disorders—see Effects on the Nervous System: Extrapyramidal Effects under Adverse Effects, above.

Carbamazepine has also been used in resistant cases of *tardive dyskinesia* (see under Extrapyramidal Disorders, p.971).

Although not licensed in the UK for movement disorders in children, the *BNFC* suggests that carbamazepine may be tried in disorders such as *paroxysmal kinesigenic choreoathetosis* in doses similar to those used for the treatment of epilepsy (see Administration in Children, above).

1. Roig M, *et al.* Carbamazepine: an alternative drug for the treatment of nonhereditary chorea. *Pediatrics* 1988; **82:** 492–5.
2. García González MM, *et al.* Corea de Sydenham: presentación de un caso tratado con carbamazepina con excelente respuesta clínica. *An Pediatr (Barc)* 2007; **66:** 80–3.
3. Roulet E, Deonna T. Successful treatment of hereditary dominant chorea with carbamazepine. *Pediatrics* 1989; **83:** 1077.
4. Anonymous. Dystonia: underdiagnosed and undertreated? *Drug Ther Bull* 1988; **26:** 33–6.

Neonatal seizures. Carbamazepine has been tried in the management of neonatal seizures (p.471).

Neuropathic pain. As well as being used to ease the pain of trigeminal neuralgia (see below) carbamazepine may be of use in other neuropathic pain including that associated with diabetic neuropathy (p.6). A systematic review[1] concluded that about two-fifths of patients who take carbamazepine for neuropathic pain will achieve moderate pain relief, but this was based on small studies. The authors found no evidence that carbamazepine was effective for acute pain.

Carbamazepine has also been tried in an attempt to prevent the painful sensory neuropathy associated with oxaliplatin treatment (p.758); results of preliminary studies have been conflicting.[2,3]

Although not licensed in the UK for neuropathic pain in children, the *BNFC* suggests that carbamazepine may be tried in doses similar to those used for the treatment of epilepsy (see Administration in Children, above).

1. Wiffen PJ, *et al.* Carbamazepine for acute and chronic pain. Available in the Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2005 (accessed 09/06/08).
2. Eckel F, *et al.* Prophylaxe der Oxaliplatin-induzierten Neuropathie mit Carbamazepin: eine Pilotstudie. *Dtsch Med Wochenschr* 2002; **127:** 78–82.
3. Wilson RH, *et al.* Acute oxaliplatin-induced peripheral nerve hyperexcitability. *J Clin Oncol* 2002; **20:** 1767–74.

Nocturnal enuresis. Carbamazepine has been reported to be of benefit in the treatment of primary nocturnal enuresis; a dose of 200 mg at night for 15 nights markedly decreased the frequency of bed-wetting episodes in 8 children.[1]

For the conventional management of nocturnal enuresis see p.2180.

1. Al-Waili NS, *et al.* Effect of carbamazepine on urinary volume and osmolality, water clearance, and serum osmolality in patients with primary enuresis. *Eur Urol* 2006; **50:** 844–9.

Psychiatric disorders. Carbamazepine has psychotropic properties and has been tried in the management of several psychiatric disorders, particularly in patients with *bipolar disorder* (see above). Carbamazepine has also been used with mixed results in various disorders for the control of symptoms such as agitation, aggression, and rage[1-4] (see Disturbed Behaviour, p.954). It may produce modest benefit when used as an adjunct to antipsychotics in the management of refractory *schizophrenia* (p.955) but any improvement appears to be related to its mood stabilising effect.[5] However, a more recent systematic review,[6] albeit based on small studies, found carbamazepine to have no significant benefit either as monotherapy or as an adjunct to antipsychotics; the authors considered that further randomised studies may be warranted. Carbamazepine also has the potential to reduce serum concentrations of antipsychotics, resulting in clinical deterioration (see under Interactions for Chlorpromazine, p.974). Carbamazepine has also been tried[7] in *post-traumatic stress disorder* (p.953).

