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Valproate risk form - surveying 215 clinicians involving 4775 encounters

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ABSTRACT

Objectives

Annual completion of a Valproate Risk Acknowledgement Form (RAF) is mandated in the United Kingdom due to neurodevelopmental risks of *in utero* valproate exposure. The number of women of childbearing potential taking valproate, the uptake of the RAF within this population and their clinical outcomes is not known or monitored. The aim of this study surveyed responses of clinicians administering the RAF to women of childbearing potential taking valproate medications.

Materials and Methods

• Study design - national online survey distributed to clinical specialists throughout the United Kingdom via their national organisations.

• Participants - clinicians qualified to counsel and administer the valproate RAF (as defined by the Medicines and Healthcare products Regulatory Agency).

• Main outcome measures – quantitative and qualitative responses regarding identification, uptake, effects and reactions to the RAF.

• Trial registration – registered at the Clinical Governance and Audit Committee at Royal Free London NHS Foundation Trust Hospital.

Results

215 respondents covering more than 4775 patient encounters were captured. Most patients continued on valproate, 90% with epilepsy as the indication. Respondents reported that seizure control deteriorated when switched to levetiracetam (33%) and lamotrigine (43%), compared to 7% when continuing valproate (P<.001).

Conclusions

33-43% of clinicians reported seizure control deterioration in women changed to alternatives to valproate. Informed consent requires women considering a change are given this information. Systematic

capture of data automated through online RAFs and linked to patient outcomes is needed. There remains little data on valproate given for indications other than epilepsy.

KEYWORDS

Valproate

Teratogenicity

congenital malformations

neurodevelopmental disability

Medicines and Healthcare products Regulatory Agency (MHRA)

Risk Acknowledgement Form (RAF)

Informed consent

INTRODUCTION

Valproate medications (valproic acid, sodium valproate, divalproex sodium and related compounds, trade names include Epilim and Depakote) are licenced for use in epilepsy, bipolar disorder and in some countries for migraine. They are the most effective treatment for idiopathic generalised epilepsies (genetic generalised epilepsies).[1,2] There are increasing restrictions of its use in many countries including United Kingdom (UK) because of concerns about teratogenicity and developmental problems in offspring exposed to valproate estimated at 10% and 40% respectively.[3] In the UK since 2018 the Medicines and Healthcare products Regulatory Agency (MHRA) mandate the completion of a valproate risk acknowledgement form (RAF) by an appropriate specialist in all females of childbearing potential who are taking valproate.[4] There are no studies evaluating implementation challenges, the uptake of this initiative and the views of patients and clinicians using the form.[5-7] The impact of changing from valproate to other medications, or avoiding valproate in females, has not been systematically assessed. This project surveyed clinicians responsible for identifying, reviewing, and counselling relevant patients, and administering the RAF.

MATERIALS and METHODS

The survey was drafted by two of the authors (HAL and MMM) taking into account key topic areas. It incorporated multiple choice and free text responses, there were 35 questions and it took 10-15 minutes to complete (online Appendix https://forms.gle/FQGRDBDCw2hLcMKq6). It was reviewed and modified by other authors and the Epilepsy Advisory Group of the Association of British Neurologists. Clinical diagnoses were defined as those ascribed by the responding clinicians. The Clinical Governance and Audit Committee at The Royal Free London NHS Foundation Trust Hospital approved and registered it. Distribution was through newsletters and websites of the Association of British Neurologists, the Epilepsy Specialist Nurse Association Intellectual Disability section of the Royal College of Psychiatry and the British Paediatric Neurology Association. The population were clinical professionals where consent was implicit by completing the questionnaire as confirmed by current guidelines.[8] The anonymous survey was carried out on Google Drive between April to July 2019. Data Handling was in accord with the Data Protection Act of 2018, incorporating General Data Protection Regulation guidance.[9]

Data Analysis

Descriptive and graphical analysis of data collected was performed to summarise key quantitative findings. Significance was measured using Chi square testing on the population as a whole. Subgroup

analysis into type of specialist and indication for valproate use was avoided because the numbers in some groups were too small for this to be meaningful. Qualitative data was analysed thematically following the steps outlined by Braun and Clarke.[10]

Patient Involvement

Requests from two patients gave the impetus to the study, and specific questions about the pregnancy related issues. The survey included questions about patient views on the RAF. A specific separate patient survey is underway.

