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PRESCRIPTION OF SODIUM VALPROATE AS A MOOD STABILISER IN PREGNANCY

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SUMMARY

This essay was submitted for the Royal College of Psychiatry's perinatal psychiatry medical student essay prize in 2017. The essay considers the choices available to women with bipolar disorder who become pregnant while taking sodium valproate to treat mania or for mood stabilisation. The implications of three options are considered: to stop all treatment, to switch to a different mood stabiliser or to continue on sodium valproate. The implications for the fetus, on the mother's wellbeing and the ethics of patient choice are discussed.

Background: *Pregnancy can be especially challenging for women with bipolar disorder, predominantly because of the heightened probability of relapse, potential fetal harm caused by bipolar medication, and a 250-fold risk of puerperal psychosis compared to the general population. Sodium valproate is a known teratogen, and is discouraged in pregnancy, but what choice is open to women who rely on this medication to stabilise their mood?*

Conclusions: *The large majority of women of childbearing age with bipolar disorder should not be prescribed sodium valproate as the risks to the unborn fetus far outweigh the benefits of the medication, as other drugs have similar if not better efficacy to stabilize the mother's mood, with lower risks to the fetus. In the small minority of women for whom valproate may be the only effective treatment, she must be fully informed of the teratogenic and neurodevelopmental risks, as well as the ways in which the pregnancy can be managed to reduce such risks.*

Key words: *bipolar disorder - sodium valproate – pregnancy - teratogen*

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> *What I would've given anything for…someone who could've helped me with both pregnancy and the psychiatric aspect. You know, that could…not treat me like I'm pregnant and I'm a psychiatric patient, but they can treat me as both, and not separate it and make it sound like I have to have one or the other.*
>
> Anonymous patient with bipolar disorder
> quoted in Richardson et al. 2016;
> *The Experience of Pregnancy for Women with Bipolar Disorder: An Exploratory Study*

Pregnancy can be especially challenging for women with bipolar disorder, predominantly because of the heightened probability of relapse, potential fetal harm caused by bipolar medication, and a 250-fold risk of puerperal psychosis compared to the general population. The lifetime prevalence of bipolar disorder is 1-3%, and the average age of diagnosis aligns with early adulthood, and therefore women's reproductive years. Sodium valproate – an established teratogen – is officially prescribed for three medical indications: epilepsy (generalized or focal), acute mania in bipolar disorder, or less commonly, migraine prophylaxis. Valproate is not licensed for mood stabilisation in bipolar disorder, although it is commonly prescribed off-license for this purpose. If pregnant women are prescribed valproate to prevent mania and stabilise mood, they are not only exposed to the intrinsic risks of this drug, but also run the additional risk of taking an unlicensed medication, which may not meet acceptable standards of quality, efficacy and safety.

The fetal implications of taking valproate[1] in pregnancy are profound, and include congenital malformations and neurodevelopmental delay. Valproate's use has been cautioned in pregnancy ever since a paper in the Lancet from 1982 linked the drug to spina bifida. But it took over 30 years in the UK for prescription-regulation to be imposed. It is now rigorously evidenced that of babies exposed to valproate in the womb, 40% go on to have neurodevelopmental problems (22% have an "exceptionally low" verbal IQ compared to 2% in the general population (Meador et al. 2009)). 11% of babies whose mothers took valproate in pregnancy have congenital malformations, compared to 2–3% in the general population. The risk of autism after valproate exposure compared to controls is almost five times higher (Table 1).

For the mother, when considered as a single entity separate from the fetus, there are no known biomedical negative implications for continuation of valproate in pregnancy other than the side effects consistent with non-pregnant patients. A pregnant woman is likely to see the benefit of continued mood control (if valproate proved efficacious before pregnancy) from a medication with which she is familiar. However, the emotional impact if medication taken in gestation results in harm to her baby can be devastating.

[1]Three formulations of valproate are available in the UK: sodium valproate and valproic acid (licensed for treatment of epilepsy) and semi-sodium valproate (licensed for treatment of acute mania).

