3. Wang J, *et al.* Low-dose naloxone in the treatment of urinary retention during extradural fentanyl causes excessive reversal of analgesia. *Br J Anaesth* 1998; **80:** 565–6.
4. Nimmo WS, *et al.* Reversal of narcotic-induced delay in gastric emptying and paracetamol absorption by naloxone. *BMJ* 1979; **2:** 1189.
5. Frame WT, *et al.* Effect of naloxone on gastric emptying during labour. *Br J Anaesth* 1984; **56:** 263–5.
6. Gan TJ, *et al.* Opioid-sparing effects of a low-dose infusion of naloxone in patient-administered morphine sulfate. *Anesthesiology* 1997; **87:** 1075–81.
7. Sykes NP. Oral naloxone in opioid-associated constipation. *Lancet* 1991; **337:** 1475.
8. Sykes NP. Oral naloxone in opioid-associated constipation. *Lancet* 1991; **338:** 582.
9. Robinson BA, *et al.* Oral naloxone in opioid-associated constipation. *Lancet* 1991; **338:** 581–2.
10. Thomas MC, Erstad BL. Safety of enteral naloxone and i.v. neostigmine when used to relieve constipation. *Am J Health-Syst Pharm* 2003; **60:** 1264–7.

DIAGNOSTIC USE. Naloxone is used to reverse opioid effects in the diagnosis of opioid overdose, although some workers have recommended that it should only be used in patients with clinical signs of opioid overdose.[1]

Naloxone has also been used in the diagnosis of opioid dependence. It has been given intravenously to precipitate withdrawal symptoms, but methods that do not induce acute withdrawal have also been investigated. Pupillary dilatation in response to topical naloxone solution (naloxone eye drops) has been suggested as a useful method, but varying results have been reported depending on the strength of the solution used. A study[2] using naloxone hydrochloride solution 1 mg/mL distinguished patients with a physical dependence from non-dependent patients who had received opioids on a single occasion as pre-operative medication, but this response was not confirmed in another study[3] using naloxone 400 micrograms/mL solution. Another study[4] reported that a 2 mg/mL solution of naloxone hydrochloride gave useful results in an outpatient setting. However, there has been a report[5] of withdrawal syndrome and pupillary dilatation in 4 opioid dependent subjects after instillation of naloxone solution 40 mg/mL.

1. Hoffman JR, *et al.* The empiric use of naloxone in patients with altered mental status: a reappraisal. *Ann Emerg Med* 1991; **20:** 246–52.
2. Creighton FJ, Ghodse AH. Naloxone applied to conjunctiva as a test for physical opiate dependence. *Lancet* 1989; **i:** 748–50.
3. Loimer N, *et al.* Conjunctival naloxone is no decision aid in opioid addiction. *Lancet* 1990; **335:** 1107–8.
4. Ghodse AH, *et al.* Evaluation of the opioid addiction test in an out-patient drug dependency unit. *Br J Psychiatry* 1999; **175:** 158–62.
5. Sanchez-Ramos JR, Senay EC. Ophthalmic naloxone elicits abstinence in opioid-dependent subjects. *Br J Addict* 1987; **82:** 313–15.

OPIOID OVERDOSAGE. Naloxone is usually given intravenously in opioid overdosage but may also be given intramuscularly if intravenous access is not available. Alternative routes have also been tried; a study[1] using intranasal naloxone found that it was effective for prehospital management of suspected opioid overdosage, although response was slower than with intramuscular injection.

1. Kelly A-M, *et al.* Randomised trial of intranasal versus intramuscular naloxone in prehospital treatment for suspected opioid overdose. *Med J Aust* 2005; **182:** 24–7.

Shock. Endogenous opioids may have a role in the pathophysiology of shock but studies investigating naloxone for the treatment of shock have produced contradictory results. A systematic review[1] concluded that naloxone does increase blood pressure in various forms of shock, but no significant effect on mortality was shown. US licensed product information has noted that the optimal dose and duration of therapy with naloxone have not been established, and that caution should be exercised before its use, particularly in patients with underlying pain or who have previously received opioids and may have developed opioid tolerance.

