(negative myoclonus). The term 'myoclonus' is non-specific and classification is important in order to decide on treatment:[1-4]

- physiological (in normal subjects)
- essential (no known cause)
- epileptic (seizures dominate)
- symptomatic (encephalopathy dominates—causes include storage diseases, neurodegenerative syndromes, toxic and drug-induced syndromes, and hypoxia)

In epileptic myoclonus, epileptic seizures (myoclonic seizures in which the motor manifestation is myoclonus) dominate. Their treatment is discussed under Epilepsy, above. Essential myoclonus may benefit from *clonazepam*. *Botulinum toxin* has been used successfully for spasmodic movements in some forms of myoclonus.

Myoclonus may also be subdivided into cortical, reticular, or spinal forms. Cortical myoclonus is considered to be a subset of epilepsy and responds best to antiepileptics, usually *valproate* and/or clonazepam; *piracetam* or *levetiracetam* are also used, usually as adjunctive therapy. Reticular myoclonus is usually caused by anoxia or acute encephalopathy and may be treated with clonazepam; *serotonin* or serotonergic agonists have also been tried. Post-hypoxic myoclonus occurring after hypoxic coma may respond to *oxitriptan* or serotonin combined with *carbidopa*; antiepileptics may help.

1. Caviness JN. Myoclonus. *Mayo Clin Proc*. 1996; **71:** 679–88.
2. Blindauer K. Myoclonus and its disorders. *Neurol Clin North Am* 2001; **19:** 723–34.
3. Agarwal P, Frucht SJ. Myoclonus. *Curr Opin Neurol* 2003; **16:** 515–21.
4. Caviness JN, Brown P. Myoclonus: current concepts and recent advances. *Lancet Neurol* 2004; **3:** 598–607.

Neonatal seizures. Neonatal seizures differ from epilepsy, and the definitions in the 1989 international classification of epilepsy and epileptic syndromes (see above) may be of little value; (a study[1] has suggested that the proposed 2001 classification may be more helpful). They are frequently subtle and difficult to recognise.[2] Causes include asphyxia, glucose or electrolyte imbalance, infection, CNS or cerebrovascular lesions, inborn errors of metabolism, and drug withdrawal or intoxication.[3-5]

Neonatal seizures represent a neurological emergency in the newborn and rapid diagnosis and treatment is essential.[3-7] Infusion of glucose or electrolytes may be of benefit.[4,5] Current practice involves giving antiepileptic drugs to control seizures, although there is no consensus on, nor good evidence for, their use.[2,7] *Phenobarbital* and *phenytoin* are the most widely used.[3-6] Traditionally, phenobarbital has been considered to be the mainstay of treatment for all types of seizures in neonates; however response rates are variable.[6-8] If seizures persist, phenytoin may be added to therapy.[8] Other drugs that have been tried include *carbamazepine*, *levetiracetam*,[9] *benzodiazepines*,[3-5,8,10,11] *lidocaine*,[3,8,10] and *primidone*.[4,5] Pyridoxine-dependent seizures can be abolished by regular large doses of the vitamin[4,5] (see p.1979).

1. Mastrangelo M, *et al.* Epileptic seizures, epilepsy and epileptic syndromes in newborns: a nosological approach to 94 new cases by the 2001 proposed diagnostic scheme for people with epileptic seizures and with epilepsy. *Seizure* 2005; **14:** 304–11.
2. Rennie J, Boylan G. Treatment of neonatal seizures. *Arch Dis Child Fetal Neonatal Ed* 2007; **92:** F148–F150.
3. Evans D, Levene M. Neonatal seizures. *Arch Dis Child Fetal Neonatal Ed* 1998; **78:** F70–F75.
4. Hill A. Neonatal seizures. *Pediatr Rev* 2000; **21:** 117–21.
5. Painter MJ, Alvin J. Neonatal seizures. *Curr Treat Options Neurol* 2001; **3:** 237–48.
6. Painter MJ, *et al.* Phenobarbital compared with phenytoin for the treatment of neonatal seizures. *N Engl J Med* 1999; **341:** 485–9.
7. Booth D, Evans DJ. Anticonvulsants for neonates with seizures. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2004 (accessed 09/06/08).
8. Boylan GB, *et al.* Second-line anticonvulsant treatment of neonatal seizures: a video-EEG monitoring study. *Neurology* 2004; **62:** 486–8.
9. Shoemaker MT, Rotenberg JS. Levetiracetam for the treatment of neonatal seizures. *J Child Neurol* 2007; **22:** 95–8.
10. Shany E, *et al.* Comparison of continuous drip of midazolam or lidocaine in the treatment of intractable neonatal seizures. *J Child Neurol* 2007; **22:** 255–9.
11. Castro Conde JR, *et al.* Midazolam in neonatal seizures with no response to phenobarbital. *Neurology* 2005; **64:** 876–9.

Porphyria. Convulsions may occur at the peak of an attack of acute porphyria (p.1448) but usually disappear as the attack resolves and therapy should be aimed at the underlying disease. However, some patients continue to have convulsions while in remission and their management poses a major therapeutic problem as all the first-line antiepileptics have been associated with acute attacks.[1,2] Barbiturates (*phenobarbital*, *primidone*), hydantoins *(phenytoin, ethotoin)*, and *carbamazepine* are considered unsafe, as is *sultiame*. There is limited evidence that the *benzodiazepines, sodium valproate*, and probably *valpromide* are porphyrinogenic but status epilepticus has been treated successfully with intravenous *diazepam*. Seizure prophylaxis may be undertaken as a calculated risk using valproate or *clonazepam* if considered essential. *Magnesium sulfate* is safe. *Clomethiazole* is also probably safe. *Gabapentin* and *vigabatrin* have each been tried in a few patients without ill-effect, although there has been a report of a bullous skin eruption in a patient with porphyria cutanea tarda given vigabatrin.[3] Of the other newer antiepileptics, *oxcarbazepine* was used successfully in one patient whilst *lamotrigine* was associated with an acute porphyric attack in another; *tiagabine* and *topiramate* have been found to increase hepatic and urinary porphobilinogen concentrations.[2] Other antiepileptics such as the succinimides *(ethosuximide, mesuximide, phensuximide)* and oxazolidinediones *(trimethadione)* are considered to be unsafe.

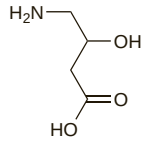
1. Gorchein A. Drug treatment in acute porphyria. *Br J Clin Pharmacol* 1997; **44:** 427–34.
2. Solinas C, Vajda FJ. Epilepsy and porphyria: new perspectives. *J Clin Neurosci* 2004; **11:** 356–61.
3. Hommel L, *et al.* Acute bullous skin eruption after treatment with vigabatrine. *Dermatology* 1995; **191:** 181.

4-Amino-3-hydroxybutyric Acid

Ácido 4-amino-3-hidroxibutírico; γ-Amino-β-hydroxybutyric acid; Buxamin; Gabob; Gamma-amino-beta-hydroxybutyric acid.

4-Амино-3-оксимасляная Кислота

$C_4H_9NO_3$ = 119.1.
CAS — 352-21-6.



Profile

Aminohydroxybutyric acid has been claimed to be of value in a variety of neurological disorders including use as an adjunct in the treatment of epilepsy. It has also been promoted as a dietary supplement for its supposed beneficial effects on the CNS and growth hormone. It should be distinguished from its isomer 3-amino-4-hydroxybutyric acid (GOBAB), which is reported to possess anti-inflammatory and antifungal activity.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Gabimex; ***Braz.:*** Gamibetal†; ***Ital.:*** Gamibetal; ***Mex.:*** Gamibetal; ***Port.:*** Gabomade; Gamibetal†.

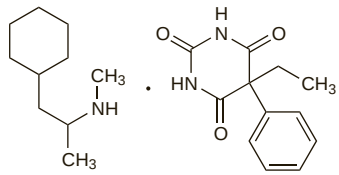
Multi-ingredient: ***Arg.:*** Gabimex Plus; ***Braz.:*** Gamibetal Complex†; ***Ital.:*** Gamibetal Complex; Gamibetal Plus; Parvisedil; ***Mex.:*** Gamibetal Complex; ***Port.:*** Gabisedil†; Gamibetal Compositum†; ***Spain:*** Cefabol; Dorken; Gamalate B6; Redutona.

Barbexaclone *(rINN)*

Barbeksaklon; Barbexaclona; Barbexaclonum. Compound of (–)-*N*,α-Dimethylcyclohexaneethylamine with 5-ethyl-5-phenylbarbituric acid .

Барбексаклон

$C_{12}H_{12}N_2O_3$,$C_{10}H_{21}N$ = 387.5.
CAS — 4388-82-3.
ATC — N03AA04.
ATC Vet — QN03AA04.



Profile

Barbexaclone is a compound of levopropylhexedrine (see under Propylhexedrine, p.2163) with phenobarbital (p.492). It is used in the treatment of various types of epilepsy (p.465). Usual adult doses are 200 to 400 mg daily given by mouth in divided doses.

Preparations

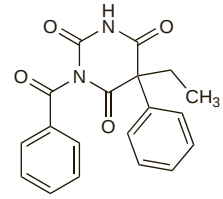
Proprietary Preparations (details are given in Part 3)
Austria: Maliasin; ***Braz.:*** Maliasin; ***Gr.:*** Maliasin; ***Ital.:*** Maliasin; ***Switz.:*** Maliasin; ***Turk.:*** Maliasin.

Benzobarbital *(rINN)*

Benzobarbitalum; Benzobarbitone; Benzonal; Benzonalum. 1-Benzoyl-5-ethyl-5-phenylbarbituric acid.

Бензобарбитал

$C_{19}H_{16}N_2O_4$ = 336.3.
CAS — 744-80-9.



NOTE. The name benzonal has also been used as a proprietary name for benzonatate (p.1552).

Pharmacopoeias. In *Int.*

Profile

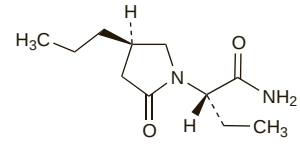
Benzobarbital is a barbiturate used in the treatment of epilepsy.

Brivaracetam *(USAN, rINN)*

Brivaracétam; Brivaracetamum; UCB-34714. (2*S*)-2-[(4*R*)-2-Oxo-4-propylpyrrolidin-1-yl]butanamide.

Бриварацетам

$C_{11}H_{20}N_2O_2$ = 212.3.
CAS — 357336-20-0.



Profile

Brivaracetam is under investigation for the treatment of various types of epilepsy including progressive myoclonic epilepsy and refractory partial seizures.

◊ References.

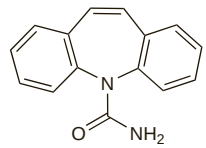
1. Sargentini-Maier ML, *et al.* The pharmacokinetics, CNS pharmacodynamics and adverse event profile of brivaracetam after single increasing oral doses in healthy males. *Br J Clin Pharmacol* 2007; **63:** 680–8.
2. Rolan P, *et al.* The pharmacokinetics, CNS pharmacodynamics and adverse event profile of brivaracetam after multiple increasing oral doses in healthy men. *Br J Clin Pharmacol* 2008; **66:** 71–5.
3. Malawska B, Kulig K. Brivaracetam: a new drug in development for epilepsy and neuropathic pain. *Expert Opin Invest Drugs* 2008; **17:** 361–9.

