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ANALYSIS

Weighing the risks of valproate in women who could become pregnant

Despite international consensus on the harmful effects of valproate during pregnancy, women should not be denied the human right to make their own decisions after fully informed discussion, say **Heather Angus-Leppan** and **Rebecca Liu**

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An estimated one million people take valproate worldwide each day.[1] Valproate is a γ-aminobutyric acid (GABA) agonist licensed for use in epilepsy, bipolar disorder, and, in some countries, migraine. In the United States in 2012, about 1.5 million outpatients received valproate, and roughly 22% (341 000) of these were women of reproductive potential (13-45 years); 67% of the total took the drug for mood and psychiatric disorders, 9% for migraine, and 9% for epilepsy.[2]

The international consensus is that valproate is a serious teratogen, but there is no agreement on the appropriate regulation of valproate in people who may become pregnant. Some advocate a ban on valproate in pregnancy and in women and girls, while others support restricted availability of valproate in certain circumstances, including during pregnancy. We summarise these positions, the implicit assumptions for each, and the implications for patients and healthcare professionals in the light of European and United Kingdom regulatory announcements made in March 2018 (box 1).[3 4]

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Box 1: Regulatory authority statements about valproate use in women of childbearing age

European Medicines Agency's Pharmacovigilance Risk Assessment Committee 2018[3]

- Migraine or bipolar disorder
  Valproate must not be used in pregnancy

  In female patients from the time they become able to have children—valproate must not be used unless pregnancy prevention programme conditions are met
- For epilepsy
  Valproate must not be used in pregnancy. However, it is recognised that for some women with epilepsy it may not be possible to stop valproate and they may have to continue treatment (with appropriate specialist care) in pregnancy

  In female patients from the time they become able to have children—valproate must not be used unless the conditions of the new pregnancy prevention programme are met. This involves pregnancy tests before starting and during treatment as needed, counselling patients about the risks of valproate treatment, effective contraception throughout treatment, reviews of treatment by a specialist at least annually, and completing a new risk acknowledgement form at each review

UK Medicines and Healthcare Products Regulatory Agency 2018[4]

- Valproate should only be used in women and girls of childbearing potential if nothing else works
- This group must follow the pregnancy prevention programme

French National Agency for the Safety of Medicines and Health Products 2017[5]

- Valproate banned for women and girls of childbearing age with bipolar disorder without effective contraception
- For epilepsy—avoid in girls, adolescents, women of childbearing age, and pregnant women, except in cases of treatment failure

US Food and Drug Administration 2016[2]

- Epilepsy and bipolar disorder: category D—potential benefit for pregnant women may be acceptable despite the potential risks, should be given to pregnant women and those of childbearing potential only if other medications have not controlled the symptoms or are otherwise unacceptable
- Migraine: category X, indicating the risk to pregnant women clearly outweighs any possible benefit

Joint Task Force of International League Against Epilepsy, Commission on European Affairs, and European Academy of Neurology (adopted China and elsewhere) 2016[6]

- Where possible valproate should be avoided in women of childbearing potential
- Need to balance teratogenic risks of valproate and treatment alternatives, the importance of seizure control, and of risks to patient and fetus from seizures, and the effectiveness of valproate and treatment alternatives for the different epilepsies
- Shared decision between clinician and patient and, where appropriate, the patient's representatives.

New Zealand Medicines and Medical Devices Safety Authority 2014[7]

- Valproate is contraindicated in pregnancy
- Valproate should not be used in women with childbearing potential unless other treatments are ineffective or not tolerated

Studying the risks

A pooled analysis reported major congenital malformations in 6.1% (range 4-10%) of children whose mothers took antiepileptic drugs during pregnancy, compared with 2.8% in children of untreated women with epilepsy and 2.2% in the general population.[8] No randomised controlled trials have been done of valproate use in pregnancy; nor will there be any. Observational data have come from population based cohort studies, pregnancy registers, and case-control studies in volunteers, mostly in people with epilepsy. Cochrane reviews conclude that the observational data are robust and that the methodological issues[9] do not affect final conclusions regarding the risks of valproate.

