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Pharmacological and Therapeutic Properties of Valproate

A Summary After 35 Years of Clinical Experience

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Abstract

Thirty-five years since its introduction into clinical use, valproate (valproic acid) has become the most widely prescribed antiepileptic drug (AED) worldwide. Its pharmacological effects involve a variety of mechanisms, including increased γ-aminobutyric acid (GABA)–ergic transmission, reduced release and/or effects of excitatory amino acids, blockade of voltage-gated sodium channels and modulation of dopaminergic and serotoninergic transmission.

Valproate is available in different dosage forms for parenteral and oral use. All available oral formulations are almost completely bioavailable, but they differ in dissolution characteristics and absorption rates. In particular, sustained-release

formulations are available that minimise fluctuations in serum drug concentrations during a dosing interval and can therefore be given once or twice daily.

Valproic acid is about 90% bound to plasma proteins, and the degree of binding decreases with increasing drug concentration within the clinically occurring range. Valproic acid is extensively metabolised by microsomal glucuronide conjugation, mitochondrial β-oxidation and cytochrome P450–dependent ω-, (ω-1)– and (ω-2)–oxidation. The elimination half-life is in the order of 9 to 18 hours, but shorter values (5 to 12 hours) are observed in patients comedicated with enzyme-inducing agents such as phenytoin, carbamazepine and barbiturates. Valproate itself is devoid of enzyme-inducing properties, but it has the potential of inhibiting drug metabolism and can increase by this mechanism the plasma concentrations of certain coadministered drugs, including phenobarbital (phenobarbitone), lamotrigine and zidovudine.

Valproate is a broad spectrum AED, being effective against all seizure types. In patients with newly diagnosed partial seizures (with or without secondary generalisation) and/or primarily generalised tonic-clonic seizures, the efficacy of valproate is comparable to that of phenytoin, carbamazepine and phenobarbital, although in most comparative trials the tolerability of phenobarbital was inferior to that of the other drugs. Valproate is generally regarded as a first-choice agent for most forms of idiopathic and symptomatic generalised epilepsies. Many of these syndromes are associated with multiple seizure types, including tonic-clonic, myoclonic and absence seizures, and prescription of a broad-spectrum drug such as valproate has clear advantages in this situation. A number of reports have also suggested that intravenous valproate could be of value in the treatment of convulsive and nonconvulsive status epilepticus, but further studies are required to establish in more detail the role of the drug in this indication.

The most commonly reported adverse effects of valproate include gastrointestinal disturbances, tremor and bodyweight gain. Other notable adverse effects include encephalopathy symptoms (at times associated with hyperammonaemia), platelet disorders, pancreatitis, liver toxicity (with an overall incidence of 1 in 20 000, but a frequency as high as 1 in 600 or 1 in 800 in high-risk groups such as infants below 2 years of age receiving anticonvulsant polytherapy) and teratogenicity, including a 1 to 3% risk of neural tube defects. Some studies have also suggested that menstrual disorders and certain clinical, ultrasound or endocrine manifestations of reproductive system disorders, including polycystic ovary syndrome, may be more common in women treated with valproate than in those treated with other AEDs. However, the precise relevance of the latter findings remains to be evaluated in large, prospective, randomised studies.

With a prevalence of about 1 : 50 in children and 1 : 100 to 1 : 200 in adults,[1] epilepsy is the most common serious neurological disorder. In the US alone, it is estimated that about 2 million persons have epilepsy.[2] Among elderly patients, both the prevalence of epilepsy (approximately 1.5% among persons 65 years of age and older) and the annual incidence of a first seizure (127 per 100 000 individuals 60 years of age and older) are considerably higher than in the average population.[3] Therefore, many primary care physicians are involved in the management of patients who have epilepsy.

Complete seizure control is the single most important determinant of good quality of life for patients with epilepsy,[4] and the chronic nature of the

disorder requires that antiepileptic drugs (AEDs) be administered for many years, often for a lifetime. Therefore, long-term experience is of particular importance in evaluating the efficacy and safety of an AED.

Since the serendipitous discovery of its anticonvulsant properties in France in 1962,[5] valproate (valproic acid) has become one of the mainstays for the treatment of different epileptic syndromes in adults and children. Initial clinical trials were carried out in Europe in the mid-1960s, and the drug was licensed first in France in 1967 and in over 100 other countries, including the US, thereafter. This article provides a concise update on current knowledge concerning its mechanisms of action, pharmacokinetic properties and interaction potential, followed by an overview of clinical efficacy, safety and pharmacoeconomic data related to its use in the treatment of epilepsy.

1. Mechanisms of Action

Valproic acid (N-dipropylacetic acid, or 2-propylpentanoic acid) is a simple branched-chain carboxylic acid, the structure of which is entirely different from that of other AEDs in clinical use. Despite extensive research, its precise mode of action has not been fully elucidated. However, in view of its wide spectrum of activity against different seizure types and results from biochemical and electrophysiological studies, it is clear that a combination of mechanisms is involved.

A comprehensive review by Löscher[6] in 1999 summarised current knowledge. There is substantial evidence that valproic acid increases γ-aminobutyric acid (GABA) synthesis and release and potentiates by these mechanisms GABAergic transmission in specific brain regions.[7] Valproic acid has also been found to reduce the release of the excitatory amino acid β-hydroxybutyric acid and to attenuate neuronal excitation mediated by activation of *N*-methyl-D-aspartate (NMDA) glutamate receptors.[8] In addition to these effects, valproic acid exerts direct actions on excitable membranes, including blockade of voltage-dependent sodium channels.[9] Microdialysis data also suggest that the drug modulates dopaminergic and serotoninergic transmission,[6] which could be relevant for its efficacy in some psychiatric disorders and in neurological disorders other than epilepsy. Certainly, valproic acid should not be considered a specific GABAergic drug, but an agent with multiple and complex modes of action.[6,10]

2. Clinical Pharmacokinetics

When administered as uncoated tablets containing the sodium salt, valproate dissociates rapidly in the stomach to the corresponding acid. The oral bioavailability of available standard formulations (including enteric-coated tablets and the sustained-release Chrono®[1] formulation) is almost complete,[11-13] but time to reach the maximum plasma concentration and the maximum concentration achieved are dependent on the pharmaceutical preparation. Peak concentrations usually occur within 2 to 3 hours for syrup, capsules and uncoated tablets, between 3 and 5 hours for enteric-coated tablets and between 5 and 10 hours for sustained-release formulations.[10-15] Maximum concentrations are considerably lower with sustained-release formulations, which ensure a reduced fluctuation in serum drug concentration during the dosing interval.

