DOI: https://doi.org/10.4038/sljon.v12i1.192

SLJoN

REVIEW

Restricting valproate prescribing in women – path forward in Sri Lanka

M Saamir Mohideen[1]

[1]National Hospital, Galle, Sri Lanka.

Correspondence

M Saamir Mohideen
National Hospital, Galle,
Sri Lanka.

E-mail: saamirms@gmail.com

Abstract

Valproate is a well-established antiseizure medication (ASM) with efficacy across multiple seizure types. However, its teratogenic effects and risks to neurodevelopment in exposed children present significant challenges in prescribing it to women of childbearing potential (WOCP). Various countries have implemented stringent guidelines to limit valproate's use among women. This article examines the pharmacological profile, efficacy, and reproductive health risks of sodium valproate, reviews international restriction practices, and proposes actionable steps for Sri Lanka.

KEYWORDS

Valproate (VPA), Anti-seizure medication (ASM), Women of childbearing potential (WOCP), Major congenital malformation (MCM)

INTRODUCTION

Globally, an estimated 5 million people are diagnosed with epilepsy each year. In high-income countries, there are estimated to be 49 per 100 000 people diagnosed with epilepsy each year. In low- and middle-income countries, this figure can be as high as 139 per 100 000.[1]

Sri Lanka is a middle-income country in Southeast Asia with a population of approximately 22 million. Its state care health system provides free health to all its citizens. Epilepsy is treated both in the private and government health sector. Anti-seizure medications (ASMs) are prescribed by junior doctors to consultants without restriction.

Women with epilepsy are at a higher risk of teratogenic effects of ASM. ASMs associated with highest teratogenicity are sodium valproate and topiramate. Drugs with the least teratogenic effects include lamotrigine, levetiracetam, oxcarbamazepine and have a lower risk than that associated with the lowest dose category of valproate.[2]

Valproic acid was first approved for the treatment of epilepsy in France in 1967. However, the first controlled trial documenting its efficacy was published in 1975.[3] The recent discovery of its ability to inhibit histone deacetylase has rekindled interest in novel potential indications, such as cancer. It is the conventional drug of choice for adults and children with a clear diagnosis of genetic generalized epilepsy, otherwise known as idiopathic generalized epilepsy (IGE).[4] Since its approval for the treatment of epilepsy decades ago, the clinical indications for valproic acid have evolved to include migraine prophylaxis and treatment of bipolar disorders.

In one study in the USA, patients with migraine and mood disorders accounted for the largest proportion of valproic acid use and had the highest pregnancy rates, while patients with epilepsy had the lowest. This is despite restrictions in the USA.[5]

Valproate, discovered in the 1960s, has been a cornerstone in epilepsy management due to its broad-spectrum efficacy,

This is an open-access article distributed under the terms of the Creative Commons Attribution 4.0 International License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

especially in generalized epilepsies. However, evidence of serious teratogenicity, including structural birth defects and neurodevelopmental disorders, warrants caution when prescribing sodium valproate to women of childbearing potential.

In response, many countries have implemented regulatory frameworks to limit its use among young females. This article assesses the necessity for similar measures in Sri Lanka.

Sodium valproate: Overview and mechanism of action

Sodium valproate has multiple mechanisms of action, including GABA potentiation, blocking of T-type calcium channels and blocking of sodium channels. This effect stabilizes neuronal firing and is beneficial across a variety of seizure types. Valproate is enzyme inhibitor and extensively metabolized by conjugation and oxidation. The half-life in adults is between 13 to 16 hours.[6]

Valproate has a broad spectrum of efficacy against all focal and generalized seizures. However, it is more effective in generalized tonic-clonic seizures, absence seizures, myoclonic seizures, and some mixed seizure types. It is less effective in focal seizures, where alternative ASMs may offer more targeted control.

Valproate is associated with a dose-related teratogenicity rate higher than any other marketed antiseizure medication, with risk of major malformations higher than 30% at doses greater than 1100 mg/d. In utero exposure is also associated with dose-dependent reduced verbal IQ, other cognitive dysfunction, and autism.

Adverse effects on reproductive health in females

The reproductive risks associated with sodium valproate are well-documented with major congenital malformations (MCM) and neurodevelopmental risks.

