withdrawal over a period of 2 to 3 weeks. For a discussion on whether or not to withdraw antiepileptic therapy in seizure-free patients, see p.465.

Administration in hepatic impairment. The initial daily maintenance dosage of tiagabine in patients with mild to moderate hepatic impairment (Child-Pugh score 5 to 9) should be reduced to 5 to 10 mg given as a single dose or in 2 divided doses. Tiagabine should not be given to patients with severe hepatic impairment.

Epilepsy. Tiagabine is one of a number of drugs that may be used as adjunctive therapy in patients with partial seizures (with or without secondary generalisation) refractory to standard treatment (p.465). It appears to be reasonably well tolerated. For the suggestion that it might be tried in refractory status epilepticus, see p.469.

References.

1. Leach JP, Brodie MJ. Tiagabine. *Lancet* 1998; **351:** 203–7.
2. Adkins JC, Noble S. Tiagabine: a review of its pharmacodynamic and pharmacokinetic properties and therapeutic potential in the management of epilepsy. *Drugs* 1998; **55:** 437–60.
3. Luer MS, Rhoney DH. Tiagabine: a novel antiepileptic drug. *Ann Pharmacother* 1998; **32:** 1173–80.
4. Loiseau P. Review of controlled trials of gabitril (tiagabine): a clinician's viewpoint. *Epilepsia* 1999; **40** (suppl 9): S14–S19.
5. Anonymous. Tiagabine: add-on treatment for partial seizures. *Drug Ther Bull* 2000; **38:** 47–8.
6. Dodrill CB, *et al.* Tiagabine versus phenytoin and carbamazepine as add-on therapies: effects on abilities, adjustment, and mood. *Epilepsy Res* 2000; **42:** 123–32.
7. Crawford P, *et al.* Tiagabine: efficacy and safety in adjunctive treatment of partial seizures. *Epilepsia* 2001; **42:** 531–8.
8. Biraben A, *et al.* Comparison of twice- and three times daily tiagabine for the adjunctive treatment of partial seizures in refractory patients with epilepsy: an open label, randomised, parallel-group study. *Epileptic Disord* 2001; **3:** 91–100.
9. Pereira J, *et al.* Tiagabine add-on for drug-resistant partial epilepsy. Available in the Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2002 (accessed 09/06/08).
10. Arroyo S, *et al.* A randomised open-label study of tiagabine given two or three times daily in refractory epilepsy. *Seizure* 2005; **14:** 81–4.

Pain. Antiepileptics are among the drugs used to manage pain (see Choice of Analgesic, p.2); tiagabine has been tried in chronic pain[1] and was found to be effective.

1. Todorov AA, *et al.* Tiagabine and gabapentin for the management of chronic pain. *Clin J Pain* 2005; **21:** 358–61.

Psychiatric disorders. Tiagabine has been tried for the treatment of *generalised anxiety disorder*[1,2] (p.952) and *major depressive disorder* with anxiety[3] (p.373), with variable results. It has also been tried in *post-traumatic stress disorder* (p.953) with some success in a case series[4] and a small open-label study[5] although a later multicentre placebo-controlled study[6] found no significant difference between tiagabine and placebo; further studies are considered warranted. A preliminary study[7] suggested that tiagabine may be effective and generally well tolerated as augmentation therapy in patients with anxiety disorders.

References.

1. Rosenthal M. Tiagabine for the treatment of generalized anxiety disorder: a randomized, open-label, clinical trial with paroxetine as a positive control. *J Clin Psychiatry* 2003; **64:** 1245–9.
2. Pollack MH, *et al.* The selective GABA reuptake inhibitor tiagabine for the treatment of generalized anxiety disorder: results of a placebo-controlled study. *J Clin Psychiatry* 2005; **66:** 1401–8.
3. Carpenter LL, *et al.* Open-label tiagabine monotherapy for major depressive disorder with anxiety. *J Clin Psychiatry* 2006; **67:** 66–71.
4. Taylor FB. Tiagabine for posttraumatic stress disorder: a case series of 7 women. *J Clin Psychiatry* 2003; **64:** 1421–5.
5. Connor KM, *et al.* Tiagabine for posttraumatic stress disorder: effects of open-label and double-blind discontinuation treatment. *Psychopharmacology (Berl)* 2006; **184:** 21–5.
6. Davidson JRT, *et al.* The efficacy and tolerability of tiagabine in adult patients with post-traumatic stress disorder. *J Clin Psychopharmacol* 2007; **27:** 85–8.
7. Schwartz TL, *et al.* An open-label study of tiagabine as augmentation therapy for anxiety. *Ann Clin Psychiatry* 2005; **17:** 167–72.

Stiff-man syndrome. There have been anecdotal reports[1] of improvement of stiff-man syndrome (see under Muscle Spasm in Uses of Diazepam, p.993) with tiagabine in patients unable to tolerate benzodiazepine therapy.

