J R Coll Physicians Edinb 2020; 50: 114–7 | doi: 10.4997/JRCPE.2020.207 ORIGINAL RESEARCH PAPER

Is the Medicines and Healthcare products Regulator Agency (MHRA) guidance on sodium valproate acceptable to women of childbearing age?

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Abstract

Background: The UK Medicines and Healthcare products Regulatory Agency (MHRA) published guidelines restricting the use of sodium valproate in women of childbearing age unless they consented to the pregnancy prevention programme (PPP), receiving counselling by an epilepsy specialist, or meeting exclusion criteria.

Method: We contacted every woman of childbearing age on valproate for epilepsy in NHS Tayside (122).

Results: Seventeen out of 122 (13.9%) responded to the initial invitation to attend, and 25 out of 122 (20.4%) responded to a letter sent to their GP. Twenty-five attended, 21 completed a consent form, seven switched to another drug and three attended to express dissatisfaction with the MHRA guidance. There were 53 patients identified with learning difficulties. Consent was only taken from three patients, with carers declining to sign consent because the patient was not sexually active.

Conclusion: Our study suggests that patients and carers do not wish to stop valproate or engage in PPP despite being made aware of MHRA guidance.

Keywords: sodium valproate, pregnancy, MHRA, PPP teratogenicity

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Introduction

Sodium valproate is well recognised as teratogenic, with reports from the early 1980s describing increased rates of spina bifida in children born to women with epilepsy (WWE) taking sodium valproate during pregnancy.[1–3] Subsequent reports identified pregnancy-related complications that included neural tube defects, cleft lip and palate, congenital heart defects or learning disabilities such as autism spectrum disorder (ASD).[4–9] The UK and Ireland epilepsy and pregnancy register reported the risk of major congenital malformations to the fetus when exposed to sodium valproate in utero was 6.7% (95% CI 5.5–8.3%).[10]

The Medicines and Healthcare products Regulatory Agency (MHRA) in the United Kingdom is a government agency that regulates medicines, medical devices and blood components for transfusion in the UK. Their patient guidance suggests that 10 in every 100 pregnancies in WWE on valproate will have a major congenital defect and 30—40 in every 100 will have developmental and learning difficulties (LD).[11]

In April 2018, the MHRA published guidelines, based on restrictions by the Pharmacovigilance Risk Assessment Committee (PRAC) of the European Medicines Agency, that restricted use of sodium valproate in women of childbearing age unless they had consented to the pregnancy prevention programme (PPP) and received preconception counselling on the teratogenic effects of sodium valproate by a clinician with an interest in epilepsy (with a risk assessment form to be completed annually thereafter), or if they met certain

