Nicergoline *(BAN, USAN, rINN)*

FI-6714; Nicergolin; Nicergolina; Nicergolinas; Nicergolinum; Nisergoliini; Nisergolin. 10α-Methoxy-1,6-dimethylergolin-8β-ylmethyl 5-bromonicotinate.

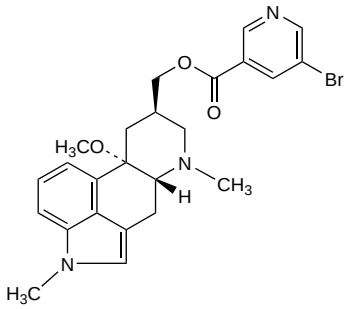
Ницерголин

$C_{24}H_{26}BrN_3O_3$ = 484.4.

CAS — 27848-84-6.

ATC — C04AE02.

ATC Vet — QC04AE02.



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

Ph. Eur. 6.2 (Nicergoline). A fine to granular white or yellowish powder. It exhibits polymorphism. Practically insoluble in water; soluble in alcohol; freely soluble in dichloromethane.

Adverse Effects and Precautions

Adverse effects that may occur after nicergoline include gastrointestinal disturbances and, particularly after parenteral doses, hypotension.

Incidence of adverse effects. Adverse effects occurred in 25 of 359 patients with cerebrovascular insufficiency treated with nicergoline for 1 month;[1] the drug had to be withdrawn in 11. The reactions included 6 cases of hot flushes, 8 of general malaise, 2 of agitation, 3 of hyperacidity, 1 of nausea, 3 of diarrhoea, and 2 of dizziness and somnolence.

1. Dauverchain J. Bedeutung von Nicergolin bei der symptomatischen Behandlung des arteriellen Hochdrucks und der chronischen, zerebro-vaskulären Insuffizienz. *Arzneimittelforschung* 1979; **29:** 1308–10.

Porphyria. Nicergoline is considered to be unsafe in patients with porphyria because it has been shown to be porphyrinogenic in *in-vitro* systems, although there is conflicting evidence of porphyrinogenicity.

Interactions

For a study indicating that nicergoline enhances the cardiac depressant action of propranolol, see Ergot Derivatives, in Interactions of Beta Blockers, p.1229.

Uses and Administration

Nicergoline is an ergot derivative. It has been used similarly to codergocrine mesilate (p.364) to treat symptoms of mental deterioration associated with cerebrovascular insufficiency (see Dementia, p.362) and has also been used in peripheral vascular disease (p.1178). Nicergoline has been given in doses of up to 60 mg daily by mouth in divided doses, and by intramuscular injection in doses of 2 to 4 mg twice daily; 4 to 8 mg daily has been given by intravenous infusion. Nicergoline tartrate has been used in parenteral dosage forms.

◊ References.

1. Ronchi F, *et al.* Symptomatic treatment of benign prostatic obstruction with nicergoline: a placebo controlled clinical study and urodynamic evaluation. *Urol Res* 1982; **10:** 131–4.
2. Bousquet J, *et al.* Double-blind, placebo-controlled study of nicergoline in the treatment of pruritus in patients receiving maintenance hemodialysis. *J Allergy Clin Immunol* 1989; **83:** 825–8.
3. Saletu B, *et al.* Nicergoline in senile dementia of Alzheimer type and multi-infarct dementia: a double-blind, placebo-controlled, clinical and EEG/ERP mapping study. *Psychopharmacology (Berl)* 1995; **117:** 385–95.
4. Herrmann WM, *et al.* A multicenter randomized double-blind study on the efficacy and safety of nicergoline in patients with multi-infarct dementia. *Dementia Geriatr Cogn Disord* 1997; **8:** 9–17.
5. Fioravanti M, Flicker L. Nicergoline for dementia and other age associated forms of cognitive impairment. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2001 (accessed 28/04/05).
6. Felisati G, *et al.* Nicergoline in the treatment of dizziness in elderly patients: a review. *Arch Gerontol Geriatr Suppl* 2004; 163–70.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Cergodun; Nicergolent†; Sermion; ***Austria:*** Ergotop; Nicergin; Sermion; ***Braz.:*** Sermion; ***Chile:*** Sermion; ***Cz.:*** Ergotop; Nilogrin†; Sermion; ***Fr.:*** Sermion; ***Ger.:*** Circo-Maren†; Ergobel; Nicergobeta; Nicerium; Sermion†; ***Gr.:*** Albotyl†; Sermion; ***Hong Kong:*** Cergodun; Qualigoline; Sermion; ***Hung.:*** Ergotop; Sermion; ***Indon.:*** Serolin; ***Ital.:*** Cebran; Nicer†; Sermion; ***Jpn:*** Sermion; ***Mex.:*** Sermion; ***Philipp.:*** Sermion; ***Pol.:*** Adavin; Circulat; Nicerin; Nilogrin; Sermion; ***Port.:*** Erg XXI†; Sermion; ***Rus.:*** Nilogrin (Нилогрин); Sermion (Сермион); ***Spain:*** Fisifax†; Sermion; Varson; ***Switz.:*** Sermion; ***Thai.:*** Sermion; ***Turk.:*** Sermion; ***Venez.:*** Sermion.