1. Murinson BB, Rizzo M. Improvement of stiff-person syndrome with tiagabine. *Neurology* 2001; **57:** 366.

Preparations

Proprietary Preparations (details are given in Part 3)

Austral.: Gabitril; ***Austria:*** Gabitril; ***Belg.:*** Gabitril; ***Cz.:*** Gabitril; ***Denm.:*** Gabitril; ***Fin.:*** Gabitril†; ***Fr.:*** Gabitril; ***Ger.:*** Gabitril; ***Gr.:*** Gabitril; ***Hung.:*** Gabitril; ***Irl.:*** Gabitril; ***Ital.:*** Gabitril; ***Mex.:*** Gabatril†; ***Pol.:*** Gabitril; ***Port.:*** Gabitril; ***Spain:*** Gabitril; ***Switz.:*** Gabitril; ***UK:*** Gabitril; ***USA:*** Gabitril.

Topiramate *(BAN, USAN, rINN)*

KW-6485; McN-4853; RWJ-17021; Topiramaatti; Topiramat; Topiramato; Topiramatum. 2,3:4,5-Di-*O*-isopropylidene-β-D-fructopyranose sulphamate.

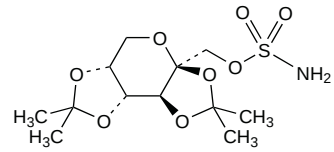
Топирамат

$C_{12}H_{21}NO_8S$ = 339.4.

CAS — 97240-79-4.

ATC — N03AX11.

ATC Vet — QN03AX11.



Pharmacopoeias. In *US.*

USP 31 (Topiramate). A white to off-white powder. Freely soluble in dichloromethane. Store in airtight containers at a temperature of 20° to 25°, excursions permitted between 15° and 30°. Protect from light.

Adverse Effects

Adverse effects associated with topiramate therapy include ataxia, impaired concentration, confusion, dizziness, fatigue, paraesthesia or hypoaesthesia, drowsiness, and difficulties with memory or cognition. Agitation, anxiety, nervousness, emotional lability, and mood disorders may also occur. Other reported adverse effects include abdominal pain, anorexia, asthenia, diplopia, leucopenia, nausea, nystagmus, insomnia, psychomotor retardation, impaired speech, altered taste, visual disturbances, and weight loss. The risk of developing renal calculi is increased, especially in predisposed patients. Reduced sweating with hyperthermia has occurred particularly in children. Rare cases of acute myopia with secondary angle-closure glaucoma have been reported.

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

Effects on electrolytes. Metabolic acidosis has been associated with topiramate treatment. Data from clinical trials estimate that the incidence of persistently decreased serum bicarbonate concentrations ranges from 23 to 67% with topiramate compared with 1 to 10% with placebo;[1] children, in particular, may be at a greater risk than adults.[1,2] A retrospective cohort study also found that 48% of adult patients developed decreased serum bicarbonate concentrations while receiving topiramate.[3] Generally, the decreases in serum bicarbonate are mild to moderate and occur soon after starting topiramate. Clinical signs such as hyperventilation may develop.

Some sources such as the US licensed product information recommend that baseline and periodic serum bicarbonate levels should be monitored during topiramate treatment. If metabolic acidosis develops or persists, it may be necessary to reduce the dose or stop topiramate although, in some cases, correcting the acidosis with alkali therapy may be more appropriate.

1. Janssen-Ortho Canada. Important drug safety information: Topamax (topiramate) use is associated with metabolic acidosis (issued 12/01/04). Available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/topamax_3_hpc-cps-eng.pdf (accessed 01/09/08)
2. Philippi H, *et al.* Topiramate and metabolic acidosis in infants and toddlers. *Epilepsia* 2002; **43:** 744–7.
3. Garris SS, Oles KS. Impact of topiramate on serum bicarbonate concentrations in adults. *Ann Pharmacother* 2005; **39:** 424–6.

Effects on the eyes. There have been rare reports of acute myopia with or without secondary angle-closure glaucoma in adults and children receiving topiramate:[1-3] as of April 2002 the UK CSM was aware of 23 cases worldwide occurring with secondary angle-closure glaucoma.[4] Symptoms include decreased visual acuity and ocular pain which generally appear within one month of starting treatment; hyperaemia and raised intra-ocular pressure may be present with or without mydriasis. Choroidal effusions resulting in anterior displacement of lens and iris have been reported. Appropriate measures to reduce intra-ocular pressure should be taken, and topiramate stopped as rapidly as is clinically feasible.[4] A later review[5] of 115 reports of ocular adverse effects associated with topiramate described 83 cases of bilateral and 3 cases of unilateral acute angle-closure glaucoma; of these, 7 sustained permanent loss of vision. Onset of glaucoma was between 1 and 49 days after starting topiramate therapy, with 85% of cases occurring within the first 2 weeks. Also reported were cases of acute bilateral myopia (17 patients), suprachoroidal effusions (9), scleritis (4), blepharospasm (2), oculogyric crisis (2), and myokymia (1). Diplopia and nystagmus were reported with daily doses of at least 200 to 400 mg topiramate.

