







## PRACTICE AND POLICY

# Paternal Valproate Treatment and Risk of Childhood Neurodevelopmental Disorders: Precautionary Regulatory Measures Are Insufficiently Substantiated

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## ABSTRACT

On January 12, 2024 the safety committee of the European Medicines Agency (EMA) recommended precautionary measures over a potential risk of neurodevelopmental disorders in children born to men treated with valproate. These new measures recommend patient supervision by a specialist in the management of epilepsy, bipolar disorder, or migraine. In the United Kingdom, the Medicines and Healthcare products Regulatory Agency (MHRA) issued a far more stringent precaution, warning against prescribing valproate to anyone under 55 years of age. We, members of the European Network of Teratology Information Services (ENTIS) and the Organization of Teratology Information Specialists (OTIS), believe that the EMA and MHRA warnings were premature. We are of the opinion that the underlying scientific data do not convincingly substantiate the inference of a paternally mediated risk from valproate to children, much less to an extent that justifies these far-reaching recommendations.

Per Damkier, Brian Cleary, Orna Diav-Citrin, Ken Hodson, Alice Panchaud, Svetlana Shechtman and Corinna Weber-Schoendorfer are members of the Scientific Committee of The European Network of Teratology Information Services (ENTIS). All other authors are Members of The Organization of Teratology Information Specialists (OTIS).



The medical community has long been aware that valproate use during pregnancy is associated with a substantially increased risk of congenital anomalies in the offspring. To date, the scientific literature does not support paternal valproate exposure as a developmental concern. However, on January 12, 2024 the safety committee of the European Medicines Agency (EMA) recommended precautionary measures over a potential risk of neurodevelopmental disorders in children born to men treated with valproate. These new measures recommend patient supervision by a specialist in the management of epilepsy, bipolar disorder, or migraine. In the United Kingdom, the Medicines and Healthcare products Regulatory Agency (MHRA) issued a far more stringent precaution, warning against prescribing valproate to anyone under 55 years of age (MHRA 2024; EMA 2024). We, members of the European Network of Teratology Information Services (ENTIS) and the Organization of Teratology Information Specialists (OTIS), believe that the EMA and MHRA warnings were premature. We are of the opinion that the underlying scientific data do not convincingly substantiate the inference of a paternally mediated risk from valproate to children, much less to an extent that justifies these far-reaching recommendations.

These recommendations were based on a report that appeared as an extended abstract of an unpublished study conducted by IQVIA, a contract research organization (Valproate EU Consortium 2024). The data used in the report came from national prescription registries in Denmark, Sweden, and Norway with exposure considered a prescription during a “risk window” for spermatogenesis (3 months prior to the estimated date of conception). The primary outcome was childhood neurodevelopmental disorders, including autism spectrum disorders, and the secondary outcome was a composite of major and minor congenital malformations based on ICD-10 codes. Outcomes in children with paternal exposure to valproate were compared to outcomes in children with paternal exposure to lamotrigine or levetiracetam.

There were 2213 children with fathers who used valproate during the spermatogenic risk window and 3740 children with fathers who used lamotrigine or levetiracetam during the spermatogenic risk window. Valproate prescriptions occurred earlier in time than prescriptions for lamotrigine or levetiracetam, resulting in a longer period of follow-up for children with paternal valproate exposure. Neurodevelopmental disorders were diagnosed in 6.6% of children with paternal exposure to valproate and 3.7% of children with paternal exposure to lamotrigine or levetiracetam. In unadjusted analysis, the pooled cumulative incidence ratio (new cases over 0–10 years of follow-up) for neurodevelopmental disorders in the children of men prescribed valproate compared to lamotrigine or levetiracetam was 1.58, 95% confidence interval 1.21–2.05. The pooled incidence rate ratio (new cases of neurodevelopmental disorders per 1000 person-years) for paternal valproate compared to paternal lamotrigine/levetiracetam was 1.26, 95% confidence interval 0.97–1.64.