Major congenital malformation (MCM)

Around 1 in 9 babies (11%) will have a birth defect in women who take valproate while pregnant. In the first trimester valproate increases the risk of major congenital malformations, independent of any contribution of the epilepsy syndrome itself.

Birth defects seen when mothers take valproate during pregnancy include neural tube-like defects (e.g., spina bifida, open lumbosacral myelocle) in 1 to 2 percent of fetuses, which represents a 10- to 20-fold increase over the general population.

Additional patterns of major malformations associated with first-trimester valproate exposure include oral clefts, cardiovascular and urogenital malformations, and multiple malformations (Table 1).[7]

The risk of MCMs during valproate treatment is highest during the first 7 weeks of pregnancy and the rates of MCMs are dose dependant (Table 2).[8]

The reasons for the teratogenic effects are not fully understood, but possibly involve epigenetic effects, including the inhibition of histone deactylase with associated changes in gene expression, increases in foetal oxidative stress, or the antagonism of folate required for DNA synthesis.[9]

TABLE 1 Odds ratios and absolute risk of congenital malformation with sodium valproate (adapted from Jentink et al., 2010)[7]

	Odds ratio (median and range) in offspring of mothers who took valproate in pregnancy	Absolute risk
Spina bifida	12.7 (7.7-20.7)	0.6%
Atrial septal defect	2.5 (1.4-4.4)	0.5%
Cleft palate	5.2 (2.8-9.9)	0.3%
Hypospadias	4.8 (2.9-8.1)	0.7%
Polydactyly	2.2 (1.0-4.5)	0.2%
Craniosynostosis	6.8 (1.8-18.8)	0.1%

TABLE 2 Prevalence of major congenital malformations (MCMs) in offspring exposed prenatally to valproate monotherapy

ASM treatment (dose range, mg/d)	Prevalence of MCMs (95% CI), %
Valproate (≤650)	6.0 (4.4-8.0)
Valproate (>650-≤1450)	11.1 (8.9-13.6)
Valproate (>1450)	25.2 (17.8-33.8)
Valproate (100-3000)	9.9 (8.5-11.5)

Neurodevelopmental risks

Of all ASMs, valproate is the drug most strongly associated with adverse neurodevelopmental outcomes. In women who take valproate while pregnant, about 3-4 children in every 10 may have developmental problems, and these disorders can be seriously debilitating and permanent.[10] Unlike major congenital malformations, antiseizure medication exposure during the last trimester may be the most detrimental for cognitive performance.[11]

Cognitive impairment

Several publications have described an association between fetal exposure to valproate and the risk of impaired IQ and cognitive developmental delay. One study found a significantly lower IQ (mean IQ score of 97) in children of women with epilepsy treated with valproate than with lamotrigine (mean IQ score of 108) and these findings persisted at six years. The effects are dose dependent with valproate doses above 800-1000 mg/day have been consistently associated with reduced IQ with doses below the 800 mg/day threshold have been linked to worse verbal IQ performance and a need for educational support.[12]

Unlike major congenital malformations, antiseizure medication exposure during the last trimester may be the most detrimental for cognitive performance.[12]

Behavioural impairment

Valproate has been consistently associated with a 2- to 4-fold increased risk of autism spectrum disorder (ASD), 2- to 5-fold increased risk of intellectual disability (ID), and poor adaptive functioning.[13]

Studies have shown that the risk of autism spectrum disorder with valproate exposure was 4.4%, compared to 1.5% in the general population. In another study, the correlation of autism spectrum disorder to fetal antiseizure medication exposure was not seen in children exposed to polytherapy without valproate, suggesting that valproate (or valproate dose) rather than polytherapy is the critical determinant of the relationship.[14,15] In addition, children with in utero exposure to valproate are also at a significantly greater risk for a diagnosis of attention deficit hyperactivity disorder (ADHD).[16]

Rationale for restricting sodium valproate in reproductive-aged females

Restricting valproate use in young, healthy females is crucial to prevent potential teratogenic effects and neuro-developmental issues in exposed children. Given the availability of alternative ASMs with lower teratogenic risks, a more selective approach in prescribing valproate can help protect the health of both women and potential offspring.