1. Gubbay SS. The occurrence of drug-induced myopia as a transient side effect of topiramate. *Epilepsia* 1998; **39:** 451.
2. Sen HA, *et al.* Topiramate-induced acute myopia and retinal striae. *Arch Ophthalmol* 2001; **119:** 775–7.
3. Rhee DJ, *et al.* Bilateral angle-closure glaucoma and ciliary body swelling from topiramate. *Arch Ophthalmol* 2001; **119:** 1721–3.
4. Committee on Safety of Medicines/Medicines Control Agency. Topiramate (Topamax): acute myopia and raised intraocular pressure. *Current Problems* 2002; **28:** 4. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON007454&RevisionSelectionMethod=LatestReleased (accessed 09/06/08)
5. Fraunfelder FW, *et al.* Topiramate-associated acute, bilateral, secondary angle-closure glaucoma. *Ophthalmology* 2004; **111:** 109–11.

Effects on the liver. For reports of hepatotoxicity associated with the addition of topiramate to antiepileptic therapy with carbamazepine or valproate see Interactions, Antiepileptics, on p.474 and p.511 respectively.

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

Effects on the nervous system. Hyperthermia was reported in 10.5% of patients taking topiramate compared with 0.15% of patients taking other antiepileptic drugs in one centre.[1] Children under the age of 6 years, patients on daily doses of 6 mg/kg or more, and those exposed to high ambient temperatures were most at risk. Licensed product information recommends that children should be monitored closely for decreased sweating and hyperthermia, especially during warm or hot weather. Caution is also advised when giving topiramate with other drugs known to cause similar effects, for example, carbonic anhydrase inhibitors and antimuscarinics.

Hemiparesis that resolved on withdrawal of topiramate has been reported[2] in 2 patients, although both already had compromised neurological function.

1. Ziad EK, *et al.* Age, dose, and environmental temperature are risk factors for topiramate-related hyperthermia. *Neurology* 2005; **65:** 1139–40.
2. Stephen LJ, *et al.* Transient hemiparesis with topiramate. *BMJ* 1999; **318:** 845.

Effects on sexual function. Topiramate has been associated with sexual dysfunction[1,2] in male and female patients; in all cases symptoms resolved with dosage reduction or withdrawal of the drug.

1. Holtkamp M, *et al.* Erectile dysfunction with topiramate. *Epilepsia* 2005; **46:** 166–7.
2. Sun C, *et al.* Reversible anorgasmia with topiramate therapy for headache: a report of 7 patients. *Headache* 2006; **46:** 1450–3.

Precautions

Topiramate should be used with caution in patients with renal or hepatic impairment. Adequate hydration is recommended to reduce the risk of developing renal calculi, especially in predisposed patients.

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

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

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

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

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.

◊ References.

1. Bialer M, *et al.* Pharmacokinetic interactions of topiramate. *Clin Pharmacokinet* 2004; **43:** 763–80.

Antiepileptics. In pharmacokinetic studies hepatic enzyme inducers such as *carbamazepine*,[1-3] *phenobarbital*,[2] and *phenytoin*[1,2] were reported to decrease the plasma concentration of topiramate.

For the effect of topiramate on phenytoin and carbamazepine, see p.498 and p.474, respectively. For reports of an increased risk of hepatic impairment in patients taking topiramate with valproate, see p.511.

1. Bourgeois BFD. Drug interaction profile of topiramate. *Epilepsia* 1996; **37:** (suppl 2): S14–S17.
2. Contin M, *et al.* Topiramate therapeutic monitoring in patients with epilepsy: effect of concomitant antiepileptic drugs. *Ther Drug Monit* 2002; **24:** 332–7.
3. Mimrod D, *et al.* A comparative study of the effect of carbamazepine and valproic acid on the pharmacokinetics and metabolic profile of topiramate at steady state in patients with epilepsy. *Epilepsia* 2005; **46:** 1046–54.

Cardiac glycosides. For the effect of topiramate on *digoxin*, see p.1261.

Sex hormones. For the effects of antiepileptics including topiramate on *oral contraceptives*, see p.2068.

Pharmacokinetics

Topiramate is readily absorbed after oral doses, with peak plasma concentrations achieved after about 2 hours. Bioavailability is not affected by the presence of food. Protein binding is about 9 to 17%. The volume of distribution in women is about half that in men. Topiramate crosses the placental barrier and is distributed into breast milk.

In healthy subjects topiramate is not extensively metabolised; however, up to 50% of a dose may undergo metabolism in the liver in patients also receiving enzyme-inducing drugs. It is eliminated chiefly in urine, as unchanged drug and metabolites; mean plasma elimination half-life is about 21 hours. Steady-state concentrations are achieved after about 4 to 8 days in patients with normal renal function. Clearance is decreased in patients with impaired renal or hepatic function, and steady-state plasma concentrations may not be achieved for 10 to 15 days in the former. Children exhibit a higher clearance and shorter elimination half-life than adults.

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

◊ References.

1. Perucca E, Bialer M. The clinical pharmacokinetics of the newer antiepileptic drugs: focus on topiramate, zonisamide, and tiagabine. *Clin Pharmacokinet* 1996; **31:** 29–46.
2. Glauser TA, *et al.* Topiramate pharmacokinetics in infants. *Epilepsia* 1999; **40:** 788–91.
3. Öhman I, *et al.* Topiramate kinetics during delivery, lactation, and in the neonate: preliminary observations. *Epilepsia* 2002; **43:** 1157–60.
4. Ferrari AR, *et al.* Influence of dosage, age, and co-medication on plasma topiramate concentrations in children and adults with severe epilepsy and preliminary observations on correlations with clinical response. *Ther Drug Monit* 2003; **25:** 700–8.
5. Battino D, *et al.* Topiramate pharmacokinetics in children and adults with epilepsy: a case-matched comparison based on therapeutic drug monitoring data. *Clin Pharmacokinet* 2005; **44:** 407–16.