1. Boeuf B, *et al.* Naloxone for shock. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2003 (accessed 04/10/05).

Preparations

BP 2008: Naloxone Injection; Neonatal Naloxone Injection;
USP 31: Naloxone Hydrochloride Injection; Pentazocine and Naloxone Tablets.

Proprietary Preparations (details are given in Part 3)

Arg.: Antiopiaz; Grayxona; Narcanti; Narxona; ***Austral.:*** Narcan; ***Austria:*** Narcanti; ***Belg.:*** Narcan†; ***Braz.:*** Narcan; ***Canad.:*** Narcan†; ***Cz.:*** Intrenon; Narcanti†; ***Denm.:*** Narcanti; ***Fin.:*** Narcanti; ***Fr.:*** Nalone†; Narcan†; ***Ger.:*** Naloselect†; Narcanti; ***Gr.:*** Narcan; ***Hong Kong:*** Mapin; Narcan†; ***Hung.:*** Narcanti†; ***India:*** Narcotan; ***Indon.:*** Nokoba; ***Irl.:*** Narcan; ***Israel:*** Narcan†; ***Ital.:*** Narcan; ***Malaysia:*** Mapin; Narcan†; ***Mex.:*** Narcanti†; ***Norw.:*** Narcanti; ***NZ:*** Narcan; ***Port.:*** Narcan†; Naxan; Naxolan; ***Rus.:*** Naloxon (Налоксон); ***S.Afr.:*** Narcan†; Zynox; ***Singapore:*** Narcan†; ***Swed.:*** Narcanti; ***Switz.:*** Narcan; ***Thai.:*** Narcan; ***UK:*** Narcan†; ***USA:*** Narcan†; ***Venez.:*** Narcan; Oxogina.

Used as an adjunct in: ***Belg.:*** Tinalox; Valtran; ***Cz.:*** Suboxone; ***Fr.:*** Suboxone; ***Ger.:*** Andolor; Celldolor; Findol N†; Gruntin Tropfen†; Nalidin; Tili Comp; Tili-Puren; Tili†; Tilicomp; Tilidalor†; Tilidin comp; Tilidin N; Tilidin plus; Tilidin-saar; Tilidura; Tiligetic†; Tilimerck†; Tilnalox; Valoron N; ***Israel:*** Talwin NX†; ***Malaysia:*** Suboxone; ***NZ:*** Suboxone; ***Port.:*** Suboxone; ***UK:*** Suboxone; ***USA:*** Suboxone; Talwin NX.

Naltrexone *(BAN, USAN, rINN)*

Naltrexona; Naltrexonum. (5*R*)-9a-Cyclopropylmethyl-3,14-dihydroxy-4,5-epoxymorphinan-6-one; 17-(Cyclopropylmethyl)-4,5α-epoxy-3,14-dihydroxymorphinan-6-one.

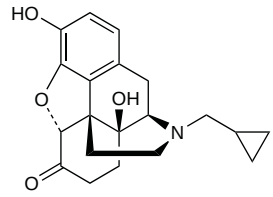
Налтрексон

$C_{20}H_{23}NO_4$ = 341.4.

CAS — 16590-41-3.

ATC — N07BB04.

ATC Vet — QN07BB04; QV03AB30.



Naltrexone Hydrochloride *(BANM, rINNM)*

EN-1639A; Hidrocloruro de naltrexona; Naltreksonihydroklorid; Naltreksono hidrochloridas; Naltrexone, chlorhydrate de; Naltrexon-hydrochlorid; Naltrexonhydroklorid; Naltrexoni hydrochloridum.

Налтрексона Гидрохлорид

$C_{20}H_{23}NO_4$,HCl = 377.9.

CAS — 16676-29-2.

ATC — N07BB04.

ATC Vet — QN07BB04.

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

Ph. Eur. 6.2 (Naltrexone Hydrochloride). A white or almost white, very hygroscopic, powder. Freely soluble in water; slightly soluble in alcohol; practically insoluble in dichloromethane. Store in airtight containers. Protect from light.

USP 31 (Naltrexone Hydrochloride). Store in airtight containers.

