The Independent
MEDICINES & MEDICAL DEVICES
Safety Review

The Independent Medicines and Medical Devices Safety Review

Written Evidence

Clinicians, Academics and Other Individuals – Sodium Valproate

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Contents

WARNING: Please be aware some evidence contains descriptions, pictures and audio of the harm suffered by individuals. Some may find this distressing.

Submission from Jeffrey K Aronson

COI:

No conflicts of interest declared.

Pharmacological aspects of the teratogenicity of sodium valproate

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Contents

A. Summary and personal statement

In this paper I discuss aspects of the teratogenicity of sodium valproate under the following headings:

1. What is sodium valproate and what are the distinctions between Epilim, sodium valproate, and related compounds?
Sodium valproate is an antiepileptic drug used to treat various types of epilepsy; it is also used to treat bipolar affective disorder and migraine (an unlicensed indication in the UK). Divalproex, which is converted to valproate in the gut before absorption, is similarly used. Epilim is one brand name of sodium valproate, available in many different types of formulation.

2. What are the pharmacokinetics of valproate in humans, including transplacental transfer and kinetics in children?
Valproate has a relatively short half-life in adults and a longer half-life in neonates, and presumably in fetuses. It is highly protein bound and its binding is saturable, being reduced at higher concentrations. Small changes in binding produce large changes in the unbound active compound. It crosses the placenta in high concentrations.

3. What are the adverse effects of valproate as listed in different sources?
Reported harms are too extensive to list here. They are summarized in a table using three different sources of information. A major harm is teratogenicity.

4. What are the pharmacological properties of sodium valproate and the mechanisms of action whereby it produces beneficial effects in epilepsy and harmful effects?
These are not known, but there are many hypotheses, discussed in the text. Teratogenicity may be mediated by inhibition of histone deacetylase, and consequent changes in gene expression, or by increased fetal oxidative stress, or by inhibition of folic acid metabolism.

5. By when was there first a testable hypothesis in relation to the teratogenicity of sodium valproate in humans?

Teratogenicity was first noted in animals in 1971. Cumulative meta-analysis, a technique that was available from 1992, shows that there was a significant twofold signal of teratogenicity in humans by 1990.

6. How is the evidence that sodium valproate is teratogenic in humans reflected in the Data Sheets and Summaries of Product Characteristics relating to Epilim?

The information given in the Data Sheets and Summaries of Product Characteristics has lagged behind the information that could have been given. I have tabulated the information given in key years and compared it with information given about two other antiepileptic drugs with teratogenic effects, phenytoin and carbamazepine.

7. What information about teratogenicity has been given in other important sources of general information about sodium valproate?

The main source of information outside of data sheets and SmPCs is the British National Formulary, which is published twice a year; I have summarized the changes in information about the teratogenicity of sodium valproate in successive issues since it was first mentioned in issue 4 (September 1982).

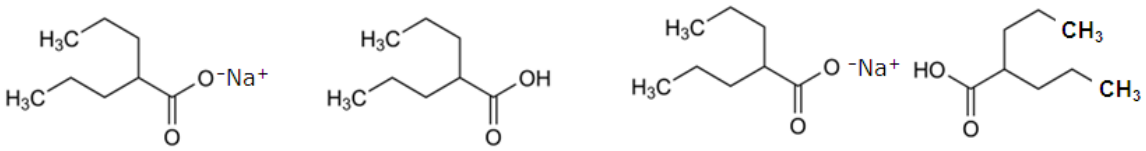
Personal statement

I am a physician and clinical pharmacologist, with interests spanning all matters to do with pharmacological interventions in general medicine. I have published widely in learned journals in these areas and especially in the area of harms from medicines (adverse drug effects and adverse drug reactions and interactions). I edited the 16th edition of *Meyler's Side Effects of Drugs—the International Encyclopedia of Adverse Drug Reactions and Interactions* (7 volumes; Elsevier, 2016) and eight volumes of *Meyler's Side Effects of Drugs* in relation to different medical specialties (Elsevier 2008–10), and I co-edited the 6th edition of *Stephens' Detection and Evaluation of Adverse Drug Reactions: Principles and Practice* (Wiley-Blackwell, 2011). I have often advised coroners and legal firms on matters concerning adverse effects of therapeutic medicines and toxic compounds. I am a President Emeritus and currently Vice-President Publications of the British Pharmacological Society, and an Emeritus Fellow of Green–Templeton College, Oxford. I currently work in the Centre for Evidence Based Medicine in the University of Oxford. My complete curriculum vitae is given in Appendix 3.

B. Main report

1. What is sodium valproate and what are the distinctions between Epilim, sodium valproate, and related compounds?

"Sodium valproate" is the recommended International Non-Proprietary Name (rINN) that the World Health Organization has allotted to the chemical compound with the systematic name of sodium 2-propylpentanoate. It is the sodium salt of valproic acid (Figure 1).



Sodium valproate | Valproic acid | Divalproex (Valproate disodium)

Figure 1. Structures

Sodium valproate and Epilim

"Epilim" is the proprietary name of a formulation manufactured and marketed by Sanofi. Epilim contains the compound sodium valproate plus a variety of other ingredients, so-called excipients, which have no pharmacological actions and generally no detectable effects. It is available in the UK as immediate-release crushable tablets, modified-release gastro-resistant tablets and modified-release granules, oral solutions, both sugar-free and syrup, and as a powder and a solvent for solution for injection. Non-proprietary versions of these are also available, as is another branded product, Episenta, marketed by Desitin Pharma Ltd, as modified-release capsule and granules and a solution for injection.

Epilim is licensed for the treatment of "generalized, partial or other epilepsy" [1]. Daily dosage requirements vary according to age and body weight. The typical recommended initial dose of the crushable tablets in adults is 600 mg/day in two divided doses, preferably after food, increased by 200 mg/day every 3 days until control is achieved to a maximum of 2.5 g/day; the usual maintenance dose is 1–2 g/day (20–30 mg/kg/day).

Divalproex

Valproate semisodium or divalproex, which contains equal molar quantities of sodium valproate and valproic acid (Figure 1), is marketed by Sanofi in a formulation called Depakote (gastro-resistant tablets)and by Pfizer Ltd as Convulex (gastro-resistant capsules). Depakote is licensed for "treatment of all forms of epilepsy [and] treatment of manic episode in bipolar disorder when lithium is contraindicated or not tolerated" [2].

Other brand names

Brand names for these compounds vary from country to country, depending on the manufacturer. Here are some examples of formulations of sodium valproate:

Australia: Epilim tablets (Sanofi-Aventis); Valpro tablets (Alphapharm)
Canada: Epival or Epiject intravenous injection (Abbott Laboratories)
Germany, Switzerland, Norway: Orfiril tablets, Orfiril IV (Desitin Pharmaceuticals)
South Africa: Convulex syrup (Byk Madaus)
USA: Depacon intravenous injection; Depakene syrup; both by Abbott Laboratories.

2. What are the pharmacokinetics of valproate in humans, including transplacental transfer and kinetics in children?

Sodium valproate is almost completely absorbed after oral administration. Valproic acid and divalproex are converted to sodium valproate in the gut before absorption. Modified-release ("sustained-release" or "slow-release") formulations minimize fluctuations in serum drug concentrations during a dosing interval [3].

Valproate is about 90% absorbed after oral administration [4]. It is about 93% bound to plasma proteins, but binding is saturable and so the extent of binding falls to about 85% with increasing drug concentrations within the therapeutic range; thus, disproportionately more valproate is unbound and therefore available for tissue distribution at higher doses.

Valproic acid is extensively metabolized in the liver by glucuronidation (about 40%) by different variants of UDP-glucuronosyltransferase (UGT) enzymes, and by oxidation, both beta-oxidation and omega-oxidation (Figure 2). [Carbon atoms are marked C, and there are also carbon atoms at each point where two lines in the structure meet.] Formation of the 4-en metabolite, said to be the most toxic, is reduced after administration of a slow-release formulation [5,6]. Only about 1–3% of valproate is excreted unchanged via the kidneys.

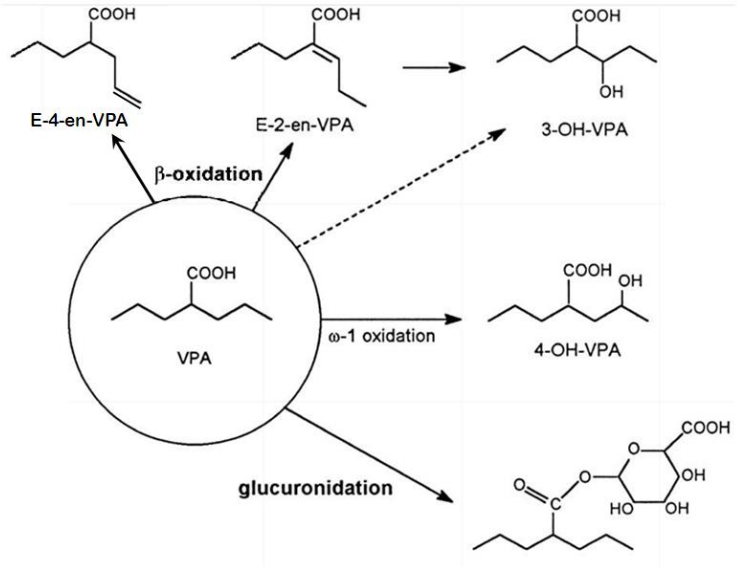


Figure 2. Some of the metabolic pathways of valproic acid (VPA)

The half-life of valproate is 4–16 hours, but enzyme-inducing agents, such as phenytoin and carbamazepine, shorten this to less than 12 hours. In neonates the half-life is considerably longer (20–67 hours) [7], and this is presumably also the case in the fetus. The difference in half-life between adults and neonates is not surprising; valproate is extensively metabolized in the liver, and hepatic function in neonates is immature, leading to a reduced rate of clearance and therefore a prolonged half-life.

Valproate inhibits the metabolism of some other drugs, including phenobarbital, lamotrigine, and zidovudine.

Valproate crosses the placenta, and concentrations in cord blood are higher than those in maternal serum [8]. In 23 pregnant women, in whom drug measurements were made during the last 3 months of pregnancy, at birth, and during the first week post-partum, the following concentrations of valproic acid were found (expressed as a percentage of the maternal serum concentration): cord blood 125–147% and amniotic fluid (derived from fetal urine) 5–11% [9].

It is a pharmacological tenet that the higher the concentration the bigger the effect, up to a maximum value (beyond which there is no further increase)—this is the principle of the dose-response (or concentration-effect) curve (Figure 3). Thus, the higher the dose taken by the mother, the more will be transferred to the fetus, and the larger the pharmacological effects. At high concentrations there is also the potential for harmful effects. For example, in a study in pregnant women the incidence of fetal malformations increased with dose and serum concentration [10].

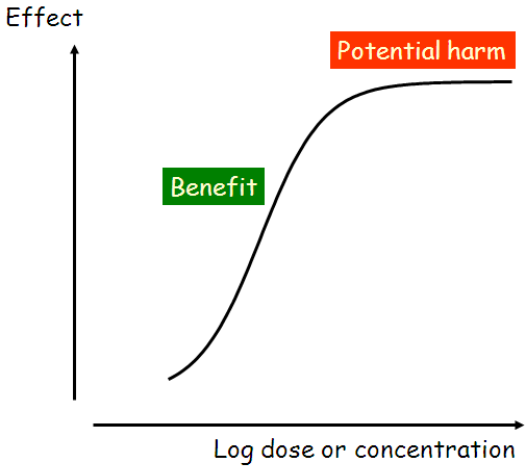


Figure 3. A schematic representation of a dose-response (concentration-effect) curve. At very low concentrations there is little or no effect; as the concentration increases, so does the effect; at very high concentrations no extra beneficial effect is seen, but there is a potential for harmful effects, either through the same pharmacological effect as the beneficial effect, or sometimes through a different pharmacological action. This analysis is not exhaustive—other relationships between beneficial and harmful effects are possible.

3. What are the adverse effects of valproate as listed in different sources?

In Table 1 I have summarized the harms that have been attributable to valproate, using three different sources: the Summary of Product Characteristics for Epilim 100 mg crushable tablets [1]; the *British National Formulary* (online version, accessed 23 October 2018) [11]; and *Meyler's Side Effects of Drugs* [12]. The data listed in the SmPC will have come from clinical trials and anecdotal reports submitted to the manufacturer. Those listed in the BNF and Meyler will have come from reviews of the published literature. In some cases drug-event associations will not have been confirmed to be true adverse effects or adverse reactions (which I shall also refer to as "harms").

The reported harms are broadly similar in the different sources. The frequencies of adverse effects and reactions are difficult to assess, and different words (such as "occasionally", "commonly", and "rarely") are often used loosely [13]. Apparent differences are therefore not noteworthy. To put this in context, about 30% of all reports of suspected adverse drug reactions are anecdotal (i.e. single case reports); only about 35% of the total come from major studies (randomized trials or observational studies) [14]. Furthermore, only about 17% of anecdotal reports are followed up in an effort to confirm or refute them; information about unconfirmed anecdotes often finds its way into SmPCs or the BNF, but the processes by which this happens are inconsistent, and such information can be conflicting in different sources [15].

Table 1. Reported adverse effects of sodium valproate
1 = common or very common
2 = uncommon
3 = rare or very rare
4 = not stated or unknown

System affected*	SmPC Epilim	BNF	Meyler
Cardiovascular			Very rarely, impaired cardiac function due to carnitine deficiency
Respiratory	Pleural effusion[2]	Pleural effusion[2]	Rarely, respiratory failure
Nervous system, psychological, psychiatric	Tremor[1]; extrapyramidal disorder[1]; stupor[1]; somnolence[1]; convulsion[1]; memory impairment[1]; headache[1]; nystagmus[1]; coma[2]; encephalopathy[2]; lethargy[2]; reversible parkinsonism[2]; ataxia[2]; paraesthesia[2]; aggravated convulsions[2]; reversible dementia associated with reversible cerebral atrophy[3]; cognitive disorder[3]; sedation[3]; increased alertness, occasionally with aggression, hyperactivity, and behavioural deterioration[3]; confusional state[1]; hallucinations[1]; aggression[1]; agitation[1]; disturbance in attention[1]; abnormal behavior[3]; psychomotor hyperactivity[3]; learning disorder[3]	Agitation[1]; behaviour abnormal[1]; concentration impaired[1]; confusion[1]; dizziness[1]; drowsiness[1]; headache[1]; memory loss[1]; movement disorders[1]; nystagmus[1]; seizures[1]; stupor[1]; tremor[1]; coma[2]; encephalopathy[2]; paraesthesia[2]; parkinsonism[2]; cerebral atrophy[3]; cognitive disorder[3]; dementia[3]; learning disability[3]; alertness increased[4]; hallucination[4]	Tremor, asterixis; less frequently, sedation, fatigue, dizziness, headache, ataxia, insomnia, encephalopathy, and behavioral problems; occasionally aggravation of seizures, impaired cognitive performance and altered behavior; uncommonly parkinsonism, encephalopathy, pseudoatrophy of the brain; rarely, gelastic seizures, cortical atrophy, psychotic reactions
Special senses	Deafness[1];	Deafness[1]	Very rarely, colour vision or visual field defects
Endocrine/metabolism/ nutrition	Weight increased[1]; Syndrome of Inappropriate Secretion of ADH (SIADH)[2]; hyperandrogenism (hirsutism, virilism, acne, male pattern alopecia, and/or androgen increase) [2]; hyperammonaemia[3];	Weight increased[1]; SIADH[2]; hyperammonaemia[3]; hypothyroidism[3]	Weight gain, raised serum lipids, hyperammonaemia, carnitine deficiency, increased plasma homocysteine concentration, reduced serum folate, subclinical hypothyroidism

	hypothyroidism[3]; obesity[3]		
Fluid balance	Non-severe peripheral oedema[3]	Peripheral oedema[2]	Rarely, peripheral oedema
Electrolyte balance	Hyponatraemia[1]	Hyponatraemia[1]	Very rarely, hyponatremia
Haematological	Haemorrhage[1]; anaemia[1]; thrombocytopenia[1]; pancytopenia[2]; leucopenia[2]; bone marrow failure, including red cell aplasia, agranulocytosis, anaemia macrocytic, macrocytosis[3]; coagulation factors decreased (at least one)[3]; abnormal coagulation tests (such as prothrombin time prolonged, activated partial thromboplastin time prolonged, thrombin time prolonged, INR prolonged)[3]; myelodysplastic syndrome[3]; reduced blood fibrinogen and/or increased prothrombin time[4]; inhibition of platelet aggregation[4]	Anaemia[1]; haemorrhage[1]; thrombocytopenia[1]; bone marrow disorders[2]; leucopenia[2]; agranulocytosis[3]; myelodysplastic syndrome[3]; red blood cell abnormalities[3]	Uncommonly, disorders of hemostasis (especially thrombocytopenia); rarely, reduced plasma fibrinogen concentrations; very rarely, deficiency of von Willebrand factor or factor XIII
Salivary glands			Very rarely, sialadenosis
Gastrointestinal	Nausea[1]; vomiting[1]; stomatitis[1]; gastralgia[1]; diarrhea[1]	Abdominal pain[1]; diarrhoea[1]; nausea[1]	Nausea, anorexia, vomiting, gastritis, and diarrhoea
Liver	Liver injury[1]; increased liver enzymes[1]; severe liver damage, including hepatic failure sometimes resulting in death[4]	Hepatic disorders[1]	Raised liver enzymes, non-alcoholic fatty liver disease; rarely, liver failure
Pancreas	Pancreatitis, sometimes lethal[2]	Pancreatitis[2]	Uncommonly pancreatitis
Urinary tract	Renal failure[2]; enuresis[3]; tubulointerstitial nephritis[3]; reversible Fanconi syndrome (a defect in proximal renal tubular function giving rise to glycosuria, amino aciduria, phosphaturia, and uricosuria)[3]	Enuresis[3]; urine abnormalities[3]	Occasionally, enuresis in children; rarely, impaired proximal tubule function (Fanconi's syndrome)
Skin/hair/teeth/gums	Gingival disorder (mainly gingival hyperplasia)[1]; transient and/or dose related alopecia (hair loss) [1]; nail and nail bed disorders[1]; rash[2]; hair disorder (such as	Alopecia (regrowth may be curly)[1]; skin reactions[2]; hirsutism[3]; severe cutaneous adverse reactions (SCARs) [3]	Hair loss and changes in hair texture or color; uncommonly, rashes; rarely, photosensitivity

	abnormal hair texture, hair colour changes, abnormal hair growth)[2]; toxic epidermal necrolysis[3]; Stevens–Johnson syndrome[3]; erythema multiforme[3]; Drug Rash with Eosinophilia and Systemic Symptoms (DRESS) syndrome[3]		
Reproductive function, breasts	Dysmenorrhea[1]; amenorrhea[2]; male infertility[3]; polycystic ovaries[3]; gynaecomastia[3]	Menstrual cycle irregularities[1]; gynaecomastia[3]; infertility male[3]; polycystic ovaries[3]	Occasionally, menstrual abnormalities, polycystic ovaries, and hyperandrogenism in women; sperm abnormalities and reduced testicular volume in men
Musculoskeletal	Bone mineral density decreased[2]; osteopenia[2]; osteoporosis and fractures[2]; rhabdomyolysis[3]	Bone disorders[2]; bone fracture[2]	Reduced bone mineral density, accumulation of microvesicular lipid droplets between myofibrils
Immunological/ autacoids	Hypersensitivity[1]; angioedema[2]; vasculitis[2]; systemic lupus erythematosus[3]	Hypersensitivity[1]; angioedema[2]; vasculitis[2]; systemic lupus erythematosus (SLE) [3]	Very rarely, hypersusceptibility reactions, DRESS syndrome, lupus-like syndrome, vasculitis
Other	Hypothermia[3]		

4. What are the pharmacological properties of sodium valproate and the mechanisms of action whereby it produces beneficial effects in epilepsy and harmful effects?