Carbamazepine *(BAN, USAN, rINN)*

Carbamazepina; Carbamazépine; Carbamazepinum; G-32883; Karbamatsepiini; Karbamazepin; Karbamazepinas; Karbamazepinum. 5*H*-Dibenz[*b,f*]azepine-5-carboxamide.

Карбамазепин

$C_{15}H_{12}N_2O$ = 236.3.
CAS — 298-46-4.
ATC — N03AF01.
ATC Vet — QN03AF01.



Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Int.*, *Jpn*, and *US*.
Ph. Eur. 6.2 (Carbamazepine). A white or almost white crystalline powder. It exhibits polymorphism. Very slightly soluble in water; sparingly soluble in alcohol and in acetone; freely soluble in dichloromethane. Store in airtight containers.
USP 31 (Carbamazepine). A white or off-white powder. Practically insoluble in water; soluble in alcohol and in acetone. Store in airtight containers.

Incompatibility. Carbamazepine suspension should be mixed with an equal volume of diluent before nasogastric use as undiluted suspension is adsorbed onto PVC nasogastric tubes.[1]

The FDA have received a report of a patient who passed an orange rubbery mass in his faeces the day after taking a carbamazepine suspension (*Tegretol*; *Novartis, USA*) followed immediately by chlorpromazine solution (*Thorazine*; *GSK, USA*). Subsequent testing showed that mixing the same carbamazepine suspension with a thioridazine hydrochloride solution (*Mellaril*; *Novartis, USA*) also resulted in the precipitation of a rubbery orange mass.

1. Clark-Schmidt AL, *et al.* Loss of carbamazepine suspension through nasogastric feeding tubes. *Am J Hosp Pharm* 1990; **47**: 2034–7.

Stability. FDA studies indicate that carbamazepine tablets could lose up to one-third of their effectiveness if stored in humid conditions.[1] This appears to be due to formation of a dihydrate form which leads to hardening of the tablet and poor dissolution and absorption.[2,3] As the dihydrate has also been detected after storage under ambient conditions some suggest that storage with silica gel sachets may be necessary to avoid physical deterioration of carbamazepine tablets.[2]

1. Anonymous. Moisture hardens carbamazepine tablets, FDA finds. *Am J Hosp Pharm* 1990; **47:** 958.
2. Lowes MMJ. More information on hardening of carbamazepine tablets. *Am J Hosp Pharm* 1991; **48:** 2130–1.
3. Wang JT, *et al.* Effects of humidity and temperature on in vitro dissolution of carbamazepine tablets. *J Pharm Sci* 1993; **82:** 1002–5.

Adverse Effects

Fairly common adverse effects of carbamazepine, particularly in the initial stages of therapy, include dizziness, drowsiness, and ataxia. Gastrointestinal disturbances, such as nausea and vomiting, and mild skin reactions are also common. These effects may be minimised by starting therapy with a low dose. Drowsiness and disturbances of cerebellar and oculo-motor function (with ataxia, nystagmus, and diplopia) are also symptoms of excessive plasma concentrations of carbamazepine, and may disappear spontaneously with continued treatment or at reduced or divided dosage.

Although rare, generalised erythematous rashes can be severe and treatment may have to be withdrawn. Photosensitivity reactions, urticaria, alopecia, exfoliative dermatitis, toxic epidermal necrolysis, erythema multiforme and Stevens-Johnson syndrome, and SLE (but see below) have also been reported.

Transient leucopenia is common and usually resolves with continued therapy; however, rarer blood disorders reported include agranulocytosis, aplastic anaemia, eosinophilia, persistent leucopenia, leucocytosis, thrombocytopenia, and purpura. Lymphadenopathy, splenomegaly, pneumonitis, abnormalities of liver and kidney function, hepatitis, and cholestatic jaundice have occurred. Some or all of these symptoms as well as fever and rashes may represent a generalised hypersensitivity reaction to carbamazepine.

Gastrointestinal symptoms reported to be less common include dry mouth, abdominal pain, anorexia, and diarrhoea or constipation. Hyponatraemia, and sometimes oedema, have occurred. Other adverse effects reported include paraesthesia, headache, arrhythmias and heart block, heart failure, impotence, male infertility, gynaecomastia, galactorrhoea, and dystonias and dyskinesias with asterixis. Rectal use has resulted in local irritation.

Overdosage may be manifested by many of the adverse effects listed above, especially those on the CNS, and may result in stupor, coma, convulsions, respiratory depression, and death.

In rare cases, carbamazepine has been reported to exacerbate seizures in patients suffering from mixed-type epilepsy—see Precautions, below.

Congenital malformations have been reported in infants born to women given carbamazepine during pregnancy.

Effects on the blood. Occasional reports of fatal haematological reactions associated with carbamazepine led the manufacturers to recommend extensive blood monitoring during therapy. However, because of the rarity of such reactions these recommendations were questioned and the manufacturers subsequently modified their guidelines (see Precautions, below).

Case reports and studies of carbamazepine's haematological effects have been reviewed.[1] The incidence of haematological reactions to carbamazepine has been estimated to range between 1:10 800 and 1:38 000 per year while one group reported the rate of bone marrow suppression to be between 1:10 000 and 1:50 000 cases. The incidence of aplastic anaemia has been calculated to be 1:200 000 per year. Another investigator indicated that 2.2 deaths per million exposures were associated with aplastic anaemia and agranulocytosis. However, of 27 reports of aplastic anaemia (16 fatal) associated with carbamazepine many were found to have had co-incidental disease or were receiving multiple-drug therapy. Benign or clinically insignificant leucopenia has occurred, usually during the first 3 months of treatment, in about 12% of children and 7% of adults but in most patients this resolved despite continuation of therapy. Mild transient thrombocytopenia has occurred in about 2% of patients; transient eosinophilia has also occurred.

The reviewers[1] suggested that all patients should have blood and platelet counts before treatment. Patients with low white cell and neutrophil counts were at risk of developing leucopenia and should be monitored every 2 weeks for the first 1 to 3 months. If counts fell further the dose should be reduced or treatment stopped. It should be noted that the *BNF* doubts the practical value of routine monitoring: in particular, aplastic anaemia, agranulocytosis, and thrombocytopenia have a rapid onset and are best monitored by instructing the patient to report warning symptoms (see Precautions, below).

For a discussion of the effects of antiepileptics, including carbamazepine, on serum folate, see Folic Acid Deficiency, under Phenytoin, p.495.

1. Sobotka JL, *et al.* A review of carbamazepine's hematologic reactions and monitoring recommendations. *DICP Ann Pharmacother* 1990; **24:** 1214–19.

Effects on bone. For the effects of antiepileptics including carbamazepine on bone and on calcium and vitamin D metabolism, see under Phenytoin, p.496.

Effects on electrolytes. There have been reports of *hyponatraemia* or *water intoxication* in patients receiving carbamazepine.[1-7] One review[8] states that although hyponatraemia occurs in 10 to 15% of patients taking carbamazepine, it is seldom symptomatic or severe enough to cause fluid retention. However, care should be taken to distinguish the confusion, dizziness, nausea and headache of water intoxication from the central and gastrointestinal effects of the drug.[2] The mechanism is uncertain; although some studies suggest an increase in secretion of antidiuretic hormone in subjects given carbamazepine,[3,4,6] others indicate the reverse,[5,9] and the fact that the hyponatraemic effects of carbamazepine can be partly reversed by demeclocycline[5] is cited as evidence for an effect on the kidney, either directly upon the distal tubule or by increasing sensitivity to the effects of antidiuretic hormone. Risk factors for developing carbamazepine-induced hyponatraemia include age of over 40 years, use of sodium-depleting drugs, and low pre-treatment plasma-sodium concentrations; it is unclear whether this adverse effect is dose-related.[7]

1. Henry DA, *et al.* Hyponatraemia during carbamazepine treatment. *BMJ* 1977; **1:** 83–4.
2. Stephens WP, *et al.* Water intoxication due to carbamazepine. *BMJ* 1977; **1:** 754–5.
3. Ashton MG, *et al.* Water intoxication associated with carbamazepine treatment. *BMJ* 1977; **1:** 1134–5.
4. Smith NJ, *et al.* Raised plasma arginine vasopressin concentration in carbamazepine-induced water intoxication. *BMJ* 1977; **2:** 804.
5. Ballardie FW, Mucklow JC. Partial reversal of carbamazepine-induced water intolerance by demeclocycline. *Br J Clin Pharmacol* 1984; **17:** 763–5.
6. Sørensen PS, Hammer M. Effects of long-term carbamazepine treatment on water metabolism and plasma vasopressin concentration. *Eur J Clin Pharmacol* 1984; **26:** 719–22.
7. Kuz GM, Manssourian A. Carbamazepine-induced hyponatremia: assessment of risk factors. *Ann Pharmacother* 2005; **39:** 1943–6.
8. Mucklow J. Selected side-effects 2: carbamazepine and hyponatraemia. *Prescribers' J* 1991; **31:** 61–4.
9. Stephens WP, *et al.* Plasma arginine vasopressin concentrations and antidiuretic action of carbamazepine. *BMJ* 1978; **1:** 1445–7.

Effects on the endocrine system. Carbamazepine may reduce serum concentrations of *thyroid* hormones through enzyme induction—see under Interactions of Levothyroxine, p.2172.

For mention of the effects of antiepileptics on *sexual function* in male epileptic patients, see under Phenytoin, p.496.

Effects on the eyes. On rare occasions lenticular opacities have been associated with carbamazepine.[1] Retinotoxicity associated with long-term carbamazepine use has been reported[2] in 2 patients. After stopping the drug visual function and retinal morphological changes improved. A review[3] of the effect of antiepileptics on the eyes noted that despite reports of colour vision disturbances and impaired contrast sensitivity associated with carbamazepine therapy, studies in healthy subjects had shown conflicting results.

1. Anonymous. Adverse ocular effects of systemic drugs. *Med Lett Drugs Ther* 1976; **18:** 63–4.
2. Nielsen NV, Syversen K. Possible retinotoxic effect of carbamazepine. *Acta Ophthalmol (Copenh)* 1986; **64:** 287–90.
3. Hilton EJR, *et al.* The effect of antiepileptic drugs on visual performance. *Seizure* 2004; **13:** 113–28.