Table 1. Effects of In Utero Sodium Valproate Therapy on the Fetus

Anatomical malformation	Neurodevelopmental effects
Dysmorphic craniofacial features: ▪ Telecanthus ▪ Wide philtrum ▪ Increased width of upper lip ▪ Trigonocephaly ▪ Epicanthic folds ▪ Infraorbital grooves	Autism spectrum disorder (ASD) Autistic traits: ▪ Lower sociability ▪ Lower verbal ability
Craniosynostosis	Lower IQ
Neural tube defects: spina bifida, anencephaly	Lower non-verbal abilities
Polydactyly	Deficit in motor skills
Heart malformations: ASD, VSD, aortic stenosis, patent ductus arteriosus	
Hypospadias	
Increased bleeding and liver disease	

The opposite scenario to a pregnant woman continuing valproate, is an expectant mother with bipolar affective disorder who stops all treatment, and thus risks relapse into worsening mood control and mania, potentially endangering both herself – in terms of morbidity or even (in rare cases) mortality – as well as the fetus.

These two extreme situations – continuation of valproate resulting in fetal abnormality or cessation of treatment with grave outcomes for mother and baby – are today uncommon (but by no means unheard of). There are very few decisions in medicine for which one path proves to be "always better." Such recipe-book practice should be anathema to both obstetrics and psychiatry, which are rich in situational nuance. There are shades of compromise between the Scylla of valproate and the Charybdis of relapse, but this middle way requires sensitive risk-benefit analysis of every patient's specific circumstances within the framework of an open and trusting relationship between doctor and patient. It is the duty of the medical profession to enable a woman with bipolar disorder to have the safest possible pregnancy for both herself and her baby, without denial of the real risks that both mental and physical illness pose in pregnancy, as well as the potential risks of treatment.

Reacting to the effects of valproate on the fetus, the National Agency for the Safety of Medicines and Health Products (ANSM) in France imposed a ban in July 2017 on valproate prescription for females who are either pregnant or of childbearing age for any bipolar disorder-related indication. Notably, the ANSM did not ban the use of valproate to control epilepsy in pregnant women. The director-general of the ANSM, Dominique Martin, stated that "Valproate is probably the most teratogenic drug around," and he hopes that the remaining 27 EU countries will follow France in 2018.

The rationale for this partial ban – refusing valproate for mania and mood stabilisation in bipolar disorder but continuing its use in specific cases of epilepsy –is due to expert witness from perinatal psychiatrists who said that in (almost) all cases of bipolar disorder, equally or more effective drugs are available to treat mania and balance mood besides valproate, such as lithium, lamotrigine, and second generation anti-psychotics (SGAs), which carry lower risks to the developing fetus. However, neurologists argued that anti-epileptic drugs (AEDs) other than valproate are not invariably effective for all cases of epilepsy. The majority of patients with epilepsy can indeed be switched to another AED (not carbamazepine, which can also cause fetal malformations) with significantly lower risk. Yet a minority of women can controls their seizures only with valproate, and in such cases the risk of uncontrolled seizures to the fetus and the mother - falling, becoming unconscious, entering status epilepticus or even dying - is potentially more harmful than valproate itself.

While the UK has not (yet) imposed a similar ban, NICE released a Quality Statement in February 2016 advising that "Women of childbearing potential are not prescribed valproate to treat a mental health problem" unless in "exceptional circumstances" after full disclosure of the risks to the patient. All clinics must have protocols in place "to ensure that women of childbearing potential are not prescribed valproate to treat a mental health problem". Valproate in epilepsy is less strongly dissuaded, and can be prescribed if there is no safer alternative drug. France's policy – and the intonation of NICE's statement – implies that implications when valproate is used to treat bipolar disorder in pregnancy are almost always worse than alternative courses of action. Unlike in epilepsy, evidence suggests that an less significant number of women rely on valproate for mood stabilisation and would be worse off without it compared to the high probability of harm to their child.

When a woman with bipolar disorder takes valproate and then becomes pregnant, she is faced with three potential courses of action:

- Stopping mood stabilisers altogether
- Switching to an alternative drug which is reported to pose less risk to the fetus
- Continuing on valproate, with or without adjustments to minimize risk to the fetus

Stopping mood stabilisers altogether

If a woman who requires mood stabilisers to stay mentally well were to stop valproate before or during pregnancy without substituting another mood stabiliser, she would be at greater risk of worsened mental wellbeing. Discontinuation of mood stabilisers in pregnancy is associated with a doubled risk of relapse compared to women who stay on their mood stabilisers (Viguera et al. 2007). The BNF states that "it is important that women do not stop taking essential treatment because of concern over harm to the fetus," due to this relapse risk.

