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EDITORIAL

Joint Position Statement from the Society for Birth Defects Research and Prevention, the Organization of Teratology Information Specialists, and the Developmental Neurotoxicology Society: A Call for Implementation of Risk Evaluation and Mitigation Strategies to Reduce Prenatal Exposure to Valproate

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1 | Introduction

Prevention of prenatal exposure to teratogenic medications is a critical challenge in clinical and regulatory decision-making. Complex benefit–risk considerations need to balance health outcomes among women of childbearing age who need treatment access with potential adverse effects on pregnancy outcomes. In recent decades, regulatory agencies worldwide have implemented risk management programs to support safe use behaviors of patients and providers that can prevent adverse outcomes and help ensure that medications can be approved and used with a favorable benefit–risk profile. Risk management programs are used for medications with known teratogenic risk (e.g., isotretinoin, thalidomide, and mycophenolate) (Brown et al. 2023), with different types of programs in place in different countries.

Valproate was initially approved in the United States for treatment of epilepsy, with later expansion of its FDA-approved indications to include acute mania in bipolar disorder and migraine prophylaxis. Several off-label uses have emerged to include treatment of alcohol withdrawal, panic disorders, and social phobias (Manoguerra et al. 2008; Romoli et al. 2019). Valproate has long been recognized as a teratogen, yet substantial numbers of prenatal exposures to valproate still occur. One role of our societies (the Society for Birth Defects Research and Prevention, the Organization of Teratology Information Specialists, and the Developmental Neurotoxicology Society) is to translate scientific evidence to inform clinical practice and public health policies to improve health outcomes. Here we review the scientific evidence for valproate as a teratogen, the efforts currently in place to reduce its utilization in pregnancy, and current levels of prenatal exposures in the United States. Based on review of this evidence, we end with a call for enhanced regulatory risk management measures to mitigate prenatal exposures to valproate in the United States.

2 | Valproate Is a Potent Teratogen

Valproate has been recognized as a teratogen for decades, with an association between maternal valproate use and an increased risk

of spina bifida first recognized in the 1980s (Lammer et al. 1987). Later studies demonstrated an association between valproate and other major congenital malformations. In 2010, a study using European Surveillance of Congenital Anomalies (EUROCAT) data reported links between maternal use of valproate monotherapy and six different congenital malformations. In this study, adjusted odds ratios were 12.7 (95% confidence interval [CI] 7.7–20.7) for spina bifida; 2.5 (95% CI, 1.4–4.4) for atrial septal defect; 5.2 (95% CI, 2.8–9.9) for cleft palate; 4.8 (95% CI, 2.9–8.1) for hypospadias; 2.2 (95% CI, 1.0–4.5) for polydactyly; and 6.8 (95% CI, 1.8–18.8) for craniosynostosis (Jentink et al. 2010).

Data from a recent Cochrane review of prospective cohort studies estimated a prevalence of major congenital malformations among children born to women taking valproate of 9.8% (95% CI, 8.1–11.9), compared to 2.1% (95% CI, 1.5–3.0) among children born to women without epilepsy and 3.0% (95% CI, 2.1–4.2) for women with untreated epilepsy. In comparison, the frequencies of congenital malformations among women taking low-risk antiepileptic medications (lamotrigine and levetiracetam) in that analysis were 2.7% (95% CI, 1.9–3.8) and 2.6% (95% CI, 1.6–4.4), respectively, not significantly higher than the baseline risk among women with epilepsy (Bromley, Adab, et al. 2023). In a recent analysis of the International Registry of Antiepileptic Drugs and Pregnancy (EURAP) data collected across 40 countries, major congenital malformations occurred in 9.9% (95% CI, 8.5%–11.5%) of pregnancies among women taking valproate compared to 3.1% (95% CI, 2.5%–3.7%) for lamotrigine and 2.5% (95% CI, 1.8%–3.5%) for levetiracetam (Battino et al. 2024). Similar findings were seen in a study using the North American Antiepileptic Drug Pregnancy Registry between 1997 and 2023 (Hernandez-Diaz et al. 2025). These analyses confirm that the risk of congenital malformations is substantially elevated with prenatal use of valproate, and that these findings are not solely due to maternal epilepsy.

Risk of congenital malformations among children born to women taking valproate increases as the dose increases. A study by Tomson et al. demonstrated a frequency of major congenital malformations of 24% among women exposed to monotherapy with valproate at doses ≥1500 mg/day (Tomson et al. 2015). Polytherapy with other antiepileptic drugs is associated with a higher risk than with use of valproate alone, with an odds ratio of 1.46 (95% CI, 1.11–1.91) for monotherapy compared to 2.06 (95% CI, 1.32–3.20) for polytherapy (Kim et al. 2026).