Effects on the heart. A review[1] of reports of cardiac effects associated with carbamazepine revealed that patients could be divided into 2 distinct groups based on their symptoms. One group consisted mainly of young patients with non life-threatening sinus tachycardia after carbamazepine overdosage while the other group was composed of older female patients with potentially life-threatening bradycardia or AV block associated with therapeutic or modestly raised blood concentrations of carbamazepine. However, there has been a report of fatal syncope, probably due to ventricular asystole, in a 20-year-old patient.[2] Carbamazepine should be avoided in patients who develop conduction abnormalities, or who have conditions such as myotonic dystrophy in which conduction abnormalities are likely.[1]

Elevation of ventricular and atrial stimulation thresholds was reported in a 59-year-old man with a permanent dual-chamber pacemaker, 5 days after starting carbamazepine for mania.[3]

For a report of carbamazepine producing fatal eosinophilic myocarditis, see under Hypersensitivity, below.

1. Kasarkis EJ, *et al.* Carbamazepine-induced cardiac dysfunction: characterization of two distinct clinical syndromes. *Arch Intern Med* 1992; **152:** 186–91.
2. Stone S, Lange LS. Syncope and sudden unexpected death attributed to carbamazepine in a 20-year-old epileptic. *J Neurol Neurosurg Psychiatry* 1986; **49:** 1460–1.
3. Ambrosi P, *et al.* Carbamazepine and pacing threshold. *Lancet* 1993; **342:** 365.

Effects on the immune system. There have been reports of hypogammaglobulinaemia associated with carbamazepine.[1-4] The authors of one report[2] stated that this was a recognised but rare adverse effect of carbamazepine and noted that the UK CSM had 9 reports on file of hypogammaglobulinaemia or gammaglobulin abnormalities related to the use of carbamazepine.

1. Moschione Castro APB, *et al.* Secondary hypogammaglobulinemia after use of carbamazepine: case report and review. *Rev Hosp Clin Fac Med Sao Paulo* 2001; **56:** 189–92.
2. Hayman G, Bansal A. Antibody deficiency associated with carbamazepine. *BMJ* 2002; **325:** 1213.
3. Rice CM, *et al.* Recurrent herpes simplex virus encephalitis secondary to carbamazepine induced hypogammaglobulinaemia. *J Neurol Neurosurg Psychiatry* 2007; **78:** 1011–12.
4. Tamada T, *et al.* Secondary bronchiolitis obliterans organising pneumonia in a patient with carbamazepine-induced hypogammaglobulinemia. *Thorax* 2007; **62:** 100.

Effects on the liver. A report in 1990 commented that of 499 reports of unwanted effects of carbamazepine on the liver about half comprised only abnormal results from liver function tests;[1] however, deaths have occurred from liver failure[1,2] or hepatic necrosis.[3] Reversible vanishing bile duct syndrome has been associated with long-term use of carbamazepine.[4]

Hepatotoxicity may form part of the antiepileptic hypersensitivity syndrome reported with carbamazepine (see below).

1. Hadžić N, *et al.* Acute liver failure induced by carbamazepine. *Arch Dis Child* 1990; **65:** 315–17.
2. Zucker P, *et al.* Fatal carbamazepine hepatitis. *J Pediatr* 1977; **91:** 667–8.
3. Smith DW, *et al.* Fatal hepatic necrosis associated with multiple anticonvulsant therapy. *Aust N Z J Med* 1988; **18:** 575–81.
4. Ramos AMO, *et al.* Reversible vanishing bile duct syndrome induced by carbamazepine. *Eur J Gastroenterol Hepatol* 2002; **14:** 1019–22.

Effects on mental function. Carbamazepine therapy has been associated in a few patients with the development of acute psychotic and paranoid symptoms[1-3] and with phobias[2] and mood disturbances, including mania[4] and melancholia.[5] One case of acute paranoid psychosis was associated with the addition of carbamazepine to long-term sodium valproate therapy in a patient subsequently diagnosed as having a schizotypal personality.[3] For nonconvulsive status epilepticus associated with carbamazepine presenting as psychiatric disorders, see under Effects on the Nervous System, below. The problems of antiepileptic therapy adversely affecting cognition and the risk of mood disorders, including suicidal ideation, are discussed on p.468.

1. Berger H. An unusual manifestation of Tegretol (carbamazepine) toxicity. *Ann Intern Med* 1971; **74:** 449–50.
2. Mathew G. Psychiatric symptoms associated with carbamazepine. *BMJ* 1988; **296:** 1071.
3. McKee RJW, *et al.* Acute psychosis with carbamazepine and sodium valproate. *Lancet* 1989; **i:** 167.
4. Reiss AL, O'Donnell DJ. Carbamazepine-induced mania in two children: case report. *J Clin Psychiatry* 1984; **45:** 272–4.
5. Gardner DL, Cowdry RW. Development of melancholia during carbamazepine treatment in borderline personality disorder. *J Clin Psychopharmacol* 1986; **6:** 236–9.

Effects on the nervous system. ***ASEPTIC MENINGITIS.*** Aseptic meningitis has developed in a patient with Sjögren's syndrome given carbamazepine. It abated when the drug was withdrawn and symptoms recurred on rechallenge.[1] Aseptic meningitis has also been associated with carbamazepine in patients without Sjögren's syndrome.[2-4]

1. Hilton E, Stroh EM. Aseptic meningitis associated with administration of carbamazepine. *J Infect Dis* 1989; **159:** 363–4.
2. Simon LT, *et al.* Carbamazepine-induced aseptic meningitis. *Ann Intern Med* 1990; **112:** 627–8.
3. Hemet C, *et al.* Aseptic meningitis secondary to carbamazepine treatment of manic-depressive illness. *Am J Psychiatry* 1994; **151:** 1393.
4. Dang CT, Riley DK. Aseptic meningitis secondary to carbamazepine therapy. *Clin Infect Dis* 1996; **22:** 729–30.

ENCEPHALOPATHY. Carbamazepine-induced encephalopathy with symptoms resembling Creutzfeldt-Jakob disease was reported in a 71-year-old man; the cognitive decline, bradykinesia, tremor, and abnormal EEG improved on stopping carbamazepine.[1]

1. Horvath J, *et al.* Carbamazepine encephalopathy masquerading as Creutzfeldt-Jakob disease. *Neurology* 2005; **65:** 650–1.

EXTRAPYRAMIDAL EFFECTS. Although carbamazepine has been associated with extrapyramidal adverse effects,[1-4] it has also been tried in the treatment of movement disorders—see under Uses and Administration, below.

1. Schwartzman MJ, Leppik IE. Carbamazepine-induced dyskinesia and ophthalmoplegia. *Cleve Clin J Med* 1990; **57:** 367–72.
2. Soman P, *et al.* Dystonia—a rare manifestation of carbamazepine toxicity. *Postgrad Med J* 1994; **70:** 54–5.
3. Lee JW. Persistent dystonia associated with carbamazepine therapy: a case report. *N Z Med J* 1994; **107:** 360–1.
4. Stryjer R, *et al.* Segmental dystonia as the sole manifestation of carbamazepine toxicity. *Gen Hosp Psychiatry* 2002; **24:** 114–15.

STATUS EPILEPTICUS. Nonconvulsive status epilepticus, misdiagnosed as behavioural and psychiatric disorders, was reported[1] to have been precipitated by carbamazepine in 2 patients; seizure control and behaviour improved when carbamazepine was stopped and replaced with valproate.

1. Marini C, *et al.* Nonconvulsive status epilepticus precipitated by carbamazepine presenting as dissociative and affective disorders in adolescents. *J Child Neurol* 2005; **20:** 693–6.

Effects on the skin. Rashes occurring with carbamazepine may form part of an antiepileptic hypersensitivity syndrome (see below). In a report,[1] erythema multiforme occurred when a generic formulation was given instead of a proprietary brand of carbamazepine. Skin lesions resolved when the patient stopped taking the generic formulation and did not recur when the proprietary brand was restarted. In another report, a 6-year-old boy developed Stevens-Johnson syndrome 5 weeks after carbamazepine was added to valproic acid, which he had been taking as sole antiepileptic therapy for several weeks.[2] Carbamazepine was stopped and the patient eventually made a full recovery; valproic acid was continued because it was not thought to be the causative agent (but see under Valproate, p.509). Fatal toxic epidermal necrolysis has been seen when carbamazepine was given to a patient who had previously had Stevens-Johnson syndrome during carbamazepine treatment.[3] Pseudo mycosis fungoides with lymphoid cell infiltration of the dermis and raised liver enzymes has been reported[4] in a 54-year-old man who was taking carbamazepine for seizures; symptoms resolved within about 2 weeks of stopping therapy.

For a warning that severe skin reactions may be more likely in patients of certain genotypes, see Skin Reactions, under Precautions, below. For the relative incidence of skin reactions to different antiepileptics, see under Phenytoin, p.496.

1. Busch RL. Generic carbamazepine and erythema multiforme: generic-drug nonequivalency. *N Engl J Med* 1989; **321:** 692–3.
2. Keating A, Blahunka P. Carbamazepine-induced Stevens-Johnson syndrome in a child. *Ann Pharmacother* 1995; **29:** 538–9.
3. Huang L-Y, *et al.* Fatal toxic epidermal necrolysis induced by carbamazepine treatment in a patient who previously had carbamazepine-induced Stevens-Johnson syndrome. *J Formos Med Assoc* 2007; **106:** 1032–7.
4. Gül Ü, *et al.* Carbamazepine-induced pseudo mycosis fungoides. *Ann Pharmacother* 2003; **37:** 1441–3.

Hypersensitivity. An antiepileptic hypersensitivity syndrome, comprising fever, rash, and lymphadenopathy and less commonly hepatosplenomegaly and eosinophilia, has been associated with some antiepileptic drugs including carbamazepine.[1-3] Although a literature search[1] was only able to find 20 published cases to 1986, 22 cases had been reported to the Australian Adverse Drug Reactions Advisory Committee between 1975 and 1990. Some have estimated the incidence at 1 in 1000 to 1 in 10 000 new exposures to aromatic anticonvulsants,[2,3] but the true incidence is uncertain due to variations in presentation and reporting. Most reactions occurred within 30 days of the start of carbamazepine treatment,[1] although symptoms may occur anywhere between 1 and 8 weeks after exposure.[2] In previously sensitised individuals the reactions may occur within 1 day of rechallenge. The potential for cross-reactivity between carbamazepine, phenobarbital, and phenytoin is approximately 75%, and patients who develop the syndrome, and their close relatives, should be warned of the risk associated with use of these antiepileptics.[2]

Carbamazepine antibodies were detected in an 8-year-old child who developed symptoms of serum sickness including fever, skin rash, oedema, and lymphadenopathy during treatment with carbamazepine.[4] Hypersensitivity to carbamazepine with multisystem effects clinically resembling a mononucleosis syndrome was reported in a 15-year-old boy 2 weeks after starting monotherapy with carbamazepine;[5] all symptoms resolved on stopping carbamazepine and giving prednisone. There have been other cases[6-8] of an infectious mononucleosis syndrome associated with hypersensitivity to carbamazepine, leading the authors to suggest that reactivation of human herpesvirus 6 or 7 infection is a cofactor and an early manifestation of carbamazepine hypersensitivity syndrome; however, further studies are warranted.

