Paternal exposure to antiseizure medications and offspring outcomes

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Is there evidence to support restrictions in the use of valproate in male patients? This issue is addressed in a *JNNP* systematic review presented in the paper by Honybun *et al*.[1] The review provides a comprehensive assessment of different teratogenic outcomes in offspring associated with paternal exposure to antiseizure medications, and the results are reassuring.

In 2014, the European Medicines Agency (EMA) issued contraindications for the use of valproate during pregnancy and imposed restrictions for its use in girls and female patients due to overwhelming evidence of its teratogenic risks. Restrictions were clearly justified, despite valproate being the most effective medication for some types of generalised epilepsies.

In November 2023, the UK Medicines and Healthcare products Regulatory Agency (MHRA) expanded these restrictions to include males stating that 'valproate must not be started in new patients, male or female, younger than 55 years unless two specialists independently consider and document that there is no other effective or tolerated treatment or there are compelling reasons that the reproductive risks do not apply'.[2] EMA, in January 2024 was less strict recommending that 'valproate treatment in male patients is started and supervised by a specialist in the management of epilepsy, bipolar disorder or migraine.' They also advised doctors to inform male patients of the possible risks and discuss the need for effective contraception for both the patient and their female partner, with regular reviews to assess the suitability of valproate treatment, particularly when planning to conceive a child.[3]

While the 2014 restriction for females were overdue in relation to the available evidence, the restrictions for male patients were primarily based on an EMA-initiated retrospective observational study using Scandinavian registry data.[4] The results of this study, yet to published after peer review, suggested 'there may be an increased risk of neurodevelopmental disorders in children born to men taking valproate in the 3 months before conception.' EMA, however, concluded that it was not possible to establish whether the increased risks were due to valproate.

In this context, the systematic review by Honybun *et al*[1] provides essential comprehensive, and mainly reassuring information, indicating no increased risks for developmental disorders with paternal valproate exposure. Unfortunately, the EMA-initiated study could not be included in the systematic review. However, the two included high-quality studies on neurodevelopmental outcomes were from Sweden[5] and Denmark,[6] apparently with cohorts partly overlapping with the EMA study, the large Danish study[6] published after the MHRA and EMA restrictions. These peer-reviewed data, highlighted in the current systematic review, contradict the observations reported from the EMA-initiated study, with its limitations, and call for a reconsideration of in particular the MHRA restrictions. It is questionable to refer to the restriction as a precautionary measure when they place male patients with generalised epilepsies at risk of inadequate seizure control with potentially fatal consequences. Potential risks with paternal exposure will remain a hot topic, but it is difficult to see how more conclusive evidence regarding valproate could be generated within the next few years.

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