BPNA, OPEN UK and RCPCH Update for Valproate Prescribing in Paediatric Neurology

31 January 2024

BPNA, OPEN UK and RCPCH Update for Valproate Prescribing in Paediatric Neurology

In this document, we will

- Highlight the key points from the national patient safety alert regarding valproate
- Examples in paediatric epilepsies where two specialists are likely to agree that valproate is the medication of choice, considering the new regulation
- What you could do from now on to prepare for the safe implementation of the new regulation
- What to expect next from BPNA/OPEN UK/RCPCH

Key points from the national patient safety alert regarding valproate

The issue of valproate teratogenicity in women is well recognised and the Pregnancy Prevention Program has been in place since 2018. There has been a reduction in the number of women prescribed valproate between 2018 and 2023 but there continue to be pregnancies exposed to valproate. For men, there is a risk of likely reversible infertility and there are also concerns of testicular toxicity. This led to the MHRA issuing a new national patient safety alert on 28th November, 2023.

This new national patient safety alert regarding valproate is for anyone under the age of 55 with reproductive capacity (https://www.gov.uk/drug-device-alerts/national-patient-safety-alert-valproate-organisations-to-prepare-for-new-regulatory-measures-for-oversight-of-prescribing-to-new-patients-and-existing-female-patients-natpsa-slash-2023-slash-013-slash-mhra#explanation-of-identified-safety-issue) states that:

As a part of phase 1 (as of 31.1.24):

- No one (male or female) under the age of 55 should be started on valproate unless two specialists (defined below) independently consider and document that there is no other "effective or tolerated" treatment, or there are compelling reasons why the reproductive risks do not apply.

- Women under 55 already on valproate: At their next scheduled review, two specialists are required to independently consider and document that there is no other effective or tolerated treatment.

Phase 2 (date to be announced) will apply to current (prevalent) valproate prescriptions for men.

The supporting material from the marketing authorisation holders (including the updated Healthcare Professional Guide, Patient Guide and Annual Risk Acknowledgement Form for females, Risk Acknowledgement Form for male patients starting valproate and a patient card) are available at Valproate (Belvo, Convulex, Depakote, Dyzantil, Epilim, Epilim Chrono or Chronosphere, Episenta, Epival, and Syonell▼): new safety and educational materials to support regulatory measures in men and women under 55 years of age - GOV.UK (www.gov.uk)

Obtaining and documenting two specialist agreement

From 31st January 2024, a second independent specialist will need to agree that there are no other effective or tolerated treatment options to prescribing valproate.

- The second specialist is defined as
    - Consultant paediatric neurologist
    - Paediatrician with Expertise in Epilepsy
    - Epilepsy Specialist Nurse (there is NO requirement for Epilepsy Specialist Nurse to be a prescriber)

- At least one signatory on the two signatory forms must be a consultant. The second signatory for initiation of valproate treatment and the decision to continue or switch valproate treatment should not be in direct line management of the primary signatory.

- Examples of how 2 signatories may be achieved in paediatric practice are:

    Example 1 a Consultant Paediatrician with an Expertise in Epilepsy working with an experienced Epilepsy Specialist Nurse could both sign the risk acknowledgement form, provided that both have the knowledge and skills to make the decision and can do so independently. The consultant should be the lead signatory with the Epilepsy Specialist Nurse countersigning as the second specialist.

    Example 2 -a review of case notes or case discussion within an MDT framework may be used to obtain the countersignature, where the presenting clinician fulfils the criteria for specialist and is the first signatory and if the MDT agrees then a second signatory meeting criteria for specialist is nominated from the MDT; face to face review by the second specialist is not specifically required.

- The updated Annual Risk Acknowledgement Form (ARAF) for females and new Risk Acknowledgement Form for male patients starting valproate are available as editable PDFs. These forms can be accessed on the MHRA website and on electronic Medicines Compendium (eMC). A wet signature is not required, forms may be edited and shared electronically.