Multi-ingredient: ***Arg.:*** Angiolit†; Sibelium Plus.

Nicotine

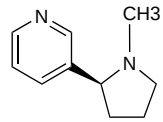
Nicotina; Nicotinum; Nikotiini; Nikotin; Nikotinas. (*S*)-3-(1-Methylpyrrolidin-2-yl)pyridine.

$C_{10}H_{14}N_2$ = 162.2.

CAS — 54-11-5.

ATC — N07BA01.

ATC Vet — QN07BA01; QP53AX13.



Description. Nicotine is a liquid alkaloid obtained from the dried leaves of the tobacco plant, *Nicotiana tabacum* and related species (Solanaceae). Tobacco leaves contain 0.5 to 8% of nicotine combined as malate or citrate.

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

Ph. Eur. 6.2 (Nicotine). A colourless or brownish, volatile, hygroscopic, viscous liquid. Soluble in water; miscible with dehydrated alcohol. Store under nitrogen in airtight containers. Protect from light.

USP 31 (Nicotine). It should be stored under nitrogen at a temperature below 25°. Protect from light and moisture.

Nicotine Polacrilex *(USAN)*

CAS — 96055-45-7.

ATC — N07BA01.

ATC Vet — QN07BA01.

Pharmacopoeias. In *US.*

USP 31 (Nicotine Polacrilex). A weak carboxylic cation-exchange resin prepared from methacrylic acid and divinylbenzene, in complex with nicotine. Store in airtight containers.

Nicotine Resinate

Nicotine, résinate de; Nicotini resinas; Nicotinresinat; Nikotiiniresinaatti; Nikotino rezinatas; Nikotin-resinát; Nikotin-rezinát.

ATC — N07BA01.

ATC Vet — QN07BA01.

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

Ph. Eur. 6.2 (Nicotine Resinate). A complex of nicotine with a weak cationic exchange resin. It may contain glycerol. A white or slightly yellowish powder. Practically insoluble in water. Store in airtight containers. Protect from light.

Nicotine Tartrate

Nicotine Bitartrate *(USAN).*

$C_{10}H_{14}N_2,2C_4H_6O_6,2H_2O$ = 498.4.

CAS — 65-31-6 (anhydrous nicotine tartrate).

ATC — N07BA01.

ATC Vet — QN07BA01.

Dependence and Withdrawal

Nicotine dependence is most commonly associated with cigarette smoking. It is characterised by a strong desire to continue taking the agent, a physical and psychological need for it, and a characteristic abstinence syndrome on withdrawal. Common symptoms seen on nicotine withdrawal include irritability, anxiety, depression, restlessness, poor concentration, increased appetite, weight gain, and insomnia. The management of smoking cessation is discussed under Uses and Administration, below.

Mild withdrawal symptoms have been reported from nicotine replacement preparations used to aid smoking cessation.

◊ References.

1. Hatsukami D, *et al.* Physical dependence on nicotine gum: effect of duration of use. *Psychopharmacology (Berl)* 1993; **111:** 449–56.
2. Benowitz NL, Henningfield JE. Establishing a nicotine threshold for addiction: the implications for tobacco regulation. *N Engl J Med* 1994; **331:** 123–5.
3. Keenan RM, *et al.* Pharmacodynamic effects of cotinine in abstinent cigarette smokers. *Clin Pharmacol Ther* 1994; **55:** 581–90.
4. Slade J, *et al.* Nicotine and addiction: the Brown and Williamson documents. *JAMA* 1995; **274:** 225–33.
5. Kessler DA. Nicotine addiction in young people. *N Engl J Med* 1995; **333:** 186–9.
6. Doll R, Crofton J, eds. Tobacco and health. *Br Med Bull* 1996; **52:** 1–223.
7. Benowitz NL. Nicotine addiction. *Prim Care* 1999; **26:** 611–31.
8. Colby SM, *et al.* Are adolescent smokers dependent on nicotine? A review of the evidence. *Drug Alcohol Depend* 2000; **59** (suppl 1): S83–S95.
9. Royal College of Physicians. *Nicotine addiction in Britain: a report of the Tobacco Advisory Group of the Royal College of Physicians.* London: Royal College of Physicians, 2000. Also available at: http://www.rcplondon.ac.uk/pubs/books/nicotine/index.htm (accessed 30/07/08)
10. West R, *et al.* A comparison of the abuse liability and dependence potential of nicotine patch, gum, spray and inhaler. *Psychopharmacology (Berl)* 2000; **149:** 198–202.

Adverse Effects and Treatment

Nicotine is a highly toxic substance and in acute poisoning death may occur within 1 hour due to respiratory failure arising from paralysis of the muscles of respiration. The fatal oral dose of nicotine for an adult is from 40 to 60 mg.

Less severe poisoning causes initial stimulation followed by depression of the autonomic nervous system. Typical symptoms include burning of the mouth and throat, nausea and salivation, abdominal pain, vomiting, diarrhoea, dizziness, weakness, hypertension followed by hypotension, mental confusion, headache, hearing and visual disturbances, dyspnoea, faintness, convulsions, sweating, and prostration. Transient cardiac standstill or paroxysmal atrial fibrillation may occur.