In addition to the evidence regarding congenital malformations, there is strong evidence that prenatal valproate exposure increases the risk of adverse neurodevelopmental outcomes in childhood (Ornoy et al. 2023). A Cochrane review of cohort studies in 2014 found that children exposed to valproate in utero had IQ scores approximately 9 points lower than unexposed children born to women without epilepsy and 8 points lower than children born to women with untreated epilepsy (Bromley et al. 2014). A 2024 systematic review in the journal *Neurology* updated these findings, confirming that valproate is consistently associated with 2- to 5-fold increased risk of intellectual disability, with clear dose-dependent effects (Honybun et al. 2024).

Prenatal valproate exposure has also been associated with an increased risk of childhood neurodevelopmental conditions. A 2025 meta-analysis of 8 cohort studies found that gestational valproate exposure was associated with a modest but significant increase in attention deficit/hyperactivity disorder (ADHD) risk (adjusted hazard ratio [HR] 1.62, 95% CI, 1.30–2.01) and a three-fold increase in the risk of autism spectrum disorder (ASD) (adjusted HR 3.10, 95% CI, 2.24–4.28), with both risks showing dose-dependent relationships (Andrade et al. 2025). The most comprehensive examination comes from a 2023 Nordic registry study among children born to mothers with epilepsy, which assessed 13 psychiatric disorders. This study found that children with prenatal valproate exposure faced an absolute risk of 42.1% (95% CI, 38.2–45.8) of being diagnosed with any psychiatric disorder by age 18, compared to 31.3% (95% CI, 28.9–33.6) among children of untreated mothers and 30.8% (95% CI, 29.2–32.3) among children exposed to any antiseizure medication. Besides intellectual and other neurodevelopmental disorders, this increase was driven by elevated risks for ASD, ADHD, and attachment disorder (Dreier et al. 2023). Long-term impacts on developmental outcomes in adulthood among those exposed to valproate in utero have not been well examined. As with the risk for congenital malformations, a consistent and significant dose–response relationship is seen with higher doses of valproate linked to both higher risk for and severity of adverse neurodevelopmental outcomes (Andrade et al. 2025).

Gestational timing of prenatal exposure is important. First-trimester exposure is a critical time for manifestation of congenital malformations during organogenesis (Fietz et al. 2024), while the timing for adverse effects on neurodevelopment spans early to late gestation (Sheehy et al. 2025). Hence, risk management measures need to focus on exposure prevention throughout pregnancy. Early pregnancy, often before women even know they are pregnant, poses the greatest challenge for prevention.

The benefits of periconceptional folic acid to decrease the risk of neural tube defects are well recognized and have led to recommendations from numerous professional groups for all women who are capable of becoming pregnant to take 400 mcg (0.4 mg) of folic acid daily to reduce the risk of neural tube defects (American College of Obstetricians and Gynecologists 2017; US Preventive Services Task Force et al. 2023). Valproate can lower folic acid levels, which has led some to recommend that women who take valproate during pregnancy, as well as women with epilepsy on other medications, take higher doses (1–5 mg daily) of folic acid before and during pregnancy to reduce valproate-associated risks (Ornoy et al. 2023; Reynolds and Green 2020). However, a recent systematic review did not demonstrate significant mitigation of the risk for valproate-associated anatomic abnormalities (e.g., neural tube defects) among women taking folic acid (Valentino et al. 2024). While some studies of women taking antiseizure medications suggest better cognitive development (Meador et al. 2020) and lower risk of autistic traits (Bjork et al. 2018) with periconceptional folic acid supplementation, other studies did not confirm these protective effects (Baker et al. 2015; Bromley, Bullen, et al. 2023; Valentino et al. 2024). Thus, it remains unclear whether higher doses of folic acid are beneficial. Consistent with this, the current joint practice guideline from the American Academy of Neurology (AAN), the American Epilepsy Society (AES), and the Society for Maternal-Fetal Medicine (SMFM) recommends "at least 0.4 mg of folic acid supplementation daily preconceptionally and during pregnancy" to any person with epilepsy of childbearing potential treated with

an antiseizure medication to decrease the risk of neural tube defects and to possibly improve neurodevelopmental outcomes such as ASD and global IQ in the offspring (Practice Guideline from the AAN, AES, and SMFM, et al. 2025).

