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ORIGINAL RESEARCH ARTICLE

Understanding and Responding to Prescribing Patterns of Sodium Valproate-Containing Medicines in Pregnant Women and Women of Childbearing Age in Western Cape, South Africa

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Abstract

Introduction Growing evidence of the teratogenic potential of sodium valproate (VPA) has changed prescribing practices across the globe; however, the impact of this research and the consequent dissemination of a Dear Health Care Professional Letter (DHCPL) in December 2015, recommending avoidance of the teratogen VPA in women of childbearing age (WOCBA) and pregnant women in South Africa, is unknown. We explored trends and reasons for VPA use among pregnant women and WOCBA in the public sector in Western Cape Province from 1 January 2015 to 31 December 2017.

Methods Using the provincial health information exchange that collates routine electronic health data via unique patient identifiers, we analysed clinical and pharmacy records from 2015 to 2017 to determine prescription patterns of VPA and other antiepileptic drug (AED) and mood-stabilising medicine (MSM) use in WOCBA and pregnant women. Senior clinicians and policy makers were consulted to understand the determinants of VPA use.

Results At least one VPA prescription was dispensed to between 8205 (0.79%) and 9425 (0.94%) WOBCA from a cohort of approximately 1 million WOCBA attending provincial health care facilities per year. Prescriptions were more likely in HIV-infected women compared with HIV-uninfected women (1.1–1.3% vs. 0.7–0.9%; $p < 0.001$). VPA use in WOCBA remained stable at 0.8–0.9% over the review period despite the 2016 DHCPL. VPA was the most prescribed AED/MSM, constituting 43.2–45.5% of all WOCBA taking at least one such agent, while lamotrigine, the other recommended first-line agent, was only prescribed in 7.8–8.9% of WOCBA. Over 3 years, approximately 663 pregnancies were exposed to VPA, with a steady rise in the number of exposures each year ($n = 204$, 214 and 245, respectively).

Conclusion Despite warnings, VPA remained the most frequently prescribed AED or MSM in WOCBA. Contributing factors are described.

1 Introduction

In recent years, the Medicines Control Council in South Africa (MCC; now known as the South African Health Products Regulatory Authority [SAHPRA]), the US Food and Drug Administration (FDA) [1], the European Medicines Agency (EMA) [2] and other regulatory authorities have highlighted the need to completely avoid sodium valproate (VPA) in pregnant women and women of childbearing age (WOCBA; unless there is no other effective treatment available) due to convincing evidence of high rates of congenital malformations (approximately 11%) [3] and neurodevelopmental impairment (30–40%) such as delayed physical milestones, memory problems, difficulties in speech and language, and lower intellectual ability associated with in utero exposure [4–11]. In addition, there is compelling evidence of an increased risk of autism and autism spectrum disorder in children exposed to VPA in utero [12–15].

Due to its poor safety profile in pregnancy, VPA is indicated for epilepsy only in WOCBA who are intolerant of or unresponsive to other antiepileptic treatments and who are compliant with an effective Pregnancy Prevention Programme (PPP) [2]. However, in HIV-infected adults in South Africa receiving antiretroviral treatment (ART), VPA has been one of two therapeutic options recommended as

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Key Points

Despite warnings, valproate use in women of childbearing age (WOCBA) has not changed in the Western Cape Province of South Africa over a 3-year period, and sodium valproate (VPA) remains the most commonly prescribed antiepileptic or mood-stabilising medicine among women of childbearing age in the Western Cape Province of South Africa.

Over 3 years, approximately 663 pregnancies were exposed to VPA, with a steady rise in the number of exposures each year ($n = 204$, 214 and 245, respectively). Contributing factors to these trends are described, including the concerns about drug–drug interactions between antiepileptic/mood-stabilising medicines and antiretrovirals.

Despite significant measures that have been taken at both a national and provincial level, the implementation of new approaches to the treatment of epilepsy in women are hindered by challenges facing clinicians in a resource-limited setting with a high burden of HIV.

first-line treatment for the management of epilepsy, the other being lamotrigine [16]. This is primarily because most other antiepileptics have clinically significant drug–drug interactions with ART, affecting the safety and efficacy of both antiepileptic and antiretroviral agents. VPA is also indicated for maintenance therapy for bipolar mood disorder, and, together with lithium, was until recently considered a first-line option in the public sector in South Africa [16]. It has also been used for migraine prophylaxis, although VPA-containing products are not registered for this indication in South Africa [1].

