

Male mediated teratogenesis-Valproate and neurodevelopmental disorders

The Pharmacovigilance Risk Assessment Committee (PRAC) of the European Medicines Agency (EMA) has reported its review of a yet unpublished, retrospective study (EUPAS34201) across three Nordic countries initiated by the EMA to investigate the risk of neurodevelopmental disorders (NDD), in offspring of fathers taking valproate (monotherapy), compared to lamotrigine or levetiracetam (composite monotherapy) treatment at the time of conception. NDD are problems with development that begin in early childhood, such as autism spectrum disorders, intellectual disability, communication disorders, attention deficit/hyperactivity disorders, and movement disorders. The primary outcome of interest is the occurrence of NDD in offspring up to twelve years of age based on ICD-10 diagnostic codes, as recorded in the National Patient Registries.

The meta-analysis of the data showed that the hazard ratio of NDD in children of fathers taking valproate in the 3 months prior to conception was 1.50 (95% CI: 1.09-2.07) compared to fathers taking levetiracetam or lamotrigine. The cumulative risk of NDD was estimated at 5% in children of fathers taking valproate compared to 3% in children of fathers taking lamotrigine or levetiracetam.

The PRAC could not establish whether these results were due to valproate intake as the study data had limitations, including differences between the groups in the conditions for which the medicines were used and in follow-up times. The results of the analysis are not conclusive, so the EMA recommends that valproate be started and supervised by a specialist, in the management of epilepsy, migraine or bipolar disorder. EMA's statement also includes the recommendation that male patients be informed of these possible risks and consider effective contraception; and that treatment with valproate be reviewed appropriately.

The Epilepsy Society of Australia agrees with these recommendations given the information at hand. Valproate has provided reliable seizure control for countless patients over more than 50 years. It is the most effective antiseizure medicine for generalised epilepsies. Doctors and patients need to continue balance the risks and adverse effects of anti-seizure medications with the importance of seizure control to optimise quality of life, safety and minimising the risk of injury and death, including SUDEP, for people with epilepsy.

Further Reading

European Medicines Agency. Potential risk of neurodevelopmental disorders in children born to men treated with valproate medicines: PRAC recommends precautionary measures. Link: <https://www.ema.europa.eu/en/news/potential-risk-neurodevelopmental-disorders-children-born-men-treated-valproate-medicines-prac-recommends-precautionary-measures> (accessed on 12-April-2024)

Berkovic SF, Perucca E. Pract Neurol 2024;pn-2024-004097 Epub ahead of print: doi: 10,1136/ pn-2024-004097.