Concerns regarding possible adverse reproductive effects of valproate are not confined to use by women. Several smaller studies suggest that men may experience a drop in fertility while using valproate, with fertility improving when use has stopped (Asghar et al. 2024; Markoula et al. 2020; Tallon et al. 2021). However, a 2025 published retrospective cohort study in more than 90,000 exposed men with bipolar disorder or epilepsy found no significant difference in lifetime risks of infertility, testicular hypofunction, testicular atrophy, or abnormal semen parameters compared to unexposed men (Mbizvo et al. 2025).

Paternal use of valproate has not been found to result in an increased risk of major congenital malformations (Garey et al. 2024). However, although evidence is inconsistent, paternal use may increase the risk of neurodevelopmental disorders in offspring. A 2025 European Medicines Agency-mandated post-authorization safety study conducted in Denmark, Norway, and Sweden and published in 2025 found that paternal valproate exposure within 3 months prior to conception was associated with a 50% increased risk of neurodevelopmental disorders compared to paternal use of lamotrigine or levetiracetam (pooled adjusted HR 1.50, 95% CI, 1.09–2.07) (Colas et al. 2025; IQVIA 2023). These concerns prompted recommendations about precautionary measures for the treatment of male patients by European regulatory authorities (European Medicines Agency 2024). However, independent Danish analyses (Christensen et al. 2024) were unable to replicate the Danish risk estimates from the post-authorization safety study, and an earlier Swedish study found insignificant results, suggesting that adverse effects are likely attributable to epilepsy-related factors rather than valproate itself (Bjork et al. 2025; Olstad et al. 2025).

3 | Regulatory Efforts to Reduce Inadvertent Prenatal Exposures in the United States and Other Countries

The US Food and Drug Administration (FDA)-approved indications for valproate include treatment of seizure disorders, acute treatment of manic or mixed episodes associated with bipolar disorder, and migraine prophylaxis. FDA has approved various formulations, ranging from capsules to injections, made by multiple different manufacturers. However, successive label changes, including addition and then expansion of a boxed warning, have restricted its use in the United States, including a contraindication for prophylaxis of migraine headaches in pregnancy and in women of childbearing potential who are not using effective contraception (Figure 1). The current label also states that valproate should not be used to treat women with epilepsy or bipolar disorder who are pregnant or plan to become pregnant unless other medications have failed to provide adequate symptom control, and it should generally not be administered to a woman of childbearing potential unless other medications have failed and only if effective contraception is used.

Besides the label, regulatory risk management to prevent prenatal exposure to valproate has been limited to several drug safety communications to health care providers (Figure 1), and the requirement for a medication guide, that is, standardized patient-directed information that must be dispensed when valproate prescriptions are filled. The 5-page medication guide, which covers a broad range of severe adverse effects, includes a half page summarizing the risk for birth defects and lower IQ, related precautions and contraindications consistent with the label, and a recommendation that in case of pregnancy, women should talk to their healthcare provider to decide whether they should continue treatment with valproate (DailyMed National Library of Medicine 2026).

In addition to issuing drug safety communications and medication guides, regulatory agencies can also require the implementation of more stringent risk management programs. With the FDA Amendments Act signed into law in 2007, FDA has the authority to require Risk Evaluation and Mitigation Strategies (REMS). Prominent examples in prevention of teratogenic effects include the REMS for isotretinoin, thalidomide, and mycophenolate (Brown et al. 2023). Each of these REMS includes "elements to ensure safe use," ranging from more restrictive components such as required pharmacy verification of negative pregnancy tests before dispensing and supplies capped at 30 days for isotretinoin and 28 days for thalidomide, to only mandatory provider training and patient counseling for mycophenolate.

While the FDA has not implemented a REMS program for valproate, other countries have implemented restrictions similar to REMS to help mitigate exposure in pregnancy. In 2018, the European Medicines Agency (EMA) developed a valproate Pregnancy Prevention Programme (PPP) in which valproate is contraindicated in women of childbearing age unless the patient and prescriber complete a mandatory risk acknowledgement form, the patient uses effective contraception throughout treatment with negative pregnancy tests before and after treatment, and other restrictions (European Medicines Agency 2018). This PPP was endorsed by the European Commission, requiring implementation by all member countries. The UK's Medicines