The mechanisms of action of valproate in producing benefits and harms are not known. The following summarizes the main current hypotheses.

The main theory about the mechanism of action of valproate in epilepsy is that it increases synaptic concentrations of the inhibitory neurotransmitter gamma-aminobutyric acid (GABA), by inhibiting GABA metabolism by the enzyme GABA transaminase and by increasing its synthesis. However, other modes of action have been proposed; these include actions on sodium channels, potassium channels, and calcium channels, reduced concentrations of excitatory neurotransmitters, such as aspartate [16,17], and effects on intracellular signalling pathways, particularly inhibition of histone deacetylase [18,19,20]. Other proposed mechanisms include altered expression and nuclear translocation of cyclin D3, causing arrest of the cell cycle in the G1 phase [21] and an antiapoptotic effect (i.e. inhibition of the mechanism commonly known as "programmed cell death") [22,23,24].

Teratogenicity due to valproate has been attributed [25] to inhibition of histone deacetylase and consequent changes in gene expression, or to increased fetal oxidative stress, or to inhibition of folic acid, a feature that valproate shares with phenytoin.

Effects on folate metabolism [26] or folate receptors [27] may be related to teratogenicity. Supplementation with folic acid during pregnancy prevents recurrence of neural tube defects in the children of women who have had a previously affected child. Valproate is thought to cause folic acid deficiency by interfering with its intestinal absorption, inducing folate-metabolizing enzymes in the liver, and inhibiting enzymes that are involved in the metabolism of folic acid. There are anecdotal reports of neural tube defects in the children of women who took folic acid supplement during pregnancy but also took valproate. It is not known whether folic acid taken during pregnancy prevents neural tube defects due to valproate, and it has been suggested that it does not [28].

A suggestion that neural tube defects due to valproate might be due to deficiency of zinc or other trace elements [29] has not been confirmed in humans.

5. By when was there first a testable hypothesis in relation to the teratogenicity of sodium valproate in humans?

The earliest antiepileptic drugs, valproic acid, phenytoin, phenobarbital, primidone, and carbamazepine are all thought to be teratogenic; of these, valproate carries the highest risks, causing about 2% of neural tube defects and an additional increase in major congenital abnormalities of 4–8% [30]. For example, major malformations in infants exposed to carbamazepine or valproic acid monotherapy in utero were analysed in a Swedish nationwide, population-based register study [31]. There were malformations in 35 of 268 valproic acid-exposed infants, of which 28 were severe, and in 46 of 703 carbamazepine-exposed infants, 28 of which were severe. Valproic acid monotherapy compared with carbamazepine monotherapy gave an odds ratio of 3.51 (95% CI = 1.43–4.68) for neonatal malformations. The malformations included neural tube defects, cardiac abnormalities, orofacial clefts, hypospadias, alimentary tract atresia, diaphragmatic hernias, and craniosynostosis. The authors concluded that the risk of a malformation after exposure to valproic acid is higher than after exposure to carbamazepine.

Teratogenicity of sodium valproate was shown in 1971 in rodents [32] and has been reported in several animal species since then, including primates, albeit in a very small study. The Data

Sheet in the *Data Sheet Compendium* published in 1975 says "This compound has been shown to be teratogenic in animals". Therefore there was already by that time a testable hypothesis that it would also be teratogenic in humans. Congenital defects associated with drug therapy are regarded as serious adverse effects [33].

The result of a cumulative meta-analysis of the teratogenic effects of valproate [34] are shown in Figure 4, with annotations, and discussed in detail in Appendix 1 [35]. A significant signal of teratogenicity in humans was present from 1990 onwards, and by 2005 the evidence for major congenital malformations was overwhelming. Since then the estimated risk ratio and its confidence intervals has remained stable. The latest estimate shows a more than doubling of the risk (RR = 2.24, 95% CI, 2.13 to 2.80) for congenital malformations based on an analysis of over 20 000 subjects.

In 1992, Antman and colleagues used cumulative meta-analysis to show that expert recommendations often lag behind pooled estimates of effect sizes in clinical trials [36]. Thus, it would have been possible after 1992 to have analysed the data on valproate to test the hypothesis that it is not teratogenic.

Cases of teratogenicity attributed to valproate continue to be reported [37].

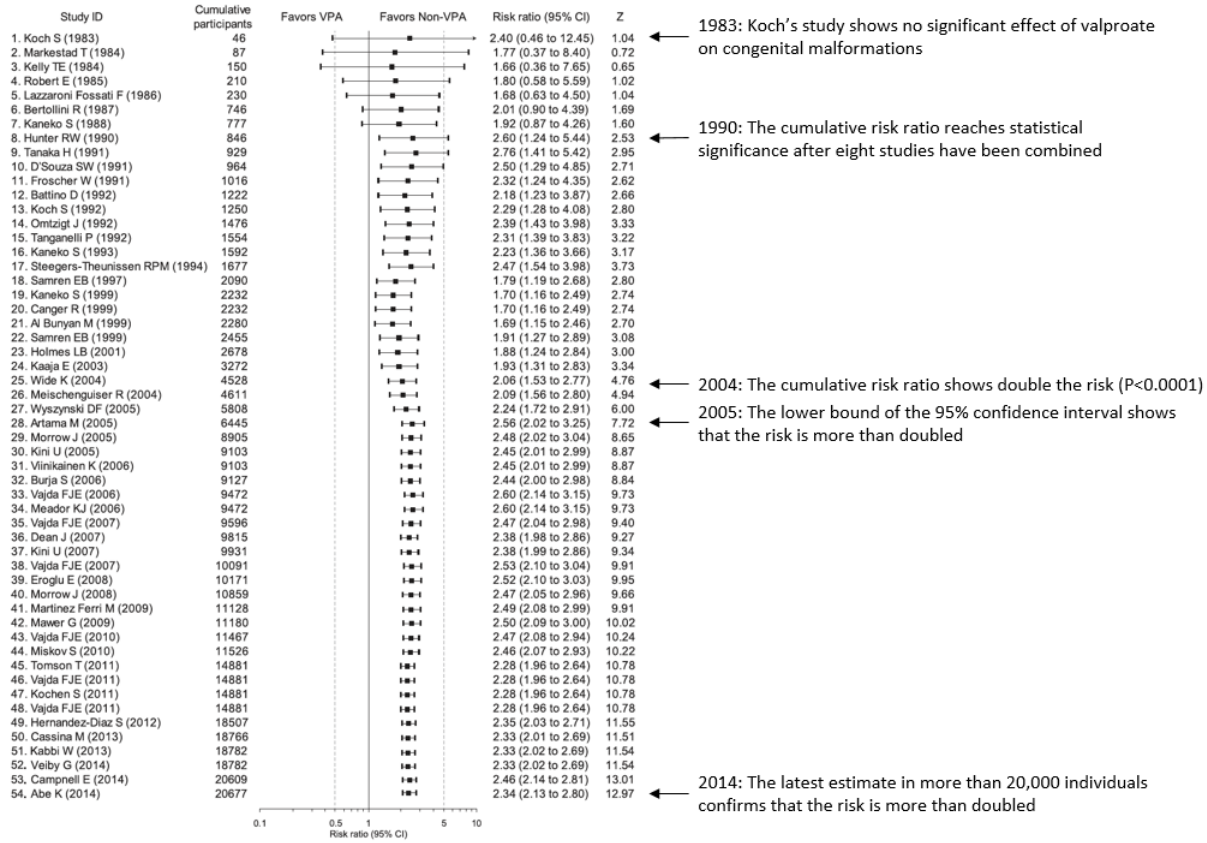


Figure 4. An annotated meta-analysis of studies of the teratogenicity of valproate (see Appendix 1 for a full explanation)

6. How is the evidence that sodium valproate is teratogenic in humans reflected in the Data Sheets and Summaries of Product Characteristics relating to Epilim?

Whatever other sources of information are available, it is a legal requirement in the EU for a pharmaceutical company to provide full information about potential harms of a medication in

its Data Sheet (since 1973 following the Medicines Act 1968) or, since 2002, its Summary of Product Characteristics (SmPC).

The Medicines (Data Sheet) Regulations 1972 [38] stated that the following should be included in Data Sheets:

> "Contra-indications, warnings, precautions and action to be taken in the event of overdosage, relating to the medicinal product and main side effects and adverse reactions likely to be associated therewith and, where there are no such particulars to be given, a statement to that effect shall be made; where required in the interests of safety, the antidote or other appropriate action to be taken."

Directive 2004/27 /EC [39] states that the following should be included in Summaries of Product Characteristics:

> "Risks related to use of the medicinal product:
> — any risk relating to the quality, safety or efficacy of the medicinal product as regards patients' health or public health"

The 1975 Data Sheet for sodium valproate says "This compound has been shown to be teratogenic in animals. Any benefit which may be expected from its use should be weighed against the hazard suggested by these findings." [Compare this with the text on phenytoin under Epanutin in the same volume: "The safe use of phenytoin during pregnancy has not been established. Therefore it should not be used as the first drug in pregnancy, especially early pregnancy, unless in the judgement of the physician the potential benefits outweigh the risk". And the text on carbamazepine under Tegretol: "Following the generally accepted policy, it is not recommended that Tegretol be administered to women during the first trimester of pregnancy unless specifically indicated."] See also Appendix 2.

The first case of the birth of an abnormal fetus to a mother taking sodium valproate was reported in 1980 [40] and further anecdotal reports subsequently appeared [41,42,43,44]

By 1982 Bjerkedal et al. had estimated that the risk of fetal abnormalities after first-trimester exposure to valproate was about 1% [45]. This was cited in the third edition of *Davies' Textbook of Adverse Drug Reactions* (1985) and in the 11th edition of *Meyler's Side Effects of Drugs* (1988), the 10th edition of which (1984) had already noted that "None of the major anticonvulsants—phenytoin, carbamazepine, valproate and phenobarbital—is to be regarded as free from teratogenic effects, and no one drug is safer than another in this regard." The *Side Effects of Drugs Annual 8* (SEDA-8, 1984) noted "Sodium valproate and congenital anomalies, particularly neural tube defects, is a controversial topic [citing 46,47]. Although not proven this is probably a true association, but further studies are awaited." The "fetal valproate syndrome" (a dysmorphic syndrome consisting of a characteristic facial appearance, neurodevelopmental delay, and limb and digital abnormalities, in particular an absent or short radius) was first described in 1984 [48]. Disorders in the autism spectrum have also been reported [49].

The 1975 text on valproate was repeated in subsequent editions of the Data Sheet, until the Data Sheet that was published in the Compendium dated 1984–85, in which the text reads "Valproic acid or sodium valproate, like certain other anti-convulsants, have been shown to be teratogenic in animals. In women of childbearing age, the benefits of these compounds should be weighed against the possible hazard suggested by these findings and their pregnancies should be carefully monitored."

Further reports appeared between 1985 and 1990 [50], and in 1988 the relative risk of neural tube defects due to valproate was estimated from a systematic review of prospective studies in infants exposed to valproate compared with other births to mothers with epilepsy at 4.4 (95%

confidence interval = 1.6–12) [51]. However, the 1984–85 text was not changed until the Data Sheet published in the Compendium dated 1990–91: "There have been reports of foetal anomalies including neural tube defects in women receiving valproate during the first trimester. This incidence has been estimated to be in region of 1%. Such pregnancies should be carefully screened by alpha-foetoprotein measurement and ultrasound and if indicated amniocentesis. In all pregnancies monotherapy is recommended and the benefits of antiepileptic therapy must be evaluated against the possible risks and patients should be informed of these and the need for screening."

7. What information about teratogenicity has been given in other important sources of general information about sodium valproate?

The most commonly used general reference about the use of drugs in the UK is the British National Formulary (BNF). It is the most widely used reference text by all prescribers. The BNF first introduced a table entitled "Prescribing in pregnancy" in issue 4 (1982). Valproate was not mentioned. The following information was given in subsequent issues:

Issues 6 & 7 (1983 & 1984): "May possibly be teratogenic."

Issues 8 & 9 (1984 & 1985): "Increased risk of neural tube defects reported but not substantiated."

Issues 10-18 (1985–Sep 1989): "Increased risk of neural tube defects reported."

Issues 19-25 (Mar 1990–Sep 1992): "Increased risk of neural tube defects (screening advised)."

Issues 26-46 (Sep 1993–Sep 2003): "Increased risk of neural tube defects (counselling and screening advised)." In addition, "women who become pregnant should be **counselled** and offered **antenatal screening** (alpha-fetoprotein measurement and a second trimester untrasound scan)" [emphasis in the original].

Issue 47-58 (Mar 2004–Sep 2009): "Increased risk of congenital malformation (counselling and screening advised)." In addition, "women who become pregnant should be **counselled** and offered **antenatal screening** (alpha-fetoprotein measurement and a second trimester untrasound scan)" [emphasis in the original].

The Table "Prescribing in pregnancy" was discontinued in issue 59, but advice continued to be included in the monograph on sodium valproate.

Thus, by 1985, the BNF considered that there was an increased risk of neural tube defects in association with valproate.

From issue 4 the BNF also included a comment under antiepileptic drugs: "Benefit of treatment outweighs risk to fetus."

From issue 26 (Sep 1993) the BNF included a statement about informing women who might become pregnant of the possible consequences of taking antiepileptic drugs during pregnancy.

The current issue of the BNF online [11] gives the following information:

> Valproate is highly teratogenic and evidence supports that use in pregnancy leads to neurodevelopmental disorders (approx. 30–40% risk) and congenital malformations (approx. 10% risk).
>
> Valproate must not be used in women and girls of childbearing potential unless the conditions of the Pregnancy Prevention Programme are met (see Conception and contraception) and only if other treatments are ineffective or not tolerated, as judged by an experienced specialist.
>
> Use of valproate in pregnancy is contraindicated for migraine prophylaxis [unlicensed] and bipolar disorder; it must only be considered for epilepsy if there is no suitable

alternative treatment (see Pregnancy).

Women and girls (and their carers) must be fully informed of the risks and the need to avoid exposure to valproate medicines in pregnancy; supporting materials have been provided to use in the implementation of the Pregnancy Prevention Programme (see Prescribing and dispensing Information). The MHRA advises that:

GPs must recall all women and girls who may be of childbearing potential, provide the Patient Guide, check they have been reviewed by a specialist in the last year and are on highly effective contraception;

Specialists must book in review appointments at least annually with women and girls under the Pregnancy Prevention Programme, re-evaluate treatment as necessary, explain clearly the conditions as outlined in the supporting materials and complete and sign the Risk Acknowledgement Form—copies of the form must be given to the patient or carer and sent to their GP;

Pharmacists must ensure valproate medicines are dispensed in whole packs whenever possible—all packs dispensed to women and girls of childbearing potential should have a warning label either on the carton or via a sticker. They must also discuss risks in pregnancy with female patients each time valproate medicines are dispensed, ensure they have the Patient Guide and have seen their GP or specialist to discuss their treatment and the need for contraception.

Citations of evidence in other sources (Davies' *Textbook of Adverse Drug Reactions*, 1985, the 10th and 11th editions of *Meyler's Side Effects of Drugs*, 1984 and 1988, and *Side Effects of Drugs Annuals*) are mentioned above.

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Appendix A1:

Heneghan C, Aronson JK. Sodium valproate: who knew what and when? Cumulative meta-analysis gives extra insights. *BMJ Evidence-Based Medicine* Published Online First: 22 October 2018.

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Appendix A2

Extracts from Data Sheets and Summaries of Product Characteristics dealing with the teratogenicity of sodium valproate, phenytoin, and carbamazepine, 1975, 1990-1, 2005, and 2018

The Medicines (Data Sheet) Regulations 1972 [1] stated that the following should be included in Data Sheets:

> "Contra-indications, warnings, precautions and action to be taken in the event of overdosage, relating to the medicinal product and main side effects and adverse reactions likely to be associated therewith and, where there are no such particulars to be given, a statement to that effect shall be made; where required in the interests of safety, the antidote or other appropriate action to be taken."

In 1996, Data Sheets started to be replaced by Summaries of Product Characteristics (SmPCs) and have been completely replaced by them since 2002. The European Union's Directive 2004/27/EC [2] states, among other things, that the following should be included in SmPCs:

> "Risks related to use of the medicinal product:
> — any risk relating to the quality, safety or efficacy of the medicinal product as regards patients' health or public health"

In Tables 1–4 are extracts from the Data Sheets and Summaries of Product Characteristics for sodium valproate as published in compendia dated 1975 (Table 1), 1990-1 (Table 2), and 2005 (Table 3), corresponding to key dates shown in Figure 4 in the main report, and the current SmPC (Table 4). The corresponding texts for phenytoin and carbamazepine, two other teratogenic antiepileptic drugs, are shown for comparison. Copies of the original Epilim Data Sheets from 1975, 1990-1, and 2005 are shown at the end. The current Summaries of Product Characteristics can be found at https://www.medicines.org.uk/emc/search?q=[brand name].

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Table 1. 1975

Drug	Text
Sodium valproate (Epilim)	This compound has been shown to be teratogenic in animals. Any benefit which may be expected from its use should be weighed against the hazard suggested by these findings.
Phenytoin (Epanutin)	The safe use of phenytoin during pregnancy has not been established. Therefore it should not be used as the first drug in pregnancy, especially early pregnancy, unless in the judgement of the physician the potential benefits outweigh the risk.
Carbamazepine (Tegretol)	Following the generally accepted policy, it is not recommended that Tegretol be administered to women during the first trimester of pregnancy unless specifically indicated.

