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

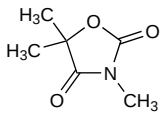
Proprietary Preparations (details are given in Part 3)
Arg.: Neutop; Topamac; Topictal; Topirex; ***Austral.:*** Topamax; ***Austria:*** Topamax; ***Belg.:*** Topamax; ***Braz.:*** Topamax; ***Canad.:*** Topamax; ***Chile:*** Topamax; Toprel; ***Cz.:*** Topamax; Topiragis; ***Denm.:*** Epitomax; Topimax; ***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

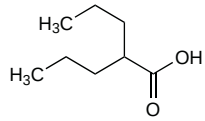
NOTE. Valproate is a generic term applied to valproic acid and its salts and esters.

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

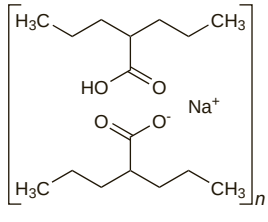
$C_{14}H_{26}O_4$ = 258.4.
CAS — 77372-61-3.
ATC — N03AG01.
ATC Vet — QN03AG01.

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

- Of the 71 children experiencing reactions, therapy continued unchanged in 56, was changed in 3 either by altering the pharmaceutical formulation (syrup, tablets, granules), by changing the frequency of dosing, or by reducing the dose in 6, and in the remaining 9 children valproate therapy was stopped

1. Herranz JL, *et al.* Side effects of sodium valproate in monotherapy controlled by plasma levels: a study in 88 pediatric patients. *Epilepsia* 1982; **23:** 203–14.

Carnitine deficiency. Carnitine deficiency may occasionally arise during long-term use of valproate; although it is unclear whether carnitine supplementation (p.1933) is of value in children receiving valproate, some neurologists consider it justified in selected cases, including those with, or at risk of, valproate-induced hepatotoxicity.[1,2]

1. De Vivo DC, *et al.* -Carnitine supplementation in childhood epilepsy: current perspectives. *Epilepsia* 1998; **39:** 1216–25.
2. Lheureux PER, *et al.* Science review: carnitine in the treatment of valproic acid-induced toxicity—what is the evidence? *Crit Care* 2005; **9:** 431–40.

Effects on the blood. A number of reports have implicated valproate as a cause of occasional neutropenia,[1-3] leucopenia,[4] and thrombocytopenia.[2] A 1-year prospective study involving 45 patients found that absolute neutropenia developed in 12 and thrombocytopenia in 15, but that the disorders were transient and self-limiting.[2] However, neutropenia has occasionally been sufficiently severe to warrant withdrawal of valproate.[5] Red cell aplasia has also been associated with valproate therapy.[6,7] A study[8] involving 30 children indicated that valproate might produce symptoms similar to those of von Willebrand's disease; 19 of the 30 had a history of minor haemorrhage during therapy, and 7 had abnormal bleeding times. Factor VIII therapy might need to be given in patients receiving valproate who underwent surgery or in whom bleeding was severe.

For a discussion of the effects of antiepileptics, including valproate, on serum folate, see under Phenytoin, p.495.

1. Jaeken J, *et al.* Neutropenia during sodium valproate treatment. *Arch Dis Child* 1979; **54:** 986–7.
2. Barr RD, *et al.* Valproic acid and immune thrombocytopenia. *Arch Dis Child* 1982; **57:** 681–4.
3. Vesta KS, Medina PJ. Valproic acid-induced neutropenia. *Ann Pharmacother* 2003; **37:** 819–21.
4. Coulter DL, *et al.* Valproic acid therapy in childhood epilepsy. *JAMA* 1980; **244:** 785–8.
5. Symon DNK, Russell G. Sodium valproate and neutropenia. *Arch Dis Child* 1983; **58:** 235.
6. MacDougall LG. Pure red cell aplasia associated with sodium valproate therapy. *JAMA* 1982; **247:** 53–4.
7. Watts RG, *et al.* Valproic acid-induced cytopenias: evidence for a dose-related suppression of hematopoiesis. *J Pediatr* 1990; **117:** 495–9.
8. Kreuz W, *et al.* Induction of von Willebrand disease type I by valproic acid. *Lancet* 1990; **335:** 1350–1.

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

Effects on the endocrine system. An early study[1] reported that menstrual disturbances were associated more often with valproate than with other antiepileptics among 238 women with epilepsy; 80% of those treated with valproate before 20 years of age had polycystic ovaries or hyperandrogenism. A later study[2] found that the occurrence of polycystic ovaries in 105 epileptic women taking carbamazepine or valproate was no greater than that in the general population, although valproate appeared to increase glucose-stimulated pancreatic insulin secretion. Subsequent studies[3-5] and reviews[6-9] support the association between valproate therapy and reproductive endocrine disorders and metabolic disturbances in female patients with epilepsy. However, a causal link could not be established since epilepsy itself affects the endocrine system. Symptoms such as hyperandrogenism, menstrual disturbances, polycystic ovaries, weight gain, and insulin resistance have been attributed to the development of polycystic ovary syndrome (p.2080) in some patients. Other adverse effects of valproate on the endocrine system include dyslipidaemia, hypocalcaemia, and hypothyroidism.

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

1. Isojärvi JIT, *et al.* Polycystic ovaries and hyperandrogenism in women taking valproate for epilepsy. *N Engl J Med* 1993; **329:** 1383–8.
2. Luef G, *et al.* Polycystic ovaries, obesity and insulin resistance in women with epilepsy: a comparative study of carbamazepine and valproic acid in 105 women. *J Neurol* 2002; **249:** 835–41.
3. Betts T, *et al.* A study of anticonvulsant medication on ovarian function in a group of women with epilepsy who have only ever taken one anticonvulsant compared with a group of women without epilepsy. *Seizure* 2003; **12:** 323–9.
4. Mikkonen K, *et al.* Long-term reproductive endocrine health in young women with epilepsy during puberty. *Neurology* 2004; **62:** 445–50.
5. Tan H, *et al.* Valproate-induced insulin resistance in prepubertal girls with epilepsy. *J Pediatr Endocrinol Metab* 2005; **18:** 985–9. Correction. *ibid.*; 1134.
6. Morrell MJ. Reproductive and metabolic disorders in women with epilepsy. *Epilepsia* 2003; **44** (suppl 4): 11–20.
7. Rasgon N. The relationship between polycystic ovary syndrome and antiepileptic drugs: a review of the evidence. *J Clin Psychopharmacol* 2004; **24:** 322–34.
8. Verrotti A, *et al.* Endocrine and metabolic changes in epileptic patients receiving valproic acid. *J Pediatr Endocrinol Metab* 2005; **18:** 423–30.
9. Isojärvi J. Disorders of reproduction in patients with epilepsy: antiepileptic drug related mechanisms. *Seizure* 2008; **17:** 111–19.

Effects on the liver. An early review[1] of the hepatotoxicity of valproate included an analysis of 42 cases with fatal hepatitis, 3 cases with a Reye's-like syndrome, and 22 instances of hyperammonaemia:

- In 19 studies the incidence of *abnormal serum aminotransferase* activity ranged from 0 to 44% with an overall incidence of 11% in the 1197 patients monitored; in the non-fatal cases activity was usually between one and three times the upper limit of normal and was not usually, except in the most severe cases, accompanied by rises in serum bilirubin or alkaline phosphatase
- In the 42 cases of *hepatitis* with a fatal outcome the age at presentation ranged from 2.5 months to 34 years with 69% aged 10 years or less. Below the age of 15 years the proportion of males was 62.5% but above this age it was 30%; the disproportionate vulnerability of young individuals, particularly boys, did not appear to be a reflection of prescribing habits in that age group. In more than two-thirds of these patients with a fatal outcome, prodromal symptoms comprised anorexia and vomiting, loss of epilepsy control, impaired consciousness, and ataxia; in about one-third there were signs of liver damage with fever, jaundice, ascites, peripheral oedema, and easy bruising. In all of the patients hepatic coma developed. In 36 patients on whom data were available the onset of hepatic illness in one-third occurred between 1 and 2 months and in only 2 patients did the onset occur after more than 5 months. Of these 42 patients with fatal hepatotoxicity 36 were also given other drugs, mostly antiepileptics
- The 3 children with a *Reye's-like syndrome* all died within 3 weeks of the first occurrence of symptoms as a result of cerebral oedema (2) or aspiration pneumonia (1)
- In the 22 patients with symptomatic *hyperammonaemia*, characterised usually by impaired consciousness and ataxia, but without overt liver disease, withdrawal of valproate resulted in all becoming asymptomatic and biochemical abnormalities returned to normal. Hyperammonaemia has also been reported in asymptomatic patients

Hyperammonaemia and encephalopathy may also be precipitated when valproate is used with certain drugs (see under Antibacterials, p.510 and Antiepileptics, p.511, in Interactions).

Various hypotheses for the cause of valproate hepatotoxicity have been discussed in detail.[2]

Analysis of deaths in the USA attributed to valproate liver toxicity identified a decline in the incidence of fatalities as use in young children and use with other antiepileptics declined.[3] However, occasional reports still occur in some countries.[4]

1. Powell-Jackson PR, *et al.* Hepatotoxicity to sodium valproate: a review. *Gut* 1984; **25:** 673–81.
2. Eadie MJ, *et al.* Valproate-associated hepatotoxicity and its biochemical mechanisms. *Med Toxicol* 1988; **3:** 85–106.
3. Dreifuss FE, *et al.* Valproic acid hepatic fatalities: II US experience since 1984. *Neurology* 1989; **39:** 201–7.
4. Koenig SA, *et al.* Valproic acid-induced hepatopathy: nine new fatalities in Germany from 1994 to 2003. *Epilepsia* 2006; **47:** 2027–31.