A hypersensitivity reaction producing fatal eosinophilic myocarditis has been reported in a 13-year-old patient; initial symptoms mimicked scarlet fever.[9] A 21-year-old woman developed fatal fulminant hepatic failure after taking carbamazepine for about 2 months; she had presented with initial symptoms of fever, breathlessness, bloody diarrhoea, and a spreading rash.[10]

Generalised erythroderma with renal, hepatic, and bone-marrow failure (characterised by hypercellularity and dyserythropoiesis) has been reported[11] in an 81-year-old man 50 days after starting carbamazepine therapy. Symptoms recurred following an inadvertent rechallenge. The presence of underlying lymphoproliferative disease may have potentiated the severe drug-induced reaction.

If the antiepileptic hypersensitivity syndrome develops, immediate withdrawal of carbamazepine is recommended. In most cases this is all that is required and does not seem to precipitate an increase in seizures, compared with gradual withdrawal.[12]

Successful desensitisation to carbamazepine was reported[13] in a 12-year-old boy who was sensitive to carbamazepine, sodium valproate, and phenytoin. Starting with a low dose of carbamazepine 100 micrograms daily the dose was doubled, generally every 2 days, up to 100 mg daily. The dose was then gradually increased over 4 weeks to a maintenance dose of 200 mg twice daily. The same technique was used to desensitise 7 patients, all of whom developed dramatic skin rashes when first exposed to carbamazepine.[14] Carbamazepine therapy in full doses was achieved without problem in about 6 weeks. Some[2] consider that desensitisation is not to be recommended in patients with full-blown antiepileptic hypersensitivity syndrome.

1. Anonymous. Anticonvulsants and lymphadenopathy. *WHO Drug Inf* 1991; **5:** 11.
2. Knowles SR, *et al.* Anticonvulsant hypersensitivity syndrome: incidence, prevention and management. *Drug Safety* 1999; **21:** 489–501.
3. Bessmertny O, *et al.* Antiepileptic hypersensitivity syndrome in children. *Ann Pharmacother* 2001; **35:** 533–8.
4. Hosoda N, *et al.* Anticarbamazepine antibody induced by carbamazepine in a patient with severe serum sickness. *Arch Dis Child* 1991; **66:** 722–3.
5. Merino N, *et al.* Multisystem hypersensitivity reaction to carbamazepine. *Ann Pharmacother* 1994; **28:** 402–3.
6. Zeller A, *et al.* Drug hypersensitivity syndrome to carbamazepine and human herpes virus 6 infection: case report and literature review. *Infection* 2003; **31:** 254–6.
7. Aihara Y, *et al.* Carbamazepine-induced hypersensitivity syndrome associated with transient hypogammaglobulinaemia and reactivation of human herpesvirus 6 infection demonstrated by real-time quantitative polymerase chain reaction. *Br J Dermatol* 2003; **149:** 165–9.
8. Oskay T, *et al.* Association of anticonvulsant hypersensitivity syndrome with Herpesvirus 6, 7. *Epilepsy Res* 2006; **70:** 27–40.
9. Salzman MB, *et al.* Carbamazepine and fatal eosinophilic myocarditis. *N Engl J Med* 1997; **336:** 878–9.
10. Syn W-K, *et al.* Carbamazepine-induced acute liver failure as part of the DRESS syndrome. *Int J Clin Pract* 2005; **59:** 988–91. Correction. *ibid.*; 1371.
11. Lombardi SM, *et al.* Severe multisystemic hypersensitivity reaction to carbamazepine including dyserythropoietic anemia. *Ann Pharmacother* 1999; **33:** 571–5.
12. Pirmohamed M, *et al.* Hypersensitivity to carbamazepine and lamotrigine: clinical considerations. *Br J Clin Pharmacol* 2000; **49:** 519P–520P.
13. Smith H, Newton R. Adverse reactions to carbamazepine managed by desensitisation. *Lancet* 1985; **i:** 753.
14. Eames P. Adverse reactions to carbamazepine managed by desensitisation. *Lancet* 1989; **i:** 509–10.

Sudden unexplained death in epilepsy. Sudden unexplained death in epilepsy (SUDEP), a common cause of seizure-related mortality in patients with chronic epilepsy, has been reviewed.[1,2] Risk factors may include early onset of epilepsy, frequent generalised tonic-clonic seizures, intractability, frequent medication changes, and polytherapy. *Carbamazepine* use has also been implicated but the evidence was considered to be tenuous although frequent dose change resulting in plasma-carbamazepine levels outside the therapeutic range was found to be an independent risk factor. Although the FDA in the USA had required data about the specific risk of SUDEP to be included in the prescribing information for the newer antiepileptic drugs *gabapentin, lamotrigine, tiagabine, topiramate,* and *zonisamide,* some commentators[3] consider that none of these antiepileptics have shown an associated change in the risk of SUDEP. It has been suggested[2,3] that the incidence of SUDEP is related to the disease rather than a specific drug effect.

1. Walczak T. Do antiepileptic drugs play a role in sudden unexpected death in epilepsy? *Drug Safety* 2003; **26:** 673–83.
2. Nashef L, *et al.* Risk factors in sudden death in epilepsy (SUDEP): the quest for mechanisms. *Epilepsia* 2007; **48:** 859–71.
3. Lathers CM, Schraeder PL. Clinical pharmacology: drugs as a benefit and/or risk in sudden unexpected death in epilepsy? *J Clin Pharmacol* 2002; **42:** 123–36.

Systemic lupus erythematosus. A review[1] of 80 cases of SLE-like syndromes associated with carbamazepine that had been reported to the manufacturer suggested that the frequency of reports (less than 0.001%) was below that for idiopathic lupus. There have been subsequent reports[2-4] of late-onset SLE occurring after up to 8 years of carbamazepine therapy without previous adverse effects. The symptoms due to carbamazepine usually resolved on stopping treatment.

1. Jain KK. Systemic lupus erythematosus (SLE)-like syndromes associated with carbamazepine therapy. *Drug Safety* 1991; **6:** 350–60.
2. Toepfer M, *et al.* Drug-induced systemic lupus erythematosus after 8 years of treatment with carbamazepine. *Eur J Clin Pharmacol* 1998; **54:** 193–4.
3. Pelizza L, *et al.* Drug-induced systemic lupus erythematosus after 7 years of treatment with carbamazepine. *Acta Biomed* 2006; **77:** 17–19.
4. Amerio P, *et al.* Drug-induced cutaneous lupus erythematosus after 5 years of treatment with carbamazepine. *Eur J Dermatol* 2006; **16:** 281–3.

Treatment of Adverse Effects

In the treatment of carbamazepine overdosage repeated doses of activated charcoal may be given orally to adults and children who have ingested more than 20 mg/kg; the aim is not only to prevent absorption but also to aid elimination. Gastric lavage may be considered if undertaken within 1 hour of ingestion. Supportive and symptomatic therapy alone may then suffice, with particular attention to correcting hypoxia and hypotension; haemoperfusion has been suggested for severe poisoning. If there is doubt about the diagnosis, or if multiple-dose oral activated charcoal is being considered, then monitoring plasma-carbamazepine concentration can be useful; it may also help determine when carbamazepine therapy should be restarted. See also Overdosage, below.

Hypersensitivity reactions. For reference to successful desensitisation in patients sensitive to carbamazepine, see Hypersensitivity under Adverse Effects, above.

Overdosage. Carbamazepine poisoning and its management has been reviewed.[1] Management is primarily supportive, with prompt attention to airway management and seizure control. Activated charcoal should be given; although multiple-dose activated charcoal has been recommended for carbamazepine overdosage, care must be taken to protect the airway since carbamazepine inhibits intestinal motility and there is a significant risk of aspiration. In patients with seizures unresponsive to benzodiazepines phenobarbital should be used; phenytoin is not a drug of choice in this situation. Hypotension is rare, and should be managed with fluid and vasopressor support; hypotension with refractory seizures should be treated aggressively as it has led to permanent neurological disability and death.

Haemodialysis or haemoperfusion may be warranted in patients with unstable cardiac status or status epilepticus complicated by bowel hypomotility and unresponsive to more conventional therapy. However, a report[2] of the use of plasmapheresis in the treatment of an acute overdose of carbamazepine concluded that plasmapheresis removed a very small percentage of the total body load of carbamazepine and could not be recommended. As carbamazepine is highly protein-bound, albumin-enhanced continuous venovenous haemodialysis was tried and found to be effective in the treatment of a 10-year-old child after ingestion of 1.4 g of carbamazepine.[3]

For a further review of the features and management of poisoning with some antiepileptics, including carbamazepine, see under Phenytoin, p.497.

1. Spiller HA. Management of carbamazepine overdose. *Pediatr Emerg Care* 2001; **17:** 452–6.
2. Kale PB, *et al.* Evaluation of plasmapheresis in the treatment of an acute overdose of carbamazepine. *Ann Pharmacother* 1993; **27:** 866–70.
3. Askenazi DJ, *et al.* Management of a severe carbamazepine overdose using albumin-enhanced continuous venovenous hemodialysis. *Pediatrics* 2004; **113:** 406–9.

Precautions

Carbamazepine should be avoided in patients with AV conduction abnormalities. It should not be given to patients with a history of bone marrow depression. Carbamazepine should be given with caution to patients with a history of blood disorders or haematological reactions to other drugs, or of cardiac, hepatic, or renal disease. Patients or their carers should be told how to recognise signs of blood, liver, and skin toxicity and they should be advised to seek immediate medical attention if symptoms such as fever, sore throat, rash, mouth ulcers, bruising, or bleeding develop. Carbamazepine should be withdrawn, if necessary under cover of a suitable alternative antiepileptic, if severe, progressive, or symptomatic leucopenia develops, or if symptoms suggestive of Stevens-Johnson syndrome or toxic epidermal necrolysis occur. Licensed product information recommends blood counts and hepatic and renal-function tests before starting carbamazepine therapy and periodically during treatment, but the *BNF* considers the evidence of practical value unsatisfactory. Clinical monitoring is of primary importance throughout treatment. Some patients of Asian ancestry may be at increased risk of severe skin reactions; for recommendations that such patients' genotype should be tested before beginning carbamazepine see Skin Reactions, below.

Care is required in identifying patients with mixed seizure disorders that include generalised absence or atypical absence seizures, who may be at risk of an increase

in generalised seizures if given carbamazepine. Carbamazepine may also exacerbate absence and myoclonic seizures.

Care is required when withdrawing carbamazepine therapy—see also Uses and Administration, below.

Since carbamazepine has mild antimuscarinic properties caution should be observed in patients with glaucoma or raised intra-ocular pressure; scattered punctate lens opacities occur rarely with carbamazepine and it has been suggested that patients should be examined periodically for eye changes.

Abuse. Overdosage requiring hospital admission has been reported after abuse of carbamazepine.[1]

1. Crawford PJ, Fisher BM. Recreational overdosage of carbamazepine in Paisley drug abusers. *Scott Med J* 1997; **42:** 44–5.

Breast feeding. The American Academy of Pediatrics considers[1] that carbamazepine is usually compatible with breast feeding, although there have been reports[2] of transient cholestatic hepatitis in breast-fed infants.

