uct information states that it should not be used in patients with acute respiratory depression. There have been occasional reports of psychiatric disorders such as hallucinations, confusion, and depression. As meptazinol has both antagonist and agonist properties its effects may be only partially reversed by naloxone, but use of the latter is still recommended in overdosage.

Meptazinol has the potential to precipitate withdrawal symptoms if given to patients who are physically dependent on opioids.

Abuse. See under Dependence and Withdrawal, above.

Effects on the respiratory system. Meptazinol is said to have a relatively low potential for respiratory depression and in healthy subjects was reported to produce substantially less respiratory depression than morphine or pentazocine at usual analgesic doses.[1] However, respiratory depression does occur in anaesthetised patients given meptazinol[2] and the effects on respiration may be similar to those of morphine[3,4] or pethidine.[5,6] Compensatory mechanisms may come into play after repeated doses of meptazinol but the intravenous use of meptazinol during anaesthesia should be viewed with as much caution as with any other opioid.[6]

Respiratory arrest occurred after an *overdose* of 50 meptazinol 200-mg tablets and a quarter of a bottle of whisky.[7] Full recovery eventually followed supportive measures although spontaneous respiration was not re-established by naloxone intravenously to a cumulative total dose of 10 mg.

1. Jordan C, *et al.* A comparison of the respiratory effects of meptazinol, pentazocine and morphine. *Br J Anaesth* 1979; **51:** 497–502.
2. Hardy PAJ. Meptazinol and respiratory depression. *Lancet* 1983; **ii:** 576.
3. Frater RAS, *et al.* Analgesia-induced respiratory depression: comparison of meptazinol and morphine in the postoperative period. *Br J Anaesth* 1989; **63:** 260–5.
4. Verborgh C, Camu F. Post-surgical pain relief with zero-order intravenous infusions of meptazinol and morphine: a double-blind placebo-controlled evaluation of their effects on ventilation. *Eur J Clin Pharmacol* 1990; **38:** 437–42.
5. Wilkinson DJ, *et al.* Meptazinol—a cause of respiratory depression in general anaesthesia. *Br J Anaesth* 1985; **57:** 1077–84.
6. Lee A, Drummond GB. Ventilatory effects of meptazinol and pethidine in anaesthetised patients. *Br J Anaesth* 1987; **59:** 1127–33.
7. Davison AG, *et al.* Meptazinol overdose producing near fatal respiratory depression. *Hum Toxicol* 1987; **6:** 331.

Interactions

For interactions associated with opioid analgesics, see p.103.

Plasma concentrations of meptazinol may be increased by ritonavir and use together should be avoided (see also p.103).

Pharmacokinetics

After oral doses of meptazinol peak plasma concentrations have been achieved within 0.5 to 2 hours, but bioavailability is low since it undergoes extensive first-pass metabolism. Systemic availability is improved after rectal doses. Peak plasma concentrations have been achieved 30 minutes after rectal or intramuscular use. Plasma protein binding has averaged only about 27%. Elimination half-lives of about 2 hours have been reported. Meptazinol is extensively metabolised in the liver and is excreted mainly in the urine as the glucuronide conjugate. Less than 10% of a dose has been recovered from the faeces. Meptazinol crosses the placenta.

◊ References.

1. Franklin RA, *et al.* Studies on the metabolism of meptazinol, a new analgesic drug. *Br J Clin Pharmacol* 1976; **3:** 497–502.
2. Franklin RA, *et al.* Studies on the absorption and disposition of meptazinol following rectal administration. *Br J Clin Pharmacol* 1977; **4:** 163–7.
3. Davies G, *et al.* Pharmacokinetics of meptazinol in man following repeated intramuscular administration. *Eur J Clin Pharmacol* 1982; **23:** 535–8.
4. Norbury HM, *et al.* Pharmacokinetics of the new analgesic, meptazinol, after oral and intravenous administration to volunteers. *Eur J Clin Pharmacol* 1983; **25:** 77–80.
5. Murray GR, *et al.* The systemic availability of meptazinol in man after oral and rectal doses. *Eur J Clin Pharmacol* 1989; **36:** 279–82.

The elderly. A lower clearance and longer elimination half-life has been reported for meptazinol in elderly patients, but dosage reduction was not considered warranted on pharmacokinetic grounds. Mean half-lives in elderly and young subjects were 3.39 and 1.94 hours, respectively after single oral doses[1] and 2.93 and 2.06 hours, respectively after intravenous doses.[2]

1. Norbury HM, *et al.* Pharmacokinetics of meptazinol after single and multiple oral administration to elderly patients. *Eur J Clin Pharmacol* 1984; **27:** 223–6.
2. Murray GR, *et al.* Pharmacokinetics of meptazinol after parenteral administration in the elderly. *Eur J Clin Pharmacol* 1987; **31:** 733–6.

Hepatic impairment. Oral bioavailability of meptazinol appeared to be enhanced in patients with liver disease. After a single oral dose of meptazinol mean peak plasma concentrations were 184 nanograms/mL, 131 nanograms/mL, and 53 nanograms/mL in cirrhotic patients, patients with non-cirrhotic liver disease, and patients with normal liver function, respectively, although there was no evidence of accumulation after chronic dosing.[1] There were no significant differences in plasma clearance after an intravenous dose. Reduced oral doses of meptazinol might be advisable in cirrhotic patients.

1. Birnie GG, *et al.* Enhanced oral bioavailability of meptazinol in cirrhosis. *Gut* 1987; **28:** 248–54.

Pregnancy. In women given an intramuscular injection of 100 to 150 mg during labour, meptazinol was found to cross the placenta readily but was rapidly eliminated from the neonate.[1] This contrasted with pethidine which was known to be excreted very slowly from neonates. As in the adult, elimination of meptazinol by the neonate appeared to take place mainly by conjugation with glucuronic acid.[2] A half-life of 3.4 hours, similar to that in adults, has been reported in the neonate,[3] in contrast to 22.7 hours for pethidine in neonates.

Disposition of meptazinol appears not to be significantly affected by pregnancy. Mean half-lives of 1.36 and 1.68 hours were reported in pregnant and non-pregnant women, respectively,[4] compared with 2.06 hours in men.

1. Franklin RA, *et al.* Preliminary studies on the disposition of meptazinol in the neonate. *Br J Clin Pharmacol* 1981; **12:** 88–90.
2. Dowell PS, *et al.* Routes of meptazinol conjugation in the neonate. *Br J Clin Pharmacol* 1982; **14:** 748–9.
3. Jackson MBA, Robson PJ. Preliminary clinical and pharmacokinetic experiences in the newborn when meptazinol is compared with pethidine as an obstetric analgesic. *Postgrad Med J* 1983; **59** (suppl 1): 47–51.
4. Murray GR, *et al.* The disposition of meptazinol after single and multiple intravenous administration to pregnant and non-pregnant women. *Eur J Clin Pharmacol* 1989; **36:** 273–7.

Uses and Administration

Meptazinol is a mixed opioid agonist and antagonist with partial opioid agonist activity at the μ_1 opioid receptor (see p.104); it also has cholinergic activity. Meptazinol is used in the treatment of moderate to severe pain. It has a shorter duration of action than morphine.