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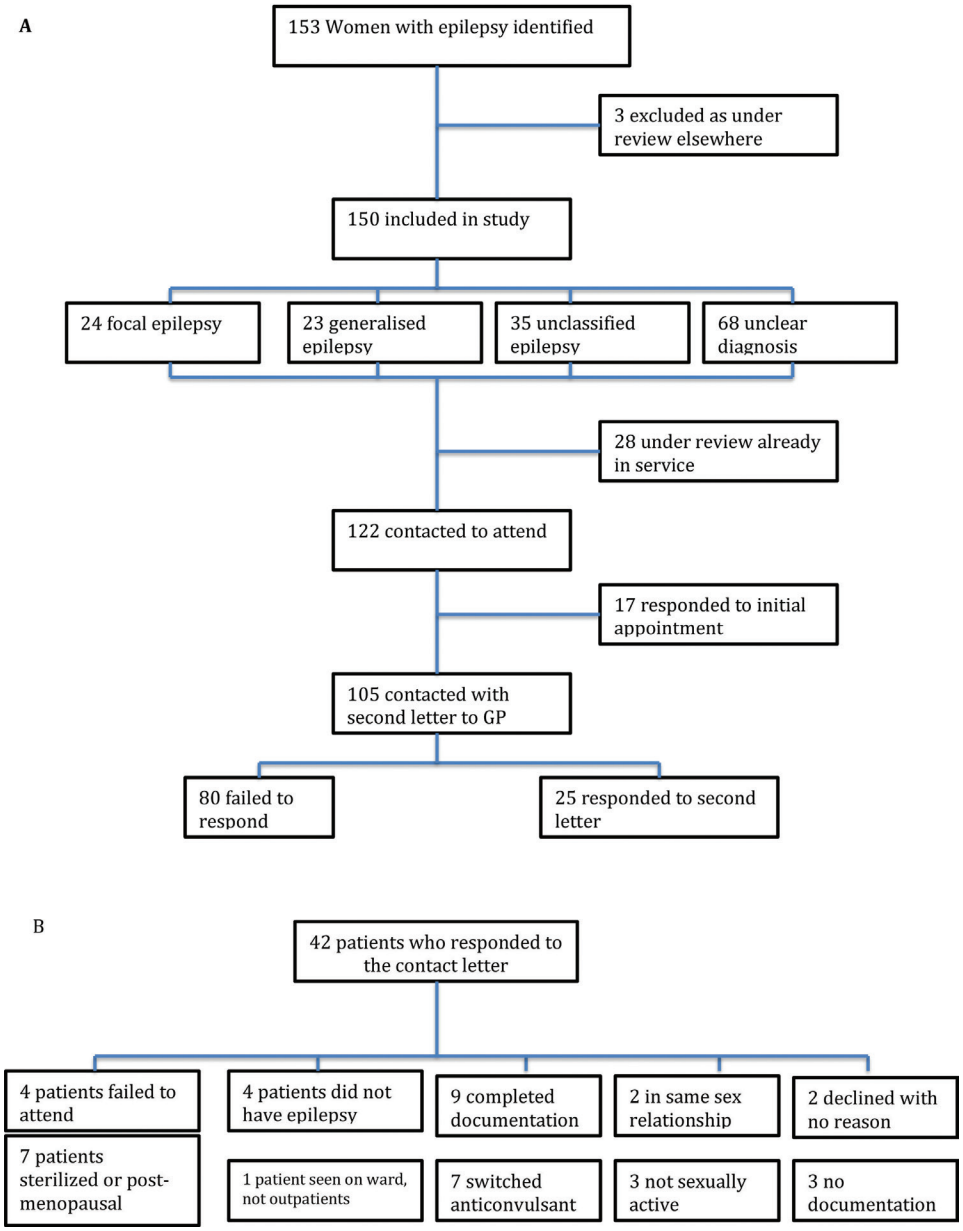

Figure 1 (a) Response to contacting patients to attend clinic. (b) Outcomes of patients who attended appointment.

exclusion criteria (appendix 1 – online only). PPP includes using an effective long-term contraception such as a coil (copper intrauterine device [IUD] or levonorgestrel intrauterine system), or a contraceptive implant (progestogen-only implant) or sterilization.[12]

Methods

NHS Tayside is a Scottish health board covering a population of 415,470 in both rural and urban settings. A local audit from 2014 identified 2,190 patients who received an anticonvulsant drug for epilepsy, of whom 1,437 (65%) were aged between 16 and 64 (50.7% female).

Using a pre-existing database in NHS Tayside (Database of Epilepsy Outcomes in Tayside – DEPOTS) and general practitioner (GP) prescription records, the authors identified all women of childbearing age with epilepsy who were prescribed sodium valproate in NHS Tayside, including those not previously known to the epilepsy service. A letter explaining MHRA guidance was sent in September 2018 to this group and their GPs, with an invitation to attend a specialist clinic to discuss the guidance (appendix 2 – online only). Clinics were available at least once a week throughout January 2019 and patients could book a time that was convenient for them. A second letter was sent in November/December 2018 to the GPs of those who didn't respond to the original letter (appendix 3 – online only). This letter included a recommendation that GPs should not stop sodium valproate without seeking specialist advice. Once a WWE attended clinic, she spent at least half an hour with an epilepsy specialist nurse (ESN) to discuss issues of pregnancy, teratogenicity and contraception, with a consultant neurologist attending in the latter stages of the consultation to reiterate advice and obtain the appropriate consent.

This study was an audit of routine clinical care and therefore specific ethical approval was not necessary.

Results

One hundred and fifty-three WWE of child-bearing age were identified within this study (Figure 1). Fifty-three patients were diagnosed as having a learning disability (IQ less than 70). Three were excluded as they were under review elsewhere.

Of the remaining 150, 95 were previously known to the epilepsy service and were seen in the preceding five years in a specialist epilepsy clinic. Twenty-eight were under regular review and had been seen within the last year while 27 hadn't been seen by the service for the last five years.

There were 24 patients documented as having focal epilepsy, 23 had a generalised epilepsy disorder, 35 had unclassified epilepsy and the remaining diagnoses were not clear from the available documentation.

Twenty-eight patients had PPP counseling at a previous appointment and were not contacted. No letters were returned with an incorrect address. Eighty patients failed to respond to either the first or second letters.