Adverse Effects

Difficulty in sleeping, loss of energy, anxiety, dysphoria, abdominal pain, nausea, vomiting, reduction in appetite, joint and muscle pain, and headache may occur with naltrexone. Dizziness, constipation, diarrhoea, skin rashes, and reduced potency and ejaculatory difficulties have also been reported. Some adverse effects may be associated with opioid withdrawal. Thrombocytopenic purpura has occurred rarely. High doses may cause hepatocellular injury. Injection site reactions, including abscesses and tissue necrosis, have been reported with use of the intramuscular preparation.

Effects on the liver. Increased liver enzyme values were reported in 6 of 40 obese patients given naltrexone 50 or 100 mg daily for 8 weeks.[1] Five of the 6 patients had minimally abnormal liver function before naltrexone was given and liver function tests returned to baseline values or better on stopping naltrexone.

Raised transaminase levels were noted in 5 of 26 obese patients after 3 weeks of treatment with naltrexone 300 mg daily; transaminase activity returned to normal when treatment was stopped.[2]

1. Atkinson RL, *et al.* Effects of long-term therapy with naltrexone on body weight in obesity. *Clin Pharmacol Ther* 1985; **38:** 419–22.
2. Mitchell JE. Naltrexone and hepatotoxicity. *Lancet* 1986; **i:** 1215.

Effects on the muscles. Asymptomatic rhabdomyolysis has been reported[1] in a patient receiving naltrexone; the condition resolved when naltrexone was withdrawn.

1. Zaim S, *et al.* Rhabdomyolysis associated with naltrexone. *Ann Pharmacother* 1999; **33:** 312–3.

Precautions

Naltrexone should be avoided in patients receiving opioids therapeutically, or in those misusing them, as an acute withdrawal syndrome may be precipitated (see Dependence and Withdrawal under Opioid Analgesics, p.101). Withdrawal symptoms may develop within 5 minutes and last up to 48 hours. Naltrexone should be discontinued at least 48 hours before elective surgery involving opioid analgesia. For further precautions when using naltrexone as an adjunct in the treatment of opioid dependence, see Uses and Administration, below.

When analgesia is required, larger doses than usual of opioids will be needed and there is an increased risk of respiratory depression and other adverse effects.

Naltrexone should be used with caution in patients with hepatic impairment and is contra-indicated in patients with acute hepatitis or hepatic failure. Regular monitoring of hepatic function has been recommended. Naltrexone should be given with caution to patients with renal impairment.

Pharmacokinetics

Naltrexone is well absorbed from the gastrointestinal tract but is subject to considerable first-pass metabolism and may undergo enterohepatic recycling. It is extensively metabolised in the liver and the major metabolite, 6-β-naltrexol, may also possess weak opioid antagonist activity. Maximum plasma concentrations of naltrexone and 6-β-naltrexol are achieved in about 1 hour and naltrexone is about 20% bound to plasma proteins at therapeutic doses. The elimination half-life of naltrexone is approximately 4 hours and that of 6-β-naltrexol about 13 hours. Naltrexone and its metabolites are excreted mainly in the urine. Less than 1% of an oral dose of naltrexone is excreted unchanged.

Hepatic impairment. A study[1] in 11 patients with hepatic cirrhosis found that the systemic availability of naltrexone was significantly increased, particularly in those with decompensated disease.

1. Bertolotti M, *et al.* Effect of liver cirrhosis on the systemic availability of naltrexone in humans. *J Hepatol* 1997; **27:** 505–511.

Uses and Administration

Naltrexone is a specific opioid antagonist with actions similar to those of naloxone (p.1454); however, it is more potent than naloxone and has a longer duration of action. It is used in the management of opioid dependence and alcohol dependence, and has also been investigated in other addictive disorders.

