## Valproate use in people of child-bearing potential

*How to balance risks and benefits*

<table>
<thead>
<tr>
<th>Journal:</th>
<th>BMJ</th>
</tr>
</thead>
<tbody>
<tr>
<td>Manuscript ID</td>
<td>BMJ.2018.044261</td>
</tr>
<tr>
<td>Article Type:</td>
<td>Analysis</td>
</tr>
<tr>
<td>BMJ Journal:</td>
<td>BMJ</td>
</tr>
<tr>
<td>Date Submitted by the Author:</td>
<td>21-Mar-2018</td>
</tr>
<tr>
<td>Complete List of Authors:</td>
<td>Angus-Leppan, Heather; Royal Free London NHS Foundation Trust, Epilepsy Initiative Group; University College London Institute of Neurology Liu, Rebecca; Royal Free London NHS Foundation Trust, Epilepsy Initiative Group; University College London Institute of Neurology</td>
</tr>
<tr>
<td>Keywords:</td>
<td>women, epilepsy, SUDEP, valproate, pregnancy, bipolar disorders, migraine, malformations</td>
</tr>
</tbody>
</table>

https://mc.manuscriptcentral.com/bmj
ANALYSIS ARTICLE

Valproate use in people of child-bearing potential

How to balance risks and benefits

Angus-Leppan H, Liu RSN Epilepsy Initiative Group, Royal Free London
centre for Research in Public Health and Community Care (CRIPACC), University of Hertfordshire

Introduction

Valproate is a gamma-Aminobutyric acid (GABA) agonist licenced for use in epilepsy, bipolar disorder and in some countries for migraine. It is estimated that 2 million people take valproate world-wide, \(^1\) an uncertain number of these are women. In the USA in 2012, approximately 1.5 million outpatients received valproate, and approximately 22% (341,000) of these were women of reproductive potential (13-45 years): 67% for mood and psychiatric disorders, 9% for migraine, and 9% for epilepsy. \(^2\) The international consensus is that valproate is a significant teratogen, independent of the indication for use. There is no consensus on the appropriate regulation of valproate in people who may become pregnant. Some advocate a ban on valproate use in pregnancy and women and girls, others support restricted availability of valproate in certain circumstances, including during pregnancy. This article summarises these positions, the implicit assumptions for each, and the implications for patients and healthcare professionals, in the light of new European and United Kingdom regulatory announcements in March 2018 (see Table 1).

Background

A pooled analysis reported major congenital malformations in 6.1% (range 4-10%) in offspring with maternal exposure to antiepileptic drugs, 2.8% in children of untreated women with epilepsy, and 2.2% in the general population. \(^3\) There are no randomised controlled trials of valproate use in pregnancy, nor will there be. Observational data is from population-based cohort studies, pregnancy registers (capturing between 1/12 to 1/3 of all relevant pregnancies \(^4,5\)) and case control studies in volunteers, mostly in people with epilepsy. These studies suggest major malformations in the offspring of those
taking valproate in up to 13.8%, developmental disorders, an increased risk of autism and attention deficit hyperactivity disorder (ADHD) compared to the general population. Cochrane reviews conclude that the observational data are robust and that the methodological issues do not affect final conclusions regarding the teratogenic and developmental risk of valproate.

There is a growing momentum from patient support groups, health care professionals and the press 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 valproate use in pregnancy to restricted use when other treatments have failed, to prohibition of valproate in women of child-bearing age coupled with a pregnancy prevention programme in all women taking it (Table I).

**Arguments to ban valproate use in pregnancy through legislation**

The main assumption is that the risks of valproate are so great that informed consent for this drug in this group of patients is over-ridden (Box 1). A complete ban in pregnancy implies a pregnancy prevention programme is enforced in any woman of child-bearing age who wishes to take valproate.

*Valproate is a major teratogen and effects are often life-long*

Some advocacy groups call for a complete ban on valproate in pregnancy “as the benefit of this product do not outweigh the risk and pregnancy is not mandatory.” Because of the severity and life-long impact of many of the teratogenic and developmental effects, they argue that no-one should be exposed to such risks.