Table 2. 1990-1

Drug	Text
Sodium valproate (Epilim)	"An increased incidence of congenital abnormalities in offspring born to mothers with epilepsy both untreated and treated has been demonstrated. There have been reports of foetal abnormalities including neural tube defects in women receiving valproate during the first trimester. The incidence has been estimated to be in the region of 1%. Such pregnancies should be carefully screened by alpha-foetoprotein measurement and ultrasound and if indicated amniocentesis. In all pregnancies monotherapy is to be recommended and the benefits of antiepileptic therapy must be evaluated against the possible risks and patients should be informed of these and the need for screening.
Phenytoin (Epanutin)	There is some evidence that phenytoin may produce congenital abnormalities in the offspring of a small number of epileptic patients , therefore it should not be used as the first drug in pregnancy, especially early pregnancy, unless in the judgement of the physician the potential benefits outweigh the risk.
Carbamazepine (Tegretol)	There is no strong evidence of a teratogenic potential and clinical experience indicates that the risk of teratogenesis with Tegretol therapy is low. In women of child-bearing potential, the need to control seizures should be carefully weighed against possible risks to the foetus. This is particularly important during the first three months of pregnancy. The incidence of congenital abnormalities in the offspring of women being treated with a combination of anti-convulsants is greater than in those mothers receiving monotherapy. Therefore, in women of child-bearing potential Tegretol should be prescribed as monotherapy wherever possible.

Table 3. 2005

Drug	Text
Sodium valproate (Epilim)	[From Section 4.4:] Women of childbearing potential should not be started on Epilim without specialist neurological advice. Epilim is the antiepileptic of choice in patients with certain types of epilepsy such as generalized epilepsy + myoclonus/photosensitivity. For partial seizures, Epilim should be used only in patients resistant to other treatment. Women who are likely to get pregnant should receive specialist advice because of the potential teratogenic risk to the foetus (see also section 4.6 Pregnancy and Lactation). [From Section 4.6:] "From experience in treating mothers with epilepsy, the risk associated with the use of valproate during pregnancy has been described as follows: ***-Risk associated with epilepsy and antiepileptics*** In offspring born to mothers with epilepsy receiving any anti-epileptic treatment, the overall rate of malformations has been demonstrated to be 2 to 3 times higher than the rate (approximately 3%) reported in the general population. Although an increased number of children with malformations have been reported in case of multiple drug therapy, the respective ole of treatment sand disease in causing the malformations has not been formally established. Malformations most frequently encountered are cleft lip and cardio-vascular malformations. Epidemiological studies have suggested an association between in-utero exposure to sodium valproate and a risk of developmental delay. Many factors including maternal epilepsy may also contribute to this risk but it is difficult to quantify the relative contributions of these or of maternal anti-epileptic treatment. Notwithstanding those potential risks no sudden discontinuation in the anti-epileptic therapy should be undertaken as this may lead to breakthrough seizures which could have serious consequences for both the mother and the foetus.

	-Risk associated with valproate In animals: teratogenic effects have been demonstrated in the mouse, rat and rabbit. There is animal experimental evidence that high plasma peak levels and the size of an individual dose are associated with neural tube defects. In humans: an increased incidence of congenital abnormalities (including cases of facial dysmorphia, hypospadias and multiple malformations, particularly of the limbs) has been demonstrated in offspring born to mothers with epilepsy treated with valproate. Valproate use is associated with neural tube defects such as myelomeningocele and spina bifida. The frequency of this effect is estimated to be 1 to 2%. ***-In view of the above data*** When a woman is planning pregnancy, this gives an opportunity to review the need for anti-epileptic treatment. Women of childbearing age should be informed of the risks and benefits of continuing anti-epileptic treatment throughout pregnancy. Folate supplementation, **prior** to pregnancy, has been demonstrated to reduce the incidence of neural tube defects in the offspring of women at high risk. Although no direct evidence exists of such effects in women receiving anti-epileptic drugs, women should be advised to start taking folic acid supplementation (5mg) as soon as contraception is discontinued. The available evidence suggests that anticonvulsant monotherapy is preferred. Dosage should be reviewed before conception and the lowest effective dose used, in divided doses, as abnormal pregnancy outcome tends to be associated with higher total daily dosage and with the size of an individual dose. The incidence of neural tube defects rises with increasing dosage, particularly above 100mg daily. The administration in several divided doses over the day and the use of a prolonged release formulation is preferable in order to avoid high peak plasma levels. During pregnancy, valproate anti-epileptic treatment should not be discontinued if it has been effective. Nevertheless, specialized prenatal monitoring should be instituted in order to detect the possible occurrence of a neural tube defect or any other ,malformation., Pregnancies should be carefully screened by ultrasound and other techniques if appropriate (see Section 4.4 Special Warnings and special Precautions for use).
Phenytoin (Epanutin)	The great majority of mothers on anticonvulsant medication deliver normal infants … Anticonvulsants including phenytoin may produce congenital abnormalities in the offspring of a small number of epileptic patients. The exact role of drug therapy in these abnormalities is unclear and genetic factors, in some studies, have also been shown to be important. Epanutin should only be used during pregnancy, especially early pregnancy, if in the judgement of the physician the potential benefits clearly outweigh the risk. In addition to the reports of increased incidence of congenital malformations, such as cleft lip/palate and heart malformations in children of women receiving phenytoin and other antiepileptic drugs, there have more recently been reports of a foetal hydantoin syndrome. This consists of prenatal growth deficiency, micro-encephaly and mental deficiency.
Carbamazepine (Tegretol)	Pregnant women with epilepsy should be treated with special care. In women of childbearing age Tegretol should, wherever possible, be prescribed as monotherapy, because the incidence of congenital abnormalities in the offspring of women treated with a combination of anti-epileptic drugs is greater than in those mothers receiving the individual drug as monotherapy. If pregnancy occurs in a women receiving Tegretol, or if the problem of initiating treatment with Tegretol arises during pregnancy, the drug's potential benefits must be carefully weighed against its possible hazards, particularly in the first three months of pregnancy. Minimum effective doses should be given and monitoring of plasma levels is recommended. Offspring of epileptic mothers with untreated epilepsy are known to be more prone to developmental disorders, including malformations. The possibility that carbamazepine, like all major anti-epileptic drugs, increases the risk has been reported, although conclusive evidence from controlled studies with carbamazepine monotherapy is lacking. However, there are reports on developmental disorders and malformations, including spina bifida, and also other congenital anomalies e.g. craniofacial defects, cardiovascular malformations and anomalies involving various body systems, have been reported in association with Tegretol. Patients should be counselled regarding the possibility of an increased risk of malformations and given the opportunity of antenatal screening. Folic acid deficiency is known to occur in pregnancy. Anti-epileptic drugs have been reported to aggravate deficiency. This deficiency may contribute to the increased incidence of birth defects in the offspring of treat epileptic women. Folic acid supplementation has therefore been recommended before and during pregnancy.

Table 4. 2018

Drug	Text
Valproate (Epilim)	[From Section 4.4:] *Pregnancy:* Women of childbearing potential should not be started on Epilim without specialist neurological advice. Adequate counselling should be made available to all pregnant women with epilepsy of childbearing potential regarding the risks associated with pregnancy because of the potential teratogenic risk to the foetus (see also section 4.6 Pregnancy and Lactation). [From Section 4.6:] *Pregnancy Exposure Risk related to valproate* Both valproate monotherapy and valproate polytherapy are associated with abnormal pregnancy outcomes. Available data suggest that anti-epileptic polytherapy including valproate is associated with a greater risk of congenital malformations than valproate monotherapy. *Congenital malformations* Data derived from a meta-analysis (including registries and cohort studies) has shown that 10.73% of children of epileptic women exposed to valproate monotherapy during pregnancy suffer from congenital malformations (95% CI: 8.16–13.29). This is a greater risk of major malformations than for the general population, for whom the risk is about 2–3%. The risk is dose dependent but a threshold dose below which no risk exists cannot be established. Available data show an increased incidence of minor and major malformations. The most common types of malformations include neural tube defects, facial dysmorphism, cleft lip and palate, craniostenosis, cardiac, renal and urogenital defects, limb defects (including bilateral aplasia of the radius), and multiple anomalies involving various body systems. *Developmental disorders* Data have shown that exposure to valproate in utero can have adverse effects on mental and physical development of the exposed children. The risk seems to be dose-dependent but a threshold dose below which no risk exists, cannot be established based on available data. The exact gestational period of risk for these effects is uncertain and the possibility of a risk throughout the entire pregnancy cannot be excluded. Studies in preschool children exposed in utero to valproate show that up to 30–40% experience delays in their early development such as talking and walking later, lower intellectual abilities, poor language skills (speaking and understanding) and memory problems. Intelligence quotient (IQ) measured in school aged children (age 6) with a history of valproate exposure in utero was on average 7–10 points lower than those children exposed to other anti-epileptics. Although the role of confounding factors cannot be excluded, there is evidence in children exposed to valproate that the risk of intellectual impairment may be independent from maternal IQ. There are limited data on the long term outcomes. Available data show that children exposed to valproate in utero are at increased risk of autistic spectrum disorder (approximately three-fold) and childhood autism (approximately five-fold) compared with the general study population. Limited data suggests that children exposed to valproate in utero may be more likely to develop symptoms of attention deficit/hyperactivity disorder (ADHD). *Female children, female adolescents and woman of childbearing potential (see above and section 4.4)* *If a Woman wants to plan a Pregnancy* • During pregnancy, maternal tonic clonic seizures and status epilepticus with hypoxia may carry a particular risk of death for the mother and the unborn child. • In women planning to become pregnant or who are pregnant, valproate therapy should be reassessed • In women planning to become pregnant all efforts should be made to switch to appropriate alternative treatment prior to conception, if possible. Valproate therapy should not be discontinued without a reassessment of the benefits and risks of the treatment with valproate for the patient by a physician experienced in the management of epilepsy. If based on a careful evaluation of the risks and the benefits valproate treatment is continued during the pregnancy, it is recommended to: - Use the lowest effective dose and divide the daily dose valproate into several small doses to be taken throughout the day. The use of a prolonged release formulation may be preferable to other treatment formulations in order to avoid high peak plasma concentrations. - Folate supplementation before the pregnancy may decrease the risk of neural tube defects common to all pregnancies. However the available evidence does not suggest it prevents the birth defects or malformations due to valproate exposure. - To institute specialized prenatal monitoring in order to detect the possible occurrence of neural tube defects or other malformations.
Phenytoin (Epanutin Infatabs)	[From Section 4.6:] <u>Pregnancy</u> Phenytoin crosses the placenta. There are intrinsic methodologic problems in obtaining adequate data on drug teratogenicity in humans. Genetic factors or the epileptic condition itself may be more important than drug therapy in leading to birth defects. The great majority of mothers on anticonvulsant medication deliver normal infants. It is important to note that anticonvulsant drugs should not be discontinued in patients in whom the drug is administered to prevent major seizures because of the strong possibility of precipitating status epilepticus with attendant hypoxia and threat to life. In individual cases where the severity and frequency of the seizure disorder are such that the removal of medication does not pose a serious threat to the patient, discontinuation of the drug may be considered prior to and during pregnancy although it cannot be said with any confidence that even minor seizures do not pose some hazard to the developing embryo or foetus. Anticonvulsants including phenytoin may produce congenital abnormalities in the offspring of a small number of epileptic patients. The exact role of drug therapy in these abnormalities is unclear and genetic factors, in some studies, have also been shown to be important. Epanutin should only be used during pregnancy, especially early pregnancy, if in the judgement of the physician the potential benefits clearly outweigh the risk. In addition to the reports of increased incidence of congenital malformations, such as cleft lip/palate and heart malformations in children of women receiving phenytoin and other antiepileptic drugs, there have more recently been reports of a foetal hydantoin syndrome. This consists of prenatal growth deficiency, micro-encephaly and mental deficiency in children born to mothers who have received phenytoin, barbiturates, alcohol, or trimethadione. However, these features are all interrelated and are frequently associated with intrauterine growth retardation from other causes. There have been isolated reports of malignancies, including neuroblastoma, in children whose mothers received phenytoin during pregnancy. An increase in seizure frequency during pregnancy occurs in a proportion of patients, and this may be due to altered phenytoin absorption or metabolism. Periodic measurement of serum phenytoin levels is particularly valuable in the

	management of a pregnant epileptic patient as a guide to an appropriate adjustment of dosage. However, postpartum restoration of the original dosage will probably be indicated. Neonatal coagulation defects have been reported within the first 24 hours in babies born to epileptic mothers receiving phenytoin. Vitamin K1 has been shown to prevent or correct this defect and may be given to the mother before delivery and to the neonate after birth. Phenytoin is teratogenic in rats, mice and rabbits (see section 5.3). [From Section 5.3:] Phenytoin causes embryofetal death and growth retardation in rats, mice, and rabbits. Phenytoin is teratogenic in rats (craniofacial defects including cleft palate, cardiovascular malformations, neural and renal defects, and limb abnormalities), mice (cleft lip, cleft palate, neural and renal defects, limb abnormalities, and digital and ocular abnormalities) and rabbits (cleft palate, limb abnormalities, and digital and ocular abnormalities). The defects produced are similar to major malformations observed in humans and abnormalities described for fetal hydantoin syndrome. The teratogenic effects of phenytoin in animals occur at therapeutic exposures, and therefore a risk to the patients cannot be ruled out.
Carbamazepine (Tegretol)	[From section 4.6:] ***Pregnancy*** Offspring of epileptic mothers with untreated epilepsy are known to be more prone to developmental disorders, including malformations. Developmental disorders and malformations, including spina bifida, and also other congenital anomalies e.g. craniofacial defects such as cleft lip/palate, cardiovascular malformations, hypospadias and anomalies involving various body systems, have been reported in association with the use of Tegretol. Patients should be counselled regarding the possibility of an increased risk of malformations and given the opportunity of antenatal screening. Based on data in a North American pregnancy registry, the rate of major congenital malformations, defined as a structural abnormality with surgical, medical, or cosmetic importance, diagnosed within 12 weeks of birth was 3.0% (95% CI 2.1 to 4.2%) among mothers exposed to carbamazepine monotherapy in the first trimester and 1.1% (95% CI 0.35 to 2.5%) among pregnant women not taking any antiepileptic drug (relative risk 2.7, 95% CI 1.1 to 7.0). Taking these data into consideration: - Pregnant women with epilepsy should be treated with special care. - If women receiving Tegretol become pregnant or plan to become pregnant, or if the problem of initiating treatment with Tegretol arises during pregnancy, the drug's expected benefits must be carefully weighed against its possible hazards, particularly in the first 3 months of pregnancy. - In women of childbearing potential Tegretol should, wherever possible, be prescribed as monotherapy, because the incidence of congenital abnormalities in the offspring of women treated with a combination of antiepileptic drugs is greater than in those of mothers receiving the individual drugs as monotherapy. The risk of malformations following exposure to carbamazepine as polytherapy may vary depending on the specific drugs used and may be higher in polytherapy combinations that include valproate. - Minimum effective doses should be given and monitoring of plasma levels is recommended. The plasma concentration could be maintained in the lower side of the therapeutic range 4 to 12 micrograms/mL provided seizure control is maintained. There is evidence to suggest that the risk of malformation with carbamazepine may be dose-dependent i.e. at a dose < 400mg per day, the rates of malformation were lower than with higher doses of carbamazepine. - Patients should be counseled regarding the possibility of an increased risk of malformations and given the opportunity of antenatal screening. - During pregnancy, an effective antiepileptic treatment should not be interrupted, since the aggravation of the illness is detrimental to both the mother and the fetus. ***Monitoring and prevention*** Folic acid deficiency is known to occur in pregnancy. Antiepileptic drugs have been reported to aggravate deficiency. This deficiency may contribute to the increased incidence of birth defects in the offspring of treated epileptic women. Folic acid supplementation has therefore been recommended before and during pregnancy.

Screenshots of Epilim Data Sheets 1975, 1990-1, and 2005, highlighting the sections on pregnancy

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EPILIM*

Presentation Epilim is available as a scored white tablet with a diameter of 11 mm. The active ingredient is sodium valproate (200 mg per tablet).

Uses For use in generalised, focal or other epilepsy. In women of child-bearing age, the product should only be used in severe cases or in those resistant to other treatment.

Dosage and administration Adults and children over 15 years: Epilim can be introduced alone or added to existing treatment.

New patients: Treatment should start with 1 tablet three times daily. Dosage may be increased after three days to 2 tablets three times daily. If, after a total period of two weeks, adequate control has not been achieved, dosage of Epilim should again be increased and one other anti-epileptic agent may be introduced commencing at a low dosage. Dosage of both Epilim and other agents should then be adjusted during the stabilisation period to obtain optimum control.

Patients receiving other therapy: Treatment should start with 1 tablet twice a day. Dosage can be increased at intervals of three days in increments of 2 tablets per day; optimum control is achieved usually within the dosage range of 4–7 tablets (800–1,400 mg) per day. (However, in several recently published controlled trials, it was found that the dose could be increased with advantage to 2.4 g per day, to achieve control in very severe cases.)

Dosage of existing medication may be reduced concomitantly to obtain optimum control on a minimum dosage combination of drugs. It may be possible to withdraw the concomitant therapy, allowing optimum control with Epilim alone (e.g. in petit mal with absences). If increased sedation is observed, dosage of barbiturates should be concomitantly reduced as the dosage of Epilim is increased.

Tablets should be swallowed whole, with a little water if necessary (but *not* with aerated mineral water).

Children under 15 years and infants: Dosage should be related to age within the range as follows:

0–3 years: Usually 20–30 mg/kg/day.

3–15 years: Dosage should range from 2 tablets to doses slightly less than those of adults.

All doses should be tailored to obtain optimum control and the treatment procedure should follow the same principle as in adults.

Contra-indications, warnings, etc *Contra-indications:* There are no specific contra-indications for Epilim, but note should be taken of the following precautions.

Precautions – General: No hepatic, renal, cardiac or haematological effects attributable to Epilim have been reported. At the start of treatment a few patients have experienced minor gastric irritation and, less frequently, nausea. Should these symptoms persist, they can be relieved by standard medication.

Combined medication: Epilim is well tolerated in combination with other anti-epileptic agents. Epilim may enhance the sedative effects of other agents, particularly barbiturates; this should be recognised when introducing Epilim to existing treatment, and may require concomitant reduction in the dosage of other agents. Similarly Epilim, in common with many other medications, may potentiate the effect of monoamine oxidase inhibitors (MAOI) and thymoleptics, and the doses of these agents should be reduced accordingly.

Diabetic patients: Epilim is partially eliminated by the renal route in the form of ketone bodies, and this may give false positives when testing the urine of possible diabetics.

Overdosage: Reports of accidental overdosage of Epilim have been rare. Recovery after the ingestion of up to 30 g has been uneventful following conservative management.

As Epilim is absorbed very rapidly, gastric lavage may be of limited value. However, as Epilim is excreted almost entirely within 24 hours (70% in the urine), it is recommended that general supportive measures be applied, paying particular attention to the maintenance of an adequate urinary output.

Precautions – women of child bearing age: This compound has been shown to be teratogenic in animals. Any benefit which may be expected from its use should be weighed against the hazard suggested by these findings.

Pharmaceutical precautions The tablets, being hygroscopic, must be kept in their protective foil until taken, and should be stored in a cool dry place.