Nicotine is rapidly absorbed through the skin or by inhalation as well as by ingestion, and nicotine poisoning may occur due to careless handling when it is used as a horticultural insecticide.

Prompt treatment of nicotine poisoning is essential. If contact was with the skin, contaminated clothing should be removed and the skin washed thoroughly with cold water without rubbing. If the patient has swallowed nicotine, gastric lavage and activated charcoal may be beneficial. Treatment is supportive and includes support of respiration and control of convulsions. Atropine may be used to suppress features of parasympathomimetic stimulation.

Apart from effects such as dizziness, headache, and gastrointestinal disturbances mentioned above, adverse effects associated with *nicotine replacement preparations* have also included cold and flu-like symptoms, palpitations, insomnia, vivid dreams, myalgia, chest pain, blood pressure changes, anxiety, irritability, somnolence, and dysmenorrhoea. Allergic reactions have been reported. Adverse effects associated with specific preparations include skin reactions with transdermal patches; nasal irritation, epistaxis, lachrymation, and sensations in the ear with the nasal spray; throat irritation with the spray, inhalator, sublingual tablets, lozenges, or chewing gum; aphthous ulceration with the inhalator, sublingual tablets, lozenges, or chewing gum; increased salivation and sometimes swelling of the tongue with chewing gum; cough, rhinitis, stomatitis, sinusitis, and dry mouth with the inhalator; and unpleasant taste with the sublingual tablets or lozenges. Excessive swallowing of nicotine released from oral replacement preparations may cause hiccups in the first few days of treatment.

◊ References.

1. Greenland S, *et al.* A meta-analysis to assess the incidence of adverse effects associated with the transdermal nicotine patch. *Drug Safety* 1998; **18:** 297–308.
2. Gourlay SG, *et al.* Predictors and timing of adverse experiences during transdermal nicotine therapy. *Drug Safety* 1999; **20:** 545–55.

Adverse effects of tobacco products. Chronic use of tobacco is linked to a variety of diseases. By the mid-1960s, epidemiological data established tobacco smoking as a cause of lung cancer (p.668). Smoking is also associated with cancers of the larynx, mouth, cervix, bladder, pancreas, oesophagus, stomach, and kidneys, and with leukaemia.[1] Smoking is a risk factor in cardiovascular, respiratory, and peripheral and cerebral vascular diseases.[1-3] Smoking also increases the risk of developing peptic ulcer disease and may affect other gastrointestinal disorders.[2] There is also evidence that smoking tobacco products increases the risk of developing age-related macular degeneration,[4] type 2 diabetes mellitus,[5] and adenomatous polyps.[6]

Maternal smoking in pregnancy is associated with low birthweight infants and increased risk of abortion, still-birth, and neonatal death (see also Pregnancy under Precautions, below).

Passive smoking refers to inhalation of secondhand tobacco smoke or environmental tobacco smoke. Risks to health from passive exposure are lower than those from active smoking. However, studies have established passive smoking as a cause of lung cancer;[7] passive smoking is also associated with increased risk of heart disease[8] and chronic respiratory disease.[9,10] Smokeless tobacco products also carry risks to health, for example the association of cancers of the head and neck (see p.666) with the use of mixtures of tobacco and areca (p.2259) and probably snuff or chewing tobacco.[11,12]

1. Wald NJ, Hackshaw AK. Cigarette smoking: an epidemiological overview. *Br Med Bull* 1996; **52:** 3–11.
2. Ashton H. Adverse effects of nicotine. *Adverse Drug React Bull* 1991; **149**: 560–3.
3. Teo KK, *et al.* INTERHEART Study Investigators. Tobacco use and risk of myocardial infarction in 52 countries in the INTERHEART study: a case-control study. *Lancet* 2006; **368:** 647–58.
4. Tan JSL, *et al.* Smoking and the long-term incidence of age-related macular degeneration: the Blue Mountains Eye Study. *Arch Ophthalmol* 2007; **125:** 1089–95.
5. Willi C, *et al.* Active smoking and the risk of type 2 diabetes: a systematic review and meta-analysis. *JAMA* 2007; **298:** 2654–64.
6. Botteri E, *et al.* Cigarette smoking and adenomatous polyps: a meta-analysis. *Gastroenterology* 2008; **134:** 388–95.
7. Lam TH. Passive smoking in perspective. *Med Toxicol Adverse Drug Exp* 1989; **4:** 153–62.

8. Steenland K. Passive smoking and the risk of heart disease. *JAMA* 1992; **267**: 94–9.
9. Law MR, Hackshaw AK. Environmental tobacco smoke. *Br Med Bull* 1996; **52:** 22–34.
10. DiFranza JR, Lew RA. Mortality and morbidity in children associated with the use of tobacco products by other people. *Pediatrics* 1996; **97:** 560–8.
11. Rodu B, Cole P. Smokeless tobacco use and cancer of the upper respiratory tract. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2002; **93:** 511–15.
12. Critchley JA, Unal B. Health effects associated with smokeless tobacco: a systematic review. *Thorax* 2003; **58:** 435–43.