Of the 42 patients who responded to the contact letter, four failed to attend despite booking an appointment, four did not have epilepsy on review and were taking valproate for other reasons (migraine) and seven were sterilised, had a hysterectomy or were postmenopausal.

A valproate safety checklist and consent form (see appendix 4 – online only) was completed by nine out of 42 WWE who attended the dedicated valproate clinic. Elsewhere, ten forms were completed during routine review by the ESN or consultant; one was completed by a GP and sent to the department, and one was obtained during an inpatient review.

Of the remaining WWE who attended the dedicated valproate clinic but didn't complete the consent form, seven out of 42 who were considered eligible elected to switch to another anticonvulsant drug; three out of 42 were not sexually active; two out of 42 were in a same-sex relationship with no plans to become pregnant; two out of 42 declined but offered no reason and no documentation was available for the remaining three patients.

Three WWE expressed dissatisfaction with the guidance. One patient was postmenopausal but had a son with an alleged valproate-related developmental delay, and two, who were in a same-sex relationship, felt the initial guidance was discriminatory.

Of the 53 patients identified with learning difficulties, 23 were not known to the service or under regular review and 12 had attended clinic in the last year. Only one out of 23 (4%) of those not under regular review responded to a request to attend clinic, with consent being obtained to continue valproate in that patient. Of the 12 under regular review, consent was obtained in two (16.7%) patients only. The carers or next of kin of the remaining patients declined to sign consent, with several explaining that the patient was not sexually active and therefore PPP was not appropriate in their opinion.

Discussion

Recent guidance from the MHRA suggests the prescription of sodium valproate in WWE of childbearing age should be restricted unless they comply with PPP. However, our study suggests that despite being told of the guidance and potential risks in pregnancy, the vast majority of women in this cohort chose not to engage in discussion about their medicine.

Our study was a retrospective review based on clinical practice and consequently was a pragmatic, 'real world' snapshot of a patient cohort using a well-established tool that is used to identify patients with epilepsy in routine clinical care. As a result, the study was limited by this approach and it proved challenging to examine other variables of potential interest including the co-prescription of other anticonvulsant drugs, seizure freedom, etc. We were also unable to identify the reasons why WWE chose not to attend the clinic. We attempted to address common causes for non-attendance by offering a range of potential appointments, providing information on why attendance was sought, and offering information to GPs to encourage attendance.

It is possible that patients were concerned that changing their anticonvulsant regime might cause an increased risk of seizure, with potential driving, lifestyle or occupational issues.

Complications of poorly controlled epilepsy in pregnancy are also well recognised, and may be a further factor. WWE have a ten-fold increased risk of maternal mortality during pregnancy compared to those without epilepsy,[7] and a lack of seizure control during pregnancy also increases the risk of other maternal complications such as haemorrhage, pre-eclampsia, placental abruption and preterm labour. Effective seizure control during pregnancy also limits potential fetal complications such as hypoxia, intrauterine growth restriction and stillbirth.[13] This is supported by Lawther et al., who published interviews with seven women on their experiences of preconception care whilst taking sodium valproate. Many women expressed concerns about balancing the risks to their health and those of their baby should they discontinue sodium valproate. Likewise, whilst fully being informed of the risks to their unborn child, some women taking sodium valproate felt it remained their choice to continue medication.[14]

The importance of seizure control to WWE was evident in our study of patients who attended clinic, with only seven electing to stop and switch to another anticonvulsant drug. Concerns about stopping valproate may also explain, albeit in part, the decision of the majority of WWE not to attend.

Our study also identified that the majority of carers of WWE who have LD felt MHRA guidance was not appropriate because they were not sexually active. Likewise, two women in same-sex relationships also expressed concern that MHRA guidance was inappropriate for them. This suggests that current guidance is

too broad ranging and may restrict the prescription of valproate unnecessarily in certain sub-groups of WWE.

Our study suggests that many WWE favour better seizure control and choice over complying with MHRA guidance, and parents or carers feel the guidance is not appropriate for WWE who have learning difficulties. Within the limitations of the study design, in our opinion, our study suggests that current MHRA guidance on the prescription of sodium valproate in WWE of child-bearing age needs to be revised to consider the needs and wishes of the patient cohort specifically, rather than focusing on the adverse outcomes in pregnancy. We suggest future guidance should recognise that while teratogenicity is devastating, most WWE spend only a small minority of their lives pregnant but the impact of their epilepsy can be felt on a daily basis.

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