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RESEARCH

Valproate Prescribing for Female Adolescents and Management of the Associated Teratogenicity Risk, Royal Children's Hospital, Melbourne, 2022–2024: A Retrospective Audit of Medical Records Data

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ABSTRACT

Objectives: To assess the frequency of valproate prescribing for female patients of childbearing age at the Royal Children's Hospital, Melbourne, and to assess the frequency of documented discussions with these patients about the teratogenicity of valproate and the discussions or prescribing of contraception.

Study Design: Retrospective audit of hospital electronic medical records data; analysis of Pharmaceutical Benefits Scheme (PBS) valproate dispensing data.

Setting, Participants: 13- to 18-year-old girls or women prescribed valproate at the Royal Children's Hospital, Melbourne during 29 May 2022–29 May 2024; PBS valproate dispensing data for Australia for the 2023 calendar year.

Main Outcome Measures: Characteristics of adolescent female patients prescribed valproate; documented discussions of valproate-related teratogenicity, and discussions or prescribing of contraception; population valproate prescribing rates for Australia and by state.

Results: Valproate was prescribed for 245 female patients aged 13–18 years during 2022–2024 (median age, 16 years; interquartile range [IQR], 14–17 years); the median prescribed daily dose was 600 mg (IQR, 400–800 mg; range, 200–2000 mg). Valproate was prescribed for treating epilepsy for 221 patients (90%), including 97 (44%) with drug-resistant epilepsy; 160 patients (65%) had neurodevelopmental disabilities. Teratogenicity was discussed with 32 patients (13%), less frequently with patients with a neurodevelopmental disability (9% vs. 20%; odds ratio [OR], 0.41; 95% confidence interval [95% CI], 0.19–0.88). Contraception was discussed with 69 patients (28%); the proportion was larger for patients with neurodevelopmental disabilities (34% vs. 16%; OR, 2.66; 95% CI, 1.37–5.14). Contraception was prescribed for 50 patients (20%); the proportion was larger for patients with neurodevelopmental disabilities (25% vs. 12%; OR, 2.50; 95% CI, 1.18–5.30). The national PBS-subsidised dispensing rate during 2023 was 621 per 100,000 girls and women aged 13–18 years; in Victoria it was 556 per 100,000 girls and women aged 13–18 years.

Conclusion: Despite the risk of teratogenicity, valproate was prescribed for a considerable number of female adolescents at the Royal Children's Hospital during 2022–2024 and across Australia during 2023. Its teratogenicity was discussed with few patients, nor were discussions or prescribing contraception frequent. Contraception was more frequently discussed and prescribed for patients with neurodevelopmental disability, but teratogenicity was discussed less often.

Plain Language Summary

The known: As sodium valproate is a teratogen, prescribing it for girls and women of childbearing age should be avoided. If prescribed, patients must be informed of the risk, alternative options and offered contraception.

The new: Valproate was frequently prescribed for female patients aged 13–18 years at the Royal Children's Hospital Melbourne and nationally. Documented discussions about its teratogenicity and contraception, and contraception prescribing were infrequent.

The implications: Coordinated national strategies for improving awareness among valproate prescribers of its risks are needed, as are counselling and shared decision making for female adolescents using valproate.

Sodium valproate (valproate) has been used as a highly effective antiseizure medication since the 1960s [1], with broad antiseizure efficacy [2]. It is also prescribed for preventing migraine and treating behaviour and mood disturbances [1].

Teratogenicity is associated with valproate use during pregnancy [3–6]; 2%–11% of valproate-exposed pregnancies result in major congenital malformations, and 30%–40% of children exposed to valproate in utero develop cognitive or neuropsychiatric conditions, including autism spectrum disorder, attention deficit hyperactivity disorder and intellectual disability [4, 7]. The risk of harm is dose-related [3, 8], but even at lower doses the risk is greater than for other antiseizure medications, such as lamotrigine and levetiracetam [3].