International registries[10-13] report rates of major malformations (an abnormality of an essential anatomical structure that substantially interferes with function or requires major intervention)[14] ranging from 6.7% (UK and Ireland Epilepsy and pregnancy registers which includes a third of relevant pregnancies)[10] to 13.8% (Australian Pregnancy Registry, which includes 1 in 12 relevant pregnancies).[13] There are few prospective reports for indications other than epilepsy. The Australian registry captured nine children of women who were taking valproate for non-epilepsy indications, one of whom had a malformation (cleft palate).[15]

Although some major malformations (polydactyly, cleft palate, hypospadias, cardiac defects) are treatable, many children are left with serious permanent disability and some require lifelong full time care.

Valproate is also associated with developmental disorders and an increased risk of autism (2.5% versus 0.5% in general population)[16] and attention-deficit/hyperactivity disorder.[17] The mean IQ of 6 year olds with maternal valproate exposure (49/62 children from 25 centres in the UK and US) was in the normal range at 97 (95% confidence interval 94 to 101), with mean maternal IQ of 96 (92 to 100), but lower than for those with lamotrigine exposure (108, 105 to 110).[18]

Arguments to ban valproate use in pregnancy

Momentum is growing from patient support groups, healthcare professionals, and the media to reduce the numbers of women taking valproate. Responses from expert advisory groups and regulators have varied, from those advocating shared decision making and informed patient choice about taking valproate in pregnancy,[6 19-21] to restricted use when other treatments have failed,[17] to prohibition of valproate in pregnancy coupled with a pregnancy prevention programme in all women taking it[5 22] (box 1).

The main assumption behind prohibition is that the risks of valproate are so great for unborn children that informed consent for this drug in pregnant women is over-ridden (box 2).[5 22] A complete ban on use in pregnancy implies a pregnancy prevention programme is enforced in any woman of childbearing age who wishes to take valproate. This includes negative pregnancy test results before starting treatment and regular review (box 1). Similar programmes have been introduced for women taking other teratogenic drugs such as oral retinoids.

Box 2: Consensus and assumptions on valproate use in people who could become pregnant

Consensus

- Valproate has significant teratogenicity
- Valproate teratogenicity is dose dependent so women of childbearing potential should take the lowest effective dose*
- Women of childbearing potential taking valproate are often advised to take folic acid 5 mg daily, but the evidence that folic acid reduces teratogenesis is equivocal
- There are effective alternative treatments for migraine during pregnancy
- The teratogenicity of some alternatives to valproate are unknown
- All women of childbearing potential taking valproate need expert advice, information about its risks, and regular review
- Women of childbearing potential taking valproate should not stop taking it suddenly but seek specialist medical advice

Assumptions by those supporting prohibition of valproate

- Valproate is a major teratogen and this consideration over-rides all others
- Polytherapy with other drugs is less harmful than valproate
- There are efficacious alternatives to valproate and these are lower risk
- Girls should not take valproate even before pregnancy is a possibility because of the risk that they will continue it into child bearing years
- Women who wished to become pregnant would not take valproate if they knew the risks
- Women taking valproate should not be permitted to become pregnant
- Women would rather have no child than a disabled child

Assumptions made by those supporting informed choice

- Some patients will place personal safety considerations over concerns about teratogenicity
- Some patients would prefer to continue valproate during pregnancy
- Individuals have the right to choose valproate treatment after informed discussion
- Alternative treatments to valproate are not risk free
- Assessment of the risk-benefit analysis for valproate is an individual judgment
- In some situations low dose valproate† plus folate 5 mg daily may be lower risk than high dose polytherapy

*Some bodies recommend slow release formulation but these are unproved.

†Low dose valproate is variably defined as 500-600 mg/day, 800 mg/day, or 1000 mg/day.