Naltrexone is used as the hydrochloride as an aid to maintaining abstinence after opioid withdrawal in detoxified, formerly **opioid-dependent** patients. Naltrexone treatment should not be started until the patient has been detoxified and abstinent from opioids for at least 7 to 10 days because of the risk of acute withdrawal; abstinence should be verified by analysis of the patient's urine. A *naloxone challenge test* should then be performed to confirm the absence of opioid dependence, as follows: naloxone hydrochloride 200 micrograms is given intravenously and the patient observed for 30 seconds for evidence of withdrawal symptoms; if none occur, a further dose of 600 micrograms is given and the patient observed for 30 minutes. A confirmatory rechallenge with naloxone hydrochloride 1.6 mg intravenously may be considered if results are ambiguous. Sources in the USA suggest a naloxone challenge test with a single dose of 800 micrograms given subcutaneously as an alternative to the intravenous route.

Once a negative naloxone challenge test has been obtained, naltrexone hydrochloride is given orally to maintain abstinence. Treatment may be initiated with a dose of 25 mg. If no signs of opioid withdrawal occur subsequent doses may be increased to 50 mg daily. The usual maintenance dose of naltrexone hydrochloride is 350 mg weekly given as 50 mg daily, but the dosing interval may be lengthened to improve compliance; for example, doses of 100 mg on Monday and Wednesday and 150 mg on Friday may be effective, and various other intermittent dosage regimens have been used. Patients should be carefully counselled and warned that attempts to overcome the opioid blockade with large doses of opioids could result in fatal opioid intoxication.

Naltrexone hydrochloride is also used as an adjunct in the management of **alcohol dependence** at a recommended oral dose of 50 mg daily. Alternatively, naltrexone (as the base) may be given as a modified-release intramuscular injection in a dose of 380 mg once every 4 weeks.

Alcohol withdrawal and abstinence. Naltrexone may be of use as an adjunct to psychotherapy in maintaining abstinence after alcohol withdrawal in patients with alcohol dependence (p.1626). Two systematic reviews[1,2] have concluded that oral naltrexone is safe and effective for the short-term treatment of alcohol dependence, although there is less evidence for long-term benefit. However, since the risk of relapse is particularly high early after alcohol withdrawal, treatment for at least 3 to 6 months has been recommended.[2,3] Compliance with oral naltrexone may be a problem,[1,2] and promising results[4,5] have been reported with a long-acting intramuscular injection given monthly.

Naltrexone appears to be more effective at reducing the amount of alcohol consumed than producing complete abstinence;[1] reports[6] from patients who continued to drink during therapy suggest that naltrexone may reduce the pleasure associated with drinking, possibly by blocking the effect of endorphins released as a result of alcohol consumption.

Although naltrexone does not appear to be hepatotoxic at the oral dosage of 50 mg daily used for alcohol dependence, caution is recommended in patients with liver disease;[3] careful monitoring is recommended if it is given with disulfiram since hepatotoxicity could potentially be increased.

Other opioid antagonists have also been studied. Preliminary results[7,8] suggest that nalmefene may also be effective, although there is insufficient evidence to recommend its use.[2]

1. Carmen B, *et al.* Efficacy and safety of naltrexone and acamprosate in the treatment of alcohol dependence: a systematic review. *Addiction* 2004; **99:** 811–28.
2. Srisurapanont M, Jarusuraisin N. Opioid antagonists for alcohol dependence. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2005 (accessed 04/10/05).
3. Berg BJ, *et al.* A risk-benefit assessment of naltrexone in the treatment of alcohol dependence. *Drug Safety* 1996; **15:** 274–82.
4. Garbutt JC, *et al.* Efficacy and tolerability of long-acting injectable naltrexone for alcohol dependence: a randomized controlled trial. *JAMA* 2005; **293:** 1617–25. Correction. *ibid.*: 1978.
5. Swainston Harrison T, *et al.* Extended-release intramuscular naltrexone. *Drugs* 2006; **66:** 1741–51.
6. Volpicelli JR, *et al.* Effect of naltrexone on alcohol "high" in alcoholics. *Am J Psychiatry* 1995; **152:** 613–15.
7. Mason BJ, *et al.* A double-blind, placebo-controlled pilot study to evaluate the efficacy and safety of oral nalmefene HCl for alcohol dependence. *Alcohol Clin Exp Res* 1994; **18:** 1162–7.
8. Mason BJ, *et al.* A double-blind, placebo-controlled study of oral nalmefene for alcohol dependence. *Arch Gen Psychiatry* 1999; **56:** 719–24.

