

Valproate in the treatment of epilepsy in women and girls

Pre-Publication Summary of

Recommendations from a joint Task Force of ILAE-Commission on European Affairs* and European Academy of Neurology (EAN)**

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The Coordination Group for Mutual Recognition and Decentralised Procedures-Human (CMDh) of the European Medicines Agency (EMA) has recently strengthened warnings on the use of valproate medicines (e.g. valproic acid, sodium valproate, divalproex sodium) in women and girls due to the risk of malformations and intellectual and cognitive developmental problems in babies who are exposed to valproate in the womb. The Summary of Product Characteristics (SmPC) therefore now states that valproate “should not be used in female children, in female adolescents, in women of childbearing potential and pregnant women unless alternative treatments are ineffective or not tolerated..” This should, however, not be interpreted to suggest that every individual female patient needs to try and fail on alternative treatments before being prescribed valproate if that is the most appropriate treatment for her epilepsy. To assist physicians, the Commission of European Affairs of the International League Against Epilepsy (CEA-ILAE) and the European Academy of Neurology (EAN) appointed a joint Task Force. The mission of the Task Force has been to make recommendations on the use of valproate for the treatment of epilepsy in female children and adolescents, and in women of childbearing potential, in the context of EMA’s new warnings. The Task Force has considered teratogenic risks associated with use valproate and treatment alternatives, the importance of seizure control and of risks to patient and foetus due to seizures, and the effectiveness of valproate and treatment alternatives for the different epilepsies. The Task Force report is under review for consideration for Epilepsia but given the urgency of the matter the recommendations are summarized in this document with the permission of ILAE, EAN and the Editors of Epilepsia

The choice of treatment for women of childbearing potential should be based on a shared decision between clinician and patient and, where appropriate, the patient’s representatives. Discussions should include a careful risk benefit assessment of reasonable treatment options for the patient’s seizure or epilepsy type. This will include discussion of the likely effectiveness of valproate compared to alternatives for the seizure types the women has (e.g. generalized tonic-clonic seizures, absence, myoclonus), and any risk those seizures pose should there be diminished or delay in achieving seizure control. This is essential inasmuch as uncontrolled epilepsy is associated with serious morbidity and excess mortality and that uncontrolled generalized tonic-clonic seizures may be harmful to the fetus. Where valproate is the most appropriate option, every patient must be fully informed of the risks associated with valproate use during pregnancy as well as of the risks and benefits of treatment alternatives. It is the Task Force’s opinion that whenever possible, valproate should be avoided in women of childbearing potential. There are, however, epilepsies for which valproate is the most effective treatment, and also situations where pregnancy is extremely unlikely, and valproate thus a reasonable choice.

General recommendations

Given the multitude of treatment alternatives with at least comparable efficacy in focal epilepsies, valproate should preferably not be used for this indication, and withdrawal of valproate or switch to treatment alternatives should be considered for women of childbearing potential that are established on treatment with valproate for focal seizures and that consider pregnancy.

When used in women of childbearing potential, valproate should be prescribed at the lowest effective dose, when possible aiming at doses not exceeding 500-600 mg/day,* though, at times, higher doses may be necessary to attain seizure control.

Women of childbearing potential who are not planning pregnancy and continue treatment with valproate should utilize effective contraception methods or otherwise ensure that unplanned pregnancies can be avoided.

Women should be informed about the possibilities and limitations of prenatal screening, which cannot identify children whose neurodevelopment will be affected.

