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Valproate pregnancy prevention scheme: what are the barriers to enrolling patients and how do we meet them?

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ABSTRACT

Background The UK Medicines Health products Regulation Agency instructs that valproate prescriptions should be restricted in women of childbearing age to those consenting to the Pregnancy Prevention Programme (PPP). We assessed the compliance and barriers to the valproate PPP.

Methods We retrospectively audited NHS Grampian's compliance with PPP guidelines among women of childbearing potential prescribed valproate between October 2017 and March 2018. Additionally, we prospectively reviewed new valproate prescriptions from February 2019 to March 2022 and compared this with our retrospective data to assess the effectiveness of our identification process using descriptive statistics.

Results We identified 351 women retrospectively and 80 women prospectively. Epilepsy, migraine and psychiatry were the main indications. There was a decline in valproate use over the years, particularly for epilepsy. Initially, only 132 (37.6%) met the PPP requirement, and eventually, 81 (23%) stopped the medication. Despite efforts, 38 (10.8%) had contact with secondary care but still did not meet PPP and 100 (28.5%) had no documentation or referral to secondary care. Patients not meeting PPP lacked capacity, most commonly with severe learning difficulties. Women treated for psychiatric purposes were less likely to meet PPP than other indications.

Conclusions A significant proportion of women continue valproate treatment without meeting the PPP requirement. This is linked to their indication for prescription and their comorbidities. Collaborative input from relevant specialities and primary care is required to fully achieve PPP if a national valproate database is to be established.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Compliance with the UK Medicines Health products Regulation Agency (MHRA) guideline on valproate Pregnancy Prevention Programme (PPP) is sparingly assessed, despite the risk of congenital malformation and learning difficulties in children when used during pregnancy.

WHAT THIS STUDY ADDS

⇒ This study shows that despite MHRA's PPP guidance, a substantial number of women of childbearing age remain with no documentation, particularly for psychiatric indications, and were not referred to secondary care. However, some not meeting PPP had learning difficulties.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This high rate of women not meeting PPP requires a multidisciplinary collaborative process and further studies to improve PPP compliance.

INTRODUCTION

Sodium valproate has proven to be a highly effective antiseizure medication (ASM), since it first came into medical use in 1962.[1 2] The *Standard and New Antiepileptic Drugs* (SANAD1) study[3] and the recent SANAD2 study confirmed it as the most efficacious and cost-effective ASM for patients with generalised epilepsy.[4] It is effective for multiple seizure types,[5] and comparable to phenytoin and levetiracetam in the treatment of status epilepticus.[6 7] It is also an effective migraine-preventative treatment and mood-stabilising medication in bipolar disorder, but less frequently used because of the availability of a wide range of alternative treatment options.[8 9]

Sodium valproate's teratogenicity became established in the 1980s.[10] The UK and Ireland pregnancy registers reported the risk of major congenital malformations in 6.7% (95% CI: 5.5% to 8.3%) of babies exposed to valproate during pregnancy, with neural tube defects, cleft lip and palate, congenital heart defects and learning disability being the most frequently reported.[11] The prospective cohort study from 42 countries contributing to the European and international registry of Anti-epileptic drugs in Pregnancy (EURAP) database showed that the risk of a neurodevelopmental anomaly in children exposed to

valproate during pregnancy may even be higher,[12] likely with higher doses.[13]

The UK Medicines Health products Regulation Agency (MHRA) in April 2018 stated that 10% of babies born to women treated with valproate will have birth defects and 30%–40% of children will have some learning difficulties in development. The MHRA, therefore, issued guidance to primary and secondary care physicians in the UK that the use of valproate should be restricted in women of childbearing age unless they consented to the Pregnancy Prevention Programme (PPP).[14] They should be referred by primary care to secondary care clinicians specialising in the management of epilepsy, migraine or psychiatry to review the continued need for valproate treatment, discuss other potential treatment options, complete the PPP consent documentation or confirm they met the exclusion criteria. The PPP mandated the use of highly effective long-term contraception including coils (copper intrauterine device or levonorgestrel intrauterine systems), the contraceptive implant (progesterone-only implant) or sterilisation. MRHA survey data in April 2019 indicated that clinicians had not adequately completed valproate PPP, necessitating the need to create a national registry for women of childbearing age taking valproate. The authors suggested that the major issue may have been a lack of clinician engagement with the process. Recently, the MHRA through the independent Commission on Human Medicines reviewed the available data and advised that no patient≤55 years either men or women should be started on valproate unless two specialists independently confirm no other effective or tolerated treatment is available or the risks do not apply.[15] Having established a local registry from available secondary care data, we assessed potential primary and secondary care barriers to enrolling patients into the PPP.