Prior to this study, valproate prescribing practices in South Africa were undocumented. In December 2015, a Dear Health Care Professional Letter (DHCPL) was disseminated to registered medical practitioners and pharmacists in South Africa warning about the high risk of congenital anomalies and developmental disorders associated with VPA use during pregnancy (See Electronic Supplementary Material 1). This study aimed to establish whether this regulatory safety alert had any impact on clinical care or prescribing. We aimed to assess the extent of VPA use among pregnant women and WOCBA seeking care in the public sector in the Western Cape Province, South Africa, using linked population-level electronic clinical and pharmacy records between January 2015 and December 2017, i.e. 1 year before and 2 years after the December 2015 DHCPL safety alert. We explored reasons for ongoing VPA use in the public sector through key informant interviews and meetings with senior clinicians and policy makers at the provincial level.

2 Methods

We conducted a retrospective review of aggregate population-level data. The Provincial Health Data Centre (PHDC) in the Western Cape is a health information exchange in which all electronic health data are linked via a unique patient identifier allocated to all patients seeking care at public health facilities in the Western Cape Province [17].

Anonymised, aggregate data extracts were provided by the PDHC for a cohort of WOCBA (13–55 years of age) over 3 years from January 2015 to December 2017. Pregnancies were identified electronically through a series of evidences implying pregnancy, categorised by various levels of confidence. These evidences included registration on MomConnect (a mobile health messaging service for South African mothers); laboratory tests (e.g. rhesus test, pregnancy test, syphilis test, Beta HCG test, and pap smear with recorded gestational age); outcome-related evidences (e.g. birth registration, diagnostic/procedure-related codes indicating a pregnancy outcome, maternal death, maternal discharge summary); electronic admission records for antenatal and obstetric ward visits; and the use of pregnancy-related medicines (e.g. misoprostol and mifepristone in combination indicating termination of pregnancy, iron and folate dispensed) [17–19]. Only high-confidence pregnancies were included in this analysis.

Antiepileptic drug/mood-stabilising medication (AED/MSM) use was identified from electronic pharmacy dispensing records and linked to women in the cohort via the unique patient identifier. We defined a pre- and intra-pregnancy period, which starts at the beginning of the calendar year before the year of delivery and ends with delivery. VPA exposure during pregnancy was defined as a WOCBA with evidence of pregnancy who has at least one prescription of VPA dispensed during the pregnancy period. The pregnancy period was defined as the estimated pregnancy start date to the pregnancy outcome (including pregnancy loss) date. Where available, the last menstrual period and reported gestational age based on ultrasound were used to estimate the pregnancy period. In the absence of this data, a period of 280 days prior to birth was considered the pregnancy period for a full-term birth. To ensure maximal ascertainment of exposure, all women identified as being prescribed valproate in pregnancy were included in our analyses even if the pregnancy outcome was unknown.

We explicitly decomposed VPA exposures during pregnancy into three types, by timing: (1) VPA initiated during pregnancy (defined as the first recorded prescription of VPA issued during the pregnancy period); (2) VPA switched

for an alternative during the course of the pregnancy (first AED/MS prescription without VPA issued after the estimated pregnancy start date and before the pregnancy outcome date); and (3) VPA used throughout pregnancy. Data on pregnancy exposures were confined to sites where the pharmacy electronic management system was present for more than 3 months prior to onset of the pregnancy, reducing the likelihood of a false date of treatment onset in relation to the pregnancy episode.

HIV infection prevalence in all pregnant women and WOCBA was compared with the HIV prevalence of those WOCBA and pregnant women exposed to VPA and alternative agents, in the Western Cape Province. HIV status was categorised as HIV-infected and, collectively, HIV-uninfected or HIV status unknown. Given the overwhelming evidence of risk in pregnancy and the incompleteness of provincial birth outcomes data, particularly stillbirths and congenital anomalies, data on birth outcomes of AED and MSM-exposed pregnancies were not systematically assessed. Daily dosage information was not available.

Descriptive statistics were used to report proportions and percentages of the outcomes. Pearson's Chi-square test was used to compare pregnancy rates among women taking VPA compared with women taking other AED and MSM regimens, as well as comparing VPA exposure rates among women living with and without HIV.