When enteric-coated tablets are used, concomitant intake with food may result in retention of the tablet in the stomach for up to several hours, with a consequent delay in drug absorption; however, when the tablet reaches the intestine, dissolution of the active principle occurs rapidly and absorption proceeds rapidly and unhindered.[16] The lag-time in absorption following coadministration with food is not seen when the sustained-release formulation is used, because the latter releases the active principle already in the stomach.[17]

Valproic acid is extensively (≥90%) bound to plasma proteins, mainly albumin. The extent of binding decreases with increasing drug concentration,[18] resulting in a nonlinear relationship between total plasma concentration and dosage.[19]

1 Use of tradenames is for product identification only and does not imply endorsement.

The relationship between unbound (pharmacologically active) drug concentration and dosage, however, does not deviate substantially from linearity.[20] The apparent volume of distribution is 0.13 to 0.19 L/kg, while brain-to-plasma concentration ratios based on total and unbound plasma concentration are on average around 0.1 and 0.5, respectively, with considerable interindividual variability.[21,22] The ratio between the CSF concentration and the unbound concentration in plasma ranges between 0.6 and 1.0.[22]

Studies on the kinetics of penetration into the CSF indicate that valproic acid, despite its hydrophilic nature, enters the CNS rapidly. The processes governing the passage of the drug across the blood-brain barrier involve both passive diffusion and a bidirectional carrier-mediated transport. Entry into the brain is mediated by an anion exchanger at the brain capillary endothelium, which accounts for two-thirds of the barrier permeability.[22] Valproic acid is also efficiently cleared out of the brain into the blood by a saturable, probenecid-sensitive transport at the blood-brain and blood-CSF barriers.[22-24] Another set of transporters exists within the brain parenchyma, which is responsible for the uptake of valproic acid into neuronal and glial cells, resulting in intracellular concentrations that are higher than interstitial fluid concentrations.[22]

The half-life of valproic acid is in the order of 9 to 18 hours, but shorter values (5 to 12 hours) are observed in patients taking enzyme-inducing comedication.[10-12] The elimination is slower in newborns, especially those born prematurely. On the other hand, children eliminate the drug at a faster rate compared with adults and therefore require larger dosages per unit of bodyweight to achieve plasma drug concentrations comparable with those observed in adults.[10]

Although total plasma valproic acid concentrations in the elderly are similar to those found in the young, unbound drug concentrations are increased in the elderly (as a result of an age-related decrease in intrinsic metabolic clearance, in the presence of a reduced plasma protein binding) and, therefore, the possibility of a reduction in dose requirements should be contemplated in these patients.[25] Alterations in the pharmacokinetics of valproic acid are also observed in pregnancy, with a progressive decrease in total concentration and little or no change in unbound concentration.[26] A discussion of the changes in the pharmacokinetics of valproic acid in disease states is beyond the scope of this review.

Only a minor fraction of the administered dose of valproic acid is excreted unchanged in the urine. The drug is extensively metabolised, primarily in the liver, through several pathways, the most important of which include microsomal glucuronide conjugation, mitochondrial β-oxidation and cytochrome P450 (CYP)–dependent ω-, (ω-1)– and (ω-2)–oxidation.[10,14,22] The CYP isoforms involved in the metabolism of valproic acid have not been elucidated fully, but direct and indirect evidence suggests a role for CYP2C9, CYP2A6, CYP2B6 and, possibly, CYP2C19.[22]

A number of unsaturated and oxygenated metabolites retain anticonvulsant activity, although their brain concentrations are probably too low to contribute significantly to therapeutic activity.[6] Some metabolites, however, particularly the 4-en and the 2,4-di-en unsaturated derivatives, could be involved in the pathogenesis of liver toxicity (see section 6.6).[14]

3. Drug Interactions

Coadministration of two or more AEDs, or of an AED with other medications, can result in clinically important drug interactions, both at pharmacokinetic and at pharmacodynamic levels. Thirty-five years of clinical experience have allowed extensive elucidation of interactions in which valproic acid is involved.

3.1 Effect of Other Drugs on the Pharmacokinetics of Valproic Acid

A list of drugs that may affect the pharmacokinetics of valproic acid is provided in table I. Among the interactions listed in the table, the most commonly observed are those involving stimulation of valproic acid metabolism by enzyme-inducing AEDs, such as carbamazepine, phenytoin and bar-

biturates. These drugs cause a marked increase in the clearance of valproic acid, resulting in a significant increase in valproic acid dose requirements.[10,12,27-32]

3.2 Effect of Valproic Acid on the Pharmacokinetics of Other Drugs

Unlike most other first-line AEDs, valproic acid is devoid of enzyme-inducing properties and, therefore, does not interfere with the metabolism of steroid oral contraceptives.[10] On the other hand, valproic acid has a potential for inhibiting drug metabolism, resulting in a number of interactions involving an elevation of plasma concentrations of concomitantly administered drugs (table II).[33-43]

The most important examples of these interactions are represented by the valproic acid–induced increase in the plasma concentrations of phenobarbital (phenobarbitone) [including phenobarbital derived from primidone][10,33] and lamotrigine;[34,35] both of these interactions are clinically important because they usually require a reduction in the dosage of the affected drug. Valproic acid may also inhibit epoxide hydrolase and by this mechanism increases the plasma concentration of carbamazepine-10,11-epoxide, an active metabolite of carbamazepine;[36-38] this may explain the occasional occurrence of signs of carbamazepine toxicity without any change in the concentration of the parent drug in patients receiving the drug combination.[37]

Valproic acid may displace other drugs from plasma protein binding sites (table II).[18,31,32,44] In particular, valproic acid displaces phenytoin from plasma proteins, and in some patients it may

Table I. Interactions whereby the pharmacokinetics of valproic acid (VPA) can be affected by other drugs (for a source of references, refer to text and published reviews)[10,13,22,31,32]