RESULTS

The survey was completed by 215 specialist clinicians responsible for the prescription of valproate and/or completion of the MHRA risk acknowledgement form (RAF) for women of childbearing potential (WCP). They were consultant neurologists (119/215 55.3%; one third with special interest in epilepsy), consultant psychiatrists (48/215, 22.3%; half with intellectual disability special interest), consultant paediatricians (22/215, 10.2%), specialty doctors (9/215, 3.3%), epilepsy clinical nurse specialists (14/215, 6.5%), and general practitioners (3/215, 1.4%) with an average of 18 years experience prescribing sodium valproate (range 0-40 years; n=215).

Identification of Women of Childbearing Potential taking Valproate

Surveyed clinicians identified or estimated they had collectively completed a total of 4775 RAFs for women of childbearing potential taking or going to start valproate. Seven percent (16/215) of responders were unable to provide any estimate.

Healthcare professionals had identified relevant individuals using a range of methodologies: one third used clinic appointments alone (32.6%); record searches (17.2%) and pharmacy searches (1.9%) were used less frequently in isolation. 100 responders (46.5%) used a combination of identification methods, (Figure 1A).

87% (n=186) specified epilepsy as the diagnostic indication for valproate; this was further categorised into “epilepsy only” (67%), “epilepsy + intellectual disability” (24.2%), “epilepsy + bipolar disorder” (15.8%), “epilepsy + migraine” (11.2%) and “epilepsy + bipolar disorder + migraine” (3.3%). Migraine alone

was an indication in nine respondents (4.2%), bipolar disorder in 28 (13%), and other mood disorders in 22 (10.2%), (Supplemental Figure 1).

Completion of Risk Acknowledgement Form in WCP taking Valproate

42.8% of respondents (n=92) stated that "all" WCP taking valproate under their practice had a completed RAF in accordance with MHRA 2018 regulations; 30.7% stated "most" (n=66), 7.9% "about half" (n=17) and 7% "minority" (n=15). 6% (n=13) of clinicians responded "none", and 6% percent were "unsure" whether WCP taking valproate in their practice had been reviewed and had a RAF completed, (Figure 1B).

Outcomes Following Completion of RAF in WCP without ID taking Valproate

68.5% (n=137) of clinicians continued valproate in women of childbearing potential following completion of the RAF, with 25% reporting "all" WCP under their care continued valproate post-RAF (n= 50), (Figure 2A). Ten percent of clinicians reported that valproate was stopped in "all" patients following review (n=20), (Figure 2A). Over 70% of clinicians reported that "all" or "most" of the WCP weaned off valproate were changed to a new medication (n=68, 37.8% and n=60, 33.3%, respectively), (Figure 2B). Lamotrigine and levetiracetam were most frequently used when valproate replaced, (Figure 2C).

Clinician estimated outcomes for WCP continuing valproate (n=167) were compared with those changed to levetiracetam (n=97) or lamotrigine (n=108) following the RAF (Figure 2D). Continuing valproate was associated with significantly better symptom control (seizure control in almost all cases) than changing to levetiracetam or lamotrigine. 48% (n=80) of clinicians reported that WCP continuing on valproate were "seizure free", in contrast to 29% (n=28) and 20% (n=20) in patients changed to levetiracetam and lamotrigine, respectively (P<.05). 61% (n=102) of clinicians reported seizure rates to be "stable" amongst patients continuing valproate, in comparison to 49% (n=48) and 41% (n=44) on levetiracetam and lamotrigine, respectively. A deterioration in seizure control was reported more frequently by clinicians caring for WCP weaned off valproate and changed to levetiracetam (n=32, 33%) or lamotrigine (n=46, 43%), than in those continuing valproate (7%) (P<.001). Clinician-reported status epilepticus in WCP was rare and similar across all three medications. There was one reported epilepsy-related death, occurring in a patient continuing valproate (n=1, 1%), (Figure 2D).

Respondents reported 4-8% of patients experienced negative mood changes or other adverse events on changing medications (Figure 2D).

Outcomes following completion of RAF in WCP with intellectual disability (ID) taking Valproate

Similar patient outcomes were reported for WCP with ID following completion of the RAF (ID; Supplemental Figure 2). 80% (n=140) of clinicians surveyed stated that valproate was continued in "all" or "most" WCP with ID (Supplemental Figure 2A); comments indicate this was because it is "efficacious", keeping seizure rates stable in WCP that are generally "not sexually active" and/or under carer supervision. 42.5% of clinicians reported that "all" or "most" of the 10% of WCP under their care weaned off valproate were changed to a new medication (n=57; Supplemental Figure 2B); usually to lamotrigine or levetiracetam (Supplemental Figure 2C).