The background rate of major malformations (an abnormality of an essential anatomical structure present at birth that significantly interferes with function and/or requires major intervention) in the general population is 2-3%. Observational pregnancy registries report congenital malformations in infants exposed to valproate in utero ranging from 6.7% (UK and Ireland Epilepsy and pregnancy registers which includes 1/3 of relevant pregnancies), 9.3% (North American Anti-Epileptic Drug Pregnancy Registry), 9.7% (International Registry of antiepileptic drugs) (EURAP) and 13.8% (Australian Pregnancy Registry which includes 1/12 of all relevant pregnancies).

There are few prospective reports for indications other than epilepsy. The Australian registry captured 9 offspring of pregnant women taking valproate for non-epilepsy indications, 1 of whom had a malformation (cleft palate).

The mean IQ of 6 year olds with maternal valproate exposure (49/62 children with maternal exposure to valproate completed examinations over 25 centres in the UK and USA) was in the normal range at 97 (95% CI 94-101) with mean maternal IQ of 96 (95% CI 92-100), but lower than for lamotrigine exposure [108 95% CI (105-110)]. Children of mothers who took valproate were at a greater risk for a diagnosis of Attention Deficit Hyperactivity Disorder (ADHD).
A population study in Denmark found the absolute risk of autism in children with prenatal valproate exposure was 2.5%, compared to 0.5% in the general population. 3% of children whose mothers with epilepsy took valproate had autism, whereas the risk was 1% for children with maternal epilepsy not exposed to valproate.6

While some major malformations (polydactyly, cleft palate, hypospadias, cardiac defects) are treatable, many of these children are left with significant permanent disability and some require life-long full-time care.

**There are effective alternatives to valproate**

Those supporting a ban point to alternatives with lower risk of teratogenesis. These are summarised in Table II.

For focal epilepsy, there are more effective alternatives to valproate for most patients21-25 (such as levetiracetam with malformations in 1.6-2.4%, lamotrigine with malformations in 1.9-4.6%, and for carbamazepine in 2.6-5.6%). For idiopathic epilepsies, there are fewer alternatives as summarised in Table II, and trials are underway to evaluate alternatives.26 For newer anti-epileptic drugs, data on teratogenesis are scant.

For bipolar disorders, lithium has similar efficacy as a mood stabiliser to valproate.27 Avoiding valproate in pregnant women with bipolar disease is “zero risk” according to ANSM director, Dominique Martin28 who claims that not all women with bipolar disease will require treatment during pregnancy (see Patient safety below).

In migraine, valproate is now rarely considered in women of child-bearing potential, given effective lower risk alternatives, (amitriptyline, beta blockers, see Table II).29

**Offspring affected by valproate will continue to be inadequately recognised, supported and compensated**

Given reports of valproate teratogenicity in animals since the 1970s and in humans since the 1980s,30 advocacy groups suggest that government, industry and medical responses are too slow. Banning valproate is suggested as the only way to avoid future problems including contentions about causality which may 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 affected with life-long disabilities.31 Inspection Générale des Affaires Sociales (IGAS)32 estimate 450/14322 exposed children born between 2006-2014 were affected by maternal valproate exposure in France,33 but a joint paper by French National Agency for the Safety of Medicines (ANSM) and the national health insurance administration estimated many more- 2150-4100 children affected between 2007 and 2014.14 There are disputes about who should be held responsible for this. Legal action on behalf of people with fetal valproate syndrome in France (Depakine victims in France) is underway, and expected to cost 424.2 million Euros, and the French government argues that Sanofi is responsible for
compensation. In the United Kingdom mass action against Sanofi Adventis on behalf of 100 children collapsed when legal advisors did not think the case had a reasonable prospect of success. A similar class action brought against an affiliate company in the United States was settled out of court. Protracted court cases about compensation and support for those affected can exacerbate the pain and suffering of the families involved.