METHODOLOGY

Study design and data collection

We conducted a retrospective and prospective audit in NHS Grampian. This NHS Trust serves a population of about 585 700 patients (2019 mid-year population estimate) from the Aberdeen, Aberdeenshire and Moray regions. There are well-established regional preconception and antenatal clinics with input from neurology, clinical genetics and obstetric colleagues. We obtained primary care prescribing data to identify patients of childbearing potential (aged 16–54 years) on treatment with all forms of sodium valproate. Any patients issued with a prescription for valproate in the period between October 2017 and March 2018 were identified in the retrospective arm. These subjects were identified through a Microsoft Access database established in 2019 to audit the board's level of compliance with the PPP guidelines and facilitate monitoring of annual documentation of PPP. We conducted reviews in December 2019, February 2021 and September 2022 to gain an overview of our progress in completing the documentation.

Our neurology database aided our prospective audit of new valproate prescriptions. Funding for an extra weekly epilepsy nursing session was approved, thus providing time to maintain the database and undertake annual follow-up discussions and documentation. We prospectively identified relevant patients newly commenced on valproate from February 2019 until March 2022 from primary care prescribing data. We compared the data from our prospective database and to our retrospective database, to review more recent prescribing trends. NHS Grampian uses an electronic records system (TRAK) to document all secondary care correspondence since 2014. Standardised primary care referrals (Sci store) are also used by all practices to document previous medical histories and drug prescriptions, often recorded over several decades. These electronic records allowed us to see all correspondence between primary and secondary care since 2014, thus identifying cases initiated on valproate without input from secondary care. In some cases, there was evidence of initiation from private clinicians or where patients had moved to the region having had treatment initiated elsewhere.

Statistical analysis

We transferred data from the Microsoft Access database to Excel (2016) spreadsheet and analysed using Stata V.15 (Stata Corp. 2017. Stata Statistical Software: Release 15. College Station, Texas: Stata Corp LLC). We compared baseline characteristics between subjects in the retrospective and prospective arm and between valproate indications using graphical and descriptive statistics. The mean±SD or for skewed data the median and IQR were used for summarising continuous variables and compared using the Student's t-test or the Wilcoxon rank-sum test, as appropriate. A χ^2 test or Fisher's exact was used to compare categorical variables. A p value of <0.05 was considered statistically significant.

Ethical considerations

A Caldicott ethical approval for use of patient identifiable data was granted in January 2019 following the MHRA guidance in July 2018. Our data retrieval, processing and analysis were done according to the guideline set by the Declaration of Helsinki.[16]

RESULTS

We identified 351 women retrospectively from 2019 and 80 women prospectively who were on treatment with valproate. The demographic characteristics of subjects treated with valproate are shown in table 1. The age distribution is significantly skewed to the older patient population with a mean age of 40.7±9.7 (range 16–45) years and 39.5±10.1 (16–53) years, respectively, (online supplemental figure 1), with no significant age difference between the two groups or indications (online supplemental table 1).

Table 1 Baseline characteristics comparing the two recruited groups

	Retrospective n=351 (%)	Prospective* n=80 (%)	P value
Age			
Mean±SD	40.7±9.7	39.5±10.1	0.3183
Median (IQR)	43 (34–49)	42 (32.5–38.5)	0.3390
Range	16–54	16–53	
Indications			
Epilepsy	229 (65.2)	24 (30.0)	<0.001
Migraine	23 (6.5)	18 (22.5)	
Psychiatry	80 (22.8)	31 (38.8)	
Others	19 (5.4)	7 (8.7)	
Meets PPP			
No (no documentation and no referral)	100 (28.5)	28 (35.0)	<0.001
Yes	132 (37.6)†	49 (61.3)	
Stopped†	81 (23.0)	3 (3.7)	
Some contact but do not meet PPP	38 (10.8)	–	

*Five subjects in the prospective arm were at some point in the retrospective arm.
†Those who eventually stopped can be assumed to have met PPP, therefore a total of 60.6% of patients met PPP eventually.
PPP, Pregnancy Prevention Programme.