Discussions were held with senior clinicians and policy makers at the provincial level, including pharmacologists, neurologists, psychiatrists, pharmacists and fetal medicine specialists, to understand the determinants of VPA use in the Western Cape Province. The aim of these discussions was to identify opportunities to reduce pregnancy exposures to VPA and to develop systems aimed at better supporting pregnant women and their infants exposed to VPA in utero. The key findings and recommendations of these meetings are also presented.

Approval for the study was granted by the University of Cape Town Faculty of Health Sciences Human Research Ethics Committee (ref: 098/2018) and the Western Cape Provincial Research Committee. The data that support the findings of this study are available from the PHDC, but restrictions apply to the accessibility of these data, which were used after approval for the current study, and are therefore not publicly available. Data are however available from the authors upon reasonable request and with permission of the Western Cape Provincial Research Committee.

3 Results

Approximately 1 million WOCBA seek care every year from a provincial health facility in the Western Cape, with HIV infection rates ranging from 17.2–19.3% per year over the course of the study period (Table 1). Over the 3 years, at least one VPA prescription was dispensed to between 0.79% and 0.94% of these WOCBA . In all 3 years, prescriptions for VPA were significantly more likely in HIV-infected WOCBA and pregnant women compared with HIV-negative women or women for whom HIV status was undocumented ($p < 0.001$) (Table 1). VPA prescriptions for WOCBP or pregnant women did not significantly decrease after the DHPCL. The data concerningly suggest no difference, or possibly an upward trend, in prescribing after the DHCP letter (Table 1).

Valproate was the most prescribed AED or MSM among WOCBA (43.2–45.5% of treated WOCBA per annum irrespective of HIV infection status) during the study period. Lamotrigine, the other recommended first-line agent, was only prescribed in 7.8–8.9% of all WOCBA using an AED or MSM (Table 2). Carbamazepine (22.6–25.7%), risperidone (21.9–24%) and phenytoin (14.8–19.3%) were the most commonly used alternatives to VPA for epilepsy and mood disorder, respectively.

Over the course of 3 years, 663 pregnancies were exposed to VPA, with a progressively increasing absolute number of exposed pregnancies each year (Table 3). Based on International Classification of Diseases (ICD) coding of health facility visits, the indication in most cases was neurological (79–81%) and was therefore likely to represent the management of epilepsy or other seizure disorders. Overall, 121 women initiated, and 87 women discontinued, VPA during pregnancy over the 3-year period. Of those women who were exposed to VPA during the year of their pregnancy, VPA was stopped prior to the estimated onset of the pregnancy in 55.5–63.9% of women (Table 4). There was no increase in the number of women discontinuing valproate preconceptually following the DHCPL. The use of the alternative agent lamotrigine remained consistent across the 3-year period.

The overall pregnancy rate in women taking AEDs and MSMs was significantly lower compared with the total provincial cohort of WOCBA (5.9% vs. 10.3%; $p < 0.001$). There were no marked differences in pregnancy rates among women taking VPA-containing AEDs/MSMs compared with non-VPA containing AEDs/MSMs, although pregnancy rates did drop from 2015 to 2016 (6.6% to 5.6%; $p < 0.001$), but not from 2016 to 2017 in women taking any AED/MSM (5.6–5.4%; $p = 0.350$) [Table 5].

We did not assess the impact of VPA pregnancy exposures on birth outcomes because of the incomplete electronic record linkage between infants and mothers, unreliable ICD coding of congenital malformations, and other adverse birth outcomes.

Discussions were held with senior neurologists, psychiatrists, members of the provincial pharmacy and therapeutics committee, and clinical pharmacologists in the Western Cape Province to determine the reason for such widespread

Table 1 Valproate use in women of childbearing age and pregnant women, by HIV status

