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National compliance with UK wide guidelines for usage of valproate in women of childbearing potential

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ABSTRACT

Valproate (VPA) is an effective treatment for epilepsy and also used in bipolar disorder. However, VPA is associated with a significant risk of birth defects and developmental disorders if used during pregnancy. This has led to the introduction of measures to reduce the use of valproate in women of childbearing potential such as the 'Prevent' pregnancy prevention program (PPP) and the completion of an annual risk acknowledgement form (ARAF). The aim of the current audit was to assess compliance with the guidance.

An audit tool was made available to neurologists registered with the Association of British Neurologists (ABN) and to epilepsy nurse specialists via the Epilepsy Nurses Association (ESNA) in the UK. Data were collected between November 2020 and March 2021.

The main indication for valproate was generalised epilepsy (55.8%), followed by focal (22.5%). For most, there was documentation that the woman had been informed about the risks associated with taking valproate during pregnancy (93.1%) and the need to be on highly effective contraception or that this was not deemed appropriate (92.2%). A signed ARAF was available in the notes for 81.2% although only 66% were <12 months old.

Although information had been made available for most women, there were still individuals where this was not documented. Further work is needed to facilitate identification of women taking valproate and implementation of a digital ARAF. For clinicians, the audit highlights a need to carefully counsel women about the teratogenic risks of continuing to take valproate versus the risk of deteriorating seizure control if the drug is withdrawn. This is particularly true of women with focal epilepsy, where there may be safer, equally effective, alternative anti-seizure medication (ASM). The aim should be to create a partnership of trust between the patient and clinician in order to arrive at the best clinical decision for that individual.

1. Introduction

Valproate is used for treatment of epilepsy and bipolar disorders. It is the most effective treatment for generalised or unclassified epilepsy [1]. However, exposure to valproate in utero is also associated with substantial teratogenic risks, including major congenital malformations (around 10%) [2], cognitive (30–40% exposed have significant reduction of IQ [3]) and neurodevelopmental disorders such as autism spectrum disorder [4]. This has led to the introduction of measures to reduce the use of valproate in women of childbearing potential. Across Europe and the United Kingdom (UK) the actions include the introduction of the 'Prevent' pregnancy prevention program (PPP) and the completion of an annual risk acknowledgement form (ARAF) by an appropriate specialist [5, 6]. Despite all the publicity and messages to healthcare professionals, there are several reports from UK patient organisations highlighting concerns that many women have not had the opportunity to discuss their use of valproate with an epilepsy specialist. For example, a survey by three UK epilepsy charities (Epilepsy Action, Epilepsy Society and Young Epilepsy) found that nearly 20% of women taking valproate reported still not being aware of the teratogenic risks of the drug, and that only 41% had signed up to the PPP [7]. A survey of specialist clinicians working in the UK reported that only around 43% of clinicians estimate that all, and 31% that most, women under their care had completed the ARAF [8]. Significant shortcomings were identified by an Independent Medicines and Medical Devices Safety Review (First do no harm) published July 2020 [9]. Through a national audit, we evaluated

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compliance with the Medicines & Healthcare products Regulatory Agency (MHRA) guidance amongst neurologists and epilepsy specialist nurses (ESNs) in the United Kingdom (UK), to identify areas for improvement.

2. Material and methods

An audit tool (Table 1) was developed by two of the authors (SHE and SMS). Following publicity to professionals, the tool was made available to neurologists registered with the Association of British Neurologists (ABN) and to ESNs via the Epilepsy Nurses Association (ESNA), using the newsletters and websites of both organisations. Clinicians were asked to audit their individual or departmental services and submit their local audit results via the survey tool or directly to one of the authors (SHE). Data were collected between November 2020 and March 2021. Data for all participating centres were analysed by one of the authors (SHE) and results reported as averages and ranges.

The audit was approved by the Clinical Audit and Quality Improvement Subcommittee (Queen Square Division, UCLH), number 124-202021-CA.

Table 1
Audit of Valproate in Women of Childbearing potential (For each option please enter a percentage, totalling to 100%).