As reported by clinicians, continuing valproate was associated with more favourable epilepsy outcomes (seizure "free", "rate stable" or "incidence reduced") and "same" or "better" mood in WCP with ID compared to outcomes when changed to levetiracetam and lamotrigine; status epilepticus occurred in two patients switched to lamotrigine (4%, n=2). No pregnancies were reported in WCP with ID continuing valproate. Two pregnancies were reported in WCP with ID switched to levetiracetam or lamotrigine, (Supplemental Figure 2D). The outcome of these, and all pregnancies reported, is unknown.

Changes to contraception methods following completion of RAF in WCP

47% of clinicians stated that "highly" efficacious" contraception (intrauterine device or depot injections) did not replace pre-existing pregnancy prevention in any WCP without ID post-RAF completion (n=87). In WCP with ID, 61% of clinicians reported that none of their patients switched to "highly efficacious" contraception (n=91). 19% of clinicians reported that "all" of their patients with ID or their carers declined "highly efficacious" contraception (n=28), in contrast to 9% for WCP without ID (n=17), (Supplemental Figure 3).

Review of the Risk Acknowledgement Form

37% (n=80) of clinicians reported that patients were satisfied with the RAF, whilst 31% (n=66) reported patients were dissatisfied or strongly dissatisfied with the form, (Figure 3A). 40% (n=87) of clinicians were dissatisfied or strongly dissatisfied with the RAF, (Figure 3B). Clinician reported patient comments include that RAF is "time-consuming", a "tick-box exercise", "invasive", "marginalizing" and "feels weighted towards the patient in terms of accountability", (Table).

45% (n=97) of respondents "disagreed" or "strongly disagreed" that they had sufficient resources to identify WCP taking valproate for recall, in contrast 28% "disagreed" or "strongly disagreed" that they

had sufficient resources to deal with filling in the RAF (n=57), (Figure 3C). 49% (n=106) of clinicians reported annotating the RAF document more than half the time (Supplemental Figure 4A). 13.5% (n=29) of those surveyed reported using and/or producing additional resources to aid in reviewing WCP on valproate, principally easy read information leaflets/booklets, (Supplemental Figure 4B).

[Table about here]

DISCUSSION

Annual completion of the newly modified risk acknowledgement form (RAF) and enrolment in the pregnancy prevention programme (PPP) is now required for continued valproate prescription in the United Kingdom, and elsewhere. Patients must first be identified and reviewed. There is no standard procedure for this. Almost half of respondents used a combination of modalities for this process (Figure 1). Whilst manual record searches, pharmacy searches and appointments were most frequently used together, comments also indicate an increase in GP referrals and demands on outpatient clinics. Importantly, completion of the risk acknowledgement form is not universal amongst WCP on valproate; 6% of respondents were unsure of their patients' RAF completion status and only 43% stated the RAF had been completed in "all" of the WCP under their care (Figure 1).

MHRA guidance mandating the enrolment of WCP taking valproate onto a pregnancy prevention programme is a consequence of the recognised risk of foetal teratogenicity and neurodevelopmental disorders with *in utero* exposure to valproate. Achieving adequate seizure control or symptom control is sometimes a difficult and dynamic balance. It is recognised that valproate may be the only medication that controls potentially dangerous symptoms, particularly for genetic generalised epilepsies. Clinicians reported that following completion of the risk acknowledgement form, the majority of WCP under their care continued valproate (68.5%, Figure 2). Many of these women had already tried or considered other medications that were ineffective. A recent survey in Poland had similar findings.[11]

Clinicians reported that patients switched from valproate to another medication (usually lamotrigine or levetiracetam) had worse clinical outcomes, with significant deterioration in seizure control, including fewer seizure free or stable patients (Figure 2 and Supplemental Figure 2). This aligns with a recent Italian

study reporting clinical deterioration in 36/51 (70.6%) of WCP with idiopathic generalized epilepsy discontinuing VPA.[12] SANAD II showed superior effectiveness of valproate over levetiracetam in generalised and unclassifiable epilepsy in an un-blinded randomised controlled trial.[2] A few clinicians reported restarting valproate following a change and deterioration of epilepsy control (despite previously being stable), however being unable to achieve the same seizure control.

There were 14 pregnancies in total reported by clinicians occurring following completion of the RAF in this group; 5 in those continuing on valproate (none occurred in WCP with ID). Their outcome is as yet unknown.