Legal category Available on prescription only.

Package quantities Carton containing 100 tablets in foil.

Further information Epilim represents a new approach in the therapy of epilepsy. Whereas most of the currently available drugs have chemical features in common, Epilim is a different entity with a simple chemical structure which (unlike existing drugs) does not contain nitrogen. Biological studies on Epilim indicate that it may have a different mode of action in that it produces an increase in the level of γ-aminobutyric acid (GABA) in the brain by inhibiting GABA transaminase, which is responsible for the breakdown of GABA. Although there is no simple correlation between convulsive activity and GABA levels, evidence linking them is growing.

Clinically Epilim is effective in treatment of petit mal, grand mal, mixed epilepsies, and those with temporal lobe (or psychomotor) components.

Product licence number 0623/0001.

**Trade Mark*

day (irrespective of weight) with spaced increases until control is achieved; this is usually within the range 20–30 mg/kg body weight per day. Where adequate control is not achieved within this range the dose may be increased to 35 mg/kg body weight per day.

Children under 20 kg: 20 mg/kg of body weight per day; in severe cases this may be increased but only in patients in whom plasma valproic acid levels can be monitored. Above 40 mg/kg/day, clinical chemistry and haematological parameters should be monitored.

Use in the elderly: Although the pharmacokinetics of Epilim are modified in the elderly, they have limited clinical significance and dosage should be determined by seizure control. The volume of distribution is increased in the elderly and, because of decreased binding to serum albumin, the proportion of free drug is increased. This will affect the clinical interpretation of plasma valproic acid levels.

Administration: Epilim tablets, syrup and liquid may be given twice daily. Uncoated tablets may be crushed if necessary.

Combined therapy: In certain cases it may be necessary to raise the dose by 5 to 10 mg/kg/day when used in combination with anticonvulsants which induce liver enzyme activity, e.g. phenytoin, phenobarbitone, and carbamazepine. Once known enzyme inducers have been withdrawn it may be possible to maintain seizure control on a reduced dose of Epilim. When barbiturates are being administered concomitantly the dosage of barbiturate should be reduced should sedation be observed.

General considerations: Optimum dosage is mainly determined by seizure control and routine measurement of plasma levels is unnecessary. However, a method for measurement of plasma levels is available and may be helpful where there is poor control or side-effects are suspected, see Further Information.

Contra-indications, warnings, etc
Contra-indication: Active liver disease.

Side-effects
Hepatic: Liver dysfunction, including hepatic failure resulting in fatalities, has occurred in patients whose treatment included valproic acid or sodium valproate. Patients most at risk are children under the age of three and those with congenital metabolic disorders, organic brain disease or severe seizure disorders associated with mental retardation. The incidents mainly occurred during the first six months of therapy, the period of maximum risk being 2–12 weeks, and usually involved multiple anticonvulsant therapy. Monotherapy is to be preferred in this group of patients.

Clinical symptoms are more helpful than laboratory investigations in the early stages of hepatic failure. The onset of an acute illness, especially within the first six months, which may include symptoms of vomiting, lethargy or weakness, drowsiness, anorexia, jaundice or loss of seizure control, is an indication for immediate withdrawal of the drug. Patients should be instructed to report any such signs to the clinician should they occur. Available evidence to date does not establish which, if any, investigation could predict this possible adverse effect. However, routine measurement of liver function should be undertaken in the first six months of therapy in those who seem most at risk, and those with a prior history of liver disease; such patients should have close clinical supervision. Raised liver enzymes are not uncommon during treatment with Epilim and are usually transient or respond to reduction in dosage of Epilim. Patients with such biochemical abnormalities should be reassessed clinically and tests of liver function should be monitored until they return to normal.

Metabolic: Hyperammonaemia without hepatic damage can occur in patients during treatment with valproic acid or sodium valproate. This is usually transient, but may occasionally present clinically as vomiting, ataxia and increasing clouding of consciousness. Should these symptoms occur Epilim should be discontinued. Oedema has been reported rarely.

Pancreatic: There have been reports of pancreatitis occurring in patients receiving valproic acid or sodium valproate, usually within the first six months of therapy. Patients experiencing acute abdominal pain should have their serum amylase estimated; if these levels are elevated treatment should be discontinued.

Haematological: Valproic acid inhibits the second stage of platelet aggregation. Reversible prolongation of bleeding time and thrombocytopenia have been reported, but are usually associated with doses above those recommended. Spontaneous bruising or bleeding is an indication for withdrawal of medication pending investigations; it is recommended that patients receiving Epilim be monitored for platelet function before major surgery. Red cell hypoplasia and leucopenia have been reported rarely; the blood picture returned to normal when the drug was discontinued.

Neurological: Ataxia and tremor have been occasionally reported and appear to be dose related effects.

Sedation has been reported occasionally, usually when used in combination with other anticonvulsants. In Epilim monotherapy it occurred early in treatment on rare occasions and is usually transient. Rare cases of lethargy and confusion occasionally progressing to stupor, sometimes with associated hallucinations have been reported. Coma has very rarely been observed. These cases have usually been in association with other anticonvulsants, notably phenobarbitone, and have been reversible on withdrawal of treatment.

An increase in alertness may occur; this is generally beneficial but occasionally aggression, hyperactivity and behavioural deterioration have been reported.

Gastro-intestinal: Increase in appetite may occur and an increase in weight is not uncommon. Minor gastric irritation and, less frequently, nausea have been observed in some patients at the start of treatment, but these problems can usually be overcome by administering Enteric Coated Epilim or administering Epilim with or after food.

Dermatological: Transient hair loss has been noted in some patients. This effect does not appear to be dose-related and regrowth normally begins within six months, although the hair may become more curly than previously. Rashes have been reported rarely.

Endocrine: There have been isolated reports of amenorrhoea.

Drug interactions: Like many other drugs, Epilim may potentiate the effect of monoamine oxidase inhibitors and other antidepressants. The enzyme inducing effect of valproate is appreciably less than that of certain other anticonvulsants and loss of efficacy of oral contraceptive agents does not appear to be a problem.

Caution is recommended when administering anticoagulants and other products which have anticoagulant properties (e.g. warfarin and aspirin). Epilim decreases protein binding of warfarin but this may not lead to clinically significant effects.

Dosage of Epilim may require adjustment when used in combination with other anticonvulsants. See Dosage, Combined Therapy Section.

Diabetic patients: Epilim is eliminated mainly through the kidneys, partly in the form of ketone bodies; this may give false positives in the urine testing of possible diabetics. In addition, care should be taken when treating diabetic patients with Epilim Syrup, as this contains 3.6 g sucrose per 5 ml; Epilim Liquid is, however, sugar-free.

Women of childbearing age: An increased incidence of congenital abnormalities in offspring born to mothers with epilepsy both untreated and treated has been demonstrated.

There have been reports of foetal anomalies including neural tube defects in women receiving valproate during the first trimester. This incidence has been estimated to be in the region of 1%. Such pregnancies should be carefully screened by alpha-foetoprotein measurement and ultrasound and if indicated amniocentesis.

In all pregnancies monotherapy is to be recommended and the benefits of antiepileptic therapy must be evaluated against the possible risks and patients should be informed of these and the need for screening.

Breast feeding: The concentration of valproic acid found in the breast milk is very low, between 1% and 10% of total maternal plasma levels. There appears to be no contra-indication to breast feeding by patients on Epilim. The decision to allow the patients to breast feed should be taken with regard to all the known facts.

Overdosage: Cases of accidental and suicidal overdosage have been reported. At plasma concentrations of up to 5 to 6 times the maximum therapeutic levels, there are unlikely to be any symptoms other than nausea, vomiting and dizziness.

In massive overdose, i.e. with plasma concentrations 10 to 20 times maximum therapeutic levels there may be serious CNS depression and respiration may be impaired. Full recovery is usual following treatment including induced vomiting, gastric lavage, assisted ventilation, and other supportive measures.

Pharmaceutical precautions Epilim tablets are hygroscopic and must be kept in their protective foil until taken; they should be stored in a dry place. Epilim Syrup and Epilim Liquid should be kept cool and away from direct sunlight.

Dilutions: if it is necessary to dilute Epilim Syrup, the recommended diluent is Syrup BP, but syrup containing SO_2 as a preservative should not be used. The diluted product will have a 14 day shelf life. Epilim Liquid should not be diluted.

Legal category POM.

Package quantities Epilim 200 Enteric-Coated, Epilim 500 Enteric-Coated tablets and Epilim 100 mg Crushable tablets are packed in foil, in cartons of 100 tablets. Epilim Syrup and Epilim Liquid are packed in 300 ml bottles.

Further information The beneficial effects of Epilim may not be clearly correlated with the total plasma valproic acid levels. The reported effective range is usually between 40–100 mg/litre (278–694 micro mol/litre) depending on time of sampling and presence of co-medication.

The percentage of free drug then is usually between 6% and 15% of the total levels. Above this range an increased incidence of adverse effects may occur.

The half-life of sodium valproate is usually reported to be within the range of 8–20 hours.

Product licence numbers

Epilim Syrup	0623/0004
Epilim 500 Enteric-Coated	0623/0005
Epilim 200 Enteric-Coated	0623/0006
Epilim 100 mg Crushable tablets	0623/0015
Epilim Liquid	0623/0016

EPILIM* INTRAVENOUS

Presentation Epilim Intravenous. Off-white sterile, freeze dried Sodium Valproate BP 400 mg in a clear glass vial supplied with an ampoule of 4 ml of solvent (Water for Injections).

Uses Epilim Intravenous may be used for epileptic patients who would normally be maintained on oral sodium valproate, and for whom oral therapy is temporarily not possible.

Dosage and administration Daily dosage requirements vary according to age and body weight.

To reconstitute, inject the solvent provided (4 ml) into the vial, allow to dissolve and extract the appropriate dose. Due to displacement of solvent by sodium valproate the concentration of reconstituted sodium valproate is 95 mg/ml.

Each vial of Epilim Intravenous is for single dose injection only. It should be reconstituted immediately prior to use and infusion solutions containing it used within 24 hours. Any unused portion should be discarded.

Epilim Intravenous may be given by direct slow intravenous injection or by infusion using a separate intravenous line in normal saline, dextrose 5%, or dextrose saline.

Patients already satisfactorily treated with Epilim may be continued at their current dosage using continuous or repeated infusion. Other patients may be given a slow intravenous injection over 3–5 minutes, usually 400–800 mg depending on body weight (up to 10 mg/kg) followed by continuous or repeated infusion up to a maximum of 2500 mg/day.

Epilim Intravenous should be replaced by oral Epilim therapy as soon as practicable.

Daily requirement for children is usually in the range 20–30 mg/kg/day and method of administration is as above. Where adequate control is not achieved within this range the dose may be increased up to 40 mg/kg/day but only in patients in whom plasma valproic acid levels can be monitored. Above 40 mg/kg/day clinical chemistry and haematological parameters should be monitored.

Use in the elderly: Although the pharmacokinetics of Epilim are modified in the elderly, they have limited clinical significance and dosage should be determined by seizure control. The volume of distribution is increased in the elderly and because of decreased binding to serum albumin, the proportion of free drug is increased. This will affect the clinical interpretation of plasma valproic acid levels.

Combined therapy: In certain cases it may be necessary to raise the dose by 5 to 10 mg/kg/day when used in combination with anticonvulsants which induce liver enzyme activity, e.g. phenytoin, phenobarbitone, and carbamazepine. Once known enzyme inducers have

The concomitant use of salicylates should be avoided in children under 3 due to the risk of liver toxicity. Additionally, salicylates should not be used in children under 16 years (see aspirin/salicylate product information on Reye's syndrome).

Monotherapy is recommended in children under the age of 3 years when prescribing Epilim, but the potential benefit of Epilim should be weighed against the risk of liver damage or pancreatitis in such patients prior to initiation of therapy

In most cases, such liver damage occurred during the first 6 months of therapy, the period of maximum risk being 2-12 weeks.

Suggestive signs:

Clinical symptoms are essential for early diagnosis. In particular the following conditions, which may precede jaundice, should be taken into consideration, especially in patients at risk (see above: 'Conditions of occurrence'):

- non specific symptoms, usually of sudden onset, such as asthenia, malaise, anorexia, lethargy, oedema and drowsiness, which are sometimes associated with repeated vomiting and abdominal pain.

- in patients with epilepsy, recurrence of seizures.

These are an indication for immediate withdrawal of the drug.

Patients (or their family for children) should be instructed to report immediately any such signs to a physician should they occur. Investigations including clinical examination and biological assessment of liver function should be undertaken immediately.

Detection:

Liver function should be measured before and then periodically monitored during the first 6 months of therapy, especially in those who seem most at risk, and those with a prior history of liver disease.

Amongst usual investigations, tests which reflect protein synthesis, particularly prothrombin rate, are most relevant.

Confirmation of an abnormally low prothrombin rate, particularly in association with other biological abnormalities (significant decrease in fibrinogen and coagulation factors; increased bilirubin level and raised transaminases) requires cessation of Epilim therapy.

As a matter of precaution and in case they are taken concomitantly salicylates should also be discontinued since they employ the same metabolic pathway.

As with most antiepileptic drugs, increased liver enzymes are common, particularly at the beginning of therapy; they are also transient.

More extensive biological investigations (including prothrombin rate) are recommended in these patients; a reduction in dosage may be considered when appropriate and tests should be repeated as necessary.

Pancreatitis: Pancreatitis, which may be severe and result in fatalities, has been very rarely reported. Patients experiencing nausea, vomiting or acute abdominal pain should have a prompt medical evaluation (including measurement of serum amylase). Young children are at particular risk; this risk decreases with increasing age. Severe seizures and severe neurological impairment with combination anticonvulsant therapy may be risk factors. Hepatic failure with pancreatitis increases the risk of fatal outcome. In case of pancreatitis, valproate should be discontinued.

4.4.2 Precautions

Haematological: Blood tests (blood cell count, including platelet count, bleeding time and coagulation tests) are recommended prior to initiation of therapy or before surgery, and in case of spontaneous bruising or bleeding (see section 4.8 Undesirable Effects).

Renal insufficiency:

In patients with renal insufficiency, it may be necessary to decrease dosage. As monitoring of plasma concentrations may be misleading, dosage should be adjusted according to clinical monitoring (see sections 4.2 Posology and Method of Administration and 5.2. Pharmacokinetic Properties).

Systemic lupus erythematosus: Although immune disorders have only rarely been noted during the use of Epilim, the potential benefit of Epilim should be weighed against its potential risk in patients with systemic lupus erythematosus (see also section 4.8 Undesirable Effects).

Hyperammonaemia: When a urea cycle enzymatic deficiency is suspected, metabolic investigations should be performed prior to treatment because of the risk of hyperammonaemia with valproate.

Weight gain: Epilim very commonly causes weight gain, which may be marked and progressive. Patients should be warned of the risk of weight gain at the initiation of therapy and appropriate strategies should be adopted to minimise it (see section 4.8 Undesirable Effects).

Pregnancy: Women of childbearing potential should not be started on Epilim without specialist neurological advice. Epilim is the antiepileptic of choice in patients with certain types of epilepsy such as generalised epilepsy + myoclonus/photosensitivity. For partial epilepsy, Epilim should be used only in patients resistant to other treatment. Women who are likely to get pregnant, should receive specialist advice because of the potential teratogenic risk to the foetus (see also section 4.6 Pregnancy and Lactation).

Diabetic patients: Valproate is eliminated mainly through the kidneys, partly in the form of ketone bodies; this may give false positives in the urine testing of possible diabetics.

4.5 Interaction with other medicinal products and other forms of Interaction

4.5.1 Effects of Valproate on other drugs

- Neuroleptics, MAO inhibitors, antidepressants and benzodiazepines

Valproate may potentiate the effect of other psychotropics such as neuroleptics, MAO inhibitors, antidepressants and benzodiazepines; therefore, clinical monitoring is advised and dosage should be adjusted when appropriate.

- Phenobarbital

Valproate increases phenobarbital plasma concentrations (due to inhibition of hepatic catabolism) and sedation may occur, particularly in children. Therefore, clinical monitoring is recommended throughout the first 15 days of combined treatment with immediate reduction of phenobarbital doses if sedation occurs and determination of phenobarbital plasma levels when appropriate.

- Primidone

Valproate increases primidone plasma levels with exacerbation of its adverse effects (such as sedation); these signs cease with long term treatment. Clinical monitoring is recommended especially at the beginning of combined therapy with dosage adjustment when appropriate.

- Phenytoin

Valproate decreases phenytoin total plasma concentration. Moreover valproate increases phenytoin free form with possible overdosage symptoms (valproic acid displaces phenytoin from its plasma protein binding sites and reduces its hepatic catabolism). Therefore clinical monitoring is recommended; when phenytoin plasma levels are determined, the free form should be evaluated.

- Carbamazepine

Clinical toxicity has been reported when valproate was administered with carbamazepine as valproate may potentiate toxic effects of carbamazepine. Clinical monitoring is recommended especially at the beginning of combined therapy with dosage adjustment when appropriate.

- Lamotrigine

Valproate may reduce lamotrigine metabolism and increase its mean half-life, dosages should be adjusted (lamotrigine dosage decreased) when appropriate. Co-administration of lamotrigine and Epilim might increase the risk of rash.

- Zidovudine

Valproate may raise zidovudine plasma concentration leading to increased zidovudine toxicity.

- Vitamin K-dependent anticoagulants

The anticoagulant effect of warfarin and other coumarin anticoagulants may be increased following displacement from plasma protein binding sites by valproic acid. The prothrombin time should be closely monitored.

- Temozolomide

Co-administration of temozolomide and valproate may cause a small decrease in the clearance of temozolomide that is not thought to be clinically relevant.

4.5.2 Effects of other drugs on Valproate

Antiepileptics with enzyme inducing effect (including ***phenytoin, phenobarbital, carbamazepine***) decrease valproic acid plasma concentrations. Dosages should be adjusted according to blood levels in case of combined therapy.

On the other hand, combination of ***felbamate*** and valproate may increase valproic acid plasma concentration. Valproate dosage should be monitored.

Mefloquine and ***chloroquine*** increase valproic acid metabolism and may lower the seizure threshold; therefore epileptic seizures may occur in cases of combined therapy. Accordingly, the dosage of Epilim may need adjustment.

In case of concomitant use of valproate and ***highly protein bound agents (e.g. aspirin)***, free valproic acid plasma levels may be increased.

Valproic acid plasma levels may be increased (as a result of reduced hepatic metabolism) in case of concomitant use with ***cimetidine*** or ***erythromycin***.

Carbapenem antibioticssuch as ***imipenem*** and ***meropenem***: Decrease in valproic acid blood level, sometimes associated with convulsions, has been observed when imipenem or meropenem were combined.If these antibiotics have to be administered, close monitoring of valproic acid blood levels is recommended.

Cholestyramine may decrease the absorption of valproate.

