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The impact and challenges of the 2018 MHRA statement on the use of sodium valproate in women of childbearing age during the first year of implementation, in a UK epilepsy centre

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Abstract

Purpose:

On 24/04/2018, the United Kingdom (UK) Medicines and Healthcare Products Regulatory Agency (MHRA) clarified previous policies by issuing a statement, that the use of sodium valproate is contraindicated in women of childbearing potential unless the conditions of a pregnancy prevention programme are met, and only if other treatments are ineffective or not tolerated. We evaluated the impact of this over the first year of implementation in a tertiary epilepsy centre.

Methods:

Cross-sectional study of all women under active follow up, or newly referred, of childbearing age (16-55 years), taking valproate for the treatment of epilepsy, over 12 months from 01/05/2018.

Results:

We identified 125 cases, with 31 newly referred in response to MHRA regulations. 9.6% of patients did not attend their appointment, 35.2% had a learning disability (LD), which in 19.2% was sufficiently severe that they could not consent to a sexual relationship. Patients with LD prescribed valproate were significantly younger, and more likely to have a focal or uncharacterised epilepsy than patients without LD. In 46.4% of patients, MHRA regulations were followed: women were already using highly active contraception (HAC), HAC was started, or valproate withdrawn. In 24.8% of cases, women elected to continue valproate, and were not willing to use HAC.

Conclusions:

In 53.6% of cases, MHRA regulations contraindicating the use valproate in women of childbearing potential could not be followed fully, due to lack of patient attendance, lack of applicability in severe LD, or ethical concerns relating to patient choice.

Introduction

Sodium valproate was first approved for use in the treatment of epilepsy in 1978. It has particular efficacy in the treatment of the genetic generalized epilepsies[1], where effective alternative treatments are limited. In 1980, a letter published in The Lancet raised concern about the teratogenic potential of valproate in animal models[2], and in 1982, a birth defects monitoring system in France detected a relatively high rate of sodium valproate use in mothers of children born with neural tube defects. A combination of features collectively termed fetal valproate syndrome was first described in a case series of seven children in 1984[3]. In 2004, a study of longer term developmental outcome of children born to mothers with epilepsy found a significantly lower verbal IQ in those whose mothers were taking sodium valproate[4]. These findings were confirmed in several subsequent studies, in which a range of neuro-developmental problems, such as autism and developmental delay were causally linked to maternal use of sodium valproate during pregnancy. Recent estimates put the total prevalence of neuro-developmental problems in children exposed to sodium valproate *in utero* at up to 40% [5; 6; 7; 8].

In France a class action lawsuit was filed in 2017 against Sanofi-Aventis, manufacturers of Depakine, by the *'Association d'Aide aux Parents d'Enfants souffrant du Syndrome de l'Anti-Convulsivant'*, and it was projected that compensation costs for Depakine victims could exceed 400 million Euros (£340 m, $450 m)[9]. Subsequently, the French national agency for the safety of medicines and healthcare products issued a ban on the use of valproate in pregnancy in women with bipolar disorder, and in February 2018, the European Medicines Agency recommended that valproate should only be used in women of childbearing age if they have epilepsy that does not respond to other antiepileptic drugs, and if they are enrolled in a pregnancy prevention programme ('Prevent'). In the UK, this was endorsed by legally binding guidelines issued by the Medicines and Healthcare Products Regulatory Agency (MHRA) in April 2018.

The MHRA's valproate-related 'Prevent' programme includes the requirement only to use valproate in women of childbearing potential, if other treatments are ineffective or not tolerated, and to enforce the use of 'highly active contraception' (HAC) while such women take valproate. The 'Prevent' guidance for health professionals stipulates that HAC needs to be a user independent methods such as a intrauterine device (IUD or IUS), progestogen-only implant and female sterilisation, all of which have a failure rate of less than 1%. The progesterone-only injectable is highly effective with perfect use, but with typical use, there is a failure rate of 6 pregnancies per 100 women per year, probably related to lack of compliance with the 3-monthly interval required. The only exception to this restriction in the MHRA guidelines is when the physician considers 'that there are compelling reasons to believe that there is no risk of pregnancy'. The regulatory measures also include '… a ban on the use of valproate to treat epilepsy during pregnancy unless there is no other effective treatment available'. Women of child-bearing potential who are taking sodium valproate are required to have yearly specialist review, in which they sign an annual risk assessment form intended to confirm compliance with all conditions of the 'Prevent' programme.