Autism. Autistic disorders have been linked with abnormalities in the endogenous opioid system and there is some evidence[1] that naltrexone may be of benefit in children with autism, especially in those with self-injurious behaviour.

1. ElChaar GM, *et al.* Efficacy and safety of naltrexone use in pediatric patients with autistic disorder. *Ann Pharmacother* 2006; **40:** 1086–95.

Opioid dependence. ***MAINTENANCE.*** Naltrexone is a long-acting, non-addictive oral opioid antagonist. It can be effective in maintaining abstinence in opioid addicts after detoxification, but compliance with therapy is difficult to maintain because although it blocks the euphoriant effects of opioids it does not block the craving for narcotics. It is thus most effective in highly motivated addicts with good sociological and psychological support to discourage impulsive use of opioids. Subcutaneous formulations have also been used but have been associated with serious complications (see Rapid Detoxification, below).

For a discussion of the management of opioid dependence, see p.101.

References.

1. Gonzalez JP, Brogden RN. Naltrexone: a review of its pharmacodynamic and pharmacokinetic properties and therapeutic efficacy in the management of opioid dependence. *Drugs* 1988; **35:** 192–213.
2. Minozzi S, *et al.* Oral naltrexone maintenance treatment for opioid dependence. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2006 (accessed 02/09/08).
3. NICE. Naltrexone for the management of opioid dependence: Technology Appraisal Guidance 115 (issued January 2007). Available at: http://guidance.nice.org.uk/TA115/guidance/pdf/English (accessed 02/05/07)
4. Lobmaier P, *et al.* Sustained-release naltrexone for opioid dependence. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2008 (accessed 21/07/08).

RAPID DETOXIFICATION. Naltrexone has been used in various regimens for rapid detoxification;[1,2] opioid withdrawal may be achieved in only a few days, although benefits for long-term outcome are not yet established. It has also been used for ultrarapid detoxification under anaesthesia, although a systematic review[3] concluded that the risks outweighed the benefits of using opioid antagonists in such procedures. A later study[4] also failed to support the use of such a regimen. After detoxification, patients may be given oral naltrexone for maintenance; subcutaneous formulations of naltrexone have also been used in an attempt to improve compliance, although serious complications, including deaths, have been reported[5-7] with their use.

1. O'Connor PG, Kosten TR. Rapid and ultrarapid opioid detoxification techniques. *JAMA* 1998; **279:** 229–34.
2. Gowing L, *et al.* Opioid antagonists with minimal sedation for opioid withdrawal. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2006 (accessed 02/09/08).
3. Gowing L, *et al.* Opioid antagonists under heavy sedation or anaesthesia for opioid withdrawal. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2006 (accessed 02/09/08).
4. Collins ED, *et al.* Anesthesia-assisted vs buprenorphine- or clonidine-assisted heroin detoxification and naltrexone induction: a randomized trial. *JAMA* 2005; **294:** 903–13.
5. Hamilton RJ, *et al.* Complications of ultrarapid opioid detoxification with subcutaneous naltrexone pellets. *Acad Emerg Med* 2002; **9:** 63–8.
6. Gibson AE, *et al.* Opioid overdose deaths can occur in patients with naltrexone implants. *Med J Aust* 2007; **186:** 152–3.
7. Lintzeris N, *et al.* Unplanned admissions to two Sydney public hospitals after naltrexone implants. *Med J Aust* 2008; **188:** 441–4.

Pruritus. For reference to the use of opioid antagonists, including naltrexone, in pruritus, see under Nalmefene, p.1453.