Meptazinol hydrochloride is given orally or by intramuscular or intravenous injection; doses are expressed in terms of the base. Meptazinol hydrochloride 115.6 mg is equivalent to about 100 mg of meptazinol. For the short-term treatment of moderate pain meptazinol is given in an oral dose of 200 mg every 3 to 6 hours, as required. The intramuscular dose is 75 to 100 mg given every 2 to 4 hours, as required; for obstetric pain a dose of 2 mg/kg (100 to 150 mg) may be used. Meptazinol is also given by slow intravenous injection in doses of 50 to 100 mg every 2 to 4 hours, as required.

Administration. ***EPIDURAL ROUTE.*** Epidural meptazinol 90 mg for postoperative pain was reported to be superior to an intramuscular dose of 90 mg.[1] However, in another study[2] a 30-mg dose was ineffective and associated with an unacceptable incidence of adverse effects. A 60-mg dose was also found to be ineffective because of its short duration of action.[3]

UK licensed product information states that the injectable formulation is not suitable for epidural or intrathecal use.

1. Verborgh C, *et al.* Meptazinol for postoperative pain relief in man: comparison of extradural and im administration. *Br J Anaesth* 1987; **59:** 1134–9.
2. Francis RI, Lockhart AS. Epidural meptazinol. *Anaesthesia* 1986; **41:** 88–9.
3. Birks RJS, Marsh DRG. Epidural meptazinol. *Anaesthesia* 1986; **41:** 883.

Administration in hepatic impairment. See under Pharmacokinetics, above for a suggestion that doses may need to be reduced in patients with cirrhosis.

Preparations

BP 2008: Meptazinol Injection; Meptazinol Tablets.

Proprietary Preparations (details are given in Part 3)
Austria: Meptidol†; ***Ger.:*** Meptid; ***Irl.:*** Meptid; ***UK:*** Meptid.

Methadone Hydrochloride

(BANM, pINNM) ⊗

Amidine Hydrochloride; Amidone Hydrochloride; Hidrocloruro de amidina; Hidrocloruro de metadona; Metadon Hidroklorür; Metadon-hidroklorid; Metadonhydroklorid; Metadonihydroklorid; Metadono hidrochloridas; Metadonu chlorowodorek; Methadon hydrochlorid; Méthadone, chlorhydrate de; (±)-Methadone Hydrochloride; Methadoni hydrochloridum; Phenadone. (±)-6-Dimethylamino-4,4-diphenylheptan-3-one hydrochloride.

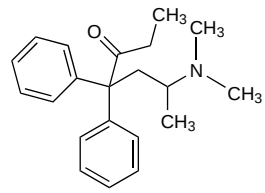
Метадона Гидрохлорид

$C_{21}H_{27}NO,HCl$ = 345.9.

CAS — 76-99-3 (methadone); 297-88-1 (±methadone); 1095-90-5 (methadone hydrochloride); 125-56-4 (±methadone hydrochloride).

ATC — N07BC02.

ATC Vet — QN07BC02.



(methadone)

NOTE. The following terms have been used as 'street names' (see p.vi) or slang names for various forms of methadone:
Amidone; Balloons; Breeze; Burdock; Buzz bomb; Dollies; Dolls; Done; Doses; Fizzies; Juice; Jungle juice; Junk; Meta; Mud; Phy; Phyamps; Tootsie roll.

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

Ph. Eur. 6.2 (Methadone Hydrochloride). A white or almost white, crystalline powder. Soluble in water; freely soluble in alcohol. Protect from light.

USP 31 (Methadone Hydrochloride). Odourless colourless crystals or white crystalline powder. Soluble in water; freely soluble in alcohol and in chloroform; practically insoluble in ether and in glycerol. pH of a 1% solution in water is between 4.5 and 6.5. Store in airtight containers at a temperature of 25°, excursions permitted between 15° and 30°. Protect from light.

Incompatibility. There appears to be adequate evidence that stable solutions containing methadone hydrochloride and hydroxybenzoate esters can be formulated but the risk of precipitation exists if syrup preserved with hydroxybenzoates is used to extemporaneously prepare a methadone mixture 1 mg/mL to the DTF formula.[1] An oral formulation of methadone hydrochloride 5 mg/mL containing methyl hydroxybenzoate 0.1% as preservative rather than chloroform has been reported stable for at least 4 months at room temperature.[2]

1. *PSGB Lab Report P/80/1* 1980.
2. Ching MS, *et al.* Stability of methadone mixture with methyl hydroxybenzoate as a preservative. *Aust J Hosp Pharm* 1989; **19:** 159–61.

Dependence and Withdrawal

As for Opioid Analgesics, p.101.

Methadone withdrawal symptoms are similar to, but more prolonged than, those produced by morphine or diamorphine. They develop more slowly and do not usually appear until 3 to 4 days after the last dose.

Methadone is used for substitution therapy in the management of opioid dependence (see Uses and Administration, below) including neonatal abstinence syndrome (see Administration in Children, below).

Adverse Effects and Treatment

As for Opioid Analgesics in general, p.102.

Methadone has a more prolonged effect than morphine and readily accumulates with repeated doses. It may have a relatively greater respiratory depressant effect than morphine and, although reported to be less sedating, repeated doses of methadone may result in marked sedation. QT prolongation and torsade de pointes have been reported rarely with methadone use, particularly at doses above 100 mg daily. After gross overdosage symptoms are similar to those of morphine poisoning. Pulmonary oedema after overdosage is a common cause of fatalities among addicts.

Methadone causes pain at injection sites; subcutaneous injection causes local tissue irritation and induration.

Effects on the cardiovascular system. Methadone prolongs the QT interval and has rarely been associated with torsade de pointes. In a retrospective case series,[1] 17 patients on high-dose methadone (mean daily dose of 397 mg) developed torsade de pointes; of these, 14 had potential risk factors for arrhythmia and 6 had had their dose increased within the last month. In another study[2] torsade de pointes developed in 5 patients taking methadone (mean daily dose 268 mg); however, they all had other contributing risk factors. Other studies[3,4] did not find instances of torsade de pointes and the increase in QT interval was considered clinically insignificant; in one study,[4] the mean daily dose of methadone was 110 mg and some patients also had risk factors for arrhythmia.

For a report of QT interval prolongation in an infant born to a mother on maintenance methadone therapy for opioid addiction, see Pregnancy, below.

In a small case-controlled study of sudden cardiac deaths,[5] the prevalence of underlying cardiac disease or structural abnormalities was lower in the 22 cases with evidence of therapeutic methadone levels when compared with the 106 cases without evidence of methadone use. The authors considered that the low prevalence of cardiac risk factors in the methadone group suggested a role for methadone itself in the pathogenesis of sudden death in this group.

1. Krantz MJ, *et al.* Torsade de pointes associated with very-high-dose methadone. *Ann Intern Med* 2002; **137:** 501–4.
2. Sticherling C, *et al.* Methadone-induced torsade de pointes tachycardias. *Swiss Med Wkly* 2005; **135:** 282–5.
3. Martell BA, *et al.* The impact of methadone induction on cardiac conduction in opiate users. *Ann Intern Med* 2003; **139:** 154–5.
4. Cruciani RA, *et al.* Measurement of QTc in patients receiving chronic methadone therapy. *J Pain Symptom Manage* 2005; **29:** 385–91.
5. Chugh SS, *et al.* A community-based evaluation of sudden death associated with therapeutic levels of methadone. *Am J Med* 2008; **121:** 66–71.

