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Prescribing valproate to female patients under 18 years of age

Update 31 January 2024

In recent years the ongoing concern about use of valproate in females who might become pregnant has resulted in changes to the licensed indication, such that valproate is contraindicated in women and girls of childbearing potential unless the conditions of a Pregnancy Prevention Programme (PREVENT) are met. PREVENT is primarily directed at women of childbearing potential, but clearly as younger females transition through adolescence into adulthood the same concerns about unintended pregnancy arise and paediatricians caring for patients under the age of 18 need to ensure that if valproate is being prescribed, the patient and/or their responsible person (usually their parent) are fully informed of the high incidence of teratogenic effects and the extreme importance of pregnancy avoidance.

PREVENT essentially comprises:

- Discussing the risks of pregnancy with patients / responsible person
- Serum pregnancy test before first prescription
- Arrange use of effective contraception (most likely IUD or implant) before first prescription and then on an ongoing basis
- Completion of an Annual Risk Acknowledgement Form by the patient or their responsible person / parent
- A minimum of annual specialist review
- Providing a copy of the Patient Guide to the patient (or parent/caregiver/responsible person)

This joint guidance from the British Paediatric Neurology Association (BPNA) and the Royal College of Paediatrics and Child Health (RCPCH) has been developed to provide greater clarity about the approach to prescribing valproate in female patients under 18-years of age. The only licensed indication for valproate in female children and young people is for the treatment of epilepsy. The PREVENT programme is not relevant for many female children and young people due to their age and learning ability. Whilst this guidance is structured around patient age and learning ability, the age ranges are not prescriptive, and the guidance has been developed to support clinicians in the implementation of an approach to practice that can support young girls as they transition through childhood to adolescence and then adulthood. Every patient and their family should have their individual needs assessed and a bespoke approach undertaken that is broadly consistent with the approach described in this guidance.

This guidance should be used in parallel with the new BPNA document - **BPNA, OPEN UK and RCPCH Update for Valproate prescribing in Paediatric Neurology** (January 2024) – which highlights the changes from 31/01/24 with regard to signatories on Annual Risk Acknowledgement Form (ARAF). **For all female patients under 55, two signatories are required at initiation of valproate (or at first review of a previously signed ARAF before 31/01/24) and then one signatory annually thereafter*.**

Patient groups

Female children under 10-years of age

Valproate can be prescribed for girls under 10 years by specialists in epilepsy if it is considered the best treatment for the patient by two specialists independently. Treatment should only be initiated by a specialist working within secondary or tertiary care and patients must be reviewed at least annually. There are no requirements for PREVENT or other special measures. If treatment with valproate is commenced parents should be aware that it is not a desirable long term treatment because of teratogenicity, and this discussion should be documented. If a girl attains menarche before 10 years they should be managed as per 10-12 age group.

Female children 10-12 years of age

Unless justifiable on clinical grounds no female patient aged over 10 years should be commenced on treatment with valproate if there is potential for future pregnancy. Patients already taking valproate should undergo formal evaluation to see if valproate can be discontinued or substituted for an alternative therapy. Existing patients must remain under specialist care and be seen at least annually. Additionally, the prescriber must ensure that:

- The parents/caregivers of female children understand the need to contact the specialist once the female child using valproate experiences menarche.
- The parents/caregivers of female children who have experienced menarche are provided with comprehensive information about the risks of congenital malformations and neurodevelopmental disorders including the magnitude of these risks for children exposed to valproate *in utero*
- An Annual Risk Acknowledgement Form should be signed by two specialists and the responsible person documenting that they are aware of the risks of teratogenicity, but no PREVENT intervention is required. The requirement for PREVENT may apply if the patient has reached menarche. A second signatory is required at initiation of valproate, but not required for annual reviews*.

Females aged 13-15 years

This patient group and their parents need to be fully counselled about the risks of pregnancy and teratogenicity with sodium valproate if there is potential for future pregnancy. The Annual Risk Acknowledgement Form should be completed annually, which should clearly document that the information regarding teratogenicity has been shared and understood and this should be countersigned by the responsible person as well as the prescriber. Existing patients on valproate must be reviewed on an at least annual basis in specialist services and start a transition process with a view to formal handover to specialist adult services between 16 and 18 years of age. In some cases, prescribers and parents / patients are likely to feel that there are “are compelling reasons to indicate that there is no risk of pregnancy” and so although the information about pregnancy risk should be documented, it is unlikely that the full PREVENT pregnancy programme of pregnancy tests and hormonal contraception will be required. In girls who are known to be or are felt likely to

become sexually active in the near future the full PREVENT programme should be implemented and confidentiality of these patients should be respected particularly in discussions about their sex life.