Preparations

USP 31: Naltrexone Hydrochloride Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Revez; ***Austral.:*** Revia; ***Austria:*** Dependex; Ethylex; Nalone†; Naltrexin; Nemexin; Revia; ***Belg.:*** Nalorex; ***Braz.:*** Revia; ***Canad.:*** Revia; ***Chile:*** Nalerona; ***Cz.:*** Nemexin; Revia; ***Denm.:*** Revia; ***Fin.:*** Revia; ***Fr.:*** Nalorex; Revia; ***Ger.:*** Nemexin; ***Gr.:*** Nalorex; ***Hong Kong:*** Revia; ***Hung.:*** Antaxon; Nemexin; Revia; ***India:*** Nodict; ***Indon.:*** Nutrexon; Phaltrexia; ***Irl.:*** Nalorex; Revia; ***Israel:*** Revia†; ***Ital.:*** Antaxone; Nalorex; Narcoral; ***Malaysia:*** Trexan†; ***Mex.:*** Revia; ***Neth.:*** Nalorex; Revia; ***Norw.:*** Revia; ***NZ:*** Revia; ***Port.:*** Antaxone; Basinal; Destoxican; Nalorex; ***Rus.:*** Antaxone (Антаксон); ***S.Afr.:*** Revia†; ***Singapore:*** Trexan†; ***Spain:*** Antaxone; Celupan; Revia; ***Swed.:*** Revia; ***Switz.:*** Naltrexin; Nemexin; ***Thai.:*** Revia; ***UK:*** Nalorex; Opizone; ***USA:*** Depade†; Revia; Trexan; Vivitrol.

Obidoxime Chloride *(USAN, rINN)*

Cloruro de obidoxima; LüH6; Obidoxime, Chlorure d'; Obidoximi Chloridum. 1,1'-[Oxybis(methylene)]bis[4-(hydroxyimino)methyl]pyridinium dichloride.

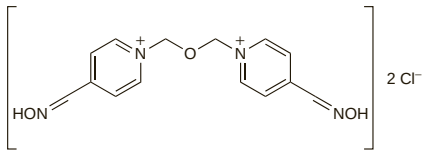
Обидоксима Хлорид

$C_{14}H_{16}Cl_2N_4O_3$ = 359.2.

CAS — 7683-36-5 (obidoxime); 114-90-9 (obidoxime chloride).

ATC — V03AB13.

ATC Vet — QV03AB13.



Profile

Obidoxime chloride is a cholinesterase reactivator with similar actions and uses to pralidoxime (p.1460). It is given with atropine in the treatment of organophosphorus poisoning in a usual initial dose of 250 mg (4 mg/kg) by slow intravenous injection. This may be followed by intravenous infusion of 750 mg over 24 hours, continued until the concentration of organophosphate is below critical levels; alternatively, repeated doses of 4 to 8 mg/kg may be given at intervals of 2 to 4 hours. It has also been given by intramuscular injection.

◊ References.

1. Thiermann H, *et al.* Cholinesterase status, pharmacokinetics and laboratory findings during obidoxime therapy in organophosphate poisoned patients. *Hum Exp Toxicol* 1997; **16:** 473–80.

Preparations

Proprietary Preparations (details are given in Part 3)
Austria: Toxogonin; ***Chile:*** Toxogonin; ***Cz.:*** Toxogonin; ***Ger.:*** Toxogonin; ***Neth.:*** Toxogonin; ***S.Afr.:*** Toxogonin; ***Swed.:*** Toxogonin; ***Switz.:*** Toxogonine.

Penicillamine *(BAN, USAN, rINN)*

Penicilamin; Penicilamina; Penicilaminas; Penicillamin; Pénicillamine; D-Penicillamine; Penicillaminum; Penicylamina; Penisilamin; Penisillamiini. D-3,3-Dimethylcysteine; D-3-Mercaptovaline.

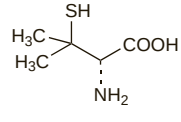
Пеницилламин

$C_5H_{11}NO_2S$ = 149.2.

CAS — 52-67-5 (penicillamine); 2219-30-9 (penicillamine hydrochloride).

ATC — M01CC01.

ATC Vet — QM01CC01.



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

Ph. Eur. 6.2 (Penicillamine). A white or almost white, crystalline powder. Freely soluble in water; slightly soluble in alcohol. A 1% solution in water has a pH of 4.5 to 5.5.

USP 31 (Penicillamine). A white or practically white, crystalline powder having a slight characteristic odour. Freely soluble in water; slightly soluble in alcohol; insoluble in chloroform and in ether. pH of a 1% solution in water is between 4.5 and 5.5. Store in airtight containers.

