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Valproic acid: reducing the risks of prenatal exposure

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Fetal valproic acid exposure is associated with higher risks for a broad spectrum of major congenital malformations compared with other widely used antiepileptic drugs.¹

Furthermore, fetal valproic acid exposure is linked to risks of reduced cognitive abilities and increased autism.^{2,3} On the basis of the present data, valproic acid is clearly the most teratogenic antiepileptic drug currently prescribed.¹ In 2014, the Pharmacovigilance Risk Assessment Committee (PRAC) of the European Medicines Agency recommended that valproic acid, “should not be used in female children, women of childbearing potential and pregnant women unless alternative treatments are ineffective or not tolerated.”⁴

In *The Lancet Neurology*, Torbjörn Tomson and colleagues⁵ review evidence on the risks of prenatal valproic acid exposure to children, including implications for management of seizure disorders, and raise concerns that in some circumstances the new restrictions are excessive. They agree that, whenever possible, valproic acid should be avoided in women of childbearing potential, especially in those with focal epilepsies and unclassified epilepsies. However, Tomson and colleagues argue that because valproic acid is the most effective antiepileptic drug for some primary generalised epilepsies, it should still be considered in specific circumstances, such as for women with severe concurrent disabilities or very severe epilepsy, who are very unlikely to become pregnant; young girls with an epilepsy type highly likely to go into remission, allowing antiepileptic drug withdrawal before puberty; and well informed and competent women who should retain the right to choose valproic acid if they understand the risks, do not plan pregnancy, and take adequate precautions against pregnancy. These circumstances are reasonable as long as the patient (or their caregiver) is well informed.

The PRAC recommended further changes to product information and additional risk-minimisation measures including educational materials to better inform patients and clinicians.⁴ Tomson and colleagues raised no concerns with these recommendations, and in fact, they state that every woman receiving valproic acid should be counselled on a regular basis about the risks of this treatment and alternative treatments should be discussed.⁵ They further state that withdrawal or switch to another antiepileptic drug should be considered in women contemplating pregnancy. Unfortunately, waiting until a pregnancy is considered will probably result in unwanted fetal valproic acid exposures since 40–50% of pregnancies are not planned.⁶ Determination of whether an antiepileptic drug other than valproic acid is effective early in the course of treatment, well before any planned or unplanned pregnancy, seems more prudent than waiting until a pregnancy is planned. In randomised head-to-head comparisons in primary generalised epilepsy,⁷ valproic acid was more effective than lamotrigine (5% more withdrawals) and topiramate (14% more withdrawals),⁸ but had

similar effectiveness to levetiracetam. In childhood absence epilepsy, valproic acid had more cognitive side-effects than ethosuximide.⁹ Several other antiepileptic drugs are effective in primary generalised epilepsy, but no randomised comparisons between these and valproic acid have been done. Teratogenic risks are low for lamotrigine and levetiracetam, intermediate for topiramate, and uncertain or unknown for other antiepileptic drugs that are effective in these seizure types, emphasising the importance of continued research on the teratogenic risks of antiepileptic drugs.¹

Teratogens act on a susceptible genetic substrate in a dose-dependent manner.² At present, we cannot predict genetic susceptibility to valproic acid. Since the teratogenic effects of valproic acid are dose-dependent, Tomson and colleagues recommend clinicians prescribe the lowest effective dose, aiming at 500–600 mg/day, for women of childbearing potential.⁵ However, as Tomson and colleagues note, a safe dose has not been defined. In a 2015 study,¹⁰ children exposed in utero to less than 800 mg/day had significantly lower verbal IQ and increased need for educational interventions.