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

Effects on the nervous system. An *extrapyramidal* syndrome of tremor and rigidity, unresponsive to benzatropine or trihexyphenidyl, developed in a 52-year-old man with schizophrenia given a therapeutic trial of sodium valproate 1 to 2 g daily.[1] Giving sodium valproate to a man with dystonic movements of the neck and spine produced a severe subjective and objective deterioration in his symptoms, which returned to their previous severity on withdrawal of the drug.[2] There have also been reports[3,4] of *parkinsonism* associated with valproate antiepileptic therapy; onset was usually insidious and progressive, occurring after several years of good tolerability. A case series[4] also reported *cognitive impairment* in 6 of 10 patients who developed parkinsonism. In most cases symptoms improved on stopping valproate.

Spasmodic dysphonia associated with valproate has been reported;[5] symptoms resolved when the dose of valproate was reduced.

A *stuporous state* associated with EEG abnormalities has been described[6,7] during valproate therapy for complex partial or mixed seizure types and it was suggested that in certain forms of epilepsy valproate may exhibit a paradoxical epileptogenic effect. Other findings[8] have argued against an epileptic origin for valproate-induced stupor.

1. Lautin A, *et al.* Extrapyramidal syndrome with sodium valproate. *BMJ* 1979; **2:** 1035–6.
2. Dick DJ, Saunders M. Extrapyramidal syndrome with sodium valproate. *BMJ* 1980; **280:** 189.
3. Easterford K, *et al.* Reversible parkinsonism with normal β-CIT-SPECT in patients exposed to sodium valproate. *Neurology* 2004; **62:** 1435–7.
4. Masmoudi K, *et al.* Parkinsonism and/or cognitive impairment with valproic acid therapy: a report of ten cases. *Pharmacopsychiatry* 2006; **39:** 9–12.
5. Oh J, *et al.* Spasmodic dysphonia induced by valproic acid. *Epilepsia* 2004; **45:** 880–1.
6. Marescaux C, *et al.* Stuporous episodes during treatment with sodium valproate: report of seven cases. *Epilepsia* 1982; **23:** 297–305.
7. Stecker MM, Kita M. Paradoxical response to valproic acid in a patient with a hypothalamic hamartoma. *Ann Pharmacother* 1998; **32:** 1168–72.
8. Aguglia U, *et al.* Negative myoclonus during valproate-related stupor: neurophysiological evidence of a cortical non-epileptic origin. *Electroencephalogr Clin Neurophysiol* 1995; **94:** 103–8.

Effects on the pancreas. An early report of 4 cases of pancreatitis associated with valproic acid therapy also reviewed 10 previously published cases.[1] None of the 14 patients, 2 of whom died, suffered other symptoms of a toxic reaction to valproic acid. Pancreatitis was not dose-related and had developed as early as one week and as late as 4.5 years after the introduction of therapy. Symptoms recurred on rechallenge in 6 of 7 patients. However, routine monitoring of serum-amylase concentrations in asymptomatic patients did not seem necessary. In February 1994 the UK CSM commented[2] in a review of drug-induced pancreatitis that they had received 29 reports of pancreatitis, including 2 fatalities, associated with sodium valproate. A later review[3] of 22 children who developed pancreatitis while taking valproate (2 of whom died) found that duration of therapy, dose, serum concentrations, and polytherapy were not risk factors. The authors advised against rechallenge as the rate of relapse is high. Serum amylase concentrations were found to be nondiagnostic in 39% of these patients, and the authors considered that serum lipase concentrations were far more likely to be elevated.

1. Wyllie E, *et al.* Pancreatitis associated with valproic acid therapy. *Am J Dis Child* 1984; **138:** 912–14.
2. Committee on Safety of Medicines/Medicines Control Agency. Drug-induced pancreatitis. *Current Problems* 1994; **20:** 2–3. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024457&RevisionSelectionMethod=LatestReleased (accessed 01/09/08)
3. Werlin SL, Fish DL. The spectrum of valproic acid-associated pancreatitis. *Pediatrics* 2006; **118:** 1660–3.

Effects on the skin, hair, and nails. Five of 250 patients developed curly hair during treatment with sodium valproate 1 g daily;[1] in 3 patients this effect followed temporary alopecia. Another report of hair curling in a patient who received sodium valproate in doses up to 3 g daily for 30 months commented that her hair started to revert to the former straight style 9 months after stopping the drug.[2]

Valproate-induced nicotinic-acid deficiency with an associated pellagra-like syndrome has been reported in a young boy;[3] the condition responded dramatically to treatment with nicotinamide.

Reduced serum-zinc concentrations and cutaneous manifestations of zinc deficiency were found in 2 patients receiving antiepileptic drugs.[4] It was thought that deficiency resulted from chelation by sodium valproate, and possibly phenytoin, in association with malabsorption and that, in one case, malabsorption was triggered by valproate.

Cutaneous vasculitis has been reported[5] in 2 patients taking sodium valproate. The reaction recurred on rechallenge.

Very rarely, skin rashes occurring with valproate may form part of an antiepileptic hypersensitivity syndrome (see below). Valproate might share the same order of risk as other antiepileptics for the development of Stevens-Johnson syndrome and toxic epidermal necrolysis,[6] although it had previously been regarded as safer in this respect. For a suggestion that skin reactions are less common with valproate than with some other antiepileptics see under Phenytoin, p.496.

Reversible yellow nail pigmentation has been reported[7] in a woman who was taking valproate semisodium.

1. Jeavons PM, *et al.* Valproate and curly hair. *Lancet* 1977; **i:** 359.
2. Gupta AK. 'Perming' effects associated with chronic valproate therapy. *Br J Clin Pract* 1988; **42:** 75–7.
3. Gillman MA, Sandyk R. Nicotinic acid deficiency induced by sodium valproate. *S Afr Med J* 1984; **65:** 986.
4. Lewis-Jones MS, *et al.* Cutaneous manifestations of zinc deficiency during treatment with anticonvulsants. *BMJ* 1985; **290:** 603–4.
5. Kamper AM, *et al.* Cutaneous vasculitis induced by sodium valproate. *Lancet* 1991; **337:** 497–8.
6. Anonymous. Drugs as risk factors in severe cutaneous diseases. *WHO Drug Inf* 1996; **10:** 33–5.
7. Buka R, *et al.* Yellow nail pigmentation following Depakote therapy. *J Drugs Dermatol* 2003; **2:** 545–7.

Enuresis. Nocturnal enuresis associated with sodium valproate therapy has been reported[1] in 2 children. Remission of the enuresis was achieved either by reducing or redistributing the doses. Several studies have recorded enuresis as an adverse effect of valproate in children,[2] the frequency being between 1 and 7%. The most likely explanations are that either it is secondary to a central effect on the thirst centre resulting in polydipsia or it is a consequence of the increased depth of sleep associated with valproate.

1. Panayiotopoulos CP. Nocturnal enuresis associated with sodium valproate. *Lancet* 1985; **i:** 980–1.
2. Choonara IA. Sodium valproate and enuresis. *Lancet* 1985; **i:** 1276.

Hypersensitivity. An antiepileptic hypersensitivity syndrome, comprising fever, rash, and lymphadenopathy and less commonly lymphocytosis, and liver and other organ involvement, has been associated with some aromatic antiepileptic drugs; however, there have also been case reports[1-3] associated with valproate, a non-aromatic compound. In one case[1] a patient developed these symptoms with carbamazepine but they resolved when the drug was stopped; however, when valproate was started 2 weeks later the symptoms reappeared. Another report[2] described a fatal case occurring in a 2-year-old girl who developed fulminant hepatitis.

1. Arévalo-Lorido JC, *et al.* Antiepileptic drug hypersensitivity syndrome in a patient treated with valproate. *Br J Clin Pharmacol* 2003; **55:** 415–16.
2. Huang Y-L, *et al.* Fatal sodium valproate-induced hypersensitivity syndrome with lichenoid dermatitis and fulminant hepatitis. *J Am Acad Dermatol* 2003; **49:** 316–19.
3. Roepke S, *et al.* Valproic acid and hypersensitivity syndrome. *Am J Psychiatry* 2004; **161:** 579.

Overdosage. A cohort study[1] of valproate poisonings reported to a regional toxicology centre between January 1991 and November 2001 reported 79 cases. Of these, valproate was the only drug taken in 15 cases with a median dose of 15 g; symptoms were mild and included drowsiness (2 patients), vomiting (4), and tachycardia (5). The authors concluded that overdoses of more than 400 mg/kg could cause severe, potentially life-threatening toxicity, but these were uncommon. Symptoms of severe toxicity include significant CNS depression, respiratory insufficiency, and multi-organ failure; fatalities have been reported.[2] Children younger than 2 years of age are considered to be at significant risk for developing fatal valproate-induced hepatotoxicity in overdose; there has been a report of a 26-day-old neonate who died 42 hours after receiving a dose of 75 mg/kg.[3]

1. Isbister GK, *et al.* Valproate overdose: a comparative cohort study of self poisonings. *Br J Clin Pharmacol* 2003; **55:** 398–404.
2. Eyer F, *et al.* Acute valproate poisoning: pharmacokinetics, alteration in fatty acid metabolism, and changes during therapy. *J Clin Psychopharmacol* 2005; **25:** 376–80.
3. Unal E, *et al.* Fatal valproate overdose in a newborn baby. *Hum Exp Toxicol* 2007; **26:** 453–6.