Pregnancy is riskier for women with untreated bipolar disorder compared to women without bipolar disorder, or those who are stabilised (though this still carries increased risk compared to the general population). Bipolar is associated with higher rates of pre-eclampsia, perinatal (preterm delivery, low birth weight) and postnatal complications (Nguyen et al. 2012) as well as poor infant neurodevelopment including motor function, IQ and social-emotional interactions (Gentile 2012).

Moreover, as evidenced in the UK's confidential enquiries into maternal deaths (now overseen by MBRRACE), women with severe mental health conditions (such as bipolar and schizophrenia) are at an increased risk of self-harm (with violent methods used in 20% of cases) and suicide during the perinatal period. Postpartum, women with uncontrolled bipolar disorder have a 25-50% risk of puerperal psychosis compared to 0.1% in the general population. Suicide linked to mental health conditions is now classified as a direct cause of maternal death, acknowledging that pregnancy is a catalyst for the arrival and worsening of mental health conditions. Among pregnant women with ICD10 diagnoses of schizophrenia, bipolar disorder or other affective psychoses, 24.5% had experience of suicidal ideation in pregnancy (Taylor et al., 2016). Bipolar patients when manic are also at higher risk of unprotected sex, substance misuse (alcohol, cigarette smoking and recreational drugs), and domestic abuse, of which all are risk factors for negative fetal outcomes as well as maternal morbidity (Stein et al. 2014). In extremis, although undoubtedly rare, both mother and fetus may die: the worst of all possible outcomes.

Discontinuing medication may also increase fetal exposure to the hormonal mediators of maternal stress (Newport, Wilcox & Stowe 2001). An area of fascinating, evolving research is the epigenetic effects of maternal stress on the fetus. The definition of stress is vague – but both depression and mania could be included here. Zucchi et al. indicate that prenatal stress modifies epigenetic signatures of disease during important phases in fetal brain development. Their rat model suggests that physiological changes in stressed mothers may be linked to altered gene expression in the offspring's brain development through microRNA regulation. However, at this nascent stage, the causal mechanisms and long-term consequences of perinatal programming are poorly understood, yet remind us that many of the influences at the maternal-fetal interface are yet to be discovered.

Switching to an alternative drug

The mood stabiliser class includes valproate, lithium carbonate, lamotrigine and second-generation antipsychotics. Lithium is the most commonly prescribed mood stabiliser in bipolar disorder, and more recently SGAs have been increasingly used (Khan et al., 2016). While patient idiosyncrasies always exist, the BALANCE (Bipolar Affective disorder: Lithium/ Anticonvulsant Evaluation) study suggests that lithium is a more effective mood stabiliser than valproate for most patients with bipolar, and is less teratogenic. While the highest risk of congenital malformations and long-term neurodevelopmental effects is associated with valproate, Galbally et al.'s systematic review reports that "[a]ll mood stabilisers were found to be associated with a risk of malformation and perinatal complications," including teratogenesis, impaired neurological development and autism. In the FDA's classification system for medications in pregnancy, mood stabilisers can be found in category C (potential evidence of human fetal risk) or category D (positive evidence of human fetal risk). Bromley et al. observed an increased rate of autism spectrum disorder among children exposed prenatally to AEDs (a proportion but not all of these prescriptions were for valproate) (Table 2).

Although the risks of lithium and SGAs are reportedly more rare and less severe than with valproate, it would be wrong to let patients believe that these drugs are safe in pregnancy. Not enough is known about the long-term effects of lithium on infant neurodevelopment, and indeed the impact of antipsychotic exposure of the fetus. As well as risk profiles of individual drugs, efficacy has to be considered. Mood stabilisers taken throughout pregnancy appear to reduce the risk of relapse, but do not remove it (Bergink et al. 2012).