Effects on the endocrine system. Hypoadrenalism has been found in chronic methadone addicts. Findings consistent with deficient ACTH production and subsequent secondary hypoadrenalism have been reported[1] although there is also evidence[2] of methadone-induced primary adrenal cortical hypofunction.

Hyperprolactinaemia and galactorrhoea have also been reported.[3] See also Effects on Sexual Function, below.

1. Dackis CA, *et al.* Methadone induced hypoadrenalism. *Lancet* 1982; **ii:** 1167.
2. Pullan PT, *et al.* Methadone-induced hypoadrenalism. *Lancet* 1983; **i:** 714.
3. Bennett J, Whale R. Galactorrhoea may be associated with methadone use. *BMJ* 2006; **332:** 1071.

Effects on the nervous system. Choreic movements occurred in a 25-year-old man on long-term methadone maintenance treatment of 45 to 60 mg daily for diamorphine addiction.[1] Similar adverse effects were seen in a 41-year-old woman taking 5 mg methadone four times daily for complex regional pain syndrome.[2] In both cases, symptoms resolved when methadone was stopped.

1. Wasserman S, Yahr MD. Choreic movements induced by the use of methadone. *Arch Neurol* 1980; **37:** 727–8.
2. Clark JD, Elliott J. A case of a methadone-induced movement disorder. *Clin J Pain* 2001; **17:** 375–7.

Effects on the respiratory system. Sleep apnoea has been reported[1,2] in patients on stable methadone maintenance treatment.

1. Teichtahl H, *et al.* Sleep-disordered breathing in stable methadone programme patients: a pilot study. *Addiction* 2001; **96:** 395–403.
2. Wang D, *et al.* Central sleep apnea in stable methadone maintenance treatment patients. *Chest* 2005; **128:** 1348–56.

Effects on sexual function. Sexual performance was impaired in 29 male diamorphine addicts receiving methadone maintenance therapy.[1] The function of secondary sex organs was markedly suppressed when compared with untreated diamorphine addicts or controls and serum-testosterone concentrations were 43% lower in those on methadone. However, in a more recent study[2] in 92 opioid addicts also receiving methadone maintenance, rates of sexual dysfunction (erectile, libido, and orgasm dysfunction) were found to be similar to that of the general population. Rates of dysfunction between patients just started on methadone and those on methadone for at least 60 days were not significantly different although new patients generally had lower rates. Mean plasma levels of testosterone and prolactin were within normal ranges and although 8 individuals had low testosterone levels, only 1 case of dysfunction was reported in this group.

1. Cicero TJ, *et al.* Function of the male sex organs in heroin and methadone users. *N Engl J Med* 1975; **292:** 882–7.
2. Brown R, *et al.* Methadone maintenance and male sexual dysfunction. *J Addict Dis* 2005; **24:** 91–106.

Overdosage. Most cases of methadone poisoning occur in persons not on maintenance,[1-4] particularly children or family members of maintenance patients.[1] Methadone is highly toxic to anyone who is not tolerant to opioids; 50 to 100 mg can be life-threatening in non-tolerant adults and 10 mg can be fatal in a young child.[1] Furthermore, life-threatening toxicity from oral doses as low as 5 mg has been reported in children.[2,4]

Various groups[5,6] have found that the risk of death from methadone toxicity is greatest during the first 2 weeks of maintenance therapy. This has been attributed to the difficulty in determining a safe and effective starting dose of methadone and unreliable accounts of a patient's recent drug use.

1. Harding-Pink D. Opioid toxicity: methadone: one person's maintenance dose is another's poison. *Lancet* 1993; **341:** 665–6.
2. Aronow R, *et al.* Childhood poisoning: an unfortunate consequence of methadone availability. *JAMA* 1972; **219:** 321–4.
3. Zador DA, Sunjic SD. Methadone-related deaths and mortality rate during induction into methadone maintenance, New South Wales, 1996. *Drug Alcohol Rev* 2002; **21:** 131–6.
4. Sachdeva DK, Stadnyk JM. Are one or two dangerous? Opioid exposure in toddlers. *J Emerg Med* 2005; **29:** 77–84.
5. Caplehorn JRM, Drummer OH. Mortality associated with New South Wales methadone programs in 1994: lives lost and saved. *Med J Aust* 1999; **170:** 104–9.
6. Buster MCA, *et al.* An increase in overdose mortality during the first 2 weeks after entering or re-entering methadone treatment in Amsterdam. *Addiction* 2002; **97:** 993–1001.

Precautions

As for Opioid Analgesics in general, p.103.

Methadone should be given with caution to patients at risk of developing prolongation of the QT interval including those with cardiac or hepatic disease, with hypokalaemia or other electrolyte imbalance, or with a family history of sudden death. It should also be used with caution in patients who are taking other potentially arrhythmogenic drugs, drugs likely to cause electrolyte imbalance, or drugs that inhibit the cytochrome P450 isoenzyme CYP3A4 (see under Interactions, below). ECG monitoring is recommended before starting methadone treatment in these patients, with a further test at dose stabilisation. ECG monitoring is also recommended before and at 7 days after dose titration above 100 mg daily in patients without recognised risk factors.

Administration. Methadone has a long half-life and accumulation may occur with repeated doses, especially in elderly or debilitated patients. An 81-year-old woman given methadone 5 mg three times daily orally for 2 days became deeply unconscious but awoke immediately when given naloxone 400 micrograms intravenously.[1]

Sudden death in 10 diamorphine addicts occurred between 2 and 6 days after starting a methadone maintenance programme.[2] The mean prescribed dose of methadone at the time of death had been about 60 mg. There was evidence of chronic persistent hepatitis in all cases and liver disease could have reduced methadone clearance resulting in higher than expected blood concentrations. Liver function tests and urine testing for the presence of drugs before entry into methadone maintenance programmes, and lower starting doses, might decrease the likelihood of such deaths. Like dextropropoxyphene, methadone has membrane stabilising activity and can block nerve conduction, and it was suggested[3] that the sudden deaths were mainly due to accumulation of methadone over several days resulting in complications such as cardiac arrhythmias or cardiovascular collapse (above). See also Overdosage, above.

For the effects of hepatic and renal impairment on the disposition of methadone, see under Pharmacokinetics, below.

1. Symonds P. Methadone and the elderly. *BMJ* 1977; **i:** 512.
2. Drummer OH, *et al.* Deaths of heroin addicts starting on a methadone maintenance programme. *Lancet* 1990; **335:** 108.
3. Wu C, Henry JA. Deaths of heroin addicts starting on methadone maintenance. *Lancet* 1990; **335:** 424.