1. Of the women of childbearing potential, you see who take Valproate, what proportion take this for
Generalised epilepsy
Focal epilepsy
Developmental and epileptic encephalopathies (DEE) including Dravetsyndrome
Unclassified
Other (please specify below)
Free text
2. In what proportion of women of childbearing potential you see who are taking valproate was there documentation in the notes/clinic letters that the woman has been informed about the teratogenic risks of valproate and that the info leaflet has been shared as per MHRA requirements?
Yes (in the last 12 months)
Yes (but more than 12 months ago)
No
3. In what proportion of women of childbearing potential taking valproate was there documentation in notes/clinic letter that the woman has been informed about the need to be on highly effective contraception or that the need for highly effective contraception is not deemed appropriate?
Yes (in the last 12 months)
Yes (but more than 12 months ago)
No
4. In what proportion of women of childbearing potential taking valproate was there a signed Annual Risk Acknowledgement form in the notes and proof it had been sent to GP/patient?
Yes (<12 months old)
Yes (>12 months old)
Yes but incorrectly completed
No
5. How many women were included in the survey?
Optional questions
A. Data submitted is from
A single Neurologist
A departmental audit
B. Data submitted is from
England
-London & Southeast
-East Anglia
-Mersey & Northwest
-Northern
-Oxford
-Southwest
-Trent
-Wessex
-West Midlands
-Yorkshire
Wales
Scotland
Northern Ireland
C. Data submitted is from
Epilepsy specialist
General neurologist

3. Results

Data were returned from 26 centres, comprising a total of 1171 patients. The number of patients audited at individual centres varied between 2 and 190. Data were mainly obtained from epilepsy specialist services (21/26 centres), rather than general neurology departments. Data were obtained from departmental audits in 24/26 centres. In the remaining two centres, an individual practitioner submitted their own data. Data were obtained from centres throughout England and Wales. Details on geographical distribution of centres and number of patients included/centre are listed in Table 2.

The main indication for valproate prescription was generalised epilepsy (55.8%), followed by focal (22.5%), or unclassified (15.3%), epilepsy. Developmental and epileptic encephalopathies were the indication in a small proportion of patients (4.3%). Other disorders (such as psychiatric disorder, usually not further specified) accounted for 2.1% of the cohort.

For most of the patients (93.1%), there was documentation in the notes or clinic letters that the woman had been informed about the teratogenic risks (of major malformations and neurodevelopmental delay) of valproate, and that the information leaflet had been shared as

Table 2
Number of patients included per centre.

Area	Number of patients included	Type of audit
England - East Anglia	54	Departmental audit
England - London & South east	22	Departmental audit
England - London & South east	190	Departmental audit
England - London & South east	20	Departmental audit
England - London & South east	37	Departmental audit
England - London & South east	17	Nurse
England - London & South east	69	Nurse
England - Mersey & North west	7	Nurse
England - Mersey & North west	37	Nurse
England - Northern	25	Nurse
England - Northern	11	Nurse
England - Northern	32	Single Neurologist
England - Oxford	115	Departmental audit
England - South west	41	Departmental audit
England - South west	49	Departmental audit
England - South west	39	Nurse
England - South west	2	Single Neurologist
England - West Midlands	36	Departmental audit
England - West Midlands	21	Departmental audit
England - West Midlands	51	Nurse
England - Yorkshire	48	Departmental audit
England - Yorkshire	38	Departmental audit
England - Yorkshire	5	Nurse
Unknown	13	Departmental audit
Wales	91	Departmental audit
Wales	101	Departmental audit

per the Medicines and Healthcare products Regulatory Agency (MHRA) requirements. For 74.1% (range by centre 20 – 100%), this information had been documented in the last 12 months. For 19% (range 0 – 77%), this information was older than 12 months and for 6.9% (range 0 – 33%) of patients, this documentation could not be found. Information about the risk associated with valproate was more likely to have been documented in the last 12 months for epilepsy specialists versus general neurologists (76% versus 66%), but there was no difference in the proportion of patients for whom this documentation could not be found in the notes or clinic letters (7% for both groups).

For most of the patients (92.2%), there was documentation in notes or clinic letters that the woman had been informed about the need to be on highly effective contraception or that the need for highly effective contraception was not deemed appropriate. For 74% (range by centre 18 – 100%), this information had been documented in the last 12 months. For 18.2% (range 0 – 78%), this information was older than 12 months and for 7.8%, (range 0 – 33%) of patients, this documentation could not be found. Again, this information was more likely to have been documented in the last 12 months for epilepsy specialists versus general neurologists (76% versus 66%) but there was little difference in the proportion of patients for whom this information could not be found (7% for epilepsy specialists versus 9% for general neurologists).

A signed ARAF was available in the notes for 81.2% of the women of childbearing potential taking valproate. For 66% (range by centre 18–100%), this was <12 months old and for 15.2% (0–66%) the document was >12 months old. In 0.4% (0–6%) the ARAF was incorrectly filled out and in 18.4% (0–67%), a signed ARAF could not be found in the notes. Results were similar for epilepsy specialists and general neurologists with a signed ARAF <12 months old found in 67% for epilepsy specialists and 63% for general neurologist and no ARAF found for 18% of women seen by epilepsy specialists versus 20% of women seen by general neurologists.