Uses and Administration

Topiramate, a sulfamate-substituted monosaccharide, is an antiepileptic used as adjunctive therapy in refractory partial seizures with or without secondary generalisation, seizures associated with the Lennox-Gastaut syndrome, and primary generalised tonic-clonic seizures. It may also be used as monotherapy in patients with newly diagnosed epilepsy who have generalised tonic-clonic seizures or partial seizures. Topiramate is also used for the prophylaxis of migraine.

In the UK, for both adjunctive and monotherapy of **epilepsy**, the initial oral dose of topiramate is 25 mg at night for 1 week increased thereafter by increments of 25 or 50 mg at intervals of 1 to 2 weeks until the effective dose is reached. Daily doses of more than 25 mg should be taken in 2 divided doses. The usual daily dose for *adjunctive therapy* is 200 to 400 mg although some patients may require up to 800 mg daily. When used as *monotherapy*, usual doses range from 100 mg daily to a maximum of 400 mg daily. Similar target doses are also used in the USA for both adjunctive and monotherapy although higher initial doses of 50 mg daily with weekly increases thereafter are recommended in the licensed product information.

For doses in children, see below.

As with other antiepileptics, withdrawal of topiramate 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 UK product information suggests decreasing the daily dose by 50 to 100 mg at weekly intervals.

In the prophylaxis of **migraine**, topiramate is given orally in initial doses of 25 mg at night for 1 week, increased by 25-mg increments every week, to a usual dose of 50 mg twice daily. UK product information suggests decreasing the daily dose by 25 to 50 mg at weekly intervals when withdrawing topiramate therapy.

Smaller increments or longer intervals between increments may be necessary if patients cannot tolerate the above regimens; US product information suggests that doses should be halved in patients with moderate to severe renal impairment regardless of indication (see also below).

Administration in children. Topiramate is used as adjunctive therapy in children for refractory partial seizures with or without secondary generalisation, seizures associated with the Lennox-Gastaut syndrome, and primary generalised tonic-clonic seizures. It may also be used as monotherapy in those with newly diagnosed epilepsy who have generalised tonic-clonic seizures or partial seizures.

In the UK, the initial oral dose for *adjunctive* therapy in children from 2 years of age is 25 mg. This is given as a single dose at night for 1 week, then increased by 1 to 3 mg/kg every 1 to 2 weeks until the effective dose is reached; these higher daily doses are divided and given twice daily. About 5 to 9 mg/kg daily is usually required, although up to 30 mg/kg has been given.

For *monotherapy*, in children from 6 years of age, the initial daily oral dose is 0.5 to 1 mg/kg at night for the first week, increased thereafter by 0.5 to 1 mg/kg every 1 or 2 weeks, to a usual dose of 3 to 6 mg/kg daily in 2 divided doses; up to 16 mg/kg daily has been used.

The adult dose (above) is recommended in those over 16 years of age.

In the USA, licensed doses for adjunctive therapy are similar to those in the UK; however, monotherapy, which is limited to those 10 years of age and over, is given at usual adult doses.

Administration in renal impairment. Patients with moderate to severe renal impairment take longer to reach steady-state plasma concentrations of topiramate than patients with normal renal function (see Pharmacokinetics, above) and the dosage regimen may need adjusting; US licensed product information recommends that usual adult doses (see above) be halved in such patients.

In patients undergoing haemodialysis a supplemental dose equal to about one-half of the daily dose should be given in divided doses (at the start and finish of the procedure).

Alcohol withdrawal and abstinence. Topiramate may be of use as an adjunct in achieving and maintaining abstinence in patients with alcohol dependence[1,2] (p.1626).

1. Johnson BA, *et al.* Oral topiramate for treatment of alcohol dependence: a randomised controlled trial. *Lancet* 2003; **361:** 1677–85.
2. Johnson BA, *et al.* Topiramate for treating alcohol dependence: a randomized controlled trial. *JAMA* 2007; **298:** 1641–51.

Bipolar disorder. Mood-stabilising antiepileptics such as carbamazepine and valproate are alternatives to lithium in the management of bipolar disorder (p.372). Topiramate has also been investigated after favourable case reports,[1,2] but randomised controlled studies[3,4] have produced disappointing results and a systematic review[5] found insufficient evidence for its use as monotherapy or adjunctive therapy.

1. Teter CJ, *et al.* Treatment of affective disorder and obesity with topiramate. *Ann Pharmacother* 2000; **34:** 1262–5.
2. Erfurth A, Kuhn G. Topiramate monotherapy in the maintenance treatment of bipolar I disorder: effects on mood, weight and serum lipids. *Neuropsychobiology* 2000; **42** (suppl 1): 50–1.
3. Kushner SF, *et al.* Topiramate monotherapy in the management of acute mania: results of four double-blind placebo-controlled trials. *Bipolar Disord* 2006; **8:** 15–27.
4. Chengappa KNR, *et al.* Adjunctive topiramate therapy in patients receiving a mood stabilizer for bipolar I disorder: a randomized, placebo-controlled trial. *J Clin Psychiatry* 2006; **67:** 1698–1706.
5. Vasudev K, *et al.* Topiramate for acute affective episodes in bipolar disorder. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2006 (accessed 09/06/08).

