President: Piero Perucca
Vice President: Lata Vadlamudi
Secretary: Hanka Laue-Gizzi
Treasurer: Josephine Chan

Administrative Office: PO Box 2137 Glenelg SA 5045 Australia
Telephone: 0400 280 811 **Email:** enquiries@epilepsy-society.org.au **Internet:** www.epilepsy-society.org.au
ABN: 73 602 950 318

EPILEPSY SOCIETY OF AUSTRALIA
Australian Chapter of the
International League Against Epilepsy

VALPROATE USE IN MEN AND OFFSPRING RISK: A STATEMENT FOR HEALTH PROFESSIONALS BY THE EPILEPSY SOCIETY OF AUSTRALIA

The Pharmacovigilance Risk Assessment Committee (PRAC) of the European Medicines Agency (EMA) has reported its review of an EMA-commissioned, retrospective, cohort study (EUPAS34201) using administrative healthcare databases from Denmark, Sweden and Norway to investigate the risk of neurodevelopmental disorders (NDDs), in offspring of fathers taking valproate (monotherapy), compared to lamotrigine or levetiracetam (composite monotherapy) treatment in the three months before conception.[1] NDDs 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 was the risk of NDDs in offspring up to 12 years of age based on ICD-10 diagnostic codes. Of note, the study has yet to undergo peer-review and publication in a scientific journal.

The meta-analysis of the data from the three Nordic countries showed that the adjusted hazard ratio of NDDs in children of fathers taking valproate was 1.50 (95% CI: 1.09-2.07) compared to fathers taking levetiracetam or lamotrigine. The cumulative risk of NDDs was estimated at 5% in children of fathers taking valproate compared to 3% in children of fathers taking lamotrigine or levetiracetam. The study acknowledged methodological limitations including differences between the groups in the conditions for which the medications were used and in duration of follow-up of exposed offspring. Furthermore, there were "some known risk factors and/or causal factors (eg, genetic abnormalities, congenital infectious diseases, paternal condition severity that required antiepileptic drug use, lifestyle factors) which were not identified nor controlled for."[1] These factors were presumed to be balanced between the paternal exposure groups.

In view of these limitations, PRAC could not establish whether the apparent increased risks of NDDs in children of fathers on valproate were causally related to valproate. PRAC still recommended precautionary measures including that in males, valproate be started and supervised by a specialist in the management of epilepsy, migraine or bipolar disorder; and that doctors inform males taking valproate about these potential risks, discuss the need to consider effective contraception, and review regularly the need for valproate particularly when males are planning to conceive a child.

Subsequent to this advice, Christensen et al.[2] reported a Danish retrospective cohort study also interrogating administrative healthcare databases and including 1,235,353 live births that occurred between 1-January-1997 and 31-December-2017. 1,336 of these children had fathers who filled valproate prescriptions within three months prior to conception (1,017 exposed to valproate monotherapy). Compared to children whose fathers were not taking valproate in the three months before conception, children of fathers on valproate were not found to be at significant increased risk of congenital malformations (adjusted relative risk 0.89 [95% CI: 0.67-1.18]) or

neurodevelopmental disorders (adjusted hazard ratio 1.10 [95% CI: 0.88-1.37]), including autism spectrum disorder (adjusted hazard ratio 0.92 [95% CI: 0.65-1.30]). Median follow up was 10 years for both groups. A number of sensitivity analyses, including a comparison between children paternally exposed to valproate and those exposed to lamotrigine, yielded similar negative findings.

Following the release of the EMA advice a systematic review of the literature on offspring outcomes of fathers exposed to antiseizure medications has been published.[3] This review found that, although data in the field were limited, there was no clear evidence for an adverse impact of paternal antiseizure medication use on offspring outcomes. Few isolated adverse findings were not replicated by other studies. Further research into this area was recommended.

The Epilepsy Society of Australia considers that the findings of EUPAS34201 remain unsubstantiated. Given the results of the rigorous analysis by Christensen et al.[2], it is not appropriate to restrict the use of valproate in males with seizure disorders nor advise them to consider effective contraception. Valproate has provided reliable seizure control for countless patients over more than 50 years. It is the most effective antiseizure medication for generalised epilepsies and restricting its use in these patients can expose them to significant risks of morbidity and mortality.[4,5] Doctors and patients need to continue to balance the risks and adverse effects of antiseizure medications with the importance of seizure control to optimise quality of life, and to minimise the risk of injury and death, including sudden unexpected death in epilepsy (SUDEP).

References

1. 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-December-2024)

2. Christensen J, Trabjerg BB, Dreier JW. Valproate Use During Spermatogenesis and Risk to Offspring. JAMA Netw Open 2024;7(6):e2414709. doi: 10.1001/jamanetworkopen.2024.14709.

3. Honybun E, Rayner G, Malpas CB, O'Brien TJ, Vajda FJ, Perucca P, Perucca E. Paternal exposure to antiseizure medications and offspring outcomes: a systematic review. J Neurol Neurosurg Psychiatry 2024:jnnp-2024-334077. doi: 10.1136/jnnp-2024-334077. [Online ahead of print].

4. Tomson T. Paternal exposure to antiseizure medications and offspring outcomes. J Neurol Neurosurg Psychiatry 2024:jnnp-2024-334474. doi: 10.1136/jnnp-2024-334474. [Online ahead of print].

5. Mbizvo GK, Bucci T, Lip GYH, Marson AG Morbidity and mortality risks associated with valproate withdrawal in young adults with epilepsy. Brain 2024;147(10):3426-3441. doi: 10.1093/brain/awae128.