4. Discussion

The audit highlighted that many women of childbearing potential included in the survey had been informed about the risks associated with taking valproate during pregnancy and the need to adhere to the PPP. However, even in this cohort, which mainly consisted of patients seen by epilepsy specialists (81%), compliance with the MHRA guidance was incomplete and for nearly one fifth of the patients, no signed ARAF was found in the notes. These are concerning and important findings, suggesting that further work is needed to improve informing, counselling and managing the patients involved.

The risks of valproate treatment for women of childbearing potential have been discussed for several years in the literature [3, 10]. This has culminated in stricter guidance and the formation of the MHRA Valproate Stakeholders Network (VSN) in the UK, with similar groups worldwide, allowing patient groups, clinicians and regulators to meet and discuss practices to further improve safety in valproate prescribing for women of childbearing potential. A radical suggestion to reduce the risk of babies being exposed to valproate in utero has been a complete ban of the drug. However, this would mean denying patients access to a treatment that has been shown to be the most effective for generalised or unclassified epilepsies [1]. In particular, it could disadvantage women with intellectual disability (ID), who are more likely to have generalised epilepsies or specific syndromes where valproate would be considered the most effective ASM. This is particularly true of women with severe or profound ID, who would be unable to consent to sexual relationship and therefore would not be at risk of pregnancy. Furthermore, deterioration of seizure control in women who were switched from valproate to an alternative agent was reported in a survey of UK clinicians [8] and generalised tonic clonic seizures were more frequent in women who withdrew or changed valproate for an alternative agent, compared to those who remained on the drug during pregnancy [11]. Poor seizure control is associated with reduced quality of life, risk of injury from seizures and, of particular importance, sudden unexpected death in epilepsy (SUDEP) [12]. The risks of inadequate seizure control during pregnancy, both to the woman and the foetus, are significant and include maternal death, SUDEP, intrauterine growth retardation, and preterm delivery [13]. Whilst overall maternal death rates have fallen in the UK, the MBRRACE report "Confidential Enquiries in Maternal Death and Morbidity 2016–18" [14] specifically mentions a small but significant increase in the number of maternal deaths due to SUDEP. The aim should therefore be on safe, informed prescribing of valproate rather than further restrictions to its licencing indications.

One of the concerns raised by clinicians participating in the audit was difficulties identifying women on valproate, particularly at specialist centres where clinicians do not directly prescribe the drug. In a recent survey of neurologists at a UK tertiary referral centre (National Hospital for Neurology and Neurosurgery, unpublished service evaluation), only two thirds of the clinicians with patients on valproate had a means of identifying them. A UK wide register of women of childbearing potential prescribed valproate has been requested for several years by clinicians participating in the VSN, to help identify women on valproate, who will need annual reviews. NHS Digital (which is the national provider of information, data and IT systems within the National Health Service in UK) has been working with MHRA to develop a registry and the first report from the Medicines in Pregnancy Registry: Valproate use in females aged 0 to 54 in England (April 2018 to September 2020) was published in February 2021 [15]. The report highlighted a reduction in valproate prescriptions in the cohort but also showed that 462 women prescribed valproate during that period had become pregnant. Although the registry is a step in the right direction, in its current form, it will still not allow identification of individual patients to facilitate annual reviews and enable further research and learning, particularly regarding those who conceive whilst taking valproate. There needs to be a way to link the register to treating clinicians in order to overcome this problem. In the summer of 2021, NHS England and NHS Improvement sent a letter to all women and girls aged 12 and over who had a current prescription for valproate, highlighting the risks to the unborn child if valproate was taken during pregnancy, the need to comply with the PPP and have a specialist review (https://www.england.nhs.uk/publication/letter-to-women-and-girls-taking-sodium-valproate/). However, even if women are identified and referred for specialist review, an audit from another UK centre found that up to 10% of women do not attend their appointment to review valproate treatment, highlighting that patient identification is only part of the problem [16].

This audit identified a higher-than-expected proportion of women with a diagnosis of focal epilepsy being prescribed valproate (22.5%). For patients with focal epilepsies as a group, valproate is often not the most effective treatment [17]. These women should have the opportunity to be involved in a careful discussion about their treatment with the possibility of switching treatment carefully explored. Nevertheless, it must not be automatically assumed that valproate can be switched in favour of another ASM. Some women will have tried several other treatments for focal epilepsy and found that valproate is the most effective drug for them as individuals. Conversely, there will be some women who continue to have focal seizures while taking valproate, and a review from a specialist may lead to improved treatment, particularly for women who have not tried one of the newer ASM. We do not know if the women with focal epilepsy in the audit had tried other ASM and found that valproate was the most effective drug for them. The MHRA review of the safety in pregnancy of other ASM, published in January 2021 [18], will facilitate discussions on risks associated with alternative drugs. Further, there are often concerns regarding breakthrough seizures when any ASM is withdrawn or altered in a person who is seizure-free, and a proportion of patients with seizure recurrence do not regain the previous level of control [19].