Table 2. Comparative teratogenic risk of Mood Stabilisers

Risks of Lithium	Risks of SGAs	Risks of Lamotrigine
Heart defects – Ebstein's anomaly	More data and research needed	Cleft lip
Risk of unpredictable lithium levels and risk of overdose	Small risk of increased congenital malformations	Autism spectrum disorder
Increased risk of stillbirth and infant death		
Low birth weight and floppy baby syndrome		

Continuing sodium valproate

If a patient had stable mood on valproate, having found that no other drug works for her, a decision to continue valproate in childbearing age should be respected, as long is she is advised about risks of pregnancy and offered full contraceptive cover. Given such a complex terrain of considerations and evidence, an individualized risk-benefit analysis must make space for a patient's circumstances and beliefs. Too many women with bipolar disorder are advised not to have children because of risk to their mental wellbeing and teratogenicity to the baby (Cohen et al. 2010). Clinical contributions to discussions about valproate should include severity of illness, risk of relapse, family history of bipolar and congenital malformations, biological, psychological and social impact of the mother's illness, family support, number of weeks gestation and other mood stabilisers that have worked in the past. This conversation should begin soon after menarche – and certainly before conception is likely to occur, bearing in mind that 50% of pregnancies are unplanned (Meador and Loring, 2016). The teratogenic effects of valproate are most potent in the first trimester, which means that fetal damage may have already been done before the prescription of valproate in pregnancy is detected if not forecast and actively monitored.

After thorough counseling with exchange of evidence and ideas from a health professional, if the patients till wants to continue with both her pregnancy and valproate treatment (dependent on capacity as outlined in the Mental Capacity Act of 2005) her autonomous choice must be respected. Clinicians need not agree with the rationale of their patients' wishes, as long as there is documentation of rigorous counseling and a signed consent form. The unborn fetus does not have rights as a patient under UK law, and so the mother must be considered to be sole patient, despite the very best outcomes for the fetus being desirable.

It is then the NHS' responsibility to minimize risks associated with this decision. Regarding a valproate regimen, slow release formula at the lowest effective divided dose to a maximum of 1g should be given daily to prevent plasma concentration spikes. Polytherapy with other AEDs should be emphatically avoided. Specialist prenatal monitoring must be instigated to check the plasma-valproate concentration in the mother (to assess concordance) and fetal growth checked. Routine ultrasound and amniocenteses is offered for prenatal diagnosis of abnormalities. Daily folic acid prophylaxis (5mg daily) must be prescribed pre-conception (if possible) and throughout the first semester to limit the risk of neural tube defects. Also, vitamin K should be administered to the mother after 36 weeks and to the baby post-delivery because increased incidence of hemorrhagic disease in the newborn has been reported after exposure to AEDs. It is also best practice for a woman with mental health conditions - particularly if on high-risk medication - to see the same midwife throughout the nine months.

However, rather than a woman choosing to enter pregnancy while taking valproate and knowing the risks, it is unfortunately more likely that she will be pregnant and unaware of endangering her baby, neither informed nor advised. Many women who have bipolar from a young age are started on medication to achieve remission. Psychotropic prescriptions are less likely to be tightly monitored after many years. If women on chronic medication in a stable state become pregnant – planned or otherwise – they may not be under regular care from a psychiatrist, and therefore may not have access to resources to make an informed choice about a medication regimen.

Such clinical negligence is unacceptable, but systemically possible. In 2016, the BMJ reported findings from the Medicines and Healthcare products Regulatory Agency (MHRA) survey which found that 50% of women questioned aged 16 to 50 with epilepsy were unaware that valproate could harm a fetus, and 20% currently taking valproate did not know about this risk either. Over a quarter of participants had not discussed risks in pregnancy with a health professional. It would be revealing to repeat this survey with women on valproate for bipolar disorder, and compare the results.

Although no excuse, healthcare professionals may say they have insufficient time and tools to facilitate these critical conversations with their patients. In a 2016 RCOG report, Judy Shakespeare (a retired GP and reviewer for MBRRACE mortality cases) explained that if doctors are not given longer than 10 minutes to facilitate ethically and medically complex dialogue, women can easily feel "rushed, judged or 'processed'." All patients making a decision about valproate therapy must have equal access to information – both printed and verbalised – particularly if they have learning disabilities. For those who do not speak or read English, an interpreter or advocate may be needed.