Regulatory agencies and advisory groups have therefore progressively strengthened safety alerts and recommended restricting the use of valproate by girls and women of childbearing age [9–12]. The 2020 Epilepsy Society of Australia position statement advised that 'valproate should not be taken by a girl or woman who could become pregnant, unless there is no other anti-seizure drug suitable for that patient that can control her seizures' [13]. The World Health Organization recently issued a revised safety statement on valproate use by women and children and continues to actively monitor its use in low and middle income countries [14, 15]. These include regional initiatives to reduce valproate-associated risks, such as the South-East Asian Regulatory Network working group, scheduled to commence in 2025 [15].

In Australia, valproate accounted for 24% of antiseizure medication prescriptions during 2019–2020 [16]. The Australian Pregnancy Register has recorded a decline in valproate prescribing over the past 20 years [17], but exposure during pregnancy remains higher than in comparable countries [11, 18]. Since January 2021, Pharmaceutical Benefits Scheme (PBS) approval indications have designated lamotrigine and levetiracetam as the first-line therapy for girls and women of childbearing age [19, 20], in alignment with local and overseas guidelines.

The objective of our audit was to assess the frequency of valproate prescribing for 13- to 18-year-old female patients at the Royal Children's Hospital, Melbourne during 2022–2024, and to assess the frequency of documented discussions with these patients about the teratogenicity of valproate, as well as the frequency of discussions or prescribing of contraception. We also analysed state and national prescribing data to assess the frequency of valproate prescribing for female adolescents across Australia.

1 | Methods

We report a retrospective audit of hospital clinical records for all people of female sex aged between 13 years and 18 years and 11 months for whom valproate was prescribed at the Royal Children's Hospital, Melbourne at least once during 29 May 2022–29 May 2024. Female sex was defined as sex assigned at birth, irrespective of current gender identity. Pubertal stage is poorly documented in clinical medical records [21]; we therefore audited all patients aged 13 years or older, as the mean age at menarche in Australia is 12.9 years (standard deviation, 1.4 years) [22]. We report our study according to the Strengthening the reporting of observational studies in epidemiology (STROBE) guidelines for cross-sectional studies [23].

Female patients aged 13–18 years who had been prescribed valproate at the hospital were identified using the Slicer Dicer function of the Epic electronic medical record. Slicer Dicer is an analytical tool with which clinicians can generate reports based on prescription or other patient data in the Epic system [24]. Individual records were then reviewed to confirm female sex, the prescribing of valproate by a Royal Children's Hospital clinician during the 24-month study period, and an inpatient or outpatient visit with a Royal Children's Hospital clinician. Patients were excluded if they had died during or since the audit period, the valproate prescription was outside the audit period or if they were prescribed only a single valproate dose.

We extracted electronic medical records data for age, indication for valproate prescribing, most recent recorded valproate dose, age at first valproate prescription, specialty of prescribing doctor, diagnosis of a neurodevelopmental disability and whether valproate treatment had ceased during the audit period. Clinical notes were searched for discussions about teratogenicity and discussions about or prescribing of contraception. We also audited documented HEEADSSS (home, education, eating, activities, drugs, sexuality, suicide safety) screens. For the purposes of this audit, neurodevelopmental disability encompassed diagnoses of intellectual disability, autism spectrum disorder, cerebral palsy or specific learning disorder. For patients with neurodevelopmental disabilities, we also extracted data on Gross Motor Function Classification System (GMFCS) score [25], ambulatory status and verbal communication skills. For patients with epilepsy diagnoses, we extracted the epilepsy syndrome, defined according to the International League Against Epilepsy classification [26], whether criteria for drug-resistant epilepsy were met, the number of concomitant antiseizure medications prescribed at the time of audit, and whether valproate was the first antiseizure medication prescribed. Drug-resistant epilepsy was defined as ongoing seizures despite adequate trials of two tolerated antiseizure medications [27].

To examine state and national valproate prescribing patterns, PBS dispensing data (number of female adolescents aged

13–18 years supplied with valproate) was obtained directly from Services Australia. We calculated the rate of valproate dispensing nationally and by state during the 2023 calendar year by dividing the dispensing number by 2023 (fourth quarter) population estimates for 13-, 14-, 15-, 16-, 17- and 18-year-old female Australians as reported by the Australian Bureau of Statistics [28].