The main indications for valproate prescription are epilepsy, migraine and psychiatric illnesses (table 1). The age demographics are similar among patients within the group prescribed valproate for various indications. However, there was a significant change (p<0.001) in indications for valproate use between the two groups and a decline in use. Epilepsy was the most frequent indication in two-thirds of the retrospective group, which dropped to less than a third in the prospective group, with an increased proportion for psychiatry and migraine indications. Although the age for epilepsy indication was younger in the prospective cohort, this was not statistically significant.

Comparing data by indications from the entire cohort (table 2) showed that those with psychiatric indication for valproate use were less likely to meet PPP compared with the other groups (p<0.001).

Despite multiple MRHA and department letters sent to primary care clinic and pharmacy colleagues asking that women of childbearing age be referred to the specialty care team that initiated the treatment by September 2022, only 132 (37.6%) meet PPP, 81 (23%) stopped the medication, 38 (10.8%) have had some contact from secondary care but do not meet PPP, 100 (28.5%) have no documentation or referral to secondary care. Showing that approximately 4 out of 10 did not meet PPP. Of these patients, 21 have severe learning difficulties or a brain injury lacking the capacity to make decisions (6% of the total population, but 21% of patients without documentation). A total of 18 patients (5%) have been referred but have not attended appointments or responded to department letters on multiple occasions. A total of 7 patients (2%) have been seen and met the PPP but failed to submit their signed documents. A total of 10 further patients (3%) do not meet PPP, despite meeting with clinicians and discussing the issues (some are not sexually active or in same-sex relationships). The clinicians opted to continue their treatment despite this.

Table 2 How each valproate indication meets PPP

	Meets PPP			
Indications	No	Yes	Total	P value
Epilepsy	44 (17.5)	116 (46.2)	251	<0.001
Migraine	8 (19.5)	22 (53.7)	41	
Psychiatry	72 (64.9)	30 (27.0)	111	
Others	5 (19.2)	5 (19.2)	26	

PPP, Pregnancy Prevention Programme.

We audited the degree of concordance in December 2019, February 2021 and September 2022 (see online supplemental table 2). Table 3 outlines the findings at two time points, December 2019 and September 2022. In the interim, the results of the first audit in December 2019 were presented to neurology, psychiatry and primary care pharmacy and clinical leads. We provided identifiable details for the psychiatry patients without documentation to their pharmacy team in January 2020 to be distributed to the clinical teams involved. Our primary care prescribing group informed us that we were not allowed to write to patients with epilepsy and migraine who had not been referred and who were no longer under active neurology follow-up. We, therefore, provided those primary care colleagues with identifiable data at a practice level to review the requirement for valproate PPP documentation. This led to further referrals to secondary care, but

Table 3 Comparison between the degree of concordance with PPP in December 2019 and September 2022 by the indication for valproate treatment

	Epilepsy (December 2019) n=219	Epilepsy (September 2022) n=233	Migraine (December 2019) n=12	Migraine (September 2022) N=26	Psychiatry (December 2019) n=72	Psychiatry (September 2022) n=81	Other (December 2019) n=17	Other (September 2022) n=11
Valproate stopped	43	50 (+7)	0	11 (+11)	4	18 (+14)	0	2
Meets PPP	77	102 (+25)	1	7 (+6)	0	21 (+21)	0	2
Meets PPP (no RAF form)	0	5 (+5)	0	0	0	2 (+2)	0	0
Review does not meet PPP	0	6 (+6)	0	0	0	4 (+4)	0	0
RAF sent to patient, no record of PPP	0	0	0	0	0	3 (+3)	0	0
DNA/letters repeatedly offering appointments	0	13 (+13)	0	4 (+4)	0	1 (+1)	0	0
No documentation	63	39 (–24)	11	4 (–7)	68	29 (–39)	17	7 (–10)
No documentation (lacks capacity)	36	18 (–18)	0	0	0	3 (+3)	0	0

DNA, did not attend; PPP, Pregnancy Prevention Programme; RAF, Risk Assessment Form.

there are still 26% (57/233) of patients with epilepsy who have not been re-referred to secondary care. Although a number may be sterilised or postmenopausal, we have no way of knowing what proportion still have childbearing potential. A proprtion of these patients are likely to have refused referrals or will not have been contactable from their GP practices for example.