No woman who might become pregnant would choose valproate if fully informed of the risk

This assumes that any fully informed woman would avoid valproate it pregnancy was a possibility. This argument is that information provision for women with epilepsy about valproate risks is not a realistic policy because it is incomplete, and will remain so, 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, will prevent future problems.

Many women with epilepsy are not informed of the risks of valproate according to asurveys- 28% of 2000 of the women ctaking sodium valproate in the United Kingdom (Epilepsy Action UK, 2017), 41% of 192 in a German survey, and 59% of 200 in Croatia. Despite regulatory warnings, toolkits and public debate, patient groups estimate that 1500 children in the United Kingdom have been affected by valproate since 2014, and 400 children since the 2016 MHRA campaign.

Arguments for allowing restricted use of valproate in women of child-bearing potential

The main assumption is that informed choice after risk benefit analysis applies to valproate as for other treatments (see Table II).

Efficacy of alternative medications is sometimes less

Valproate has the most evidence for efficacy for idiopathic epilepsies (genetic generalised epilepsies), 25% of all epilepsies but twice as common in women than men. It may be the only effective treatment in certain patients, sometimes justifying first line use (see Table II). Case reports of harmful seizure related complications in young women with subsequent seizure freedom on valproate are an important signal. We do not know how many women with active epilepsy would become seizure free on valproate. A nested population study suggests an increased risk of SUDEP in women with epilepsy taking lamotrigine, a commonly used alternative. Withdrawal from valproate or change to another medication in the first trimester of pregnancy doubled the risk of tonic-clonic seizures in one observational register study. Valproate is also the treatment of choice for some rare life-threatening childhood epilepsy syndromes.

The number of treatments used for bipolar disorders, with variable evidence bases, attributes to the complexity of the condition (see Table II). 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. Valproate use has increased although its efficacy is similar to lithium as maintenance therapy. An estimated 80% of patients with bipolar
disorders require treatment during pregnancy, and relapse risk in untreated was twice that of treated women in pregnancy. Untreated bipolar disease is an independent risk factor for pregnancy complications, malformations and developmental problems in offspring. Post partum psychosis is a medical emergency, posing a risk to mother and baby, and more common in untreated women.

In migraine there are effective alternatives to valproate considered safe in pregnancy. Migraine per se does not appear to cause excess morbidity in pregnancy, but is associated with increased risks of thrombosis and pregnancy related hypertension.

Negative effects on cognition of poorly controlled epilepsy

Avoidance of valproate in girls with idiopathic generalised (genetic generalised) epilepsies even before they reach child-bearing potential may result in poor seizure control affecting their cognition and behaviour with long-term medical and social consequences.

Patient safety and maternal outcomes

1/200 pregnant women have epilepsy, with mortality is almost 10 times greater than those without epilepsy (100 versus 11 per 100,000 maternities respectively). Maternal mortality has fallen but epilepsy-related deaths increased over the past 30 years. Valproate had been stopped before pregnancy in 2/9 United Kingdom episodes of Sudden unexpected death in epilepsy (SUDEP) in 2013-2015.

There are no data on the impact of valproate use on maternal safety issues in bipolar disorders. There is no evidence of increased maternal morbidity caused by migraine per se, or whether migraine treatment modifies pregnancy risks.

Informed consent

WHO, General Medical Council guidance and the Montgomery Judgement in the United Kingdom stress patient’s rights to informed choice based on full disclosure of relevant risks and benefits. For epilepsy, the potential for increased seizures and even death (most through SUDEP risk ranging from ~0.1-9.3/1000 person years) is material information, by any standards. Banning valproate imposes less effective treatment for some female patients than other people for a similarly potentially life-threatening or serious condition, without their consent. Patient 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. VanMcCrary discusses an ethical model facilitating individual patient’s own risk-benefit assessment, and warns about unintended prescriptive guidance,
including multiple trials of unsuccessful medication and potential medicolegal consequences arising if a woman suffers injury or death ascribed to avoiding valproate without adequate information.\textsuperscript{55}

**Will research change the situation?**

Maternal seizure frequency during pregnancy and caesarean rate are primary outcome measures in one prospective study (MONEAD –Table 3).\textsuperscript{56} The EMPIRE study\textsuperscript{57} (Table 3) investigated the impact of therapeutic drug monitoring during pregnancy on seizures and maternal outcome, and results are awaited. There are little prospective data on outcomes in bipolar disease and migraine.