Alternatives are available

Those supporting a ban point to alternatives with lower risk of teratogenesis (table 1), though the availability of effective alternatives depends on the indication.

For most people with focal epilepsy, alternatives such as levetiracetam, lamotrigine, and carbamazepine are more effective than valproate.[12 35] Fewer alternatives exist for idiopathic epilepsies, as well as some rare but severe childhood epilepsies. Trials are under way to evaluate new treatments.[36] However, few data are available on teratogenesis in newer anti-epileptic drugs such as lacosamide, zonisamide or perampanel.

For bipolar disorders, lithium has similar efficacy as a mood stabiliser to valproate.[24] Avoiding valproate in pregnant women with bipolar disease is "zero risk" according to the director of the French National Agency for the Safety of Medicines (ANSM), Dominique Martin,[37] who claims that not all women with bipolar disease will require treatment during pregnancy.

In migraine, valproate is now rarely considered in women of childbearing potential, given effective lower risk alternatives.[31]

Inadequate recognition, support, and compensation

Given that there have been reports of valproate teratogenicity in animals since the 1970s and in humans since the 1980s,[38] advocacy groups suggest that government, industry, and medical responses are too slow. Some suggest that banning valproate is the only way to avoid future problems, including contentions about causality that can result in lengthy legal proceedings. Parents of children with fetal valproate syndrome express grief and anger at delays in recognition of the problem, delays in diagnosis, and inadequate support for those with lifelong disabilities.[39] The French government agency Inspection Générale des Affaires Sociales (IGAS)[40] estimates that 450/14 322 of exposed children born between 2006 and 2014 were affected by valproate in France,[41] but a joint paper by ANSM and the national health insurance administration estimated many more (2150 to 4100) children were affected between 2007 and 2014.[5]

Who should be held responsible for this harm is disputed. Legal action on behalf of people with fetal valproate syndrome in France is under way, and is expected to cost €424m (£370m; $520m). The French government argues that Sanofi, which produces valproate, is responsible for compensation.[37] In the UK mass action against Sanofi Adventis on behalf of 100 children collapsed because legal advisers did not think the case had a reasonable prospect of success.[42] A similar class action brought against an affiliate company in the United States was settled out of court.[42] Protracted court cases about compensation and support for those affected can exacerbate the distress for families.[39] Because of concerns about perceived delays in action on valproate and other treatments, the UK government has appointed an independent committee to review procedures in consultation with patient groups.[43]

No woman would take the risk if fully informed

A valproate ban assumes that any fully informed woman would avoid valproate if pregnancy was a possibility. The argument is that providing people with epilepsy about the full risks of valproate is not a realistic policy since it is difficult to contact everyone, thus a ban is the safest option. Some patient advocacy groups argue that only a ban, coupled with explicit written and pictogram warnings on packaging,[41] will prevent future problems.

Many women with epilepsy are unaware of the risks of valproate in pregnancy according to surveys: 28% of 2000 women taking valproate surveyed in the UK,[44] 41% of 192 in a German survey,[45] and 59% of 200 in Croatia.[46] Despite regulatory warnings, toolkits, and public debate, patient groups estimate that 1500 children in the UK have been affected by valproate since 2014, and 400 children since the 2016 Medicine and Healthcare Products Regulatory Agency campaign to increase public awareness.[22]

Arguments for restricted use

The main assumption behind allowing restricted use of valproate is that informed choice after a risk-benefit analysis applies to valproate as it does to other treatments. Several arguments support using valproate in specific circumstances.

Alternative drugs are sometimes less effective

Valproate has the most evidence for efficacy for idiopathic epilepsies (genetic generalised epilepsies), which comprise 25% of all epilepsies and are twice as common in women than men.