1. Mattes JA. Comparative effectiveness of carbamazepine and propranolol for rage outbursts. *J Neuropsychiatr Clin Neurosci* 1990; **2:** 159–64.
2. Gleason RP, Schneider LS. Carbamazepine treatment of agitation in Alzheimer's outpatients refractory to neuroleptics. *J Clin Psychiatry* 1990; **51:** 115–18.
3. Tariot PN, *et al.* Efficacy and tolerability of carbamazepine for agitation and aggression in dementia. *Am J Psychiatry* 1998; **155:** 54–61.
4. Cueva JE, *et al.* Carbamazepine in aggressive children with conduct disorder: a double-blind and placebo-controlled study. *J Am Acad Child Adolesc Psychiatry* 1996; **35:** 480–90.
5. Okuma T. Use of antiepileptic drugs in schizophrenia: a review of efficacy and tolerability. *CNS Drugs* 1994; **1:** 269–84.
6. Leucht S, *et al.* Carbamazepine for schizophrenia. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2007 (accessed 09/06/08).
7. Wolf ME, *et al.* Posttraumatic stress disorder in Vietnam veterans: clinical and EEG findings; possible therapeutic effects of carbamazepine. *Biol Psychiatry* 1988; **23:** 642–4.

Restless legs syndrome. The aetiology of restless legs syndrome (see Sleep-associated Movement Disorders, p.958) is obscure and treatment has been largely empirical. In a double-blind study involving 174 patients carbamazepine appeared to be more effective than placebo.[1] Oxcarbazepine has been reported[2] to be of benefit in restless legs syndrome induced by paroxetine.

1. Telstad W, *et al.* Treatment of the restless legs syndrome with carbamazepine: a double blind study. *BMJ* 1984; **288:** 444–6.
2. Öztürk Ö, *et al.* Oxcarbazepine treatment for paroxetine-induced restless leg syndrome. *Gen Hosp Psychiatry* 2006; **28:** 264–5.

Tinnitus. Treatment of tinnitus (p.1866) is difficult, and many drugs have been tried. Although carbamazepine has been reported to be effective in some patients, it is rarely used because of its adverse effects.

Trigeminal neuralgia. Carbamazepine is the drug of choice in the treatment of the acute stages of trigeminal neuralgia (p.9). Satisfactory pain relief may be achieved in 70% or more of patients, although increasingly larger doses may be required and adverse effects can be troublesome.

Withdrawal syndromes. Carbamazepine has been tried in the prophylaxis and treatment of various withdrawal syndromes. Reduction in *cocaine use* associated with carbamazepine treatment was found in one short-term controlled study,[1] although a systematic review[2] of data from later studies concluded that there was no evidence to support the use of carbamazepine in the treatment of cocaine dependence (p.1860). It has been reported[3,4] to be of benefit in some patients during *benzodiazepine withdrawal* but such adjunct therapy is not usually indicated (see p.987). Carbamazepine has been shown[5,6] to be effective in the treatment of symptoms of the *alcohol withdrawal syndrome* (p.1626) but as there are limited data on its efficacy in preventing associated delirium tremens and seizures it is usually recommended that it should only be used as an adjunct to benzodiazepine therapy. Carbamazepine has also been studied[7] as an aid in the treatment of alcohol dependence.

1. Halikas JA, *et al.* Cocaine reduction in unmotivated crack users using carbamazepine versus placebo in a short-term, double-blind crossover design. *Clin Pharmacol Ther* 1991; **50:** 81–95.
2. Lima Reisser A, *et al.* Carbamazepine for cocaine dependence. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2002 (accessed 01/09/08).
3. Schweizer E, *et al.* Carbamazepine treatment in patients discontinuing long-term benzodiazepine therapy: effects on withdrawal severity and outcome. *Arch Gen Psychiatry* 1991; **48:** 448–52.
4. Klein E, *et al.* Alprazolam withdrawal in patients with panic disorder and generalized anxiety disorder: vulnerability and effect of carbamazepine. *Am J Psychiatry* 1994; **151:** 1760–6.
5. Malcolm R, *et al.* Double-blind controlled trial comparing carbamazepine to oxazepam treatment of alcohol withdrawal. *Am J Psychiatry* 1989; **146:** 617–21.
6. Stuppaeck CH, *et al.* Carbamazepine versus oxazepam in the treatment of alcohol withdrawal: a double-blind study. *Alcohol Alcohol* 1992; **27:** 153–8.
7. Mueller TI, *et al.* A double-blind, placebo-controlled pilot study of carbamazepine for the treatment of alcohol dependence. *Alcohol Clin Exp Res* 1997; **21:** 86–92.