The introduction of these regulations led to difficulties in the clinic, which were highlighted in an open letter, signed by many epileptologists, and published in the BMJ[10]. The authors provided examples of special circumstances (such as status epilepticus, and severe learning disability), which they felt should be considered an exception to the regulations. They expressed concern that cessation of sodium valproate in women for whom this provides good seizure control carries a risk of recurrence of seizures, with their serious complications of sudden unexpected death in epilepsy

(SUDEP), status epilepticus and injury, and of adverse social consequences, particularly loss of eligibility to drive. In March 2019, a document was produced by Shakespeare and Sisodiya, which aimed to provide practical information and guidance regarding the application of the MHRA regulations[11]. It was endorsed by several of the Royal Colleges, the Association of British Neurologists and other professional bodies in the UK and addressed many of the challenging situations faced by clinicians, when trying to balance the requirement to act in their patient's best interests, whilst seeking to limit the potential harm from a pregnancy exposed to sodium valproate.

The current study aims to determine the impact of the 2018 MHRA regulations on the prescribing of sodium valproate to women of childbearing potential, over first year of their use, in a tertiary UK epilepsy referral centre. We aimed to quantify the impact of the regulations on the service; their effect on patient management - the proportion of patients who changed treatment or who started HAC; and to determine both quantitatively and qualitatively, the extent of ethical and clinical dilemmas posed by the application of the 'Prevent' programme.

Methods

Study population

The reference population comprised all patients with epilepsy (aged ≥ 16 years) in South Yorkshire, North Derbyshire and North Nottinghamshire. This area is covered by neurology services based in Sheffield, which operates a hub and spoke system to serve surrounding district general hospitals. The total population within this catchment is approximately 1.8 million. The Sheffield-based service is the only adult neurology service provider in this region. Patients living outside this geographical area, or still under the care of paediatric services were excluded from the study. The adult neurology service received 1,940 new referrals over the one-year study period.

Case identification

From this reference population we identified women of childbearing age, who were taking valproate as an anti-epileptic drug (AED), and who were offered a new or follow-up neurology clinic appointment between 01/05/2018 and 30/04/2019. The MHRA regulations do not stipulate an age range that is considered to be childbearing. For the purpose of this study, we defined it as 16-55, the lower limit being the youngest age covered by adult services, and the upper age limit is the age at which 95% of women have gone through the menopause. Pregnancies after the age of 50 are extremely rare[12]. Cases were ascertained by multiple overlapping methods. The primary method was a text search of all outpatient clinic letters generated by consultant neurologists with a specialist interest in epilepsy, within the study period, for the words 'Epilim' and 'valproate' (109 patients). The clinic referral letters for women between the ages of 16 and 55 who failed to attend their clinic appointment were obtained to establish whether the referral was made to address MHRA regulations (6 patients). These screening methods were cross-referenced with the database of patients who were referred for discussion at an epilepsy consultant team meeting, which was established to provide peer support for cases in which the MHRA regulations were difficult to apply (25 patients), and with the pre-existing Epilepsy Specialist Nurse database of women taking valproate (33 patients seen by the epilepsy services during the study period). All but 2 patients referred to the epilepsy consultant team meeting had also been ascertained by clinic letter screening (these 2 patients were seen by non-epileptologists in a district general hospital). Of patients identified from the epilepsy nurse screening list, 14 had not been identified by screening of clinic

letters. All were follow-up patients. In 4 cases, this was because the patients were seen in a general neurology clinic in a district general hospital, and in the remaining cases, because valproate was not mentioned in the latest clinic letter. The omission of this information appeared on review of the cases to be because the risk of pregnancy was considered low, either due to patient age (6 patients over age of 45), lack of a sexual partner (due to the presence of severe learning disability or learning disability with constant supervision, 4 patients) or in two cases, because patients had been sterilised.

Data collection

Cases were anonymised by allocation of a study number, and the following data collected: Age at consultation; new/ follow-up appointment; source and purpose of referral (new patients only), whether patient attended, total daily dose of valproate, length of treatment with valproate, indication for treatment (focal or generalised epilepsy); presence and degree of learning disability; whether or not patient was sexually active; contraception used; intention for pregnancy; and outcome of the consultation. In patients with a learning disability, whether or not they had capacity to consent to a sexual relationship was determined by the consulting physician, and documented in the clinical correspondence, or on the MHRA risk assessment form.