Newly diagnosed epilepsy, or valproate naïve female patients who failed other treatments

- Valproate should not be prescribed for focal seizures in women except as a last resort.
- Valproate as well as alternatives should be considered as appropriate treatment option for the generalized epilepsies where it is more effective than other drugs (e.g. juvenile myoclonic epilepsy, or juvenile absence epilepsy). If following discussion of risks and benefits the woman who is not planning pregnancy chooses valproate, it should be initiated.
- Valproate may be considered as appropriate treatment option for the generalized epilepsies where it is more effective than other drugs (e.g. juvenile myoclonic epilepsy, or juvenile absence epilepsy) in women that have failed to attain seizure control on treatment alternatives.
- When most appropriate for the seizure or epilepsy type, valproate may be considered as initial treatment for female children with epilepsies that have a high likelihood of remission and treatment withdrawal before puberty.
- When most appropriate for the seizure or epilepsy type, valproate may be considered as initial treatment when the epilepsy is of such a severe nature or the patient has concurrent severe disabilities, that future pregnancy is extremely unlikely.
- Ensure effective contraception whenever relevant if valproate is prescribed.

Female patients already established on valproate treatment and not considering pregnancy

- In women with focal epilepsies withdrawal of valproate or a switch to an alternative treatment should always be considered.
- Valproate can be continued when the patient and clinician agree that the benefits of staying on valproate outweigh the risks of withdrawal or switch to an alternative.
- For women who wish to stay on valproate but are willing to accept the risks associated with a dose reduction, the dose should be reduced to the lowest possible to achieve acceptable seizure control, aiming for doses not exceeding 500-600mg/day* if possible.
- For women whose seizures were controlled only after failing other appropriate treatment alternatives, and for whom the risks of withdrawal are not acceptable, valproate can be continued.
- For women in remission on valproate, withdrawal of treatment should be considered if the likelihood of relapse on withdrawal is acceptable to the woman.
- For women on valproate with suboptimal seizure control or adverse effects, a switch to another treatment should be considered.
- Women of childbearing potential that continue treatment with valproate should utilize effective contraception or otherwise ensure that unplanned pregnancies can be avoided.

Female patients already established on valproate treatment considering future pregnancy

- Treatment should be reassessed and changes carefully considered for every woman on valproate treatment that is considering pregnancy.
- In women with focal epilepsies withdrawal of valproate or a switch to an alternative treatment should always be considered.
- Treatment changes should be completed and adequately evaluated before conception. For valproate as well as for other treatments the lowest effective dose should be established before conception.

- Withdrawal of valproate treatment should be considered in women with epilepsy in remission, for whom the risk of relapse on withdrawal is acceptable.
- A switch from valproate to alternative treatments should be considered for every woman who is not suitable for, or who has failed, treatment withdrawal.
- Continued valproate treatment can be considered for women that are well controlled on a low dose of valproate (up to 500-600 mg/day*) and who consider the risks associated with attempts to withdrawal or switch of treatment to be unacceptable. These women as well as those who need to continue valproate treatment at higher doses must be carefully informed about the teratogenic risks and the limitations of prenatal screening.

Woman already on valproate treatment while pregnant, unplanned pregnancy

- The general rule is to continue treatment with valproate in a woman who discovers that she is pregnant.
- Withdrawal of valproate treatment in a pregnant woman with good seizure control should only be initiated if the risks of doing so are acceptable to the women, and after careful consideration of the risks to both mother and foetus. This is usually only the case when there is agreement that valproate treatment is not needed to maintain acceptable seizure control.
- A reduction in valproate dose can be considered in women when the risks of doing so are acceptable to the woman. This applies when prior history suggests that the current dose is higher than needed to maintain acceptable seizure control.
- A switch from valproate to another AED is generally not recommended during pregnancy of a woman with good seizure control while taking valproate.

*The dose level of 500-600 mg/day is based on data from the North American Antiepileptic Drug and Pregnancy Registry¹ and the UK Ireland Pregnancy Register² reporting increased risk of major congenital malformations in children exposed to valproate doses exceeding these levels in early pregnancy. Another registry (EURAP)³ reported increased risks at valproate doses from 700 mg/day and above. The suggested dose level should be seen as a guide for the prescriber, although it is acknowledged that valproate tablet strengths vary between countries so that it sometime can be difficult to prescribe a specific dose.

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