Breast feeding. The American Academy of Pediatrics considers that the use of methadone in breast-feeding mothers is usually compatible with breast feeding.[1] The *BNF* also permits breast feeding by mothers on methadone maintenance although the dose should be as low as possible and the infant monitored to avoid sedation. Others have suggested that the amount of methadone in breast milk is unlikely to have any pharmacological effect on the infant.[2-8] However, in the past, there has been a report of the death of a 5-week-old breast-fed infant whose mother was on methadone maintenance.[9]

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 26/06/08)
2. Blinick G, *et al.* Methadone assays in pregnant women and progeny. *Am J Obstet Gynecol* 1975; **121:** 617–21.
3. Wojnar-Horton RE, *et al.* Methadone distribution and excretion into breast milk of clients in a methadone maintenance programme. *Br J Clin Pharmacol* 1997; **44:** 543–7.
4. Geraghty B, *et al.* Methadone levels in breast milk. *J Hum Lact* 1997; **13:** 227–30.
5. McCarthy JJ, Posey BL. Methadone levels in human milk. *J Hum Lact* 2000; **16:** 115–20.
6. Begg EJ, *et al.* Distribution of R- and S-methadone into human milk during multiple, medium to high oral dosing. *Br J Clin Pharmacol* 2001; **52:** 681–5.
7. Jansson LM, *et al.* Methadone maintenance and breastfeeding in the neonatal period. *Pediatrics* 2008; **121:** 106–14.
8. Jansson LM, *et al.* Methadone maintenance and long-term lactation. *Breastfeed Med* 2008; **3:** 34–7.
9. Smialek JE, *et al.* Methadone deaths in children. *JAMA* 1977; **238:** 2516–17.

Pregnancy. Methadone is not recommended for use in labour because its prolonged duration of action increases the risk of neonatal respiratory depression.

Neonatal abstinence syndrome and low birth-weight are immediate problems in infants born to women receiving methadone for the management of opioid addiction; increased still-birth rates have also been noted.[1-3] In the neonatal period moderate to severe opioid abstinence syndrome occurred in 75% of infants in a study,[2] as well as reduced head circumference and raised systolic blood pressure. At follow-up over 18 months these children had a higher incidence of otitis media, of reduced head circumference, and of abnormal eye findings when compared with drug-free controls. Neurobehavioural abnormalities and lower scores on mental and motor developmental indices were thought to be possible predictors of later learning and behavioural problems. In a later study,[4] the use of methadone alone during pregnancy as part of a maintenance program was claimed to increase the risk of prematurity twofold, of intra-uterine growth retardation fourfold, and of microcephaly threefold when compared with a normal population. In addition, in those mothers who continued to abuse other drugs, as well as receive methadone, the risks of these events were further increased. However, an earlier study[5] has reported that methadone or diamorphine had no specific effect on intra-uterine and postnatal growth.

The relationship between maternal methadone dose and the incidence and severity of neonatal abstinence syndrome is unclear. Although a retrospective study[6] found a correlation in some pregnancies, others[7,8] did not and there was no evidence of an increased incidence of neonatal withdrawal symptoms even with high maternal doses of 100 mg or more daily.[8]

A small retrospective study[9] comparing the use of methadone during pregnancy for the treatment of chronic pain with use in maintenance therapy for opioid addiction found a lower incidence of neonatal abstinence syndrome and better growth parameters in infants born to the former group of mothers; however, a higher rate of slight prematurity was also found in this group of infants. The authors suggested that lower maternal doses and shorter durations of treatment may account for the favourable findings, in addition to better maternal health, nutrition, and socio-economic status.

Clinically significant prolongation of the QT interval has been reported[10] in an infant born to a mother taking methadone 50 mg daily for maintenance therapy; the infant had mild withdrawal symptoms and follow-up at 2 months of age was normal.

1. Blinick G, *et al.* Methadone maintenance, pregnancy, and progeny. *JAMA* 1973; **225:** 477–9.
2. Rosen TS, Johnson HL. Children of methadone-maintained mothers: follow-up to 18 months of age. *J Pediatr* 1982; **101:** 192–6.
3. Kalter H, Warkany J. Congenital malformations. *N Engl J Med* 1983; **308:** 491–7.
4. Arlettaz R, *et al.* Methadone maintenance program in pregnancy in a Swiss perinatal center (II): neonatal outcome and social resources. *Acta Obstet Gynecol Scand* 2005; **84:** 145–50.
5. Lifschitz MH, *et al.* Fetal and postnatal growth of children born to narcotic-dependent women. *J Pediatr* 1983; **102:** 686–91.
6. Dashe JS *et al.* Relationship between maternal methadone dosage and neonatal withdrawal. *Obstet Gynecol* 2002; **100:** 1244–9.
7. Berghella V, *et al.* Maternal methadone dose and neonatal withdrawal. *Am J Obstet Gynecol* 2003; **189:** 312–17.
8. McCarthy JJ, *et al.* High-dose methadone maintenance in pregnancy: maternal and neonatal outcomes. *Am J Obstet Gynecol* 2005; **193:** 606–10.
9. Sharpe C, Kuschel C. Outcomes of infants born to mothers receiving methadone for pain management in pregnancy. *Arch Dis Child Fetal Neonatal Ed* 2004; **89:** F33–F36.
10. Hussain T, Ewer AK. Maternal methadone may cause arrhythmias in neonates. *Acta Paediatr* 2007; **96:** 768–9.

Interactions

For interactions associated with opioid analgesics, see p.103.

Methadone is metabolised in the liver mainly via the cytochrome P450 isoenzyme CYP3A4; the isoenzymes CYP2B6, CYP2D6, CYP2C9, CYP2C19, and CYP1A2 are also thought to be involved. Consequently, use with other drugs that induce or inhibit these isoenzymes may result in changes in plasma concentrations of methadone and, possibly adverse effects. There is a risk of cardiac events in patients receiving methadone who are also taking drugs that affect cardiac conduction or electrolyte balance.

◊ Drugs that *acidify* or *alkalinise* the urine may have an effect on methadone pharmacokinetics since body clearance is increased at acidic pH and decreased at alkaline pH.[1]

1. Nilsson M-I, *et al.* Effect of urinary pH on the disposition of methadone in man. *Eur J Clin Pharmacol* 1982; **22:** 337–42.

Antibacterials. Withdrawal symptoms have been reported in patients maintained on methadone when they were given the enzyme inducer *rifampicin*.[1-3] Conversely, the use of *ciprofloxacin*, which inhibits CYP1A2 and CYP3A4, has resulted in signs of methadone toxicity.[4]

1. Kreek MJ, *et al.* Rifampin-induced methadone withdrawal. *N Engl J Med* 1976; **294:** 1104–6.

2. Bending MR, Skacel PO. Rifampicin and methadone withdrawal. *Lancet* 1977; **i:** 1211.
3. Raistrick D, *et al.* Methadone maintenance and tuberculosis treatment. *BMJ* 1996; **313:** 925–6.
4. Herrlin K, *et al.* Methadone, ciprofloxacin, and adverse drug reactions. *Lancet* 2000; **356:** 2069–70.