The PRAC called for a drug-utilisation study to assess the effectiveness of their proposed risk-minimisation measures.⁴ Measurement of effectiveness should be a crucial component of any health-care policy. Recently published data suggest that previous publications and health-care policies have not been effective in reducing fetal valproic acid exposures. For example, the UK Statistics Authority published statistics on drug prescriptions in England from 2004 to 2014.¹¹ Valproic acid was the third most prescribed antiepileptic drug in 2014, with 2.7 million items dispensed in the UK. Furthermore, valproic acid prescriptions increased from 2004 to 2014, which should have been sufficient time to see a change in prescription practices in response to the growing scientific literature on fetal valproic acid risks. Although these numbers are not stratified by sex, valproic acid should no longer be the third most widely used antiepileptic drug—with prescriptions continuing to increase—in view of the large portion of the epilepsy population that are women of childbearing potential and the number of alternative antiepileptic drugs. These data suggest that women in this population are not receiving adequate information for informed consent.

The continued high use of valproic acid justifies the PRAC recommendation against its first-line use in most women of childbearing potential, but limited exceptions noted by Tomson and colleagues are valid as long as these women (or their caregivers) are appropriately educated about valproic acid's risks and informed consent is documented.

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References

1. Meador KJ, Loring DW. Developmental effects of antiepileptic drugs and the need for improved regulations. *Neurology* 2015; published online Oct 30. DOI:10.1212/WNL.0000000000002119.

2. Meador KJ, Baker GA, Browning N, et al. Fetal antiepileptic drug exposure and cognitive outcomes at age 6 years (NEAD study): a prospective observational study. *Lancet Neurol* 2013; 12: 244–52. [PubMed: 23352199]
3. Christensen J, Gronborg TK, Sorensen MJ, et al. Prenatal valproate exposure and risk of autism spectrum disorders and childhood autism. *JAMA* 2013; 309: 1696–703. [PubMed: 23613074]
4. European Medicines Agency. Assessment report. Procedure under article 31 of directive 2001/83/EC resulting from pharmacovigilance data. http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/Valproate_and_related_substances_31/Recommendation_provided_by_Pharmacovigilance_Risk_Assessment_Committee/WC500177352.pdf(accessed Nov 14, 2015).
5. Tomson T, Battino D, Perucca E. Valproic acid after five decades of use in epilepsy: time to reconsider the indications of a time-honoured drug. *Lancet Neurol* 2015; published online Dec 4. 10.1016/S1474-4422(15)00314-2.
6. Sedgh G, Singh S, Hussain R. Intended and unintended pregnancies worldwide in 2012 and recent trends. *Stud Fam Plann* 2014; 45: 301–314. [PubMed: 25207494]
7. Trinka E, Marson AG, Van Paesschen W, et al. KOMET: an unblinded, randomised, two parallel-group, stratified trial comparing the effectiveness of levetiracetam with controlled-release carbamazepine and extended-release sodium valproate as monotherapy in patients with newly diagnosed epilepsy. *J Neurol Neurosurg Psychiatry* 2013; 84: 1138–47. [PubMed: 22933814]
8. Marson AG, Al-Kharusi AM, Alwaidh M, et al. The SANAD study of effectiveness of valproate, lamotrigine, or topiramate for generalised and unclassifiable epilepsy: an unblinded randomised controlled trial. *Lancet* 2007; 369: 1016–26. [PubMed: 17382828]
9. Glauser TA, Cnaan A, Shinnar S, et al. Ethosuximide, valproic acid, and lamotrigine in childhood absence epilepsy. *N Engl J Med* 2010; 362: 790–99. [PubMed: 20200383]
10. Baker GA, Bromley RL, Briggs M, et al. IQ at 6 years after in utero exposure to antiepileptic drugs: a controlled cohort study. *Neurology* 2015; 84: 382–90. [PubMed: 25540307]
11. Prescribing and Medicines Team of Health and Social Care Information Centre. Prescriptions dispensed in the community, England 2004–14. July 7, 2015 <http://www.hscic.gov.uk/catalogue/PUB17644/pres-disp-com-eng-2004-14-rep.pdf> (accessed Nov 14, 2015).