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EDITORIALS

Dangers of valproate in pregnancy

New measures expected to improve protection for unborn children

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In the UK, valproate is licensed for the treatment of all forms of epilepsy and manic episodes in bipolar disorder when lithium is contraindicated or not tolerated. In patients whose manic symptoms have responded, valproate can be continued to prevent recurrence. In practice, valproate is also prescribed for unlicensed indications, including prophylaxis against migraine, prevention of clozapine induced seizures, and reduction of aggression, impulsivity, and other symptoms in adults with severe mental disorders.

On 9 February this year, the Pharmacovigilance Risk Assessment Committee of the European Medicines Agency[1] published its recommendation that valproate should not be used in pregnancy unless the woman has a form of epilepsy that is unresponsive to other anti-epileptic drugs. The committee also recommended that the drug should not be prescribed to patients with childbearing potential unless they follow a comprehensive "pregnancy prevention programme." These recommendations, which go further than previous European and UK guidance, were adopted by the Coordination Group for Mutual Recognition and Decentralised Procedures of the European Union on 23 March.[2] The European Commission will decide within two months of this date whether the recommendations will become legally binding across the EU. A positive decision would be desirable, and looks likely.

Why have these steps been taken?

There is consistent evidence that valproate exposure is a major risk to the intrauterine development of children. About 11% of exposed children are born with congenital malformations,[3] a roughly three times higher risk than in the general population. Anomalies can be severe and affect several organ systems. Compared with children of mothers without epilepsy or who have untreated epilepsy, exposed children have been reported to be intellectually less able,[4] seven times more likely to have developmental delay,[5] and three and five times more likely to have autism spectrum disorder or autism, respectively.[6] Taking into account other developmental problems, it has been estimated that 30-40% of exposed preschool children may be affected.[7] The spectrum of harm suggests that the developing child is vulnerable to valproate throughout pregnancy. A safe dose has not been identified, and concomitant folic acid provides, at best, only partial protection from adverse effects.[8]

Despite these well known safety concerns, limited data suggest that valproate prescribing has not shown a consistent large decline across Europe or across indications. Recent audits and surveys conducted in the UK and other European countries also indicate that substantial proportions of girls and women of childbearing age taking valproate have not been informed of the risks by health professionals, or are not aware of them.[9-14]

If the European Commission accepts the recommendations, all women of childbearing age who are being prescribed valproate will probably have to be identified and their treatment reviewed within a specified time frame. Recent prescribing data from England[15] indicate that on average there will be less than one patient per general practitioner. Close collaboration between primary and secondary care will be needed.

Women must not stop taking valproate without first consulting their doctor. If they are not currently not pregnant, a specialist should review whether valproate is still needed or can be replaced by another drug. All those who continue treatment with valproate must follow the pregnancy prevention programme.[2] This includes an assessment of their potential to become pregnant, pregnancy tests before and during treatment, and counselling about the risks of valproate to unborn children and the importance of effective contraception throughout treatment. Patients will be required to have specialist reviews and complete a risk acknowledgement form every year.[2] Valproate packaging will carry a visual warning of the pregnancy risks and patients will receive a warning card with each prescription.[2] Pharmacists will be required to discuss the risks every time they dispense valproate to women of childbearing age.[2]

Urgent action

Patients who are pregnant and taking valproate should be reviewed urgently by a specialist—ideally within 72 hours. Unless the woman has epilepsy and has not responded to alternative medication, the aim is to discontinue valproate, replace it with another drug if required, and put a management

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plan in place to minimise the risk of a deterioration in mental state or seizure control.

It has taken half a century since valproate was first introduced to understand the full extent of harm to unborn children. Current regulatory systems are clearly inadequate at identifying and assessing the reproductive risks of medicines. Pregnant women are usually excluded from drug development studies on ethical grounds, and postmarketing surveillance of pregnancy outcomes is largely unplanned and uncoordinated. Although challenging to achieve, we urgently need a regulatory system for the standardised and timely collection of pregnancy outcome data for new and existing drugs that may harm offspring. Mandatory pregnancy registers, targeted data mining of other resources, and regular evaluation of all available evidence would be key elements to achieve this aim.