Antidepressants. *SSRIs* such as fluoxetine[1] and fluvoxamine[1,2] may enhance the effects of some opioid analgesics; such interactions may lead to methadone toxicity. *St John's wort* reduced the plasma-methadone concentration to dose ratios by 47% in 4 patients on methadone maintenance therapy for opioid addiction; 2 patients reported symptoms suggestive of a withdrawal syndrome.[3]

1. Eap CB, *et al.* Fluvoxamine and fluoxetine do not interact in the same way with the metabolism of the enantiomers of methadone. *J Clin Psychopharmacol* 1997; **17:** 113–17.
2. Bertschy G, *et al.* Probable metabolic interaction between methadone and fluvoxamine in addict patients. *Ther Drug Monit* 1994; **16:** 42–5.
3. Eich-Höchli D, *et al.* Methadone maintenance treatment and St. John's Wort: a case report. *Pharmacopsychiatry* 2003; **36:** 35–7.

Antiepileptics. Opioid withdrawal symptoms have been reported in patients maintained on methadone when they were given *carbamazepine*,[1,2] *phenobarbital*,[3] or *phenytoin*.[4,5] Conversely, methadone-induced respiratory depression developed in a patient on carbamazepine, gabapentin, and methadone for neuropathic pain, after carbamazepine was stopped.[6]

1. Bell J, *et al.* The use of serum methadone levels in patients receiving methadone maintenance. *Clin Pharmacol Ther* 1988; **43:** 623–9.
2. Saxon AJ, *et al.* Valproic acid, unlike other anticonvulsants, has no effects on methadone metabolism: two cases. *J Clin Psychiatry* 1989; **50:** 228–9.
3. Liu S-J, Wang RIH. Case report of barbiturate-induced enhancement of methadone metabolism and withdrawal syndrome. *Am J Psychiatry* 1984; **141:** 1287–8.
4. Finelli PF. Phenytoin and methadone tolerance. *N Engl J Med* 1976; **294:** 227.
5. Tong TG, *et al.* Phenytoin-induced methadone withdrawal. *Ann Intern Med* 1981; **94:** 349–51.
6. Benítez-Rosario MA, *et al.* Methadone-induced respiratory depression after discontinuing carbamazepine administration. *J Pain Symptom Manage* 2006; **32:** 99–100.

Antifungals. Use of methadone with *fluconazole* has been reported[1] to increase serum concentrations of methadone although the authors considered that for patients being treated for opioid dependence the interaction was unlikely to require adjustment of the methadone dose. However, respiratory depression has been reported[2] after intravenous doses of fluconazole were given to a 60-year-old man also taking oral methadone for pain relief in advanced gastric cancer. Although a randomised placebo-controlled study[3] found that giving *voriconazole* to patients on methadone maintenance therapy for opioid addiction was generally safe and well tolerated, the authors recommended monitoring and possible dose reduction of methadone when the 2 drugs are used together. Similar recommendations are also given in the licensed product information for voriconazole.

1. Cobb MN, *et al.* The effect of fluconazole on the clinical pharmacokinetics of methadone. *Clin Pharmacol Ther* 1998; **63:** 655–62.
2. Tarumi Y, *et al.* Methadone and fluconazole: respiratory depression by drug interaction. *J Pain Symptom Manage* 2002; **23:** 148–53.
3. Liu P, *et al.* Pharmacokinetic interaction between voriconazole and methadone at steady state in patients on methadone therapy. *Antimicrob Agents Chemother* 2007; **51:** 110–18.

Antivirals. The potential for interaction between antiretrovirals and methadone has been reviewed.[1] Available evidence for HIV-protease inhibitors suggests that *atazanavir*, *indinavir*, and, possibly, *saquinavir* alone have no effect on plasma concentrations of methadone; *amprenavir*, *nelfinavir*, *ritonavir*, and *ritonavir-boosted saquinavir* may reduce plasma-methadone concentrations but the effect is unlikely to be clinically significant. *Lopinavir-ritonavir* may also reduce methadone concentrations and, although most studies found the interaction to be insignificant, one study reported opioid withdrawal symptoms in some patients. Unpublished data [also referred to in the licensed product information] on *tipranavir* (boosted with ritonavir) in healthy, opioid-naive subjects suggest that it may decrease plasma-methadone; licensed product information for tipranavir recommends that patients are monitored for symptoms of opioid withdrawal.

The NNRTIs *nevirapine* and *efavirenz* have both been reported to reduce plasma-methadone levels and withdrawal symptoms have occurred when they were given to patients receiving methadone. Conversely, *delavirdine* may increase methadone concentrations although the effect is unlikely to be clinically significant. Methadone possibly increases plasma concentrations of the NRTI *zidovudine* (see p.915).

1. Bruce RD, *et al.* Pharmacokinetic drug interactions between opioid agonist therapy and antiretroviral medications: implications and management for clinical practice. *J Acquir Immune Defic Syndr* 2006; **41:** 563–72.

Gastrointestinal drugs. Histamine H_2-antagonists such as *cimetidine* (see p.103) may enhance the effects of some opioid analgesics; such interactions may lead to methadone toxicity.

Grapefruit juice. Grapefruit juice, an inhibitor of the cytochrome P450 isoenzyme CYP3A4, has been shown to modestly increase the bioavailability of methadone;[1] although no symptoms of methadone toxicity were seen in the studied patients, the authors commented that such effects may occur in patients with reduced opioid tolerance, particularly when starting methadone treatment.

1. Benmebarek M, *et al.* Effects of grapefruit juice on the pharmacokinetics of the enantiomers of methadone. *Clin Pharmacol Ther* 2004; **76:** 55–63.

Pharmacokinetics

Methadone hydrochloride is readily absorbed from the gastrointestinal tract and from subcutaneous or intramuscular injections. It is widely distributed in the tissues, diffuses across the placenta, and is distributed into breast milk. It is extensively protein bound. Methadone is metabolised in the liver, mainly by *N*-demethylation and cyclisation, and the metabolites are excreted in the bile and urine. Metabolism is primarily catalysed by CYP3A4, although other cytochrome P450 isoenzymes also play a role (see Interactions, above). It has a prolonged half-life and is subject to accumulation.

◊ In reviews of the pharmacokinetics of methadone[1-5] particular reference has been made to its long elimination half-life, accumulation after repeated doses, and wide interindividual variations.

Methadone is rapidly absorbed after oral doses and has high oral bioavailability. Peak plasma concentrations have been reported 1 to 5 hours after a single tablet by mouth. It undergoes considerable tissue distribution and protein binding is reported to be 60 to 90% with α_1-acid glycoprotein being the main binding protein in plasma. Metabolism to the major metabolite 2-ethylidine-1,5-dimethyl-3,3-diphenylpyrrolidine and the minor metabolite 2-ethyl-3,3-diphenyl-5-methylpyrrolidine, both of them inactive, occurs in the liver. These metabolites are excreted in the faeces and urine with unchanged methadone. Other metabolites, including methadol and normethadol, have also been described. The liver may also serve as a major storage site of unchanged methadone which is taken up, bound non-specifically by the liver, and released again mainly unchanged. Urinary excretion of methadone is pH-dependent, the lower the pH the greater the clearance.

In addition to marked interindividual variations there are differences in the pharmacokinetics of methadone after single or multiple doses. Elimination half-lives vary considerably (a range of 15 to 60 hours has been quoted) and may be much longer than the 18 hours reported following a single dose. Careful adjustment of dosage is necessary with repeated doses.

Most studies have been in addicts. Plasma concentrations have been found to vary widely during methadone maintenance therapy with large differences between patients and wide fluctuations in individual patients. These variations in kinetics have also been seen in cancer patients.