Epilepsy. Topiramate is used[1-5] in epilepsy (p.465) for refractory partial seizures, for primary generalised tonic-clonic seizures,[6] and in patients with the Lennox-Gastaut syndrome;[7] in the UK, it may be a first-line option in some circumstances. Starting topiramate therapy gradually improves tolerability without delaying therapeutic response.[8]

Topiramate has also been investigated in children with infantile spasms (as for example in West's syndrome),[9] severe myoclonic epilepsy,[10] and juvenile myoclonic epilepsy;[11] it has been tried as a second-line drug in absence seizures and for tonic or atonic seizures. A retrospective review[12] and later studies[13,14] of the use of topiramate in such drug-resistant childhood epilepsies have concluded that it is efficacious and well tolerated.

Topiramate has also been investigated as an alternative antiepileptic in the management of refractory status epilepticus (p.469).[15,16]

1. Lyseng-Williamson KA, Yang LPH. Topiramate: a review of its use in the treatment of epilepsy. *Drugs* 2007; **67:** 2231–56.
2. Sachdeo RC, *et al.* Topiramate: clinical profile in epilepsy. *Clin Pharmacokinet* 1998; **34:** 335–46.
3. Garnett WR. Clinical pharmacology of topiramate: a review. *Epilepsia* 2000; **41** (suppl 1); S61–S65.
4. Glauser TA, *et al.* Topiramate monotherapy in newly diagnosed epilepsy in children and adolescents. *J Child Neurol* 2007; **22:** 693–9.
5. Jette NJ, *et al.* Topiramate add-on for drug-resistant partial epilepsy. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2008 (accessed 27/08/08).
6. Biton V. A randomized, placebo-controlled study of topiramate in primary generalized tonic-clonic seizures. *Neurology* 1999; **52:** 1330–7.
7. Sachdeo RC, *et al.* A double-blind, randomized trial of topiramate in Lennox-Gastaut syndrome. *Neurology* 1999; **52:** 1882–7.
8. Biton V, *et al.* Topiramate titration and tolerability. *Ann Pharmacother* 2001; **35:** 173–9.
9. Glauser TA, *et al.* Long-term response to topiramate in patients with West syndrome. *Epilepsia* 2000; **41** (suppl 1): S91–S94.
10. Nieto-Barrera M, *et al.* Topiramate in the treatment of severe myoclonic epilepsy in infancy. *Seizure* 2000; **9:** 590–4.
11. Biton V, Bourgeois BFD. Topiramate in patients with juvenile myoclonic epilepsy. *Arch Neurol* 2005; **62:** 1705–8.
12. Yeung S, *et al.* Topiramate for drug-resistant epilepsies. *Eur J Paediatr Neurol* 2000; **4:** 31–3.
13. Al Ajlouni S, *et al.* The efficacy and side effects of topiramate on refractory epilepsy in infants and young children: a multicenter clinical trial. *Seizure* 2005; **14:** 459–63.
14. Grosso S, *et al.* Efficacy and safety of topiramate in refractory epilepsy of childhood: long-term follow-up study. *J Child Neurol* 2005; **20:** 893–7.
15. Towne AR, *et al.* The use of topiramate in refractory status epilepticus. *Neurology* 2003; **60:** 332–4.
16. Bensalem MK, Fakhoury TA. Topiramate and status epilepticus: report of three cases. *Epilepsy Behav* 2003; **4:** 757–60.

Headache. Topiramate is used for the prophylaxis of *migraine* (p.616). Results from placebo-controlled studies[1-5] have shown a significant reduction in frequency of migraines in those patients receiving prophylactic topiramate.

Topiramate has been tried for prophylaxis of *cluster headache* attacks[6] (p.616) and chronic *tension-type headache*[7] (p.617). It has also been used to control headache due to *raised intracranial pressure* (see p.1181).

1. Storey JR, *et al.* Topiramate in migraine prevention: a double-blind, placebo-controlled study. *Headache* 2001; **41:** 968–75.
2. Brandes JL, *et al.* Topiramate for migraine prevention: a randomized controlled trial. *JAMA* 2004; **291:** 965–73.
3. Silberstein SD, *et al.* Topiramate in migraine prevention: results of a large controlled trial. *Arch Neurol* 2004; **61:** 490–5.
4. Silberstein SD, *et al.* Efficacy and safety of topiramate for the treatment of chronic migraine: a randomized, double-blind, placebo-controlled trial. *Headache* 2007; **47:** 170–80.
5. Diener H-C, *et al.* Topiramate reduces headache days in chronic migraine: a randomized, double-blind, placebo-controlled study. *Cephalalgia* 2007; **27:** 814–23.
6. Láinez MJA, *et al.* Topiramate in the prophylactic treatment of cluster headache. *Headache* 2003; **43:** 784–9.
7. Lampl C, *et al.* A prospective, open-label, long-term study of the efficacy and tolerability of topiramate in the prophylaxis of chronic tension-type headache. *Cephalalgia* 2006; **26:** 1203–8.