2 | Statistical Analyses

Group-level findings are reported as numbers and proportions. Associations between categorical variables were assessed using 2 × 2 contingency tables and the standard log odds formula; we report odds ratios (OR) with 95% confidence intervals (CI). Analyses were unadjusted. Statistical analyses were undertaken in R 1.4.1106 (R Foundation for Statistical Computing).

2.1 | Ethics Approval

The Human Research and Ethics Committee at the Royal Children's Hospital approved the study and waived the requirement for individual patient consent to data access (HREC 36328).

3 | Results

We identified 327 adolescent female patients who were prescribed valproate at the Royal Children's Hospital at least once during 2022–2024. After excluding 11 who had died, 68 for whom the prescription date was before the audit period, and three who had received one-off valproate doses, we included 245 people in our audit. Their median age was 16 years (interquartile range [IQR], 14–17 years); 168 were older than 15.0 years, the 95th centile for menarche in Australia [29]. The median prescribed daily dose of valproate was 600 mg (IQR, 400–800 mg); total daily doses ranged from 200 to 2000 mg. Valproate had been prescribed in 152 cases by paediatric neurologists (62%), in 76 by general paediatricians (31%) and in 17 by other medical practitioners (7%).

Valproate was prescribed for treating epilepsy for 221 patients (90%); other indications for prescribing it were post-traumatic stress disorder (five patients), bipolar disorder (four), challenging behaviour (four), headache (four), generalised anxiety (four) and pain (three patients). First prescribing of valproate was at age 13 years or older for 15 of 24 patients prescribed valproate for indications other than epilepsy, and for 22 of 221 patients with epilepsy.

Among the 221 female patients prescribed valproate for the treatment of epilepsy, the most frequent epilepsy diagnoses were genetic generalised epilepsy (96, 43%) and focal epilepsy (54, 24%) (Table 1). Ninety-seven (44%) met the criteria for drug-resistant epilepsy. Valproate was used as monotherapy by 94 patients (43%), in combination with one other antiseizure medication by 55 (25%), and in combination with two or more other antiseizure medications by 72 patients (32%) (Table 2). Fifty-seven of the patients using valproate as monotherapy (61%) had genetic generalised epilepsy, 22 (23%) had focal epilepsy, seven (7%) non-epileptic events and eight (9%) had unknown epilepsy syndromes. Valproate was the first antiseizure medication prescribed for 110 patients (50%) (Table 2), for 102 of whom (93%) it had been prescribed before the age of 13 years.

TABLE 1 | Epilepsy syndromes for which sodium valproate was prescribed for girls or women aged 13–18 years at the Royal Children's Hospital, Melbourne, 29 May 2022–29 May 2024.

Epilepsy syndrome	Number
Valproate prescribed to treat epilepsy	221
Genetic generalised epilepsy	96 (43%)
Juvenile absence epilepsy	39 (18%)
Juvenile myoclonic epilepsy	8 (4%)
Generalised tonic–clonic seizures alone	2 (1%)
Unspecified (or other) generalised syndrome	47 (21%)
Focal epilepsy	54 (24%)
Self-limited epilepsy with centrotemporal spikes	16 (7%)
Other	38 (17%)
Developmental and epileptic encephalopathy	49 (22%)
DEE-SWAS	14 (6%)
Dravet syndrome	4 (2%)
Lennox–Gastaut syndrome	10 (5%)
Other	21 (10%)
Non-epileptic events[a]	9 (4%)
Unknown syndrome	13 (6%)

Abbreviation: DEE-SWAS = developmental and epileptic encephalopathy with spike wave activation in sleep.
[a]Including syncope, psychogenic non-epileptic seizures, episodes of unresponsiveness.

Neurodevelopmental disabilities were documented for 160 of 245 patients prescribed valproate (65%), including intellectual disability (146, 60%), autism spectrum disorder (56, 23%) and specific learning disorders (22, 9%). Among the 160 patients with neurodevelopmental disabilities, 147 patients (92%) could walk and 115 (72%) had adequate verbal skills. Forty-five patients (18%) had diagnoses of cerebral palsy (Global Motor Function Classification System [GMFCS] level I, five; II, seven; III, seven; IV, seven; V, 19 patients).