Effects on carbohydrate metabolism. Hyperinsulinaemia and insulin resistance have been associated with long-term use of nicotine gum.[1] Smoking tobacco products may increase the risk of developing type 2 diabetes mellitus (see above).

1. Eliasson B, *et al.* Long-term use of nicotine gum is associated with hyperinsulinemia and insulin resistance. *Circulation* 1996; **94:** 878–81.

Effects on the cardiovascular system. As mentioned above, nicotine from tobacco products is associated with increased risk of cardiovascular disease. It would not be surprising, therefore, if nicotine replacement preparations were also associated with cardiovascular adverse effects, and there are anecdotal reports of cardiovascular events, including myocardial infarction,[1,2] stroke,[3,4] and cerebral haematoma,[5] associated with use of such products. However, a case-control study in the general population,[6] and both cohort studies[7] and short-term placebo-controlled trials[8,9] in patients with cardiovascular disease have failed to show any increased cardiovascular risk associated with transdermal nicotine.

1. Warner JG, Little WC. Myocardial infarction in a patient who smoked while wearing a nicotine patch. *Ann Intern Med* 1994; **120:** 695.
2. Arnaot MR. Nicotine patches may not be safe. *BMJ* 1995; **310:** 663–4.
3. Pierce JR. Stroke following application of a nicotine patch. *Ann Pharmacother* 1994; **28:** 402.
4. Ang R, *et al.* Nicotine replacement therapy and ischaemic stroke. *Hosp Med* 2005; **66:** 366–7.
5. Riche G, *et al.* Intracerebral haematoma after application of nicotine patch. *Lancet* 1995; **346:** 777–8.
6. Kimmel SE, *et al.* Risk of acute first myocardial infarction and use of nicotine patches in a general population. *J Am Coll Cardiol* 2001; **37:** 1297–1302.
7. Meine TJ, *et al.* Safety and effectiveness of transdermal nicotine patch in smokers admitted with acute coronary syndromes. *Am J Cardiol* 2005; **95:** 976–8.
8. Working Group for the Study of Transdermal Nicotine in Patients with Coronary Artery Disease. Nicotine replacement therapy for patients with coronary artery disease. *Arch Intern Med* 1994; **154:** 989–95.
9. Joseph AM, *et al.* The safety of transdermal nicotine as an aid to smoking cessation in patients with cardiac disease. *N Engl J Med* 1996; **335:** 1792–8.

Vasculitis. Vasculitis occurring in 2 patients was associated with transdermal nicotine patches.[1]

1. van der Klauw MM, *et al.* Vasculitis attributed to the nicotine patch (Nicotinell). *Br J Dermatol* 1996; **134:** 361–4.

Precautions

Nicotine preparations should not be used in patients who have experienced recent cerebrovascular accident. They should be used with caution in patients with cardiovascular disease. Use should preferably be avoided completely in severe cardiovascular disease, including during the immediate postmyocardial infarction period, and in patients with severe arrhythmias or unstable angina pectoris, although use under medical supervision may be considered if the patient is otherwise unable to stop smoking. They should be used with caution in those with peripheral vascular disease, in endocrine disorders including phaeochromocytoma, hyperthyroidism, and diabetes mellitus, in peptic ulcer disease, or renal or hepatic impairment. They should also be used with caution, and avoided if possible, during pregnancy or breast feeding (see below).

Skin patches should not be used on broken skin.

Breast feeding. The American Academy of Pediatrics[1] notes that there have been reports of decreased milk production in breast-feeding mothers who smoke, and of decreased weight gain in the infant. There is, however, controversy regarding the effects of nicotine on infant size at 1 year of age. Although nicotine and its metabolite cotinine have been shown to be distributed into breast milk there are hundreds of compounds in tobacco smoke; nicotine is not necessarily the only component that might be detrimental to the breast-fed infant. Nicotine is present in breast milk in concentrations between 1.5 to 3 times the maternal plasma concentration, but there is no evidence documenting whether this amount of nicotine presents a health risk to the infant. Indeed, one study reported that the incidence of acute respiratory illness in infants whose mothers smoked was decreased in those who were breast fed when compared with those infants who were bottle fed.

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 02/07/04)

Exercise. Physical exercise increased mean peak plasma concentrations of nicotine in 8 healthy subjects treated with a transdermal nicotine patch.[1] The effect was thought to be most likely due to increased skin perfusion resulting in increased uptake.

1. Klemsdal TO, *et al.* Physical exercise increases plasma concentrations of nicotine during treatment with a nicotine patch. *Br J Clin Pharmacol* 1995; **39:** 677–9.

Myasthenia gravis. A patient with myasthenia gravis noted worsening of his symptoms after application of transdermal nicotine patches, the effects being most severe about 1 hour after application, and resolving within 3 hours once the patch was removed.[1] Previous heavy smoking had not produced similar adverse effects, despite the fact that blood-nicotine concentrations are typically higher just after finishing a cigarette than when using the patch.[2]

1. Moreau T, *et al.* Nicotine-sensitive myasthenia gravis. *Lancet* 1994; **344:** 548–9.
2. Pethica D. Nicotine-sensitive myasthenia gravis. *Lancet* 1994; **344:** 961.