4.5.3 Other Interactions

Caution is advised when using Epilim in combination with newer anti-epileptics whose pharmacodynamics may not be well established.

Valproate usually has no enzyme-inducing effect; as a consequence, valproate does not reduce efficacy of oestroprogestative agents in women receiving hormonal contraception, including the oral contraceptive pill.

4.6 Pregnancy and lactation

4.6.1 Pregnancy

From experience in treating mothers with epilepsy, the risk associated with the use of valproate during pregnancy has been described as follows:

- Risk associated with epilepsy and antiepileptics

In offspring born to mothers with epilepsy receiving any anti-epileptic treatment, the overall rate of malformations has been demonstrated to be 2 to 3 times higher than the rate (approximately 3 %) reported in the general population. Although an increased number of children with malformations have been reported in cases of multiple drug therapy, the respective role of treatments and disease in causing the malformations has not been formally established. Malformations most frequently encountered are cleft lip and cardio-vascular malformations.

Epidemiological studies have suggested an association between *in-utero* exposure to sodium valproate and a risk of developmental delay. Many factors including maternal epilepsy may also contribute to this risk but it is difficult to quantify the relative contributions of these or of maternal anti-epileptic treatment. Notwithstanding those potential risks, no sudden discontinuation in the anti-epileptic therapy should be undertaken as this may lead to breakthrough seizures which could have serious consequences for both the mother and the foetus.

- Risk associated with valproate

In animals: teratogenic effects have been demonstrated in the mouse, rat and rabbit.

There is animal experimental evidence that high plasma peak levels and the size of an individual dose are associated with neural tube defects.

In humans: an increased incidence of congenital abnormalities (including cases of facial dysmorphia, hypospadias and multiple malformations, particularly of the limbs) has been demonstrated in offspring born to mothers with epilepsy treated with valproate.

Valproate use is associated with neural tube defects such as myelomeningocele and spina

bifida. The frequency of this effect is estimated to be 1 to 2%.

- In view of the above data

When a woman is planning pregnancy, this provides an opportunity to review the need for anti-epileptic treatment. Women of childbearing age should be informed of the risks and benefits of continuing anti-epileptic treatment throughout pregnancy.

Folate supplementation, **prior** to pregnancy, has been demonstrated to reduce the incidence of neural tube defects in the offspring of women at high risk. Although no direct evidence exists of such effects in women receiving anti-epileptic drugs, women should be advised to start taking folic acid supplementation (5mg) as soon as contraception is discontinued.

The available evidence suggests that anticonvulsant monotherapy is preferred. Dosage should be reviewed before conception and the lowest effective dose used, in divided doses, as abnormal pregnancy outcome tends to be associated with higher total daily dosage and with the size of an individual dose. The incidence of neural tube defects rises with increasing dosage, particularly above 1000mg daily. The administration in several divided doses over the day and the use of a prolonged release formulation is preferable in order to avoid high peak plasma levels.

During pregnancy, valproate anti-epileptic treatment should not be discontinued if it has been effective.

Nevertheless, specialised prenatal monitoring should be instituted in order to detect the possible occurrence of a neural tube defect or any other malformation. Pregnancies should be carefully screened by ultrasound, and other techniques if appropriate (see Section 4.4 Special Warnings and Special Precautions for use).

- Risk in the neonate

Very rare cases of haemorrhagic syndrome have been reported in neonates whose mothers have taken valproate during pregnancy. This haemorrhagic syndrome is related to hypofibrinogenemia; afibrinogenemia has also been reported and may be fatal. These are possibly associated with a decrease of coagulation factors. However, this syndrome has to be distinguished from the decrease of the vitamin-K factors induced by phenobarbitone and other anti-epileptic enzyme inducing drugs.

Therefore, platelet count, fibrinogen plasma level, coagulation tests and coagulation factors should be investigated in neonates.

4.6.2

Lactation

Excretion of valproate in breast milk is low, with a concentration between 1 % to 10 % of total maternal serum levels; up to now children breast fed that have been monitored during the neonatal period have not experienced clinical effects. There appears to be no contra-indication to breast feeding by patients on valproate.

4.7 Effects on ability to drive and use machines

Use of Epilim may provide seizure control such that the patient may be eligible to hold a driving licence.

Submission from Professor Jill Clayton-Smith, Dr Rebecca Bromley, Professor Peter Turnpenny, Professor Amanda G Wood

Submission to the Independent Medicines and Medical Devices Safety Review: evidence pertaining to in utero exposure to sodium valproate

Authors:

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Version 1 October 2018

This document has been written by the authors for the purpose of the Independent Medicines and Medical Devices Safety Review and incorporates the request references RYKTVG, BFZADD and TNFFYA**.**

Conflicts of interest

Professor Turnpenny accepts private referrals to assess children and young people who have been exposed to AEDs. He has also provided medico-legal reports as an expert witness in claims relating to prenatal exposure to VPA.

Professor Clayton-Smith and Dr Bromley have previously provided information on behalf of the families in UK class action regarding Fetal Valproate Syndrome. They have both been involved in research work funded by Sanofi Aventis and UCB Pharma into AED teratogenesis.

Professor Wood does not have any conflicts of interest.

Introduction

This document has been written by the authors listed on page one, all of who have been involved in the assessment of individuals with a history in utero exposure to sodium valproate (valproic acid; VPA)

and other antiepileptic drugs (AEDs). All authors have published scientific papers on the topic and Professor Turnpenny, Dr Bromley and Professor Clayton-Smith see individuals with a history of VPA exposure through their NHS work. Short bio's are included for the authors in appendix 1. The evidence provided in this document is based on both published research data and our collective clinical experience. Where the information is based upon research evidence references have been provided.

In our invitation to submit evidence we were asked to answer specific questions. We have addressed each of these below in turn.

1. Would you use the term 'Fetal Valproate Spectrum Disorder'? If so, please define.

The term used to associate a constellation of physical and neurodevelopmental abnormalities with exposure in utero to VPA has been termed Fetal Valproate Syndrome (FVS) and in 2000 Dean and Colleagues(1) provided a diagnostic framework for this condition. In March 2018 however, individuals from 27 institutions across Europe provided wide ranging expert clinical input into a consensus guideline document(2) regarding FVS. This initiative was undertaken as one of the activities of the European Reference Network on Rare Congenital Malformations and Rare Intellectual Disability (ERN ITHACA). This document is still under editing but a summary of the new proposed diagnostic criteria is provided below; it is expected that the full document will be published in 2019. The aim of the document is to update the previous diagnostic guidelines(1) and outline best practice care pathways for FVSD.

Given that there are a number of developmental risks associated with VPA exposure, and that there are many varied presentations across individuals, this expert consensus group suggested that we move towards using the term Fetal Valproate Spectrum Disorder (FVSD), a situation akin to that used when discussing adverse effects of exposure to alcohol in utero(3). This seems appropriate since children with severe neurodevelopmental effects of VPA exposure, but without significant malformations, can be just as impaired in their everyday functioning as children with classical FVS, and need to be identified in order to be offered the appropriate management. The authors now use the term FVSD and from this point onwards the term FVSD will be used in place of FVS in this document.

Published data has characterised FVSD as a consistent pattern of major and minor malformations, facial dysmorphism and impaired neurodevelopment(1, 4-13). Risks are increased in particular for neural tube defects(9), congenital heart disease(12), cleft palate[8, 12], upper limb (radial ray) defects(14-16), ophthalmological problems (17-19) and genitourinary anomalies(13, 20-22). Associated minor anomalies include inguinal hernia(23), overlapping toes and other minor digital anomalies(8) and scalp defects(23, 24). The facial dysmorphism is characterised by a broad nasal

bridge, short nose with forward-facing nostrils, small mouth with thin upper lip, everted lower lip, flat philtrum (the area between the nose and the lip), ridging of the metopic suture (midline of the forehead) and neatly arched eyebrows(1, 6, 8, 13, 23, 25). Problems with impaired neurodevelopment, including an increased risk for poorer intellectual ability (i.e. Intelligence Quotient (IQ)) and autism spectrum disorder (ASD), went unrecognised initially but are now proven to be part of the FVSD phenotype(26-34). The prevalence of the neurodevelopmental deficits after VPA exposure is higher than that of the prevalence of VPA associated malformations, suggesting that an individual can demonstrate adverse effects of VPA exposure without necessarily having all of the physical features seen in FVSD. In fact, impairment of functioning is known to occur at lower doses and at increased frequency than structural malformations, across teratogenic exposures(35). Further, studies have specifically excluded VPA exposed children with major congenital malformations and still find the increased risk of both reduced IQ (34, 36) and autistic spectrum disorder(29).

Kini et al., (25) raised the question of whether it was possible to have impaired neurodevelopment as a result of VPA exposure in the absence of dysmorphic facial features. In their study of the facial dysmorphism associated with antiepileptic drug exposure in utero, although the risk of impaired IQ was higher in those with a typical dysmorphic facial presentation, cases without a clear facial features were also noted to have a lower IQ. From a practical clinical point of view, the dysmorphic features associated with VPA exposure can be subtle and age dependent, and designating individuals as having the characteristic dysmorphism or not can be difficult, especially for those with limited expertise in this area. Due to these points the authors and the aforementioned Expert Consensus Group felt that whilst the presence of a typical facial presentation makes the diagnosis more certain, they are not absolutely required for the diagnosis of FVSD.

The diagnosis of FVSD is difficult, as there is no specific biomarker that can be assayed in this condition, though there are conditions with overlapping features which need to be excluded(21). Important considerations include the dose, timing and duration of the VPA exposure, whether it was a monotherapy exposure or whether it was in combination with another AED. All of these factors could alter the phenotype seen in the exposed individual. For example, the onset of VPA use in the second or third trimester would not be able to induce structural congenital malformations or facial dysmorphism as the structure of the major organs and the face are complete. However, the brain remains susceptible throughout the second and third trimesters and therefore an impact on cognition from exposure later in pregnancy is possible. Currently, the diagnostic criteria for Fetal Anticonvulsant Syndrome published by Dean and colleagues(1) are used by most Clinical Geneticists in the UK and our expert consensus group reviewed these prior to developing new criteria for FVSD which reflect our current knowledge of the condition. The suggested revised criteria from the group, presented in

Table 1, have been divided into “essential criteria”, defined as those which must be present for an FVSD diagnosis, “suggestive” features which are seen at significantly increased frequency (>10%) in FVSD, and “supportive” features which occur independently within the general population but are more common in FVSD. The supportive criteria are weighted according to their frequency in the general population (the more common they are in the general population the less weight they are given). Dysmorphic facial features are a strong diagnostic handle for FVSD(25) as these are considered specific for the disorder if present. For diagnostic criteria to be met all essential criteria in Table 1 must be fulfilled in addition to two suggestive criteria, or one suggestive plus a supportive score of 3 or more.

Table 1 Proposed Diagnostic Criteria For Fetal Valproate Spectrum Disorder

Grade	Criterion	Comments
Essential	Confirmed exposure to VPA during pregnancy	Any dose or duration
Essential	Has no other recognisable diagnosis which would explain the phenotype	As evidenced on assessment by a clinical geneticist or other professional with relevant expertise
Essential	Normal microarray-CGH and Fragile X studies	Part of diagnostic work-up
Essential	Other teratogenic disorders with clinical overlap excluded	In particular fetal alcohol syndrome / spectrum disorder
Suggestive	Facial dysmorphism consistent with VPA exposure (flat philtrum, thin upper lip, full, everted lower lip, short anteverted nose, small mouth, epicanthic folds, neat arched eyebrows, broad nasal root) see Figure 3	Include review of photographs at a younger age and take into account variability of phenotype with age (see Fig 3)
Suggestive	Cognitive profile consistent with current knowledge of that associated with valproate exposure	a) discordant from parents b) in infancy: motor and speech delay, c) school aged: IQ, verbal reasoning, communication and executive functioning deficits
Suggestive	Diagnosed social communication difficulties/autism spectrum disorder	Occurs in 7-15%

Suggestive	Spina bifida	20 fold risk	
			Score
Supportive	Congenital cardiac defect	Confirmed on echo	2
Supportive	Cleft palate		2
Supportive	Metopic suture ridging or synostosis		2
Supportive	Radial ray defect	Includes mild variants with flat thenar eminences	2
Supportive	Genitourinary malformations	Hypospadias, abnormal collecting system, hydronephrosis	2
Supportive	Laryngomalacia/stridor		2
Supportive	Joint laxity	Beighton 6 or more	1
Supportive	Talipes requiring surgery		1
Supportive	Digital anomalies	Overlapping toes, camptodactyly, clinodactyly	1
Supportive	Ophthalmological anomalies	Coloboma, strabismus, astigmatism, refractive error	1
Supportive	Enuresis/poor bladder control beyond pre-school years	Requiring investigation	1

Given the prominence of the cognitive, social and motor difficulties within the presentation of FVSD, individuals with the condition should be referred to a Clinical Psychologist or Neuropsychologist as part of the diagnostic process, unless the child clearly has severe neurodevelopmental impairment. The age-appropriate neuropsychological assessment focus will vary by age, but should cover cognitive, speech and motor development in infancy, and then IQ, language, memory, attention and executive functioning in school aged children or older. Neurodevelopmental difficulties, as measured by poor performance on neuropsychological assessments, are present in a large number of neurological conditions and therefore careful expert workup and interpretation by an experienced clinician is required, taking into account the expected phenotypic pattern for FVSD.

The number of fetuses exposed to VPA that go on to meet the criteria for FVSD is unknown currently. Estimates to date regarding the risk of major congenital malformation and neurodevelopmental difficulties (as discussed below) come from cohorts of children with a history of exposure to VPA and are not a confirmed population with FVSD.

2. Please could you provide a timeline outlining your understanding and recognition of risks of valproate damage in utero? This may include: initial recognition of the risk, dates of consequential and significant research studies, and communication of regulatory and professional guidance to clinicians and patients

Major congenital malformations

Dickinson et al., (37) and Nau et al., (38) documented early on in its use that VPA crossed the human placenta and was present in higher concentrations in the fetus than in the mother. Throughout the 1980's case reports were published, often as letters to major medical journals, presenting children with a history of VPA exposure and a major congenital malformation, often spina bifida(9, 10, 39-46). In 1982, the first group report came from a French Birth Defect Register and suggested an increased risk of spina bifida associated with VPA exposure(42) which was replicated by birth defect registers in Italy (47) and Spain (48) and then others (49). In their case report to the Lancet in 1989, Oakeshott and Hunt reported three cases of spina bifida from the East Anglian region of the UK and additionally documented that a personal communication from the Committee on Safety of Medicines, indicated that the committee had received 26 such notifications of spina bifida following VPA exposure (50). In addition to this early emerging human data, in their 1986 paper Nau reported that VPA had been demonstrated to be teratogenic in the mouse, rabbit, hamster, monkey(38) suggesting early availability of animal data signalling concern about VPAs teratogenic potential.

From 1983, prospective studies, which followed-up children ascertained during pregnancy, and not just because they had presented with problems, began to be established, and these provided information on risks associated with VPA exposure, which was less subject to ascertainment bias. Early investigations were limited in their reporting as often all AED exposure children were reported as a single group. However, in 1997, a collaboration by a number of European groups was published highlighting an increased association between VPA exposure (n=184) and an increased risk of major congenital malformations (51). For the first time, the issue of a dose dependent relationship was noted; suggesting that doses above 1000 mg daily carried an increased risk for major congenital malformations(51). An interesting cumulative meta-analysis carried out by Tanoshima and colleagues(52) highlighted that this early data was sufficient for certain associated risk with VPA exposure, such as spina bifida, to be demonstrated. This meta-analysis was conducted in a manner by which data was added to the analysis by year of its publication, which clearly shows the accumulation of data over time. Recently, a review of Tanoshima's cumulative meta-analysis has led to the call, that from the 1990s onwards, patients should have been offered alternative treatments and pre conceptual counselling (53). Whilst the authors here agree that the emerging risks associated with

VPA treatment should have been more comprehensively and routinely conveyed to patients, the context should be considered. In 1990, lamotrigine (LTG) was not yet licenced in the UK and research to that point, had suggested teratogenic concern regarding phenytoin (PHT), phenobarbital (PB) and primidone (54-56) which were the available alternatives. What disappointingly did not happen at this point was a large programme of research aimed at delineating these risk and understanding them more rapidly.

National and International Pregnancy Registers have been central to establishing both risk and relatively safety of AEDs in terms of major congenital malformations. Established in the late 1990's, the North American Antiepileptic Drug Register (57-61), the UK Epilepsy and Pregnancy Register (62-64), the Australian Pregnancy Register of Antiepileptic Drugs (65-67), and EURAP- International Register of Antiepileptic Drugs and Pregnancy(68-70), have provided the most data historically. This data has been rigorously summarised, along with data from smaller prospective observational studies, in the Cochrane Review by Weston and Colleagues (71). In this review, children exposed to VPA were compared to children from two control groups; 1) women with epilepsy who were not medicated, and 2) women from the general population who did not have epilepsy and who were not taking an AED. Twenty-six studies were included in the review's meta-analyses, reporting on 2565 babies exposed to VPA in the womb. The incidence of a major congenital malformation (of any type or any body region) following exposure to VPA was 10.9%. Children exposed to VPA were found to have an additional 8% risk (RD 0.08, 95% CI 0.05 to 0.11) when compared to the children born to women from the general population, and an additional 7% risk (RD0.07, 95% CI 0.03 to 0.10) compared to the children born to women with epilepsy but who were untreated during their pregnancies(71). Data were far scarcer for individual types of malformations but this review confirmed the suggestions from the early case reports that neural tube defects (e.g. spina bifida), cardiac, oro-facial, as well as skeletal and limb malformations, were all increased following exposure in the womb to VPA (71). Based on these findings, around 11% of children exposed to VPA in utero can be expected to be born with a major congenital malformation. The risk associated with VPA has been documented to be dose dependent, as would be predicted from the principles of teratology(35, 56, 72). The most robust demonstration of this association comes from the EURAP collaboration which demonstrated that at doses above 1500 mg daily the prevalence of major malformation increased to 25.2% from 6.3%, when the dose was no more than 650 mg daily(73). It should also be noted that timing of the exposure and individual susceptibility will play a role in mediating whether an individual has a major malformation following exposure(35, 56, 72). Additional evidence regarding an association between VPA and increased levels of malformation, has come from national population datasets. With the benefit or large numbers and

sequential case ascertainment national register studies have provided results consistent with those of the observational and pregnancy register cohorts (74, 75).

There is therefore a multitude of evidence demonstrating that prenatal VPA exposure is associated with an increased risk of major congenital malformations such as spina bifida, cardiac, limb and orofacial clefts. It should be pointed out however, that rates of major congenital malformations represent only the most severe structural abnormalities and are thus the 'tip of the iceberg'. Children with a history of VPA exposure are also at an increased risk of more minor malformations, ie physical health problems which do not require surgical intervention or significant treatment, and may not be obvious on brief health screenings. However, such problems may still have an impact on the daily functioning of the child. These problems are seen in VPA exposed groups more frequently than in the background population and include facial dysmorphism, hypotonia, overlapping digits, and bladder function difficulties.