Statistical analysis

Descriptive statistics was produced using Microsoft Excel. Statistical analysis was performed using GraphPad Prism software.

Ethical approval

The study was registered with and approved as a service evaluation by the Clinical Effectiveness Unit, Sheffield University Hospitals NHS Foundation Trust.

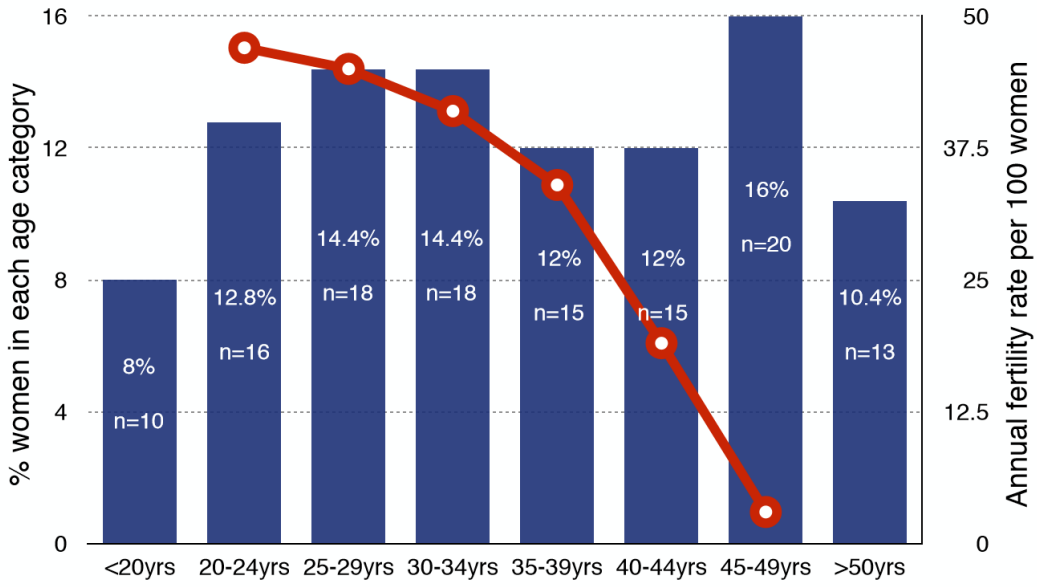
Results

Study population

The age distribution of the 125 patients who met our inclusion criteria is shown in Figure 1. Of those identified, 47 (37.6%) were new referrals, with the majority (31, 24.8% of total population) being from general practice in order to fulfil the requirements of the MHRA regulations. 12 patients (9.6%) fulfilled the inclusion criteria but did not attend their appointment.

Figure 1:

Bar chart to show the number and percentage of patients seen in 5-year age categories. The superimposed line graph shows the annual fertility rates per 100 women (adapted from NICE CG156[13])



Learning disability in patients taking sodium valproate

Of the 113 women who attended their appointment, 44 (38.2%) had a documented learning disability (LD). In 24 patients, this was deemed sufficient for them not to have capacity to consent to a sexual relationship, and the MHRA regulations were not applied, as this is a compelling reason to believe that there is no risk of pregnancy.

The indication for and use of sodium valproate differed between patients with and without learning disability (see table 1). Women on valproate without LD, were significantly older than those with LD. They were significantly more likely to have a diagnosis of generalised epilepsy, and to have a characterised and documented epilepsy subtype. There was a non-significant trend toward valproate being used more commonly in monotherapy in the non-LD group, but no significant differences between the two groups in the dose of valproate taken.

Table 1: Characteristics of women taking valproate, categorised by presence or absence of learning disability

		Learning disability	No learning disability	Analysis of group differences
Mean age		32.1	37.8	p=0.005 (Unpaired t test)
Mean valproate dose		1,305 mg	1,455 mg	p=0.27 (Unpaired t test)
Valproate dose range		100-2800 mg	200-3000 mg	
		No. (%) patients	No. (%) patients	
Valproate monotherapy		13 (29.5)	33 (47.8)	p=0.056 (Chi square)
Indication	Generalised epilepsy	10 (22.7)	53 (76.8)	p<0.0001 (Chi square)
	Focal epilepsy	16 (36.4)	8 (11.6)	
	Unknown / not documented	18 (40.9)	8 (11.6)	

Patient management decisions

Of the 89 women who attended their appointment and had capacity to consent to a sexual relationship, 31 (34.8%) were already using HAC, had been sterilized, had had a hysterectomy, were in a stable monogamous relationship with a vasectomized partner, or were post-menopausal.