Hyperhidrosis. Reduced sweating has been associated with topiramate therapy (see Effects on the Nervous System under Adverse Effects, above). There have been 2 case reports[1,2] of the use of topiramate in the treatment of hyperhidrosis.

1. Owen DB, Meffert JJ. The suppression of primary palmarplantar hyperhidrosis by topiramate. *Br J Dermatol* 2003; **148:** 826–7.
2. Hoehn-Saric R. Facial hyperhidrosis-induced social fear alleviated with topiramate. *J Clin Psychiatry* 2006; **67:** 1157.

Motor neurone disease. Topiramate has been tried as a potential therapy for amyotrophic lateral sclerosis (see Motor Neurone Disease, p.2380) but with disappointing results.[1]

1. Cudkowicz ME, *et al.* A randomized, placebo-controlled trial of topiramate in amyotrophic lateral sclerosis. *Neurology* 2003; **61:** 456–64.

Neuropathic pain. Although carbamazepine is the drug of choice in the treatment of *trigeminal neuralgia* (p.9), topiramate has also been tried successfully.[1] It has also been tried[2,3] in the treatment of *diabetic neuropathy* (p.6) and of *phantom limb pain*[4] (p.9).

1. Zvartau-Hind M, *et al.* Topiramate relieves refractory trigeminal neuralgia in MS patients. *Neurology* 2000; **55:** 1587–8.
2. Raskin P, *et al.* Topiramate vs placebo in painful diabetic neuropathy: analgesic and metabolic effects. *Neurology* 2004; **63:** 865–73.
3. Donofrio PD, *et al.* Safety and effectiveness of topiramate for the management of painful diabetic peripheral neuropathy in an open-label extension study. *Clin Ther* 2005; **27:** 1420–31.
4. Harden RN, *et al.* Topiramate for phantom limb pain: a time-series analysis. *Pain Med* 2005; **6:** 375–8.

Obesity. Weight loss has been associated with topiramate therapy (see Adverse Effects, above) and it has been tried as an adjunct in the treatment of obesity (p.2149) and in overweight patients; topiramate appears to be reasonably well tolerated. It has also been tried in binge eating (see below).

References.

1. Astrup A, Toubro S. Topiramate: a new potential pharmacological treatment for obesity. *Obes Res* 2004; **12** (suppl): 167S–173S.

2. Kirov G, Tredget J. Add-on topiramate reduces weight in overweight patients with affective disorders: a clinical case series. *BMC Psychiatry* 2005; **5:** 19. Available at: http://www.biomedcentral.com/content/pdf/1471-244X-5-19.pdf (accessed 09/06/08)
3. Khazaal Y, *et al*. Long-term topiramate treatment of psychotropic drug-induced weight gain: a retrospective chart review. *Gen Hosp Psychiatry* 2007; **29:** 446–9.
4. Eliasson B, *et al*. Weight loss and metabolic effects of topiramate in overweight and obese type 2 diabetic patients: randomized double-blind placebo-controlled trial. *Int J Obes* 2007; **31:** 1140–7.

Psychiatric disorders. Topiramate has been tried in several psychiatric disorders, including *schizophrenia*[1] (p.955), *disturbed behaviour*[2] (p.954), *post-traumatic stress disorder*[3] (p.953), and *social anxiety disorder*[4] (see Phobic Disorders, p.953). It has also been tried in *binge eating*.[5-7] For its use in *bipolar disorder* see above.

1. Tiihonen J, *et al*. Topiramate add-on in treatment-resistant schizophrenia: a randomized, double-blind, placebo-controlled, crossover trial. *J Clin Psychiatry* 2005; **66:** 1012–15.
2. Nickel MK, *et al*. Topiramate treatment of aggression in female borderline personality disorder patients: a double-blind, placebo-controlled study. *J Clin Psychiatry* 2004; **65:** 1515–19.
3. Berlant JL. Prospective open-label study of add-on and monotherapy topiramate in civilians with chronic nonhallucinatory posttraumatic stress disorder. *BMC Psychiatry* 2004; **4:** 24. Available at: http://www.biomedcentral.com/content/pdf/1471-244X-4-24.pdf (accessed 09/06/08)
4. Van Ameringen M, *et al*. An open trial of topiramate in the treatment of generalized social phobia. *J Clin Psychiatry* 2004; **65:** 1674–8.
5. Nickel C, *et al*. Topiramate treatment in bulimia nervosa patients: a randomized, double-blind, placebo-controlled trial. *Int J Eat Disord* 2005; **38:** 295–300.
6. Tata AL, Kockler DR. Topiramate for binge-eating disorder associated with obesity. *Ann Pharmacother* 2006; **40:** 1993–7.
7. Claudino AM, *et al*. Double-blind, randomized, placebo-controlled trial of topiramate plus cognitive-behavior therapy in binge-eating disorder. *J Clin Psychiatry* 2007; **68:** 1324–32.

Tremor. A beta blocker is often the first drug used in patients with essential tremor who require regular treatment (p.1231); however, topiramate[1,2] has also been tried.