Interacting drug	Interaction	Comment
Carbamazepine, phenytoin, phenobarbital (phenobarbitone), primidone	These drugs stimulate VPA metabolism and cause a marked reduction in serum VPA concentration	VPA dosage may need to be increased up to 2- to 3-fold to achieve serum VPA concentrations comparable to those found in patients not receiving enzyme inducers; patients receiving enzyme inducers are also more susceptible to VPA-induced liver toxicity
Ethosuximide	Ethosuximide may cause a modest decrease in serum VPA concentrations	This possible pharmacokinetic interaction is probably of little clinical significance; more importantly, ethosuximide and VPA show a synergistic pharmacodynamic interaction that may be usefully exploited in patients with absence seizures refractory to monotherapy
Felbamate	Felbamate may increase VPA concentrations by approximately 30-50% by inhibiting VPA β-oxidation	A reduction in VPA dosage may be required to avoid toxicity
Lamotrigine	Lamotrigine may cause a modest decrease in serum VPA concentrations	Although this interaction is of little or no significance, the reverse interaction (inhibition of the metabolism of lamotrigine by VPA) is clinically important (table II); these drugs also show a positive pharmacodynamic interaction leading to synergistic antiepileptic effects
Topiramate	Topiramate may cause a modest decrease in serum VPA concentrations	This interaction is probably of little clinical significance
Antidepressants	Fluoxetine has been reported to increase serum VPA concentrations to a clinically important extent	Evidence is anecdotal, but patients should be monitored for potential signs of VPA toxicity
Antituberculosis agents	Isoniazid may increase VPA concentrations by inhibiting VPA metabolism; conversely, rifampicin reduces VPA concentrations by inducing its metabolism	Both interactions may be clinically relevant; VPA dose requirements may be decreased by isoniazid and increased by rifampicin
Nonsteroidal anti-inflammatory drugs	Aspirin (salicylic acid) and naproxen displace VPA from plasma proteins; aspirin may also compete with VPA for mitochondrial oxidation	Although the interaction with naproxen is probably clinically insignificant, patients comedicated with aspirin should be monitored for possible VPA toxicity; total serum VPA concentrations may underestimate the concentrations of unbound (pharmacologically active) VPA in patients taking these drugs

also inhibit phenytoin metabolism.[10,45] The usual consequence of this interaction is a decrease in total plasma phenytoin concentration, whereas the concentration of unbound (pharmacologically active) phenytoin is unchanged or may even be increased.[10,44,45] As a result of this interaction, in

Table II. Interactions where valproic acid (VPA) may affect the pharmacokinetics of other drugs (for a source of references, refer to text and published reviews)[10,13,22,31,32]

Affected drug	Interaction	Comment
Carbamazepine	VPA causes a modest increase in the serum concentrations of CBZ-E by inhibiting epoxide hydrolase	The increase in CBZ-E concentrations may occasionally result in CNS adverse effects; valpromide, an amide derivative of VPA, causes a much greater increase in CBZ-E concentrations, leading frequently to signs of toxicity
Ethosuximide	VPA has variable effects (increase, decrease or no change) on serum ethosuximide concentrations	This possible pharmacokinetic interaction is usually of little clinical significance; more importantly, ethosuximide and VPA show a synergistic pharmacodynamic interaction that may be usefully exploited in patients with absence seizures refractory to monotherapy
Felbamate	VPA may cause a modest increase in serum felbamate concentrations, possibly by inhibiting felbamate metabolism	This interaction is probably of limited clinical significance
Lamotrigine	VPA increases serum lamotrigine concentrations by inhibiting lamotrigine glucuronidation	Patients receiving VPA require lower dosages of lamotrigine (a slower rate of lamotrigine up-titration is also necessary to minimise the risk of skin reactions); lamotrigine and VPA also exhibit a positive pharmacodynamic interaction leading to synergistic antiepileptic effects
Phenobarbital (phenobarbitone)	VPA increases serum phenobarbital concentrations by inhibiting the *N*-glucosidation and the p-hydroxylation of phenobarbital	The increase in phenobarbital concentrations is usually in the range of 15-45%; a reduction in phenobarbital dosage may be required to avoid toxicity
Primidone	VPA may increase serum concentrations of metabolically derived phenobarbital; primidone concentrations may increase or remain unchanged	A reduction in primidone dosage may be required to avoid toxicity
Phenytoin	VPA displaces phenytoin from plasma protein binding sites and may inhibit phenytoin metabolism	Usually the interaction results in decreased total serum phenytoin concentration with little or no change in unbound phenytoin concentrations and clinical effect; in some patients, free phenytoin concentrations may increase, leading to potentiation of phenytoin effects
Antidepressants	VPA may increase amitriptyline and nortriptyline concentrations in patients receiving amitriptyline; VPA may also elevate nortriptyline concentrations in patients receiving nortriptyline	Patients receiving amitriptyline and nortriptyline should be monitored for potential signs of toxicity
Antipsychotics	VPA increases by about 20% serum chlorpromazine concentrations; VPA may variably affect the plasma concentrations of clozapine and decreases those of the metabolite norclozapine	Both interactions are probably of little clinical significance, though there have been reports of adverse effects in patients given VPA and clozapine in combination
Benzodiazepines	VPA increases serum lorazepam concentrations by about 20%; VPA also displaces diazepam from plasma protein binding sites	Both interactions are probably of little clinical significance; theoretically, the effects of IV diazepam may be transiently potentiated
Calcium channel antagonists	VPA may cause a moderate increase in serum nimodipine concentration	The possibility of VPA potentiating the effects of nimodipine (and possibly other dihydropyridines) should be considered
Nucleoside reverse transcriptase inhibitors	VPA may increase 2- to 3-fold the serum concentration of zidovudine by inhibiting its glucuronidation	Patients receiving zidovudine and VPA should be monitored for zidovudine toxicity; no significant interactions are expected with other nucleoside reverse transcriptase inhibitors (didanosine, lamivudine and zalcitabine)

CBZ-E = carbamazepine-10,11-epoxide; **IV** = intravenous.

patients comedicated with valproate, therapeutic (and toxic) effects occur at total plasma phenytoin concentrations lower than usual.

As indicated in table II, valproic acid may increase the serum concentration of certain coadministered drugs, including some tricyclic antidepressants, nimodipine and zidovudine. This could result in potentiation of the pharmacological effects of these agents.