As neuropsychological assessments are expensive, time-consuming,\textsuperscript{32} one observational study\textsuperscript{58} investigates parental questionnaires in assessing child development, aiming to facilitate larger and longer follow-up studies of neurodevelopmental effects. This information is equally important for alternatives to valproate in pregnancy in randomised blinded studies of offspring.

Pharmacogenomics studies may help delineate individual susceptibility to valproate induced teratogenesis and neurodevelopmental abnormalities, and its alternatives.\textsuperscript{56}

**What should we do?**

**Nuanced guidance for clinicians and patients**

The MHRA toolkit and other regulatory bodies provide patients with a summary of the risks of valproate, and Box 2 is an information sheet used by the authors for women with epilepsy. Generic handouts are not enough, and a Czech survey suggests most patients prefer a consultation with a healthcare professional.\textsuperscript{36} ILAE provides structured reflections for clinicians on relevant scenarios faced by patients with epilepsy\textsuperscript{59} and others discuss situations when women may choose valproate as their treatment.\textsuperscript{60, 61}

**Identifying patients**

The unknown number of women taking long-term valproate who are not under specialist follow-up are at particular risk of sub-optimal decisions. Generating fear and anxiety without guidance may result in women stopping their treatment without support.\textsuperscript{61} 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 offspring is critical, and will require considerable additional resources.
Conclusions

The decision making surrounding valproate will remain complex and requires thoughtful individualised discussions with our patients. Such discussions should include specialists with appropriate knowledge and experience of the relevant conditions. This will maximise the ability of health care professionals to equip our patients for truly informed decision making. 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

*The international consensus is that valproate carries a significant risk for foetal and developmental problems in offspring of those taking it.

*Sodium valproate is sometimes the only effective medication for certain 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, and this requires adequate resources.

*We have a duty to monitor consequences of reduced valproate use in women along with standardised outcomes of their pregnancies.

Search strategy

We searched PubMed, Cochrane collaborations and personal databases. We spoke with colleagues and patients regarding resources. We searched international epilepsy, drug regulatory and patient support group websites. We searched research trials databases through UK Clinical Trials Gateway - https://www.ukctg.nihr.ac.uk/trials, which includes Clinical Trials.gov register and ISRCTN Register; and https://clinicaltrials.gov.

Search terms relating to anti-epileptic drugs, sodium valproate, birth defects, teratogenesis, development, malformation, autism, epilepsy, seizure, pregnancy, bipolar disease.

The article inadvertently neglects articles and websites written in languages other than English.
How patients and colleagues were involved in this article

Two patients, who had come to different conclusions about their medication (one continues valproate, one changed to another medication), were involved in this article. They said it was very important topic, advised on the wording of the information sheet and both approved the final version (Box 2). Dr Gavin Angus-Leppan, MBBS FRACPsych, consultant psychiatrist in Sydney Australia, advised on bipolar disorders.

Funding: Royal Free Charity

Competing Interests: see BMJ website.

Contributions: HAL is Consultant Neurologist and Epilepsy Initiative Group Lead, Royal Free Hospital, and Honorary Senior Lecturer, University College London and Honorary Consultant, Institute of Neurology. RSNL is Consultant Neurologist and Neurology Audit Lead, Royal Free Hospital and Honorary Consultant Neurologist, Institute of Neurology. HAL conceived the idea for the article, HAL and RSNL contributed to researching and writing the paper.
Table I: Examples of regulatory authority statements about valproate use in people of childbearing potential

European Medicines Agency’s Pharmacovigilance Risk Assessment Committee (EMA PRAC) 2018
- Migraine or bipolar disorder:
  - In pregnancy - valproate must not be used.
  - 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:
  - In pregnancy - valproate must not be used. 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.