	HIV uninfected/ status unknown	HIV-infected	Total	*p*-Value
WOCBA taking VPA				
2015				
Number of WOCBA taking VPA (%)	6208 (0.72)	1997 (1.11)	8205 (0.79)	<0.001
Total number of WOCBA	864,222	180,599	1,044,821	
2016				
Number of WOCBA taking VPA (%)	6957 (0.86)	2468 (1.28)	9425 (0.94)	< 0.001
Total number of WOCBA	812,401	193,446	1,005,847	
2017				
Number of WOCBA taking VPA (%)	7145 (0.81)	2757 (1.31)	9902 (0.91)	< 0.001
Total number of WOCBA	880,667	211,051	1,091,718	
Pregnancies while taking VPA				
2015				
Number of pregnant women taking VPA (%)	125 (0.15)	79 (0.56)	204 (0.21)	< 0.001
Total number of pregnancies	84,697	14,131	98,828	
2016				
Number of pregnant women taking VPA (%)	152 (0.18)	62 (0.41)	214 (0.21)	< 0.001
Total number of pregnancies	86,360	15,174	101,534	
2017				
Number of pregnant women taking VPA (%)	149 (0.16)	96 (0.53)	245 (0.22)	< 0.001
Total number of pregnancies	92,861	18,067	110,928	

WOCBA women of childbearing age, *VPA* sodium valproate

Table 2 Use of antiepileptic drugs and mood-stabilising medicines in women of childbearing age

AED or MSM used	2015[a] (%)[b]	2016[a] (%)[b]	2017[a] (%)[b]
Sodium valproate	8205 (43.2)	9425 (45.5)	9902 (44.8)
Carbamazepine	4874 (25.7)	4930 (23.8)	5001 (22.6)
Risperidone	4162 (21.9)	4906 (23.7)	5308 (24.0)
Phenytoin	3653 (19.3)	3505 (16.9)	3284 (14.8)
Lamotrigine	1482 (7.8)	1673 (8.1)	1962 (8.9)
Olanzapine	992 (5.2)	1374 (6.6)	1813 (8.2)
Lithium	903 (4.8)	1024 (4.9)	1042 (4.7)
Levetiracetam	64 (0.8)	65 (0.3)	88 (0.4)
Total number of WOCBA taking AEDs or MSMs (%)	18,974 (1.82[c])	20,701 (2.06[c])	22,120 (2.03[c])
Total number of WOCBA not taking AEDs or MSMs	1,025,847	985,147	1,069,598
Total number of WOCBA	1,044,821	1,005,847	1,091,718

AEDs antiepileptic drugs, *MSMs* mood-stabilising medicines, *WOCBA* women of childbearing age

[a] Many women were exposed to more than one AED or MSM, either concurrently or consecutively, during the course of each year

[b] Percentage of all WOCBA taking either an AED or an MSM

[c] Percentage of all WOCBA

use of VPA among WOCBA. Table 6 summarises the key reasons identified.

4 Discussion

This analysis of prescription practices from 2015 to 2017, derived from population-level data, indicates that despite the known significant risks that VPA poses to the foetus, it remained the most frequently prescribed AED/MSM in WOCBA and pregnant women in public health facilities in the Western Cape Province. Over 3 years, VPA use in WOCBA and pregnant women did not decrease, despite nationwide dissemination of a DHCPL by its manufacturers in December 2015. Up to 245 women per year (Table 3) were exposed to VPA during the course of their pregnancy in this province alone.

Based on the electronic record of the prescribing clinical specialty, it appears that VPA's primary use is in the management of epilepsy and possibly other neurological conditions. Women with bipolar mood disorder also continue to be prescribed VPA despite international consensus on the need to reduce the use of this agent for mood disorders in WOCBP [1, 2, 21–30]. This may be because there are also concerns about the safety of lithium therapy in pregnancy, both in terms of challenges in optimal dosing during pregnancy and concerns about the risk of Ebstein's

Table 3 Sodium valproate use in pregnancy, by clinical service accessed

	Year pregnancy ended		
	2015 (%)	2016 (%)	2017 (%)
Neurology service only	161 (79)	182 (85)	199 (81)
Mental health service only, or both[a]	43 (21)	32 (15)	46 (19)
Total number of pregnancies exposed to VPA	204	214	245

VPA sodium valproate

[a] Mental health service, or both neurology and mental health services, accessed by the patient

Table 4 Prescribing of AED/MSM in the pre- and intra-pregnancy period[a]