Treatment of Adverse Effects

The value of gastric decontamination for overdose is uncertain since valproic acid and its salts are rapidly absorbed. Activated charcoal may be given orally to adults and children who present within 1 hour of ingesting more than 100 mg/kg; alternatively gastric lavage may be considered in adults within 1 hour of a potentially life-threatening overdose. Supportive therapy alone may then suffice although haemodialysis should be considered in very severe poisoning.

◊ A variety of active treatments including forced diuresis, whole bowel irrigation, naloxone, and haemodialysis or haemoperfusion have been advocated for valproate overdose;[1,2] however, supportive measures provided sufficient treatment for a patient who had taken 25 g of sodium valproate.[1] For a further review of the features and management of poisoning with some antiepileptics such as valproate, see under Phenytoin, p.497.

1. Lakhani M, McMurdo MET. Survival after severe self poisoning with sodium valproate. *Postgrad Med J* 1986; **62:** 409–10.
2. Sztajnkrycer MD. Valproic acid toxicity: overview and management. *J Toxicol Clin Toxicol* 2002; **40:** 789–801. Correction. *ibid.* 2003; **41:**215.

Precautions

Valproate is contra-indicated in patients with pre-existing liver disease or a family history of severe hepatic dysfunction. Children under 3 years of age and those with congenital metabolic or degenerative disorders, organic brain disease, or severe seizure disorders associated with mental retardation may be at particular risk of hepatotoxicity and the drug should be used with particular caution in these groups. Use with other antiepileptics, which may also increase the risks of liver damage, should be avoided if possible. Liver function tests should be carried out, particularly in those most at risk, before and during the first 6 months of therapy. Raised liver enzymes are not uncommon during treatment and are usually transient or respond to reduction in dosage, but patients should be reassessed clinically and liver function, including prothrombin time, monitored until they return to normal. An abnormally prolonged prothrombin time, particularly in association with other relevant abnormalities, requires treatment to be stopped. If given with salicylates, these should also be stopped. Treatment should also be stopped if pancreatitis is diagnosed.

Patients or their carers should be told how to recognise signs of blood and liver toxicity or pancreatitis, and they should be advised to seek immediate medical attention if symptoms develop.

Patients should be monitored for potential bleeding complications before major elective surgery; some licensed product information suggests regular monitoring before and during therapy.

Valproate should be used with caution if the patient is at risk of SLE.

Patients should be warned of the risk of weight gain and appropriate strategies adopted to minimise the effect.

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

The protein binding of valproate is saturable and thus shows concentration dependency; significant increases in free drug occur at high total plasma concentrations.

Because valproate is partly excreted in the form of ketone bodies, it may cause false positives in urine tests for diabetes mellitus.

Dosage adjustments may be necessary in severe renal impairment in accordance with free serum valproate levels.

Breast feeding. Thrombocytopenic purpura and anaemia occurred in a breast-fed infant whose mother was being treated with valproic acid.[1] The baby recovered when breast feeding was stopped. Low serum-valproate levels were detected[2] in 6 breast-fed infants whose mothers had been taking valproate semisodium post partum; no adverse effects were seen in the infants. Similar results have previously been obtained for patients taking sodium valproate[3] or valproic acid.[4] The American Academy of Pediatrics considers[5] that valproate is, therefore, usually compatible with breast feeding.

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

1. Stahl MMS, *et al.* Thrombocytopenic purpura and anemia in a breast-fed infant whose mother was treated with valproic acid. *J Pediatr* 1997; **130:** 1001–3.
2. Piontek CM, *et al.* Serum valproate levels in 6 breastfeeding mother-infant pairs. *J Clin Psychiatry* 2000; **61:** 170–2.
3. Alexander FW. Sodium valproate and pregnancy. *Arch Dis Child* 1979; **54:** 240.
4. von Unruh GE, *et al.* Valproic acid in breast milk: how much is really there? *Ther Drug Monit* 1984; **6:** 272–6.
5. 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)

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

HIV infection and AIDS. Limited data from several small *in-vitro* studies have found that valproic acid may induce viral replication of HIV;[1] some clinicians have therefore suggested increased monitoring of viral load in HIV-positive patients treated with valproic acid. For the use of this effect to reduce latent viral load see under Uses and Administration, below.

1. Jennings HR, Romanelli F. The use of valproic acid in HIV-positive patients. *Ann Pharmacother* 1999; **33:** 1113–16.

Porphyria. Valproate is considered to be unsafe in patients with porphyria because it has been shown to be porphyrinogenic in *animals* or *in-vitro* systems. There is conflicting evidence of the porphyrinogenicity of valpromide, although it has also been shown to be porphyrinogenic in *in-vitro* systems.

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

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 valproate and craniofacial and digital abnormalities and, less commonly, cleft lip and palate have been described, which may form part of a fetal antiepileptic syndrome.[1] In an unselected series[2] of 17 infants whose epileptic mothers had received valproate during pregnancy, 9 had minor abnormalities and of these 5 also had major abnormalities, including congenital heart defect in 4. In another series,[3] involving 149 women whose offspring were exposed to valproate monotherapy in the first trimester, 16 infants with major malformations were identified (a relative risk calculated at about 7 times that in the population at large). The abnormalities reported included craniosynostosis, spina bifida, and pulmonary atresia. A population-based study[4] of 2350 births to epileptic women between 1991 and 2000 found that the offspring of mothers who were given valproate, as mono- or polytherapy, in the first trimester had a fourfold increase in risk for congenital malformations compared with untreated mothers; the risk was tenfold in those who were given daily doses of more than 1.5 g. The risk of malformations was not increased in the offspring of mothers taking carbamazepine, oxcarbazepine, or phenytoin as mono- or polytherapy without valproate.

Neonatal bleeding, attributed to fibrinogen depletion and sometimes fatal, has been reported after exposure *in utero* to valproate.[5,6] Hypoglycaemia was recorded[7] in 13 of 22 neonates whose mothers had taken valproate during pregnancy. Valproate-withdrawal symptoms, including irritability, jitteriness, hypertonia, seizures, and feeding problems were also noted.

1. Genton P, *et al.* Valproic acid in epilepsy: pregnancy-related issues. *Drug Safety* 2006; **29:** 1–21.
2. Thisted E, Ebbesen F. Malformations, withdrawal manifestations, and hypoglycaemia after exposure to valproate in utero. *Arch Dis Child* 1993; **69:** 288–91.
3. Wyszynski DF, *et al.* Increased rate of major malformations in offspring exposed to valproate during pregnancy. *Neurology* 2005; **64:** 961–5.
4. Artama M, *et al.* Antiepileptic drug use of women with epilepsy and congenital malformations in offspring. *Neurology* 2005; **64:** 1874–8.
5. Majer RV, Green PJ. Neonatal afibrinogenaemia due to sodium valproate. *Lancet* 1987; **ii:** 740–1.
6. Bavoux F, *et al.* Neonatal fibrinogen depletion caused by sodium valproate. *Ann Pharmacother* 1994; **28:** 1307.
7. Ebbesen F, *et al.* Neonatal hypoglycaemia and withdrawal symptoms after exposure in utero to valproate. *Arch Dis Child Fetal Neonatal Ed* 2000; **83:** F124–F129.

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. Caution is recommended when giving valproate with other drugs liable to interfere with blood coagulation, such as aspirin or warfarin. Use with other hepatotoxic drugs should be avoided. Use of highly protein bound drugs with valproate may increase free valproate plasma concentrations.

◊ General references.

1. Levy RH, Koch KM. Drug interactions with valproic acid. *Drugs* 1982; **24:** 543–56.

Analgesics. The free fraction of valproate was increased eightfold in a 76-year-old man[1] who was also given *aspirin* 325 mg daily, resulting in signs of clinical toxicity. Aspirin displaces valproate from plasma protein binding sites, as well as inhibiting its metabolism by inhibition of beta-oxidation. Similarly, the valproic acid free fraction was reported to be increased, as was the half-life, when aspirin was given in a study in 6 epileptic children.[2] Furthermore, salicylates have been associated with an increased risk of Reye's syndrome (p.22) in children, and combination with another hepatotoxic drug such as valproate is clearly undesirable. In addition, both aspirin and valproate affect blood coagulation and platelet function.

Naproxen has also been reported to produce a slight displacement of protein-bound valproic acid but the effect is probably not sufficiently marked for it to have a clinical effect.[3]

1. Sandson NB, *et al.* An interaction between aspirin and valproate: the relevance of plasma protein displacement drug-drug interactions. *Am J Psychiatry* 2006; **163:** 1891–6.
2. Orr JM, *et al.* Interaction between valproic acid and aspirin in epileptic children: serum protein binding and metabolic effects. *Clin Pharmacol Ther* 1982; **31:** 642–9.
3. Grimaldi R, *et al.* In vivo plasma protein binding interaction between valproic acid and naproxen. *Eur J Drug Metab Pharmacokinet* 1984; **9:** 359–63.