Females aged 16-18 years

Young women in this age group, if they have potential for future pregnancy, should be managed as adult women in line with PREVENT programme. Every effort should be made by the specialist to switch females who have potential for future pregnancy to alternative treatment before they reach 18 years of age. Any young women in this age group who remains on valproate must be seen on at least annual basis in specialist services and must undergo a formal transition handover to specialist adult services.

With regard to young women in this age group with moderate to severe intellectual disability whom the **prescriber and the carer** agree that there are compelling reasons to indicate that there is no chance of sexual activity and hence no risk of pregnancy, this should be documented and signed within the Annual Risk Acknowledgement Form*. In these cases there is no need to implement a pregnancy PREVENT programme. This assessment should be repeated and documented annually on an ongoing basis. If the reproductive risks are not applicable and there is no risk of pregnancy, the patient and or her responsible person does not need to sign the ARAF each year. However, the specialist should complete the first part of the form.

Further information regarding the programme and all professional and patient information leaflets are available at https://www.gov.uk/guidance/valproate-use-by-women-and-girls.

Summary

Whilst it is clear that, if at all possible, female patients over 10 years of age should not be treated with valproate, there are a small number of patients with epilepsy who remain on this therapy and in whom transition to other treatment options should be undertaken as a matter of urgency. If this is not possible because other treatments are ineffective or not tolerated, then an assessment of pregnancy risk should be undertaken, and in patients over 16 years of age (and younger if sexually active or likely to become sexually active before next review) a full pregnancy prevention programme should be implemented in line with MHRA guidance unless there are compelling reasons to indicate that there is no risk of pregnancy e.g. if a young woman has severe intellectual disability. In some patients the opportunities to switch medications are much more limited and ongoing treatment with valproate is likely to be necessary. Particularly in the more profoundly disabled patient groups, clinicians and carers can undertake a realistic assessment of pregnancy risk, and assess the risk: benefit ratio on an individualised basis. In a number of patients whose carer can give fully informed consent a full pregnancy PREVENT programme may not be necessary, but the decision making behind this needs to be clearly documented by both the prescriber and the responsible person or patient. All female patients should undergo documented annual review in specialist services where the issues relating to ongoing prescription of valproate and the risk of pregnancy are reviewed and documented, and an annual risk acknowledgement form should be completed to document this discussion.

Female patient <18 years old possibly requiring treatment with sodium valproate

- Sodium valproate should be initiated by a Consultant with specialist training / expertise in epilepsy only. A second specialist must agree that this is the most appropriate treatment at initiation* and sign the Annual Risk Acknowledgement Form (ARAF)
- Patients must be reviewed by a specialist at least annually and ARAF completed

<10 years old

- Teratogenicity risk must be discussed and documented
- PREVENT programme NOT required

10 - 12 years old

- For patients already taking valproate, unless families and clinicians are satisfied that there are compelling reasons to consider there is no pregnancy risk and that this is unlikely to change, transfer to alternative therapy or discontinuation of valproate should be undertaken if at all possible.
- If valproate continued, remind parents of teratogenicity risk and instruct them to inform Consultant at onset of menarche
- Post menarche: complete risk acknowledgement form documenting awareness of teratogenicity and confirming that both parents and specialist agree that there are compelling reasons to suggest no sexual activity / pregnancy risk so PREVENT programme not required.
- Complete this assessment annually

13 – 15 years old

- Switch from valproate / discontinue valproate if possible and potential to become sexually active and pregnant
- If Valproate continued, discuss teratogenicity risk and document at every annual review, parents also to inform Consultant at onset of menarche
- If parents / teenager / Consultant feel there is a chance of patient becoming or already being sexually active, then complete acknowledgement form and implement PREVENT programme **OR**
- Complete acknowledgement form documenting awareness of teratogenicity and confirming that both parents and specialist agree that there are compelling reasons to suggest no pregnancy risk so PREVENT programme not required
- Young people participate in transition process to plan handover of care to adult services at 16-18 years

16 – 18 years old, Normal IQ / capacity

- Switch from valproate/discontinue valproate if possible
- If valproate therapy is ongoing complete acknowledgement form with patient +/- parent
- Highly likely to also undergo PREVENT programme
- Transition handover to adult specialist services

16 – 18 years old, without capacity

- Complete acknowledgement form documenting awareness of teratogenicity and confirming that both parents and specialist agree that there are compelling reasons to suggest no pregnancy risk so PREVENT programme not required (majority of patients)
- OR: IF there is a chance of patient becoming or already being sexually active, then complete acknowledgement form and implement PREVENT programme
- Transition handover to specialist adult services