1. Säwe J. High-dose morphine and methadone in cancer patients: clinical pharmacokinetic considerations of oral treatment. *Clin Pharmacokinet* 1986; **11:** 87–106.
2. Moore RA, *et al.* Opiate metabolism and excretion. *Baillieres Clin Anaesthesiol* 1987; **1:** 829–58.
3. Eap CB, *et al.* Interindividual variability of the clinical pharmacokinetics of methadone: implications for the treatment of opioid dependence. *Clin Pharmacokinet* 2002; **41:** 1153–93.
4. Ferrari A, *et al.* Methadone—metabolism, pharmacokinetics and interactions. *Pharmacol Res* 2004; **50:** 551–9.
5. Lugo RA, *et al.* Pharmacokinetics of methadone. *J Pain Palliat Care Pharmacother* 2005; **19:** 13–24.

Administration. Methadone is considerably more lipid-soluble than morphine. A study of plasma concentrations and analgesia after intramuscular injection indicated that more rapid and greater relief of pain might be achieved if lipid-soluble opioid analgesics were injected into the deltoid rather than the gluteal muscle; there was no significant difference in absorption of morphine from the two sites.[1]

Other routes investigated in pharmacokinetic studies include continuous intravenous infusion[2] and continuous epidural infusion.[3] Rectal administration[4] has also been studied.

1. Grabinski PY, *et al.* Plasma levels and analgesia following deltoid and gluteal injections of methadone and morphine. *J Clin Pharmacol* 1983; **23:** 48–55.
2. Denson DD, *et al.* Pharmacokinetics of continuous intravenous infusion of methadone in the early post-burn period. *J Clin Pharmacol* 1990; **30:** 70–5.
3. Shir Y, *et al.* Plasma concentrations of methadone during postoperative patient-controlled extradural analgesia. *Br J Anaesth* 1990; **65:** 204–9.
4. Dale O, *et al.* Bioavailabilities of rectal and oral methadone in healthy subjects. *Br J Clin Pharmacol* 2004; **58:** 156–62.

Hepatic impairment. Overall hepatic dysfunction does not seem unduly to disrupt methadone metabolism[1] and it has been suggested[2] that maintenance dosage of methadone need not be changed in stable chronic liver disease, although abrupt changes in hepatic status might result in substantial alterations in methadone disposition requiring dosage adjustments.

In a study of patients on methadone maintenance therapy[2] apparent terminal half-life of methadone was prolonged from a mean of 18.8 hours in those with healthy livers to 35.5 hours in patients with severe chronic liver disease. However, plasma concentrations were not increased in such patients.

1. Moore RA, *et al.* Opiate metabolism and excretion. *Baillieres Clin Anaesthesiol* 1987; **1:** 829–58.
2. Novick DM, *et al.* Methadone disposition in patients with chronic liver disease. *Clin Pharmacol Ther* 1981; **30:** 353–62.

Pregnancy. Plasma concentrations of methadone were reduced in methadone-maintained pregnant women, probably due to enhanced metabolism.[1,2] It was suggested that the dose of methadone might need to be increased in such patients.

1. Pond SM, *et al.* Altered methadone pharmacokinetics in methadone-maintained pregnant women. *J Pharmacol Exp Ther* 1985; **233:** 1–6.
2. Wolff K, *et al.* Changes to methadone clearance during pregnancy. *Eur J Clin Pharmacol* 2005; **61:** 763–8.

Renal impairment. The urinary excretion of methadone was reduced in renal failure,[1] but plasma concentrations were within the usual range and faecal excretion accounted for the majority of the dose. Very little methadone was removed by peritoneal dialysis or haemodialysis.

1. Kreek MJ, *et al.* Methadone use in patients with chronic renal disease. *Drug Alcohol Depend* 1980; **5:** 197–205.

Uses and Administration

Methadone hydrochloride, a diphenylheptane derivative, is an opioid analgesic (p.104) that is primarily a μ opioid agonist. Single doses of methadone have a less marked sedative action than single doses of morphine. Methadone is a racemic mixture and levomethadone (p.77) is the active isomer.

Methadone hydrochloride is used in the treatment of moderate to severe pain; it may be of use for those patients who experience excitation or exacerbation of pain with morphine. Methadone is also used in the management of opioid dependence. It has a depressant action on the cough centre and has been used as a cough suppressant in terminal illness, although the *BNF* discourages this use because of the risks of accumulation.

For **pain relief** starting oral doses of methadone hydrochloride may range from 2.5 to 10 mg given every 6 to 8 hours or longer and thereafter adjusted as necessary. Methadone may also be given parenterally. In the UK, the subcutaneous and intramuscular routes are licensed with the intramuscular route being recommended for prolonged use; US licensed product information states that the intravenous, intramuscular, and subcutaneous routes may be used although it gives doses for the intravenous route only. Initial dose ranges for parenteral routes are similar to those used orally; however, if transferring between oral and parenteral methadone, US product information states that the initial conversion dose should be based on the guide that 10 mg of oral methadone is equivalent to about 5 mg of parenteral methadone. The analgesic effect of methadone begins about 10 to 20 minutes after parenteral injection and about 30 to 60 minutes after oral doses, the effect of a single dose usually lasting about 4 hours. As accumulation occurs with repeated doses, the effects become more prolonged. Consequently, to avoid the risk of opioid overdose, it is recommended that in prolonged use methadone should not be given more than twice daily.

Methadone is used as part of the treatment of **opioid dependence**, although prolonged use of methadone itself may result in dependence. Initially, methadone hydrochloride is given in doses sufficient to suppress signs of opioid withdrawal but avoid toxicity; the *BNF* and US licensed product information recommended a starting dose of 10 to 40 mg daily. Subsequent dose adjustments should be made cautiously because of the risks of accumulation; the *BNF* suggests adjusting the dose in steps of 10 mg to a maximum weekly increase of 30 mg. Once the dose has been stabilised, patients may choose to receive prolonged therapy with a carefully selected methadone dose for each individual; most patients in such maintenance programmes are stabilised on once-daily doses of 60 to 120 mg. Alternatively, detoxification may be appropriate with the dose of methadone being gradually decreased until total withdrawal is achieved. Methadone is usually given orally for the treatment of dependence although

parenteral routes may be used, particularly when oral therapy is not possible; the doses stated above may be given orally or parenterally. In the UK, oral treatment is commonly given as a mixture containing 1 mg/mL of methadone hydrochloride.

For details of doses in children, see below.

For the control of intractable **cough** associated with terminal lung cancer, methadone hydrochloride is usually given in the form of a linctus in a dose of 1 to 2 mg every 4 to 6 hours, but reduced to twice daily on prolonged use.

Administration. Although duration of action after single doses of methadone is similar to that of morphine, it increases considerably with multiple dosing of methadone because of the long elimination half-life (see under Pharmacokinetics, above). The minimum effective dose of methadone can be difficult to titrate for the individual patient. A fixed 10-mg oral dose with a flexible patient-controlled dosage interval has been used in patients with chronic cancer pain.[1] Dosage not more frequently than every 4 hours during the first 3 to 5 days, followed by a fixed dose every 8 to 12 hours depending on the patient's requirements, was advised.