Preparations

BP 2008: Carbamazepine Tablets;
USP 31: Carbamazepine Extended-Release Tablets; Carbamazepine Oral Suspension; Carbamazepine Tablets.

Proprietary Preparations (details are given in Part 3)

Arg.: Actinerval; Carbagramon; Carbamat; CMP†; Conformal; Elebe; Tegretol; ***Austral.:*** Tegretol; Teril; ***Austria:*** Deleptin; Neurotop; Sirtal; Tegretol; ***Belg.:*** Tegretol; ***Braz.:*** Carmazin; Convulsan; Tegretard; Tegretol; Tegrex; Tegrezin; Uni Carbamaz; ***Canad.:*** Novo-Carbamaz; Tegretol; ***Chile:*** Carbactol Retard†; Eposal; Tegretal; ***Cz.:*** Biston; Neurotop; Tegretol; Timonil; ***Denm.:*** Nordotol†; Tegretol; Trimonil; ***Fin.:*** Neurotol; Tegretol; ***Fr.:*** Tegretol; ***Ger.:*** Carba; Carbabeta; Carbadura; Carbaflux; Carbagamma; Carbium†; espa-lepsin; Finlepsin; Fokalepsin; Sirtal; Tegretal; Timonil; ***Gr.:*** Tegretol; ***Hong Kong:*** Carzepin; CP-Carba; Tegretol; Teril; ***Hung.:*** Azepal†; Finlepsin†; Neurotop; Stazepine; Tegretol; Timonil; ***India:*** Carbacontin; Cizetol; Mazetol; Tegrital; ***Indon.:*** Bamgetol; Tegretol; Teril; ***Irl.:*** Gericarb; Tegretol; Temporol†; ***Israel:*** Carbi; Tegretol; Teril; Timonil; ***Ital.:*** Tegretol; ***Malaysia:*** Taver; Tegretol; ***Mex.:*** Adepril†; Apobace†; Bioneuril; Bioreuni†; Carbalan; Carbasal; Carbaval; Carbazep; Carbazina; Carpin; Clostedal; Dateril; Neugeron; Neurolep; Sepibest; Tegretol; Trepina; Ultrepyl; Volutol†; Zepiken; ***Neth.:*** Tegretol; ***Norw.:*** Tegretol; Trimonil; ***NZ:*** Tegretol; Teril; ***Philipp.:*** Carbilepp; Epazin; Epikor; Tegretol; ***Pol.:*** Amizepin; Finlepsin; Neurotop; Tegretol; Timonil; ***Port.:*** Tegretol; ***Rus.:*** Carbalepsin (Карбалепсин); Carbapin (Карбапин); Finlepsin (Финлепсин); Tegretol (Тегретол); Zeptol (Зептол); ***S.Afr.:*** Degranol; Tegretol; ***Singapore:*** Carbatol; Neurotop; Tegretol; ***Spain:*** Tegretol; ***Swed.:*** Hermolepsin; Tegretol; Trimonil; ***Switz.:*** Carsol; Neurotop; Tegretol; Timonil; ***Thai.:*** Antafit; Carbatol†; Carbazene; Carmapine; Carpine; Carzepine; Mapezine; Panitol; Taver; Tegretol; Zeptol; ***Turk.:*** Karazepin; Karbalex; Karbasif; Karberol; Kazepin; Tegretol; ***UAE:*** Fitzecalm; ***UK:*** Arbil; Carbagen; Epimaz; Tegretol; Teril†; Timonil†; ***USA:*** Atretol†; Carbatrol; Epitol; Equetro; Tegretol; Teril; ***Venez.:*** Convulex; Gabox†; Tanfedin; Tegretol.

Clobazam *(BAN, USAN, rINN)*

Clobazamum; H-4723; HR-376; Klobatsaami; Klobazam; Klobazamas; LM-2717. 7-Chloro-1,5-dihydro-1-methyl-5-phenyl-1,5-benzodiazepine-2,4(3*H*)-dione.