For further comment on antiepileptic therapy and breast feeding, see p.467.

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 09/06/08)
2. Frey B, *et al.* Neonatal cholestatic hepatitis from carbamazepine exposure during pregnancy and breast feeding. *Ann Pharmacother* 2002; **36:** 644–7.

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

Multiple sclerosis. Exacerbation of symptoms of multiple sclerosis has been reported[1] in 5 patients on starting carbamazepine therapy for paroxysmal neurological symptoms and pain. There was a close temporal association between starting carbamazepine and worsening of symptoms, followed by resolution when it was stopped. A 3-year follow-up observational study[2] found that out of 36 multiple sclerosis patients who received carbamazepine therapy, 12 developed neurological adverse effects that mimicked a relapse. The authors concluded that carbamazepine was associated with higher rates of adverse effects and stopping therapy than gabapentin or lamotrigine.

1. Ramsaransing G, *et al.* Worsening of symptoms of multiple sclerosis associated with carbamazepine. *BMJ* 2000; **320:** 1113.
2. Solaro C, *et al.* Antiepileptic medications in multiple sclerosis: adverse effects in a three-year follow-up study. *Neurol Sci* 2005; **25:** 307–10.

Porphyria. Carbamazepine has been associated with acute attacks of porphyria and is considered unsafe in porphyric patients.

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

There is an increased risk of neural tube defects in infants exposed *in utero* to antiepileptics including carbamazepine; syndromes such as craniofacial and digital abnormalities and, less commonly, cleft lip and palate have also been described. Exposure to carbamazepine has been calculated to carry a 1% risk of spina bifida.[1] A 'carbamazepine syndrome' characterised by facial dysmorphic features and mild mental retardation has been described;[2] such syndromes are now often seen as aspects of a single 'fetal antiepileptic syndrome'. There is also a risk of neonatal bleeding.

1. Rosa FW. Spina bifida in infants of women treated with carbamazepine during pregnancy. *N Engl J Med* 1991; **324:** 674–7.
2. Ornoy A, Cohen E. Outcome of children born to epileptic mothers treated with carbamazepine during pregnancy. *Arch Dis Child* 1996; **75:** 517–20.

Skin reactions. The FDA has issued a warning[1] that severe and potentially fatal skin reactions such as Stevens-Johnson syndrome and toxic epidermal necrolysis are significantly more common in patients with the HLA allele HLA-B*1502, which occurs almost exclusively in persons of Asian ancestry. They recommend that patients with such ancestry should be screened for the presence of this allele before beginning therapy with carbamazepine, and if present the risks and benefits of therapy should be considered with particular care; those who have already taken carbamazepine for more than a few months without developing skin reactions are, however, at low risk of them ever developing, regardless of genotype. Similar recommendations have since been issued in the UK by the MHRA.[2]

1. FDA. Information for healthcare professionals: carbamazepine (marketed as Carbatrol, Equetro, Tegretol, and generics). Issued 12th December, 2007. Available at: http://www.fda.gov/cder/drug/InfoSheets/HCP/carbamazepineHCP.htm (accessed 09/06/08)
2. MHRA/CHM. Carbamazepine: genetic testing recommended in some Asian populations. *Drug Safety Update* 2008: **1** (9): 5. Available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON014506&RevisionSelectionMethod=Latest (accessed 09/06/08)

Interactions

There are complex interactions between antiepileptics and toxicity may be enhanced without a corresponding increase in antiepileptic activity. Such interactions are very variable and unpredictable and plasma monitoring is often advisable with combination therapy.

The metabolism of carbamazepine is reported to be less susceptible to inhibition by other drugs than that of phenytoin but a few drugs are reported to inhibit its metabolism by the cytochrome P450 isoenzyme CYP3A4, resulting in raised plasma concentrations and associated toxicity. Conversely, drugs that induce CYP3A4 may increase the metabolism of carbamazepine, leading to reduced plasma concentrations and potentially a decrease in therapeutic effect. Licensed product information advises that, in such situations, the dose of carbamazepine should be adjusted accordingly and/or the plasma concentrations monitored.

Carbamazepine is itself a hepatic enzyme inducer, and induces its own metabolism as well as that of a number of other drugs including some antibacterials (notably, doxycycline), anticoagulants, and sex hormones (notably, oral contraceptives). Carbamazepine and phenytoin may also mutually enhance one another's metabolism. The metabolism of carbamazepine is similarly enhanced by enzyme inducers such as phenobarbital.

◊ General references.

1. Spina E, *et al.* Clinically significant pharmacokinetic drug interactions with carbamazepine: an update. *Clin Pharmacokinet* 1996; **31:** 198–214.

Alcohol. Alcohol may exacerbate the CNS adverse effects of carbamazepine and vice versa.

Analgesics. *Dextropropoxyphene* has been reported to cause substantial elevation of serum-carbamazepine concentrations[1] and carbamazepine toxicity,[1,2] probably due to inhibition of carbamazepine metabolism.[1]

Use of enzyme-inducing antiepileptics such as carbamazepine affects the threshold for use of antidote in the treatment of *paracetamol* poisoning, see p.110.

For the effect of carbamazepine on *tramadol*, see p.131.

1. Dam M, Christiansen J. Interaction of propoxyphene with carbamazepine. *Lancet* 1977; **ii:** 509.
2. Yu YL, *et al.* Interaction between carbamazepine and dextropropoxyphene. *Postgrad Med J* 1986; **62:** 231–3.

Anthelmintics. For the effect of carbamazepine on *mebendazole* and *praziquantel*, see p.149 and p.154, respectively.

Antibacterials. The antimycobacterial *isoniazid*[1,2] and macrolides[3] such as *clarithromycin*, *erythromycin*, and *troleandomycin* have been reported to cause substantial elevations of serum concentrations of carbamazepine and symptoms of carbamazepine toxicity. Clarithromycin has also been reported to have caused hyponatraemia when added to carbamazepine therapy in a 30-year-old epileptic woman.[4] *Rifampicin* and isoniazid decreased the serum concentrations of carbamazepine in a 44-year-old woman being treated for bipolar disorder and suspected tuberculosis, resulting in hypomania.[5]

Use of carbamazepine with isoniazid may increase the risk of isoniazid-induced hepatotoxicity.

1. Valsalan VC, Cooper GL. Carbamazepine intoxication caused by interaction with isoniazid. *BMJ* 1982; **285:** 261–2.
2. Wright JM, *et al.* Isoniazid-induced carbamazepine toxicity and vice versa. *N Engl J Med* 1982; **307:** 1325–7.
3. Pauwels O. Factors contributing to carbamazepine-macrolide interactions. *Pharmacol Res* 2002; **45:** 291–8.
4. Kanbay M, *et al.* Hyponatremia due to an additive effect of carbamazepine and clarithromycin. *South Med J* 2007; **100:** 222.
5. Zolezzi M. Antituberculosis agents and carbamazepine. *Am J Psychiatry* 2002; **159:** 874.

Anticoagulants. For the effect of carbamazepine on *warfarin*, see p.1429.

Antidepressants. As with all antiepileptics, antidepressants may antagonise the antiepileptic activity of carbamazepine by lowering the convulsive threshold.

Antidepressants such as *desipramine*,[1] *fluoxetine*,[2] *fluvoxamine*,[3] *nefazodone*[4] (and perhaps *trazodone*[5]), and *viloxazine*[6] increase plasma concentrations of carbamazepine and may induce carbamazepine toxicity. A toxic serotonin syndrome (see p.416) has been reported in a patient who received fluoxetine with carbamazepine.[7] Severe neurotoxicity reported during therapy with *lithium* and carbamazepine[8,9] may be due to a synergistic effect as reports indicate that either drug was tolerated when not given with the other and measured plasma concentrations did not indicate overdosage.[9] However, toxic serum concentrations of lithium have also been reported, due to carbamazepine-induced acute renal failure (see p.404).

Because of the structural similarity to tricyclic antidepressants licensed product information suggests that carbamazepine should not be given to patients taking an *MAOI* or within 14 days of stopping such treatment.

St John's wort has been shown to induce several drug metabolising enzymes (see p.423) and consequently it has been suggested that it might reduce the blood concentrations of carbamazepine leading to an increased risk of seizure.[10] However, a multiple-dose study[11] in healthy subjects reported that St John's wort had no significant effect on the pharmacokinetics of carbamazepine or its active epoxide metabolite.

For the effect of carbamazepine on antidepressants, see Bupropion (p.384), Fluoxetine (p.396), Mianserin (p.409), Nefazodone (p.413), and Amitriptyline (p.380).

1. Lesser I. Carbamazepine and desipramine: a toxic reaction. *J Clin Psychiatry* 1984; **45:** 360.
2. Pearson HJ. Interaction of fluoxetine with carbamazepine. *J Clin Psychiatry* 1990; **51:** 126.
3. Fritze J, *et al.* Interaction between carbamazepine and fluvoxamine. *Acta Psychiatr Scand* 1991; **84:** 583–4.
4. Ashton AK, Wolin RE. Nefazodone-induced carbamazepine toxicity. *Am J Psychiatry* 1996; **153:** 733.
5. Sánchez Romero A, *et al.* Interaction between trazodone and carbamazepine. *Ann Pharmacother* 1999; **33:** 1370.
6. Scarpello JHB, Cottrell N. Overuse of monitoring of blood concentrations of antiepileptic drugs. *BMJ* 1987; **294:** 1355.
7. Dursun SM, *et al.* Toxic serotonin syndrome after fluoxetine plus carbamazepine. *Lancet* 1993; **342:** 442–3.
8. Andrus PF. Lithium and carbamazepine. *J Clin Psychiatry* 1984; **45:** 525.
9. Chaudhry RP, Waters BGH. Lithium and carbamazepine interaction: possible neurotoxicity. *J Clin Psychiatry* 1983; **44:** 30–1.
10. Committee on Safety of Medicines/Medicines Control Agency. Reminder: St John's wort (Hypericum perforatum) interactions. *Current Problems* 2000; **26:** 6–7. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON007462&RevisionSelectionMethod=LatestReleased (accessed 09/06/08)
11. Burstein AH, *et al.* Lack of effect of St John's Wort on carbamazepine pharmacokinetics in healthy volunteers. *Clin Pharmacol Ther* 2000; **68:** 605–12.

Antiepileptics. Interactions of varying degrees of clinical significance have been reported between carbamazepine and other antiepileptics.

Serum concentrations of carbamazepine are reported to be reduced by *phenobarbital*, but without loss of seizure control;[1,2] this reduction is probably due to induction of carbamazepine metabolism.