Antibacterials. Raised valproate blood concentrations and symptoms consistent with valproate toxicity have been reported in a patient also given *erythromycin*.[1]

There is a theoretical possibility that carnitine deficiency may be increased in patients receiving *pivampicillin* and valproate. Hyperammonaemic encephalopathy developed in a 72-year-old woman who had been taking valproate for 10 months when she was given *pivmecillinam* for a urinary-tract infection. It was suggested that valproate's propensity to produce hyperammonaemia had been exacerbated by a secondary hyperammonaemia induced by both drugs reducing carnitine concentrations.[2]

Decreases in plasma concentrations of valproate to subtherapeutic levels (and sometimes with loss of seizure control) have been noted in patients during therapy with antibacterial treatment containing *ertapenem*,[3] *imipenem*,[4] or *meropenem*.[4-8] Marked reductions in valproate concentrations have also been reported in 3 children given *panipenem* (with betamipron).[9]

Increased serum-valproate concentrations resulting in signs of valproate toxicity occurred in a child after beginning therapy with *isoniazid*;[10] the child was a slow acetylator of isoniazid and valproate dosage had to be reduced by about 60% to maintain satisfactory concentrations. When isoniazid was subsequently stopped, valproate dosage had to be increased to its previous value in order to maintain a therapeutic effect.

1. Redington K, *et al.* Erythromycin and valproate interaction. *Ann Intern Med* 1992; **116:** 877–8.
2. Lokrantz C-M, *et al.* Hyperammonemic encephalopathy induced by a combination of valproate and pivmecillinam. *Acta Neurol Scand* 2004; **109:** 297–301.
3. Lunde JL, *et al.* Acute seizures in a patient receiving divalproex sodium after starting ertapenem therapy. *Pharmacotherapy* 2007; **27:** 1202–5.

4. Llinares Tello F, *et al.* Interacción farmacocinética entre ácido valproico y antibióticos carbapenémicos: descripción de tres casos. *Farm Hosp* 2003; **27:** 258–63.
5. De Turck BJG, *et al.* Lowering of plasma valproic acid concentrations during concomitant therapy with meropenem and amikacin. *J Antimicrob Chemother* 1998; **42:** 563–4.
6. Coves-Orts FJ, *et al.* Acute seizures due to a probable interaction between valproic acid and meropenem. *Ann Pharmacother* 2005; **39:** 533–7.
7. Fudio S, *et al.* Epileptic seizures caused by low valproic acid levels from an interaction with meropenem. *J Clin Pharm Ther* 2006; **31:** 393–6.
8. Spriet I, *et al.* Interaction between valproate and meropenem: a retrospective study. *Ann Pharmacother* 2007; **41:** 1130–6.
9. Nagai K, *et al.* Decrease in serum levels of valproic acid during treatment with a new carbapenem, panipenem/betamipron. *J Antimicrob Chemother* 1997; **39:** 295–6.
10. Jonville AP, *et al.* Interaction between isoniazid and valproate: a case of valproate overdosage. *Eur J Clin Pharmacol* 1991; **40:** 197–8.

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

There have been conflicting reports of the effect of *fluoxetine* on serum concentrations of valproate. While some reported an increase,[1-3] others have reported a decrease[4] in valproate-serum concentrations when the 2 drugs were used together.

For the effect of valproate on *amitriptyline*, see p.380.

1. Sovner R, Davis JM. A potential drug interaction between fluoxetine and valproic acid. *J Clin Psychopharmacol* 1991; **11:** 389.
2. Lucena MI, *et al.* Interaction of fluoxetine and valproic acid. *Am J Psychiatry* 1998; **155:** 575.
3. Cruz-Flores S, *et al.* Valproic toxicity with fluoxetine therapy. *Mo Med* 1995; **92:** 296–7.
4. Droulers A, *et al.* Decrease of valproic acid concentration in the blood when coprescribed with fluoxetine. *J Clin Psychopharmacol* 1997; **17:** 139–40.

Antiepileptics. The barbiturate antiepileptic *phenobarbital* is reported to decrease serum-valproate concentrations when given together,[1] apparently by induction of valproate metabolism.[2] This effect is overshadowed, however, by the marked increase in serum-phenobarbital concentrations caused by valproate inhibition of phenobarbital metabolism—see p.493. It has been suggested that phenobarbital may also increase the risk of valproate-induced hyperammonaemic encephalopathy.[3]

Carbamazepine and *phenytoin* are also enzyme-inducing drugs and, as might be expected, are reported to increase the metabolism and decrease the serum concentration of valproate.[4-6] The effect may be clinically significant.[7] The reciprocal effects of valproate on both drugs are complex, with conflicting effects on metabolism and protein binding, and the clinical outcome is difficult to predict. For more details see under Carbamazepine, p.474 and Phenytoin, p.498.

Serum concentrations of valproic acid were reduced, with considerable interpatient variability, when *ethosuximide*[8] or *mesuximide*[9] was added to the antiepileptic therapy of some patients.

Raised serum concentrations of valproic acid have been reported in patients given *felbamate*.[10]

Reversible hepatic impairment has been reported[11,12] when *topiramate* was added to valproate therapy in patients who had previously tolerated valproate well. Use of valproate with topiramate has also been associated with hyperammonaemia and encephalopathy.[13]

Valproate inhibits the metabolism of *lamotrigine* which may result in serious toxic reactions—see p.486. There is limited evidence that valproic acid may affect the metabolism of *ethosuximide* in some patients—see p.480. Valproate reduces the half-life of *zonisamide*—see p.515.

For interactions with benzodiazepines, see under Diazepam, p.990.

1. Perucca E. Pharmacokinetic interactions with antiepileptic drugs. *Clin Pharmacokinet* 1982; **7:** 57–84.
2. Levy RH, Koch KM. Drug interactions with valproic acid. *Drugs* 1982; **24:** 543–56.
3. Segura-Bruna N, *et al.* Valproate-induced hyperammonemic encephalopathy. *Acta Neurol Scand* 2006; **114:** 1–7.
4. Panesar SK, *et al.* The effect of carbamazepine on valproic acid disposition in adult volunteers. *Br J Clin Pharmacol* 1989; **27:** 323–8.
5. Reunanen MI, *et al.* Low serum valproic acid concentrations in epileptic patients on combination therapy. *Curr Ther Res* 1980; **28:** 456–62.
6. Cramer JA, *et al.* Variable free and total valproic acid concentrations in sole- and multi-drug therapy. *Ther Drug Monit* 1986; **8:** 411–15.
7. Jann MW, *et al.* Increased valproate serum concentrations upon carbamazepine cessation. *Epilepsia* 1988; **29:** 578–81.
8. Sälke-Kellermann RA, *et al.* Influence of ethosuximide on valproic acid serum concentrations. *Epilepsy Res* 1997; **26:** 345–9.
9. Besag FMC, *et al.* Methsuximide reduces valproic acid serum levels. *Ther Drug Monit* 2001; **23:** 694–7.
10. Wagner ML, *et al.* The effect of felbamate on valproic acid disposition. *Clin Pharmacol Ther* 1994; **56:** 494–502.
11. Longin E, *et al.* Topiramate enhances the risk of valproate-associated side effects in three children. *Epilepsia* 2002; **43:** 451–4.
12. Bumb A, *et al.* Adding topiramate to valproate therapy may cause reversible hepatic failure. *Epileptic Disord* 2003; **5:** 157–9.
13. Latour P, *et al.* Drug induced encephalopathy in six epileptic patients: topiramate? valproate? or both? *Hum Psychopharmacol* 2004; **19:** 193–203.

Antimalarials. Low serum concentrations of valproate have been reported[1] in patients taking *mefloquine.* Also, mefloquine and *chloroquine* may antagonise the antiepileptic activity of valproate by lowering the convulsive threshold.

1. Anonymous. Mefloquine for malaria. *Med Lett Drugs Ther* 1990; **32:** 13–14.

Antineoplastics. A marked reduction in serum-valproate concentration occurred in a 6-year-old child after a high-dose 24-hour infusion of *methotrexate*.[1]

1. Schrøder H, Østergaard JR. Interference of high-dose methotrexate in the metabolism of valproate? *Pediatr Hematol Oncol* 1994; **11:** 445–9.

Antipsychotics. As with all antiepileptics, antipsychotics may antagonise the antiepileptic activity of valproate by lowering the convulsive threshold. Although a study[1] found that *risperidone* had no significant effect on the pharmacokinetics of valproate, 2 earlier case reports showed conflicting results; one[2] described increased serum-valproate concentrations, and the other[3] decreased concentrations, when risperidone was added to valproate therapy. For the effect of valproate on *clozapine*, see p.984.

1. Ravindran A, *et al.* Risperidone does not affect steady-state pharmacokinetics of divalproex sodium in patients with bipolar disorder. *Clin Pharmacokinet* 2004; **43:** 733–40.
2. van Wattum PJ. Valproic acid and risperidone. *J Am Acad Child Adolesc Psychiatry* 2001; **40:** 866–7.
3. Bertoldo M. Valproic acid and risperidone. *J Am Acad Child Adolesc Psychiatry* 2002; **41:** 632.

Antivirals. There have been 2 reports that describe a reduction in plasma-valproate concentrations in HIV-positive patients who were taking valproate for bipolar disorder and were given *efavirenz* in one case[1] and *ritonavir-boosted lopinavir* in another,[2] resulting in mania. However, an earlier study[3] in a small number of HIV-positive patients did not find any clinically significant interactions between these drugs and valproic acid. For the effect of *aciclovir* on valproate, see under Interactions of Phenytoin, p.499.

For the effect of valproate on *zidovudine*, see p.915.

1. Saraga M, *et al.* Reduced valproate plasma levels possible after introduction of efavirenz in a bipolar patient. *Bipolar Disord* 2006; **8:** 415–17.
2. Sheehan NL, *et al.* Possible interaction between lopinavir/ritonavir and valproic acid exacerbates bipolar disorder. *Ann Pharmacother* 2006; **40:** 147–50.
3. DiCenzo R, *et al.* Effects of valproic acid coadministration on plasma efavirenz and lopinavir concentrations in human immunodeficiency virus-infected adults. *Antimicrob Agents Chemother* 2004; **48:** 4328–31.