A suggested initial dose for patients who need to switch from oral morphine to methadone because of poor pain control is one tenth of the total daily dose of morphine, but not greater than 100 mg, given at intervals determined by the patient, typically every 8 hours.[2]

When switching from oral to parenteral use it was suggested[3] that the dose of methadone should be halved and adjusted thereafter as necessary.

Evidence of the prolonged effect of methadone was demonstrated when a single intravenous bolus dose of 20 mg resulted in postoperative analgesia lasting about 25 hours.[4] An initial 2-hour loading intravenous infusion of methadone 100 to 200 micrograms/kg per hour to provide rapid analgesia followed by infusion at a lower maintenance rate of 10 to 20 micrograms/kg per hour for continuous pain relief has been used in burn patients.[5] Methadone has also been given by continuous subcutaneous infusion for severe cancer pain[6,7] although this route has been associated with local tissue irritation and induration. Epidural methadone has been used successfully in doses of up to 5 mg for analgesia in association with bupivacaine.[8,9] Intermittent and continuous epidural infusion of methadone has also been tried[10] in postoperative analgesia.

A small case series[11] found topical methadone powder to be effective for pain relief of open, exudative wounds.

1. Säwe J, *et al.* Patient-controlled dose regimen of methadone for chronic cancer pain. *BMJ* 1981; **282:** 771–3.
2. Morley JS, *et al.* Methadone in pain uncontrolled by morphine. *Lancet* 1993; **342:** 1243.
3. Säwe J. High-dose morphine and methadone in cancer patients: clinical pharmacokinetic considerations of oral treatment. *Clin Pharmacokinet* 1986; **11:** 87–106.
4. Gourlay GK, *et al.* Methadone produces prolonged postoperative analgesia. *BMJ* 1982; **284:** 630–1.
5. Denson DD, *et al.* Pharmacokinetics of continuous intravenous infusion of methadone in the early post-burn period. *J Clin Pharmacol* 1990; **30:** 70–5.
6. Mathew P, Storey P. Subcutaneous methadone in terminally ill patients: manageable local toxicity. *J Pain Symptom Manage* 1999; **18:** 49–52.
7. Makin MK, Morley JS. Subcutaneous methadone in terminally-ill patients. *J Pain Symptom Manage* 2000; **19:** 237–8.
8. Drenger B, *et al.* Extradural bupivacaine and methadone for extracorporeal shock-wave lithotripsy. *Br J Anaesth* 1989; **62:** 82–6.
9. Martin CS, *et al.* Extradural methadone and bupivacaine in labour. *Br J Anaesth* 1990; **65:** 330–2.
10. Prieto-Alvarez P, *et al.* Continuous epidural infusion of racemic methadone results in effective postoperative analgesia and low plasma concentrations. *Can J Anaesth* 2002; **49:** 25–31.
11. Gallagher RE, *et al.* Analgesic effects of topical methadone: a report of four cases. *Clin J Pain* 2005; **21:** 190–2.

Administration in children. Methadone is not licensed for use in children. However, it has been tried[1] intravenously in children aged 3 to 7 years to prevent postoperative **pain**; a dose of 200 micrograms/kg was given perioperatively followed postoperatively by 50 micrograms/kg every 10 minutes until the patient was both comfortable and adequately alert. Methadone has also been tried[2] orally for the treatment of severe pain in hospitalised children; daily doses ranged from 200 to 600 micrograms/kg for up to 6 weeks.

Methadone is used for the management of **neonatal abstinence syndrome** (p.102). The *BNFC* suggests an initial oral dose of 100 micrograms/kg increased by 50 micrograms/kg every 6 hours until symptoms are controlled; once stabilised, the total daily dose is given in 2 divided doses for maintenance. When withdrawing methadone, the dose should be reduced over 7 to 10 days.

1. Berde CB, *et al.* Comparison of morphine and methadone for prevention of postoperative pain in 3- to 7-year-old children. *J Pediatr* 1991; **119:** 136–41.
2. Shir Y, *et al.* Oral methadone for the treatment of severe pain in hospitalized children: a report of five cases. *Clin J Pain* 1998; **14:** 350–3.

Cancer pain. Methadone is used as an alternative to morphine in the treatment of severe cancer pain (p.5). A better understanding of its pharmacokinetics and of equianalgesic doses may address early concerns about the risk of cumulative toxicity associated with prolonged use. However, its long terminal half-life makes it less suitable for the treatment of breakthrough pain.

Methadone has been given by the oral, rectal, and parenteral routes.

References.

1. Ayonrinde OT, Bridge DT. The rediscovery of methadone for cancer pain management. *Med J Aust* 2000; **173:** 536–40.
2. Bruera E, Sweeney C. Methadone use in cancer patients with pain: a review. *J Palliat Med* 2002; **5:** 127–38.
3. Bruera E, *et al.* Methadone versus morphine as a first-line strong opioid for cancer pain: a randomized, double-blind study. *J Clin Oncol* 2004; **22:** 185–92.
4. Moryl N, *et al.* Methadone in the treatment of pain and terminal delirum [sic] in advanced cancer patients. *Palliat Support Care* 2005; **3:** 311–17.
5. Mannino R, *et al.* Methadone for cancer-related neuropathic pain: a review of the literature. *J Opioid Manag* 2006; **2:** 269–76.
6. Nicholson AB. Methadone for cancer pain. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2007 (accessed 26/06/08).

Opioid dependence. The treatment of opioid dependence is discussed on p.101. In the UK, oral liquid preparations of methadone hydrochloride 1 mg/mL are widely used for this purpose. It is important to note that these preparations are 2.5 times **stronger** than Methadone Linctus (BP 2008), and although some are licensed for analgesia in severe pain, many are licensed for the treatment of opioid dependence only. Methadone Oral Solution (1 mg/mL) (BP 2008) is available as a ready-to-use solution or may be prepared from Methadone Hydrochloride Oral Concentrate. However, most commercially available preparations in the UK still follow an earlier formula formerly listed in the Drug Tariff Formulary (DTF):

Methadone Mixture 1 mg/mL
methadone hydrochloride 10 mg
Green S and Tartrazine Solution (BP 1980) 0.02 mL
Compound Tartrazine Solution (BP 1980) 0.08 mL
syrup, unpreserved 5 mL
chloroform water, double-strength to 10 mL.

Some commercially available forms of DTF Methadone Mixture 1 mg/mL use a preservative system based on hydroxybenzoate esters rather than chloroform; however, syrup preserved with hydroxybenzoate esters may be unsuitable for extemporaneous dispensing (see under Incompatibility, above).

References.