In 27 women (30.3%), management was changed in line with the MHRA regulations. In 8 cases (8.9%), women agreed to start using HAC, as defined by the MHRA. Three of these women had a degree of LD, of which two were not sexually active, and in the third, the occurrence of probable sexual exploitation by strangers was disclosed in the consultation. In two cases, an adverse outcome of the use of HAC was documented: one woman was very upset by the conversation which adversely affected the relationship with her neurologist, the other was distressed about having an IUD placed, and subsequently developed non-epileptic attacks. In 19 cases (21.3%), women elected to withdraw from valproate, and in 14 of these, this decision was documented to be at least in part due to concerns about teratogenicity. Four of the women changing from valproate to reduce risk in pregnancy were planning a pregnancy in the near future.

In 31 patients (34.8%), patient management did not follow the MHRA regulations. These patients continued to take sodium valproate, without enrolment in the 'Prevent' programme. In 3 cases, no reason for this was documented in the clinical notes, and the risk assessment form was not completed. All three patients were under long term follow up by the epilepsy services, had been taking valproate for many years, and were over the age of 40. In 10 (11.2%) women, the risk of pregnancy was deemed to be very low because they were not sexually active and under constant supervision related to mild to moderate learning disability, and it was agreed between the neurologist, patient and carer that they would not start HAC.

In 18 cases, women declined to use HAC, or to change medication. The reasons for this, where documented, were variable and included a lack of efficacy of other medications, long term stability on sodium valproate and concern by the patient about the impact on driving, or risk of seizures; or an unwillingness to risk side effects from changing medication. Women declined to take HAC for a number of reasons. Seven were happy using other forms of contraception (barrier methods or OCP); one had primary infertility and was approaching the menopause. Eight patients were sexually inactive, and therefore saw no need or had no desire to enrol in a pregnancy prevention programme. One woman was already pregnant when seen, and had had a previous successful pregnancy on Epilim (800mg / day); another was planning a pregnancy, and taking high dose sodium valproate for genetic generalised epilepsy, despite having had a previous pregnancy in which the child was affected by fetal valproate syndrome.

Characteristics of the patients and management strategies are summarised in table 2. Patients in whom an active management decision was made in accordance with the MHRA regulations (to stop valproate, or start HAC) had a lower mean age than women already taking HAC, and women for whom MHRA regulations were not followed ($p=0.0087$, one-way ANOVA). A higher proportion of these women were new patient referrals to the service ($p=0.0125$, Chi-squared).

Table 2: Characteristics of patients according to management decisions

		Number (%)			Mean age	% New patients
MHRA regulations followed	Valproate stopped	19	(21.3)	58 (65.1)	31.9	62.9%
	Started HAC	8	(8.9)			
	Already using HAC	31	(34.8)		40.5	25.8 %
MHRA regulations not followed	LD under constant supervision	10	(11.2)	31 (34.8)	37.4	22.3%
	Declined HAC	18	(20.2)			
	MHRA regulations not addressed	3	(3.4)			

Patients specifically referred for the MHRA risk assessment process

The 31 patients who were newly referred to the service specifically to address the MHRA regulations represented 1.6% of the 1,940 patients referred to the epilepsy service over this period. Of these, 8 (25.8%) did not attend the appointment. Of the 23 patients who attended, 3 (13.0%) had learning disability without capacity to consent, 4 (17.4%) were already using HAC, and 6 (26.0%) declined to use it, despite continuing valproate. In 10 patients (43.4%), management was changed, with 3 women starting HAC, and 7 stopping valproate.

Limitations

Although several approaches were taken to ensure that all women on valproate of childbearing age, seen by the epilepsy services, were identified for the study, it is likely that some cases, particularly those under long-term follow up in district general hospitals by non-epileptologists, were missed by our collection methods. Given that multiple complementary methods were used to identify cases and that we are unaware how many patients in total (or how many patients with epilepsy) are under the care of our regional neurology service, we can only provide approximate information about the size of the reference population by referring to the whole population our services serves.