The reasons for the lack of concordance with PPP may differ between the treatment groups. All epilepsy and migraine patients under follow-up at this stage have either stopped the medication, meet PPP criteria or have not engaged with follow-up despite being offered appointments and letters outlining the need for review. The remaining 57 patients have not been referred for review, but it is unclear if they still have childbearing potential from secondary care documentation. Of these patients, four have a history of previous alcohol misuse and another four have significant depression. Both may well influence their engagement with health services. A total of 18 patients with epilepsy lack the capacity to consent either due to brain injuries or significant learning disabilities and have no PPP documentation. The level of impairment experienced by these patients makes it difficult for them to engage with even remote follow-up arrangements. These patients should not be sexually active. A list of these patients has been given to primary care pharmacy and learning disability psychiatry colleagues. There are also seven patients for whom there is no evidence of a secondary care input since 2014, in whom the reason for valproate prescription and initiating clinician was unclear.

Although some patients with psychiatric conditions stopped valproate treatment, this was often due to improvement in the clinical state, a revision in diagnosis or a lack of efficacy of treatment. Concern about the risks relating to pregnancy may have been an undocumented factor in the decisions to change to alternative treatments in some of these patients. The reviews in February 2021 and September 2022 outlined that some patients met PPP, as they no longer had childbearing potential (23%, 19/81). It is only since January 2020 that there has been evidence within secondary care psychiatry correspondence of any discussion of PPP in these patients. Only two met PPP with a Risk Assessment Form and documentation of appropriate contraception. Three patients have been sent the MHRA patient guides and the risk acknowledgement forms, but there has been no documentation of the patient's contraceptive treatment or advice given regarding contraception. There may be separate paper records reflecting this, but if this is the case then PPP is still not being fully met, as there is no evidence of primary care colleagues having been informed of such documentation.

Comparing this with our second smaller cohort (80 women), fewer patients stopped or did not have documentation; however, 21 (25.9%) meet PPP, 27 (33.33%) stopped valproate and 33 (40.7%) did not meet PPP.

The prospective data confirmed 24 new patients with epilepsy being well enrolled on PPP (online supplemental table 3). Despite our efforts, two patients fell pregnant while on treatment with valproate. Both patients had undertaken consultant reviews and completed PPP documentation. The first had become pregnant soon after the removal of her coil in the intervening period before her annual follow-up. The coil was removed by gynaecology colleagues, with no contact with neurology services. The second patient became pregnant while awaiting sterilisation; she had agreed to use two forms of contraception

pending the procedure, having had a negative pregnancy test on initiation of treatment for highly refractory epilepsy. For the patients with migraine (18), a significant number had short periods of treatment with valproate, often for a few months and 4 had this treatment initiated in primary care with no secondary care involvement. This was also true of the seven patients in which there was insufficient secondary care data to know the indication for commencing valproate treatment. We identified that these patients' treatment was initiated by either primary care or private clinicians with no secondary care involvement. Four of the psychiatry cases had valproate treatment initiated by private psychiatrists and two had treatment initiated in other countries before moving to the region.

DISCUSSION

Our audits show that despite efforts to comply with MHRA guidance for PPP, there remain a significant number of patients who remain on treatment without documentation of meeting PPP, but more so in those with psychiatric indications.

In line with other studies, the demographic distribution of patients on valproate treatment is significantly skewed to the older patient population and the prescription prevalence of valproate in women is known to have been falling over several years, especially for epilepsy.[17–22]

Despite multiple MRHA and department letters being sent to primary care clinics and pharmacy colleagues asking that patients of childbearing age be referred to the specialty care team who initiated the treatment, some patients have not been referred.