1. Ghodse AH, *et al.* Comparison of oral preparations of heroin and methadone to stabilise opiate misusers as inpatients. *BMJ* 1990; **300:** 719–20.
2. Wolff K, *et al.* Measuring compliance in methadone maintenance patients: use of a pharmacologic indicator to "estimate" methadone plasma levels. *Clin Pharmacol Ther* 1991; **50:** 199–207.
3. Wilson P, *et al.* Methadone maintenance in general practice: patients, workload, and outcomes. *BMJ* 1994; **309:** 641–4.
4. Farrell M, *et al.* Methadone maintenance treatment in opiate dependence: a review. *BMJ* 1994; **309:** 997–1001.
5. Henry JA. Methadone: where are we now? *Hosp Med* 1999; **60:** 161–4.
6. Faggiano F, *et al.* Methadone maintenance at different dosages for opioid dependence. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2003 (accessed 28/08/08).
7. Mattick RP, *et al.* Methadone maintenance therapy versus no opioid replacement therapy for opioid dependence. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2003 (accessed 26/06/08).
8. Amato L, *et al.* Methadone at tapered doses for the management of opioid withdrawal. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2005 (accessed 26/06/08).
9. NICE. Methadone and buprenorphine for the management of opioid dependence: Technology Appraisal Guidance 114 (issued January 2007). Available at: http://www.nice.org.uk/nicemedia/pdf/TA114Niceguidance.pdf (accessed 26/06/08)

Preparations

BP 2008: Methadone Injection; Methadone Linctus; Methadone Oral Solution (1 mg per mL); Methadone Tablets;
USP 31: Methadone Hydrochloride Injection; Methadone Hydrochloride Oral Concentrate; Methadone Hydrochloride Oral Solution; Methadone Hydrochloride Tablets; Methadone Hydrochloride Tablets for Oral Suspension.

Proprietary Preparations (details are given in Part 3)
Arg.: Gobbidona; ***Austral.:*** Biodone†; Physeptone; ***Austria:*** Heptadon; ***Belg.:*** Mephenon; ***Braz.:*** Metadon; Mytedom; ***Canad.:*** Metadol; ***Chile:*** Amidona†; ***Fin.:*** Dolmed; ***Hong Kong:*** Physeptone†; ***Hung.:*** Depridol; Metadon; ***Irl.:*** Phymet DTF; Physeptone†; Pinadone DTF; ***Israel:*** Adolan; ***Ital.:*** Eptadone; ***Malaysia:*** Aseptone; ***Neth.:*** Symoron; ***NZ:*** Biodone; Methatabs; Pallidone; ***S.Afr.:*** Physeptone; ***Singapore:*** Physeptone†; ***Spain:*** Metasedin; ***Switz.:*** Ketalgine; ***UK:*** Eptadone; Martindale Methadone Mixture DTF; Methadose; Physeptone; Synastone; ***USA:*** Diskets; Dolophine; Methadose.

Methyl Butetisalicylate

Butetisalicilato de metilo; Methyl Diethylacetylsalicylate. Methyl *O*-(2-ethylbutyryl)salicylate.

$C_{14}H_{18}O_4$ = 250.3.

Profile

Methyl butetisalicylate is a salicylic acid derivative that has been used similarly to methyl salicylate (p.85) as a rubefacient for the relief of musculoskeletal, joint, and soft-tissue pain.

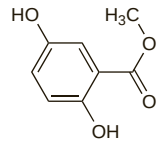
Preparations

Proprietary Preparations (details are given in Part 3)
Ital.: Dolodermi.

Methyl Gentisate

Gentisato de metilo. 2,5-Dihydroxybenzoic acid methyl ester.

$C_8H_8O_4$ = 168.1.
CAS — 2150-46-1.



Profile

Methyl gentisate has been used topically for the relief of musculoskeletal and joint pain.

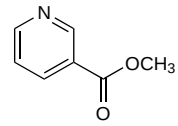
Preparations

Proprietary Preparations (details are given in Part 3)
Multi-ingredient: ***Ital.:*** Reumacort.

Methyl Nicotinate *(USAN)*

Méthyle, nicotinate de; Methyli Nicotinas; Methylis nicotinas; Methyl-nikotinát; Metilo nikotinatas; Metylnikotinat; Metyylinikotinaatti; Nicotinato de metilo. Methyl pyridine-3-carboxylate.

$C_7H_7NO_2$ = 137.1.
CAS — 93-60-7.



Pharmacopoeias. In *Eur.* (see p.vii).
Ph. Eur. 6.2 (Methyl Nicotinate). A white or almost white powder. M.p. 40° to 42°. Very soluble in water, in alcohol, and in dichloromethane. Protect from light.

Profile

Methyl nicotinate is used in topical preparations as a rubefacient.

Preparations

Proprietary Preparations (details are given in Part 3)
UK: Pickles Chilblain Cream.

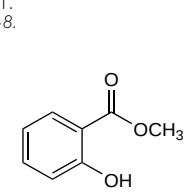
Multi-ingredient: ***Arg.:*** Infrarub†; Medex Rub; ***Austral.:*** Deep Heat; ***Austria:*** Berggeist; ***Belg.:*** Algipan; Emerxil; Percutalgine; Rado-Spray†; ***Canad.:*** Arthricare for Women Multi-Action†; Arthricare Triple Medicated†; Midalgan†; ***Chile:*** Frixio; Konirub; Mentobalsam; ***Fr.:*** Algipan; Capsic; Cliptol Sport†; Decontractyl; Gel Rubefiant; Percutalgine; Sedartryl†; ***Ger.:*** Doloneuro†; Forapin E†; Kytta-Balsam f; Rheuma Bad; Spondylon; Tetesept Badekonzentrat Rheuma Bad†; ***Gr.:*** Faragel-Forte; ***India:*** Algipan; Flamar; Medicreme; Relaxyl; ***Indon.:*** Remakrim; ***Irl.:*** Algipan; ***Israel:*** Deep Heat Spray; ***Ital.:*** Altadrine; Balsamo Sifcamina; Relaxar; Sedalpan; ***Neth.:*** Cremor capsici comp; Cremor Capsici compositus; Kruidvat Spierbalsem; ***Pol.:*** Deep Heat; ***Port.:*** Midalgan†; ***S.Afr.:*** Deep Heat Spray; Infrarub; Sloan's Heat Rub; ***Singapore:*** Deep Heating Spray†; ***Spain:*** Doctofril Antiinflamat; Doctomitil†; Radio Salil; ***Switz.:*** Kytta Baume; Midalgan; Radalgin; ***Thai.:*** Percutalgine†; ***UK:*** Cremalgin; Deep Heat Spray; Dubam; Fiery Jack; Radian-B Red Oils; Ralgex; Ralgex Heat Spray (low-odour); Red Oil; Transvasin Heat Spray; ***USA:*** Arthricare Odor Free; Arthricare Triple Medicated; Musterole.

Methyl Salicylate

Methyl Sal.; Méthyle, salicylate de; Methyli Salicylas; Methylis salicylas; Methyl-salicylát; Metilsalicilatas; Metilsalisilat; Metil-szalicilát; Metylsalicylat; Metylu salicylan; Metyylisalisylaatti; Salicilato de metilo. Methyl 2-hydroxybenzoate.

Метилсалицилат

$C_8H_8O_3$ = 152.1.
CAS — 119-36-8.



NOTE. Methyl salicylate and methyl salicylate liniment have been known previously as oil of wintergreen, wintergreen, and wintergreen oil. Wintergreen oil has also been known as sweet birch oil.

Pharmacopoeias. In *Eur.* (see p.vii), *Jpn*, and *Viet.* Also in *US-NF.*
Ph. Eur. 6.2 (Methyl Salicylate). A colourless or slightly yellow