Feasibility and effectiveness of interventions: the valproate case study- EAN-ILAE joint task force

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CMDh agrees to strengthen warnings on the use of valproate medicines in women and girls

Women to be better informed of risks of valproate use in pregnancy and need for contraception

The CMDh,* a regulatory body representing EU Member States, has agreed to strengthen warnings on the use of valproate medicines in women and girls due to the risk of malformations and developmental problems in babies who are exposed to valproate in the womb. The warnings aim to ensure that patients are aware of the risks and that they take valproate only when clearly necessary.

Doctors in the EU are now advised not to prescribe valproate for epilepsy or bipolar disorder in pregnant women, in women who can become pregnant or in girls unless other treatments are ineffective or not tolerated. Those for whom valproate is the only option for epilepsy or bipolar disorder should be advised on the use of effective contraception and treatment should be started and supervised by a doctor experienced in treating these conditions.

Concerns from the Epilepsy Community

- Treatment alternatives are few for idiopathic/genetic generalized epilepsies
  - → Only EMA approved for monotherapy of primary GTCS are lamotrigine, phenobarbital, phenytoin, topiramate; levetiracetam not approved for this indication
  - → Efficacy may not be comparable to VPA, and/or teratogenic risks significant, or not yet fully assessed
- Unlike men, women with epilepsy risk to be denied the most effective treatment
- The risks with uncontrolled seizures may be neglected
- Women may be encouraged to rapid discontinuation or switch from VPA, even during pregnancy
  - → With potentially serious consequences for them and for fetus
  - → With lack of evidence for reduced teratogenic risks

SPECIAL REPORT

Valproate in the treatment of epilepsy in girls and women of childbearing potential

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Task Force appointed by ILAE-CEA and EAN

Wherever possible, valproate should be avoided in the treatment of girls and women of childbearing potential

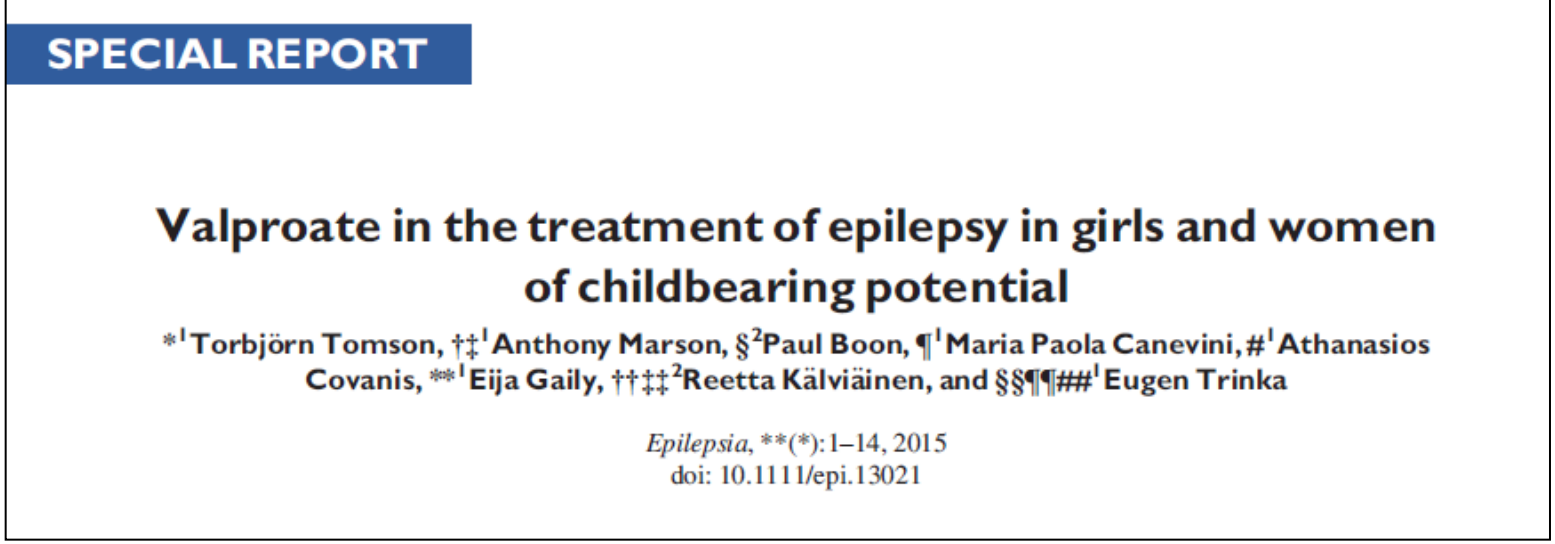
…but which are the situations when valproate cannot be avoided? And when can valproate still be used within the remit of the new EMA restrictions?