Anxiolytics. For interactions between valproate and *benzodiazepines*, see under Diazepam, p.990. For an interaction between valproate and *zolpidem*, see p.1038.

Calcium-channel blockers. For the effect of sodium valproate on *nimodipine*, see under Nifedipine, p.1353.

Colestyramine. Colestyramine may decrease the absorption of valproate.

Gastrointestinal drugs. Use with an *antacid* (aluminium and magnesium hydroxides) significantly increased the bioavailability of a valproic acid preparation in healthy subjects;[1] other antacids in this study (calcium carbonate and an aluminium magnesium trisilicate mixture) had a lesser, insignificant effect.

Cimetidine significantly increased the half-life and decreased the clearance of sodium valproate in another study;[2] *ranitidine* had no effect on valproate pharmacokinetics.[2]

These interactions have not been reported to be of clinical significance, although the possibility must exist, particularly in patients on high-dose therapy.

1. May CA, *et al.* Effects of three antacids on the bioavailability of valproic acid. *Clin Pharm* 1982; **1:** 244–7.
2. Webster LK, *et al.* Effect of cimetidine and ranitidine on carbamazepine and sodium valproate pharmacokinetics. *Eur J Clin Pharmacol* 1984; **27:** 341–3.

Ginkgo biloba. For a report of a fatal breakthrough seizure occurring when phenytoin and valproate semisodium were used with ginkgo biloba, see under Phenytoin, p.500.

Sex hormones. A 26-year-old woman who was taking valproate for epilepsy and a combined *oral contraceptive* had lower serum-valproate concentrations and an increase in seizure frequency during the active pill phase when compared with the inactive pill phase.[1] A subsequent study[2] in 9 epileptic women who were taking valproate and a combined oral contraceptive found that the apparent oral clearance of total and unbound valproic acid increased during contraceptive intake compared with the pill-free interval; the authors suggested that this effect was due to the induction of glucuronidation of valproate by ethinylestradiol.

1. Herzog AG, *et al.* Serum valproate levels with oral contraceptive use. *Epilepsia* 2005; **46:** 970–1.
2. Galimberti CA, *et al.* Increased apparent oral clearance of valproic acid during intake of combined contraceptive steroids in women with epilepsy. *Epilepsia* 2006; **47:** 1569–72.

Pharmacokinetics

Valproic acid and its salts are rapidly and completely absorbed from the gastrointestinal tract; the rate, but not the extent, of absorption is delayed if given with or after food.

Valproic acid is extensively metabolised in the liver, a large part by glucuronidation and the rest by a variety of complex pathways. It does not appear to enhance its own metabolism, but metabolism may be enhanced by other drugs that induce hepatic microsomal enzymes. It is excreted in the urine almost entirely in the form of its metabolites; small amounts are excreted in faeces and expired air.

Valproic acid is extensively bound to plasma proteins. The extent of protein binding is concentration dependent and is stated to be about 90 to 95% at total concentrations of 50 micrograms/mL, falling to about 80 to 85% at 100 micrograms/mL. Reported half-lives for valproic acid have ranged from about 5 to 20 hours; the shorter half-lives have generally been recorded in epileptic patients receiving multiple drug therapy. Clearance is usually higher in children than in adults.

The 'target' range of total plasma-valproic acid is usually quoted as being 40 to 100 micrograms/mL (280 to 700 micromoles/litre) but routine monitoring of plasma concentrations is not generally considered to be of use as an aid to assessing control.

Valproic acid crosses the placental barrier and small amounts are distributed into breast milk.

Valpromide is an amide derivative of valproic acid and its absorption is slower and its bioavailability somewhat less than that of valproic acid. Valpromide is rapidly and almost completely metabolised in the liver to valproic acid.

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

◊ References.
1. Zaccara G, *et al.* Clinical pharmacokinetics of valproic acid—1988. *Clin Pharmacokinet* 1988; **15:** 367–89.
2. Bialer M. Clinical pharmacology of valpromide. *Clin Pharmacokinet* 1991; **20:** 114–22.
3. Cloyd JC, *et al.* Valproic acid pharmacokinetics in children IV: effects of age and antiepileptic drugs on protein binding and intrinsic clearance. *Clin Pharmacol Ther* 1993; **53:** 22–9.
4. Yukawa E, *et al.* Population-based investigation of valproic acid relative clearance using nonlinear mixed effects modeling: influence of drug-drug interaction and patient characteristics. *J Clin Pharmacol* 1997; **37:** 1160–7.
5. Dutta S, *et al.* Absolute bioavailability and absorption characteristics of divalproex sodium extended-release tablets in healthy volunteers. *J Clin Pharmacol* 2004; **44:** 737–42.
6. Dutta S, *et al.* Comparative absorption profiles of divalproex sodium delayed-release versus extended-release tablets: clinical implications. *Ann Pharmacother* 2006; **40:** 619–25.
7. Reed RC, *et al.* Every-12-hour administration of extended-release divalproex in patients with epilepsy: impact on plasma valproic acid concentrations. *Epilepsy Behav* 2006; **8:** 391–6.
8. Dutta S, *et al.* Valproate protein binding following rapid intravenous administration of high doses of valproic acid in patients with epilepsy. *J Clin Pharm Ther* 2007; **32:** 365–71.

Uses and Administration

Valproate is an antiepileptic used particularly in the treatment of primary generalised seizures, has notable benefit in absence and myoclonic seizures, and is also used for partial seizures. Its actions are complex and its mode of action in epilepsy is not fully understood. Valproate is also used to treat the acute manic phase of bipolar disorder and for the prophylaxis of migraine.

Forms used include the sodium salts (valproate semisodium and sodium valproate), the amide derivative (valpromide), and valproic acid. Magnesium valproate has also been tried as has calcium valproate. Valproate should preferably be taken with or after food.

In the treatment of **epilepsy** the dose should be adjusted to the needs of the individual patient to achieve adequate control of seizures. Plasma concentrations of valproate (see Pharmacokinetics, above) are not considered to be a useful index of efficacy and thus their routine monitoring is generally not helpful.

- A suggested initial *oral* daily dose of ***sodium valproate*** is 600 mg given in 2 divided doses. The daily dose may be increased by 200 mg every 3 days to a usual range of 1 to 2 g daily (20 to 30 mg/kg daily); up to a maximum of 2.5 g daily may be necessary if adequate control has not been achieved.

  When oral dosage is not possible, sodium valproate may be given *intravenously* to start therapy or to continue therapy previously given orally. A suggest-

ed dose to *begin* therapy is up to 10 mg/kg by intravenous injection over 3 to 5 minutes followed by intravenous infusion, as necessary, up to a maximum of 2.5 g daily. To *continue* therapy intravenously, doses are the same as the patient's previous oral dose. In the USA, intravenous sodium valproate is given in doses equivalent to those used orally for valproic acid (see below).

- A suggested initial oral dose of ***valproic acid*** is 10 to 15 mg/kg daily increased at one-week intervals by 5 to 10 mg/kg. The maximum recommended dose of valproic acid in the UK is 30 mg/kg daily whereas in the USA it is 60 mg/kg daily. Valproic acid may be given in 2 to 4 divided doses.
- ***Valproate semisodium*** is given orally in doses equivalent to those used for oral valproic acid (see above).
- The amide derivative of valproic acid, ***valpromide***, is also used in some countries. Usual oral doses have ranged from 600 mg to 1.8 g daily, in divided doses.

For details of valproate doses in children, see below.

As with other antiepileptics, withdrawal of valproate 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.

In the treatment of acute manic episodes of **bipolar disorder**, the initial oral dose of ***valproate semisodium*** is the equivalent of valproic acid 750 mg daily in 2 to 3 divided doses. Thereafter, the dose is increased as rapidly as possible to achieve the optimal response, up to a maximum of 60 mg/kg daily. Patients receiving doses higher than 45 mg/kg daily should be carefully monitored. ***Valpromide*** has also been used in some countries for bipolar disorder in doses similar to those for epilepsy (see above).

In the prophylaxis of **migraine** valproate semisodium is given orally in a dose equivalent to valproic acid 250 mg twice daily; up to 1 g daily may be necessary in some patients.

Action. The actions of valproate are complex and not well understood. As well as enhancing central GABAergic neurotransmission and inhibiting neuronal sodium channels, it affects cellular signalling systems such as the Wnt/β-catenin and extracellular signal-regulated kinase (ERK) pathways, and has actions on inositol and arachidonate metabolism. In addition it has potent effects on transcription of a number of genes, mediated at least in part by its action as a direct histone deacetylase inhibitor. It is probable that its clinical effects in different disorders depend on a combination of such properties.[1]

1. Rosenberg G. The mechanisms of action of valproate in neuropsychiatric disorders: can we see the forest for the trees? *Cell Mol Life Sci* 2007; **64:** 2090–2103.

Administration in children. Valproate is used as an antiepileptic in children in the treatment of primary generalised seizures, notably for absence and myoclonic seizures, and also for partial seizures. Available forms include the sodium salts (valproate semisodium and sodium valproate) or as valproic acid. The *BNFC* suggests that sodium valproate may also be used for infantile spasms.