Amongst the comments raised by clinicians participating in the audit were concerns about difficulties managing valproate treatment in women with ID. People with ID are more likely to have refractory

epilepsy but there is only limited specific guidance on epilepsy treatment in this group of patients [20]. Women with ID may also be more likely to be prescribed valproate in view of potential beneficial effects on mood and behaviour, particularly if the chance of pregnancy is deemed to be low; around a third of women in a previous audit on MHRA valproate regulations compliance had ID [16]. Although the ARAF has been amended to accommodate the scenario where the PPP is not deemed appropriate or necessary, further guidance was requested for this group of women, an issue that has been raised by other groups previously [21]. A specific concern raised related to women living in residential care, particularly when attending appointments with carers who might not know the patient well and could not make decisions for them or sign the ARAF.

Other comments related to the paper version of the ARAF. Clinicians commented on the difficulties in getting a signed ARAF returned from patients following virtual clinics performed during the pandemic. A digital ARAF, that could be completed and subsequently be available online for all involved in each patient's care (including the specialist doctor or nurse, prescribing GP, and dispensing pharmacist) would remove this obstacle and improve safety. The need for a digital ARAF has been raised by UK clinicians participating in the VSN. NHS Digital are currently working on a solution. However, progress has been slow and no date has yet been provided on when this will become available.

There are several limitations with the audit. The invitation to participate was sent out to all members of the ABN and ESNA, with replies received from 26 centres only. Most of the replies were received from departments rather than individuals. Still, the number of neuroscience centres and district general hospitals with neurology provision in England is nearly 120, suggesting that most centres did not participate. If we estimate from the valproate prescribing data that 19 695 women (aged 16–54 years) are prescribed valproate in a given month, that means that the audit included 5.9% of women prescribed valproate. The audit was carried out during the second wave of COVID-19, with many clinicians being redeployed to alternative clinical activities or working from home, with, for example, limited access to physical notes which may have reduced the number of participants. Further, most of the replies were from epilepsy specialists, who are likely to be more aware of valproate guidelines. This may bias results, with the real spectrum of practice potentially being even less satisfactory as non-specialists may not be fully aware of the guidance and may be less easily able to identify their patients on valproate. Continued national awareness campaigns and strategies to engage healthcare professionals ranging from GPs, sexual health clinicians, specialist nurses and neurologists to pharmacists, as well as patients themselves, are needed to improve safe prescribing.

5. Conclusion

Although information about risks and need for effective contraception had been made available for most women, there were still individuals where this was not documented and only two thirds had an ARAF completed in the last year, suggesting that further efforts need to be made to improve compliance with the MHRA valproate guidelines. Based on the findings, and comments from participants, we urge the MHRA to rapidly implement and modify the valproate register to facilitate the identification of patients and NHS Digital to prioritise implementation of a digital ARAF and similar measures should be sought in other countries. For clinicians, the audit highlights a particular opportunity to engage patients who have focal epilepsy. Careful discussion of the continued use of valproate can significantly improve the care of women with epilepsy, both from a seizure control and pregnancy perspective. Digital solutions should make it easier for clinicians to identify patients on valproate, record their wishes, level of knowledge of the risks of valproate and contraceptive status. Ultimately, the aim should be to use the PPP to establish a therapeutic partnership between patient and clinician that reduces risk and enhances patient choice. There is clearly much work left to be done and progress has been slower than patient groups and clinicians would have liked. However, there is a willingness on the part of the entire epilepsy community to address this issue. A further audit, following the introduction of the digital ARAF and more comprehensive valproate register, would be helpful.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

SHE has received speaker honoraria from UCB, Eisai and Lincoln Pharma; served on advisory board for Eisai and received funding for educational activities from Fidia, Lincoln and UCB pharma.

SMS has received speaker honoraria from UCB, Eisai and Zogenix; and served on advisory boards, consulted or spoken at sponsored events for Eisai, GW Pharma, Stoke Therapeutics and Zogenix events, with all funding to the institution; and received institutional research support from UCB.

PT has received Speaker fees from UCB Pharma, Eisai, Bial; funding for other educational activities from Veriton, GW Pharma and Honoraria or consultation fees from Arvelle, Sanofi.

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PT has received Speaker fees from UCB Pharma, Eisai, Bial; funding for other educational activities from Veriton, GW Pharma and Honoraria or consultation fees from Arvelle, Sanofi.

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