Pregnancy. Cigarette smoking during pregnancy is associated with an increased risk of low birth-weight, spontaneous abortion, and perinatal mortality.[1] There is also some evidence of a possible association between smoking during pregnancy and the sudden infant death syndrome (SIDS).[2] In addition to nicotine, cigarette smoke contains many other chemicals, which are also fetal toxins, including carbon monoxide and lead.[3] Although smoking poses a far greater risk than pure nicotine, nicotine replacement therapy (NRT) is not without potential risks and should be reserved for mothers unable to quit with behavioural therapy alone.[3] It has been suggested that where NRT is required, the intermittent delivery formulations such as nicotine gum or inhalator, which expose the fetus to a lower total dose of nicotine, are preferable to continuous use formulations such as patches.[3]

1. British Medical Association. *Smoking and reproductive life: the impact of smoking on sexual, reproductive and child health.* London: British Medical Association, 2004. Available at: http://www.bma.org.uk/ap.nsf/AttachmentsByTitle/PDFsmokingreproductivelife/06.00file/Smoking.pdf (accessed 06/08/08)
2. Wisborg K, *et al.* A prospective study of smoking during pregnancy and SIDS. *Arch Dis Child* 2000; **83:** 203–6. Corrections. *ibid.* 2001; **84:** 93 and 187.
3. Dempsey DA, Benowitz NL. Risks and benefits of nicotine to aid smoking cessation in pregnancy. *Drug Safety* 2001; **24:** 277–322.

Interactions

Tobacco smoking induces hepatic metabolic enzymes and the pharmacokinetics of many drugs are altered. Drugs such as methoxsalen which inhibit the cytochrome P450 isoenzyme CYP2A6 may decrease the metabolism of nicotine, resulting in increased plasma concentrations.

◊ References.

1. Miller LG. Cigarettes and drug therapy: pharmacokinetic and pharmacodynamic considerations. *Clin Pharm* 1990; **9:** 125–35.
2. Zevin S, Benowitz NL. Drug interactions with tobacco smoking: an update. *Clin Pharmacokinet* 1999; **36:** 425–38.
3. Sellers EM, *et al.* Inhibition of cytochrome P450 2A6 increases nicotine's oral bioavailability and decreases smoking. *Clin Pharmacol Ther* 2000; **68:** 35–43.

Nicotinic acid. As described on p.1958, a possible interaction between nicotinic acid and nicotine from a transdermal patch has been reported.

Pharmacokinetics

Nicotine is readily absorbed through mucous membranes and the skin; bioavailability of oral nicotine is low due to extensive first-pass metabolism. Nicotine is widely distributed; it crosses the blood-brain barrier and the placenta and is found in breast milk. The elimination half-life is about 1 to 2 hours. Nicotine is metabolised mainly in the liver via the cytochrome P450 isoenzyme CYP2A6 to cotinine and nicotine-*N*-oxide. Nicotine and its metabolites are excreted in the urine.

◊ References.

1. Gorsline J, *et al.* Steady-state pharmacokinetics and dose relationship of nicotine delivered from Nicoderm (nicotine transdermal system). *J Clin Pharmacol* 1993; **33:** 161–8.
2. Gupta SK, *et al.* Bioavailability and absorption kinetics of nicotine following application of a transdermal system. *Br J Clin Pharmacol* 1993; **36:** 221–7.
3. Schneider NG, *et al.* Clinical pharmacokinetics of nasal nicotine delivery: a review and comparison to other nicotine systems. *Clin Pharmacokinet* 1996; **31:** 65–80.
4. Benowitz NL, *et al.* Sources of variability in nicotine and cotinine levels with the use of nicotine nasal spray, transdermal nicotine and cigarette smoking. *Br J Clin Pharmacol* 1997; **43:** 259–67.
5. Zins BJ, *et al.* Pharmacokinetics of nicotine tartrate after single-dose liquid enema, oral, and intravenous administration. *J Clin Pharmacol* 1997; **37:** 426–36.
6. Schneider NG, *et al.* The nicotine inhaler: clinical pharmacokinetics and comparison with other nicotine treatments. *Clin Pharmacokinet* 2001; **40:** 661–84.

Uses and Administration

The main physiological action of nicotine is paralysis of all autonomic ganglia, preceded by stimulation. Centrally, small doses cause respiratory stimulation, while larger doses produce convulsions and arrest of respiration. The effects on skeletal muscle are similar to those on ganglia.

Nicotine chewing gum, transdermal patches, lozenges, sublingual tablets, nasal spray, or inhalator are used as aids for smoking cessation (below) and many such products are also used to reduce the amount smoked. For smoking *cessation*, treatment is usually continued for up to 3 months, then gradually withdrawn. For smoking *reduction*, it may be continued for up to 6 months, and an attempt to quit then made. If use is to be continued beyond 9 months, additional advice from a healthcare professional should be sought.