The interaction with *phenytoin* is somewhat more complex and the consequences vary. There is evidence of a lowering of serum-carbamazepine concentrations, presumably due to induction of metabolism by phenytoin;[1-3] in return carbamazepine has been reported both to lower and increase serum phenytoin—see p.498. Again, these reports do not indicate a loss of seizure control or toxicity resulting from the interaction, although the possibility presumably exists. Gradually withdrawing phenytoin from 2 patients who had been receiving carbamazepine and phenytoin resulted in a dramatic increase in plasma-carbamazepine concentrations;[4] one patient exhibited neurotoxic symptoms. The authors recommended that plasma-carbamazepine monitoring should be carried out whenever phenytoin is withdrawn in patients taking these two drugs together.

Valproic acid produces an increase in serum concentrations of the active epoxide metabolite of carbamazepine. This is usually attributed to inhibition of its hydrolysis by epoxide hydrolase, although an additional proposed mechanism[5] is inhibition of the glucuronidation of carbamazepine-10,11-trans-diol, the compound to which the epoxide is converted under normal circumstances. Adverse effects may be a problem if unusually high epoxide concentrations arise but, in general, this interaction is of limited clinical significance. However, *valpromide*, the amide derivative, is a much more powerful inhibitor of epoxide hydrolase than valproic acid,[6-8] and therefore produces greater increases in epoxide plasma concentrations with clinical signs of toxicity.[7] Switching from sodium valproate to valpromide has resulted in toxicity in patients also receiving carbamazepine.[7] Neither valproic acid nor valpromide have any significant effect on plasma concentrations of the parent drug, carbamazepine. *Valnoctamide*, an isomer of valpromide, appears to be at least as potent as valpromide in inhibiting the elimination of the epoxide metabolite of carbamazepine.[9] Valnoctamide has been used as an anxiolytic, although it does appear to possess some antiepileptic activity. For a report of acute psychosis associated with the combination of carbamazepine and sodium valproate, see Effects on Mental Function under Adverse Effects, above. For the effects of carbamazepine on valproate, see p.511.

Of the other antiepileptics *stiripentol*[10,11] has been reported to inhibit carbamazepine metabolism, while *felbamate* causes a significant fall in plasma-carbamazepine concentrations which may require an increase in the dose of carbamazepine.[12] However, another study[13] has shown a significant increase in plasma-concentrations of the active epoxide metabolite, which may counteract the effect of the decrease in plasma concentrations of the parent compound. Neurotoxicity has been seen after use of carbamazepine with *lamotrigine*.[14] The suggestion that this was due to raised concentrations of carbamazepine epoxide was not confirmed in a controlled study in which the 2 drugs were used together safely and effectively.[15] Toxic epidermal necrolysis occurred[16] when lamotrigine was added to carbamazepine therapy in a patient who had been taking carbamazepine for 3 years; symptoms resolved progressively when both drugs were stopped. Symptoms of carbamazepine toxicity have been reported[17] when *levetiracetam* was added to carbamazepine therapy; this interaction appeared to be due to a pharmacodynamic mechanism as blood levels of carbamazepine and its epoxide metabolite were not altered. There have also been reports[18] of

carbamazepine toxicity when *topiramate* was added to carbamazepine therapy; symptoms resolved when the dose of carbamazepine was reduced. Fulminant liver failure has been reported[19] after an increase in adjunctive topiramate dose in a patient maintained on carbamazepine for 2 years without any signs of hepatotoxicity. The GABA agonist *progabide* has increased plasma concentrations of the epoxide metabolite, probably due to inhibition of microsomal epoxide hydrolase.[20] *Vigabatrin* is reported[21] to increase the clearance of carbamazepine by about 35%.

For the effects of carbamazepine on *ethosuximide*, see p.480, on *lamotrigine*, see p.486, on *oxcarbazepine*, see p.491, on *primidone*, see p.503, on *tiagabine*, see p.505, and on *topiramate*, see p.506. For interactions with benzodiazepines, see below.

1. Cereghino JJ, *et al.* The efficacy of carbamazepine combinations in epilepsy. *Clin Pharmacol Ther* 1975; **18:** 733–41.
2. Rane A, *et al.* Kinetics of carbamazepine and its 10,11-epoxide metabolite in children. *Clin Pharmacol Ther* 1976; **19:** 276–83.
3. Christiansen J, Dam M. Influence of phenobarbital and diphenylhydantoin on plasma carbamazepine levels in patients with epilepsy. *Acta Neurol Scand* 1973; **49:** 543–6.
4. Chapron DJ, *et al.* Unmasking the significant enzyme-inducing effects of phenytoin on serum carbamazepine concentrations during phenytoin withdrawal. *Ann Pharmacother* 1993; **27:** 708–11.
5. Bernus I, *et al.* The mechanism of the carbamazepine-valproate interaction in humans. *Br J Clin Pharmacol* 1997; **44:** 21–7.
6. Levy RH, *et al.* Inhibition of carbamazepine epoxide elimination by valpromide and valproic acid. *Epilepsia* 1986; **27:** 592.
7. Meijer JWA, *et al.* Possible hazard of valpromide-carbamazepine combination therapy in epilepsy. *Lancet* 1984; **i:** 802.
8. Pisani F, *et al.* Effect of valpromide on the pharmacokinetics of carbamazepine-10,11-epoxide. *Br J Clin Pharmacol* 1988; **25:** 611–13.
9. Pisani F, *et al.* Impairment of carbamazepine-10,11-epoxide elimination by valnoctamide, a valpromide isomer, in healthy subjects. *Br J Clin Pharmacol* 1992; **34:** 85–7.
10. Levy RH, *et al.* Stiripentol level-dose relationship and interaction with carbamazepine in epileptic patients. *Epilepsia* 1985; **26:** 544–5.
11. Cazali N, *et al.* Inhibitory effect of stiripentol on carbamazepine and saquinavir metabolism in human. *Br J Clin Pharmacol* 2003; **56:** 526–36.
12. Albani F, *et al.* Effect of felbamate on plasma levels of carbamazepine and its metabolites. *Epilepsia* 1991; **32:** 130–2.
13. Wagner ML, *et al.* Effect of felbamate on carbamazepine and its major metabolites. *Clin Pharmacol Ther* 1993; **53:** 536–43.
14. Warner T, *et al.* Lamotrigine-induced carbamazepine toxicity: an interaction with carbamazepine-10,11-epoxide. *Epilepsy Res* 1992; **11:** 147–50.
15. Stolarek I, *et al.* Vigabatrin and lamotrigine in refractory epilepsy. *J Neurol Neurosurg Psychiatry* 1994; **57:** 921–4.
16. Mansouri P, *et al.* Toxic epidermal necrolysis associated with concomitant use of lamotrigine and carbamazepine: a case report. *Arch Dermatol* 2005; **141:** 788–9.
17. Sisodiya SM, *et al.* Carbamazepine toxicity during combination therapy with levetiracetam: a pharmacodynamic interaction. *Epilepsy Res* 2002; **48:** 217–19.
18. Mack CJ, *et al.* Interaction of topiramate with carbamazepine: two case reports and a review of clinical experience. *Seizure* 2002; **11:** 464–7.
19. Bjøro K, *et al.* Topiramate and fulminant liver failure. *Lancet* 1998; **352:** 1119.
20. Kroetz DL, *et al.* In vivo and in vitro correlation of microsomal epoxide hydrolase inhibition by progabide. *Clin Pharmacol Ther* 1993; **54:** 485–97.
21. Sánchez-Alcaraz A, *et al.* Effect of vigabatrin on the pharmacokinetics of carbamazepine. *J Clin Pharm Ther* 2002; **27:** 427–30.

Antifungals. Malaise, myoclonus, and trembling were reported[1] to have developed in a patient receiving carbamazepine after the addition of *miconazole* to therapy. *Ketoconazole* was associated with a significant increase in plasma-carbamazepine concentrations in 8 epileptic patients stabilised on carbamazepine;[2] plasma concentrations of the epoxide metabolite were unchanged. A threefold increase in serum-carbamazepine concentrations, reported[3] in a patient after addition of *fluconazole* to carbamazepine therapy, was asymptomatic; however, carbamazepine toxicity has been reported[4,5] in 2 patients stabilised on carbamazepine who were given fluconazole. *Terbinafine* has also been reported[6] to cause possible carbamazepine toxicity.

For the effect of carbamazepine on *itraconazole*, see p.537.

1. Loupi E, *et al.* Interactions médicamenteuses et miconazole. *Therapie* 1982; **37:** 437–41.
2. Spina E, *et al.* Elevation of plasma carbamazepine concentrations by ketoconazole in patients with epilepsy. *Ther Drug Monit* 1997; **19:** 535–8.
3. Finch CK, *et al.* Fluconazole-carbamazepine interaction. *South Med J* 2002; **95:** 1099–1100.
4. Nair DR, Morris HH. Potential fluconazole-induced carbamazepine toxicity. *Ann Pharmacother* 1999; **33:** 790–2.
5. Ulivelli M, *et al.* Clinical evidence of fluconazole-induced carbamazepine toxicity. *J Neurol* 2004; **251:** 622–3.
6. Baath NS, *et al.* Possible carbamazepine toxicity with terbinafine. *Can J Clin Pharmacol* 2006; **13:** e228–e231.

Antihistamines. *Terfenadine* and carbamazepine are both highly protein bound and therefore may compete for protein binding sites. An 18-year-old woman receiving carbamazepine as an antiepileptic experienced symptoms of neurotoxicity shortly after starting treatment with terfenadine for rhinitis.[1] The concentration of free carbamazepine in the plasma was higher than normal and returned to normal on stopping terfenadine.

1. Hirschfeld S, Jarosinski P. Drug interaction of terfenadine and carbamazepine. *Ann Intern Med* 1993; **118:** 907–8.

Antimalarials. *Chloroquine* and *mefloquine* may antagonise the antiepileptic activity of carbamazepine by lowering the convulsive threshold.

Antiprotozoals. A patient receiving carbamazepine for bipolar disorder developed dizziness, diplopia, and nausea 4 days after the addition of *metronidazole* for diverticulitis.[1]

1. Patterson BD. Possible interaction between metronidazole and carbamazepine. *Ann Pharmacother* 1994; **28:** 1303–4.

Antipsychotics. As with all antiepileptics, antipsychotics may antagonise the antiepileptic activity of carbamazepine by lowering the convulsive threshold.

Increased plasma concentrations of carbamazepine epoxide have been reported to occur during therapy with carbamazepine and *loxapine*[1] or *quetiapine*,[2] possibly due to induction of carbamazepine metabolism or inhibition of metabolism of the epoxide. Raised serum concentrations of carbamazepine have also been reported in patients receiving *haloperidol*.[3]

For the effect of carbamazepine on antipsychotics, see under Chlorpromazine, p.974.

1. Collins DM, *et al.* Potential interaction between carbamazepine and loxapine: case report and retrospective review. *Ann Pharmacother* 1993; **27:** 1180–3.
2. Fitzgerald BJ, Okos AJ. Elevation of carbamazepine-10,11-epoxide by quetiapine. *Pharmacotherapy* 2002; **22:** 1500–3.
3. Iwahashi K, *et al.* The drug-drug interaction effects of haloperidol on plasma carbamazepine levels. *Clin Neuropharmacol* 1995; **18:** 233–6.