It may be the only effective treatment in certain patients, sometimes justifying first line use.[6] Case reports of seizure related complications in young women who are subsequently seizure-free on valproate are an important signal.[47] We do not know how many women with active epilepsy would become seizure-free with valproate. A nested population study suggests an increased risk of sudden unexpected death in women with epilepsy taking lamotrigine, a commonly used alternative.[48] Withdrawal from valproate or change to another drug in the first trimester of pregnancy doubled the risk of tonic-clonic seizures in one observational register study, showing that valproate is more effective than other drugs in controlling seizures in some pregnancies.[49] Valproate is also the treatment of choice for some rare life threatening childhood epilepsy syndromes.[22]

The number of drugs used for bipolar disorders, with variable evidence bases, shows the complexity of the condition (table 1).[50] The relapse rate for bipolar disease is 30% over one year even with treatment, polytherapy may be needed, and treatment must be individualised and modified over time.[27] Valproate use has increased,[27] although its efficacy is similar to lithium as maintenance therapy.[51] An estimated 80% of patients with bipolar disorders require treatment during pregnancy, and relapse risk in untreated women was twice that of treated women in pregnancy.[52] Untreated bipolar disease is an independent risk factor for pregnancy complications, malformations, and developmental problems in offspring.[53] Postpartum psychosis is a medical emergency, posing a risk to mother and baby, and is more common in untreated women.[54]

Negative effects of poorly controlled epilepsy

Avoidance of valproate in girls with idiopathic generalised (genetic generalised) epilepsies even before they reach childbearing potential[5 17 22] may result in poor seizure control. Frequent seizures during important periods of intellectual and social development may adversely affect cognition[55] and behaviour.[55 56]

Patient safety and maternal outcomes

One in 200 pregnant women have epilepsy. Maternal mortality is almost 10 times greater for women with epilepsy than for those without epilepsy (100 versus 11/100 000 pregnancies).[57] Maternal mortality has fallen, but epilepsy related deaths increased over the past 30 years.[58] Valproate had been stopped before pregnancy in two of the nine cases of sudden unexpected death in epilepsy reported in the UK during 2013-15.[59]

Untreated bipolar disease is associated with increased maternal complications. There are no specific data on the effect of valproate on maternal safety in bipolar disorders. A population study reports increased vascular complications associated with peripartum migraine (an atypical population with migraine recorded in only 0.19% of pregnant women).[60] There are no data on whether this association is causal or whether treatment of migraine modifies this risk in pregnancy.

Informed consent

The World Health Organization,[61] General Medical Council,[62] and Montgomery judgment in UK courts[63] stress patients' rights to informed choice based on full disclosure of relevant risks and benefits. For epilepsy, the potential for increased seizures and even death (mostly sudden unexpected death: risk 0.1-9.3/1000 person years)[64] is material information by any standards.[63] Banning valproate imposes less effective treatment for some female patients than for other people with a similar life threatening or serious condition, without their consent. Patients' decisions are individual and may change as their lives change. Some people never want children or are unable to have them. Seizure freedom and safety considerations outweigh other factors for some, but they may still wish to conceive. Mandating contraception for all women taking valproate could be considered an infringement of patient autonomy and liberty.

Women with serious autosomal dominant hereditary diseases and a 50% chance of having a child with their condition are given a range of options, including getting pregnant, prenatal diagnosis where available, termination if the fetus is affected, or electing to have a child without intervention. Van McCrary discusses an ethical model facilitating patients to assess their personal risks and benefits, and warns about unintended prescriptive guidance, including multiple trials of unsuccessful medication and potential medicolegal consequences arising if a woman is injured or dies because of avoiding valproate without adequate information.[65]

Will research change the situation?

Further research into alternatives to valproate may help guide treatment in the future. A major problem with treatment of idiopathic generalised epilepsies, including juvenile myoclonic epilepsy, is the lack of robust comparisons of efficacy of valproate and alternatives. The results of the SANAD II trial comparing levetiracetam, zonisamide, and valproate in idiopathic epilepsies are awaited. Like SANAD I, which compared lamotrigine, topiramate, and valproate, it is randomised but unblinded and subject to this methodological limitation.