Unplanned pregnancy while on valproate: what can be done?

Pregnancy while taking valproate presents significant challenges and requires careful management based on a risk-benefit assessment. Poor seizure control during pregnancy poses substantial risks to both the mother and baby, underscoring the importance of individualized care. The priority in the first trimester should probably be to withdraw the drug or reduce the dose to prevent cognitive impairment in the newborn.[17] If a switch is decided, levetiracetam is preferable to lamotrigine, as it can be quickly loaded, either orally or intravenously.

The evidence is unclear whether to switch to another ASM while pregnant, as switching form valproate to another ASM is associated with risk. One study had shown that generalised tonic-clonic seizures were twice as common in those where valproate was withdrawn (33%; n=93) or replaced (29%; n=38) in pregnancy, compared with those

who stayed on it (16%; n=1588). This needs to be kept in mind while considering the risk vs benefit of switching to another ASM during pregnancy.[18]

In some circumstances, you may not be able to switch to another medication. In such cases, the pregnancy should be closely monitored (e.g., with high-resolution ultrasound). The consequences of any MCM detected should be discussed in depth and women should be offered counselling to help them take the best possible decision.

Prescription of valproate in paediatric age group

Initiation of valproate before menarche is not recommended, although there are circumstances when it might be acceptable. Valproate can be prescribed as first-line therapy for potentially self-limited epilepsy syndromes, such as focal epilepsy with centrotemporal spikes, childhood absence epilepsy, and benign myoclonic epilepsy in infancy.[19]

It should not be the first choice in patients with chronic childhood-onset epilepsy syndromes likely to remain active into adolescence and adulthood (e.g., Jeavons syndrome). If starting valproate, adequate information must be given to both patients and their parents/legal guardians regarding future implications.

Contraception while on valproate

Contraception in women of childbearing potential (WOCP) with epilepsy on valproate is crucial and family planning is important. WOCP on valproate should use at least one effective method of contraception (preferably a user-independent method such as an intrauterine device or implant) or two complementary methods including a barrier method.

Pregnancy planning while on valproate

Pregnancy should be planned approximately one year in advance to allow sufficient time to safely withdraw valproate and find an effective alternative. The minimum period recommended for switching from valproate to any other ASM is 3 months.

As a general recommendation, contraception should be maintained for three months after valproate discontinuation to ensure full clearance and allow time to adapt to the new ASM. Folic acid supplementation is recommended for at least one month before conception, regardless of valproate treatment. The recommended dose for patients taking ASM is 4-5 mg/day, which is higher than doses recommended for women at low risk.[20]

Switching valproate in focal epilepsy and generalized epilepsy

Sodium valproate has not shown to be superior to other ASM in focal onset epilepsy.

For generalized epilepsy syndromes

In those with epilepsy with GTCS, monotherapy with lamotrigine and levetiracetam should be tried first, followed by combination therapy with the two drugs if necessary. For those with juvenile myoclonic epilepsy, levetiracetam, followed by lamotrigine, is the first-line alternative to valproate. Combination therapy with lamotrigine and levetiracetam can be considered. Ethosuximide, followed by lamotrigine, should be the first option for childhood absence epilepsy. If absence seizures persist, levetiracetam should be tried. The first-line options for juvenile absence epilepsy are lamotrigine and levetiracetam. Ethosuximide can be considered as a later alternative.

Switching from valproate to lamotrigine

Switching from valproate to lamotrigine requires on average 2-3 months or longer.

LTG dose starting at 12.5mg with dose escalation every two weeks with the aim to reach target dose in 8 weeks followed by sodium valproate withdrawal over six to eight weeks.

Switching from valproate to levetiracetam

Switching from valproate to levetiracetam is faster, as titration is not always needed

The target dose for levetiracetam is between 1000 and 2000 mg/day depending on the valproate dose. Valproate should not be decreased abruptly due to the risk of breakthrough GTCS. Selection of these alternatives should be based on seizure type, individual response, and safety profile.[4]

Situations when valproate could be continued

Focal onset epilepsy

In self-limited focal childhood epilepsy syndromes such as focal epilepsy with centrotemporal spikes) valproate should be both started and stopped before the patient reaches reproductive age. Four ASMs can be recommended as alternatives for focal epilepsy based on known risks of MCMs from the EURAP registry. These are levetiracetam, lamotrigine, oxcarbazepine, and carbamazepine.

