta; Equasym; Ritalin; ***NZ:*** Concerta; Ritalin; Rubifen; ***Philipp.:*** Concerta; ***Pol.:*** Concerta; ***Port.:*** Concerta; Ritalina; Rubifen; ***S.Afr.:*** Adaphen; Concerta; Ritalin; Ritaphen†; ***Singapore:*** Concerta; Ritalin; Rubifen; ***Spain:*** Concerta; Rubifen; ***Swed.:*** Concerta; Ritalin; ***Switz.:*** Concerta; Ritaline; ***Thai.:*** Concerta; Rubifen†; ***Turk.:*** Concerta; Ritalin; ***UK:*** Concerta; Equasym; Medikinet; Ritalin; Tranquilyn†; ***USA:*** Concerta; Daytrana; Metadate; Methylin; Ritalin; ***Venez.:*** Concerta; Ritalin.

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# Modafinil *(BAN, USAN, rINN)* ⊗

CEP-1538; CRL-40476; Modafinilo; Modafinilum. 2-[(Diphenylmethyl)sulfinyl]acetamide.

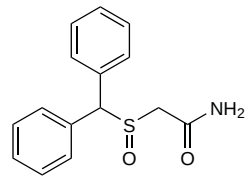
Модафинил

$C_{15}H_{15}NO_2S$ = 273.4.

*CAS — 68693-11-8.*

*ATC — N06BA07.*

*ATC Vet — QN06BA07.*



**Pharmacopoeias.** In *Eur.* (see p.vii) and *US.*

**Ph. Eur. 6.2** (Modafinil). A white or almost white, crystalline powder. It exhibits polymorphism. Very slightly soluble or practically insoluble in water; sparingly soluble in methyl alcohol; slightly soluble in alcohol.

**USP 31** (Modafinil). A white, odourless, crystalline powder. Practically insoluble in water; slightly soluble in alcohol; sparingly soluble in methyl alcohol. Store at a temperature of 20° to 25°, excursions permitted between 15° and 30°.

## Adverse Effects, Treatment, and Precautions

The most commonly reported adverse effect of modafinil, affecting about 21% of patients, is headache, which is usually mild or moderate, dose-dependent, and disappears within a few days. Other adverse effects may be a result of CNS stimulation and effects such as nervousness, insomnia, agitation, confusion, personality disorder, tremor, and anxiety have been noted. There may also be gastrointestinal disturbances, including nausea and abdominal pain, dry mouth, diarrhoea, dyspepsia, and constipation, dizziness, and anorexia. Cardiovascular effects such as hypertension, palpitations, and tachycardia have been reported.

Rare cases of serious or life-threatening rash, including Stevens-Johnson syndrome, erythema multiforme, and toxic epidermal necrolysis, have been reported (see also Effects on the Skin, below). Benign pruritic rashes have also occurred and since it is not possible to predict which skin rashes will become serious, modafinil should be stopped at the first sign of rash unless it is clearly not drug-related. Other hypersensitivity reactions such as angioedema have also been reported rarely.

Psychiatric symptoms including psychosis, depression, hallucinations, suicidal ideation, and mania have been reported. Abnormal liver function tests including dose-related increases in alkaline phosphatase, and dyskinesia have been observed.

Modafinil is contra-indicated in patients with uncontrolled, moderate to severe hypertension or cardiac arrhythmias. It is not recommended in patients with a history of left ventricular hypertrophy or ischaemic ECG changes, chest pain, or other signs of mitral valve prolapse. Modafinil should be given with caution to those with a history of psychosis, depression, or mania.