Responses suggest more clinicians than patients report dissatisfaction with the new process/form (40% versus 31% respectively, Figure 3). Some patients commented to their nurses and doctors that they were grateful to have time dedicated to explaining the risks associated with valproate and that such information should be delivered face to face, allowing patients to ask questions and explore their options. The majority of respondents leaving comments reported that patients were confused and often irritated by having to have an additional appointment to discuss risks that has already been explained to them prior to starting treatment especially when they are not permitted to decide about their treatment and methods of contraception/pregnancy prevention. Comments also highlight that the form fails to account for or make adjustment for individual circumstances such as severe ID, same-sex couples, hysterectomy or sterilisation. Some patients describe feeling offended and discriminated against. Recent modifications to the RAF will allow "opt out" of the PPP form when pregnancy is not considered possible and should reduce this problem.[13]

Strengths and limitations of the study

This is the first survey of outcomes and views by professional users of the valproate RAF. A survey of patient views is underway. The key shortfall is that it does not capture the views of all prescribers, nor all females taking or considering valproate. Like all surveys, and the pregnancy registers, participants cannot be randomly selected. Neither the total number of specialist clinicians responsible for reviewing relevant patients and completing the RAF, nor the number of women of childbearing age taking valproate is known. There are no government measures in place to capture these data prospectively. The best way to do this is a nationwide or multi-nation study using data linkage. Despite this limitation, an estimated 4775 patient outcomes are reflected in this survey, a substantial number and more than in many pregnancy registries.

Policy implications

To prevent associated congenital malformations and developmental delay, the MHRA recommendations aim to prevent all pregnancies in women taking valproate. This survey found five reported pregnancies in women taking valproate, in comparison to nine in those weaned off valproate.

The surveyed clinicians reported that changing from valproate to another medication worsened symptoms (more seizures in 33-43%, worse mood in 4-6%) of their patients. Informed consent, the Montgomery ruling, and GMC requirements mandate full disclosure of risk.[14,15] To align with these principles, the MHRA must add to the risk of worsening symptoms (for seizures is in the order of 30-40%) on changing from valproate to other medications to the patient information booklet and their websites. The risk of valproate to fetal development is at the forefront of the MHRA concerns. Women's reproductive potential should not eclipse the impacts of incomplete seizure control on premature mortality and quality of life.

Unanswered questions and further research

The true impact of the changes in legislation and practice following the introduction of the valproate risk acknowledgement form and pregnancy prevention programme is unknown and there is no systematic gathering of this data. The valproate RAF should be online, and all patient outcomes (seizure control, safety, mood, longitudinal effects on IQ and cognition of girls and women), as well as pregnancy-related outcomes, collected nationally and systematically. We have the technology and systems to do this. There should be provisions also for patient, carer and clinician feedback on the forms and the process. This information is essential for both patients and clinicians to inform current and future decision making.

Data sharing statement

Data will be made available in anonymised form to researchers on contacting the Corresponding Author.

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TABLES

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Table. *Clinician Comments on Risk Acknowledgement Form for Women of Childbearing Potential*

"[the RAF] is heavy-handed and feels weighted towards the patient in terms of accountability."
"Not designed for women who want to make an informed choice…Major issues with enforced contraception, consent in children, consent in learning disability, bodily autonomy in adults without LD and same sex couples."
"It is useful to document VPA and WWE issues, however I am not sure that this form improves what I was doing before."
"Most of the patients are willing to engage with this and grateful for the support. Those who are cross about the PPP are less likely to be satisfied and feel this is further marginalising them."
"Significant increase in referrals and demands on outpatient appointments."
"Not really appropriate for GP use and yet with long waits for neurology review we are the docs prescribing valproate."
"No section to comment on individual circumstances."
"For the women who are stable and well controlled they find it irritating that they know the risks but are not allowed to make informed decisions and are required to attend a hospital appointment."
"Mandates annual forms, even if pregnancy is impossible e.g. hysterectomy or sterilisation which individual patients have found frustrating."
"Carers in severe ID especially feel idea of enforced invasive contraception inappropriate."

FIGURE LEGENDS

Figure 1*. Identification of WCP taking Valproate and RAF Completion Requires Combining Multiple Search Methods*

(A) Methods utilized by surveyed healthcare professionals to identify women of childbearing potential (WCP) taking valproate that require review and completion of risk acknowledgement form (RAF); orange bars indicate where combinations of methods have been used. (B) Diagrammatic representation of the proportion of WCP for which a RAF has been completed. *N= number of responses. N=215, with approximately 4775 WCP on valproate under active care.*

Figure 2. *Worse Clinical Outcomes Reported when Valproate was Discontinued Following Completion of the RAF in WCP without ID*

Diagrammatic representation of the proportion of patients (A) continued on valproate and the proportion (B) weaned off valproate and initiated on new medication after review and completion of the risk acknowledgement form (RAF) for women of childbearing potential without intellectual disability (ID). N= number of responses. N=200 and N=180 for Figures 2A and 2B, respectively. Medications used to replace valproate shown in (C). (D) Clinician estimated outcomes for patients continued on valproate (red, n=167), changed from valproate to levetiracetam (dark blue; n=97) or lamotrigine (light blue; n=108), with focus on seizure frequency and duration, epilepsy related death, mood and incidence of pregnancy.