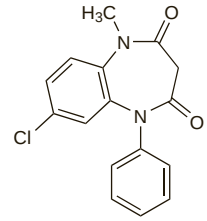
Клобазам

$C_{16}H_{13}ClN_2O_2$ = 300.7.

CAS — 22316-47-8.

ATC — N05BA09.

ATC Vet — QN05BA09.



Pharmacopoeias. In *Eur.* (see p.vii).
Ph. Eur. 6.2 (Clobazam). A white or almost white crystalline powder. Slightly soluble in water; sparingly soluble in alcohol; freely soluble in dichloromethane.

Dependence and Withdrawal

As for Diazepam, p.987.

Adverse Effects, Treatment, and Precautions

As for Diazepam, p.987.

Breast feeding. Benzodiazepines, such as clobazam, given to the mother may cause neonatal sedation and breast feeding should be avoided. For comments on antiepileptic therapy and breast feeding, see p.467.

Driving. For a comment on antiepileptic drugs and driving, see p.468.

Effects on menstruation. Occasionally the use of clobazam before menstruation for catamenial epilepsy appeared to delay the period.[1]

1. Feely M. Prescribing anticonvulsant drugs 3: clonazepam and clobazam. *Prescribers' J* 1989; **29:** 111–15.

Effects on mental function. For a review of the effects of antiepileptic therapy, including clobazam, on *cognition* and *mood*, including risk of suicidal ideation, see p.468.

Effects on the skin. Report[1] of toxic epidermal necrolysis that developed in light-exposed areas in a patient being treated with clobazam.

1. Redondo P, *et al.* Photo-induced toxic epidermal necrolysis caused by clobazam. *Br J Dermatol* 1996; **135:** 999–1002.

Porphyria. Clobazam is considered to be unsafe in patients with porphyria although there is conflicting evidence of porphyrinogenicity.

For comments on the use of benzodiazepines in porphyria, see p.471.

Pregnancy. For comments on the management of epilepsy during pregnancy, see p.468.

Interactions

As for Diazepam, p.989.

Antiepileptics. For reference to the interactions of clobazam with *felbamate* and *stiripentol*, see under Diazepam, p.990.

Pharmacokinetics

Clobazam is well absorbed from the gastrointestinal tract and peak plasma concentrations are reached 1 to 4 hours after oral doses. It is about 85% bound to plasma proteins. Clobazam is highly lipophilic and rapidly crosses the blood-brain barrier. It is metabolised in the liver by demethylation and hydroxylation but unlike the 1,4-benzodiazepines such as diazepam, clobazam, a 1,5-benzodiazepine, is hydroxylated at the 4-position rather than the 3-position (see also Metabolism under Diazepam, p.992). Clobazam is excreted unchanged and as metabolites mainly in the urine. Mean half-lives of 18 hours and 42 hours have been reported for clobazam and its main active metabolite *N*-desmethylclobazam, respectively.

◊ References.

1. Greenblatt DJ, *et al.* Clinical pharmacokinetics of the newer benzodiazepines. *Clin Pharmacokinet* 1983; **8:** 233–52.
2. Ochs HR, *et al.* Single and multiple dose kinetics of clobazam, and clinical effects during multiple dosage. *Eur J Clin Pharmacol* 1984; **26:** 499–503.

Uses and Administration

Clobazam is a long-acting 1,5-benzodiazepine with uses similar to those of diazepam (a 1,4-benzodiazepine; see p.992). It may be used as an adjunct in the treatment of epilepsy with other antiepileptics, although its use may be limited by the development of

tolerance or sedation (but see below). It is also used in the short-term treatment of acute anxiety.

As an adjunct in **epilepsy** usual oral doses in the UK are 20 to 30 mg daily, increased if necessary to a maximum of 60 mg daily.

For doses in children, see below.

As with other antiepileptics, withdrawal of clobazam therapy or transition to or from another type of antiepileptic therapy should be made gradually to avoid precipitating an increase in the frequency of seizures. For a discussion on whether or not to withdraw antiepileptic therapy in seizure-free patients, see p.465 and under Clonazepam, below.