- *Chewing gum* is available in strengths of 2 mg and 4 mg; the nicotine may be present in the gum in the form of a complex with methacrylic acid polymer (nicotine polacrilex). Individuals who smoke 20 cigarettes or less per day should start with the 2-mg strength gum chewed slowly over about 30 minutes when the urge to smoke occurs. Those who smoke over 20 cigarettes a day or require more than 15 pieces daily of the 2-mg gum should receive the 4-mg strength. Not more than 15 pieces should be used per day.
- *Sublingual tablets* containing the equivalent of 2 mg of nicotine as a β-cyclodextrin complex may be used: the recommended dose is 1 or 2 tablets sublingually every hour, increased to a maximum of 40 tablets daily if necessary.
- *Lozenges* containing 1 or 2 mg of nicotine (as the polacrilex or as the tartrate) are available. The initial dose is 1 lozenge every 1 to 2 hours increased to a maximum daily dose of 30 of the 1-mg lozenges or 15 of the 2-mg lozenges.
- Adhesive *transdermal patches* are designed to be worn for 16 or 24 hours and are available in different strengths that deliver from 5 to 21 mg during the recommended wearing time. One patch should be applied daily, on waking, to a dry, non-hairy area of skin on the hip, trunk, or upper arm, usually beginning with the highest strength or with a dose determined by the previous daily consumption of cigarettes. A different site of application should be used each day with several days elapsing before the patch is applied to the same area of skin.
- A suggested initial dosage for a *nasal spray* containing 500 micrograms per spray is one spray administered into each nostril up to twice hourly as required up to a maximum of 80 sprays daily for the first 8 weeks and reduced gradually thereafter. Treatment for more than 3 months is not recommended.
- Nicotine *inhalator cartridges* contain nicotine 10 mg for use in an appropriate inhaler mouthpiece. The initial dose is 6 to 16 cartridges daily for up to 12 weeks and is reduced gradually over a further 4 to 12 weeks.

Nicotine has been used as a horticultural insecticide.

Alzheimer's disease. The use of nicotine as a cholinergic agonist is one of a number of methods being studied[1] to overcome brain cholinergic deficits in patients with Alzheimer's disease (see Dementia, p.362). Preliminary studies[2,3] using nicotine patches have been of limited duration and were inconclusive. Transdermal nicotine has been used for the control of behavioural symptoms such as agitation in a small number of patients with Alzheimer's disease.[4] A systematic review[5] was unable to present any conclusions on the efficacy and safety of nicotine in Alzheimer's disease because of a lack of adequate randomised controlled studies.

1. Baldinger SL, Schroeder DJ. Nicotine therapy in patients with Alzheimer's disease. *Ann Pharmacother* 1995; **29:** 314–15.
2. Wilson AL, *et al.* Nicotine patches in Alzheimer's disease: pilot study on learning, memory, and safety. *Pharmacol Biochem Behav* 1995; **51:** 509–14.
3. Snaedal J, *et al.* The effects of nicotine in dermal plaster on cognitive functions in patients with Alzheimer's disease. *Dementia* 1996; **7:** 47–52.
4. Rosin RA, *et al.* Transdermal nicotine for agitation in dementia. *Am J Geriatr Psychiatry* 2001; **9:** 443–4.
5. López-Arrieta JLA, Sanz FJ. Nicotine for Alzheimer's disease. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2001 (accessed 28/04/05).

Blepharospasm. Nicotine nasal spray was reported to be of benefit in a patient with blepharospasm (p.1891) refractory to botulinum A toxin.[1] However, a subsequent study in 4 patients with blepharospasm reported no improvement with the use of nicotine nasal spray.[2]

1. Dursun SM, *et al.* Treatment of blepharospasm with nicotine nasal spray. *Lancet* 1996; **348:** 60.
2. Dressler D, *et al.* Nicotine nasal spray is not reliable treatment for blepharospasm: results of a pilot study. *Mov Disord* 1998; **13:** 190.

Extrapyramidal disorders. Nicotine transdermal patches have been reported to produce beneficial effects[1] in schizophrenic patients with antipsychotic-induced akathisia (p.971). Because of an apparent inverse association between smoking and Parkinson's disease (p.791), transdermal nicotine patches have been investigated in the treatment of parkinsonian symptoms, but with little evidence of overall benefit.[2,3]

1. Anfang MK, Pope HG. Treatment of neuroleptic-induced akathisia with nicotine patches. *Psychopharmacology (Berl)* 1997; **134:** 153–6.
2. Vieregge A, *et al.* Transdermal nicotine in PD: a randomized, double-blind, placebo-controlled study. *Neurology* 2001; **57:** 1032–5.
3. Lemay S, *et al.* Lack of efficacy of a nicotine transdermal treatment on motor and cognitive deficits in Parkinson's disease. *Prog Neuropsychopharmacol Biol Psychiatry* 2004; **28:** 31–9.

Skin disorders. There have been anecdotal reports of nicotine producing beneficial effects in various skin disorders, including pyoderma gangrenosum,[1] and dermatitis due to fluorouracil therapy.[2]

1. Kanekura T, *et al.* Nicotine for pyoderma gangrenosum. *Lancet* 1995; **345:** 1058.
2. Kingsley EC. 5-Fluorouracil dermatitis prophylaxis with a nicotine patch. *Ann Intern Med* 1994; **120:** 813.