Medicines and Healthcare products Regulatory Agency, UK (MHRA) 2017
- Not for epilepsy or bipolar disorder in women and girls unless other treatments are ineffective or not tolerated; migraine is not a licensed indication

French National Agency for the Safety of Medicines and Health Products (ANSM) 2017
- Valproate banned for women and girls of child-bearing 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

MHRA 2016
- Not for female children, in female adolescents, in women of childbearing potential and in pregnant women unless other treatments are ineffective or not tolerated.
- Women of childbearing potential must use effective contraception during treatment.

Federal Drug Agency (FDA), USA 2016
- Epilepsy & 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

Recommendations from a joint Task Force of ILAE-Commission on European Affairs and European Academy of Neurology (EAN): adopted in other countries including China, 2016
- Need to balance teratogenic risks of valproate and treatment alternatives, the importance of seizure control and of risks to patient and foetus due to 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 (Medsafe), 2014
- Valproate is contraindicated in pregnancy.
- Valproate should not be used in women of child bearing potential unless other treatments are ineffective or not tolerated.

MHRA 2013
- Not for use in pregnancy unless there is no effective alternative.
**Box 1: consensus and assumptions**

**Consensus**

- Valproate has significant teratogenicity
- Valproate teratogenicity is dose dependent so women of childbearing potential should take the lowest effective dose in slow release form
- That women taking valproate should take folic acid 5mg daily
- There are effective alternative treatments for migraine during pregnancy
- That the teratogenicity of some alternatives to valproate are unknown
- That all women of child bearing potential taking valproate need expert advice, information about its risks and regular review
- That women taking valproate should seek urgent medical advice rather than stop it suddenly

**Assumptions made by those supporting a prohibition on valproate use in women of child-bearing age**

- That valproate is a major teratogen and this consideration overrides all others
- That polytherapy with other medications is less harmful than valproate
- That there are efficacious alternatives to valproate and these are lower risk
- That girls should not take valproate even before pregnancy is a possibility because of the risk that they will continue it into child bearing years
- That women who wished to become pregnant would not take valproate if they knew the risks
- That women taking valproate should not be permitted to become pregnant
- That women would rather have no child than a disabled child

**Assumptions made by those supporting informed choice for women regarding valproate use**

- That some patients will place safety considerations over concerns about teratogenicity
- That some people would prefer to continue valproate during pregnancy
- That individuals have the right to choose valproate treatment after informed discussion
- That alternative treatments to valproate are not risk free
- That assessment of the risk benefit analysis for valproate use is an individual judgement
- That in some situations low dose valproate (<800mg daily) plus folate 5mg daily may be lower risk than high dose polytherapy
TABLE II- valproate and alternatives in pregnancy

