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# Valproate prescribing practices for women with intellectual disability across Europe

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# Valproate prescribing practices for women with intellectual disability across Europe


## Abstract

Background:

Valproate (VPA) is a known teratogen associated with greater risk of major congenital malformations and other neurodevelopmental sequelae than all other licensed antiepileptic medicines. To reduce the potential for VPA-related teratogenicity the European Medicines Agency issued recommendations in 2018. Over two-thirds of women/girls with Intellectual Disability (ID) may have treatment resistant epilepsy that could benefit from VPA treatment.

Aims:

This investigation compared VPA prescribing practice for women/girls with ID between European countries, specifically evaluating the practice in the UK with that in other countries.

Methods:

An expert working group with representation from key stake holding organisations developed a survey for dissemination to relevant professionals across Europe.

Results:

71 responses were received (27 UK, 44 Europe). Clinicians in the UK were more likely to report that they are working to mandatory regulations compared to European respondents ($p=0.015$). European respondents were less likely to be aware of user-independent contraception options ($p=0.06$). In The UK, VPA regulations were more likely to be applied to women with ID than in Europe ($p=0.024$).

Conclusion:

There is heterogeneity in the application of VPA regulations across Europe for women/girls with ID. In both the UK and Europe the regulations lack suitable adjustments for specific ID-related factors.

## Introduction

Valproate (VPA) is an established teratogen with an estimated risk of 10% major congenital malformation (MCM) and up to 40% neurodevelopmental disorders including autistic traits and cognitive deficits.[1,2] The VPA MCM risk is influenced by dose and polypharmacy.[3] Foetal Anticonvulsant Syndrome (FACS) and VPA embryopathy are defined by developmental delay, attention deficits, and intellectual disability (ID).[4,5]

In February 2018, the European Medicines Agency (EMA) recommended that VPA should only be used in women of child-bearing age if they have epilepsy that does not respond to other AEDs, and if they are enrolled in a pregnancy prevention programme ('PREVENT'). One month later, the Coordination Group for Mutual Recognition and Decentralised Procedures-Human (CMDh) endorsed new measures to avoid in-utero Valproate exposure.[6] In the UK, the Medicines and Healthcare products Regulatory Agency (MHRA) updated its VPA prescription regulations to contraindicate VPA use in women/girls of child-bearing age without restrictions.[7] The UK regulations align with those proposed by the EMA.

### *Girls/women with Intellectual disability (ID)*

Girls/women with ID require specific consideration. ID is commonly associated with co-morbid epilepsy (22%) which is treatment resistance in over two thirds of cases.[8] In terms of seizure control, VPA remains the drug of first choice for generalised epilepsy.[9] It has been shown to be effective in people with ID.[10] A recent survey suggests a mean 30-40% deterioration in seizure control when patients are changed from VPA to alternatives.[11] VPA also conveys mood stabilising properties, which are particularly relevant in those with ID given the high prevalence of psychiatric co-morbidities in this population.[12] A recent UK investigation examining the implementation of the MHRA statement at a tertiary epilepsy centre (N=125) found that over one-third of women using VPA had an ID, and one-fifth could not consent to a sexual relationship. In one in three patients, VPA treatment did not comply with the MHRA regulations.[13]

The aim of this study was to gain an understanding of how measures to restrict VPA in girls/women of child-bearing age with ID have been implemented and regulated in clinical practice across Europe. The investigation will compare VPA prescribing between Europe and the UK.

## Methods

A working group was assembled comprising of expert members from the Faculty of Psychiatry of Intellectual Disability of the Royal College of Psychiatrists (RCPsych) (RS, KC, and LW), International League against Epilepsy (ILAE) (MR), European Psychiatric Association, Mental Health in Intellectual Disability (EPA-MHID) Section (BP), European Association for Mental Health In Intellectual Disability (EAMHID) (RB), Association of British Neurologists (ABN) (HAL), and representation from IN-FACT (Independent Foetal Anticonvulsant Trust) and FACS Association (EM).

The STROBE checklist was used to guide reporting of this cross-sectional study. An initial draft questionnaire was prepared (LW) and refined by the working group over three rounds of consultations using a Delphi method. The finalised survey was sent electronically to key members of different stake-holding organisations across the UK and Europe for distribution among other members.

The survey questions focused on specific aspects of the current regulations governing VPA use and how these were applied to girls/women with ID of child-bearing age (supplementary-information 1). The survey results were analysed as a whole and findings also compared between the UK and other European countries. Content analysis of the qualitative data was performed to identify themes. The *z*-score test was used to compare UK with other European responses, with a two-tailed hypothesis and significance accepted at $p<0.05$. This study included European countries expected to take account of the EMA statement, even if they were not part of the European Union.

*Ethics*

Participants were advised that participation was voluntary and that responses would be anonymised and analysed. No identifiable data were collected. Consent was implicit by participation.

**Results**

*Demographics*

A total of 71 respondents representing 17 countries from a wide range of clinical specialties (supplementary information 2) responded. Twenty seven of the 71 respondents were based in the UK. The majority of respondents (93%) work with girls or women with ID. VPA was prescribed for epilepsy (79%), bipolar affective disorder (51%), migraine (7%), or other psychiatric / behavioural presentations (9%).