Discussions regarding the teratogenicity of valproate were documented by clinicians for 32 of 245 patients (13%); the proportion was smaller for patients with neurodevelopmental disabilities than for those without such disabilities (9% vs. 20%; OR, 0.41 [95% CI, 0.12–0.88]). Discussions regarding contraception (not necessarily related to the prescribing of valproate) were documented by clinicians for 69 patients (28%); the proportion was larger for patients with neurodevelopmental disabilities than for those without such disabilities (34% vs. 16%; OR, 2.66 [95%

CI, 1.37–5.14]). Fifty patients (22%) had active prescriptions for contraception or were on waiting lists for long-acting reversible contraception; the proportion was larger for patients with neurodevelopmental disabilities than for those without such disabilities (25% vs. 12%; OR, 2.50 [95% CI, 1.18–5.30]) (Table 3). HEEADSSS screens were documented for 16 patients (6%). Documented reasons for not using contraception included 'mother says [the patient] is not going to have children' and 'periods are well tolerated'. One patient using valproate became pregnant.

During the audit period, valproate treatment was ceased for 51 patients; the documented reasons were inefficacy in six cases, adverse effects in eight, concerns about teratogenicity in seven, and prolonged seizure freedom in 20 patients; no reason was recorded in ten cases.

TABLE 2 | Antiseizure medication use by girls or women aged 13–18 years prescribed valproate at the Royal Children's Hospital, Melbourne, 29 May 2022–29 May 2024.

Characteristic	Number
Valproate prescribed to treat epilepsy	221
People with drug-resistant epilepsy[a]	97 (44%)
Medications tried before commencing valproate	
0	110 (50%)
1	40 (18%)
2	23 (10%)
3 or more	31 (14%)
Unknown	17 (8%)
Concomitant antiseizure medications (other than valproate)	
0	94 (43%)
1	55 (25%)
2	42 (18%)
3 or more	30 (14%)

[a]Seizures after adequate trials of two tolerated antiseizure medications.

4 | Pharmaceutical Benefits Scheme Dispensing

During the 2023 calendar year, 5997 valproate prescriptions were dispensed to people of female sex aged 13–18 years in Australia, or 621 per 100,000 population. The estimated rate of valproate dispensing by state ranged from 405 (Northern Territory) to 1591 per 100,000 people of female sex aged 13–18 years (Tasmania); in Victoria, the dispensing rate was 556 per 100,000 people of female sex aged 13–18 years (Figure 1).

5 | Discussion

Valproate was prescribed at the Royal Children's Hospital in Melbourne for a considerable number of 13- to 18-year-old female patients during 2022–2024. Epilepsy was the predominant indication for prescribing valproate (221 patients, 90%), including for 124 patients (56%) with drug-responsive epilepsy. Neurodevelopmental disabilities were recorded for 160 of 245 patients (65%), including autism spectrum disorder, intellectual disability and specific learning disorders. Documented discussions about valproate-associated teratogenicity were recorded for only 32 patients (13%) and were particularly infrequent for those with neurodevelopmental disabilities. Discussions about contraception and the prescribing of contraception were also infrequent, but more frequent for adolescents with neurodevelopmental disabilities. The disparities between the risks of valproate treatment, guideline recommendations, and valproate prescribing and counselling practices is a systemic problem that is inadequately understood.

Genetic generalised epilepsies were the most frequent epilepsy syndromes for which valproate was prescribed; its efficacy for treating generalised tonic–clonic, myoclonic and absence seizures is well established [2]. Valproate monotherapy was frequent among patients with genetic generalised epilepsies, often without prior trials of alternatives such as lamotrigine or levetiracetam [30], which suggests that some prescribers are unaware of the updated 2021 PBS indications for these agents. Valproate was also prescribed for people with focal epilepsies, although these conditions often respond better to alternative agents [2], as well as for adolescents with non-epileptic events, including syncope and psychogenic non-epileptic seizures. Few patients had developmental or epileptic encephalopathies, and

TABLE 3 | Discussions with girls or women aged 13–18 years prescribed valproate about its teratogenicity, and discussions of or prescribing of contraception, by neurodevelopmental disability status: Univariate analyses.