3.3 Pharmacodynamic Drug Interactions

Potentially favourable pharmacodynamic drug interactions have been reported when valproate is administered with a number of other AEDs. For example, the combination of valproate and ethosuximide has been found to be useful in controlling absence seizures that are refractory to either drug given alone.[46] Similar interactions have been reported with carbamazepine in patients with partial seizures[47] and with lamotrigine in patients with partial and generalised seizure types.[48-50] These interactions are rather complex in nature, and adjustments in dosage are often required to optimise therapeutic response and decrease the risk of adverse effects.

4. Dosage and Administration

Valproate is available in a parenteral form and in various other formulations, including an oral solution, capsules, plain tablets, enteric-coated tablets and sustained-release formulations. These preparations contain either the free acid, various salts or a complexation product [divalproex sodium (valproate semisodium)]. Enteric coating ensures an improved gastric tolerability, whereas use of sustained-release formulations or divalproex sodium reduces the fluctuation in plasma drug concentrations and allows a prolongation of the dosing interval, with inherent benefits in terms of patient compliance.[10,51-53]

In adults, the starting dosage is usually 250mg twice daily, which is then increased at intervals of 2 to 3 days according to clinical response.[54] The usual effective dosage is 500 to 2500 mg/day in two or three divided doses with conventional formulations or two divided daily doses with sustained-release formulations.[54,55] In some patients, particularly those with idiopathic generalised epilepsies managed on valproate monotherapy, once daily administration may be feasible.[56] In general, dosage requirements are lower in patients with primarily generalised seizures than in those with partial seizures.[57]

In children, treatment may be initiated with 10 to 15 mg/kg/day and increased, if necessary, by 10 to 15 mg/kg/day at intervals of about 2 weeks according to clinical response. The usual effective dosage is 10 to 30 mg/kg/day (20 to 40 mg/kg/day in infants) in three divided doses (or two divided daily doses with sustained-release formulations). If dosages above 40 mg/kg/day are required, clinical chemistry and haematological parameters should be monitored with special care.[10]

There is considerable variability in plasma valproic acid concentrations among patients receiving the same dosage, largely as a result of interindividual differences in the rate of drug metabolism. The correlation between plasma drug concentrations and clinical response has been investigated in many studies and has been generally found to be relatively poor. An optimal plasma concentration range of 50 to 100 mg/L (350 to 700 mmol/L) has been proposed, but many patients respond well at concentrations outside this range.[10,58,59] Because of this, the value of monitoring plasma valproic acid concentrations tends to be limited, even though at times concentration measurements can be useful in the evaluation of patients with suspected toxicity or patients receiving high-dosage therapy.

5. Efficacy in the Treatment of Epilepsy

The initial trials of valproate were conducted in the late 1960s and early 1970s in patients with epilepsy refractory to the other AEDs available at the time. In these patients, adjunctive therapy with valproate was found to be efficacious in reducing the incidence of both generalised and partial seizures.

Forty-one mostly noncomparative trials of varying duration were reviewed by Pinder et al.[60] in 1977. Efficacy rates, defined as the percentage of patients showing a >75% reduction in seizure frequency compared with baseline, indicated that valproate, used mostly as adjunctive therapy, was effective in 61% of patients overall, with the response being usually greater in patients with generalised seizures compared with those with partial seizures. Equally favourable outcome data were reported in a more recent review by Davis et al.[10] on efficacy rates from 15 noncomparative trials performed between 1977 and 1993. In these studies, 70% of patients received monotherapy, and the findings confirmed the broad-spectrum efficacy of valproate in patients with a wide variety of seizure types.

The most valuable evidence on the clinical usefulness of valproate, however, comes from several randomised, controlled studies, the results of which are summarised in sections 5.1 to 5.3.

5.1 Partial Seizures (With and Without Secondary Generalisation) and Primarily Generalised Tonic-Clonic Seizures

A number of studies have compared valproate monotherapy with other AEDs as first-line treatment of patients with newly diagnosed partial seizures (with or without secondary generalisation) and/or primarily generalised tonic-clonic seizures (table III).

Turnbull et al.[62] in 1985 were the first to perform a relatively large-scale, randomised trial comparing valproate with phenytoin as initial monotherapy in 140 adults with recent-onset, previously untreated epilepsy. In agreement with earlier findings from the same group,[70] no major differences in efficacy were found between the two drugs, but phenytoin was more frequently associated with idiosyncratic adverse reactions leading to withdrawal (five patients, compared with none in the valproate group). Similar results were reported by Callaghan et al.,[63] who found no major differences in efficacy among valproate, phenytoin and carbamazepine in patients with newly diagnosed epilepsy. There was, however, a trend for complete seizure control to be observed less commonly in the carbamazepine group, particularly among patients with generalised seizures. With all three drugs, response rates were greater in patients with generalised tonic-clonic seizures than in those with partial seizures.

The efficacy of valproate monotherapy in adults with newly diagnosed partial or primarily generalised tonic-clonic seizures was further confirmed in a randomised controlled trial sponsored by the UK Medical Research Council in the early 1990s.[66] In this trial, 243 patients were randomised to treatment with valproate, carbamazepine, phenytoin or phenobarbital and followed up for 3 years. All drugs were similarly efficacious in controlling seizures but, as expected, there were appreciable differences in tolerability profile. Adverse effects leading to discontinuation of treatment were found in 5% of patients randomised to valproate compared with 3, 11 and 22% of those randomised to phenytoin, carbamazepine and phenobarbital, respectively. The results indicated that phenobarbital, as a result of its CNS adverse effects, is not the most desirable choice for the initial treatment of patients with newly diagnosed epilepsy.

These findings were reinforced by the results of a similar randomised trial in 167 children with partial or generalised tonic-clonic seizures.[68] No major differences in efficacy were identified between valproate, carbamazepine and phenytoin, but withdrawals as a result of adverse effects were more common in the phenytoin group (9%) than in the valproate and carbamazepine groups (4% each). More importantly, six of the first ten children randomised to phenobarbital dropped out as a result of unacceptable, mostly behavioural or cognitive, adverse effects, and the phenobarbital arm was eliminated from the study because the investigators considered it unethical to assign further children to treatment with a barbiturate.

Phenytoin and phenobarbital were included in another paediatric study carried out in India with a total of 151 children with generalised tonic-clonic

Table III. Prospective, randomised comparative studies on the efficacy of valproate monotherapy in the treatment of adults and children with newly diagnosed epilepsy (partial and/or generalised tonic-clonic seizures) [reproduced and modified from Seino,[61] with permission from Blackwell Science Ltd.]