Facial dysmorphism

In 1984 Di Liberti et al.,(13) published a report documenting the findings in seven patients who had been exposed to VPA in utero. They described a similar and specific facial appearance in all seven patients, and the occurrence of congenital malformations and/or developmental delay in four of them. The facial features which they emphasised included a flat nasal bridge, folds of skin at the inner corners of the eyes (epicanthic folds) which continued on to form pronounced grooves under the eyes, a short nose with forward facing nostrils, a flattened area between the mouth and the nose, and a small down-turned mouth with a thin upper lip. The authors commented specifically that this facial appearance was quite different to that which had been reported with exposure to other AEDs. In addition, two patients had developmental delay and, following a review of the previous literature, the authors ascertained five other patients with developmental delay amongst previous reports of VPA-exposed infants. This pattern was referred to in 1984 as "Fetal Valproate Syndrome" (FVS).

This first report was followed in 1986 by a small prospective study by Jäger-Roman et al., (4) which included 14 infants exposed to VPA monotherapy in utero. They stated that, *"… seven infants had a pattern of craniofacial and digital anomalies that was distinctly different to that observed after in utero exposure to other anticonvulsant medications"*. In 1987 Winter et al., (10) reported four further cases of FVS in the Journal of Medical Genetics, a widely read British genetic journal, agreeing that these children had a distinctive appearance, similar to that reported by Di Liberti (13). Winter et al., (10) pointed out specifically that ridging of the metopic suture in the midline of the forehead was a distinctive feature of FVS. They also pointed out that two of their four cases had developmental delay and that this should be considered part of the FVS pattern and needed to be explored further.

The following year Ardinger et al., (6) reported a series of 19 patients exposed to VPA in an attempt to delineate FVS further. Their findings were *"… in agreement with those of Di Liberti"*. They also reported a 71% incidence of developmental delay. Again, they pointed out specifically that whilst some of the facial features seen following VPA exposure could also be seen with exposures to other antiepileptic drugs, there were several features, such as a prominent metopic ridge, which were *"peculiar to VPA exposure"* and not seen with exposure to other AEDs.

Neurodevelopment

The term 'neurodevelopment' refers to a wide range of brain functioning and developmental processes. It covers skills such as reasoning and IQ, language development, and proficiency with motor skills, as well as psychiatric and behavioural diagnoses such as ASD. Children may have a deficit in one area but function well in other areas, or they may have difficulties in a number of areas. The question of whether VPA exposure in pregnancy could cause developmental delay/learning disability first arose in the early case reports where frequently, alongside the description of the malformation there would also be a reference to a poorer developmental profile(6, 44) . Investigations into the health and development of children born to women with epilepsy were underway in Finland (76) and Germany(77) at this time, however they had very few VPA exposed cases, and therefore could not provide clear early evidence. In fact, all of the early studies which looked at development/IQ in the offspring of mothers taking AEDs during pregnancy could be criticised because of inadequate study design, for example analysing all AED exposed children together, or due to the small size of the VPA exposed group. At the turn of the century, research into the neurodevelopment of children exposed to VPA in the womb gained momentum. In a review of 57 children who met the diagnostic criteria for an anticonvulsant syndrome, Moore and colleagues (11) reported that in the children who were school age or older (n= 38), 74% required educational support. Whilst it is unclear how many of these 38 were VPA exposed and therefore had FVS specifically, the majority of the cohort was VPA exposed. A year later in a study by Adab et al., (78), which looked retrospectively at educational outcomes in children born to mothers with epilepsy, it was reported that in those exposed to VPA monotherapy (n = 56), 45% needed additional help in school, which was 3.4 times more likely than unexposed children. The proportion requiring additional school support was also significantly raised in the group exposed to polytherapy that included VPA. In 2002 Dean and colleagues (23) in the North East of Scotland reviewed the medical records of all children with a history of VPA exposure in the womb and found that there were high levels of what they termed 'developmental delay', with delays most commonly reported in the domains of speech development (29%). In the Dean study, 34% of monotherapy VPA exposed children had either developmental delay or a congenital malformation. Adab and colleagues (79) undertook a follow up to their original study and retrospectively recruited families from the North

West where there had been a known exposure to an AED. This study was the first of its size to employ standardised assessment of IQ and therefore had greater precision for identifying cognitive difficulties. In 42 children with VPA exposure the rate of below average IQ was 30% and the mean of the group differed significantly from the untreated group, even after controlling for other influencing variables(79). These studies were retrospective, and there were calls that the samples were highly selective, but importantly they supported the need for further prospective studies examining the neurodevelopmental outcome of children exposed to AEDs including VPA to reduce bias.

Prospective studies were established which improved scientific rigor in terms of recruitment, reduction of certain biases, and statistical approaches. Data from these prospective studies now makes it very clear that children exposed to VPA are at increased risk of a range of neurodevelopmental sequelae. In infancy, children exposed to VPA are delayed in their language and motor development(80). In the NEAD study(32, 33), a prospective follow-up of children born to women with epilepsy who had been treated with a number of different AEDs as monotherapy, and which controlled for confounding factors, demonstrated that the reasoning or IQ of children exposed to VPA (n=49) were up to 9 IQ points lower than that of children exposed to other AEDs; with 37% placed below the average range for their IQ. When the same group of children were reassessed at the age of 6 years similar results were found; the children exposed to VPA continued to have lower reasoning and IQ scores than children exposed to other AEDs (33). IQ is the primary outcome in many studies and an association between VPA exposure and lower IQ has now been reported in a number of prospective studies (26, 27, 30, 33, 34, 81, 82). Not all studies have found this association however (83, 84) but in studies which have failed to demonstrate a difference between the VPA exposed children and control children there appear to be methodological reasons. These include low dose of VPA (83) and a lower than population norm IQ in the control group(84).

Consistent with what is expected for a teratogen, the effects on IQ were shown to be dose-related, with children exposed to higher doses of VPA having lower scores(26, 34). A UK study (26) reported that exposure in the womb to VPA at doses greater than 800 mg daily was associated with a 9.7 point reduction in IQ once other contributing factors had been taken into account by statistical analysis. If the dose of VPA was 800 mg daily or less the associated reduction in IQ points was, on average, reduced to 5.0 IQ points (26). Similarly, dose relationship between the level of valproate exposure and IQ have been found in cohorts from America (32, 33), Australia(34) and Georgia(36); and reflects the clear dose association seen for major congenital malformations reported above.

The data above all comes from studies of groups of children ascertained through a history of VPA exposure and shows that there is an increased risk of poorer IQ associated with VPA exposure.

However, Bromley and colleagues (85) have recently investigated the IQ outcomes in individuals ascertained through a diagnosis of FVS (using the criteria by Dean et al(1). In participants diagnosed with FVSD (both children and young adults), a similar pattern of lower IQ is observed, however the magnitude of difference was far greater in the FVSD population than had been reported from populations with a history of VPA exposure. The discrepancy for IQ, for example, was 19 points different from the expected mean with 52% falling below the average range in comparison to 9% expected to fall within this range based on the normative sample(85). This demonstrated what has been our clinical experience, that cognitive difficulties are a central feature of FVSD.

The associated impact on the brain from prenatal exposure to VPA appears to have a greater impact on verbal related skills, with studies frequently reporting poorer verbal reasoning skills in comparison to non-verbal reasoning skills (26, 33, 34, 85). Other, non-IQ, cognitive skills have also been demonstrated to be altered by VPA exposure. Children exposed to VPA are more likely to have poorer abilities in their language development (33, 34), aspects of executive functioning skills (33) and in their memory skills(86) in a dose dependent manner. Deficits in the key cognitive skills of reasoning, language, executive and memory functioning, either alone or in combination with each other, are likely to lead to the increased need for educational support noted in the published literature for VPA exposed children. The rates of educational support range from 74% for children with a confirmed FVSD (11, 85) to 37% down to 19% for children exposed higher and lower doses of VPA respectively (26). In a recent population based study, which utilised routinely collected health records and educational outcomes, the children exposed to VPA (n=55) were found to have poorer national examination results for Danish and Mathmatics (87); highlighting the real life impact of the cognitive difficulties.

There has been long-standing concern regarding the diagnosis of ASD in children exposed to VPA in pregnancy. There is a wealth of data from rodent studies which demonstrate an increase in rodent pups displaying ASD type symptomatology following exposure to VPA(88); in fact, the 'valproate autism model' is a frequently utilised tool in autism research(89). Initially individuals reported with ASD were the subjects of single, anecdotal case reports(90, 91) but 6/57 (11%) patients exposed to VPA in the series reported by Moore et al., (11) had ASD. Rasalam et al.,(28) found that the prevalence of ASD in a population of children exposed to AEDs in utero was 8 to 18 times higher that the prevalence of 0.25% calculated for the general population; the prevalence being highest (8.9%) for children exposed to VPA alone. Data from a prospective observational study in the UK reported that the incidence of ASD in the group exposed to VPA monotherapy was around 6%, substantially higher than for other monotherapy groups, and more than seven times higher compared to the control population in which only 0.9% were affected (31, 92). Further strong evidence came from a population study in Denmark by Christensen et al.,(29) in 2013 which demonstrated that the risk of ASD in a

population of children exposed to VPA was more than double that of the general population. However, clinical diagnoses of ASD may only report on the most affected individuals. Wood and colleagues(93) demonstrated that screening for ASD symptoms produced higher levels of difficulties. This is consistent with our clinical experience with FVSD, that many individuals have sub-diagnostic levels of social and communication difficulties but that there is a clear impact on their daily functioning.

An important final observation is that neurodevelopmental difficulties are not restricted to those VPA exposed children with a major congenital malformation. Whilst children with a physical malformation are at a greater risk of having poor IQ scores(26), the exact pattern of reported neurodevelopmental deficits have been demonstrated in three studies which *excluded* children with major congenital malformations (29, 34, 36).

The majority of data reviewed above comes from individuals exposed to monotherapy VPA. However, similar results across all malformation and neurodevelopmental outcomes are seen for children exposed to VPA in a polytherapy combination(26, 62), compared to exposure to VPA as monotherapy, with the dose of VPA remaining an important mediator of risk.

Summary

Accumulated evidence demonstrates that children exposed to VPA in the womb, whether as monotherapy or polytherapy, are at an increased risk of being born with major congenital malformations, a constellation of facial features typical for the exposure, having reduced intellectual, language, memory and executive functioning skills, as well as an increased risk of ASD. Whilst these risks are substantially higher than the general unexposed population, and higher than the rates seen in children exposed to other AEDs, adverse effects are not seen in 100% of exposed individuals. The timing and dose of the exposure, as well as unspecified individual differences (possibly genetic susceptibilities), are all factors that affect the chance of physical and neuro-development being altered by VPA exposure in the womb.

3. How does the in utero effect of valproate compare to other antiepileptic drugs?

There is highly consistent evidence that VPA exposure in the womb carries a higher risk of major congenital malformation and risk to neurodevelopment than all other AEDs researched to date. Weston et al.,(71) undertook a systematic review of all of the published prospective observational studies and where possible pooled the data together in meta-analysis. In these meta-analyses a consistent pattern emerged: the risk of having a major congenital malformation was increased compared with children exposed to carbamazepine (CBZ), gabapentin (GBP), levetiracetam (LEV),

lamotrigine (LTG), topiramate (TPM), oxcarbazepine (OXC), phenobarbitone (PB) and phenytoin (PHT). The risk estimates range from a two-fold to six-fold increase in risk. The level of additional absolute risk ranged from 4% to 8% depending on the comparator AED, however this analysis does not take into account the dose of VPA exposure. The increased risk of spina bifida seen following VPA exposure is also seen in children exposed to CBZ, albeit to a much lesser degree(71). To date no clear evidence of an increased risk of major congenital malformations has been demonstrated for either LTG or LEV(71, 94); two medications often used these days in women with idiopathic generalized epilepsy. The large EURAP collaboration has demonstrated that even lower doses of VPA (defined as less than 650 mg daily) carry an increased risk compared to lower dose LTG (defined as equal or less than 325 mg daily)(70). Differential outcomes between VPA and other AED types have been demonstrated in large population datasets also(74, 75).

In direct comparison to children exposed to other AEDs, those exposed to VPA were at an increased risk of poorer IQ. Meador and colleagues(32, 33) have provided the most comprehensive data set on this to date and note that there was an IQ reduction for the VPA exposed children at both three and six years of age in comparison to children exposed to either LTG, CBZ or PHT, of the magnitude of 6-11 IQ points. This level of difference is similar to the IQ difference noted when the IQ of VPA exposed children is compared to general population control group(27). The Cochrane Review into the neurodevelopmental outcomes of children exposed to AEDs in utero(27) highlights that there is a relative lack of evidence in comparison to that pertaining to malformations. However, available data from prospective observational studies and population datasets demonstrated better neurodevelopmental outcomes for children exposed to CBZ and LTG than for those exposed to VPA (26, 29, 32, 33, 81, 87). In direct comparison to LEV, children exposed to VPA have poorer levels of early development (95, 96) and school aged IQ(30). There is no doubt that more research is required into the cognitive functioning of children exposed to newer AEDs such as LTG and LEV; however, based on currently available evidence they do not appear to be associated with the neurodevelopmental impact which pertain to VPA.

4. In your expert opinion, what factors contribute to the aetiology of in utero fetal valproate damage?

a. AED taken, including dosage and co-prescriptions

Key principles of teratology outline that the type of agent or chemical (in this case AED), the dose, timing and duration of the exposure, as well as individual susceptibility (both across different tissue types and different people), will influence the fetal outcome(72). Thus, the risks associated with an

exposure will vary across the exposed population and across tissue types within one person. This is true for all human teratogens.

Research to date has demonstrated a very clear dose-dependent risk for VPA exposure for major malformations(51, 62, 66, 70) and the neurodevelopmental outcomes, including reduced IQ(26, 32, 33) and the increased risk of ASD(29). As noted in section 2 of this document, the risk of major congenital malformations rises from 6.3% to 25.2% as the dose rises(70), and that the risk to IQ can be almost halved by reducing the dose of VPA to equal or under 800 mg daily(26). Whilst the risk level is mediated by the dose taken by the mother this is not to say the adverse outcomes are not seen at lower doses in our experience. This is likely due to individual susceptibility and pharmacokinetic variability(97).

The first 12 weeks of gestation is termed the period of organogenesis and during this time the major organ structures are formed. During this gestational time period the fetus is susceptible and exposure to a teratogen at this point increases the risk of both minor and major congenital malformations(72). Exposure to VPA after the first 12 weeks would be unlikely to induce a major structural malformation, as these processes are already complete. Research into the timing of the effects of VPA exposure on brain development is non-existent in humans, as the majority of research cases to date have continued the use of VPA throughout gestation. The brain, however, grows throughout gestation in humans and therefore its period of susceptibility both includes and extends beyond the period of organogenesis leaving the brain susceptible to AED teratogenesis throughout gestation(35).

It has been shown that in polytherapy VPA combinations, exposure is associated with an increased risk of major congenital malformation above that seen for monotherapy VPA; but in contrast the EURAP collaboration did not replicate this in one of the largest studies to date(68). The UK and the Australian Pregnancy Registers report an increase in major malformation risk for polytherapy combinations including VPA (13.3% and 9.0%(98) respectively) when compared to those exposed to monotherapy (9.8% and 6.2%(62) respectively). However, what is not clear is the influence of VPA dose on this trend. As noted elsewhere in this document, higher doses of VPA have been associated with a higher risk of major congenital malformations and data from the EURAP collaboration highlights that dose of VPA was a key driver the VPA polytherapy increased rate of malformation(68). This may not be the sole driver as there is evidence that polytherapy combinations not including VPA also carry an increased risk(98); However, the rate of malformation occurrence in non-VPA polytherapy very much depends on the particular AEDs which are combined(62).

b. Maternal seizures during pregnancy

The studies of potential medication teratogenicity must always consider whether there are influences of the maternal, or in some cases paternal, disease. Where epilepsy is concerned this includes consideration of whether there is a direct impact on fetal development of exposure to maternal seizures and the more indirect influence of the parental epilepsy itself, and whether these convey risk in terms of neurodevelopmental outcomes. Animal studies are key to understanding the influence of variables in this context as the impact of the medication can be assessed in isolation from the maternal disease. As noted in section 2, there is replicated evidence for both malformations and neurodevelopmental risks, that there is a risk associated with VPA exposure that is independent of either the exposure to seizures or the background maternal disease(88, 99, 100).

However, species differences mean that we also need to ascertain this information in humans. Randomised controlled trials are not ethical for investigating potential fetal harms. Therefore, well-designed observational studies with adequate control of variables likely to influence the outcome are considered to be the gold standard. In the most notable study which investigated whether the increased malformation risk was independent from influence of the maternal disease, Bromfield and colleagues(101) demonstrated, using data from the North American Pregnancy Register, that the risk of malformations was similar across maternal epilepsy types and concluded, that the risk was associated with the VPA exposure and not the maternal epilepsy itself. Further, early investigations by Steinhausen and colleagues(77) found paternal epilepsy carried no increased risk I comparison to control children. Indirect evidence to support a role for VPA teratogenicity rather than maternal epilepsy, comes from the differences now seen between the malformation rate for VPA in comparison to LTG and LEV, two medications which are now widely used for idiopathic generalised epilepsy and for which current evidence fails to find an increased risk of major malformations(71, 94, 102). For neurodevelopment, the findings from animal data have been replicated in humans by Meador and colleagues(33), who found no difference in mean IQ at six years of age across the different epilepsy types.

Prenatal exposure to seizures has not been associated with increased risk of major congenital malformations, and in fact the North American Pregnancy Register data highlights that seizure control in their LTG group was poorer, yet they demonstrated lower rates of malformation in comparison to VPA exposed children(58). Whether transient seizure exposure in pregnancy increases the risk of poorer neurodevelopmental outcomes is less clear as the data has been contradictory and this is most likely attributable to the differences in methodologies and a failure to investigate seizure exposure as the primary research question. Adab et al.,(79) demonstrated an association between exposure to five-or-more generalised tonic-clonic seizures and child verbal IQ, which is the most often cited reference regarding this issue. Shallcross et al(96) also found an association between seizure exposure

but they collected information on seizures retrospectively from parents and so it was open to recall bias. In contrast, others, including data from large prospective studies, failed to find such an association(26, 32, 63, 81). Current evidence, from both animals and humans, would suggest that the risk associated with VPA exposure in utero is not due to the risk of maternal seizures or maternal disease. Whether frequent exposure to transient seizures in utero presents an additional risk to neurodevelopmental outcomes is unclear, due to a lack of evidence, and is something, which the authors are currently investigating.