<table>
<thead>
<tr>
<th><strong>Valproate indications, efficacy, alternatives</strong></th>
<th><strong>migraine prophylaxis</strong></th>
<th><strong>bipolar disease (BD)</strong></th>
<th><strong>(idiopathic generalised) epilepsy</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>strength of evidence</strong></td>
<td>valproate effective cf placebo-level</td>
<td>same time to recurrence -lithium/ valproate/placebo******</td>
<td>valproate superior efficacy to lamotrigine******</td>
</tr>
<tr>
<td><strong>efficacy of alternatives</strong></td>
<td>propranolol, flunarizine, topiramate Level 1-effective cf placebo</td>
<td>lithium and valproate reduce number of relapses</td>
<td>evidence on levetiracetam and topiramate awaited (SANAD II)</td>
</tr>
<tr>
<td></td>
<td>topiramate superior to - Level 2</td>
<td>treatment often complex and non-homogenous esp depressive symptoms</td>
<td></td>
</tr>
<tr>
<td><strong>teratogenicity of valproate</strong></td>
<td>little specific data for migraine - see idiopathic epilepsy ***</td>
<td>little specific data for bipolar - see other indications***</td>
<td></td>
</tr>
<tr>
<td><strong>neurodevelopmental delay</strong></td>
<td>little specific data - see epilepsy</td>
<td>lower IQ, autism 3% level III (vs 1% epilepsy - level I/II), ADHD</td>
<td></td>
</tr>
<tr>
<td><strong>teratogenicity of alternatives</strong></td>
<td>uncertain for flunarizine/for topiramate - see other indications:</td>
<td>lithium 4-12% *</td>
<td></td>
</tr>
<tr>
<td></td>
<td>propranolol - stop &gt;3 days before delivery to avoid perinatal hypoglycaemia</td>
<td>lamotrigine 3.91%</td>
<td></td>
</tr>
<tr>
<td><strong>perinatal complications of valproate</strong>**</td>
<td>nil specific data- see epilepsy- jitters, coagulation problems</td>
<td>nil specific data- see epilepsy- jitters, coagulation problems</td>
<td></td>
</tr>
<tr>
<td><strong>perinatal complications of alternative treatment</strong></td>
<td>propranolol- infant hypoglycaemia(monitor in frist days)</td>
<td>antipsychotics acutely for manic/ psychotic symptoms/</td>
<td></td>
</tr>
<tr>
<td></td>
<td>minimal breast milk excretion for propranolol, amitriptyline, valproate*</td>
<td>antidepressants - variable</td>
<td></td>
</tr>
<tr>
<td><strong>morbidity of uncontrolled symptoms</strong></td>
<td>direct-nil significant;</td>
<td>40-70% untreated women have post partum exacerbation</td>
<td></td>
</tr>
<tr>
<td></td>
<td>increased risk thrombosis, PET, hypertension***</td>
<td>neurodevelopmental problems in offspring</td>
<td></td>
</tr>
<tr>
<td></td>
<td>untreated BD is risk factor for poor maternal and fetal outcomes</td>
<td>80% if migraineurs improve in 2nd and 3rd trimester</td>
<td></td>
</tr>
<tr>
<td></td>
<td>levels vary (0-30%) can be individualised (Moretti 2003)</td>
<td>40-70% untreated women have post partum exacerbation</td>
<td></td>
</tr>
<tr>
<td></td>
<td>seizures causing injury to mother and fetus</td>
<td>neurodevelopmental problems in offspring</td>
<td></td>
</tr>
<tr>
<td></td>
<td>neurodevelopmental problems in offspring</td>
<td>2.3 x increased recurrence risk untreated versus treated (Level II): 85% vs 37%</td>
<td></td>
</tr>
<tr>
<td><strong>mortality of uncontrolled symptoms</strong></td>
<td>very low for migraine per se</td>
<td>increased perinatal suicide risk of general peripartum population</td>
<td></td>
</tr>
<tr>
<td></td>
<td>mortality for associations - thrombosis / eclampsia/ hypertension</td>
<td>SUDEP- 1/1000, for epilepsy pregnancies</td>
<td></td>
</tr>
<tr>
<td></td>
<td>not quantified</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Lin et al, Cochrane 2013

**Such as low birth weight/ haemorrhage/abortion

Levels of evidence -

***MacGregor, 2009
cf=compared to

****Cochrane 2001, Macritchie// bowden 2000

*****Bowden

******SANAD

cross- rare valproate responsive epilepsies

---

1. Lin et al, Cochrane 2013
2. MacGregor 2000
3. Bowden
4. Sanad

---

*Bipolar lithium malformations-5.73% vs lamotrigine 3.91% vs 3.26% controls in US insured cohort total

**Such as low birth weight/ haemorrhage/abortion

---

https://mc.manuscriptcentral.com/bmj
**BOX 2**

Information sheet for women and girls with epilepsy

Why might I still consider taking sodium valproate (valproate, valproic acid, Epilim) with all the concerns about it?