Generalized epilepsy

Valproate may be continued in specific situations where its benefits outweigh the risks. These include cases where it is the only effective medication after other antiseizure medications (ASMs), whether as monotherapy or polytherapy, have failed, or when alternative ASMs are contraindicated due to severe psychiatric disorders or allergies. It may also be considered when seizures are expected to resolve, such as in childhood absence epilepsy, benign myoclonic epilepsy in infancy, or when the patient is a candidate for epilepsy surgery. Additionally, valproate may be used in severely disabled females with little to no likelihood of pregnancy or when the risk of seizure exacerbation is deemed more critical than the potential teratogenic effects.

How can we minimize the risks for women who require valproate after attempting alternative treatments?

To minimize risks in women who require valproate after considering and trying alternatives, several measures can be implemented. Valproate should be prescribed at the minimum effective dose, preferably no higher than 600-800 mg/day, while avoiding high peak concentrations by utilizing prolonged-release formulations and fractionating the dose. High-dose folic acid (4-5 mg/day) is recommended before conception and should be continued for at least the first three months of pregnancy to reduce the risk of neural tube defects. Additionally, if valproate cannot be completely withdrawn, combining it in polytherapy with the lowest possible dose is preferable to using higher-dose monotherapy. These strategies aim to balance the need for seizure control with minimizing potential adverse effects.[21]

International guidelines and restriction models

Many countries have introduced stringent measures to control the prescription of sodium valproate for women of childbearing potential due to its high teratogenic risk and potential for neurodevelopmental harm in children exposed in utero.

In the European Union (EU), a Pregnancy Prevention Program (PPP) mandates that healthcare providers offer educational materials to patients and providers, obtain signed risk acknowledgment forms, and limit valproate prescriptions to specialists, who must conduct annual reviews and provide contraceptive counselling.[22]

Since 2018, in the UK valproate is not to be used in any female able to have children unless there is a Pregnancy Prevention Programme (PPP) in place. This is designed to make sure patients are fully aware of the risks and the need to avoid becoming pregnant. Healthcare professionals who seek to prescribe or dispense valproate to their female patients must make sure this is within the terms of the PPP. This includes the completion of a signed risk acknowledgement form when their treatment is reviewed by a specialist, at least annually.[23] These regulatory changes are further supported by smaller pack sizes to encourage monthly prescribing and a pictogram or warning image on valproate labelling. Regulations introduced in 2023 are to ensure all patients receive the whole pack of valproate with warnings on the box.

The United States Food and Drug Administration (FDA) has issued a boxed warning emphasizing that valproate should not be administered to women of childbearing potential unless other medications have failed to provide adequate symptom control or are deemed unacceptable, however it stops short of mandating annual reviews or signed acknowledgment forms.[24]

Australia's Therapeutic Goods Administration (TGA) has adopted a Pregnancy Prevention Program akin to the EU's, restricting prescribing to specialists and providing risk acknowledgment forms and educational materials to improve patient understanding.

In Southeast Asia (e.g., Malaysia, Singapore)

In Malaysia, the national pharmaceutical regulatory agency (NPRA) has issued warnings about valproate's teratogenicity and have contraindicated valproate use in epilepsy and bipolar affective disorder if no PPP (pregnancy prevention program) is in place. In addition, healthcare providers are urged to ensure informed decision-making by patients, with a focus on contraception use.[25] In Singapore too, valproate is contraindicated during pregnancy unless no alternative is available. Women on valproate are advised to use effective contraception, and regular reviews are conducted. These regulatory frameworks have helped reduce the incidence of foetal valproate exposure. There are no legal restrictions placed in our neighbouring countries in India, Pakistan, Bangladesh, Maldives, Bhutan, Nepal and Myanmar.

Current challenges in Sri Lanka

In Sri Lanka, several unique challenges complicate the implementation of valproate restrictions.

1. Limited awareness: Among both healthcare providers and patients, there is limited awareness of valproate's teratogenic risks. Inadequate counselling facilities further exacerbate the problem, leaving many women unaware of the associated risks.