Adverse Effects and Treatment

Adverse effects of penicillamine are frequent. Gastrointestinal disturbances including anorexia, nausea, and vomiting may occur; oral ulceration and stomatitis have been reported and impaired taste sensitivity is common.

Skin rashes occurring early in treatment are commonly allergic and may be associated with pruritus, urticaria, and fever; they are usually transient but temporary drug withdrawal and use of corticosteroids or antihistamines may be required. Lupus erythematosus and pemphigus have been reported. A Stevens-Johnson-like syndrome has been observed during penicillamine treatment. Prolonged use of high doses may affect skin collagen and elastin, resulting in increased skin friability, eruptions resembling elastosis perforans serpiginosa, and a late rash or acquired epidermolysis bullosa (penicillamine dermatopathy) that may necessitate dosage reduction or discontinuation.

Haematological adverse effects have included thrombocytopenia and, less frequently, leucopenia; these are usually reversible, but agranulocytosis and aplastic anaemia have occurred and fatalities have been reported. Haemolytic anaemia has also occurred.

Proteinuria occurs frequently and in some patients may progress to glomerulonephritis or nephrotic syndrome. Penicillamine-induced haematuria is rare but normally requires immediate discontinuation.

Other adverse effects associated with penicillamine include Goodpasture's syndrome, bronchiolitis and pneumonitis, myasthenia gravis, polymyositis (rarely with cardiac involvement), intrahepatic cholestasis, and pancreatitis.

Incidence of adverse effects. References describing the range and incidence of adverse effects associated with of D-penicillamine.[1-3] The L- or DL-forms are much more toxic.[4]

1. Kean WF, *et al.* Efficacy and toxicity of -penicillamine for rheumatoid disease in the elderly. *J Am Geriatr Soc* 1982; **30:** 94–100.
2. Steen VD, *et al.* The toxicity of -penicillamine in systemic sclerosis. *Ann Intern Med* 1986; **104:** 699–705.
3. Munro R, Capell HA. Penicillamine. *Br J Rheumatol* 1997; **36:** 104–9.
4. Kean WF, *et al.* Chirality in antirheumatic drugs. *Lancet* 1991; **338:** 1565–8.

Effects on the blood. Of the 18 deaths ascribed to penicillamine reported to the UK CSM between January 1964 and December 1977, 14 were apparently due to blood disorders, at least 7 of them being marrow aplasias. The myelotoxicity of penicillamine was reviewed in 10 patients with confirmed or suspected marrow depression during penicillamine treatment for rheumatoid arthritis or scleroderma; 6 died.[1]

An incidence of 12 to 27% has been reported for penicillamine-induced thrombocytopenia in patients with rheumatoid arthritis, possibly due to bone-marrow suppression and a reduced platelet-production rate.[2]

There have been isolated reports[3-5] of thrombotic thrombocytopenic purpura attributed to the use of penicillamine, with some fatalities.

1. Kay AGL. Myelotoxicity of D-penicillamine. *Ann Rheum Dis* 1979; **38:** 232–6.
2. Thomas D, *et al.* Thrombokinetics in patients with rheumatoid arthritis treated with D-penicillamine. *Ann Rheum Dis* 1984; **43:** 402–6.
3. Ahmed F, *et al.* Thrombohemolytic thrombocytopenic purpura during penicillamine therapy. *Arch Intern Med* 1978; **138:** 1292–3.
4. Speth PAJ, *et al.* Thrombotic thrombocytopenic purpura associated with D-penicillamine treatment in rheumatoid arthritis. *J Rheumatol* 1982; **9:** 812–13.
5. Trice JM, *et al.* Thrombotic thrombocytopenic purpura during penicillamine therapy in rheumatoid arthritis. *Arch Intern Med* 1983; **143:** 1487–8.

Effects on the breasts. Breast enlargement has been reported both in women[1-5] and in men[6] taking penicillamine and may be a rare adverse effect. In some patients breast enlargement was prolonged with poor resolution and others required surgery.