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1 European Medicines Agency. PRAC recommends new measures to avoid valproate exposure in pregnancy. Press release, 9 Feb 2018. http://www.ema.europa.eu/docs/en_GB/document_library/Press_release/2018/02/WC500243555.pdf.
2 European Medicines Agency. New measures to avoid valproate exposure in pregnancy endorsed. Press release, 23 March 2018. http://www.ema.europa.eu/docs/en_GB/document_library/Press_release/2018/03/WC500246391.pdf
3 Meador K, Reynolds MW, Crean S, Fahrbach K, Probst C. Pregnancy outcomes in women with epilepsy: a systematic review and meta-analysis of published pregnancy registries and cohorts. *Epilepsy Res* 2008;81:1-13. 10.1016/j.eplepsyres.2008.04.022 18565732
4 Bromley R, Weston J, Adab N, etal . Treatment for epilepsy in pregnancy: neurodevelopmental outcomes in the child. *Cochrane Database Syst Rev* 2014;10:CD010236.25354543
5 Veroniki AA, Rios P, Cogo E, etal . Comparative safety of antiepileptic drugs for neurological development in children exposed during pregnancy and breast feeding: a systematic review and network meta-analysis. *BMJ Open* 2017;7:e017248. 10.1136/bmjopen-2017-017248 28729328
6 Christensen J, Grønborg TK, Sørensen MJ, etal . Prenatal valproate exposure and risk of autism spectrum disorders and childhood autism. *JAMA* 2013;309:1696-703. 10.1001/jama.2013.2270 23613074
7 European Medicines Agency. CMDh agrees to strengthen warnings on the use of valproate medicines in women and girls. Press release, 21 Nov 2014. http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/Valproate_and_related_substances_31/Position_provided_by_CMDh/WC500177637.pdf
8 Wieck A, Reis M. Pharmacological treatment of mental health problems in pregnancy and lactation. In: Castle DJ, Abel KM, eds. *Comprehensive women's health*. Cambridge University Press, 2016: 122-3610.1017/CBO9781107045132.012.
9 Wieck A, Rao S, Sein K, Haddad PM. A survey of antiepileptic prescribing to women of childbearing potential in psychiatry. *Arch Womens Ment Health* 2007;10:83-5. 10.1007/s00737-007-0175-y 17380253
10 Langan J, Perry A, Oto M. Teratogenic risk and contraceptive counselling in psychiatric practice: analysis of anticonvulsant therapy. *BMC Psychiatry* 2013;13:234. 10.1186/1471-244X-13-234 24066860
11 Royal College of Psychiatrists, Centre for Care Quality Improvement. Topic 15a baseline audit report. Prescribing valproate for bipolar disorder. 2016. https://www.covwarkpt.nhs.uk/download.cfm?doc=docm93jijm4n2406.pdf&ver=3039
12 Epilepsy Society. Women still not aware of epilepsy medicine risk in pregnancy. 2017. https://www.epilepsysociety.org.uk/news/women-not-aware-epilepsy-medicine-risk-pregnancy-27-09-2017
13 Friedrich L, Sruk A, Bielen I. Women with epilepsy in childbearing age: Pregnancy-related knowledge, information sources, and antiepileptic drugs. *Epilepsy Behav* 2018;80:122-8. 10.1016/j.yebeh.2018.01.002 29414541
14 Dierking C, Porschen T, Walter U, Rösche J. Pregnancy-related knowledge of women with epilepsy - An internet-based survey in German-speaking countries. *Epilepsy Behav* 2018;79:17-22. 10.1016/j.yebeh.2017.11.013 29223932
15 NHS England. Sodium valproate prescribing. 2017. https://www.england.nhs.uk/publication/prescribing-for-sodium-valproate/.