For the short-term management of acute **anxiety** usual oral doses of 10 to 30 mg daily may be taken in divided doses or as a single dose at night; up to 80 mg daily has been used in hospitalised patients with severe anxiety states. Low initial doses and cautious increments to a usual daily dose of 10 to 20 mg are recommended in elderly or debilitated patients.

Administration in children. In the UK, clobazam is licensed for use as an adjunct in epilepsy in children over 3 years of age; no more than half the adult dose (see above) should be given. Alternatively, the *BNFC* suggests the following oral doses according to age:

- 1 month to 12 years: initially 125 micrograms/kg twice daily, increased every 5 days to a usual maintenance dose of 250 micrograms/kg twice daily. The maximum dose is 500 micrograms/kg twice daily and should not exceed 15 mg twice daily
- 12 to 18 years: initially 10 mg twice daily, increased every 5 days to a usual maintenance dose of 10 to 15 mg twice daily. The dose should not exceed 30 mg twice daily

The *BNFC* also suggests that clobazam may be given for cluster seizures and as monotherapy under specialist supervision for catamenial seizures (usually for 7 to 10 days each month just before and during menstruation).

Epilepsy. Benzodiazepines are sometimes used in the management of epilepsy (p.465), but their long-term use is limited by problems of sedation, dependence, and tolerance to the antiepileptic effects.

Clobazam, a 1,5-benzodiazepine, is considered to be somewhat better tolerated than conventional benzodiazepines, and has been widely used for adjunctive oral therapy in patients with epilepsy.[1,2] Clobazam is active against partial and generalised seizures in epilepsy of widely differing aetiology in patients of all ages and has also been used for short-term cover in patients with intermittent seizures, including in women with catamenial epilepsy (seizures associated with menstruation) or patients whose epileptic attacks occur in clusters. Clobazam has also been tried with some success in children, including those with refractory epilepsy[3-5] and epileptic encephalopathy.[6] However, a recent systematic review[7] concluded that although clobazam may reduce seizure frequency and may be most effective in partial onset seizures, it was not clear who would best benefit from its use and over what time-frame.

1. Trimble MR. On the use of tranquillisers in epilepsy. *Epilepsia* 2002; **43** (suppl 2): 25–7.
2. Ng Y-T, Collins SD. Clobazam. *Neurotherapeutics* 2007; **4:** 138–44.
3. Munn R, Farrell K. Open study of clobazam in refractory epilepsy. *Pediatr Neurol* 1993; **9:** 465–9.
4. Sheth RD, *et al.* Clobazam for intractable pediatric epilepsy. *J Child Neurol* 1995; **10:** 205–8.
5. Canadian Study Group for Childhood Epilepsy. Clobazam has equivalent efficacy to carbamazepine and phenytoin as monotherapy for childhood epilepsy. *Epilepsia* 1998; **39:** 952–9.
6. Silva RC, *et al.* Clobazam as add-on therapy in children with epileptic encephalopathy. *Can J Neurol Sci* 2006; **33:** 209–13.
7. Michael B, Marson AG. Clobazam as an add-on in the management of refractory epilepsy. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2008 (accessed 16/06/08).

Neuropathic pain. There has been a mention[1] of the complete relief of *phantom limb pain* (p.9) refractory to other therapy in an elderly patient given clobazam 10 mg three times daily.

1. Rice-Oxley CP. The limited list: clobazam for phantom limb pain. *BMJ* 1986; **293:** 1309.

Preparations

BP 2008: Clobazam Capsules.