Antivirals. *Ritonavir* inhibits several microsomal liver enzymes and therefore may potentially increase plasma concentrations of carbamazepine. Licensed product information for ritonavir advises that such combinations may require monitoring. Carbamazepine toxicity has been reported[1,2] after interaction with ritonavir. In one report,[2] the patient was also taking *nelfinavir* and *lopinavir*, both of which are substrates and inhibitors of CYP450 isoenzymes.

For the effect of carbamazepine on HIV-protease inhibitors, see p.883.

1. Mateu-de Antonio J, Grau S. Ritonavir-induced carbamazepine toxicity. *Ann Pharmacother* 2001; **35:** 125–6.
2. Bates DE, Herman RJ. Carbamazepine toxicity induced by lopinavir/ritonavir and nelfinavir. *Ann Pharmacother* 2006; **40:** 1190–5.

Anxiolytics. For a discussion of the potential interaction between carbamazepine and the anxiolytic *valnoctamide*, an isomer of the antiepileptic valpromide, see Antiepileptics, above.

See also Benzodiazepines, below.

Benzodiazepines. The metabolism of benzodiazepines may be enhanced by induction of hepatic drug-metabolising enzymes in patients who have received long-term therapy with carbamazepine; benzodiazepine plasma concentrations are reduced, half-life is shorter, and clearance is increased[1,2] (see also Antiepileptics, under Interactions of Diazepam, p.990).

Some benzodiazepines may also affect carbamazepine. One group of workers reported that after addition of *clobazam* to carbamazepine therapy a dose reduction for the latter was required due to increased blood concentrations.[3] In a later study[4] it appeared that clobazam could produce a moderate increase in the metabolism of carbamazepine. The plasma ratio of metabolites of carbamazepine, including carbamazepine-10,11-epoxide, to parent compound was increased in patients taking clobazam and carbamazepine.

1. Dhillon S, Richens A. Pharmacokinetics of diazepam in epileptic patients and normal volunteers following intravenous administration. *Br J Clin Pharmacol* 1981; **12:** 841–4.
2. Lai AA, *et al.* Time-course of interaction between carbamazepine and clonazepam in normal man. *Clin Pharmacol Ther* 1978; **24:** 316–23.
3. Franceschi M, *et al.* Clobazam in drug-resistant and alcoholic withdrawal seizures. *Clin Trials J* 1983; **20:** 119–25.
4. Muñoz JJ, *et al.* The effect of clobazam on steady state plasma concentrations of carbamazepine and its metabolites. *Br J Clin Pharmacol* 1990; **29:** 763–5.

Calcium-channel blockers. Six patients with steady-state carbamazepine concentrations had symptoms of neurotoxicity consistent with carbamazepine intoxication within 36 to 96 hours of the first dose of *verapamil*.[1] In 5 patients, in whom plasma concentrations were measured, there was a mean increase of 46% in total carbamazepine and 33% in free carbamazepine; no effect on the plasma protein binding of carbamazepine was seen. The results suggested that verapamil inhibits the metabolism of carbamazepine to an extent likely to have important clinical repercussions. There has also been a report[2] of a patient in whom *diltiazem*, but not *nifedipine*, precipitated carbamazepine neurotoxicity.

For the effect of carbamazepine on dihydropyridine calcium-channel blockers, see under Nifedipine, p.1353.

1. Macphee GJA, *et al.* Verapamil potentiates carbamazepine neurotoxicity: a clinically important inhibitory interaction. *Lancet* 1986; **i:** 700–703.
2. Brodie MJ, Macphee GJA. Carbamazepine neurotoxicity precipitated by diltiazem. *BMJ* 1986; **292:** 1170–1.

Ciclosporin. For the effect of carbamazepine on ciclosporin, see p.1826.

Corticosteroids. For the effect of carbamazepine on corticosteroids, see p.1494.

Danazol. Use of danazol with carbamazepine has been reported to increase the half-life and decrease clearance of carbamazepine,[1] resulting in increases in plasma-carbamazepine concentrations of up to 100%[1,2] and resultant toxicity in a number of patients.[2]

1. Krämer G, *et al.* Carbamazepine-danazol drug interaction: its mechanism examined by a stable isotope technique. *Ther Drug Monit* 1986; **8:** 387–92.
2. Zielinski JJ, *et al.* Clinically significant danazol-carbamazepine interaction. *Ther Drug Monit* 1987; **9:** 24–7.

Dermatological drugs. Addition of *isotretinoin* to regular carbamazepine therapy appeared to reduce plasma concentrations of the latter and its active epoxide metabolite.[1] However, no adverse events were noted during a 6-week period of treatment with isotretinoin. Nonetheless, licensed product information for carbamazepine recommends that the levels of carbamazepine are monitored if both are used together.

1. Marsden JR. Effect of isotretinoin on carbamazepine pharmacokinetics. *Br J Dermatol* 1988; **119:** 403–4.

Diuretics. There has been a report of symptomatic hyponatraemia associated with use of carbamazepine and a diuretic (*hydrochlorothiazide* or *furosemide*—see under Interactions of Furosemide, p.1293). Carbamazepine serum concentrations are increased by *acetazolamide*.[1]

1. McBride MC. Serum carbamazepine levels are increased by acetazolamide. *Ann Neurol* 1984; **16:** 393.

Gastrointestinal drugs. *Cimetidine* is reported to produce a transient increase in plasma-carbamazepine concentrations, with a return to pre-cimetidine values within about a week;[1] some increase in adverse effects was seen. *Ranitidine* does not appear to affect plasma-carbamazepine concentrations.[2] Neurotoxicity has been seen in a patient receiving carbamazepine and *metoclopramide*.[3]

1. Dalton MJ, *et al.* Cimetidine and carbamazepine: a complex drug interaction. *Epilepsia* 1986; **27:** 553–8.
2. Dalton MJ, *et al.* Ranitidine does not alter single-dose carbamazepine pharmacokinetics in healthy adults. *Drug Intell Clin Pharm* 1985; **19:** 941–4.
3. Sandyk R. Carbamazepine and metoclopramide interaction: possible neurotoxicity. *BMJ* 1984; **288:** 830.

Grapefruit juice. The bioavailability and plasma concentrations of carbamazepine have been reported[1] to be increased by grapefruit juice.

1. Garg SK, *et al.* Effect of grapefruit juice on carbamazepine bioavailability in patients with epilepsy. *Clin Pharmacol Ther* 1998; **64:** 286–8.

Levothyroxine. For the effect of carbamazepine on levothyroxine, see p.2172.

Neuromuscular blockers. For the effect of carbamazepine on *suxamethonium*, see p.1911 and on *competitive neuromuscular blockers*, see under Atracurium, p.1904.

Sex hormones. For the effect of carbamazepine on *oral contraceptives*, see p.2068 and for the possible effect on *tibolone*, see p.2134.

See also Danazol, above

Theophylline. A decrease in serum-carbamazepine concentrations of about 50% was reported[1] in an epileptic patient given theophylline. The patient experienced seizures and the proposed mechanism was that theophylline had increased the metabolism of carbamazepine.

For the effect of carbamazepine on theophylline, see p.1143.

1. Mitchell EA, *et al.* Interaction between carbamazepine and theophylline. *N Z Med J* 1986; **99:** 69–70.

Vitamins. The plasma concentration of carbamazepine was increased in 2 patients given *nicotinamide*.[1]

For the effect of antiepileptics, including carbamazepine, on *vitamin D* concentrations, see Effects on Bone under the Adverse Effects of Phenytoin, p.496.

1. Bourgeois BFD, *et al.* Interactions between primidone, carbamazepine, and nicotinamide. *Neurology* 1982; **32:** 1122–6.

Pharmacokinetics

Carbamazepine is slowly and irregularly absorbed from the gastrointestinal tract and has a bioavailability of 85 to 100%. It is extensively metabolised in the liver, notably by the cytochrome P450 isoenzymes CYP3A4 and CYP2C8. One of its primary metabolites, carbamazepine-10,11-epoxide, is also active. Carbamazepine is excreted in the urine almost entirely in the form of its metabolites; some are also excreted in faeces. Elimination of carbamazepine is reported to be more rapid in children and accumulation of the active metabolite may often be higher than in adults.

Carbamazepine is widely distributed throughout the body and is about 70 to 80% bound to plasma proteins. It induces its own metabolism so that the plasma half-life may be considerably reduced after repeated dosage. The mean plasma half-life of carbamazepine on repeated dosage is about 12 to 24 hours; it appears to be considerably shorter in children than in adults.

Moreover, the metabolism of carbamazepine is readily induced by drugs that induce hepatic microsomal enzymes (see Interactions, above).

Monitoring of plasma concentrations may be performed when clinically indicated and the therapeutic range of total plasma-carbamazepine is usually quoted as being about 4 to 12 micrograms/mL (17 to 50 micromoles/litre), although this is subject to considerable variation. It has been suggested by some, but not all investigators, that measurement of free carbamazepine concentrations in plasma may prove more reliable, and concentrations in saliva or tears, which contain only free carbamazepine, have also been measured.

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

The pharmacokinetics of carbamazepine are affected by use with other antiepileptics (see under Interactions, above).

◊ References.

1. Schmidt D, Haenel F. Therapeutic plasma levels of phenytoin, phenobarbital, and carbamazepine: individual variation in relation to seizure frequency and type. *Neurology* 1984; **34:** 1252–5.
2. Bertilsson L, Tomson T. Clinical pharmacokinetics and pharmacological effects of carbamazepine and carbamazepine-10,11-epoxide: an update. *Clin Pharmacokinet* 1986; **11:** 177–98.
3. Gilman JT. Carbamazepine dosing for pediatric seizure disorders: the highs and lows. *DICP Ann Pharmacother* 1991; **25:** 1109–12.
4. Kodama Y, *et al.* In vivo binding characteristics of carbamazepine and carbamazepine-10,11-epoxide to serum proteins in paediatric patients with epilepsy. *Eur J Clin Pharmacol* 1993; **44:** 291–3.
5. Bernus I, *et al.* Early stage autoinduction of carbamazepine metabolism in humans. *Eur J Clin Pharmacol* 1994; **47:** 355–60.
6. Caraco Y, *et al.* Carbamazepine pharmacokinetics in obese and lean subjects. *Ann Pharmacother* 1995; **29:** 843–7.
7. Mahmood I, Chamberlin N. A limited sampling method for the estimation of AUC and C of carbamazepine and carbamazepine epoxide following a single and multiple dose of a sustained-release product. *Br J Clin Pharmacol* 1998; **45:** 241–6.
8. Cohen H, *et al.* Feasibility and pharmacokinetics of carbamazepine oral loading doses. *Am J Health-Syst Pharm* 1998; **55:** 1134–40.
9. Bondareva IB, *et al.* Population pharmacokinetic modelling of carbamazepine in epileptic elderly patients: implications for dosage. *J Clin Pharm Ther* 2006; **31:** 211–21.