Reference	Year of study	No. of patients (PS/all)	Age (y)	Seizure type	Seizure frequency at entry	Follow-up (mo)	Main efficacy
Turnbull et al.[62]	1985	64/140	16-70	PS (±SGTC), GTC	≥2 over previous 36mo	24-48	VPA ≈ PHT
Callaghan et al.[63]	1985	79/181	4-72 [mean 25]	PS (±SGTC), PGTC	≥2 over previous 6mo	14-24	VPA ≈ CBZ ≈ PHT
Mattson et al.[64]a	1992	480/480	18-70	CPS (±SGTC)	Not stated	Mean 40	VPA ≈ CBZ for SGTC; VPA inferior to CBZ for CPS
Ramsay et al.[65]	1992	0/136	Mean 21	GTC	≥2 within 14d after enrolment	6	VPA ≈ PHT (trend for better efficacy of VPA)
Richens et al.[57]	1994	143/300	≥16 [mean 34]	PS (±SGTC), PGTC	≥2 over previous 6mo	36	VPA ≈ CBZ
Heller et al.[66]	1995	102/243	≥16 [median 29]	PS (±SGTC), PGTC	≥2 over previous 12mo	Median 30	VPA ≈ PB ≈ PHT ≈ CBZ
Verity et al.[67]	1995	111/260	5-15	PS (±SGTC), PGTC	≥2 over previous 6mo	36	VPA ≈ CBZ
De Silva et al.[68]	1996	89/167	3-16	PS (±SGTC), PGTC	≥2 over previous 12mo	Median 44	VPA ≈ PHT ≈ CBZ
Thilothammal et al.[69]	1996	0/151	4-12	GTC	≥2	22-36	VPA ≈ PB ≈ PHT

a 50% of the patients had been suboptimally treated previously.

CBZ = carbamazepine; **CPS** = complex partial seizures; **GTC** = generalised tonic-clonic seizures; **PB** = phenobarbital (phenobarbitone); **PGTC** = primary generalised tonic-clonic seizures; **PHT** = phenytoin; **PS** = partial seizures; **SGTC** = secondary generalised tonic-clonic seizures; **VPA** = valproate; ≈ indicates no statistical difference in between-group comparisons.

seizures.[69] In this study, no differences in efficacy emerged among these drugs, but tolerability findings tended to favour valproate. Hyperactivity was the major adverse effect of phenobarbital, being observed in 22% of the children assigned to that drug.

Three additional, larger scale randomised monotherapy trials focused on a comparison of valproate with carbamazepine. The UK adult EPITEG trial evaluated 300 patients with newly diagnosed, previously untreated epilepsy, of whom approximately one-half had partial seizures and the remaining were diagnosed as having primarily generalised tonic-clonic seizures.[57] After 3 years of follow-up, valproate and carbamazepine were found to be equally efficacious, irrespective of seizure type. Both drugs were well tolerated, although a somewhat higher incidence of adverse effects (particularly skin rashes) at initiation of therapy with carbamazepine led to significantly more patients remaining on valproate for at least 6 months (90% compared with 75% in the carbamazepine group).

In a separate trial conducted according to an identical design involving 260 children at 63 centres in the UK and Ireland, valproate and carbamazepine were also found to be very effective in controlling partial and primarily generalised tonic-clonic seizures.[67] A trend for superiority of valproate in the 12- and 24-month remission rates did not reach statistical significance. As far as adverse effects were concerned, increased appetite was more common in the valproate group, whereas somnolence and dizziness were more common in the carbamazepine group.

A third major randomised trial comparing valproate with carbamazepine was carried out by the Veterans Administration (VA) Collaborative Group in the US.[64] This large-scale (480 patients),

double-blind trial differed from the UK studies in several ways: (i) only patients with complex partial seizures and secondarily generalised tonic-clonic seizures were included; (ii) 97% of the patients were male; (iii) the average age (47 years) was higher than in the other studies; and (iv), perhaps most importantly, only half of the patients were treatment naïve, the other half having experienced suboptimally treated epilepsy for an average of 8 years. Possibly because many patients had partially refractory epilepsy, the mean dosage of valproate at the end of the 12-month follow-up was higher than in the European studies (2099 mg/day compared with 924 mg/day at 24 months in the adult EPITEG trial[57]). Valproate was found to be as effective as carbamazepine in controlling generalised tonic-clonic seizures, but carbamazepine provided better control of complex partial seizures and had fewer long-term adverse effects. In particular, tremor, hair loss or changes in hair texture, and bodyweight gain were more common in the valproate group, whereas carbamazepine was associated with a higher incidence of skin rashes at the beginning of treatment. The conclusions of this study, however, have been questioned, mainly in view of the high dosages used, the somewhat arbitrary allocation of patients to subgroups based on the predominant seizure type and the high number of patients (about one-third) lost to follow-up in the first 12 months.[61,71,72]

Although the higher efficacy of carbamazepine in comparison with valproate in controlling complex partial seizures in the VA trial[64] could be explained by recruitment of patients with a more severe partial epilepsy, it should be pointed out that in other studies the efficacy of valproate has also been clearly established in patients with refractory epilepsy. The most recent of such trials used a conversion-to-monotherapy, double-blind design, where patients with refractory partial seizures uncontrolled by carbamazepine, phenytoin or barbiturates were randomised to divalproex sodium at dosages designed to achieve plasma valproic acid concentrations in a high range (80 to 150 mg/L) and low range (25 to 50 mg/L).[73] Proof of efficacy was obtained by demonstrating that patients randomised to high concentrations had better seizure control than those randomised to low concentrations, even though there were more adverse effects in the former group. It should be stressed, however, that this trial was not designed to assess the efficacy of valproate under optimal dose conditions; indeed, the high-concentration group received dosages far in excess of those that are usually appropriate, whereas the low-concentration group received suboptimal dosages.