MHRA has taken a step in the right direction by producing a toolkit with a checklist of important discussion points and a video to prompt GPs to review female patients on valproate. Counseling should be based in evidence but must always elicit women's opinions and values. If she consents, the decision may benefit from the baby's other parent's contribution, and that of wider family members. It is imperative as more is discovered about the risks of teratogenic drugs, that GPs and specialists keep up-to-date with the latest evidence to provide the best care possible.

Conclusion

The large majority of women of childbearing age with bipolar disorder should not be prescribed sodium valproate as the risks to the unborn fetus far outweigh the benefits of the medication, as other drugs have similar if not better efficacy, with lower risks to the

fetus. In the small minority of women for whom valproate may be the only effective treatment, she must be fully informed of the teratogenic and neurodevelopmental risks, as well as the ways in which the pregnancy can be managed to reduce such risks. Women with bipolar disorder should never be made to feel that their mental health forecloses the prospect of motherhood, or is incompatible with the safety of any future baby.

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References

1. *Beck, CT.: Predictors of postpartum depression: an update. Nursing research 2001; 50(5) 275-285.*
2. *Beck, CT.: The effects of postpartum depression on maternal-infant interaction: a meta-analysis. Nursing research 1995; 44(5) 298-304.*
3. *Bergink V, Bouvy PF, Vervoort JS, Koorengevel KM, Steegers EA, Kushner SA.: Prevention of postpartum psychosis and mania in women at high risk. Am J Psychiatry. 2012 Jun; 169(6):609-15.*
4. *Boden R, Lundgren M, Brandt L, Reutfors J, Andersen M, Kieler H.: Risks of adverse pregnancy and birth outcomes in women treated or not treated with mood stabilisers for bipolar disorder: population based cohort study. BMJ (Clinical research ed.) 2012; 345 e7085.*
5. *Bromley RL, Calderbank R, Cheyne CP, Rooney C, Trayner P, Clayton-Smith J, García-Fiñana M, Irwin B, Morrow JI, Shallcross R, Baker GA; UK Epilepsy and Pregnancy Register.: Cognition in school-age children exposed to levetiracetam, topiramate, or sodium valproate. Neurology. 2016 Nov 1; 87(18):1943-1953.*
6. *Bromley R, Weston J, Adab N, et al.: Treatment for epilepsy in pregnancy: neurodevelopmental outcomes in the child (Review). Cochrane Database Syst Rev2014; 10:CD010236.*
7. *Campbell E, Kennedy F, Irwin B, Morrison P, Delanty N, Hunt S, Craig J, Morrow J.: Malformation Risks of Antiepileptic Drug Monotherapies in Pregnancy. Journal of neurology, neurosurgery, and psychiatry 2013; 84(11) e2.*
8. *Casassus B.: France bans sodium valproate use in case of pregnancy. Lancet. 2017 Jul 15; 390(10091):217.*
9. *Cohen LS, Wang B, Nonacs R, Viguera AC, Lemon EL, Freeman MP.: Treatment of mood disorders during pregnancy and postpartum. Psychiatr Clin North Am. 2010 Jun; 33(2):273-93.*
10. *Galbally M, Roberts M, Buist A; Perinatal Psychotropic Review Group.: Mood stabilisers in pregnancy: a systematic review. Aust N Z J Psychiatry. 2010 Nov; 44(11):967-77.*
11. *Gentile S. Lithium in pregnancy: the need to treat, the duty to ensure safety.: Expert opinion on drug safety 2012;11(3) 425-437.*
12. *Haskey C, Galbally M: Mood stabilisers in pregnancy and child developmental outcomes: A systematic review. Aust N Z J Psychiatry. 2017 Aug 1:4867417726175.*
13. *Holmes LB, Mittendorf R, Shen A, et al.: Fetal effects of anticonvulsant polytherapies: different risks from different drug combinations. Arch Neurol 2011; 68:1275–1281.*