- Sodium valproate may be the only medication that stops your seizures. Other antiepileptic drugs may not work or given you bad side effects.
- The risks to the mother and baby of a serious seizure need to be balanced with any risks of valproate to the development of the unborn child.
- Controlling seizures is important as they can be harmful, occasionally life-threatening.
- Seizures during pregnancy can harm the mother, and can also damage the unborn baby through lack of oxygen, premature delivery or even miscarriage. There is also a risk of Sudden Unexpected Death in Epilepsy (SUDEP) in pregnancy due to poor seizure control or to stopping medication suddenly.

What can I do? Please consider the following suggestions:

- Plan your pregnancy and discuss with your doctors and nurses, including your GP and specialist.
- Use effective birth control to avoid unplanned pregnancies whilst taking valproate.
- Take 5mgs Folic Acid daily if you are of child-bearing age. This may reduce the general risk of spina bifida and may reduce the impact of valproate on the learning and development of your child.
- Do not stop taking your medication if you are planning a pregnancy or become pregnant. Discuss with your specialist as soon as possible.

For More Information, the following websites are useful starting points:

- International League against Epilepsy
- Epilepsy Action – Having a Baby [https://www.epilepsy.org.uk/info/women/having-baby](https://www.epilepsy.org.uk/info/women/having-baby)

_Epilepsy Initiative Group, Royal Free Hospital, 2018_


7. MHRA. 2017


10. (ADRAC) AADRAC. Valproate in pregnancy. 2009


13. MHRA. 2016


15. PRAC E. Consultation on valproate in pregnancy. 2017


32. 14,000 pregnant women in France took 'birth defect drug'. *TheLocal* 2016.


Valproate indications, efficacy and alternatives

migraine prophylaxis

strength of evidence
valproate effective cf placebo - Level 1

efficacy of alternatives
propranolol, flunarazine, topiramate - Level 1-effective cf placebo
propranolol equivalent to valproate - Level 2
flunarazine equivalent to valproate - Level 2
topiramate superior to - Level 2

teratogenicity of valproate
little specific data for migraine - see idiopathic epilepsy ***

neurodevelopmental delay
little specific data - see epilepsy

teratogenicity of alternatives
uncertain for flunarazine/ for topiramate - see other indications:
propranolol - stop >3 days before delivery to avoid perinatal hypoglycaemia
aspirin 75mg - safe until 36 weeks
amitriptyline 10-25mg daily - no recorded teratogenicity

perinatal complications of valproate****
il specific data - see epilepsy, jitteriness, coagulation problems

perinatal complications of alternative treatments
propranolol- infant hypoglycaemia (monitor in first days)

minimal breast milk excretion for porpranolol, amitriptyline, valproate***

morbidity of uncontrolled symptoms
direct-nil significant;
increased risk thrombosis, PET, hypertension***
80% if migraineurs improve in 2nd and 3rd trimester, MacGregor 2009

mortality of uncontrolled symptoms
very low for migraine per se
mortality for associations - thrombosis / eclampsia / hypertension

1 Linde et al, Cochrane 2013

*bipolar lithium malformations-5.73% vs lamotrigine 3.91% vs 3.26% controls in US insured cohort total
**such as low birth weight / haemorrhage/abortion

Levels of evidence -
****MacGregor, 2009
cf= compared to
****Cochrane 2001, Macritchie// bowden 2000
*****Bowden
******SANAD

cross- rare valproate responsive epilepsies

https://mc.manuscriptcentral.com/bmj
bipolar disease (BD)
same time to recurrence - lithium/ valproate/ placebo*****
lithium and valproate reduce number of relapses
treatment often complex and non-homogenous esp depressive symptoms
lithium -50% decrease suicidal ideation/ 38% decrease mana
lithium and valproate similar efficacy****
antipsychotics acutely for mania/ psychotic symptoms/
antidepressants - inconclusive evidence,
little specific data for bipolar - see other indications***
little specific data - see epilepsy
lithium 4-12% *
lamotrigine 3.91%
controls 3.26%
antidepressants - variable
nil specific data- see epilepsy- jitteriness, coagulation problems
lithium- uncertain
minimal breast milk excretion for, valproate***
lithium traditionally contraindicates breastfeeding but
levels vary (0-30%)/ can be individualised (Moretti 2003)
untreated BD is risk factor for poor maternal and fetal outcomes
neurodevelopmental problems in offspring
40-70% untreated women have post partum exacerbation
2.3 x increased recurrence risk untreated versus treated (Level II): 85% vs 37% Viguera 2007
increased perinatal suicide risk cf general peripartum population
not quantified*not 2016
(idiopathic generalised) epilepsy