We relied on clinical documentation to determine the level of learning disability, the reasons for changes in management and the reasons for non-compliance with MHRA regulations. The decisions made in these cases are complex, and their interpretation and classification for the purpose of this study may therefore have been susceptible to bias on the part of the investigators. As this was a cross-sectional study, no information was collected, for example, about the consequences of stopping valproate, in those women who did so, which would require a follow-up study.

Discussion

This study evaluated the impact and practical consequences of implementing the 2018 MHRA regulations regarding the prescribing of sodium valproate in women of childbearing age. We found that the regulation led to an increase in the number of new referrals to a tertiary epilepsy service in the north of England, by 1.6% in the first year of implementation, with 25% of new patients referred to address the regulations, not attending their appointment. A recent audit[14] of 80 General Practices (GP) in the Sheffield area, covering an approximate population of 609,000 patients, carried out over a 6 month period from Jan to July 2019, identified 115 women of childbearing potential taking sodium valproate for epilepsy, of which only 54 (47%) were under the care of a Sheffield Hospital Trust, and only 42 (37%) had been reviewed by a specialist since April 2018. The number of cases identified in this audit (1 woman of childbearing age on sodium valproate for epilepsy per 5,300 population, 1 woman per 14,300 population reviewed within the last year) suggests that case ascertainment in our study was relatively complete. The finding that only just over 1/3 of patients who should have been reviewed by a specialist had been seen within the last year shows that, in the event of 100% compliance with the regulations, the demand on our service would have increased by nearly 5%.

We found that 38% of women taking sodium valproate during the study period had a learning disability, which is very similar to the finding in the audit of Sheffield GPs, in which 32% of women on valproate for epilepsy were on the learning disability register. Women on valproate with a LD were younger than those without, most likely due to a reluctance to use valproate in women without LD when they are of childbearing age. Women with LD were also significantly more likely to be taking valproate for a focal or unclassified epilepsy syndrome. Possible explanations for this include a higher prevalence of focal epilepsy in the LD population; in those with a low likelihood of childbearing, valproate may be used in preference to other antiepileptic medications, as it may have positive effects on psychiatric comorbidities, more common in this population, and a lower incidence of behavioural side effects seen than with some of the newer antiepileptic drugs; where valproate was started many years ago, when the formulary was more restricted, patients with LD with a low probability of pregnancy may also have been less likely to change to newer licensed medications, if seizure control was adequate.

In over one half (53.6%) of the women taking valproate for epilepsy in our study, the MHRA regulations could not be, or were not followed. 9.6% of patients did not attend their appointment, and the risk assessment process could not therefore be completed by the specialist. The 2018 MHRA regulations did not provide guidance as to how to manage those patients who decline specialist review. The Shakespeare and Sisodiya guidance document emphasizes the importance of good communication between the specialist, GP and patient in this circumstance, and of proactively attempting to encourage attendance[11]. However, ultimately the prescriber will need to make a decision about the further management, and how to resolve the potential conflict between legal and ethical considerations: while the MHRA regulations mean that valproate would be prescribed off licence if the 'Prevent' programme had not been followed, it may be unethical (and possibly illegal) to withhold an effective antiepileptic drug treatment from a woman with epilepsy who wants to continue to take valproate without taking HAC.

In the LD population, the decision that HAC as defined in the 'Prevent' guidelines was not required was straightforward in just over half of all cases because patients were not sexually active, requiring permanent care and lacked capacity to consent to a sexual relationship. However, the spectrum of

severity of disability meant that there were grey cases in whom it is far less clear whether a patient could consent to intercourse. Even when capacity is deemed to be absent, this does not mean that intercourse will not occur, as was the case in one patient in this study, who was probably a victim of sexual exploitation uncovered by the application of the 'Prevent' procedure. Non-abusive sexual relationships may also occur, for example, among service users at care facilities, and these cases can lead to ethical and practical difficulties in applying the MHRA regulations. In 11% of patients in our study, a discussion of these risks and a consideration of the level of supervision and social contact of the woman taking valproate resulted in the joint decision of the neurologist and carer/ patient that the risk of pregnancy was sufficiently low that the 'Prevent' programme need not apply. There has been considerable debate around the issue of the blanket application of MHRA guidance especially in special populations such as the LD population[15; 16]