Proprietary Preparations (details are given in Part 3)
Arg.: Karidium; ***Austral.:*** Frisium; ***Austria:*** Frisium; ***Belg.:*** Frisium; ***Braz.:*** Frisium; Urbanil; ***Canad.:*** Frisium; ***Chile:*** Frisin†; Grifoclobam; ***Cz.:*** Frisium; ***Denm.:*** Frisium; ***Fin.:*** Frisium; ***Fr.:*** Urbanyl; ***Ger.:*** Frisium; ***Gr.:*** Frisium; ***Hong Kong:*** Frisium; ***Hung.:*** Frisium; ***India:*** Frisium; ***Indon.:*** Asabium; Clobium; Frisium; Proclozam; ***Irl.:*** Frisium; ***Israel:*** Frisium; ***Ital.:*** Frisium; ***Malaysia:*** Frisium; ***Mex.:*** Frisium; ***Neth.:*** Frisium; ***NZ:*** Frisium; ***Pol.:*** Frisium; ***Port.:*** Castilium; Urbanil†; ***S.Afr.:*** Urbanol; ***Singapore:*** Frisium†; ***Spain:*** Noiafren; ***Switz.:*** Urbanyl; ***Thai.:*** Frisium; ***UK:*** Frisium; ***Venez.:*** Frisium.

Clonazepam *(BAN, USAN, rINN)*

Clonazépam; Clonazepamum; Klonatsepaami; Klonazepám; Klonazepam; Klonazepamas; Ro-5-4023. 5-(2-Chlorophenyl)-1,3-dihydro-7-nitro-1,4-benzodiazepin-2-one.

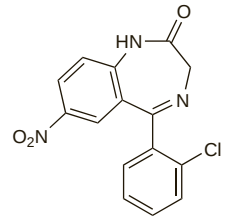
Клоназепам

$C_{15}H_{10}ClN_3O_3$ = 315.7.

CAS — 1622-61-3.

ATC — N03AE01.

ATC Vet — QN03AE01.



NOTE. The following terms have been used as 'street names' (see p.vi) or slang names for various forms of clonazepam:
K-Pins; Klondike Bars; Klonnies; Klons; La Roche; Pins; R2; R-2; Roaches; Roachies; Roche.

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

Ph. Eur. 6.2 (Clonazepam). A slightly yellowish, crystalline powder. Practically insoluble in water; slightly soluble in alcohol and in methyl alcohol. Protect from light.

USP 31 (Clonazepam). A light yellow powder having a faint odour. Insoluble in water; slightly soluble in alcohol and in ether; sparingly soluble in acetone and in chloroform. Store in airtight containers. Protect from light.

Sorption. Significant loss of clonazepam (up to 50% over 24 hours) has been reported[1] from solutions infused through PVC tubing; the effect was concentration dependent. The authors recommended that non-PVC tubing should always be used.

1. Schneider JJ, *et al.* Effect of tubing on loss of clonazepam administered by continuous subcutaneous infusion. *J Pain Symptom Manage* 2006; **31:** 563–7.

Dependence and Withdrawal

As for Diazepam, p.987.

Withdrawal. A study[1] of the withdrawal of clonazepam therapy in 40 epileptic children found that 19 had withdrawal symptoms of increased seizure frequency, either alone or with other symptoms but that this effect was transient. Withdrawal seizures and status might become an obstacle to the removal of useless or even deleterious therapy with clonazepam because the transient nature of these effects was not always recognised. Clonazepam should not be used for more than 3 to 6 months and should be stopped if clear and lasting therapeutic benefit could not be shown.

See also Uses and Administration, below.

1. Specht U, *et al.* Discontinuation of clonazepam after long-term treatment. *Epilepsia* 1989; **30:** 458–63.

Adverse Effects, Treatment, and Precautions

As for Diazepam, p.987.

The principal adverse effect of clonazepam is drowsiness, which occurs in about 50% of all patients when starting therapy. Salivary or bronchial hypersecretion may cause respiratory problems in children. Thrombophlebitis has been associated with intravenous use and may be avoided by injection into a large vein at a rate not exceeding 500 micrograms/minute. Respiration and blood pressure should also be monitored.

Care is required when withdrawing clonazepam therapy—see above.

Breast feeding. Benzodiazepines, such as clonazepam, given to the mother may cause neonatal sedation and breast feeding should be avoided. For comments on antiepileptic therapy and breast feeding, see p.467.

Driving. For a comment on antiepileptic drugs and driving, see p.468.

Effects on the endocrine system. Precocious development of secondary sexual characteristics occurred in a 15-month-old girl 2 months after starting treatment with clonazepam 500 micrograms twice daily for convulsions.[1] Symptoms regressed upon withdrawal of clonazepam.