- Once two signatures have been obtained, all female patients under 55 years continuing valproate must be reviewed annually to confirm that valproate remains the most suitable treatment (i.e. there is no other effective or tolerated treatment), and that the patient is aware of the potential risks. The ARAF can be completed by a single specialist and if there is a permanent reason why the patient is not at risk of becoming pregnant, the patient or their representative is not required to sign the form each year. All prescribing decisions should occur under the guidance/care of a Consultant Paediatric Neurologist or Paediatrician with Expertise in Epilepsy.

- Female children and women already treated with valproate should be reviewed at least annually. At their next scheduled review an updated Annual Risk Acknowledgement Form for females

should be discussed and completed with a countersignature by a second specialist obtained. Once the second signature is obtained, subsequent annual reviews/ARAFs require a single signature.

- While currently there is no requirement for male patients to have Risk Acknowledgement Form signed annually, it is recommended they are reviewed annually to confirm that valproate remains the most suitable treatment (i.e. there is no other effective or tolerated treatment), and that the patient is aware of the potential risks.

The only licensed indication for valproate in paediatric practice is in the treatment of the epilepsies.

Some examples in paediatric epilepsies where two specialists are likely to agree that valproate could be used as the first line medication, in light of the new safety alert:

- Patients under 55 years with intellectual disability where clinicians and their parents/legal guardians agree that the patient lacks capacity to consent for sexual activity, and therefore they agree that there are compelling reasons to suggest that the absence of pregnancy risk is permanent, then valproate can be chosen as the first line treatment, if it is the most appropriate treatment. Examples include patients with genetic/structural developmental epileptic encephalopathies (DEE), severe congenital brain malformation, severe acquired brain injury following hypoxic-ischaemic encephalopathy.

- Patients with phenotype of specific genetic epilepsies, such as SCN1A where valproate is the most effective treatment, and the risk of SUDEP is higher than the standard SUDEP risk.

- Patients with frequent night-time generalised tonic-clonic seizures, where valproate is the most effective treatment, and the risk of SUDEP is higher than the standard SUDEP risk.

- Patients with self-limiting generalised epilepsies where we expect seizures to remit before puberty e.g. self-limiting myoclonic epilepsy in infancy.

If two specialists agree that valproate is the medication of choice, then documentation of the discussion with parents/carers around risks and benefits of valproate is required, as well as the actions mandated by MHRA.

The BPNA/RCPCH Prescribing valproate to female patients under 18 years of age has been updated to reflect the requirement for two signatories at initiation of valproate

https://bpna.org.uk/_common/show_unpro_doc.php?doc=February2024Prescribingvalproatetofemalepatientsunder18yearsofage_158a2c44dd60d669754ea44e9d18e787.pdf

What you could do from now to prepare for the safe implementation of the new regulation

- https://assets.publishing.service.gov.uk/media/6565ddf162180b0012ce82fd/NatPSA-2023-013-MHRA.pdf specifies the actions required by each organisation in response to the new regulatory measures.
- It states that implementation should be coordinated by an executive lead for quality (or equivalent) in Integrated Care Boards in England, Health Boards in Scotland, Health Boards in Wales, and Health and Social Care Trusts in Northern Ireland, alongside the Chief Pharmacist (or equivalent) and supported by the Medical Directors of organisations involved in the prescribing of valproate and clinical leads in neurology, psychiatry, paediatrics, intellectual disability and/or autism, contraception and sexual health, and general practice, with others included to meet local needs and clinical situations.
    - If you are not already aware of your ICB (or equivalent) implementation-coordination group, please ask your clinical leads/regional colleagues.
    - Map out what your local pathways are likely to be, and what challenges you are likely to face.
    - Seek help from the ICB/equivalent to find solutions to the challenges.
    - If there are likely to be ongoing challenges, discuss whether this needs to be on the trust/health board risk register.

What to expect next from BPNA/OPEN UK/RCPCH?

- If there are further information from MHRA or other organisations (including NICE and SIGN) we will update this guidance

The ABN have additional helpful guidance:
https://cdn.ymaws.com/www.theabn.org/resource/resmgr/guidelines/abn_guidelines_for_valproate.pdf with extensive FAQs.