5. What is your understanding of the effects of in utero exposure to valproate over time on those affected?

Few studies have been carried out on adolescents and adults with FVSD, and much of the information is limited to anecdotal reports and our clinical experience. Bromley et al., (85) have studied intellectual functioning in 18 individuals over the age of 16 with a confirmed diagnosis of FVSD and identified increased rates of intellectual disability (IQ <70), with poor verbal comprehension and reasoning, impaired auditory working memory and processing speed deficits. This provided research evidence that the neurodevelopmental deficits are persistent into adulthood. Information gathered from individual families support the fact that difficulties continue into adult life, affecting independence and employment opportunities as well as mental health and ability to form relationships.

At the present time there does not appear to be an increased incidence of any specific adult medical disorders, though long term effects of congenital malformations and sequelae of joint hypermobility can remain problematic. Weight increase may be an associated feature but has not yet been studied formally. In most cases the family doctor or general practitioner will be the person responsible for the care of adults who were exposed to VPA in utero.

It is our clinical experience that individuals with FVSD continue to develop their cognitive and social skills but that this is not at the rate seen within their peer group, and in most cases they remain poorer at certain cognitive and social skills than the general population.

6. Is there any indication of intergenerational effects of in utero exposure to valproate?

To date, there has only been a single animal study on this question. This investigation(103) reported transgenerational effects in rodents for autism type symptomatology and not for the rodent malformation of a crooked tail. Whilst the study appeared to be well designed, it is in rodents and not

humans and it has neither been replicated in the same species nor another species. There is no formal evidence of an intergenerational effect currently in humans. The authors are aware of anecdotal reports of families with children born to mothers with possible FVSD who themselves display some neurodevelopmental difficulties; however, we are, as yet, unaware of any cases where full genetic review to exclude other conditions has taken place. The importance of excluding other influences is demonstrated by Jackson et al.,(104) who found that in 2/15 cases of malformation and/or significant neurodevelopmental delays there was a genetic variant which could account, at least in part, for the child's difficulties. It should also be noted that there is currently a debate in the wider epigenetic literature as to whether the case for intergenerational transfer has been made fully, or whether results are due to consistent methodological limitations(105). Therefore, it is our opinion, currently, that the case for transgenerational transfer of VPA related difficulties has not yet been made, but that there is a need for research in this area.

7. Do you have any recommendations for the care of valproate affected individuals going forward?

It is our opinion that all children with a history of VPA exposure in the womb who are found to have either physical or neurodevelopmental difficulties should be reviewed for FVSD. The signs and symptoms of FVSD will vary across individuals and with age, and therefore it is of paramount importance that any such review should be undertaken by a health professional (Clinical Geneticist or Paediatrician) with clinical experience of FVSD. A careful family, medical and developmental history should be taken and appropriate genetic testing should be undertaken to rule out other potential influencing factors. Where there is a suggestion of neurodevelopmental difficulties a formal neuropsychological opinion should be sought, unless the delay is severe and therefore easily documented. Post- diagnosis referrals to particular specialists should be made according to individual needs and contact with charities or family associations may be beneficial.

In view of the fact that multiple organ systems are affected in FVSD the need for a multidisciplinary model of care was acknowledged and strongly supported by the aforementioned Expert Consensus Group when they met, and the authors of this document support this suggested multidisciplinary approach for the individual with FVSD. We would recommend that children exposed to VPA in utero should undergo a number of checks during childhood, timed to fit in with routine health checks and specific developmental stages. At each of these, growth, development, hearing and vision should be checked, and referrals made to specialists as appropriate. In addition to the normal baby health checks it is recommended that a Paediatrician should review the baby at 6-8 weeks of age. This provides an

opportunity to look for any malformations, which may have become apparent since birth and check that the necessary screening investigations have been arranged.

A review with a Paediatrician is recommended again at eighteen months of age, as this is a critical time, in particular for language development. Thereafter, annual health checks should be carried out by a community paediatrician until school age with monitoring of growth and enquiry about hearing and eyesight problems being undertaken at each visit. These visits provide an opportunity to check for symptoms known to occur with increased frequency in FVSD, such as joint hypermobility, hyperacusis and bladder problems. As there is an increased risk for genito-urinary malformations a one-off scan of the kidneys and urinary tract is recommended in infancy to look for undetected structural malformations. In later childhood and adolescence enquiry regarding enuresis and urinary problems should be made with referral to appropriate specialists. As with other paediatric checks, enquiries about school progress, behaviour and social interaction, should be undertaken, with referrals made to appropriate specialists (i.e. psychology or psychiatry) where necessary. Reports of academic difficulties should be considered as potential markers for the neuropsychological difficulties associated with FVSD and a referral made for a neuropsychological assessment.

The neurodevelopmental features of FVSD require specialist attention. It should be considered that children can 'grow into' the cognitive difficulties and therefore a single review in childhood of neurodevelopment is not adequate. The phrase 'grow into' is used to highlight that as children mature the complexity of information processing undertaken by the brain increases in typically developing individuals. However, in certain conditions this expansion of ability does not occur and the individual's trajectory of development for that specific skill begins to deviate from that of their peers. Thus a child viewed as typically developing at 2 years of age may later be found to have marked difficulties in their reasoning and memory skills in later childhood. A school-aged child should be reviewed to make sure that any cognitive or social problems associated with FVSD are recognised and managed appropriately during the period of the child's education to maximise educational outcome. The consensus group recommended that reviews of neurodevelopment or more specifically neuropsychological functioning should occur early in the child's primary education, in the school year prior to the move to high/secondary school, and the school year prior to taking senior public examinations.

Individuals with FVSD should be referred to a psychologist qualified to undertake a neuropsychological assessment (e.g. a clinical/neuropsychological or educational), which includes, but is not limited to, IQ, memory, language, executive and attention abilities, and to allow recommendations to the school and the family to be tailored, creating a more bespoke intervention. In many cases, such assessments will be used to inform a child or young person's Education Health and Care Plan (EHCP), which will

detail the optimum educational set up. It is our clinical experience that optimising the educational environment can have important positive influence, not just on the child's academic progress but also on their mood and behavioural presentation. Teachers should be provided with general information about the condition as well as information specific to the individual child and how FVSD has impacted upon them, and the suggested management strategies.

As well as cognitive difficulties the emergence of behavioural difficulties and social communication difficulties can become more pronounced as the child ages. Although there is a lack of clear research evidence, it is the authors' experience, that individuals with FVSD have difficulties with emotional regulation, which can sometimes lead to extreme outbursts, or 'tantrum' type, behaviours which outlast infancy. Challenges such as these should be enquired about in the paediatric checks throughout childhood, and referrals made to Child and Adolescent Mental Health Services (CAMHS) where possible for intervention. Further, in both animal and human research there is evidence that being exposed to VPA in the womb raises the risk of having social communication difficulties and ASD. Given that there are now early intervention programmes for ASD, screening and formal assessment for this is warranted so that symptoms can be detected early, appropriate help can be put in place, and a diagnosis of ASD can be factored in when planning school placements.

Transition to adult care can be particularly challenging as many services differ in their set up and coverage from their paediatric equivalents. A planned and careful approach to handover should be provided with a clear list of symptoms of FVSD and the challenges this presents for the individual and their family. Any provision for specialist educational support should continue throughout the individual's educational career. In some cases a referral to a Social Worker may be required if the adult with FVSD has a learning disability or ASD. Although no comprehensive research has been completed on adults with FVSD to date it is our clinical experience that many adults with FVSD may need a form of support in the community; too often this is met entirely by the parents. There is an overwhelming challenge to delivering the above recommendations. Given the relative rarity of FVSD and the lack of a specific diagnostic test, the diagnosis needs to be made by a Clinical Geneticist or Paediatrician with experience of the condition. However, the reality is that such expertise is very limited. Given the central nature of neurodevelopmental difficulties an experienced neuropsychological opinion will also usually be required for diagnosis but paediatric neuropsychologists are small in number and few have experience of FVSD.

There is a strong argument for the establishment of a small number of strategically located expert centres functioning as a Networked Specialised Service. As a minimum the expert team should comprise a Clinical Geneticist, Paediatrician, and Neuropsychologist. Ideally, specialist services should

also be multidisciplinary in nature, incorporating expertise from Speech and Language therapy, Physiotherapy, Occupational Therapy, and others. These specialist centres should link together to share experiences and develop standards across the network. Due to the lack of research evidence regarding individuals with FVSD specifically, and especially their prognosis in adult life, provision to conduct research to enhance our understanding of assessment and treatment of affected individuals should also be incorporated within these services.

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Appendix 1. Information on the authors.

Professor Peter D Turnpenny

Professor Turnpenny is a Consultant Clinical Geneticist, Peninsula Clinical Genetics (Devon & Cornwall), based at the Royal Devon & Exeter NHS Foundation Trust, Exeter. He is also Honorary Clinical Professor, University of Exeter Medical School. He has held this NHS post since 1993, immediately prior to which he was Senior Registrar in Clinical Genetics for three years at Aberdeen Royal Infirmary and the Department of Medical Genetics, Aberdeen University Medical School. Prior to this he had a career in paediatric medicine spanning 10 years. His clinical work may involve almost any aspect of medical genetics. He has major interests in the genetics of congenital spinal malformations, fetal anticonvulsant syndromes, hypermobility syndromes, and gene discovery in rare disease. He is the author of three books, including the 12th (2005), 13th (2007), 14th (2011) and 15th (2017) editions of 'Emery's Elements of Medical Genetics' (publ. Elsevier). The 13th edition won the BMA Student Textbook Award for 2008. He has authored or co-authored some 15 chapters and reviews, and ~130 peer-reviewed articles. He regularly reviews manuscripts submitted to international genetics journals. He was President of the Clinical Genetics Society (UK), March 2011 – March 2013. From 2012-16 he was a question-setter and examiner of the Clinical Genetics Specialty Certificate Examination and now represent UK Clinical Genetics at the European Union of Medical Specialities, and is a Board member. He Chairs the Examination Committee which is working towards delivering the first Clinical Genetics Specialty Examination in Europe in 2019.

Professor Jill Clayton-Smith is a Consultant Clinical Geneticist working within the North Western Regional Genetic Service at Manchester Centre For Genomic Medicine, St Mary's Hospital, Manchester. She is also and Honorary Professor in Medical Genetics at the University of Manchester. Having qualified in medicine in Manchester in 1982 she trained in both adult and paediatric medicine prior to embarking on a career in Clinical Genetics in 1987. She trained at the Institute of Child Health in London and in Manchester, taking up a consultant post in 1994. Special interests include rare multiple malformation and intellectual disability syndromes, neurodevelopmental disorders, genetic causes of oro-facial clefting and paediatric genetic eye disorders in addition to an interest in teratogenic effects of antiepileptic drugs which has spanned more than 20 years. She has researched widely in the field of malformations and intellectual disability syndromes with more than 200 peer-reviewed publications in this area. She was instrumental in setting up one of the first prospective studies of effects of exposure in utero to antiepileptic drugs, bringing together researchers in Liverpool and Manchester in 1999. She is an active educator in genomic medicine, acting as clinical lead for the Manchester MSc in Genomic Medicine and Faculty member of the Joint Peking University/Manchester University Genomic Course. Currently she leads the European Reference Network for Rare Congenital Malformations and Intellectual Disability, ERN ITHACA.

Professor Wood is Professor of Developmental Neuropsychology and Director of the Aston Brain Centre, Aston University, Birmingham, UK. She also holds a position as Principal Research Fellow at Murdoch Children's Research Institute, Australia. Prior to working in the UK, Professor Wood trained in Australia as a Clinical Neuropsychologist and held a part-time role in practice as a Registered Psychologist. She has experience in paediatric neuropsychology assessments as well as adult case loads. She was a full member of the Australian Psychological Society, including membership of the College of Clinical Neuropsychologists. She led the Australia-wide long-term neurodevelopmental follow up study of children born to women taking antiepileptic medications, in collaboration with the Australian Pregnancy Register for Women with Epilepsy. Her group provided independent replication

of IQ impairments in children exposed to sodium valproate, provided evidence of core language processing impairments and screened prospectively for autism traits. Professor Wood also has expertise in computational quantitative brain image analysis and she published the first magnetic resonance imaging study of valproate-exposed children. Since moving to the UK (2010) she is unable to practice clinically but she was Secretary to the British Psychological Society, Division of Neuropsychology's Professional Standards Unit (2012-2017). She served on the Scientific Advisory Committee of Epilepsy Research UK (2012-2017) and prior to moving to Aston University (2016) was Director of Birmingham University Imaging Centre. She has developed collaborations with the co-authors of this submission, including ongoing funded studies led by Dr Bromley. She contributed to MHRA stakeholder meetings, and EMA scientific sessions regarding the behavioural teratogenesis of sodium valproate.

Dr Rebecca Bromley is a Neuropsychologist working both in research and NHS practice. Her interest in this topic began in 2005 as a research assistant and she went on to complete her PhD on the neurodevelopment of children exposed to antiepileptic drugs, and in particular valproate. She has now published over 30 papers on this topic, including two Cochrane reviews. Dr Bromley is currently serving on the International League Against Epilepsy (ILAE) Women and Pregnancy Task Force and is a committee member of the UK Epilepsy and Pregnancy Register and she has contributed to All Party Parliamentary Meetings and European Medicines Agency meetings on the topic of antiepileptic drug use in pregnancy. She is the principle investigator on two studies currently, both into the outcomes of children born to pregnant women with epilepsy. In her NHS work, Dr Bromley sees a small number of patients exposed to valproate in utero each year. She is currently working alongside Prof Clayton-Smith to establish a designated multidisciplinary clinic for children with physical and developmental difficulties following exposure to antiepileptic drugs in pregnancy.

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Submission from Dr Frances Elmslie

Dr Elmslie is a consultant in genetics at St George's University Hospitals NHS Foundation Trust who specialises in paediatric genetics, the genetics of epilepsy and developmental brain malformations and also tuberous sclerosis.

COI:

None provided.

Submission

1. **Would you use the term 'Fetal Valproate Spectrum Disorder' (FVSD)? If so, how is it diagnosed? Is there any way to screen prenatally?**

   Fetal Valproate Spectrum Disorder is not a term that has been used widely in the medical literature which has usually referred to Fetal Valproate Syndrome. However, the term FVSD strikes me as a reasonable one to describe a condition that encompasses a range of different malformations in association with a risk of developmental delay with autistic features. This term would encompass the variability of the phenotype, and would include those who have little to no physical manifestations but may have cognitive impairment/autism spectrum disorder likely to be a consequence of exposure to Valproate in utero.

   There are no accepted criteria for diagnosing FVSD. However, the spectrum of malformations that can occur in FVSD are well-delineated, so this condition would be suspected in a child that was known to have been exposed to Valproate, and who exhibits some of these characteristic features. These are:

   Facial features – epicanthic folds, infraorbital grooves, flat nasal bridge, downturned mouth, thin upper lip, long smooth philtrum
   Hypospadias
   Neural tube defects
   Cleft lip +/- palate
   Cardiac defects
   Skeletal defects especially digital abnormalities

   These may be accompanied in time by evidence of neurodevelopmental delay/intellectual disability with or without autism spectrum disorder.

   None of these features is specific to exposure to Valproate and will occur in the general population, but are known to occur at increased frequency in children exposed to VPA in utero. The facial features overlap with those seen in children

exposed to other teratogens including alcohol, so obtaining a clear history of exposure is important. Furthermore, it would be important to ask about a family history of malformation or neurodevelopmental problems.

However, in the absence of accepted diagnostic criteria it is difficult to be categorical about when one can make this diagnosis. I will assume for the remainder of this paper that the presence of one malformation in this spectrum + history of exposure to VPA is sufficient to make this diagnosis. This would inevitably lead to some over-diagnosis (because of the presence of these malformations in the general population).

The only method of prenatal diagnosis is by detailed scanning. Neural tube defects are frequently detected as early as 12 weeks, but other abnormalities may not be detected until the detailed anomaly scan at around 20 weeks, and some malformations may not be evident even then (eg cleft palate).

2. **What proportion of children exposed to valproate during pregnancy are affected by this disorder?**

The malformation rate in children exposed to Valproate monotherapy documented in prospective registries is between 6.7% and 9.7% (Campbell et al 2014) ie 2.5-3.5 times that seen in the general population. The risk of autism/autism spectrum disorder appears to be around 7-9%, but there is not necessarily an overlap between these two groups. It is difficult to estimate what proportion are affected by neurodevelopmental delay and/or intellectual disability because studies tend to be biased in their ascertainment. However, a recent prospective study in a large cohort of children exposed to anticonvulsant drugs suggested a reduction in IQ of 7-10 points at age 6 years amongst those exposed to VPA compared with other anticonvulsant drugs (Meador et al, 2013), although all IQs were >90 – ie would not be classified as intellectual disability.

If the risks are independent of one another, then the maximum risk of FVSD appears to be approximately 18%, but is more likely to be in the range of 12-15%, but with a additional separate effect on cognitive development.

3. **Are there overlaps between the different features of FVSD, for example neurodevelopment and facial dysmorphia?**

I have addressed this in 2 above. This is difficult to answer definitively because propspective studies have addressed one or other aspect of the condition, rather than all features combined. The early case reports that described children with facial dysmorphia, malformations and neurodevelopmental delay were all biased in their ascertainment. However, from these reports and personal experience, there is certainly some overlap between these two groups, but it is possible to have dysmorphia and malformations without delay and probably vice versa.

4. **How does this compare with the rates of malformation of other anti-epileptic drugs?**

   Data from the registries (Campbell E et al, 2014) indicate that the rate of malformation associated with exposure to Carbamazepine is around 2.6% to 5.6%, and that associated with Lamotrigine is 2.2%-2.9% (ie within the range of the general population). Historically, both phenobarbitone and phenytoin have been linked to malformations, but neither drug is used widely now and insufficient data has been collected in the prospective registries to draw definite conclusions. Data on newer anti-epileptics is either lacking, or no increased malformation rate has been demonstrated.

5. **What is the association between epilepsy and autism?**

   There is an increased risk of autism in patients with epilepsy and vice versa. This association is stronger amongst those with intellectual disability and some of this risk is likely to be to due to genetic disorders that result in all three features – and increasing numbers of these conditions are being described with the availability of new genomic technologies. (Amiet et al 2008).

6. **What types of genetic testing are offered to families, and what do they test for?**

   There is no 'test' for FVSD – it is a clinical diagnosis. However, most geneticists would offer some form of genetic testing in order to exclude common genetic conditions. Families should be offered array-CGH (comparative genome hybridisation) testing. This test can detect subtle copy number variants (CNVs) known as deletions (missing bits) and duplications (extra bits) in the chromosomes at a significantly increased level of resolution compared with standard chromosome analysis (karyotype). However, not all CNVs necessarily cause problems and we know that around 15% of healthy individuals will carry a CNV, so the results of testing should be interpreted with caution. In addition, it is possible that the problems in the child may be caused by a combination of factors, so the detection of a pathogenic CNV does not preclude an effect of VPA exposure.

   Depending on the clinical findings, testing for fragile X syndrome and other specific genetic disorders may be offered.