Uses and Administration

Carbamazepine is a dibenzazepine derivative with antiepileptic and psychotropic properties. It is used to control secondarily generalised tonic-clonic seizures and partial seizures, and in some primary generalised seizures. Carbamazepine is also used in the treatment of trigeminal neuralgia and has been tried with variable success in glossopharyngeal neuralgia and other severe pain syndromes associated with neurological disorders such as tabes dorsalis and multiple sclerosis. Another use of carbamazepine is in the management of bipolar disorder unresponsive to lithium.

In the treatment of **epilepsy**, the dose of carbamazepine should be adjusted to the needs of the individual patient to achieve adequate control of seizures; this usually requires total plasma-carbamazepine concentrations of about 4 to 12 micrograms/mL (17 to 50 micromoles/litre). A low initial dose of carbamazepine is recommended to minimise adverse effects. The suggested initial oral dose is 100 to 200 mg once or twice daily gradually increased by increments of up to 200 mg daily every week to a usual maintenance dose of 0.8 to 1.2 g daily in divided doses; up to 2 g daily may occasionally be necessary. For details of doses in children, see below.

Oral carbamazepine is usually given in divided doses 2 to 4 times daily. A twice-daily regimen may be associated with improved compliance but can produce widely fluctuating plasma-carbamazepine concentrations that lead to intermittent adverse effects. Twice-daily dosage may nonetheless be suitable for patients receiving carbamazepine monotherapy; modified-release formulations can minimise fluctuations in plasma concentration and may also allow effective twice-daily use. Different preparations vary in bioavailability and it may be prudent to avoid changing the formulation.

The time and manner of taking carbamazepine should be standardised for the patient since variations might affect absorption with consequent fluctuations in the plasma concentrations.

Carbamazepine may be given by the rectal route in doses up to a maximum of 250 mg every 6 hours to patients for whom oral treatment is temporarily not possible. The dosage should be increased by about 25% when changing from an oral formulation to suppositories, and it is recommended that the rectal route should not be used for longer than 7 days.

As with other antiepileptics, withdrawal of carbamazepine 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.

The treatment of **trigeminal neuralgia** is typically begun with low oral doses, such as 100 mg of carbamazepine twice daily (although up to 200 mg twice daily has been suggested in the UK), and increased gradually as needed to maintain freedom from pain. This is usually at maintenance doses of 400 to 800 mg in divided doses; up to 1.2 g daily is considered standard maintenance in the USA, while UK licensed product information considers that up to 1.6 g daily may be needed in some patients. When pain relief has been obtained attempts should be made to reduce, and if possible stop, therapy, until another attack occurs.

For the management of **bipolar disorder**, carbamazepine is given in an initial oral dose of 400 mg daily in divided doses, increased gradually as necessary up to a maximum of 1.6 g daily; the usual maintenance dose range is 400 to 600 mg daily.

Administration. A modified-release formulation of carbamazepine can reduce fluctuations in carbamazepine concentrations,[1] and tolerability and seizure control in patients with epilepsy may be improved.[2,3] Such formulations should be considered in patients receiving high doses who suffer intermittent adverse effects, and might also permit a reduction to twice- or even, in some patients, once-daily dosage.[2,4] However, bioavailability appears to be slightly less than conventional preparations and dosage adjustments may be required when changing between formulations.[1]

1. McKee PJW, *et al.* Monotherapy with conventional and controlled-release carbamazepine: a double-blind, double-dummy comparison in epileptic patients. *Br J Clin Pharmacol* 1991; **32:** 99–104.
2. Anonymous. Carbamazepine update. *Lancet* 1989; **ii:** 595–7.
3. Ryan SW, *et al.* Slow release carbamazepine in treatment of poorly controlled seizures. *Arch Dis Child* 1990; **65:** 930–5.
4. McKee PJW, *et al.* Double dummy comparison between once and twice daily dosing with modified-release carbamazepine in epileptic patients. *Br J Clin Pharmacol* 1993; **36:** 257–61.

Administration in children. In the UK, the usual recommended oral dose of carbamazepine for generalised tonic-clonic and partial seizures in children is 10 to 20 mg/kg daily in divided doses. Alternatively the daily dose may be given according to age as follows:

- up to 1 year: 100 to 200 mg
- 1 to 5 years: 200 to 400 mg
- 5 to 10 years: 400 to 600 mg
- 10 to 15 years: 0.6 to 1 g

As with adults, children should be started on a low initial dose of carbamazepine to minimise adverse effects; the *BNFC* suggests that those aged 1 month to 12 years may initially be given 5 mg/kg at night or 2.5 mg/kg twice daily, increasing by 2.5 to 5 mg/kg every 3 to 7 days as necessary to a usual maintenance dose of 5 mg/kg 2 or 3 times daily. Older children may be given the usual adult dose (see above) although a maximum of 1.8 g daily has been suggested.

The *BNFC* also states that these doses may be used for the treatment of neuropathic pain and some movement disorders, and for mood stabilisation.

Carbamazepine may be given rectally to children in whom oral treatment is temporarily not possible; the *BNFC* suggests this route may be used from 1 month of age. Doses should be about 25% greater than the corresponding oral dose, to a maximum of 250 mg, and given up to 4 times daily.

Bipolar disorder. Carbamazepine may be given as an alternative to lithium or valproate in patients with bipolar disorder (p.372). Studies of its efficacy have been conflicting; although clearly effective in some patients, at least one early study suggested that short-term benefit was not sustained in the longer term.[1] More recent results[2,3] have suggested that lithium or valproate are generally more effective, but that carbamazepine may conceivably have a role in patients with nonclassical features. Carbamazepine has also been used with lithium, particularly in patients unresponsive to either drug alone; although there are suggestions that the combination may be more effective than monotherapy, particularly in patients with a history of rapid cycling,[4] it is associated with a potential risk of serious neurotoxicity—see Antidepressants, under Interactions, above. While some commentators have suggested that carbamazepine is falling out of favour with specialists prescribing for bipolar disorder,[5] a more recent literature review[6] concluded that it was still a feasible treatment option.

1. Frankenburg FR, *et al.* Long-term response to carbamazepine: a retrospective study. *J Clin Psychopharmacol* 1988; **8:** 130–2.
2. Kleindienst N, Greil W. Differential efficacy of lithium and carbamazepine in the prophylaxis of bipolar disorder: results of the MAP study. *Neuropsychobiology* 2000; **42** (suppl 1): 2–10.
3. Vasudev K, *et al.* Carbamazepine and valproate monotherapy: feasibility, relative safety and efficacy, and therapeutic drug monitoring in manic disorder. *Psychopharmacology (Berl)* 2000; **150:** 15–23.
4. Denicoff KD, *et al.* Comparative prophylactic efficacy of lithium, carbamazepine, and the combination in bipolar disorder. *J Clin Psychiatry* 1997; **58:** 470–8.
5. Ferrier IN. Developments in mood stabilisers. *Br Med Bull* 2001; **57:** 179–92.
6. Stoner SC, *et al.* Historical review of carbamazepine for the treatment of bipolar disorder. *Pharmacotherapy* 2007; **27:** 68–88.

Depression. Carbamazepine has been tried[1-3] for the augmentation of antidepressant therapy in the treatment of resistant depression (p.373). However, such combined therapy may lead to interactions—see also Antidepressants under Interactions, above.

1. De la Fuente JM, Mendlewicz J. Carbamazepine addition in tricyclic antidepressant-resistant unipolar depression. *Biol Psychiatry* 1992; **32:** 369–74.
2. Otani K, *et al.* Carbamazepine augmentation therapy in three patients with trazodone-resistant depression. *Int Clin Psychopharmacol* 1996; **11:** 55–7.
3. Ciusani E, *et al.* Combination therapy with venlafaxine and carbamazepine in depressive patients not responding to venlafaxine: pharmacokinetic and clinical aspects. *J Psychopharmacol* 2004; **18:** 559–66.

Diabetes insipidus. Cranial diabetes insipidus is usually treated by replacement therapy with antidiuretic hormone (ADH) in the form of desmopressin (see p.2179). Carbamazepine is one of a variety of other drugs that have been tried to promote ADH secretion, although some consider that it is usually ineffective and has unwanted effects.[1,2] Doses of 200 to 400 mg daily by mouth have been given. See also Effects on Electrolytes under Adverse Effects, above.

1. Seckl J, Dunger D. Postoperative diabetes insipidus. *BMJ* 1989; **298:** 2–3.
2. Singer I, *et al.* The management of diabetes insipidus in adults. *Arch Intern Med* 1997; **157:** 1293–1301.

Epilepsy. Carbamazepine is one of the drugs of choice for partial seizures with or without secondary generalisation (see p.465). It has been used for generalised tonic-clonic seizures (although valproate is the drug of choice where these occur in primary generalised epilepsy), but it may exacerbate absence and myoclonic seizures.

Hemifacial spasm. Carbamazepine has been reported to have been of help in the treatment of hemifacial spasm (p.1892).

Hiccup. For the management of intractable hiccups see under Chlorpromazine, p.976. Carbamazepine may be of value for the treatment of neurogenic hiccups such as those that occur in multiple sclerosis.[1] Carbamazepine has also been reported to have been of benefit in 3 patients with diaphragmatic flutter,[2] a rare disorder associated with involuntary contractions of the diaphragm.

1. McFarling DA, Susac JO. Hoquet diabolique: intractable hiccups as a manifestation of multiple sclerosis. *Neurology* 1979; **29:** 797–801.
2. Vantrappen G, *et al.* High-frequency diaphragmatic flutter: symptoms and treatment by carbamazepine. *Lancet* 1992; **339:** 265–7.

Hyperactivity. When drugs are indicated for attention deficit hyperactivity disorder (p.2148) initial treatment is usually with a central stimulant but meta-analysis of a small number of trials has provided evidence that carbamazepine may be effective.[1]

1. Silva RR, *et al.* Carbamazepine use in children and adolescents with features of attention-deficit hyperactivity disorder: a meta-analysis. *J Am Acad Child Adolesc Psychiatry* 1996; **35:** 352–8.

Lesch-Nyhan syndrome. The severe self-mutilation that occurs in patients with Lesch-Nyhan syndrome (p.976) has been reported to improve in those given antiepileptics such as carbamazepine.[1]

1. Roach ES, *et al.* Carbamazepine trial for Lesch-Nyhan self-mutilation. *J Child Neurol* 1996; **11:** 476–8.

Movement disorders. Carbamazepine is one of many drugs that have been tried in the symptomatic treatment of *chorea* (p.953); there have been anecdotal reports of benefit in both non-hereditary[1,2] and hereditary choreas.[3] Carbamazepine is also among the drugs that have been tried in the treatment of *dystonias* that have not responded to levodopa or antimuscarinics (p.809). Although some patients may benefit from carbamazepine, it is not generally recommended because of a relatively low success rate and the possibility of adverse effects.[4] Carbamazepine therapy has also been associated with movement

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.

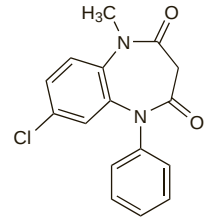
Клобазам

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