Smoking cessation. Smoking is the single most important cause of preventable illness and premature death in the UK and USA; it is estimated that around 1 in 5 deaths are due to smoking-related illnesses. The financial burden of smoking-related diseases on healthcare providers is also substantial. Many governments have undertaken initiatives to promote smoking cessation for which there is substantial evidence of a decline in the risk of disease[1] and death.[2] As the abstinence period increases, the reduced risk of disease in former smokers may even approach, although rarely does it ever equal, that of people who have never smoked.[1].

Nicotine dependence and the development of a characteristic withdrawal syndrome (see Dependence and Withdrawal, above) make stopping smoking very difficult. Many individuals relapse when trying to give up or need several attempts before successfully stopping. Both nonpharmacological and pharmacological treatments can improve the abstinence rate and are most effective when the two approaches are combined.[3-12]

Nonpharmacological methods include counselling, training in coping skills, and support groups; although the abstinence rate increases with the intensity of the support, even brief advice is effective in encouraging cessation.

The first-line pharmacological intervention is *nicotine replacement therapy* (NRT) which is an effective treatment for reducing the cravings associated with stopping smoking. NRT is available in numerous formulations: chewing gum, transdermal patches, inhalators, nasal sprays, sublingual tablets, and lozenges. A systematic review[10] of NRT found abstinence was more than doubled when compared with controls, regardless of the intensity of any additional nonpharmacological support.

Choice of formulation is based on patient preference, tolerance, and previous treatments, if any. The transdermal patch is easiest to use and compliance is greatest with this route but local effects may be troublesome. The gum has an unpleasant taste initially and some find the chewing action difficult. The sublingual tablet may be useful for those who have difficulty chewing the gum. The nasal spray has a fast onset of action but may cause local irritation. The inhalator has the advantage of simulating cigarette smoking but may cause local irritation of the mouth and throat. The lozenge has the advantage that it can be sucked discreetly. Patients who are unable to tolerate one type of NRT may benefit from a course of an alternative NRT preparation.

Combination therapy with different types of NRT (patches with either the nasal spray, inhalator, or chewing gum) has also been tried as a means of increasing efficacy.

NRT for smoking cessation is usually continued for about 3 months before being withdrawn. Although the manufacturers advise gradual withdrawal, others[6,8] have found that this offers no advantage and recommend abrupt withdrawal. NRT for smoking reduction is typically continued for longer periods. NRT has also been used long-term and may be of particular benefit in those patients who feel they would relapse if NRT was stopped or in those who have persistent withdrawal symptoms.

There has been concern over the use of NRT in patients with cardiovascular disease (see Effects on the Cardiovascular System, above) but clinical experience and studies have shown that NRT can be used with caution in these patients. The use of NRT in those who have suffered a recent myocardial infarction or those with severe arrhythmias or unstable angina is, however, contraindicated as such patients have not been adequately studied.

A number of other drugs have also been used to achieve abstinence from smoking.[13-15] *Bupropion* is effective and recommended by some as a first-line alternative to NRT; its action is said to be independent of its antidepressant activity. Bupropion in combination with NRT has been used successfully. Evidence to support the use of most other antidepressants is lacking,[16] but *nortriptyline* appears to be effective and is used as a second-line drug. A study[17] found, however, that there was no advantage in combining nortriptyline with NRT. *Clonidine* is also effective but adverse effects limit its usefulness.[15] Preliminary investigations suggest that *selegiline* and *mecamylamine* may be effective.[13,15] The cannabinoid-1 receptor antagonist *rimonabant* has produced promising results in early studies,[13,14] although a systematic review[18] of 3 randomised controlled studies found the evidence to be inconclusive. A systematic review[19] of studies on the use of the oral nicotine receptor partial agonists *varenicline* and *cytisine* concluded that both drugs have a potential place in smoking cessation. Varenicline compared favourably with placebo and bupropion in helping smokers to quit, but its efficacy in preventing relapse still remains to be fully established. Like bupropion, varenicline is recommended by some as a first-line alternative to NRT. Cytisine is widely used in central and eastern Europe but the current evidence for efficacy is limited and better designed studies are required to test earlier findings. There is little or no evidence to support the efficacy of other treatments such as *silver acetate*, *lobeline*, or *anxiolytics* such as *buspirone*, and their use is not recommended. A *vaccine* for the prevention of smoking relapse is under investigation.[13,14]

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Spasticity. There have been anecdotal reports[1] of beneficial responses to nicotine in spastic dystonia.

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Tics. Tourette's syndrome (see Tics, p.954) is characterised by motor and vocal tics and behavioural disturbances. Nicotine[1-5] has been reported to be of benefit when used alone or with the more usual treatment of haloperidol in patients with Tourette's syndrome whose symptoms were not satisfactorily controlled with haloperidol alone. It is hoped that the use of transdermal nicotine patches will avoid the reported problems of compliance associated with the taste and gastrointestinal effects of nicotine gum.

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Ulcerative colitis. Investigation of the use of nicotine in ulcerative colitis (see Inflammatory Bowel Disease, p.1697) has been prompted by the observation that this condition is rare in smokers.[1] A systematic review[2] found that transdermal nicotine was more effective than placebo in producing remission in patients with active ulcerative colitis, but appeared to be no more effective than standard therapy with a corticosteroid or aminosalicylate, and was associated with more adverse effects. It appears to be ineffective in maintaining disease remission.[3] Any role is likely to be limited to patients who do not respond to standard therapy and who can tolerate the adverse effects.[2] Local delivery to the colon, in the form of enemas[4-6] and oral modified-release capsules,[7] is under investigation as a means of reducing the adverse effects of nicotine.