7. **Is there any indication of intergenerational effects of in utero exposure to valproate?**

   Currently, there is no evidence that valproate can affect subsequent generations.

8. **What should be put in place to further support affected families?**

   Children that have been exposed to VPA who have obvious malformations should be assessed by someone with expertise in malformation syndromes, likely to be a clinical geneticist. Consideration should be given to alternative causes of the

malformations. All parents of children exposed to VPA should be warned of the possibility of developmental problems, and the health visitor and GP should be alerted to ensure early referral should problems emerge. Children should be able to access appropriate therapies and expertise, ideally locally.

A network of supra-regional clinics could be considered to ensure availability of accurate diagnosis and guidance, but this would need to be complemented by input from a local team.

9. References

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Submission from Professor David Healy

Professor of Psychiatry, Bangor University

COI: Research interests and regularly asked for views as expert.

Evaluation of Medicines & Devices: Valproate

I have been consulted by several Valproate support groups, have given expert testimony in legal cases on birth defects linked to antidepressant medication, have been consulted by the MHRA Primidos review and have spent most of the last 20 years working on issues linked to the evaluation of drugs – both their benefits and adverse effects.

In the case of valproate, I have interviewed the physician responsible for the discovery of both its epileptic and its psychotropic effects, Pierre Lambert, and published this interview in The Psychopharmacologists.

This brief paper offers a position on the more general issue of the evaluation of medicines and devices rather than on the specifics of valproate and birth defects.

The Emergence of Evaluation

An appreciation of the need to standardise the evaluation of new medicines emerged around 1762. The primary emphasis was on standardising the input of the investigator as the assessing instrument. He should be seasoned, conversant with the clinical conditions and patients being investigated, as well as streetwise, and aware that patients might resist the treatment, undermine or seek to “assist” the investigation.

There was a recognition that any assessment needed to be undertaken multiple times involving hundreds or possibly thousands of patients, under both the same and diverse conditions, and over extended periods of time. All procedures and observations needed to be well documented, so others could test claims made. Observation-based assessments that would have general validity and be reproducible were the goal.

In 1906, the American Medical Association (AMA) created a Council on Pharmacy with expert clinicians to undertake controlled trials of this type. Endorsement by AMA offered the then new pharmaceutical companies an incentive to cooperate.

The evaluation of medicines evolved further in 1935, when Gold introduced placebos and then the double-blind placebo-controlled trial, as he became aware of differences in the way patients presented to researchers and clinicians.

From 1832 through to 1962 there were debates about the role of numerical methods in clinical trials. For some the individuality of patients meant numerical methods should not trump clinical judgment. When tied to effectiveness, however, they clearly had a place.

In 1945, clinical trials of streptomycin in tuberculosis began in America. These trials, run by seasoned investigators in matched samples of patients, demonstrated that streptomycin had benefits, but tolerance developed to it, and it had hazards such as hearing loss.

In Britain, the introduction of streptomycin underpinned a proposal by Bradford Hill to test Fisher’s proposal that randomisation could offer a support for expert judgment. This trial

came to similar conclusions about streptomycin's benefit as American investigators but missed its hazards. In principle, it showed randomisation offered a further support for investigators, a reduction in the numbers of patients needed for trials and the possibility of interrogating one outcome statistically. Nothing about randomization supported doing away with seasoned investigators. It was not widely adopted.

The 1950s saw an introduction of surrogate markers such as blood sugar or blood pressure lowering, and rating scales in trials of drugs. Scales were viewed as checklists to improve the documentation of trials; they were not viewed as a replacement for a clinical interview.

Regulation

From automobiles to stock exchanges, regulation focuses on safety not efficacy. The Food and Drugs Act in 1938 centred on the Safety of Drugs. In 1962, following the thalidomide crisis, as a contribution to safety a new Act required manufacturers to demonstrate "Effectiveness". At the behest of Louis Lasagna, randomised placebo-controlled trials (RCTs), then a novel technique, whose epistemological and even statistical foundations still remain uncertain, were installed as a test of effectiveness.

Initially the trials of novel compounds were run by senior clinical investigators in teaching hospitals, who knew the patients, were alert to drug effects other than the headline effect and held the trial data in their files.

By 1972, a divide had opened up between medical and industrial trials, exemplified by an NIMH study of oral hypoglycaemics reporting in 1970 in which tolbutamide, despite lowering glucose, was linked to more deaths than comparators. This trial, which with its lengthy follow-up period took over 5 years to run, distinguished between surrogate efficacy and clinical effectiveness. Trials like this are important for medical practice but are not a realistic gateway to the market.

Industrial trials in contrast ran for 4 to 6 weeks, too brief to test effectiveness or pick up most of a treatment's effects. A turn to rating scales and designated surrogates underpinned a progressive replacement of seasoned clinicians by junior personnel. A turn to multi-centred trials, dictated largely by marketing considerations, led to a storing of trial data centrally with medical writers representing the trial outcomes. As a result, "investigators" reporting study outcomes at academic meetings from the 1980s might have never observed a single patient.

As industry trials became mechanical exercises, a mantra that RCTs provided gold standard medical evidence took hold, even though RCTs are only designed to provide good evidence on one designated outcome. They can contribute to safety, if, in failing to find effectiveness, they prevent drugs from entering the market, but in practice the creation of the idea of a failed trial has obviated that possibility. Tying findings of efficacy to claims the only valid information on medicines comes from RCTs makes RCTs a gold standard way to hide adverse events.

Pharmacovigilance

As regulators put RCTs in place to contribute to the safety of medicines, they also set up Adverse Event Reporting Systems (AERS) – Medwatch in America and Yellow Cards in Britain. Clinical knowledge of drug effects remained largely derived from clinical experience, reported in journals, these systems had a poor pick-up.

In 1965, Bradford Hill elaborating on Koch's postulates for determining clinical causality, emphasizing factors such as challenge-dechallenge and rechallenge (CDR), made clear his view that if RCTs were ever seen as the only way to evaluate a drug, the pendulum swinging

from idiosyncratic to controlled clinical observations “would not only have swung too far it would have come off its hook”.

Nevertheless, the rise of mechanical observing and sequestration of trial data slowly relegated clinical evaluations that drug X causes problem Y, even when buttressed by evidence of CDR, to the status of anecdotes. Journals no longer took these observations. AERS reports meanwhile did not incorporate causality algorithms and were anonymous which gives them hearsay status in legal and other settings.

Harms vanished. Where in 1960, it took two to three years for unanticipated side effects of a drug to be established, it now takes two to three decades. Linked to this disappearance, and a selling of efficacy, supported by a de facto regulatory willingness to avoid deterring patients from treatment benefits by placing warnings on drugs, the numbers of patients on treatments began rising with 50% of the population between 45 and 64 now on 3 or more medicines and 45% of over 65s on 5 or more. Recent reports of a stalled improvements in life expectancy may indicate that we have reached a point where effectiveness and safety need to be rethought.

Regulators have since extended AERS systems to take reports from non-medical clinicians and the public. Even anonymous reports can offer important information through the use of proportional reporting ratios and related metrics. These systems can be enhanced by incorporation of cause and effect algorithms and.by encouragement to clinicians and patients to submit named reports, ideally from both patient and clinician. Credible reports from named sources with input from more than one reporter on an event cannot be dismissed.

Since the first AERS systems, we have developed capabilities to register multiple effects of a newly started medicine. Registries like this could be adopted for all drugs given in pregnancy and all vaccines. Dermatologists and other specialists increasingly use registries to monitor the effects of new high cost treatments and these practices can be built on.

We can also now mine electronic medical records (EMR) for new events and new methods to control for confounders are being developed.

Current rates of polypharmacy have triggered a clinical turn to judicious deprescribing. In addition to detecting a treatment’s effects on first exposure, deprescribing opens dechallenge opportunities to explore these effects. Beyond the deprescribing doctors can initiate, we need data systems that allow patients on multiple medicines to explore whether the falls, fatigue, memory issues, weight gain, depressive symptoms or other problems they have, that are among the most common presentations to medical services, might stem from the fact that several of their medicines are linked to their problem.

In scrutinising registry or EMR data, a key question is where objectivity comes from. Science traditionally generates data and challenges believers and non-believers to interpret them. New techniques can throw up new observations, but while new data can challenge prior judgments, the mission of science has not been to replace judgment by technique. In the case of a pregnancy registry, provided there is a full dataset to which everyone has access, objectivity would arise from the combined scrutiny of women of child-bearing years, doctors, pharmacologists, pharmaceutical company personnel and others, rather than from signal detection methods operating on data “detached” from all human traces.

Restoring confidence in clinical and patient judgments about drug effects is critical to rehabilitating safety. It is appropriate to use RCTs to raise the bar to those who would make money from one effect of a drug given to people at their most vulnerable. Seasoned

clinicians, allied to increasingly health-literate patients, are much better placed to determine cause in the case of the 99 other effects every drug has than RCTs are. These effects, often discounted as rare, may be more common than the headline effect of a drug and still be missed in RCTs.

In 1983, Lasagna, like Hill in 1965, more aware of the drawbacks of RCTs than in 1962, faced with claims "that spontaneous reporting is usually viewed as the least sophisticated and scientifically rigorous method of detecting new adverse drug reactions", replied: "This may be true in the Webster's dictionary sense of sophisticated meaning "adulterated" but I submit spontaneous reporting is more wordly wise, knowing, subtle and intellectually appealing than expensive Phase IV schemes (RCTs)".

The evaluation of both the effectiveness and safety of drugs has been compromised since 1962 by the irruption of regulation into evaluation, and subsequently by company a sequestration of clinical trial and other data. While new signal detection methods and investigative approaches are always welcome, the problems cannot be solved without collaboration.

Submission from Kim Morley

Epilepsy Specialist Nurse and Midwife.

COI: None declared.

Introduction:

I set up a unique, unfunded specialist epilepsy preconception and pregnancy service 18 years ago with the aim of trying to prevent any woman embarking on pregnancy taking an antiepileptic drug if they were incorrectly diagnosed with epilepsy or uninformed about the potential risk of fetal anticonvulsant syndrome. My intention was to save at least one child being harmed and I believe I have now saved thousands of birth defects through my work and on-going dedication and to helping these women.

I have been committed in raising professional and public awareness about the potential teratogenic effects of drugs like sodium valproate. This has involved lecturing nationally to GPs, neurologists, psychiatrists, midwives, obstetricians, practice nurses, epilepsy specialist nurses and patient groups. I have provided support to Epilepsy Action for a decade and been responsible for writing many of the pregnancy leaflets over the years. I have also promoted the work of the UK Epilepsy and Pregnancy Register and fetal anticonvulsant groups far and wide. I have written countless articles and written a RCM i-module to inform midwives. I represent the RCM at the valproate stakeholders meetings.

The service I provide is accessible to all women with epilepsy and professionals and until 2007 it was totally unfunded. I have supported many women who have come forward for this review in order their voices will be heard and I represented them and the experience I have gained from sharing their journeys at the EMA meeting in 2017 (attached).

During this journey linking with other healthcare professionals has been challenging. I had no idea before I started this service how women's journeys depended on who they met on the way and who diagnosed and treated their epilepsy. Many women had not received preconception counselling before previous pregnancies. Many women I have met have never been told their babies slow development was as a result of the valproate exposure in pregnancy and this only came to light when I discussed the potential impact of these drugs when they have been referred to me.

The issues I would like the review to consider are:

1. Why did many medical professionals conceal the truth from so many women when it seems they were notified about the effect of valproate in the 70's.
2. When a human being has suffered harm as a result of an iatrogenic injury or teratogen, why do the medical profession deny those harmed a diagnosis and therefore, proactive treatment?
3. What can the review body do to change this allegiance within the medical profession?

Suggestions

- All babies, children and adults exposed and harmed by this drug should receive expert genetic and physical assessment to confirm diagnosis. Babies and children should receive support from portage, physiotherapy, occupational therapy and statement for schools assessment and other services as required.
- Valproate syndrome should be a diagnosis in itself. These children do not respond to treatment in the same way as children with conditions like autism, aspergers syndrome and attention deficit disorder and therefore the extent of their disability can be under-estimated and under treated.
- These children and families should be entitled to tailored support emotionally, financially and physically.
- Women who have been counselled, signed the annual risk assessment and still made the very difficult, emotive decision to have babies despite the knowledge of the harm valproate can do (because their life could be at stake if they were to stop valproate), should not be penalised for this decision making or stigmatised by health professionals.
- Women who continually do not attend for specialist review for diagnosis and treatment reassessment who are taking valproate and refuse to use contraception, should be counselled fully by their GP who is prescribing the valproate and if necessary, be directed by the specialist either on the phone or by video call to do a full reassessment of their diagnosis and treatment.

EMA Presentation (2017)

Question 1 What is your view of the risks of taking valproate during pregnancy, including its potential effect on the child?

Q1: As a practitioner specializing in the management of anti-epileptic drugs (AEDs), I have mixed views about the risks of valproate due to the potential devastating harm caused by pregnancy exposure versus lives destructed and sometimes lost because of women not taking their AEDs or other AEDs not controlling their seizures.

I set up a unique specialist service 17 years ago to be a voice for women with epilepsy and to raise professional and public awareness about the potential teratogenic risks of drugs like sodium valproate. By effectively linking with other healthcare professionals, I have ensured women are correctly diagnosed with epilepsy and taking an antiepileptic drug regime that carries the least risk of harming their baby whilst protecting them from uncontrolled seizures. For the majority of women this holistic approach starts long before pregnancy is considered. Women are fully informed of potential risks from the available research evidence and empowered with their decision making in preparation of motherhood. Evidence demonstrates that women receiving this type of support are more likely to have healthy pregnancies and less likely to have adverse outcomes. It upsets me greatly when women become pregnant never having received this type of care; with modern communication this is unacceptable. Furthermore, if disclosure about risk is not handled by a knowledgeable practitioner, the consequences can be profound. This is because women instinctively put their baby's well-being before their own and this can lead to a sudden discontinuance of AEDs;

very sadly, as identified in the maternal mortality reports, this can result in some pregnant women never getting to see their babies because they have died as a result of a convulsive seizure.

I have witnessed the profound effects of valproate syndrome on childhood development and behaviour and the challenges women face trying to obtain a diagnosis. This can deny children of appropriate proactive specialist support and impact further on their potential development. One woman was referred to me from another NHS Trust to gain support for her child who had severe fetal valproate syndrome. She said even though my ambition was to prevent this syndrome, she would never have tried an alternative AED or a lower dose of valproate; the risks to her were too great, but she did want to be a mum. She was so grateful that I had been the first person to offer her support; no-one would acknowledge that valproate caused her child harm. I have developed deep understanding of why some women choose to stay on valproate. As well as having to refrain from driving and the subsequent impact on quality of life, changing antiepileptic drugs can result in complete loss of seizure control, serious adverse effects, and very sadly in some cases, an increased risk of death. Motherhood itself raises a further dilemma for women if they are taking a drug like valproate because the consequence of a change of drug at this stage and a loss of seizure control could compromise their ability to parent safely.

Seeing children with valproate abnormalities including metopic craniosynostosis where the skull bones fuse prematurely, is extremely worrying. This condition in milder forms can go undetected but still impact seriously on neuro-development. How can we possibly know the extent of the adverse effects caused by valproate unless every child exposed to this drug in utero receives expert assessment and childhood follow-up?

Question 2 What are your views on the measures currently in place to reduce the risks of using valproate during pregnancy?

As one consequence of the measures in place there are now some young women with generalised epilepsy coming through transition whose lives have been destructed by the cocktail of other AEDs they have been prescribed without achieving seizure control. Invariably valproate has never been mentioned as an alternative because of the potential risks in pregnancy, yet it may be the only drug that will provide seizure control. One case a young girl was being home schooled as she was having clusters of uncontrolled convulsive seizures, problems with word finding and angry outbursts; her cognitive skills were reduced and she was at increased risk of sudden unexpected death in epilepsy. Following our joint specialist support, her four AEDs were gradually withdrawn and substituted for a low dose of valproate. An effective contraceptive device is in place; this young woman returned to school then college and is at university, seizure free. She has a boyfriend and is fully informed of possible adverse effects of valproate and the consequences of exposure in future pregnancy. She wants to achieve her goals before considering any changes and we will continue to support her on that journey to motherhood.

The measures in place will continue to fall short because of the lack of expertise in supporting women with epilepsy with prescribing decisions. AEDs are the most complex drugs to prescribe in the formulary; incorrect management can result in morbidity and mortality. Epilepsy services in the UK are fragmented due to lack of neurologists specialising in epilepsy, shortage of epilepsy specialist nurses, paucity of GP's with a specialist interest in epilepsy & lack of knowledge about epilepsy & the management of AEDs in maternity services. For the purpose of reducing this disparity, I provide expert advice to professional and charitable groups and have developed my own website

www.womenwithepilepsy.co.uk which showcases resources and information as a strategy to increase knowledge about risk assessment and reduction.

Question 3 What other measures should be taken to reduce the risks of using valproate during pregnancy?

The voices of thousands of women and families, represented by the speakers today are proof that more needs to be done to reduce the risks of valproate during pregnancy. It is imperative that women taking AEDs for any condition should receive a continuum of expert support to inform their decision making. As there is a shortage of professionals specialising in the management of AEDs, an expert European panel should be formed to guide professionals how to manage AEDs in women of child-bearing potential. I would be happy to be part of that panel.

Pharmacists have expert pharmaceutical knowledge and are in an optimal position to help increase knowledge about valproate risks. Providing additional training and funding for this group of professionals would be optimal in order they are all experts in AED medicines management and pharmacovigilance. Each time a woman of child-bearing potential collects her prescription there should be an additional check as to whether she has received the patient valproate guide and had the opportunity of a medication review. Pharmacists should be encouraged to refer all women of child-bearing potential taking valproate for preconception specialist support and provide information resources in an appropriate format about contraception, folic acid, risk assessment and medicines management.

Submission from Jonathan Sher

Independent Consultant and Visiting Expert at Edinburgh University's Scottish Collaboration for Public Health Research and Policy (SCPHRP)

COI:

No conflicts of interest declared.

Comments:

Clearly, major progress has been made during the past year in terms of the European and UK regulations, guidance and broader awareness-raising about the risks of valproate. The remaining challenge is to monitor and report on the actual implementation (including enforcement) of the regulations/guidance, as well as the perceptions/experiences of women of childbearing potential on what has changed in relation to information and behaviour about valproate. For example, all women of childbearing potential are now 'required' to sign up for, and adhere to, a Pregnancy Prevention Plan (PPP) in order to keep receiving valproate . . . but are they really doing so (and what happens if they are not)?

Attached papers:

Sher (2018) Taking valproate during pregnancy is a serious risk: An update on practice implications. International Journal of Birth and Parent Education. 5(3): 11-14

Sher, Frank, Doi, de Caestecker (2018) Perspectives Failures in reproductive health policy: overcoming the consequences and causes of inaction. Journal of Public Health, fdy131