Our data outline that full compliance with PPP will only be possible with collaborative input from colleagues in primary care, learning disability psychiatry, adult psychiatry and neurology services. If the MRHA is to build a national database, then primary care data will need to be submitted to confirm that unreferred patients have no childbearing potential. Engagement will be required from all the specialities listed. At present, we have no process to determine if unreferred patients no longer have childbearing potential (postmenopausal, sterilised), are unwilling to be referred for assessment or have other barriers to assessment. Our data do indicate that there are groups of vulnerable patients who cannot engage in a process undertaken in secondary care, potentially due to their disabilities. Patients with significant alcohol dependence and psychiatric conditions may be less likely to actively engage with health services. Therefore, appropriate methods to facilitate engagement with such patients will be required if we are to achieve better PPP concordance.

There are a further small group of patients with no recorded contact with secondary care for several years, where it is unclear if any secondary care specialty initiated their prescriptions. Some may have had treatments initiated in primary care, some private clinicians and some in other regions or countries, thus it is not possible for all patients to be identified purely in secondary care to complete the PPP process they will need to be identified in primary care. The recent pan-college guidance indicates that General practioners (GPs) as prescribers need to decide whether to continue their prescriptions in the context of patients who do not engage. However, given the risk of sudden unexplained death in epilepsy (SUDEP) if valproate prescriptions are stopped, as a department we have indicated the requirement for discussion with patients before considering this. Ultimately, there is an important ethical question as to who is responsible for the decision to continue valproate in these non-engaging patients. We have an obligation to provide patients with the relevant information and offer the opportunity to discuss other treatment options; however, the best response to patients who opt to continue treatment and not engage with PPP is debatable.

Our retrospective data showed that psychiatry patients often received valproate treatment for several months, with the treatment stopped and changed to alternative medical treatments. It was unclear how often pregnancy prevention was a factor in these decisions, as there would need to be a plan to wean off valproate before planning pregnancy,[23] but this will remain unclear without PPP documentation or the current contraception being recorded. There may be documentation from these other services unavailable in the local secondary care notes; however, there also has been no prospective documentation of PPP or plans for annual review in these patients. However, this again indicates that any process purely undertaken by secondary care psychiatry services will miss such cases.

Colleagues from Tayside identified 151 epilepsy patients from primary and secondary care data and found that only 13.9% responded to a letter from secondary care and 20.4% responded to a letter from their GP referring them for assessment. They concluded that patients were actively favouring good seizure control over compliance with MHRA guidance.[24] A UK national survey of 215 clinicians in 2020 confirmed significant variation in the processes undertaken to audit PPP compliance and the level of documentation between regions and services.[25] Some services reported complete compliance, while others reported no compliance or that they had no data on this issue. The author's view was that a national register should be established.[24] The Association of British Neurologists has requested epilepsy services undertake a standardised audit of their epilepsy patients. Recently published data from this audit process indicated high compliance; 93.1% of patients under epilepsy follow-up were informed of pregnancy prevention and 92.2% had documentation of the need for highly effective contraception if remaining on valproate.[26] However, our data indicate this alone will miss a significant number of patients not currently under clinic follow-up. As identified in our study, a review noted that it is important to include patients and carers in the decision process as highlighted, noting that the MRHA

guideline did not consider the impact on special populations such as those with learning disability.[27] Our study recommends collaboration between primary care and various specialities to improve PPP compliance. This is in line with a recent editorial,[28] suggesting that for the PPP to be successful, it is necessary for the health system to have established communication and integration of care across multiple primary and secondary care services and to help not to compromise safety for people with epilepsy.

CONCLUSION

This audit reveals that despite our neurology department's efforts, we are far from fully complying with the MHRA PPP guidance for all patients. A large percentage of patients who remain on valproate treatment fail to meet PPP, particularly among the psychiatric indications and those not under active secondary care follow-up. A collaborative process needs to be established between primary care and prescribing specialities to improve PPP compliance. It is important that vulnerable patients, in particular those with reduced cognitive abilities, have access to appropriate comprehensive multidisciplinary services.

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