1. Galvez-Jimenez N, Hargreave M. Topiramate and essential tremor. *Ann Neurol* 2000; **47:** 837–8.
2. Ondo WG, *et al*. Topiramate in essential tremor: a double-blind, placebo-controlled trial. *Neurology* 2006; **66:** 672–7.

Preparations

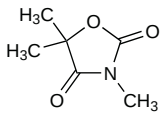
Proprietary Preparations (details are given in Part 3)
Arg.: Neutop; Topamac; Topictal; Topirex; ***Austral.:*** Topamax; ***Austria:*** Topamax; ***Belg.:*** Topamax; ***Braz.:*** Topamax; ***Canad.:*** Topamax; ***Chile:*** Topamax; Toprel; ***Cz.:*** Topamax; Topiragis; ***Denm.:*** Epitomax; Topimax; ***Fin.:*** Topimax; ***Fr.:*** Epitomax; ***Ger.:*** Topamax; ***Gr.:*** Topamac; ***Hong Kong:*** Topamax; ***Hung.:*** Topamax; ***India:*** Topamac; Topamate; ***Indon.:*** Topamax; ***Irl.:*** Topamax; ***Israel:*** Topamax; ***Ital.:*** Topamax; ***Malaysia:*** Topamax; ***Mex.:*** Topamax; ***Neth.:*** Epitomax; Topamax; ***Norw.:*** Topimax; ***NZ:*** Topamax; ***Philipp.:*** Topamax; ***Pol.:*** Topamax; ***Port.:*** Topamax; Toptrix; ***Rus.:*** Topamax (Топамакс); ***S.Afr.:*** Topamax; ***Singapore:*** Topamax; ***Spain:*** Bipomax; Topamax; ***Swed.:*** Topimax; ***Switz.:*** Topamax; ***Thai.:*** Topamax; ***Turk.:*** Topamax; ***UK:*** Topamax; ***USA:*** Topamax; ***Venez.:*** Topamax.

Trimethadione *(BAN, rINN)*

Trimetadion; Trimetadiona; Trimetadionas; Trimetadioni; Trimethadion; Triméthadione; Trimethadionum; Trimethinum; Troxidone. 3,5,5-Trimethyl-1,3-oxazolidine-2,4-dione.

Триметадион

$C_6H_9NO_3$ = 143.1.
CAS — 127-48-0.
ATC — N03AC02.
ATC Vet — QN03AC02.



Pharmacopoeias. In *Eur.* (see p.vii), *Int.*, and *Jpn.*
Ph. Eur. 6.2 (Trimethadione). Colourless or almost colourless crystals. Soluble in water; very soluble in alcohol. Protect from light.

Profile

Trimethadione is an oxazolidinedione antiepileptic that has been given in the treatment of absence seizures refractory to other antiepileptics. However, because of its potential toxicity, other antiepileptics are preferred (see under Epilepsy, p.465).

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

Pregnancy. Characteristic congenital malformations, termed the fetal trimethadione syndrome, have been associated with the use of trimethadione in pregnancy.

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

Preparations

Valproate

Valproato.

Вальпроат

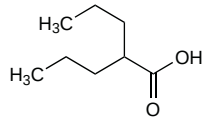
NOTE. Valproate is a generic term applied to valproic acid and its salts and esters.

Valproic Acid *(BAN, USAN, rINN)*

Abbott-44089; Acide valproïque; Ácido dipropilacético; Ácido valproico; Acidum valproicum; Kyselina valproová; Valproiinihappo; Valproik Asit; Valproiné rūgštis; Valproinsav; Valproinsyra. 2-Propylvaleric acid; 2-Propylpentanoic acid.

Вальпроевая Кислота

$C_8H_{16}O_2$ = 144.2.
CAS — 99-66-1.
ATC — N03AG01.
ATC Vet — QN03AG01.



Pharmacopoeias. In *Eur.* (see p.vii) and *US.*
Ph. Eur. 6.2 (Valproic Acid). A colourless or very slightly yellow, slightly viscous, clear liquid. Very slightly soluble in water; miscible with alcohol and with dichloromethane. It dissolves in dilute solutions of alkali hydroxides. Store in airtight containers.
USP 31 (Valproic Acid). A colourless to pale yellow, slightly viscous, clear liquid having a characteristic odour. Slightly soluble in water; freely soluble in alcohol, in acetone, in chloroform, in ether, in methyl alcohol, in benzene, in *n*-heptane, and in 1N sodium hydroxide; slightly soluble in 0.1N hydrochloric acid. Store in airtight glass, stainless steel, or polyethylene containers.

Sodium Valproate *(BANM, rINNM)*

Abbott-44090; Natrii valproas; Natrio valproatas; Natriumvalproaatti; Natriumvalproat; Nátrium-valproát; Natrium-valproát; NIK-240; Sodium, valproate de; Sodyum Valproat; Valproate de Sodium; Valproate Sodium *(USAN)*; Valproato sódico. Sodium 2-propylvalerate; Sodium 2-propylpentanoate.

Натрий Вальпроат

$C_8H_{15}NaO_2$ = 166.2.
CAS — 1069-66-5.
ATC — N03AG01.
ATC Vet — QN03AG01.