The Task Force took the following into consideration

- The teratogenic risks with valproate AND with treatment alternatives
  - → Noted the pronounced risks with valproate and the dose-dependency
- The importance of seizure control and of patient and fetal risks with seizures
  - → Noted the serious risks associated with poor control of GTCSs
- The effectiveness of valproate AND treatment alternatives in the treatment of different epilepsies
  - → Noted the multitude of alternatives for focal epilepsies
  - → Noted the limited options for some generalized epilepsies
- Risks and benefits of different treatment alternatives in specific clinical situations
- The informed patient's right to express a preference
- The principle of shared decision between physician and patient

General Recommendations for use of Valproate in female patients

1. VPA should preferably not be used for focal epilepsy. Withdrawal or switch to alternatives should be considered for women of childbearing potential established on VPA for focal seizures and those who consider pregnancy.
2. When used in women of childbearing potential, VPA should be prescribed at the lowest effective dose, when possible aiming at doses not exceeding 500-600 mg/day.
3. Women of childbearing potential who are not planning pregnancy and continue treatment with VPA should utilize effective contraception methods or otherwise ensure that unplanned pregnancies can be avoided.
4. Women should be informed about the possibilities and limitations of prenatal screening, which cannot identify children whose neurodevelopment will be affected.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1. Newly diagnosed epilepsy
2. Female patients who have failed to respond to valproate alternatives
3. Female patient already established on valproate, not considering pregnancy
4. Female patients already established on valproate considering pregnancy
5. Women already on valproate while pregnant

1. Newly diagnosed epilepsy

- VPA and alternatives should be considered for generalized epilepsies where VPA is more effective than other drugs
  VPA can be prescribed
  → If the fully informed woman chooses VPA, and
  → Is not planning pregnancy
- When most appropriate for seizure/epilepsy type, VPA may be considered for girls with epilepsies with high likelihood of remission and AED withdrawal before puberty
- When most appropriate for seizure/epilepsy type VPA may be considered when epilepsy is so severe, or concurrent disabilites so severe that pregnancy is extremely unlikely

2. Patients who have failed to respond to valproate alternatives

- VPA should be considered for women who have failed other reasonable alternatives and who have generalized epilepsies where VPA is likely to be more effective

3. Patient established on valproate, not considering pregnancy

- Withdrawal or switch should be considered in women on VPA for focal epilepsy
- VPA can be continued when patient and clinician agree that benefits of remaing outweigh risks of withdrawal or switch
- Women who wish to continue on VPA, but are willing to accept risks with dose reduction, aim for doses not exceeding 500-600 mg/day
- Those whose seizures were only controlled after failing other appropriate alternatives, and for whom risks of withdrawal are not acceptable, can continue on VPA
- For those in remission on VPA, withdrawal should be considered if likelihood of relapse is acceptable to patient
- For those with suboptimal seizure control or adverse effects on VPA, a switch should be considered

4. Patient established on valproate considering future pregnancy

- Treatment should be reassessed and changes carefully considered for every women considering pregnancy
- Switch or withdrawal should always be considered in focal epilepsy
- Treatment changes shuld be completed and evaluated before conception. Lowest effective dose established before conception
- For those in remission on VPA, withdrawal should be considered if likelihood of relapse is acceptable to patient
- Switch from VPA to alternative should be considered for those not suitable for, or who have failed, treatment withdrawal
- Continued VPA can be considered for those well controlled on low dose VPA (up to 500-600 mg/day), AND who consider risk of withdrawal or switch unacceptable

5. Women already on valproate while pregnant

- The general rule is to continue treatment with VPA in patients discovering that they are pregnant
- Withdrawal of VPA in a pregnant woman should only be initiated if the risk of doing so is acceptable to the patient. Usually the case only when there is agreement that treatment is not needed for acceptabe seizure control
- Reduction in VPA dose can be considered when the risk of doing so is acceptable to the patient. Usually only the case when prior history suggests that dose is higher than needed for acceptable seizure control
- Switch to other treatment generally not recommended during pregnancy in patient with good seizure control

Withdrawal of VPA or Switch during pregnancy?

Strategy	Risk	Benefits	Conclusion
Withdrawal	Maternal and fetal risks of uncontrolled seizures	Possible reduction of the risk of neuro-developmental delay	No effect on MCM Risks outweigh possible benefits
Switch to other AEDS	Maternal and fetal risks of uncontrolled seizures Risk of MCM and neurodevelopmental delay by VPA Teratogenicity of new drug and combination with VPA Adverse effects of the substituted drug	Possible reduction of the risk of VPA associated neuro-developmental delay	No data available on treatment outcomes after switch Exchange of VPA during pregnancy is unlikely to reduce the risk of MCM Risks outweigh possible benefits

After Tomson et al., Epilepsia 2015

Conclusions and Implications

Wherever possible, valproate should be avoided in the treatment of girls and women of childbearing potential

- If continued VPA treatment is considered
  - → All women must be carefully informed of the teratogenic risks
  - → All women should be informed of the possibilities and limitations of prenatal diagnostic tests
  - → Lowest effective dose should be established
  - → Effective contraception prescribed

The Disclaimers

The (medical) information in this manuscript is provided as a general information resource for physicians caring for patients with epilepsy. The Task Force of the ILAE and the EAN expressly disclaim(s) responsibility, and shall have no liability for any damages, loss, injury, or liability whatsoever suffered as a result of any reliance or negligence on the information contained herein.

The current recommendations in this manuscript have been reviewed by EMA to ensure that they are not in conflict with the revised valproate SmPC. It is not within the Agency's remit to discuss the implementation in clinical practice of product-specific regulatory recommendations. Although the Agency can identify some areas where consistency may be improved, it is not possible to unequivocally confirm full regulatory consistency due to the nature of the recommendations and the fact that their implementation in clinical practice will remain, ultimately, with those exercising their clinical judgment on the basis of their experience and the individual patient circumstances.