More clinically relevant information on the usefulness of valproate in the management of refractory partial seizures comes from conventional adjunctive therapy trials, where the drug was found to be superior to placebo[74,75] and as effective as vigabatrin[48] in patients whose epilepsy failed to respond to other AEDs. As discussed above in section 3, it has been suggested that in patients with refractory epilepsy, the best responses are often found when valproate is combined with either carbamazepine[47,48] or, in particular, with lamotrigine,[48-50] even though coadministration with the latter drug requires special precautions to minimise the risk of lamotrigine-induced skin rashes.[4]

The Cochrane Collaboration Group has recently completed a meta-analysis of randomised, controlled, comparative trials of valproate, phenytoin and carbamazepine given as monotherapy to patients with newly diagnosed partial and primarily generalised tonic-clonic seizures. The comparison of valproate with phenytoin was based on data from 669 patients, and no overall difference was found between the two drugs for the main outcomes examined (i.e. time to withdrawal from the allocated treatment, time to 12-month remission, time to 6-month remission and time to first seizure).[76] The comparison between valproate and carbamazepine was based on analysis of individual data from 1265 patients from five trials.[77] For partial seizures, the two drugs were found to have comparable efficacy for all endpoints tested, except for time to first seizure (a parameter of questionable clinical significance, being strongly influenced by the somewhat arbitrary choice of the starting dosage), which was in

favour of carbamazepine. For primary generalised tonic-clonic seizures, efficacy endpoints tended to favour valproate, but confidence limits were too wide to allow detection of statistically significant differences. The authors also presented evidence that analysis of data for generalised epilepsies could have been confounded by the fact that at least in some patients seizures were probably misclassified.

There is little information on how valproate compares with newly introduced AEDs in the management of patients with previously untreated epilepsy. In one trial, 249 patients with newly diagnosed partial and primarily generalised tonic-clonic seizures were randomised to either oxcarbazepine or valproate monotherapy and followed up for 1 year.[78] The two drugs were found to have comparable efficacy, and no significant differences were found in their overall tolerability, an interesting observation in view of the fact that in similar trials oxcarbazepine was found to be better tolerated than either carbamazepine or phenytoin (see review by Perucca and Tomson[79]).

5.2 Other Generalised Seizure Types

Valproate is regarded as the first-choice agent for most forms of idiopathic and symptomatic generalised epilepsies.[80-82] Many of these syndromes are associated with multiple seizure types, including tonic-clonic, myoclonic and absence seizures, and prescription of a broad-spectrum drug such as valproate has obvious advantages in this situation.[83] For the same reason, valproate represents a reasonable choice in patients with a history of generalised seizures in whom a precise syndromic diagnosis is uncertain, even though this should not be regarded as a reason to neglect all possible investigations that could lead to a precise diagnosis of the type of epilepsy.[83,84] On the other hand, carbamazepine, phenytoin, oxcarbazepine and the GABAergic drugs vigabatrin and tiagabine should be used very cautiously in patients with generalised epilepsies, since these drugs have a potential for precipitating or aggravating myoclonic jerks and absence seizures[85-87] and may even be responsible for inducing refractory nonconvulsive status.[88] The effectiveness of valproate in protecting against a variety of seizure types in patients with generalised epilepsies is supported by decades of extensive clinical experience, even though controlled comparative trials are rarely conducted in these patients.

In patients with typical and atypical absence seizures, the efficacy of valproate has been demonstrated both by clinical observation and documentation of a reduced frequency and duration of discharges in the EEG.[89-91] Although in comparative trials, valproate and ethosuximide have been found to be equally effective in suppressing seizures in at least 80% of patients with childhood or juvenile absence epilepsy,[92,93] valproate is usually considered the drug of choice for the treatment of these patients because, unlike ethosuximide, it is also effective in preventing generalised tonic-clonic seizures, which may coexist or develop at a later time in these patients.[94] Valproate has also been found to be efficacious in preventing the recurrence of absence status.[95]

Valproate is efficacious against all types of seizures associated with juvenile myoclonic epilepsy, and it is also generally regarded as the treatment of choice for this condition (see review by Wolf[81]). Seizure control is obtained in a large majority of patients with juvenile myoclonic epilepsy, and treatment needs to be continued for life because there is a high risk of relapse when the drug is discontinued.

Valproate is widely used in the management of a variety of seizure types, including atypical absences, tonic, atonic and myoclonic seizures, which are associated with cryptogenic and symptomatic generalised epilepsies. Syndromes in which valproate has been found to be useful include the Lennox-Gastaut[10,96] and West[97-99] syndromes. Caution, however, is required in infants and young children because of the risk of liver toxicity, which is especially elevated in patients with inborn metabolic defects (see section 6.6).

Although valproate is effective in reducing the risk of recurrence of febrile convulsions,[100-103]

the risk-to-benefit ratio is against the use of continuous pharmacological prophylaxis in children with a history of febrile seizures.[4,104]

5.3 Status Epilepticus

Valproate has been made available recently in a dosage form suitable for intravenous use, the approved therapeutic indication for which is replacement therapy in patients temporarily unable to take the drug orally. Some clinicians, however, have evaluated this formulation as a potential treatment against convulsive and nonconvulsive status epilepticus, with favourable preliminary results.[105-120] Compared with other drugs used in the management of status epilepticus, such as benzodiazepines and phenytoin, valproate has potential safety advantages because of a lower risk of hypotension and respiratory depression.[105,106]

Further studies are required to establish in more detail the value of valproate in the management of status epilepticus. At present, there is insufficient evidence to recommend the use of the drug as first-line therapy in the management of this condition.

6. Adverse Effects

The adverse effects profile of valproate has been evaluated in clinical studies and in extensive postmarketing experience.[10,121,122]

6.1 Gastrointestinal Adverse Effects

Among dose-dependent adverse effects, gastrointestinal disturbances such as nausea, vomiting and indigestion and, more rarely, diarrhoea, abdominal cramps and constipation are observed more commonly at initiation of treatment; they are usually transient and do not generally require discontinuation of treatment.[10,123] Manifestations of gastric intolerance may be minimised by using an enteric-coated formulation or by administering the drug at meal times.