1. Choonara IA, *et al.* Clonazepam and sexual precocity. *N Engl J Med* 1985; **312:** 185.

Effects on mental function. For a review of the effects of antiepileptic therapy, including clonazepam, on *cognition* and mood, including the risk of suicidal ideation, see p.468.

Effects on the mouth. A 52-year-old woman developed burning mouth syndrome after starting clonazepam;[1] some improvement was noted when the dose was reduced but symptoms were still intolerable and clonazepam was withdrawn. Subsequently, symptoms resolved within 3 weeks.

1. Culhane NS, Hodle AD. Burning mouth syndrome after taking clonazepam. *Ann Pharmacother* 2001; **35:** 874–6.

Effects on sexual function. Sexual dysfunction was reported[1] in 18 of 42 male patients receiving clonazepam for the treatment of post-traumatic stress disorder; symptoms resolved when therapy was changed to diazepam in 17 patients and lorazepam in the remaining patient.

1. Fossey MD, Hamner MB. Clonazepam-related sexual dysfunction in male veterans with PTSD. *Anxiety* 1994-95; **1:** 233–6.

Extrapyramidal disorders. For reference to extrapyramidal disorders associated with the use of benzodiazepines including clonazepam, see Effects on the Nervous System in Diazepam, p.988. However, clonazepam is also used in the treatment of some extrapyramidal disorders as discussed under Uses and Administration, below.

Porphyria. Clonazepam is considered to be unsafe in patients with porphyria although there is conflicting evidence of porphyrinogenicity.

For comments on the use of benzodiazepines in porphyria, see p.471.

Pregnancy. For comments on the management of epilepsy during pregnancy, see p.468.

Interactions

As for Diazepam, p.989.

Antiepileptics. For reference to possible interactions between clonazepam and other antiepileptics, see under Diazepam, p.990 and Benzodiazepines under Interactions of Phenytoin, p.499.

Pharmacokinetics

Clonazepam is quickly absorbed after oral doses with a bioavailability of about 90%; peak plasma concentrations are reached between 1 and 4 hours after ingestion. It is extensively metabolised in the liver, its principal metabolite being 7-aminoclonazepam, which has no antiepileptic activity; minor metabolites are the 7-acetamido- and 3-hydroxy-derivatives. It is excreted mainly in the urine almost entirely as its metabolites in free or conjugated form. It is about 85% bound to plasma proteins and estimations of its elimination half-life range from about 20 to 40 hours, and occasionally more.

A therapeutic range of plasma concentrations has not been established.

Clonazepam crosses the placental barrier and is distributed into breast milk.

The pharmacokinetics of clonazepam may be affected by use with other antiepileptics (see under Interactions, above).

◊ A single-dose pharmacokinetic study[1] in healthy subjects found that absorption of clonazepam was slower and intersubject variability was greater after intramuscular injection than after an oral dose. The pharmacokinetics of a modified-release subcutaneous injection have also been studied in healthy subjects;[2] plasma-clonazepam concentrations were sustained and elimination occurred slowly over 13 days.

1. Crevoisier C, *et al.* Comparative single-dose pharmacokinetics of clonazepam following intravenous, intramuscular and oral administration to healthy volunteers. *Eur Neurol* 2003; **49:** 173–7.
2. Greenblatt DJ, *et al.* Clonazepam pharmacokinetics: comparison of subcutaneous microsphere injection with multiple-dose oral administration. *J Clin Pharmacol* 2005; **45:** 1288–93.

Bioavailability. It has been suggested, on the basis of anecdotal evidence,[1] that there may be differences in bioavailability, and hence in clinical effect, between formulations of clonazepam tablets.

1. Rapaport MH. Clinical differences between the generic and non-generic forms of clonazepam. *J Clin Psychopharmacol* 1997; **17:** 424.

Uses and Administration

Clonazepam is a benzodiazepine derivative similar to diazepam (p.992), with marked antiepileptic properties.

It may be used in the treatment of all types of epilepsy and seizures (p.465), including status epilepticus (p.469), but its usefulness in chronic treatment is sometimes limited by the development of tolerance and by sedation, and other antiepileptics are often preferred. It may also be used in myoclonus (p.470) and associated