	Year pregnancy ended		
	2015 (%)	2016 (%)	2017 (%)
Total number of women exposed to any AED/MSM	1260	1161	1195
Number of women exposed to lamotrigine[b] (% of exposure to AED/MSM)	116 (9)	105 (9)	104 (9)
Number of women exposed to VPA[b] (% of exposure to AED/MSM)	566 (45)	544 (47)	551 (46)
VPA stopped before pregnancy (% of women exposed to VPA)	362 (64)	330 (61)	306 (56)
Pregnancy exposed to VPA (% of women exposed to VPA)	204 (36)	214 (39)	245 (44)
Exposed *throughout* pregnancy (% of pregnancies exposed)	132 (65)	149 (70)	174 (71)
Initiated *during* pregnancy[b] (% of pregnancies exposed)	42 (21)	37 (17)	42 (17)
Switched off *during* pregnancy (% of pregnancies exposed)	30 (15)	28 (13)	29 (12)

VPA sodium valproate, *AED* antiepileptic drug, *MSM* mood-stabilising medication

[a]The pre- and intra-pregnancy period starts at the beginning of the calendar year before the year of delivery, and ends with delivery

[b]Exposures to any AED/MSM are not exclusive

Table 5 Proportion of women of childbearing age who received antiepileptic drugs or mood-stabilising medicines in the year of conception

	Year pregnancy ended					
	2015	%	2016[a]	%	2017	%
Total number of WOCBA receiving AEDs and MSMs	18,974		20,701		22,120	
Number of women receiving any AED/MSM in the year of conception[b]	1260	6.6	1161	5.6	1195	5.4
Total number of WOCBA receiving VPA	8205		9425		9902	
Number of women receiving VPA in the year of conception	566	6.9	544	5.8	551	5.6
Total number of WOCBA receiving non-VPA AEDs and MSMs	10,769		11,276		12,218	
Number of women receiving non-VPA AEDs or MSMs in the year of conception	694	6.4	617	5.5	644	5.3
Total number of WOCBA accessing care at a health facility	1,044,821		1,005,847		1,091,718	
Number of WOCBA who had a pregnancy	101,865	9.7	105,286	10.5	114,837	10.5

WOCBA women of childbearing age, *AEDs* antiepileptic drugs, *MSMs* mood-stabilising medications, *VPA* sodium valproate

[a]Dear Health Care Professional Letter on sodium valproate safety in pregnancy was issued in December 2015

[b]Were receiving AEDs/MSMs prior to conception

anomaly (albeit much rarer than VPA-associated fetal complications) [31]. Despite recent reports suggesting that the teratogenic risk of lithium is dose-related and much lower than previously hypothesised [31], the exaggerated perception of lithium's teratogenic risks may have contributed to a preference for VPA over lithium. Similar trends of high

Table 6 Reasons cited by key informants on the widespread use of sodium valproate in women of childbearing age and pregnant women

1. VPA and lamotrigine are very effective treatments for both focal and generalised forms of epilepsy, and represent a valuable therapeutic option for both epilepsy and mood disorder patients
2. VPA and lamotrigine have a better drug interaction profile compared with phenytoin and carbamazepine, and hence are safer to use in HIV-infected patients receiving antiretroviral therapy[a]
3. Lamotrigine requires more intensive clinical management as it must be titrated slowly (6–7 weeks) to the therapeutic dosage to reduce the likelihood of serious skin reactions. This increases the burden on the healthcare system by increasing patient visits with limited specialist and therapeutic monitoring resources
4. Any interruption in therapy (i.e. in the case of non-compliance or in the event of stock-outs) requires lamotrigine titration to be re-initiated, resulting in a risk of breakthrough seizures as well as the need for additional treatment, facility visits and monitoring
5. The impact of switching treatment on quality of life and seizure control in epilepsy patients is significant—a patient is not allowed to drive or operate heavy machinery for 1 year after any treatment switch, even if the patient has remained seizure-free. In addition, during the switchover period, there may be a greater risk of breakthrough seizures, which are also associated with risks to both the mother and the foetus
6. Mood disorder patients are often non-adherent, and concerns were raised about the mood-stabilising effects of alternative agents available in the public sector in South Africa, including antipsychotics and lithium
7. Lithium use for mood disorders in pregnancy is also challenging given its narrow therapeutic range, and hence the need for careful dose titration and monitoring during pregnancy and the increased perceived risk of congenital disorders such as Ebstein's anomaly following in utero exposure
8. At the time of these consultations, access to the safer alternative AED, levetiracetam, was restricted to specialist use at tertiary hospitals due to prohibitive costs
9. Information on the performance of levetiracetam in South African patients is limited. Referral links between neurology and psychiatry, and women's health services such as family planning and antenatal care are not always optimal and could be strengthened. This is to ensure that women receive adequate family planning and utilise effective contraception when prescribed VPA

