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

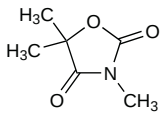
Proprietary Preparations (details are given in Part 3)
Arg.: Neutop; Topamac; Topictal; Topirex; ***Austral.:*** Topamax; ***Austria:*** Topamax; ***Belg.:*** Topamax; ***Braz.:*** Topamax; ***Canad.:*** Topamax; ***Chile:*** Topamax; Toprel; ***Cz.:*** Topamax; Topiragis; ***Denm.:*** Epitomax; Topimax;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

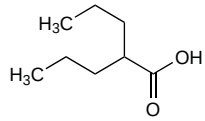
NOTE. Valproate is a generic term applied to valproic acid and its salts and esters.

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

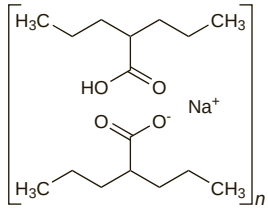
$C_{14}H_{26}O_4$ = 258.4.
CAS — 77372-61-3.
ATC — N03AG01.
ATC Vet — QN03AG01.

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