Small scale studies are ongoing into the effect of antiepileptic drugs on seizure frequency during pregnancy and caesarean rates,[66] the effect of drug monitoring during pregnancy on seizure control and maternal outcome, and the neurodevelopment of babies born to women with epilepsy (table 2).[68] Pharmacogenomics studies may also help delineate individual susceptibility to teratogenesis and neurodevelopmental abnormalities induced by valproate and its alternatives. In many countries, including the UK, there are no current or planned population studies to monitor how the regulation changes affect morbidity and mortality of women with epilepsy or bipolar disorders and their children. This is particularly important for idiopathic epilepsy, where alternative treatments are sometimes much less effective; and is despite a 70% increase in epilepsy related deaths in the UK from 2001 to 2014.[69]

What should we do?

The MHRA and other regulatory bodies provide patients with a summary of the risks of valproate and epilepsy organisations have useful information (box 3). Generic handouts are not enough, and a Czech survey suggests most patients prefer a consultation with a healthcare professional.[46] The International League Against Epilepsy provides structured reflections for clinicians on relevant scenarios faced by patients with epilepsy,[70] and others discuss situations when women may choose to take valproate.[71 72]

Box 3: Additional resources

- Medicines and Healthcare Products Regulatory Agency (MHRA): www.gov.uk/guidance/valproate-use-by-women-and-girls
- Epilepsy Foundation: www.epilepsy.com/living-epilepsy/women/epilepsy-and-pregnancy
- International League against Epilepsy: www.ilae.org/patient-care/epilepsy-and-pregnancy
- Epilepsy Action—Having a baby: www.epilepsy.org.uk/info/women/having-baby
- Epilepsy Society—Pregnancy and parenting: www.epilepsysociety.org.uk/pregnancy-and-parenting#.VRhSifnF-uI

The unknown number of women taking long term valproate who are not under specialist follow-up are at particular risk. Publicity that generates fear and anxiety without guidance may result in women stopping their treatment without support.[72] Resources to identify patients through their primary care physicians and dispensing pharmacists are essential. Monitoring of the effects of changing legislation and changing prescribing on both affected patients and their children is critical and will require considerable additional resources.

The decision making surrounding valproate will remain complex and requires thoughtful individualised discussions with patients. Such discussions should include specialists with appropriate knowledge and experience of the relevant conditions in order to help patients make truly informed decisions. Regulatory guidance should reflect the full range of risks and benefits of valproate and be based on both ethical and practical considerations for the individual, not just the population.

Key messages

Valproate in pregnancy carries a significant risk of fetal and developmental problems

Valproate may be the only effective medication for some people with potentially life threatening conditions, particularly some epilepsies

Women need specialist information about the risks and benefits of valproate and its alternatives to make informed decisions

Population based monitoring of the effects of valproate regulations in women and their offspring is essential but currently lacking