2. Resource constraints: Sri Lanka faces significant resource constraints in access to alternative anti-seizure medication, particularly newer-generation options.

3. Sociocultural factors: Discussing contraception remains a sensitive topic in Sri Lanka. Women may be reluctant to disclose their reproductive plans, and healthcare providers may hesitate to engage in these discussions due to cultural norms.

4. Reluctance of the healthcare providers to change their lifelong practises with emerging new evidence.

The path forward for Sri Lanka

Given the international precedent and the known risks associated with sodium valproate, Sri Lanka should consider adopting a structured approach to minimize its use among women of childbearing potential. Firstly, and most importantly we need to support and develop a pregnancy registry documenting birth, and developmental defects associated with antiseizure medications during pregnancy.

These are some of the proposals which could be considered for implementation.

1. **Developing national guidelines:** Create guidelines specifically addressing the use of valproate in women of childbearing potential, including recommendations for alternative treatments.

2. **Educational programs for healthcare providers:** Train healthcare providers on the reproductive risks associated with valproate and encourage the discussion of safer alternatives with patients.

3. **Informed consent and mandatory counselling:** Implement a formal consent process where prescribers are required to discuss the risks with patients and document consent.

4. **Restricting prescription to specialists:** Limit initial valproate prescriptions to specialists in neurology and epilepsy, with a focus on informed decision-making.

5. **Alternative ASM Access:** Ensure availability and affordability of alternative ASMs, such as lamotrigine and levetiracetam, which have lower teratogenic risks.

6. **Discourage** use of sodium valproate for migraine and bipolar affective disorder when suitable alternatives are available.

7. **Other options** such as smaller pack size to encourage monthly prescriptions and pictural warning for valproate.

Sri Lanka's health sector also should be mindful and should implement practical solutions to restrict valproate use in women of reproductive age. This is essential to prevent major congenital malformations (MCM) and adverse neurodevelopmental outcomes, which place a significant burden on individuals, families, and healthcare facilities already under severe economic constraints. To adopt the above, we would need consensus among stakeholders and a national policy based on evidence.

CONCLUSION

Restricting sodium valproate prescribing among females of reproductive age in Sri Lanka is an essential step to reduce teratogenic risks and improve reproductive health outcomes. Implementing guidelines for limited and well-informed valproate use, combined with educational initiatives and availability of alternative ASMs, can contribute to a safer, more effective approach in epilepsy management for this demographic.

REFERENCES

1. Epilepsy: a public health imperative. Geneva: World Health Organization; 2019.

2. Battino D, Tomson T, Bonizzoni E, et al. Risk of major congenital malformations and exposure to antiseizure medication monotherapy. *JAMA Neurol.* 2024;81(5):481-89. doi: 10.1001/jamaneurol.2024.0258.

3. Tomson T, Battino D, Perucca E. The remarkable story of valproic acid. *Lancet Neurol.* 2016;15(2):141. doi: 10.1016/S1474-4422(15)00398-1

4. Toledo M, Mostacci B, Bosak M, et al. Expert opinion: use of valproate in girls and women of childbearing potential with epilepsy: recommendations and alternatives based on a review of the literature and clinical experience-a European perspective *J Neurol.* 2021;268(8):2735-2748. doi: 10.1007/s00415-020-09809-0.

5. Smolinski NE, Sarayani A, Thai TN, et al. Prenatal exposure to valproic acid across various indications for use. *JAMA Netw Open.* 2024;7(5):e2412680. doi: 10.1001/jamanetworkopen.2024.12680.

6. Abou-Khalil BW. Update on Antiseizure Medications 2022 Continuum (Minneap Minn). 2022;28(2):500-535. doi: 10.1212/CON.0000000000001104.

7. Jentink J, Loane MA, Dolk H, et al. Valproic acid monotherapy in pregnancy and major congenital malformations. *N Engl J Med.* 2010;362(23):2185-2193. doi: 10.1056/NEJMoa0907328.

8. Tomson T, Battino D, Perucca E. Teratogenicity of antiepileptic drugs. *Curr Opin Neurol.* 2019;32(2):246-52. doi: 10.1097/WCO.0000000000000659.