6.2 CNS Adverse Effects

CNS adverse effects are observed less commonly with valproate than with other AEDs (see review by Davis et al.[10]). Sedation may be observed, but generally it is not prominent and may result from interactions with concomitantly given AEDs, particularly phenobarbital.[122] Valproate has a minimal impact on cognitive function[124] and, for this reason, it has been proposed among the AEDs to be used preferentially in the elderly.[125]

The most commonly observed neurological adverse effect associated with valproate is a postural tremor, which resembles essential tremor and tends to be dose related. In the adult EPITEG trial, 6% of patients assigned to valproate developed tremor, compared with 2% of patients allocated to carbamazepine.[57] Tremor was observed much more commonly in the VA study,[64] where it was reported in 45% of patients assigned to valproate, compared with 22% of those randomised to carbamazepine. The higher incidence in the latter trial may be ascribed to use of larger dosages but also to evaluation of adverse effects by means of a checklist, a methodology that may lead to over-reporting.[126] In some patients, particularly those in whom the tremor has a 'flapping' pattern, an underlying valproate-induced hyperammonaemia may contribute to its aetiology.

Less common CNS adverse effects of valproate include headache, nystagmus, dizziness, diplopia, amblyopia, blurred vision, incoordination, parkinsonian symptoms and behavioural or psychiatric disorders.[121,127] A reversible, dementia-like syndrome, at times associated with magnetic resonance imaging (MRI) findings suggestive of cortical atrophy, has been reported. The syndrome is extremely rare, but physicians should be aware of its existence, because both the mental and MRI signs disappear rapidly following discontinuation of treatment or a reduction in dosage.[128] Occasional cases of encephalopathy have also been reported, which may involve development of a confusional state, stupor and even coma, particularly in patients comedicated with other AEDs.[14,127] These symptoms are fully reversible and need to be differentiated from those caused by valproate-

induced hyperammonaemia or by severe liver toxicity.

6.3 Bodyweight Gain and Polycystic Ovary Syndrome

An adverse effect that may be troublesome during long-term treatment with valproate is bodyweight gain.[129] Caloric restriction does not necessarily eliminate the problem.

In the EPITEG trial, the incidence of bodyweight gain during valproate treatment was 15%,[57] whereas in the VA study the percentage of patients who gained more than 5.5kg (12lb) was 20%.[64] Hyperinsulinism has been described in association with valproate-induced excessive bodyweight gain.[130]

Some studies have associated valproate with an increased incidence of polycystic ovaries, polycystic ovarian dysfunction and hyperandrogenism,[131] which are discussed in this section as they seem to be at least in part related to bodyweight gain. Polycystic ovaries alone are a relatively common finding in the general population and should be differentiated from polycystic ovary syndrome (i.e. a condition involving hyperandrogenic chronic anovulation, associated with menstrual disorders, hypofertility and, often, hirsutism, acne and obesity).

As pointed out by Frank,[132] 'few subjects have provoked such controversy in the field of reproductive endocrinology as policystic ovary syndrome', and this appears to be equally true for the role of valproate in the pathogenesis of this syndrome.[133-136] Some authors consider available evidence to indicate a causative role of valproate in increasing the incidence of polycystic ovaries, anovulation and hyperandrogenism in women with epilepsy (particularly in those who are obese),[135] whereas others point out that the evidence is less than compelling, that the described ovarian and endocrine changes may be simply a consequence of valproate-induced bodyweight gain, and that studies conducted to date failed to fully account for the role of confounding factors, including epilepsy *per se*.[134] For a detailed discussion, the reader is referred to two recent articles where these viewpoints are hotly debated.[134,135] As summarised in an associated commentary,[136] the bulk of the evidence indicates that polycystic ovary syndrome occurs in 13 to 25% of women with epilepsy, which is higher than the 4 to 6% prevalence most commonly found in the general population; the broad extent of this range may well represent differences in classification criteria and characteristics of the assessed population, including the type of drug exposure.

Overall, menstrual disorders, certain clinical, ultrasound or endocrine manifestations of reproductive system disorders, and polycystic ovary syndrome appear to be more common with the use of valproate than with other AEDs. Although these findings do implicate a role of valproate, the precise incidence of the observed abnormalities, their clinical relevance and the influence of confounders remain to be established and should be evaluated in large, prospective randomised studies.[136]

As for the implications for current prescribing, drug selection in the individual patient should always take into account predicted benefits versus expected risks.[136] When valproate is prescribed to women with epilepsy, monitoring of bodyweight, menstrual cycle and potential reproductive endocrine abnormalities is recommended.[133-136] Should endocrine problems emerge, switching to an alternative drug (for example, carbamazepine in partial epilepsy or lamotrigine in generalised epilepsies) should be considered, even though in well controlled patients there is always a risk that a change in therapy could result in seizure recurrence.[137]

6.4 Hyperammonaemia and Other Metabolic Adverse Effects

A rise in blood ammonia level has been reported in 20 to 50% of patients treated with valproate, being more common among those comedicated with enzyme-inducing AEDs.[10] In most patients, this biochemical abnormality is asymptomatic, at times transient and of negligible clinical significance, but symptoms of encephalopathy, confusion,

nausea/vomiting and ataxia have been noted in occasional cases, which necessitated withdrawal of the drug (see review by Davis et al.[10]).

Valproate may also cause a decrease in plasma carnitine levels.[138] L-carnitine supplementation is currently recommended for valproate-induced liver toxicity, valproate overdose, other acute metabolic disorders associated with carnitine deficiency and primary plasmalemmal carnitine transport defect.[105] Other indications proposed for L-carnitine supplementation include the presence of a secondary carnitine-deficiency syndrome, symptomatic valproate-associated hyperammonaemia, multiple risk factors for valproate-associated hepatotoxicity, use of valproate in infants and young children and those undergoing dialysis, and conditions associated with hypocarnitaemia.[139]

Metabolic adverse effects that have been occasionally reported in association with valproate include alterations in lipid metabolism[127] and reduced bone mineral density.[140]

6.5 Haematological Adverse Effects

Thrombocytopenia, platelet dysfunction, fibrinogen depletion and coagulation abnormalities have also been reported with valproate use and may be associated with altered bleeding time, bruising or epistaxis.[121,122,141] Increased blood loss during surgery in valproate-treated patients has been reported in some series[142] but not in others.[143]

Bone marrow depression has been reported in a few patients treated with valproate, but it is extremely rare.[127]

6.6 Pancreatitis and Liver Toxicity

The two most important idiosyncratic reactions ascribed to valproate therapy are pancreatitis and liver failure.[127]

Acute pancreatitis may rarely lead to fatalities, and most published cases have been reviewed.[144,145] Pre-existing mental retardation[146] and end-stage renal failure[147] have been suggested to be among the risk factors for valproate-induced pancreatitis.

