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.

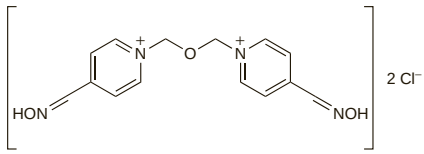
Обидоксима Хлорид

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

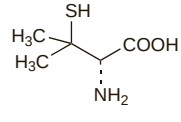
Пеницилламин

$C_5H_{11}NO_2S$ = 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.