In 14% of cases, the lack of compliance with the 'Prevent' programme resulted from simple patient choice, in women who understood the teratogenic risks of sodium valproate and elected to continue to take it, off licence, without the use of HAC. The ethical difficulties posed by these consultations was reduced by the publication of the Shakespeare and Sisodiya guidance document, which highlights that women's own views should be taken into account when making this decision, and emphasized the importance of the GMC consent process in applying the MHRA regulations, that 'you must respect a patient's decision to refuse a … treatment, even if your think their decision is wrong or irrational'. They also state that 'even if a woman is non-compliant with 'Prevent', it is unsafe to withhold the prescription of valproate'[11]. Nevertheless, while these principles of consent are clear when a patient is making a decision from which they may come to harm, they are ethically more challenging when harm may caused to another, as in the case of teratogenicity.

Approximately 1/3 of the study population were already using HAC, or did not have childbearing potential for another reason. The use of HAC is, of course, not the only requirement of 'Prevent', as it is also necessary to confirm that other antiepileptics are ineffective or not tolerated. As this was a retrospective study, it was not possible in many cases to confirm whether this requirement was fulfilled, and it is not clear in the risk assessment process how many other treatments need to have been trialled before valproate is accepted as the most effective or best-tolerated drug. The teratogenic potential of valproate has been recognised for over 35 years. Valproate has also been linked to the risk of polycystic ovarian syndrome and hypofertility[17]. It was therefore uncommon for women in our study population to be taking valproate without either a diagnosis of genetic generalized epilepsy, or refractory epilepsy (only 13 patients were taking valproate as monotherapy for an epilepsy of unknown or focal onset).

The management of 30% of women in the study was changed in line with the MHRA regulations, and this proportion was higher in patients referred specifically to address the regulations. A limitation of this study is that we cannot say how often the antiseizure medicine of these women would have been similarly altered in the absence of the introduction of the regulations. For many years, it has been usual practice for neurologists to change women of childbearing age from valproate to an alternative antiepileptic if possible, particularly if they are planning a pregnancy or if there is evidence of hypofertility or menstrual dysfunction[17]. In many of the patients who stopped taking valproate in this study, the decision took into account other factors, not only teratogenicity, but also efficacy, side effects and seizure frequency. Valproate has potential long-term health consequences, as it is often associated with substantial weight changes that may increase morbidities, such as hyperinsulinemia/insulin resistance, dyslipidemia, polycystic ovary and metabolic syndrome that are associated with long-term vascular complications and reduced fertility. In a minority of patients, the risks of valproate in pregnancy played no role in the decision to switch, as the patient was at low risk

of pregnancy. Relatively few patients in this study elected to start HAC. This may reflect the many factors that women take into account in deciding the form of contraception that suits them, that the majority of women who wished to prevent a pregnancy on valproate had already taken measures to do so, or women having a higher level of personal confidence in the reliability of more 'user-dependent' contraceptive methods than is suggested by population-based studies.

The authors' subjective experiences of the first year of implementation of the MHRA 'Prevent' programme were that the original 2018 regulations were difficult to apply in practice, provoking many ethical dilemmas, challenging consultations and distress on the part of patients and physicians. Over the period of this study, two changes were introduced, in the form of a second edition of the annual risk assessment form , which enabled the exclusion of some patients from the programme as a whole, and the production of the document by Shakespeare and Sisodiya, which provided clarification and guidance about the practical application of the regulations[11]. This study provides data supporting our perception that the regulations could not be applied to a significant proportion of our patients, in many cases simply due to the principle of patient choice. However, some patients, particularly those identified by the GP screening programme and referred for medical review, did change their management to reduce the risk of a valproate-affected pregnancy. Several studies have looked at the changing patterns of valproate use over time, and noted reductions in frequency of prescriptions for this medication in women of childbearing potential in response to measures to raise awareness of its risks[18; 19; 20], and it remains to be seen whether the recent MHRA regulations will have a similar beneficial effect. The process of 'retrospectively' completing the risk assessment process with women, 40% of whom were over the age of 40, and therefore coming to the end of their childbearing years, has been a resource-intensive, and often difficult process. The requirement for annual specialist of all women of childbearing age receiving valproate within the 'Prevent' programme will represent an additional burden on epilepsy services in the UK. However, in the future, as this process becomes embedded in practice, it should ensure that the pregnancy-related risks of valproate, and how to reduce affected pregnancies, are at the forefront of every discussion about introducing it as a treatment.

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