VPA sodium valproate, *AED* antiepileptic drug, *ART* antiretroviral therapy

[a]Known interactions between efavirenz and carbamazepine, phenytoin and phenobarbital, through cytochrome P450 system induction. VPA has no inducing effects on ART metabolism but has been shown to displace protein binding of the antiretroviral dolutegravir, which is not clinically important as it does not change the free, active dolutegravir concentrations. Levetiracetam is not metabolised by the cytochrome P450 system as it is eliminated unchanged in the urine after undergoing enzymatic hydrolysis [20]

rates of valproate use have been noted in other countries [32, 33]. Shorter and less continuous VPA prescribing patterns for non-epileptic indications, such as bipolar mood disorder, could explain the more limited teratovigilance research in the psychiatric literature. This could have further contributed to lower awareness of these risks among clinicians involved in the care of patients with non-epileptic disorders [32].

We found that the prescribing rates of VPA in WOCBA were higher among HIV-infected versus HIV-uninfected women. This is probably because the older South African national treatment guidelines recommended VPA and lamotrigine as first-line treatments for epilepsy and mood disorders in women receiving ART, driven by concerns of pharmacokinetic interactions between AEDs and antiretroviral agents (including dolutegravir, which has recently been introduced as part of first-line HIV treatment in South Africa) [20, 34]. Although lamotrigine is the other recommended agent for WOCBA and pregnant women, the complicated initiation regimen, the need for intensive therapeutic drug monitoring particularly during the pregnancy and after delivery [35], and concerns regarding the risk of severe skin reactions, has contributed to the preferential prescribing of VPA in this population. Only 9% of women who experienced a pregnancy in that year and who were taking any type of AED/MSM were exposed to lamotrigine, compared with 45–47% who were exposed to VPA (Table 4).

In resource-constrained health care settings, rational and safe prescribing of medicines is challenging for multiple reasons: access to specialist services are limited; medicines formularies are often confined to the most cost-effective options; medicine stock-outs are commonplace; and referral linkage between clinical services (e.g. between neurology and family planning) may be suboptimal. The prescribing of risky or suboptimal treatments in challenging patient subgroups can occur despite the presence of safer alternatives on the market.

The pregnancy rate of WOCBA taking AEDs and MSMs was significantly lower than the pregnancy rate of WOCBA not taking these agents, suggesting that either women tend to be aware of the risks of taking AEDs/MSMs in pregnancy, or the underlying condition directly or indirectly impacts fertility. As contraceptive use is not routinely recorded on the provincial electronic platform, we were unable to compare contraceptive use among WOCBA in the different treatment groups.

This analysis has demonstrated the value of the linked population-level data in identifying problematic prescribing practices in high-risk groups. A validation study previously conducted on the quality of exposure data comparing clinical maternity records with the electronic pharmacy system has demonstrated that chronic medications are reliably recorded

and accessible in the electronic pharmacy management system compared with paper-based records [36].

This investigation identified special challenges typical of low- to middle-income settings, such as limited access to alternative treatment options due to prohibitive costs, and the lack of easily accessible local data to motivate for revision of treatment guidelines. Moreover, in the absence of widespread and intensive advocacy efforts, the DHCPL alone did not appear to improve VPA prescribing patterns.

Levetiracetam is recognised as an alternative with a lower risk of congenital malformations, as well as a low risk of drug–drug interactions with other medications, including antiretrovirals [37]. However, due to the significantly increased cost and the risk of neuropsychiatric adverse effects (depression, aggression, suicidality and psychosis) [38], access to this alternative treatment has been limited to higher levels of care. In the Western Cape province, where data on high rates of VPA exposure in pregnancy were made available to the Provincial Pharmacy and Therapeutics Committee, the coding status of levetiracetam was amended in 2019. As a result, levetiracetam may be initiated by certain clinicians (specialist family physicians, neurologists, psychiatrists, paediatricians, neurosurgeons and physicians) and is now more easily available as a treatment option for women receiving ART and women who were previously taking VPA. In both these situations, lamotrigine would be recommended as the first choice and levetiracetam would be reserved for women who are intolerant or unresponsive to lamotrigine. At a national level, discussions are being held within the Essential Medicines Programme on the critical need and feasibility of including additional treatment options for epilepsy and mood disorders in the public sector. Until more practical alternatives are available to prescribers in the public sector, first-line use of lamotrigine for the treatment of epilepsy is being encouraged. International data suggest that local training initiatives aimed at educating doctors, pharmacists and patients on the risks of VPA should be developed [26]. Similar reluctance among health care providers to change prescribing practices, and challenges encountered in communicating these risks to patients, has been repeatedly described in other settings [26, 29, 30, 39, 40].