A suggested initial *oral* dose of ***sodium valproate*** for children weighing over 20 kg is 400 mg daily (irrespective of weight) in 2 divided doses. This may be gradually increased to a usual dose of 20 to 30 mg/kg daily; up to a maximum of 35 mg/kg daily may be necessary if adequate control has not been achieved. Children weighing under 20 kg may be given 20 mg/kg daily in 2 divided doses, which may be increased to 40 mg/kg daily or more if necessary (but see below). Alternatively the *BNFC* suggests the following *oral* or *rectal* doses, given according to age:

- neonates: initially 20 mg/kg once daily followed by a usual maintenance dose of 10 mg/kg twice daily
- 1 month to 12 years: initially 5 to 7.5 mg/kg twice daily followed by a usual maintenance dose of 12.5 to 15 mg/kg twice daily; up to 30 mg/kg twice daily may be given for infantile spasms (but see below)
- over 12 years: usual adult doses (see above)

When used rectally, the *BNFC* recommends that sodium valproate oral solution may be used and retained for 15 minutes; dilution with water may be required, if necessary.

When oral dosage is not possible, sodium valproate is licensed for use *intravenously* to start therapy or to continue therapy previously given orally. The usual dose is in the range of 20 to 30 mg/kg daily by intravenous injection over 3 to 5 minutes or by infusion; up to 40 mg/kg daily or more may be necessary if adequate control is not achieved (but see below). When switching from oral to intravenous therapy, the intravenous dose should be the same as the established oral dose.

Alternatively, the *BNFC* suggests giving neonates, children, and adolescents up to 18 years of age 10 mg/kg twice daily by intravenous injection; those aged from 1 month to 12 years may also be given 10 mg/kg initially by intravenous injection, followed by continuous infusion of 20 to 40 mg/kg daily, and older children may be given the usual adult doses (see above).

When a dose over 20 mg/kg daily is given, regardless of route, it is recommended that plasma-valproate concentrations should be monitored. If the dose exceeds 40 mg/kg daily, the patient's clinical chemistry and haematological parameters should also be monitored.

The *BNFC* states that children of all ages may be given ***valproic acid*** in doses as for sodium valproate (see above). In the USA, valproic acid is only licensed for children aged 10 years and older, who may be given the adult dose.

In the USA, ***valproate semisodium*** may also be given to children aged 10 years and over in the usual adult doses (see above) for the treatment of epilepsy.

Bipolar disorder. Valproate, usually as valproate semisodium, is increasingly being used as an alternative to lithium in patients with bipolar disorder (p.372).[1-9] Most guidelines consider it to be a first-line alternative to lithium particularly in those who have rapid cycling disease with 4 or more affective episodes a year or in those with mixed or dysphoric states. However, a study[9] failed to show particular benefit in rapid cycling disease, and systematic reviews considered that any shift in prescribing practice in favour of valproate was not based on reliable evidence of efficacy,[10] although it was effective in acute mania.[8]

1. Pope HG, *et al.* Valproate in the treatment of acute mania: a placebo-controlled study. *Arch Gen Psychiatry* 1991; **48:** 62–8.
2. Joffe RT. Valproate in bipolar disorder: the Canadian perspective. *Can J Psychiatry* 1993; **38** (suppl 2): S46–S50.
3. Schaff MR, *et al.* Divalproex sodium in the treatment of refractory affective disorders. *J Clin Psychiatry* 1993; **54:** 380–4.
4. Bowden CL, *et al.* Efficacy of divalproex vs lithium and placebo in the treatment of mania. *JAMA* 1994; **271:** 918–24. Correction. *ibid.*; 1830.
5. Stoll AL, *et al.* Neurologic factors predict a favorable valproate response in bipolar and schizoaffective disorders. *J Clin Psychopharmacol* 1994; **14:** 311–13.
6. Swann AC, *et al.* Depression during mania: treatment response to lithium or divalproex. *Arch Gen Psychiatry* 1997; **54:** 37–42.
7. Müller-Oerlinghausen B, *et al.* Valproate as adjunct to neuroleptic medication for the treatment of acute episodes of mania: a prospective, randomized, double-blind, placebo-controlled, multicenter study. *J Clin Psychopharmacol* 2000; **20:** 195–203.
8. Macritchie K, *et al.* Valproate for acute mood episodes in bipolar disorder. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2003 (accessed 09/06/08).
9. Calabrese JR, *et al.* A 20-month, double-blind, maintenance trial of lithium versus divalproex in rapid-cycling bipolar disorder. *Am J Psychiatry* 2005; **162:** 2152–61.
10. Macritchie KA, *et al.* Valproic acid, valproate and divalproex in the maintenance treatment of bipolar disorder. Available in The Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2001 (accessed 09/06/08).

Cushing's syndrome. Sodium valproate has been used in the management of Cushing's syndrome (p.2344).

Epilepsy. Valproate is one of the drugs of choice in partial seizures, primary generalised tonic-clonic seizures, absence seizures, and myoclonic seizures (see p.465), although evidence for some of these is lacking. It is also the drug of choice in epileptic syndromes such as the Lennox-Gastaut syndrome because of its wide therapeutic spectrum, and it may be useful in tonic or atonic seizures and infantile spasms.

References.

1. Mattson RH, *et al.* A comparison of valproate with carbamazepine for the treatment of complex partial seizures and secondarily generalized tonic-clonic seizures in adults. *N Engl J Med* 1992; **327:** 765–71.
2. Richens A, *et al.* A multicentre trial of sodium valproate and carbamazepine in adult onset epilepsy. *J Neurol Neurosurg Psychiatry* 1994; **57:** 682–7.
3. Verity CM, *et al.* A multicentre comparative trial of sodium valproate and carbamazepine in paediatric epilepsy. *Dev Med Child Neurol* 1995; **37:** 97–108.
4. Beydoun A, *et al.* and the Depakote Monotherapy for Partial Seizures Study Group. Safety and efficacy of divalproex sodium monotherapy in partial epilepsy: a double-blind, concentration-response design clinical trial. *Neurology* 1997; **48:** 182–8.
5. Brodie MJ, Mumford JP. Double-blind substitution of vigabatrin and valproate in carbamazepine-resistant partial epilepsy. *Epilepsy Res* 1999; **34:** 199–205.
6. Posner EB, *et al.* Ethosuximide, sodium valproate or lamotrigine for absence seizures in children and adolescents. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2005 (accessed 09/06/08).
7. Guerrini R. Valproate as a mainstay of therapy for pediatric epilepsy. *Paediatr Drugs* 2006; **8:** 113–29.
8. Aldenkamp A, *et al.* Role of valproate across the ages: treatment of epilepsy in children. *Acta Neurol Scand* 2006; **184** (Suppl): 1–13.
9. Ben-Menachem E, *et al.* Role of valproate across the ages: treatment of epilepsy in adults. *Acta Neurol Scand* 2006; **184** (Suppl): 14–27.
10. Perucca E, *et al.* Role of valproate across the ages: treatment of epilepsy in the elderly. *Acta Neurol Scand* 2006; **184** (Suppl): 28–37.
11. Marson AG, *et al.* SANAD Study Group. The SANAD study of effectiveness of valproate, lamotrigine, or topiramate for generalised and unclassifiable epilepsy: an unblinded randomised controlled trial. *Lancet* 2007; **369:** 1016–26.

Extrapyramidal disorders. Valproate is one of several drugs with GABAergic action that has been tried in the management of tardive dyskinesia (see under Extrapyramidal Disorders on p.971).

Febrile convulsions. Sodium valproate has been used prophylactically in children thought to be at risk of recurrence of febrile convulsions (p.470), but routine use of antiepileptics is no longer recommended.

References.

1. Newton RW. Randomised controlled trials of phenobarbitone and valproate in febrile convulsions. *Arch Dis Child* 1988; **63:** 1189–91.

Headache. Valproate, as valproate semisodium, may be used for the prophylaxis of *migraine* (p.616) in patients refractory to drugs such as propranolol.[1-7] Valproate has also been shown to be effective and well-tolerated for the prophylaxis of migraine in children aged between 7 and 16 years.[8,9] Intravenous valproate has been tried in the treatment of acute migraine but a review[10] concluded that its use could not be recommended. To date, published studies had mostly been small, open-label, and non-placebo controlled and had used variable doses. Valproate had not been shown to be superior to other antimigraine drugs and had been inferior to prochlorperazine in one study.

Valproate has also been tried in the prophylaxis of persistent chronic daily headache including *tension-type headache* (p.617) unresponsive to other drugs.[11]

It has also been tried for prevention of *cluster headache* (p.616).

1. Sørensen KV. Valproate: a new drug in migraine prophylaxis. *Acta Neurol Scand* 1988; **78:** 346–8.
2. Hering R, Kuritzky A. Sodium valproate in the prophylactic treatment of migraine: a double-blind study versus placebo. *Cephalalgia* 1992; **12:** 81–4.
3. Coria F, *et al.* Low-dose sodium valproate in the prophylaxis of migraine. *Clin Neuropharmacol* 1994; **17:** 569–73.
4. Mathew NT, *et al.* Migraine prophylaxis with divalproex. *Arch Neurol* 1995; **52:** 281–6.
5. Kaniecki RG. A comparison of divalproex with propranolol and placebo for the prophylaxis of migraine without aura. *Arch Neurol* 1997; **54:** 1141–5.
6. Erdemoglu AK, Ozbakir S. Valproic acid in prophylaxis of refractory migraine. *Acta Neurol Scand* 2000; **102:** 354–8.
7. Freitag FG. Divalproex in the treatment of migraine. *Psychopharmacol Bull* 2003; **37** (suppl 2): 98–115.
8. Caruso JM, *et al.* The efficacy of divalproex sodium in the prophylactic treatment of children with migraine. *Headache* 2000; **40:** 672–6.
9. Ashrafi MR, *et al.* Sodium valproate versus propranolol in paediatric migraine prophylaxis. *Eur J Paediatr Neurol* 2005; **9:** 333–8.
10. Frazee LA, Foraker KC. Use of intravenous valproic acid for acute migraine. *Ann Pharmacother* 2008; **42:** 403–7.
11. Mathew NT, Ali S. Valproate in the treatment of persistent chronic daily headache: an open label study. *Headache* 1991; **31:** 71–4.