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Preparations

USP 31: Nicotine Polacrilex Gum; Nicotine Transdermal System.

Proprietary Preparations (details are given in Part 3)

Arg.: Nicorette; Nicotinell TTS; ***Austral.:*** Nicabate; Nicorette; Nicotinell; QuitX; ***Austria:*** Nicorette; Nicotinell; Nicotrol; ***Belg.:*** Nicorette; Nicotinell; NiQuitin; ***Braz.:*** Nicorette; Nicotinell TTS; NiQuitin; ***Canad.:*** Habitrol; Nicoderm; Nicorette; Nicotrol; Prostep; ***Chile:*** Nicorette; Nicotinell; ***Cz.:*** Nicopass; Nicopatch; Nicorette; Nicotinell; NiQuitin; ***Denm.:*** Nicorette; Nicotinell; NiQuitin†; ***Fin.:*** Nicorette; Nicotinell; ***Fr.:*** Nicogum; Nicopass; Nicopatch; Nicorette; Nicotinell; NiQuitin; ***Ger.:*** Nicorette; Nicotinell; nikofrenon; NiQuitin; ***Gr.:*** Nicopass; Nicorette; Nicotinell; ***Hong Kong:*** Nicorette; Nicotinell; ***Hung.:*** Nicopass; Nicorette; Nicotinell; NiQuitin; ***India:*** Nicotinell TTS†; ***Irl.:*** Nicorette; Nicotinell; NiQuitin; ***Israel:*** Nicorette; Nicotinell; NiQuitin; ***Ital.:*** Nicorette; Nicotinell; NiQuitin; ***Malaysia:*** Nicorette; Nicotinell; ***Mex.:*** Nicorette; Nicotinell TTS†; NiQuitin; ***Neth.:*** Nicorette; Nicotinell; NiQuitin; ***Norw.:*** Nicorette; Nicotinell; ***NZ:*** Habitrol; Nicabate; Nicorette; Nicotinell; Nicotrol; ***Pol.:*** Nicorette; Nicotinell; NiQuitin; ***Port.:*** Nicopass; Nicopatch; Nicorette; Nicotinell TTS; NiQuitin; ***Rus.:*** Nicorette (Никоретте); ***S.Afr.:*** Nicorette; Quit; ***Singapore:*** Nicorette; Nicotinell; ***Spain:*** Nicomax; Nicorette; Nicotinell; Nicotrol†; NiQuitin; ***Swed.:*** Nicorette; Nicotinell; Nikotugg; NiQuitin; ***Switz.:*** Nicorette; Nicotinell; ***Thai.:*** Nicorette; Nicotinell; ***Turk.:*** Nicotinell; ***UK:*** Nicopass; Nicopatch; Nicorette; Nicotinell; NiQuitin; ***USA:*** Commit; Habitrol; Nicoderm; Nicorette; Nicotrol; Prostep; ***Venez.:*** Nicorette†.

Nitisinone *(USAN, rINN)*

Nitisinonum; NTBC; SC-0735. 2-(α,α,α-Trifluoro-2-nitro-*p*-toluoyl)-1,3-cyclohexanedione.

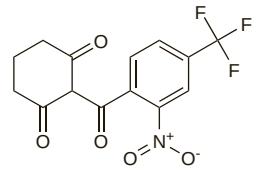
Нитизинон

$C_{14}H_{10}F_3NO_5$ = 329.2.

CAS — 104206-65-7.

ATC — A16AX04.

ATC Vet — QA16AX04.



Profile

Nitisinone is a 4-hydroxyphenylpyruvate dioxygenase inhibitor used in the management of hereditary tyrosinaemia type 1; dietary restriction of tyrosine and phenylalanine is also necessary. An initial daily dose of 1 mg/kg given orally is recommended; daily dosage should be given in 2 divided doses, which may be unequally split. Monitoring of urine succinylacetone and plasma alpha-fetoprotein, as well as liver function tests, must be carried out. If necessary, the daily dose may be increased to 1.5 mg/kg after one month; the maximum daily dose is 2 mg/kg. If satisfactory results are obtained from biochemical testing, doses should only be increased in line with body-weight gain.

Adverse effects have included granulocytopenia, leucopenia, and thrombocytopenia; regular monitoring of platelet and white cell counts is recommended. Eye disorders may occur due to increases in plasma tyrosine; they include conjunctivitis, corneal opacity, keratitis, photophobia, and eye pain. Slit-lamp examination of the eyes is recommended before starting treatment; patients developing visual disturbances during treatment should be referred to an ophthalmologist immediately, and further dietary restrictions implemented if plasma tyrosine is too high. Although it is not known if nitisinone is excreted into human milk, breast feeding is contra-indicated because of the potential effects on a suckling child.

Nitisinone is under investigation for the treatment of alkaptonuria, another hereditary metabolic disorder.

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