Decision making around the prescription of valproate and other antiepileptics in pregnant women and WOCBA is complex and involves the consideration of multiple factors. The reproductive risks of VPA have to be weighed against the need for optimal seizure control. Early reports of the SANAD II study suggest that levetiracetam may be an inferior antiepileptic to VPA [41], while Angus-Leppan and colleagues found that between 33 and 43% of clinicians surveyed in the UK noted deterioration in among women who were switched from VPA to an alternative agent [42]. The risks of inadequate seizure control during pregnancy, both to the woman and the foetus, are significant and include maternal death, sudden unexpected death, small for gestational age, and preterm delivery [43].

Women need to be provided with up-to-date information on the risks and benefits of various treatment options, including the risks of switching therapy, in order to make informed decisions. While the implementation of the PPP will provide clinicians with a framework for engaging women in informed decision making around the use of valproate in pregnancy, it may not adequately provide women with information on the potential risks of switching therapy. Moreover, women with learning disabilities may be unable to engage with the informed consent process required by the PPP [44]. Therefore, the impact of these regulatory warnings and revised treatment guidelines will need to be monitored more holistically through prescribing trends, indicators of seizure control, and rates of adverse maternal and pregnancy outcomes.

The shortcomings of the DHCPL as a regulatory risk communication tool has been highlighted by others [45–47]. Therefore, the apparent lack of response in valproate prescribing patterns, despite the dissemination of the DHCPL, has highlighted the need for improved risk communication strategies by regulatory authorities. Regulators and pharmaceutical manufacturers must assess the clinical value of the DHCPL and explore additional, more accessible, clinically relevant approaches to communicating risk, particularly in resource-limited settings.

This study had several limitations. The PHDC consolidates electronic data sources and dispensing data were limited to those facilities with an electronic pharmacy management system, and, as such, the dispensing data may be incomplete. However, AEDs and MSMs are most commonly dispensed from referral facilities and, in the Western Cape, it is only primary health care clinic sites that are not digitised.

Drug exposures were based on prescriptions dispensed in relation to the estimated onset of pregnancy. In the absence of clinical evidence of gestational age (i.e. expected date of delivery by ultrasound, last menstrual period and symphysis fundal height), this was determined using birth weight and date of delivery. Therefore, pregnancy exposures are estimated in some cases. The timing of exposure during pregnancy may be problematic given the sparse data recorded electronically on which to estimate the gestational dating of the exposures. This is a common challenge encountered by others [48]. In the case of well-described teratogens such as VPA, the absence of reliable local outcome data does not diminish the value of determining the extent of exposure. In Europe, prescribing patterns monitored over a longer period of 14 years have noted pronounced changes in VPA prescribing and, consequently, significant reductions in teratogenic events [49].

Only pregnancies with evidence in the PHDC were included; thus, importantly, pregnancies that ended in miscarriage prior to an antenatal visit were not included.

Pharmacy data in the PHDC represents dispensing data and we cannot be certain that these medicines were taken as prescribed, only that they were collected; nor could we assess whether advice on contraception was provided or adhered to. The indications for use of these medicines in each patient are not routinely captured in the electronic pharmacy system, and diagnostic codes are not reliably captured province-wide to allow for analysis of VPA use in WOCBA and pregnant women by indication. We had to rely on the crude indicator of clinical service accessed by the patient to differentiate whether VPA was being used for a psychiatric versus neurological indication (Table 3).

The findings were only based on data from one province of South Africa, where electronic patient registers and record linkage facilitated the analysis. In other provinces, HIV prevalence rates among WOCBA and pregnant women are much higher (up to 44.4%, compared with 19.3% in our cohort), likely resulting in higher rates of VPA prescribing in order to avoid interactions with ART [50].

The dialogue initiated in response to the high rates of VPA prescribing in WOCBA resulted in formal action at both the national and provincial levels.