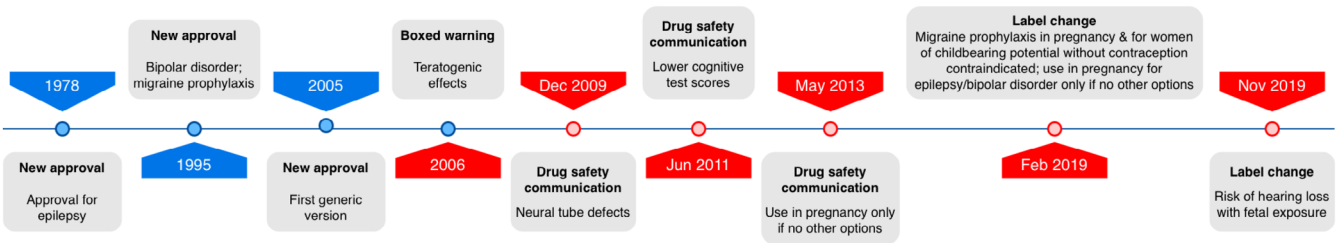

FIGURE 1 | Overview of US regulatory approvals and action addressing valproate safety concerns in pregnancy.

and Healthcare Products Regulatory Agency (MHRA) (Iacobucci 2018) and Health Canada have adopted similar PPPs (BGP Pharma ULC 2020).

4 | Other Efforts to Decrease Prenatal Exposures to Valproate

For years, US-based professional medical organizations have acknowledged the risks associated with valproate use in pregnancy and suggested mitigation strategies. As early as 2009, the AAN and the AES issued practice updates warning about the use of valproate in pregnant women and suggesting changing to another antiepileptic medication before pregnancy, if possible (Harden, Meador, Pennell, Allen Hauser, et al. 2009; Harden, Meador, Pennell, Hauser, et al. 2009). The current joint practice guideline from AAN, AES, and the SMFM regarding women with epilepsy of childbearing potential recommends avoiding the use of valproate if clinically feasible (Practice Guideline from the AAN, AES, and SMFM, et al. 2025).

In 2023 the World Health Organization published an addendum to their Mental Health Gap Action Program (mhGAP) guidelines suggesting that valproate not be used in women and girls of reproductive potential, that those taking valproate be advised to use effective contraception and have their medication reviewed by a specialist on a periodic basis, and that every effort be made to switch to an alternative treatment prior to pregnancy (World Health Organization 2023).

Finally, in 2025, several members of the American Psychiatric Association's Committee on Women's Mental Health met with FDA officials to request a REMS program for valproate products (Richmond 2025). This action, initiated by healthcare providers, is particularly noteworthy because certain components of REMS such as mandatory training might pose an additional burden on prescribers. It suggests that prescribers might value the reassurance provided by a REMS program when prescribing valproate to women of childbearing age, which is consistent with recent survey results about other REMS programs that include Elements To Assure Safe Use (Sarpatwari et al. 2023) and reports of clinician-initiated REMS-like processes such as patient informed consent when prescribing valproate (Suleiman et al. 2026).

5 | Prenatal Valproate Exposures Continue Despite Current Efforts

Several studies assessing valproate use over one or more decades have documented a decline, although it has remained the most widely used antiepileptic agent globally in 2022, with stronger growth observed in lower- and middle-income compared to higher-income countries (Chan et al. 2025). Studies describing decreases in use have typically focused on female populations of childbearing age and have attributed changes to the implementation of risk management programs or other regulatory action (Battino et al. 2024; Di Vito et al. 2023; Kim et al. 2019). However, while decreases in use have been more pronounced among female patients, use among males has also declined, likely attributable to the increasing availability of second-generation antiepileptic agents. Analyses in national private insurance claims data have estimated that about 3.6 per 10,000 women of childbearing age used valproate in 2020 in the US, compared to 6.4 of their male counterparts at a similar age range (Al-Bahou et al. 2022). Importantly, valproate remains one of the top ten known teratogenic medications used during pregnancy. A study examining prenatal exposure to a range of teratogenic medications between 2011 and 2018 found 49 pregnancies with at least one prescription fill during gestation per 100,000 pregnancy-years (32 per 100,000 pregnancy-years ending in live birth) (Wang et al. 2024). A follow-up study from 2014 to 2018 assessing risk for prenatal exposure among teratogenic medication users of childbearing potential reported the risk for prenatal exposure to valproate at 17.0 (95% CI, 16.4–17.6) per 1000 user-years (Wang et al. 2026). Exposure during pregnancy resulted mostly from conception during treatment rather than initiation of the medication during pregnancy and was twice as high among women with public insurance compared to those in employer-sponsored plans.

Given the risk for teratogenicity from valproate regardless of the indication for use, benefit–risk analyses for use among women of childbearing potential (or during pregnancy) could be more heavily weighted toward benefit considerations, that is, the seriousness of the indication being treated, valproate effectiveness in treating this indication, and whether safer, equally effective or more effective alternatives are available. Hence, valproate use would be expected to vary across indications, for example, with greater use among women with epilepsy than with migraine. However, studies have shown a different trend.