Characteristic	All people	Patients with neurodevelopmental disability	Patients with no neurodevelopmental disability	Odds ratio (95% CI)
Number of people	245	160	85	
Teratogenicity discussed	32 (13%)	15 (9%)	17 (20%)	0.41 (0.19–0.88)
Contraception discussed	69 (28%)	55 (34%)	14 (16%)	2.66 (1.37–5.14)
Contraception prescribed	50 (20%)	40 (25%)	10 (12%)	2.50 (1.18–5.30)

Abbreviation: CI, confidence interval.

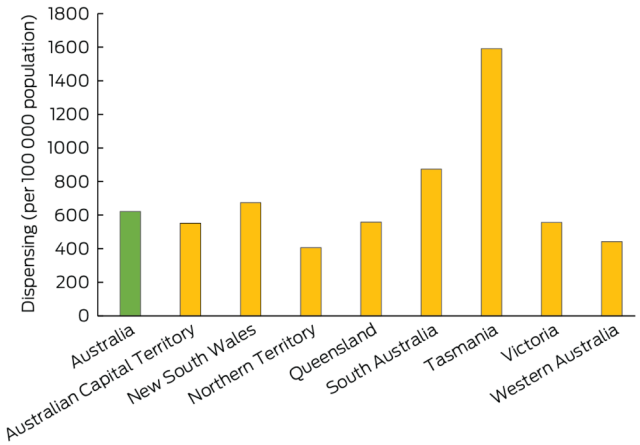

FIGURE 1 | Pharmaceutical Benefits Scheme-subsidised of dispensing of valproate to girls or women aged 13–18 years, Australia, 2023: rate per 100,000 population. Based on the 2023 population estimate for 13- to 18-year-old people of female sex [27].

only 44% had drug-resistant epilepsy, for which prescribing a potentially teratogenic antiseizure medication could be more justifiable. In contrast, a recent audit in a paediatric hospital in north-west England found that only seven female patients aged 12 years or older were using valproate, all of whom had drug-resistant epilepsies and were using multiple antiseizure medications [31].

A large proportion of initial prescriptions of valproate for indications other than epilepsy (nine of 24 patients) were at age 13 years or older, probably indicating that the prescribers were unaware of valproate-associated teratogenicity. In contrast, most patients who were prescribed valproate for epilepsy commenced valproate treatment before the age of 13 years. This suggests that one reason valproate continues to be prescribed for female adolescents, despite the abundance of safety information, is lack of foresight at the time of initial prescribing that a primary school-age girl could still need antiseizure medication during adolescence. Lack of active review of pubertal status and therapeutic inertia may subsequently contribute to continued valproate prescribing despite clinicians being aware of valproate-associated teratogenicity. Further, a considerable number of patients received valproate for self-limited epilepsies of childhood or non-epileptic events (25 of 221 adolescents prescribed valproate for epilepsy), possibly indicating lack of active review of epilepsy diagnoses and consideration of antiseizure medication withdrawal at clinical review or loss to follow-up [10].

The median prescribed daily dose of valproate (any indication) was 600 mg, but some people were prescribed 2000 mg per day. Several registry studies have established that the risk of valproate-associated teratogenicity is dose-dependent, and that daily doses beyond 800–1100 mg are associated with high rates of neurodevelopmental disability (about 30%) and autism spectrum disorder (about 10% [32]); the risk is lower with lower doses [8, 33]. There is no safe valproate dose for female patients of childbearing age, but its benefits may outweigh the teratogenic risk in some people with frequent generalised tonic–clonic seizures or who have other risk factors for sudden unexplained death in epilepsy (SUDEP).