Excluding 232 children who had a diagnosis of epilepsy, who had received antiepileptic drugs, or whose mothers were taking valproate, lamotrigine, or levetiracetam, neurodevelopmental disorders were diagnosed in 5.4% of children with paternal exposure to valproate and 3.5% of children with paternal exposure

to lamotrigine or levetiracetam for a crude hazard ratio of 1.13, 95% confidence interval 0.85–1.49, consistent with the null. The propensity score adjusted hazard ratio for all countries was 1.34, 95% confidence interval 0.79–2.25, also consistent with the null. In contrast, another calculation of the propensity score adjusted pooled hazard ratio was 1.50, 95% confidence interval 1.09–2.07, consistent with a statistically significant association with paternal valproate.

It is not clear why there was a difference between the two calculations. One of the results may have been from a meta-analysis of the individual country data. Various sensitivity analyses did not add clarity to the results, although some of these analyses showed results in opposite directions in one of the three countries.

Analyses for the secondary outcome of congenital malformations were consistent with the null and will not be further discussed here.

The authors admitted to weaknesses in their study. They explained that the earlier date of prescription of valproate compared to lamotrigine or levetiracetam may have provided more opportunity to diagnose neurodevelopmental disorders in the valproate group. The authors also called attention to the lack of information on genetic abnormalities, infectious disease, severity of paternal illness, or lifestyle factors. In the current study, there were differences between groups in the indications for paternal treatment, and the authors did not know how often the valproate prescriptions in men were for idiopathic generalized epilepsy, a type of epilepsy known to have a genetic basis, and which the authors indicated may be associated with neurodevelopmental disorders.

Warnings such as those issued by MHRA and EMA have a significant impact on both patients and healthcare practitioners. Limiting access to the appropriate antiepileptic medication is potentially harmful, as the consequences of untreated epileptic seizures can include trauma, drowning, and increased morbidity/mortality. Insufficiently substantiated warnings and precautions may result in unwarranted uncertainty and concerns among patients. In addition to study weaknesses described by the authors, we believe that the warnings were made without adequate consideration of the following:

First, slight increases in risk (i.e., RR/OR = a value >1 and <2) in health studies should be interpreted with great caution as such weak associations are especially sensitive to residual confounding (Nicholich and Gamble 2011).

Second, although there is an experimental study suggesting paternal exposure to valproate can alter the male germ cell (Sakai, Hara, and Tanemura 2023), the published epidemiology literature has not confirmed an association between paternal valproate and offspring malformations or neurodevelopmental disorders (Tomson et al. 2020; Christensen, Trabjerg, and Dreier 2024). Sundelin et al. (2016) showed that autism spectrum disorder is common in the siblings and offspring of individuals with epilepsy (Sundelin et al. 2016). Although no information on medication use was available in the Sundelin et al. study, the authors indicate that the risk of autism spectrum disorder was



similar in both offspring and siblings of patients with epilepsy. An increased risk of attention-deficit/hyperactivity disorder (ADHD) has also been reported for children of parents with epilepsy (Brikell et al. 2018). Moreover, a greater percentage of men were using valproate for epilepsy compared to men taking lamotrigine/levetiracetam. The mean percentages from the three countries were 66.2% for valproate and 48.9% for lamotrigine/levetiracetam.

Given the consequences of poorly managed epilepsy and the frequent necessity of using valproate to achieve adequate treatment for some patients, waiting for an appropriately analyzed and detailed report prior to issuing a warning would have been prudent. Valproic acid is a first-line treatment for idiopathic generalized epilepsies. We recommend that regulators think carefully about the implications of their actions and that other countries avoid hasty decision-making based on limited and inadequate evidence. We also recommend that MHRA reverses its decision.

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### Disclosure

Dr. Scialli has consulted for the defense in litigation involving valproic acid and in litigation involving paternal exposures.

### Data Availability Statement

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

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