First, women with epilepsy contribute a comparably small proportion to valproate users of childbearing potential. In a 2024 study of women of childbearing age (12–44 years) in the United States with private insurance spanning 2005–2020, bipolar disorder accounted for 42.5% of valproate use, followed by migraine or headache (20.1%), while epilepsy represented only 14.9% of treatment episodes (Smolinski et al. 2024). Similarly, a 2025 analysis of Medical Expenditure Panel Survey (MEPS) data found that among women age 12–49 years filling valproate prescriptions between 2017 and 2022, the most common indication was migraine or other headache syndromes (27.2%), followed by bipolar disorder (24.6%), with convulsions or epilepsy accounting for only 20.7% (Vadiei et al. 2026). Second, decreases in valproate use among women of childbearing age have been indication-specific with use for migraine showing no decrease over the past decade (Al-Bahou et al. 2022). Finally, pregnancy rates during valproate use among women in private insurance in the United States with migraine or bipolar disorder were more than double those of users with epilepsy. Importantly, pregnancy rates have remained steady across the study period, from 1.74 per 100 user-years in 2005 to 1.90 in 2019, suggesting no improvement in pregnancy prevention during use (Smolinski et al. 2024). In this study, less than one quarter of valproate use episodes overlapped with exposure to hormonal contraceptives or copper intrauterine devices, suggesting that the teratogenic risk was likely unknown or the need for effective contraception underappreciated.

Studies on risk factors for exposure to teratogenic medications have shown that women at the extremes of childbearing age,

those living in states in the United States with lower healthcare quality ranking, and those with public versus private insurance are at higher risk, stressing the importance of pregnancy prevention programs (Albogami et al. 2021; Sarayani et al. 2022; Smolinski et al. 2022). With most exposure to teratogenic medications occurring early in pregnancy, unintended pregnancy and delays in prenatal care initiation are other important risk factors that place vulnerable populations with limited healthcare access at particular risk (Winterstein et al. 2024).

6 | Recommendations

Recent data suggest that approximately 42% of pregnancies in the United States are unplanned, with estimates reaching up to 51% among certain demographic groups (CDC National Center for Health Statistics 2026). For this reason, awareness about the potential harmful effects of valproate use in pregnancy, and efforts to mitigate risk, cannot focus solely on pregnancy, but rather broadly on women of reproductive age who can become pregnant. In addition, many women of reproductive age see healthcare providers inconsistently and have limited access to specialists (DiPietro Mager et al. 2021; Gilchrist et al. 2024; Schuldt and Jinnett 2024). Providing valproate risk education to providers in a range of specialties beyond obstetrics, neurology, and psychiatry to include primary care, urgent care, pharmacy, and others can help ensure that women of reproductive age taking valproate or who may be prescribed valproate can be identified at opportune points of care, counseled about associated risks, and transitioned to alternate medications when possible. As with any medication before and during pregnancy, informed treatment decisions should be tailored to the individual, considering the severity of their condition, medication history, effective alternatives, pregnancy intentions, maternal health, and fetal risks.

There is consistent, high-quality evidence that valproate is a potent teratogen that causes serious harm, with lifelong consequences for the offspring of exposed mothers, their families and caregivers. Although utilization of valproate has decreased in both sexes over time in the US, the risk for prenatal exposure among users has not, suggesting that current risk management efforts have been unsuccessful in ensuring that women use effective contraception during use and that providers do not prescribe valproate to women who may be pregnant. Comparing the certainty of evidence, frequency of prenatal exposure, and severity of harm, it appears that valproate falls in a similar risk category as isotretinoin or thalidomide, raising questions about currently dissimilar risk management approaches. Given its significant detrimental public health impact, implementation of pregnancy prevention programs in peer countries, and the fact that relevant medical societies have openly requested such programs to ensure an appropriate safety net for providers when valproate is the only treatment option for a patient, we call for implementation of a REMS for valproate. Given the etiology of prenatal exposure, a valproate REMS would mandate the use of contraception or abstinence during treatment and require a monthly negative pregnancy test when prescribing valproate to a woman of childbearing potential. In cases of desired or needed use during pregnancy, both provider and patient should document that benefit–risk has been discussed and found favorable. Given the inadequacies of the available data, we do not consider it advisable to create a REMS that covers paternal use of valproate.

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Data Availability Statement

Data availability is not applicable to this article as no new data sets were generated or analyzed.

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