Hiccup. Valproic acid may be of value in the treatment of intractable hiccups,[1] especially those of neurogenic origin. For the management of intractable hiccups see under Chlorpromazine, p.976.

1. Jacobson PL, *et al.* Treatment of intractable hiccups with valproic acid. *Neurology* 1981; **31:** 1458–60.

HIV infection and AIDS. As mentioned under Precautions, above, valproate appears to induce replication of HIV, and this effect has been used to reduce latent, and therefore treatment-resistant, HIV-infection in resting CD4+ T-cells. In a preliminary study,[1] 4 HIV-positive patients on HAART were started on the fusion inhibitor enfuvirtide to intensify their HIV treatment and prevent viral spread due to valproate; oral valproic acid (500 to 750 mg twice daily) was then introduced a few weeks later and continued for 3 months. In 3 of these patients, the frequency of latent infection in resting T-cells significantly declined after enfuvirtide and valproate treatment when compared with pretreatment values. However, a later study[2] found the levels of latently infected T-cells in 9 HIV-positive patients receiving HAART and oral valproic acid for at least 3 months to be similar to those of patients receiving HAART alone. A case report[3] also described rapid rebound viraemia occurring in a 54-year-old man when HAART and sodium valproate were stopped after more than 2 years of therapy, suggesting little benefit in eradicating latent infection.

1. Lehrman G, *et al.* Depletion of latent HIV-1 infection in vivo: a proof-of-concept study. *Lancet* 2005; **366:** 549–55.
2. Siliciano JD, *et al.* Stability of the latent reservoir for HIV-1 in patients receiving valproic acid. *J Infect Dis* 2007; **195:** 833–6.
3. Steel A, *et al.* No change to HIV-1 latency with valproate therapy. *AIDS* 2006; **20:** 1681–2.

Malignant neoplasms. Valproate appears to have anti-tumour activity, thought to be mediated through the inhibition of cellular histone deacetylase. It has been tried[1-6] usually as an adjunct to

other antineoplastics in the treatment of various malignancies, with some reported benefit.

1. Bug G, *et al.* Clinical trial of valproic acid and all-trans retinoic acid in patients with poor-risk acute myeloid leukemia. *Cancer* 2005; **104:** 2717–25.
2. Raffoux E, *et al.* Treatment of elderly acute myeloid leukemia with valproic acid and all-trans retinoic acid. *Haematologica* 2005; **90:** 986–8.
3. Pilatrino C, *et al.* Increase in platelet count in older, poor-risk patients with acute myeloid leukemia or myelodysplastic syndrome treated with valproic acid and all-trans retinoic acid. *Cancer* 2005; **104:** 101–9.
4. Chavez-Blanco A, *et al.* Histone acetylation and histone deacetylase activity of magnesium valproate in tumor and peripheral blood of patients with cervical cancer: a phase I study. *Mol Cancer* 2005; **4:** 22. Full version: http://www.molecular-cancer.com/content/pdf/1476-4598-4-22.pdf (accessed 09/06/08)
5. Münster P, *et al.* Phase I trial of histone deacetylase inhibition by valproic acid followed by the topoisomerase II inhibitor epirubicin in advanced solid tumors: a clinical and translational study. *J Clin Oncol* 2007; **25:** 1979–85.
6. Blum W, *et al.* Phase I study of decitabine alone or in combination with valproic acid in acute myeloid leukemia. *J Clin Oncol* 2007; **25:** 3884–91.

Migraine. See under Headache, above.

Muscle spasm. The mainstay of management of *spasticity* is physiotherapy and an antispastic drug (see p.1887). Valproate has been tried for its GABAergic activity and case reports[1] of 4 patients with spastic conditions of various aetiologies indicated that the addition of valproate to the existing regimen of antispastic drugs might produce improvements in spasticity and pain; further studies are warranted.

Valproate has also been tried[2] in the management of *stiff-man syndrome* (see under Muscle Spasm, p.993) unresponsive to diazepam.

1. Zachariah SB, *et al.* Positive response to oral divalproex sodium (Depakote) in patients with spasticity and pain. *Am J Med Sci* 1994; **308:** 38–40.
2. Spehlmann R, *et al.* Improvement of stiff-man syndrome with sodium valproate. *Neurology* 1981; **31:** 1162–3.

Myoclonus. Valproate is used alone or in combination with clonazepam for cortical myoclonus (see p.470).

Neuropathic pain. Although carbamazepine is the drug of choice in the treatment of *trigeminal neuralgia* (p.9), sodium valproate is an alternative antiepileptic that may be used in carbamazepine-intolerant patients. Valproate has also been tried, with some success, in painful *diabetic neuropathy*[1] (p.6), *postherpetic neuralgia*[2] (p.9), and neuropathic *cancer pain*[3] (p.5). However, a placebo-controlled study[4] did not find any benefit with valproate therapy in the treatment of pain in diabetic and nondiabetic polyneuropathy.

1. Kochar DK, *et al.* Sodium valproate for painful diabetic neuropathy: a randomized double-blind placebo-controlled study. *QJM* 2004; **97:** 33–8.
2. Kochar DK, *et al.* Divalproex sodium in the management of post-herpetic neuralgia: a randomized double-blind placebo-controlled study. *QJM* 2005; **98:** 29–34.
3. Hardy JR, *et al.* A phase II study to establish the efficacy and toxicity of sodium valproate in patients with cancer-related neuropathic pain. *J Pain Symptom Manage* 2001; **21:** 204–9.
4. Otto M, *et al.* Valproic acid has no effect on pain in polyneuropathy: a randomized, controlled trial. *Neurology* 2004; **62:** 285–8.

Psychiatric disorders. Valproate has psychotropic properties and has been used in the management of bipolar disorder (see above) and in some countries as a mood stabiliser for augmentation of antidepressant therapy in the treatment of resistant depression (p.373). Valproate has also been tried in various disorders for the control of symptoms such as agitation, aggression, and rage[1,2] (see Disturbed Behaviour, p.954). However, a systematic review of the use of valproate for agitation in dementia found no convincing evidence of efficacy at low doses, and adverse effects may be unacceptable at higher doses.[3] Valproate has also been reported[4,5] to be efficacious as adjunctive therapy to antipsychotics, but again, systematic review[6] has thrown doubt upon its effectiveness. It has also been tried in anxiety disorders such as panic disorder[7-9] (p.952), and post-traumatic stress disorder[10,11] (p.953).

1. Geracioti TD. Valproic acid treatment of episodic explosiveness related to brain injury. *J Clin Psychiatry* 1994; **55:** 416–17.
2. Narayan M, *et al.* Treatment of dementia with behavioral disturbances using divalproex or a combination of divalproex and a neuroleptic. *J Clin Psychiatry* 1997; **58:** 351–4.
3. Lonergan ET, Luxenberg J. Valproate preparations for agitation in dementia. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2004 (accessed 09/06/08).
4. Wassef AA, *et al.* Randomized, placebo-controlled pilot study of divalproex sodium in the treatment of acute exacerbations of chronic schizophrenia. *J Clin Psychopharmacol* 2000; **20:** 357–61.
5. Grove VE, *et al.* Improvement of Huntington's disease with olanzapine and valproate. *N Engl J Med* 2000; **343:** 973–4.
6. Basan A, *et al.* Valproate as an adjunct to antipsychotics for schizophrenia: a systematic review of randomized trials. *Schizophr Res* 2004; **70:** 33–7.
7. Primeau F, *et al.* Valproic acid and panic disorder. *Can J Psychiatry* 1990; **35:** 248–50.
8. Keck PE, *et al.* Valproate treatment of panic disorder and lactate-induced panic attacks. *Biol Psychiatry* 1993; **33:** 542–6.
9. Woodman CL, Noyes R. Panic disorder: treatment with valproate. *J Clin Psychiatry* 1994; **55:** 134–6.
10. Fesler FA. Valproate in combat-related posttraumatic stress disorder. *J Clin Psychiatry* 1991; **52:** 361–4.
11. Petty F, *et al.* Valproate therapy for chronic, combat-induced posttraumatic stress disorder. *J Clin Psychopharmacol* 2002; **22:** 100–101.

