Patient Safety Notice

PSN037 / April 2017

Resources to support the safety of girls and women who are being treated with Valproate

To: All NHS Wales Chief Executives, Medical Directors, Directors of Nursing and Patient Safety Teams.

Valproate, also known as valproic acid (brand names include Epilim and Depakote) is an effective medication used to treat epilepsy[1] and bipolar disorder.[2] Although unlicensed for treatment of other conditions in the UK, we are aware of 'off-label' use for migraine or chronic pain.[3]

In girls and women of childbearing potential, valproate should be initiated and supervised by a specialist and **only** when other medications have not been tolerated or have been found to be ineffective.

Unborn babies exposed to valproate during pregnancy are at very high risk (30-40 in every 100)[4,5,6,7] of neurodevelopment disability - such as lower intelligence and autistic spectrum disorders, and also at risk (10 in every 100) of other birth defects.[8] This has been increasingly recognised and reflected in strengthened regulatory guidance issued in 2014.[9]

In 2015 the Medicines and Healthcare products Regulatory Agency (MHRA) published the valproate toolkit, providing a set of resources for patients, GPs, pharmacists and specialists.[3] This was added to in February 2016 and April 2017 www.gov.uk/government/publications/toolkit-on-the-risks-of-valproate-medicines-in-female-patients.[11] Welsh language versions of the toolkit resources are also available from the same source.

These resources emphasise the need to avoid the use of valproate in girls and women of childbearing potential; warn women of the very high risks to the unborn child of valproate in pregnancy; and emphasise the need for effective contraception planning and specialist oversight of changes to medication when planning a pregnancy, as abrupt changes to medication can be harmful.

Actions

When: As soon as possible but no later than 6 October 2017

Who: GP practices, community pharmacies, local health boards and NHS trusts providing NHS funded-care where valproate is prescribed or dispensed.

1. Identify how the resources signposted in this alert can be used to support fully informed decisions on the use of valproate by girls and women of childbearing age

2. Develop an action plan to ensure all girls and women of or nearing childbearing age taking valproate are systematically identified so that all relevant resources can be used to plan care.

3. Ensure relevant resources are embedded in clinical practice for current and future patients by revising local training, procedures and protocols.

4. By circulating this notice or through local alternatives (such as newsletters and local awareness campaigns) ensure staff are aware of the MHRA resources and understand their role in local plans to identify girls and women of childbearing age taking valproate.

*Community pharmacies should deliver all actions that are within their remit, but systematic identification will typically need to be taken by the organisation prescribing valproate.

The MHRA resources have had widespread dissemination. This has resulted in a change of clinical practice in some organisations but evidence suggests a further concerted effort is needed to ensure professionals are informing all girls and women of childbearing age. This evidence includes:

- a survey of women in April 2016 that found of those taking valproate (n=624), 20% were not aware of any of the risks of valproate in pregnancy and <20% had received any of the educational materials[12]

- a National Reporting and Learning System (NRLS) search for incidents involving valproate and reported since January 2015 identified 13 reports that indicated valproate had been prescribed, including two that specifically reported no discussion of the risks in pregnancy had occurred. For example:

  "Patient … on valproate. No discussion in notes about information or risks given to young female patient taking valproate."

The actions in this alert ask all organisations to undertake systematic identification of girls and women who are taking valproate, and ensure the MHRA resources are used to support them to make informed choices.

Technical notes

Patient safety incident reporting

National Reporting and Learning System (NRLS) searches for incident dates between 1 January 2015 and 31 December 2016 exported to the NRLS on or before 27 February 2017. Extraction used drug and brand names and misspells of valproate, valproic, Depakote, Convulex, Epilim, Episenta, Epival. Three searches were conducted; on incidents reported as death and severe harm for all settings and specialties; on no harm, low harm and moderate harm incidents in obstetric specialities; and on no harm, low harm and moderate harm incidents outside obstetric specialties where the medication keywords occurred alongside keywords related to pregnancy or contraception.