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Tables

Table 1| Evidence on valproate and alternatives

	Migraine prophylaxis	Bipolar disorder	(Idiopathic generalised) epilepsy
Evidence of effectiveness			
Valproate	Effective compared with placebo (level 1)[23]	No better than placebo and lithium in reducing the time to any mood episode Similar time to recurrence and similar reduction in relapses compared to lithium (level 1 and 2).[42] Treatment is often complex and non-homogeneous, especially for depressive symptoms [24]	More effective than lamotrigine and topiramate for the outcome "time to treatment failure"[7] Levetiracetam has the same time to treatment withdrawal and a shorter time to first seizure compared with valproate (level 2)[25]
Other treatments	Propranolol, flunarazine, topiramate are each effective compared with placebo (level 1)[22 23] Propranolol is equivalent to valproate (level 2)[23] Flunarazine is equivalent to valproate (level 2)[23] Topiramate is superior to valproate (level 2)[23]	Lithium is effective at reducing suicide risk (level 1)[2 26] Antipsychotics may be effective when used acutely for mania/psychotic symptoms (level 2 and 3)[24] Evidence for antidepressants is inconclusive (level 3) [24 27]	Lamotrigine is less effective at controlling seizures in pregnancy in women who were switched from valproate during the first trimester of pregnancy [9] Further evidence on levetiracetam awaited[6]
Risks to offspring			
Valproate	Few specific data for migraine	Few specific data for bipolar disorder	Associated with major congenital malformations: 6.7-13.8% (level 1-3)[10-13] Associated with neurodevelopmental effects: lower IQ (level 3), autism 3% (compared with 1% in offspring of people with epilepsy, level 1 and 2), and ADHD[16]
Teratogenicity of other treatments (% = frequency of major congenital malformations)	Uncertain for flunarizine Topiramate 2.4-6.8% (level 2,3)- Aspirin 75 mg—safe until 36 weeks,[31] amitriptyline 10-25 mg daily—-no recorded teratogenicity (level 3)[32]	Lithium 5.7%-12% (level 2 and 3)[28 29]; lamotrigine 3.9% (level 2/3)[28] controls 3.3%-level 2/3[28]; antidepressants, variable[27 30]	Lamotrigine 1.9-4.6% (level 2); carbamazepine 2.6-5.6%; levetiracetam 0.7-2.4% (level 2.3); topiramate 2.4-6.8%, (level 2, 3); newer agents: insufficient data[10-13]
Perinatal complications			
Valproate	Few specific data (see epilepsy) Minimal breast milk excretion (level 2)[30]	No specific data (see epilepsy)	Jitteriness, coagulation problems (level 2)[5]
Other treatments	Propranolol stop over 3 days before delivery to avoid perinatal hypoglycaemia and monitor for infant hypoglycaemia in first day (level 2)[32] Minimal breast milk excretion for propranolol and amitriptyline (level 2)[17]	Lithium associated with perinatal complications—rate uncertain (level 3)[30] Breast feeding is traditionally contraindicated for lithium but levels vary (0-30%), (level 3)[34]	Anti-epileptic drugs are associated with reduced birth weight, especially polytherapy (level 1-3)[12] Levetiracetam and phenobarbital are excreted into breast milk (level 2-3)[33]

Table 2| Ongoing trials investigating maternal and neurodevelopmental outcomes after anti-epileptic drug exposure during pregnancy

Title; setting; trial registration or ID; funder	Population	Comparator(s)	Assessments	Primary outcome	Comments
NaME: Neuro-development of Babies Born to Mothers with Epilepsy: an observational cohort study; UK multicentre (IRAS ID 143279); NIHR	Children born to women with epilepsy who took anti-epileptics in the first or second trimester	Children born to women with epilepsy who did not take anti-epileptics during pregnancy	Ages and Stages Questionnaire, Vineland Adaptive Behaviour Scale at 12 and 24 months; developmental assessment at 24 months.	Reliability of parental questionnaires in assessing child development: behaviour and cognitive skills at 12 and 24 months	Evaluation of potentially cost effective way of assessing effect of anti-epileptics on child development across large populations
MONEAD: Maternal and Neuro-developmental Outcomes in Utero Antiepileptic Drug Exposure; US multicentre; ISRCTN98260309; NIHR	Females aged 14-45, pregnant women with epilepsy	Pregnant women without epilepsy, non-pregnant women with epilepsy	Electronic seizure diaries, child verbal IQ; anticonvulsant blood levels; genetic samples	Changes in seizure frequency during pregnancy *v* postpartum; caesarean section rate, child verbal IQ	Estimated study completion date July 2017, not yet published
EMPIRE: Anti-epileptic drug management in pregnancy: an evaluation of effectiveness, cost effectiveness, and acceptability of dose adjustment strategies: UK multicentre; NIHR HTA Programme (project number 09/55/38)[67]	Pregnant women taking carbamazepine, lamotrigine, levetiracetam, or phenytoin	—	Serum and umbilical cord drug concentrations, monitoring of clinical features	Seizure rate	Evaluation of the relation between exposure (as measured by serum drug levels) and seizure control and effects on the fetus. Small numbers, recruitment difficult