Provincial level Within the Western Cape Province, several steps were taken to reduce VPA use in WOCBA. These included:

1. Increasing access to safer alternatives such as lamotrigine, clobazam (as a temporary adjunct agent to provide cover during the slow dose-escalation phase when lamotrigine is initiated), and levetiracetam. In the case of the latter, this involved reducing the guideline restrictions for both prescriber and patient. Only the lower dose of levetiracetam 250 mg is procured to facilitate ease of dose titration and adjustment.
2. Training of designated prescribers of lamotrigine by district clinical specialists on the adverse effects of available AEDs, and a titration regimen for helping women transition from VPA to lamotrigine.
3. Providing a provincial clinical guideline to all heads of clinical neurology and psychiatry units on the most appropriate use of AEDs and MSMs in adolescent and adult WOCBA for both epilepsy and bipolar mood disorder.
4. Distribution of an Acknowledgement of Risk form for completion by all prescribers and women initiated on VPA, and again annually thereafter.

To monitor trends in VPA prescribing in the province, a set of key indicators were developed that could be provided to the provincial Pharmacy and Therapeutics Committee, on a regular basis, by the PHDC to assess the impact of these measures on VPA prescribing in WOCBA.

As is already a mainstay of practice for other clinical scenarios in the province, an automated notification system is being envisioned whereby the PHDC is able to notify the facility of any pregnancies with identified teratogenic exposures so that these women can be referred for relevant clinical specialist services. The clinical genetics unit will serve as a referral point for all VPA-exposed infants so that these infants can be properly assessed, their parents counselled, and the children can receive appropriate access to relevant long-term care such as occupational therapy, if required.

National level In 2018, VPA use was continued by the National Essential Medicines List Committee (NEMLC) as first-line use in children on the condition that, in girls, treatment be switched to an alternate anticonvulsant when they reached childbearing age. Similarly, VPA was contraindicated in WOCBA unless alternate treatment could not be used, in which case reliable contraception was required [51]. The NEMLC, appointed by the Minister of Health, is responsible for formulating and revising the National List of Essential Medicines based on clinical need, evidence of efficacy, quality, safety, affordability and implications for practice. The SAHPRA required VPA manufacturers to support a PPP. This will enable programmatic units to be guided on how to implement measures aimed at reducing pregnancy exposures to VPA in the public sector.

5 Conclusions

Our analysis of VPA prescribing practice in WOCBA using population-level provincial data identified potentially unsafe practices. In response, stakeholder discussions explored a response to therapeutic challenges in the context of AED and MSM use in pregnant women and WOCBA in South Africa. The investigation has highlighted how, in this resource-constrained setting with a high burden of HIV-infected women taking antiretroviral therapy, lack of awareness of the extent of the problem in the local setting, and the high cost of and consequent poor access to alternative medicines and specialised care can contribute to the continued use of potentially harmful treatments in WOCBA. Within this context, the DHCPL disseminated by the manufacturers appears not to have any significant impact on valproate prescribing in WOCBA.

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Declarations

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Conflicts of interest Ushma Mehta, Mariette Smith, Emma Kalk, Helen Hayes, Annoesjka Swart, Lawrence Tucker, Renier Coetzee, Andrew Boulle, and Marc Blockman have no conflicts of interest to disclose.

Ethics approval Approval for this study and its subsequent publication was granted by the University of Cape Town Faculty of Health Sciences Human Research Ethics Committee (ref: 098/2018) and the Western Cape Provincial Research Committee.

Consent to participate Not applicable. Anonymised, aggregate data extracts and statistics aimed at addressing the key objectives of the study will be generated by the PHDC for review by the investigators. The research is retrospective, observational, part of standard of care, and involves no additional risk to patients. Only anonymised data will be provided to the investigators.

Consent for publication Not applicable.

Availability of data and material The datasets generated during and/or analysed during the current study are not publicly available as these data are in the custody of the Provincial Government of the Western Cape of South Africa and permission for access to such data would need to be sought directly from the Provincial authorities.

Code availability (software application or custom code) SQL Server 2017 was used to generate the relevant outputs from the PHDC. This code can be made available on request from the corresponding author.

Author contributions UM, MS, AB, MB and EK developed the study concept; MS and UM conducted the data mining and analysis; and UM drafted the manuscript, which was reviewed and edited by all authors.

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