These searches identified 15 relevant incidents (nine where there was the potential for pregnancy, and six where pregnancy occurred). Valproate was actually prescribed in 13 of the 15 incidents reported, and two of those reports noted that no contraceptive advice was given.

Share any learning from local investigations or locally developed good practice resources by emailing:

ImprovingPatientSafety@Wales.gsi.gov.uk

References

1. National Institute for Health and Care Excellence. Epilepsies. Clinical guideline [CG137] 2012 (Jan) Update 2016 (Feb) www.nice.org.uk/guidance/cg137 (accessed 8 March 2017)
2. National Institute for Health and Care Excellence. Bipolar disorder. Clinical guideline [CG185] 2014 (Sept) Update 2016 (Feb) www.nice.org.uk/guidance/cg185 (accessed 8 March 2017)
3. Medicines and Healthcare products Regulatory Agency. Medicines related to valproate: risk of abnormal pregnancy outcomes. www.gov.uk/drug-safety-update/medicines-related-to-valproate-risk-of-abnormalpregnancy-outcomes (accessed 24 February 2017)
4. Bromley RL et al Epilepsia 2010;51(10):2058-65. http://onlinelibrary.wiley.com/doi/10.1111/j.15281167.2010.02668.x/abstract;jsessionid=B2C2D9BE6390851E5F1C38B0B85C79AB.f02t03 (accessed 28 March 2017)
5. Cummings et al. Archives of Disease in Childhood 2011;96(7):643-7. http://adc.bmj.com/content/96/7/643?ijkey=0aa3242c8817f43620d88cbdabfb967c8cd560a2&keytype2=tf_ipsecsha (accessed 28March 2017)
6. Meador K et al. The New England Journal of Medicine 2009;360(16):1597-605. www.nejm.org/doi/full/10.1056/NEJMoa0803531 (accessed 28 March 2017)
7. Thomas S.V et al. Epilepsy & Behaviour 2008;13(1):229-36. www.sciencedirect.com/science/article/pii/S1525505008000115 (accessed 28 March 2017)
8. Meador K et al. Pregnancy outcomes in women with epilepsy: a systematic review and meta-analysisof published pregnancy registries and cohorts. Epilepsy Research. 2008 Sep;81(1):1-13. doi: 10.1016/j. eplepsyres.2008.04.022. Epub 2008 Jun 18
9. European Medicines Agency. CMDh agrees to strengthen warnings on the use of valproate medicines in women and girls. www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/referrals/Valproate_and_related_substances/human_referral_prac_000032.jsp&mid=WC0b01ac05805c516f (accessed 24 February 2017)
10. Medicines and Healthcare products Regulatory Agency. Valproate and risk of abnormal pregnancy outcomes:new communication materials. www.gov.uk/drug-safety-update/valproate-and-of-risk-of-abnormal-pregnancyoutcomes-new-communication-materials (accessed 24 February 2017)
11. Medicines and Healthcare products Regulatory Agency. Toolkit on the risks of valproate medicines in female patients. www.gov.uk/government/publications/toolkit-on-the-risks-of-valproate-medicines-in-female-patients (accessed 28 March 2017)
12. Epilepsy Society. Worrying lack of knowledge over epilepsy medicine risks in pregnancy. www.epilepsysociety.org.uk/worrying-lack-knowledge-over-epilepsy-medicine-risks-pregnancy#.WNkvWm_ysdU (accessed 28 March 2017)

Stakeholder engagement

• National Patient Safety Response Advisory Panel (for a list of members and organisations represented on the panel, see improvement.nhs.uk/resources/patient-safety-alerts/)

Advice for Patient Safety Teams

This alert asks for a systematic approach to contacting all affected patients, and therefore needs co-ordinated implementation rather than separate action by individual teams or departments. We recommend that health boards and trusts seek advice from their medical director, and where appropriate, clinical director for neurology, clinical director for paediatrics and medication safety officer who will be able to identify who to direct this alert to. We recommend that GP practices and community pharmacies consider who would be the most appropriate person to co-ordinate local action before wider dissemination of the alert.