Figure 3. *Clinicians Lack Confidence and Satisfaction with the RAF Process for WCP on Valproate*

Diagrammatic representation of (A) patient/carer and (B) clinician satisfaction with the risk acknowledgement form (RAF). N= number of clinicians surveyed; N=215. (C) Diagrammatic representation of confidence with completing the RAF; 215 healthcare professionals were asked to grade how strongly they agree with "`I have sufficient resources to deal with…" + various statements relating to the patient review and RAF completion process. The asterix indicates statements for which "neutral," disagree" and/or "strongly disagree" responses outnumber "agree" responses.

Supplemental Figure 1*. Diagnosis of Women of Childbearing Potential Taking Valproate*

215 clinicians were asked to select all relevant diagnostic indications for valproate in the approximately 4775 women of childbearing potential under active care: diagrammatic representation of the frequency

that epilepsy (purple), migraine (red), bipolar disease (yellow), other mood disorder (green), intellectual disability (ID; blue) was reported is shown, with overlapping areas indicating co-morbidities.

Supplemental Figure 2. *Worse Clinical Outcomes Reported when Valproate Discontinued Following Completion of the RAF in WCP with ID*

Diagrammatic representation of the proportion of patients (A) continued on valproate and the proportion (B) weaned off valproate and initiated on new medication after review and completion of the risk acknowledgement form (RAF) for women of childbearing potential with intellectual disability (ID). N= number of responses. N=175 and N=134 for Supplemental Figure 2A and 2B, respectively. Replacement medications following weaning of Valproate shown in (C). (D) Clinician estimated outcomes for patients continued on valproate (red; n= 132), changed from valproate to levetiracetam (dark blue; n=55) or lamotrigine (light blue; n=56), with focus on seizure frequency and duration, epilepsy related death, mood and incidence of pregnancy.

Supplemental Figure 3. *Completion of the RAF is not Associated with Increased Use of "Highly Efficacious" Contraception*

Each clinician was asked to report the proportion of WCP taking valproate under their care in which:

(A-B) "highly efficacious" contraception (intrauterine device or depot injection) was continued post-RAF; diagrammatic representation of patients (A) without intellectual disability (n=191) and (B) with intellectual disability (n=156).

(C-D) "highly efficacious" contraception had replaced another pre-existing contraception; diagrammatic representation of patients (C) without intellectual disability (n=184) and (D) with intellectual disability (n=150).

(E-F) "highly efficacious" contraception has been declined; diagrammatic representation of patients (E) without intellectual disability (n=188) and (F) with intellectual disability (n=150)

N= number of clinicians surveyed.

Supplemental Figure 4. *Annotation to the RAF and Information Aids are Frequently Required when Reviewing WCP on Valproate*

Diagrammatic representation of (A) how frequently healthcare professionals annotated the RAF and (B) whether additional resources were used/produced to aid in reviewing women of childbearing potential on Valproate. N= number of clinicians surveyed (n=215).

COMPETING INTERESTS

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work. HAL is a member of the Epilepsy Advisory Group of the Association of British Neurologists, has been an Association of British Neurologists representative on the MHRA Valproate Stakeholders' Network meeting (2018) and UK representative on the Sanofi European Valproate educational programme Advisory Board (2018). She holds Eisai Investigator initiated non-pharmaceutical grants (2017) and has received Honoraria for non-promotional lectures from Eisai (2017, 2019) and UCB (2016). HALs research salary is partly supported by the National Institute Health Research and Royal Free Charity. HRC reports in the last 3 years non-financial support from European Academy of Neurology; personal fees from Sage Pharmaceuticals Ltd, Eisai Europe Ltd, UCB Pharma Ltd, European Medicines Agency, from UK Epilepsy Nurse Specialist Association, non-financial support from Special Products Ltd, outside the submitted work. RS is a stakeholder of the 'SUDEP and Seizure Safety Checklist'. RS is a principal developer & key stakeholder of EpSMon. RS has received institutional and research support and personal fees from LivaNova, UCB, Eisai, Special Products, Bial and Desitin outside the submitted work. Other authors declare no competing influences.

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