Medicines & Healthcare products Regulatory Agency

Healthcare Improvement Scotland

Patient Safety Alert

Ref: SCOT/NHS/PSA/2017/001 **Date:** 23 May 2017

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

Source: This Patient Safety Alert is issued in association with MHRA and NHS Improvement in NHS England. The content is based on Patient Safety Alert NHS/PSA/RE/2017/002 issued by NHS Improvement on 6 April 2007 and contextualised for NHSScotland use. Information is also available on NHS Inform.

Summary

In girls and women of childbearing potential, all forms and all brands of 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.

As unborn babies exposed to valproate are at very high risk of neurodevelopment disability and other birth defects, this alert signposts providers to updated MHRA resources to support patients, GPs, pharmacists and specialists in ensuring patients being prescribed valproate are aware of the risks, the need for effective contraception planning, and the requirement for specialist oversight if they are planning a pregnancy to safely change their medication.

Action

Attention is drawn to the communication resources referred to in this alert. Consideration should be given as how best these can be highlighted to prescribers to support fully informed decisions on the use of valproate by girls and women of child-bearing age.

NHS boards are advised to:

- implement systems 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 their care
- ask NHS board governance committee to monitor progress on the implementation of systems to ensure all girls and women on valproate receive the highest quality care
- ensure resources are easily accessible and embedded in clinical practice for current and future patients at a local level, and
- circulate this Alert or through local alternatives (such as newsletters or local awareness campaigns) ensure that staff are aware of the MHRA resources and understand their role in local plans to identify all girls and women of childbearing age taking valproate.

Actions

- Healthcare Improvement Scotland- responsible for ensuring that the alert is fit for purpose in NHSScotland, dissemination of alert to service via Directors of Pharmacy and Medical Directors, and dissemination to liaison contacts in NHS boards for awareness and independent healthcare services for action.

- NHS boards - responsible for governance of implementation through the appropriate governance committee ensuring that systems to identify patients are in place

- Directors of Pharmacy/Medical Directors - responsible for dissemination to the relevant professionals and services for action (see suggested distribution list).

- Lead Clinicians and Pharmacists in primary and secondary care - responsible for developing a plan of action to ensure that all current patients are identified and every patient receives advice about safety issues and also MHRA support materials to make an informed choice. Also a system put in place when new patients present for treatment.

- Every prescribing clinician - responsible for ensuring communication of risks and support material to the patient, helping them to come to a decision about whether they wish to take the medicine and annotating the discussion in notes.

Problem / background

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[9] and April 2017 www.gov.uk/government/publications/toolkit-on-the-risks-of-valproate-medicines-in-female-patients[11]. 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.

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], and

- 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.

Distribution

If you are responsible for disseminating these alerts in your organisation, these are our suggested distribution lists. There may be additional or different groups within your local board who should be notified.

- CAMHS
- Community Pharmacists
- GP practices
- Gynaecologists
- Mental Health Services
- Neurologists/Paediatric Neurologists
- Paediatricians
- Sexual Health Clinics

References

Patient safety incident reporting

NHS England's 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.

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 26 April 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 26 April 2017)

3 Medicines and Healthcare products Regulatory Agency. Medicines related to valproate: risk of abnormal pregnancy outcomes. https://www.gov.uk/drug-safety-update/medicines-related-to-valproate-risk-of-abnormal-pregnancy-outcomes

(accessed 26 April 2017)
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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 26 April 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 26 April 2017)
7 Thomas S.V et al. Epilepsy & Behaviour 2008;13(1):229-36. www.sciencedirect.com/science/article/pii/S1525505008000115 (accessed 26 April 2017)
8 Meador K et al. Pregnancy outcomes in women with epilepsy: a systematic review and meta-analysis of 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 26 April 2017)
10 Medicines and Healthcare products Regulatory Agency. Valproate and risk of abnormal pregnancy outcomes: new communication materials. https://www.gov.uk/drug-safety-update/valproate-and-of-risk-of-abnormal-pregnancy-outcomes-new-communication-materials (accessed 26 April 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 26 April 2017)
12 Epilepsy Society. Worrying lack of knowledge over epilepsy medicine risks in pregnancy. https://www.epilepsysociety.org.uk/worrying-lack-knowledge-over-epilepsy-medicine-risks-pregnancy#.WQCEck2V-po (published 26 October 2016)

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/)

Enquiries

Enquiries should be addressed to: hcis.adtc-collaborative@nhs.net