As far as liver toxicity is concerned, its incidence in an unselected population of patients is in the order of 1 in 20 000 treated patients.[148-150] However, several conditions are known to be associated with an increased risk, most notably age below 2 years (particularly when valproate is used in polytherapy and in children with mental retardation), coexistence of certain metabolic defects (e.g. β-oxidation disorders and mitochondrial diseases, conditions for which valproate is clearly contraindicated) and pre-existing liver disease or elevated liver enzyme levels.[148-150] In children younger than 2 years receiving polytherapy, the risk of valproate-induced liver toxicity is as high as 1 : 600 or 1 : 800, but the incidence decreases with increasing age.

Over the past years, there has been a decrease in the occurrence of fatal liver toxicity, probably owing to the recognition of risk factors, avoidance of valproate in high-risk groups and, possibly, rapid discontinuation after early identification of the disorder.[150] Although monitoring of liver enzyme levels, particularly during the first 6 months of therapy, should not be neglected, it may not allow early detection of hepatotoxicity. Therefore, it is important to inform the patient and relatives about the most common heralding signs, which include apathy, somnolence, anorexia, vomiting and increased seizure frequency, especially in the presence of febrile infections.[150] A bleeding tendency and jaundice may be additional early signs in some patients. Management involves rapid discontinuation of the offending drug, and the use of intravenous carnitine has also been advocated.[151,152] In a recent report, 20 of 42 patients with valproate-induced hepatotoxicity treated with L-carnitine survived, compared with a survival rate of only 10% among 50 patients treated solely with aggressive supportive care.[153]

6.7 Skin and Appendages

Skin rashes are very uncommon with valproate, and other immune-mediated reactions such as systemic lupus erythematosus are exceedingly rare.[127]

Valproate may be associated with hair loss or changes in hair texture. These effects are usually

reversible and may remit even when therapy is continued.[10]

6.8 Effects on the Offspring

An important adverse effect of valproate is an increased risk of major malformations and, possibly, dysmorphic syndromes in the offspring of women exposed to the drug in the first trimester of pregnancy.[121,153-160] In addition to other malformations, an estimated 1 to 3% risk of neural tube defects, including spina bifida, has been reported, and there is some evidence that the increase in risk is highest when valproate is taken in high dosages (≥1000 mg/day) or in combination with certain other AEDs, particularly carbamazepine.[156,157] One recent study has also reported that children exposed prenatally to valproate were more likely to require additional educational support compared with children exposed prenatally to other AEDs,[161] but because of the retrospective nature of this survey, selection bias could not be excluded. Overall, there is a striking paucity of information on the comparative effects of prenatal AED exposure on postnatal development, and this represents an important priority for future prospective studies.

The treatment of epilepsy in women of childbearing potential raises important concerns with respect to the well-being of the offspring.[162] In addition to valproate, other old-generation AEDs have been associated with an increased incidence of birth defects (including a 0.5 to 1% risk of neural tube defects with carbamazepine[162]). The potential teratogenic risks associated with the use of newer AEDs in women are unknown.[162] Collaborative multicentre prospective registries have been set up around the world to collect essential prospective information on the relative risks associated with the various AEDs and their combinations, and it should be a duty of all practising physicians to collaborate in these studies.[163]

Since convulsive seizures are also considered harmful to the developing embryo, no one questions the need for anticonvulsant prophylaxis in women of childbearing potential. In the absence of sound evidence on potential differences in teratogenic risks between AEDs, physicians differ in their perception of risk/benefits ratios of the various drugs and, therefore, in prescribing practices. One justifiable approach involves choosing the AED that is most likely to control the patient's seizure type(s) at relatively low dosages.

Prenatal diagnosis with ultrasound at gestation weeks 18 to 20 can be used for the early detection of most major malformations, including neural tube defects.[162] In patients at risk for neural tube defects, amniocentesis at weeks 15 to 16 for the determination of α-fetoprotein may be considered, but amniocentesis is not without risks, and its use has declined following the introduction of improved ultrasound techniques (including transvaginal ultrasonography).

In animal models, the teratogenic effects of valproate are attenuated by avoiding high peak plasma concentrations.[164] In women of childbearing potential who require therapy with valproate, it is advisable to rationalise treatment prior to pregnancy by using the lowest dosage that controls convulsive seizures, possibly as monotherapy, and by dividing the total dose of valproate into three daily administrations (or two daily administrations for sustained-release formulations).[162] Folic acid should be administered before and during pregnancy in all women taking valproate and/or other AEDs. Folic acid has been shown to reduce the risk of neural tube defects in the offspring when there was a history of a previously affected pregnancy,[165] and it is possible that it could also reduce the risk of spina bifida associated with valproate or carbamazepine, even though this has not been formally tested.

7. Pharmacoeconomic Considerations

Currently available AEDs differ greatly in their cost, and the price of medication is an important consideration in designing therapeutic algorithms, even in affluent societies. Recent surveys used a cost-minimisation analysis to compare direct medical costs associated with the use of valproate, phenytoin, carbamazepine and lamotrigine in the

treatment of newly diagnosed patients in 12 countries.[166,167] Not surprisingly, the costs associated with the use of the three older drugs were one-half to one-third of those associated with the use of lamotrigine.

Economic appraisals providing data to orient therapeutic practice have clearly shown that, at least in patients with newly diagnosed epilepsy, optimal cost-effectiveness can be achieved with older generation AEDs.[166] This conclusion is supported by evidence that in these patients, new AEDs are not more efficacious than older agents.[79] Although differences in tolerability profile between these agents do exist, they do not appear to justify the first choice use of new AEDs in the vast majority of patients with recent-onset epilepsy, even though there may be exceptions to this rule.[79]

8. Conclusions

Among available AEDs, valproate is distinguished by its broad spectrum of efficacy against all seizure types and syndromes, low risk of causing paradoxical seizure exacerbation, good CNS tolerability and over 35 years of clinical experience in millions of patients worldwide. Because of these characteristics, valproate remains a mainstay for the treatment of epilepsy in all age groups, with the exception of infants and very young children where its potential benefits need to be carefully weighed against the risk of liver toxicity. In all types of epilepsy, the efficacy of valproate is comparable with that of alternative AEDs, and it is mainly the differences in tolerability profile that determine which drug has to be preferentially used in an individual patient.

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