9. Macfarlane A, Greenhalgh T. Sodium valproate in pregnancy: What are the risks and should we use a shared decision-making approach? *BMC Pregnancy Childbirth.* 2018;18(1):200. doi: 10.1186/s12884-018-1842-x.

10. Medicines and Healthcare products Regulatory Agency, UK Government. Valproate and risk of abnormal pregnancy outcomes. https://www.gov.uk/government/collections/valproate-safety-measures (accessed 2024)

11. Reinisch JM, Sanders SA, Mortensen EL, et al. In utero exposure to phenobarbital and intelligence deficits in adult men. *JAMA.* 1995;274(19):1518-25.

12. Meador KJ, Baker GA, Browning N, et al. Fetal antiepileptic drug exposure and cognitive outcomes at age 6 years (NEAD study): a prospective observational study. *Lancet Neurol.* 2013;12(3):244-52. doi: 10.1016/S1474-4422(12)70323-X.

13. Honybun E, Cockle E, Malpas CB, et al. Neurodevelopmental and functional outcomes following in utero exposure to antiseizure medication: A systematic review. *Neurology.* 2024;102(8):e209175. doi: 10.1212/WNL. 0000000 000209175.

14. Christensen J, Gronborg TK, Sorensen MJ, et al. Prenatal valproate exposure and risk of autism spectrum disorders and childhood autism. *JAMA.* 2013;309(16):1696-1703. doi: 10.1001/jama.2013.2270.

15. Bromley RL, Mawer G, Clayton-Smith J, et al. Autism spectrum disorders following in utero exposure to antiepileptic drugs. *Neurology.* 2008;71(23):1923-24. doi: 10.1212/01.wnl.0000339399.64213.1a.

16. Wood AG, Nadebaum C, Anderson V, et al. Prospective assessment of autism traits in children exposed to antiepileptic drugs during pregnancy. *Epilepsia.* 2015;56(7):1047-55. doi: 10.1111/epi.13007.

17. Beezhold JN, Fagard D, Harabajiu C. Valproate used during pregnancy: What should be done? *Eur Psychiatry.* 2017;41:S419-S419.

18. Tomson T, Battino D, Bonizzoni E, et al. Withdrawal of valproic acid treatment during pregnancy and seizure outcome: Observations from EURAP. *Epilepsia.* 2016;57(8):e173-77. doi: 10.1111/epi.13437.

19. Åberg KM, Surén P, Soraas CL, et al. Seizures, syndromes, and etiologies in childhood epilepsy: The International League Against Epilepsy 1981, 1989, and 2017 classifications used in a population-based cohort. *Epilepsia.* 2017; 58(11): 1880-91. doi: 10.1111/epi.13913.

20. European Medicines Agency. Valproate and related substances. https://www.ema.europa.eu/en/medicines/human/referrals/valproate-related-substances (accessed 2024)

21. Stephen LJ, Harden C, Tomson T, et al. Management of epilepsy in women. *Lancet Neurol.* 2019;18(5):481-91. doi: 10.1016/S1474-4422(18)30495-2.

22. European Medicines Agency. PRAC recommends new measures to avoid valproate exposure in pregnancy. https://www.ema.europa.eu/en/news/prac-recommends-new-measures-avoid-valproate-exposure-pregnancy (accessed 2024)

23. Medicines and Healthcare products Regulatory Agency, UK Government. Guidance on valproate use by women and girls. https://www.gov.uk/guidance/valproate-use-by-women-and-girls (accessed 2024)

24. U.S. Food and Drug Administration. Sodium valproate label. https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/018723s068lbl.pdf (accessed 2024)

25. National Pharmaceutical Regulatory Agency (Malaysia). New safety measures for sodium valproate. https://www.npra.gov.my/index.php/en/component/content/article/419-english/safety-alerts-main/safety-alerts-2020/1527061-new-safety-measure-for-sodium-valproate-i-risk-of-congenital-malformation-in-neonates-and-neurodevelopmental-problems-in-children-exposed-to-sodium-valproate-during-pregnancy-ii-additional-educational-material-for-healthcare-professionals-and-patients-caretakers.html?Itemid=1391 (accessed 2024)