We found that informed discussions about valproate-related teratogenicity and contraception and the prescribing of contraception were infrequent. No clinical records documented use of the Epilepsy Society of Australia valproate checklist [34] or written informed consent. It is possible that some conversations about teratogenicity were not documented, but the small number of HEEADSS screens suggests that conversations about sex and contraception in general were rare. The PREVENT Programme in the United Kingdom requires that patients or their caregivers sign an annual risk acknowledgement form and at least annual specialist review if valproate treatment is continued after 13 years of age [11]. The programme includes developmentally appropriate guidance to help clinicians discuss valproate teratogenicity with patients aged 10–18 years [11]. In Australia, there is no requirement for the treatment of female patients of childbearing age to be reviewed by a neurologist or to provide written consent, and no specific guideline for the treatment of adolescents, factors that probably contribute to the high rate of valproate prescribing for female adolescents.

Discussions about teratogenicity with adolescents with neurodevelopmental disabilities were particularly infrequent, although many of these patients had only mild intellectual disability, being able to both walk and to communicate adequately. In contrast, the prescribing of contraception was more frequent for patients with a neurodisability, but we assume it was mainly for menstrual suppression and management. Women with neurodevelopmental and intellectual disabilities have poorer access to adequate sexual education than those without neurodisability [7]. It is possible that this problem extends to discussions about the teratogenic effects of medications they use. Additionally, decisions to withdraw or continue valproate treatment or to provide contraception to women with intellectual disability often raise ethical questions, such as conflict between the autonomy or decision-making capacity of the patient and their caregiver's desire to protect them. Specific strategies that assist clinicians and caregivers to undertake conversations with young people about these topics are needed.

Our review of PBS dispensing data indicated that Victorian patterns of valproate dispensing to 13- to 18-year-old female patients during 2023 were similar to those in most other Australian states. The higher valproate dispensing rate in Tasmania could reflect its smaller population size rather than an actual difference. These findings suggest that problems of shared decision making and informed discussions about valproate-related teratogenicity are unlikely to be limited to the Royal Children's Hospital in Melbourne. A national adolescent-specific guideline for the use of valproate is needed, including guidance regarding the assessment of pubertal status, indications for dose reduction or withdrawal and appropriate alternatives. Adolescent-specific resources and guidance for conversations about teratogenicity and sexuality, including with young people with neurodisability, need to be developed. The increased use of electronic prescribing could also make an alert system feasible; for example, a warning pop-up when doctors prescribe valproate.

6 | Limitations

Our single centre retrospective audit may not have captured all conversations between adolescents, parents, and clinicians about

valproate-associated teratogenicity. Similarly, some clinicians may have not updated medication charts or documented teratogenicity as a reason for ceasing valproate treatment. We could make inferences about why valproate treatment was commenced or continued, but we could not ascertain whether it was prescribed because of lack of knowledge of its teratogenicity, whether there was a plan to cease valproate treatment at a later age or whether it was intentionally continued. The proportion of patients with neuro-disability may be larger among those prescribed valproate in tertiary services than among adolescent female patients prescribed valproate by general practitioners or private paediatricians. Statistical comparisons of audit data with PBS data were not possible because of methodological incompatibility.

7 | Conclusion

Despite strong evidence for its teratogenic risk, valproate is prescribed for many female patients aged 13–18 years at the Royal Children's Hospital in Melbourne and across Australia. Documented discussions with patients about valproate-related teratogenicity and contraception were infrequent. Informed discussions with young female patients should begin during adolescence and should be frequent, well before the transition of their care to adult care providers. National strategies for raising clinician awareness of valproate-related teratogenicity, including adolescent-specific Australian guidelines and integrated electronic medical record prescribing alerts, are needed.

Author Contributions

Briana Davis: data curation, investigation, formal analysis and writing (original draft); **Monica S. Cooper:** formal analysis and writing (review and editing); **Michael South:** conceptualisation, formal analysis and writing (review and editing); **Jeremy L. Freeman:** conceptualisation and writing (review and editing); **Emma Macdonald-Laurs:** conceptualisation, data curation, formal analysis, investigation, visualisation and supervision.

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The study data can be accessed by contacting the corresponding author.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Data S1:** mja270126-sup-0001-supinfo.pdf.