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Int.*, *Jpn.*, and *US.*
Ph. Eur. 6.2 (Sodium Valproate). A white or almost white, hygroscopic, crystalline powder. Very soluble in water; slightly to freely soluble in alcohol. Store in airtight containers.
USP 31 (Divalproex Sodium). A white to off-white powder. Soluble in acetone; practically insoluble in acetonitrile; very soluble in chloroform; freely soluble in ethyl ether and in methyl alcohol. Store in airtight containers.

Valproate Pivoxil *(rINN)*

CHF-1504; Valproato de pivoxilo; Valproato pivoxilo; Valproatum Pivoxilum. Hydroxymethyl 2-propylvalerate pivalate.

Вальпроат Пивоксил

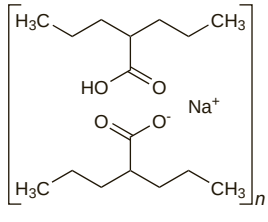
$C_{14}H_{26}O_4$ = 258.4.
CAS — 77372-61-3.
ATC — N03AG01.
ATC Vet — QN03AG01.

Valproate Semisodium *(rINN)*

Abbott-50711; Divalproex Sodium *(USAN)*; Semisodium Valproate *(BAN)*; Valproate Semisodique; Valproato semisódico; Valproatum Seminatricum. 2-Propylvaleric acid—Sodium 2-propylvalerate (1:1); Sodium hydrogen bis(2-propylvalerate) oligomer.

Вальпроат Семинатрий

$C_{16}H_{31}NaO_4$ = 310.4.
CAS — 76584-70-8.
ATC — N03AG01.
ATC Vet — QN03AG01.



Valpromide *(rINN)*

Dipropilacetamida; Dipropylacetamide; Valpromida; Valpromidum. 2-Propylvaleramide.

Вальпромид

$C_8H_{17}NO$ = 143.2.
CAS — 2430-27-5.
ATC — N03AG02.
ATC Vet — QN03AG02.

Adverse Effects

The most frequently reported adverse effects associated with valproate therapy are gastrointestinal disturbances, particularly at the start of therapy; enteric-coated formulations, taking doses with meals, and starting with low doses may minimise symptoms. There may be increased appetite, and weight gain is common.

Less common adverse effects include oedema, headache, reversible prolongation of bleeding time, and thrombocytopenia. Leucopenia and bone marrow depression have been reported. Neurological adverse effects including ataxia, tremor, sedation, lethargy, confusion, and more rarely encephalopathy and coma, have occasionally been reported, although these are often associated with too high a starting dose, increasing doses too rapidly, or use with other antiepileptics. Very rare cases of extrapyramidal symptoms or reversible dementia associated with cerebral atrophy have been reported. Increased alertness may occur, which is generally considered beneficial, but occasionally aggression, hyperactivity, and behavioural disturbances have been reported. Hearing loss has been noted. There may occasionally be rashes, and, rarely, hirsutism, acne, toxic epidermal necrolysis and Stevens-Johnson syndrome or erythema multiforme. Transient hair loss, sometimes with regrowth of curly hair, has occurred. Irregular periods, amenorrhoea, and gynaecomastia have been reported rarely.

Liver dysfunction including hepatic failure has occasionally been reported, usually in the first few months of treatment, and requires valproate withdrawal; there have been fatalities. Elevation of liver enzyme values is common but normally transient and dose-related. Hyperammonaemia has occurred, even in the absence of overt hepatic failure, and is sometimes associated with neurological symptoms; hyperglycinaemia has also been reported. Pancreatitis has also been reported rarely, and fatalities have occurred; plasma amylase should be measured if there is acute abdominal pain, although the value of serum amylase as a diagnostic tool has been questioned—see Effects on the Pancreas, below. In a few patients there have been reports of reversible defects in renal tubular function (Fanconi's syndrome).

Congenital malformations have been reported in infants born to women who had received antiepileptics including valproate during pregnancy.

Inflammatory reactions and pain have been reported at the injection site after intravenous doses.

Incidence of adverse effects. Adverse effects were present in 71 of 88 children receiving sodium valproate monotherapy[1] and, although average doses in these patients were significantly higher than in the 17 with no adverse effects, no difference in the plasma concentrations was observed between the 2 groups.

- Behavioural alterations seen in 56 included irritability, longer and deeper sleep, superficial sleep, hyperactivity, being more alert, lassitude, drowsiness, being more sociable, calmness, being happier, absent mindedness, being sadder, aggressiveness, being more skillful, and docility; it was emphasised that stimulatory reactions were as frequent as depressant effects
- Digestive disorders occurred in 43 children with anorexia, abdominal pain, and nausea and vomiting being the most frequent; diarrhoea, constipation, an increase in appetite, and a gain in weight also occurred. With the exception of a temporary increase in plasma transaminase concentrations in 2 patients, hepatic or pancreatic dysfunction was not seen
- Neurological changes in the form of tremor, paraesthesia, or ataxia, occurring in only 4 patients, were less frequent than either behavioural or digestive reactions
- Miscellaneous reactions including polydipsia, polyuria, diaphoresis, enuresis, hair loss, change in hair colour or texture, and rash were seen in 23 children