Status epilepticus. Valproate has been used in *absence* status epilepticus once the initial attack has been brought under control with intravenous benzodiazepines[1] and has been considered to be the drug of choice to prevent its recurrence.[2] Its place in the management of *convulsive* status epilepticus (p.469) is less clear, but it has been tried, mainly as a second- or third-line drug in benzodiazepine-refractory patients,[3-12] and some centres have included it in management protocols.[5]

1. Bauer J, Elger CE. Management of status epilepticus in adults. *CNS Drugs* 1994; **1:** 26–44.
2. Berkovic SF, *et al.* Valproate prevents the recurrence of absence status. *Neurology* 1989; **39:** 1294–7.
3. Giroud M, *et al.* Use of injectable valproic acid in status epilepticus: a pilot study. *Drug Invest* 1993; **5:** 154–9.
4. Hovinga CA, *et al.* Use of intravenous valproate in three pediatric patients with nonconvulsive or convulsive status epilepticus. *Ann Pharmacother* 1999; **33:** 579–84.
5. Campistol J, *et al.* Estado de mal convulsivo en el niño: experiencia con valproato endovenoso, actualización del protocolo de tratamiento. *Rev Neurol* 1999; **29:** 359–65.
6. Peters CNA, Pohlmann-Eden B. Intravenous valproate as an innovative therapy in seizure emergency situations including status epilepticus—experience in 102 adult patients. *Seizure* 2005; **14:** 164–9.
7. Limdi NA, *et al.* Efficacy of rapid IV administration of valproic acid for status epilepticus. *Neurology* 2005; **64:** 353–5.
8. Limdi NA, *et al.* Efficacy of rapid IV administration of valproic acid for status epilepticus. *Neurology* 2005; **64:** 353–5.
9. Misra UK, *et al.* Sodium valproate vs phenytoin in status epilepticus: a pilot study. *Neurology* 2006; **67:** 340–2.
10. Olsen KB, *et al.* Valproate is an effective, well-tolerated drug for treatment of status epilepticus/serial attacks in adults. *Acta Neurol Scand* 2007; **187** (Suppl): 51–4.
11. Agarwal P, *et al.* Randomized study of intravenous valproate and phenytoin in status epilepticus. *Seizure* 2007; **16:** 527–32.
12. Mehta V, *et al.* Intravenous sodium valproate versus diazepam infusion for the control of refractory status epilepticus in children: a randomized controlled trial. *J Child Neurol* 2007; **22:** 1191–7.

Preparations

BP 2008: Gastro-resistant Sodium Valproate Tablets; Sodium Valproate Oral Solution; Sodium Valproate Tablets;
USP 31: Divalproex Sodium Delayed-Release Tablets; Valproate Sodium Injection; Valproic Acid Capsules; Valproic Acid Syrup.

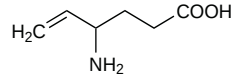
Proprietary Preparations (details are given in Part 3)
Arg.: Depakene; Exibral; Logical; Tekaval†; Valcote; Valnar; ***Austral.:*** Epilim; Valpro; ***Austria:*** Convulex; Depakine; Depakine Chrono; Depakine Chronosphere; Epival†; ***Belg.:*** Convulex; Depakine; ***Braz.:*** Depakene; Depakote; Epilenil; Torval; Valpakine; Valprene; ***Canad.:*** Depakene; Epiject; Epival; ***Chile:*** Atemperator; Depakene; DI VP; Leptilan†; Neuractin; Valcote; ***Cz.:*** Absenor; Convulex; Convulsofin†; Depakine; Depakine Chrono; Everiden; Orfiril; ***Denm.:*** Delepsine; Deprakine; Orfiril; ***Fin.:*** Absenor; Deprakine; Deprakine Depot; Orfiril; ***Fr.:*** Depakine; Depakine Chrono; Depakote; Depamide; Micropakine; ***Ger.:*** Convulex; Convulsofin; Ergenyl; Ergenyl Chrono; Espa-Valept†; Leptilan; Orfiril; Valpro; Valpro Beta; Valprodura; Valproflux†; Valprolept†; ValproNa†; ***Gr.:*** Depakine; Depakine Chrono; ***Hong Kong:*** Epilim; Valpro; ***Hung.:*** Convulex; Depakine; Depakine Chrono; Everiden†; Orfiril; ***India:*** Diproex; Epilex; Valcontin; Valparin; Valrate CR; Valtec; ***Indon.:*** Depakene; Depakote; ***Irl.:*** Epilim; Epilim Chrono; ***Israel:*** Depalept; Depalept Chrono; Orfiril; Valporal; ***Ital.:*** Depakin; Depakin Chrono; Depamag; Depamide; ***Jpn:*** Depakene; ***Malaysia:*** Epilim; Orfiril; ***Mex.:*** Atemperator; Criam; Depakene; Edorame; Epival; Leptilan; Pimiken; Provetal†; Trankitec; Valprosid†; ***Neth.:*** Convulex†; Depakine; Depakine Chrono; Orfiril; Propymal; ***Norw.:*** Deprakine; Orfiril; ***NZ:*** Epilim; ***Philipp.:*** Depakene; Depakote; Epival; ***Pol.:*** Convulex; Depakine; Depakine Chrono; Depakine Chronosphere; Depamide; Dipromal; Orfiril; ***Port.:*** Depakine; Depakine Chrono; Depakine Chronosphere; Diplexil; Diplexil-R; Valprolim; ***Rus.:*** Apilepsin (Апилепсин); Convulex (Конвулекс); Convulsofin (Конвульсофин); Depakine (Депакин); Depakine Chrono (Депакин Хроно); Encorate (Энкорат); Encorate Chrono (Энкорат Хроно); Valparin XR (Вальпарин ХР); ***S.Afr.:*** Convulex; Epilim; ***Singapore:*** Convulex; Epilim; Orfiril†; Valparin; ***Spain:*** Depakine; Depakine Crono; Depamide; Milzone; ***Swed.:*** Absenor; Ergenyl; Orfiril; ***Switz.:*** Convulex; Depakine; Depakine Chrono; Orfiril; ***Thai.:*** Depakine; Desorate; Encorate; Valparin; ***Turk.:*** Convulex; Depakin; ***UAE:*** Valopin; ***UK:*** Convulex; Depakote; Epilim; Epilim Chrono; Episenta; Orlept; ***USA:*** Depacon; Depakene; Depakote; Mendatrex; ***Venez.:*** Depakine; Valcote; Valpron.

Vigabatrin *(BAN, USAN, rINN)*

4-Amino-5-hexenoic Acid; MDL-71754; RMI-71754; Vigabatriini; Vigabatrina; Vigabatrine; Vigabatrinum; γ-Vinyl Aminobutyric Acid; γ-Vinyl-GABA. 4-Aminohex-5-enoic acid.

Вигабатрин

$C_6H_{11}NO_2$ = 129.2.
CAS — 60643-86-9.
ATC — N03AG04.
ATC Vet — QN03AG04.



Pharmacopoeias. In *Br.*
BP 2008 (Vigabatrin). A white to almost white powder. Very soluble in water.

Adverse Effects, Treatment, and Precautions

About half of all patients experience adverse effects with vigabatrin. The most common are drowsiness and fatigue, although in children excitation and agitation occur more frequently. The incidence of these effects is generally higher at the start of therapy and decreases over time. Other CNS-related adverse effects include dizziness, headache, ataxia, paraesthesia, tremor, impaired concentration, confusion, and memory disturbances. Other reported adverse effects include weight gain, gastrointestinal disturbances, oedema, alopecia, angioedema, urticaria, and skin rash. Haemoglobin and liver enzyme values may be decreased. Rarely marked sedation, stupor and confusion, together with other symptoms suggestive of encephalopathy, have occurred.

About one-third of all patients receiving vigabatrin have developed irreversible visual field defects, ranging from mild to severe and usually occurring after months or years of therapy. Blurred vision, diplopia, or nystagmus are somewhat less common. Retinal disorders such as peripheral retinal atrophy, or very rarely optic neuritis or atrophy have also been reported (see also below). Visual field function should be assessed before beginning treatment and during routine follow-up (ideally at 6-month intervals), and patients should be warned to report any new visual symptoms that develop during therapy. Vigabatrin should not be used in patients with pre-existing visual field defects.

Psychiatric reactions such as agitation, aggression, irritability, nervousness, depression, and paranoid reactions have occurred in patients with or without a psychiatric history; psychosis, hypomania, or mania have been reported rarely. Patients receiving vigabatrin should be observed carefully for any signs of adverse effects on neurological function. Caution is warranted in patients with a history of psychosis, depression, or behavioural problems.

Vigabatrin may exacerbate myoclonic or absence seizures.

Vigabatrin should be given with caution to the elderly and patients with renal impairment.

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

Breast feeding. Licensed product information states that breast feeding is not recommended in women receiving vigabatrin. For comment on antiepileptic therapy and breast feeding, see p.467.

Driving. For a comment on antiepileptic drugs and driving, see p.468.
Particular care should be taken in view of the possible effects of vigabatrin on visual acuity.

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

Effects on the eyes. A report of 3 patients who developed bilateral severely constricted visual fields 2 to 3 years after vigabatrin was added to their antiepileptic regimens[1] prompted publication of similar anecdotal reports.[2-5] Peripheral retinal atrophy rather than optic nerve damage appeared to be the cause. Symptoms showed no improvement on stopping the drug, although there was no further deterioration. At that time (1997) the manufacturers replied[6] stating that it was a rare occurrence (less than 0.1%) and was being monitored in further clinical studies. The UK CSM subsequently stated[7] (in March 1998) that it had received 41 reports of visual field defects since December 1989, which persisted in most cases despite stopping treatment. The evidence suggested that the onset of symptoms varied from 1 month to several years after starting vigabatrin. In most cases, visual field defects have persisted despite stopping vigabatrin.[8,9] Interim results of a Prescription Event Monitoring Study[10] in the UK stated that vigabatrin was considered to be probably or possibly associated with objective evidence of a visual field defect in 0.2% of patients. However, subsequent evidence appears to have confirmed that the incidence of visual field defects is much higher;[11-14] revised product literature issued in late 1999 indicated that visual field defects occurred in about one-third of all patients receiving vigabatrin. Male patients appear to be at an increased risk of developing defects.[15,16] Whether cumulative dose may be considered a risk factor remains unclear.[16,17]

The CSM considered[14] that vigabatrin should only be prescribed by a specialist, and only where all other combination therapies have failed. Ophthalmological consultation and visual field as-