valproate superior efficacy to lamotrigine*****
evidence on levetiracetam and topiramate awaited (SANAD II)

lamotrigine - 1/3 breakthrough seizures in pregnancy

evidence on levetiracetam and topiramate awaited (SANAD II)

6.7-13.8% - Level I-III
lower IQ, autism 3% level III (vs 1% epilepsy - level I/II), ADHD
lamotrigine 1.9-4.6% -level II// carbamazepine 2.6-5.6%
levetiracetam - 0.7-2.4%-level II,III
tioramate - 2.4-6.8% - level II, III
newer agents - insufficient data// untreated epilepsy-1.1-3.3%
jitteriness, coagulation problems
reduced birth weight, esp polytherapy- level I-III,
minimal breast milk excretion all except levetiracetam and phenobarb, level II-III**

seizures causing injury to mother and fetus

SUDEP- 1/1000, for epilepsy pregnancies
<table>
<thead>
<tr>
<th>Title; setting; trial registration or ID; funder</th>
<th>Population</th>
<th>Intervention</th>
<th>Comparator(s)</th>
<th>Primary outcome</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NaME: Neurodevelopment of Babies Born to Mothers with Epilepsy: an observational cohort study; UK multicenter (IRAS ID 143279); NIHR</strong></td>
<td>Children born to women with epilepsy in their first or second trimester taking AEDs</td>
<td>Ages and Stages Questionnaire, Vineland Adaptive Behaviour Scale at 12 and 24 months; Developmental assessment at 24 months.</td>
<td>Children born to women with epilepsy in their first or second trimester not taking AEDs during pregnancy</td>
<td>Reliability of parental questionnaires in assessing child development: behavior and cognitive skills at 12 and 24 months</td>
<td>Evaluation of potentially cost effective way of assessing impact of AEDs on child development across large populations.</td>
</tr>
<tr>
<td><strong>MONEAD: Maternal and Neurodevelopmental outcomes of in Utero Antiepileptic Drug Exposure; US multicenter; ISRCTN98260309; NIHR</strong></td>
<td>Aged 14-45 females. Pregnant women without epilepsy, Pregnant women with epilepsy, Non-pregnant women with epilepsy</td>
<td>Electronic seizure diaries, Assessment of child verbal IQ; Anticonvulsant blood levels; genetic samples.</td>
<td>Pregnant women without epilepsy, non-pregnant women with epilepsy</td>
<td>Changes in seizure frequency over pregnancy vs post-partum, C-section rate of depression, child Verbal IQ, breastfeeding effect on verbal IQ of child, small for gestational age rate</td>
<td>Estimated study completion date July 2017, not yet published</td>
</tr>
<tr>
<td><strong>EMPIRE: Anti-epileptic drug management in pregnancy: an evaluation of effectiveness, cost effectiveness, and acceptability of dose adjustment strategies: UK multicenter; NIHR HTA Programme (project number 09/55/38)</strong></td>
<td>Pregnant women taking either carbamazepine, lamotrigine, levetiracetam, phenytoin</td>
<td>Serum AED levels, umbilical cord AED levels.</td>
<td>Clinical features monitoring</td>
<td>Seizure outcome</td>
<td>Evaluation of the relationship between exposure (as measured by serum AED levels) and seizure control and effects on the fetus. Small numbers Recruitment difficult</td>
</tr>
</tbody>
</table>

Table III
Ongoing relevant trials investigating maternal and neurodevelopmental outcomes following AED exposure during pregnancy.