14. *Kmietowicz Z.: Women are unaware of pregnancy risks linked with sodium valproate. BMJ. 2016 Oct 30.*
15. *Man SL, Petersen I, Thompson M, Nazareth I.: Antiepileptic drugs during pregnancy in primary care: a UK population based study. PLoS One. 2012; 7(12):e52339.*
16. *Meador KJ, Baker GA, Browning N, Clayton-Smith J, Combs-Cantrell DT, Cohen M, Kalayjian LA, Kanner A, Liporace JD, Pennell PB, Privitera M, Loring DW.: Cognitive function at 3 years of age after fetal exposure to antiepileptic drugs. N. Engl. J. Med. 2009, 360 (16): 1597–1605.*
17. *Meador KJ, Loring DW.: Developmental effects of antiepileptic drugs and the need for improved regulations. Neurology. 2016 Jan 19; 86(3):297-306.*
18. *Meijer JL, Bockting CL, Beijers C, Verbeek T, Stant AD, Ormel J, Stolk RP, de Jonge P, van Pampus MG, Burger H: Pregnancy Outcomes after a Maternity Intervention for Stressful Emotions (PROMISES): study protocol for a randomised controlled trial. Trials 2011; 12 157-6215-12-157.*
19. *National Institute for Clinical Excellence. Antenatal and postnatal mental health (NICE clinical guideline 45). [Online]*
20. *Newport DJ, Wilcox MM, Stowe ZN: Antidepressants during pregnancy and lactation: defining exposure and treatment issues. Semin Perinatol 2001; 25:177-90.*
21. *Nguyen HT, Sharma V, McIntyre RS.: Teratogenesis associated with antibipolar agents. Advances in Therapy 2009; 26(3) 281-294.*
22. *Petersen I, McCrea RL, Sammon CJ, Osborn DP, Evans SJ, Cowen PJ, Freemantle N, Nazareth I. Risks and benefits of psychotropic medication in pregnancy: cohort studies based on UK electronic primary care health records. Health Technol Assess. 2016 Mar; 20(23):1-176.*
23. *Pinelli JM, Symington AJ, Cunningham KA, Paes BA.: Case report and review of the perinatal implications of maternal lithium use. American Journal of Obstetrics and Gynecology 2002; 187(1) 245-249.*
24. *Price SK, Bentley KJ.: Psychopharmacology decision-making among pregnant and postpartum women and health providers: informing compassionate and collaborative care women's health. Women & health 2013; 53(2) 154-172.*
25. *Stadelmaier R, Nasri H, Deutsch CK, Bauman M, Hunt A, Stodgell CJ, Adams J, Holmes LB.: Exposure to Sodium Valproate during Pregnancy: Facial Features and Signs of Autism. Birth Defects Res 2017; 109:1134-1143.*
26. *Stein A, Pearson RM, Goodman SH, Rapa E, Rahman A, McCallum M, Howard LM, Pariante CM: Review Effects of perinatal mental disorders on the fetus and child. Lancet. 2014 Nov 15; 384(9956):1800-19.*
27. *Taylor CL, van Ravesteyn LM, van denBerg MP, Stewart RJ, Howard LM. The prevalence and correlates of self-harm in pregnant women with psychotic disorder and bipolar disorder. Arch Womens Ment Health. 2016 Oct; 19(5):909-15.*
28. *Tomson T, Battino D, Bonizzoni E, et al.: Dose-dependent risk of malformations with antiepileptic drugs: an analysis of data from the EURAP epilepsy and pregnancy registry. Lancet Neurol 2011; 10:609–617.*

29. Viguera AC, Whitfield T, Baldessarini RJ, Newport DJ, Stowe Z, Reminick A, Zurick A, Cohen LS.: Risk of recurrence in women with bipolar disorder during pregnancy: prospective study of mood stabiliser discontinuation. Am J Psychiatry. 2007 Dec; 164(12):1817-24.
30. Yonkers KA, Wisner KL, Stowe Z, Leibenluft E, Cohen L, Miller L, Manber R, Viguera A, Suppes T, Altshuler L.: Management of bipolar disorder during pregnancy and the postpartum period. Am J Psychiatry. 2004 Apr; 161(4):608-20.
31. Zucchi FC, Yao Y, Ward ID, Ilnytskyy Y, Olson DM, Benzies K, Kovalchuk I, Kovalchuk O, Metz GA.: Maternal stress induces epigenetic signatures of psychiatric and neurological diseases in the offspring. PLoS One. 2013;8(2):e56967.

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