*UK compared to Europe*

Quantitative Data

The interpretation of regulations varies considerably between clinicians working in the UK and those working in other European countries (Table 1/figure 1). A significantly higher proportion of UK-based clinicians reported they were working to mandatory regulations than in the other European countries , suggesting lower awareness levels of VPA-related regulations among European respondents or more flexible interpretation of the regulations. In this context 'mandatory' means "legally binding" (i.e. if mandatory prescribing rules are not followed the medication is essentially used off-license and without the usual medicolegal protections provided by the licensed use of the drug). In Europe, over one third of clinicians were not aware of formal recommendations on user independent contraception. This suggests that specific advice on highly reliable contraception may be offered less often in other European countries compared to the UK.

Self-reported compliance with regulations in women and girls with ID was greater in the UK compared to Europe. However, in both the UK and other European countries the majority of respondents (71%) reported a lack of specific guidance for prescribing VPA to girls or women with ID who are not sexually active with no difference between the UK and Europe.

In the UK, clinicians were more likely to report having access to patient information resources.. but 'Easy Read' patient information was no more likely to be available in the UK than other European countries.

Qualitative Data (Supplementary information 2)

Across European countries, 41% of respondents stated that they were working in regions without mandatory VPA prescribing regulation for women and girls of child-bearing age and 32% of respondents stated the prescribing guidelines that are in place for women are not followed in practice. A themed content analysis of free comment responses identified three distinct categories that suggest reasons for this lack of adherence.

Reasons for lack of adherence to VPA regulation: -

1. Knowledge - there is a general lack of awareness of VPA regulations, more specifically regarding mental capacity, informed consent, and how to assess more complex scenarios.
2. Treatment factors - clinicians and/or patients are hesitant to change effective AED treatment, particularly if it has been difficult to achieve treatment success. The balance of risk is multifactorial and often based on a limited evidence base. For some there may be a lack of suitable alternative treatments either because of previous failure, side effects, or due to access and financial constraints.

3. Ethical considerations -patient choice is often not considered within regulations, whether an individual can provide informed consent or not. Contraception advice may be inappropriate for people who are not sexually active, particularly girls/women with ID who may lack the mental capacity to consent to sexual activity.

European respondents consider a wide range of exceptional circumstances in which the prescription of VPA is necessary and appropriate in this population (Table 2). The exceptional scenarios raised are consistent with the expert opinion consensus amalgamated in the UK.[14]

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**Discussion**

The survey results demonstrate heterogeneous interpretation, regulation, and implementation of VPA EMA guidelines for childbearing age girls/women across Europe.

The regulations described in the responses from across Europe can be classified into four categories, with category 3 being the most common and consistent with the EMA and UK-MHRA regulations.

Categories (1-4) of VPA regulation currently in place around Europe based on clinician feedback.

1. *No guidance - unaware of EMA warning*
2. *No guidance - aware of EMA warning*
3. *Do not prescribe for girls or women of child-bearing age with exceptions and restrictions*
4. *Do not prescribe for girls or women of child-bearing age without exception*

Regulation adherence appears more rigid in the UK than in Europe. However, in the UK clinicians still lack a clear understanding of the regulations which make no specific reference to patients with ID. Not all UK respondents were aware that the regulations are mandatory; some (9/25) stated there is specific guidance for people with ID who are not sexually active, although this is not actually included in the regulation. For those not sexually active because of their disabilities, participation in a user-independent contraceptive programme could add unnecessary risk and lead to emotional distress to both individuals and their families. In Europe, a proportion of clinicians reported that, where regulation is in place, it may not be followed, particularly for women with ID. Specifically, there is a lack of understanding of mental capacity assessment.

The EMA recommendations lack consideration of specific ID related factors including: individuals who lack the mental capacity to provide informed consent to sexual relationships; individuals who are not sexually active; and easy-read/accessible information. The same deficits are apparent in the UK regulations.[15]

*Limitations*

The survey response rate was low considering the number of potential responders. Information derived from a single respondent may not have been representative therefore could be biased towards the views of those with an interest in this field. The discussion of European results is based upon respondents' views in practice and not a review of regulations.

The results if this survey demonstrates heterogeneity in the application of VPA regulations across Europe for women/girls with ID. In both the UK and Europe the regulations lack suitable adjustments for specific ID-related factors. From these findings we conclude that improvements are needed in four areas to optimise the safe use of VPA in women with ID and epilepsy.

Recommendations for women/girls of child-bearing age with ID -

1. **Education** - increase clinician awareness, developing knowledge, and improve regulation adherence.
2. **Regulations** - explicit exceptional circumstances where VPA may be appropriate should be identified. Provide clear guidance/pathways on switching from VPA to alternatives and how decisions for individuals with ID should be considered.
3. **Surveillance-** establishes national VPA registers for all VPA childbearing women/girls.
4. **Shared Decision making –** arrangements at local level for decision making to involve the patient or patient representative. The clinical decision-maker should have sufficient expertise to weigh up the risks and benefits of VPA treatment and use of safe contraception using accessible information, including documents in easy-read format to facilitate patient participation in decision making (Table 3).

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Table 1 Comparison of respondents views between UK and Europe

| Parameter | Total sample (n =71)** | UK | Europe | P value |
|---|---|---|---|---|
| Awareness of VPA regulations | 63/70 | 25/27 | 37/43 | 0.4009 |
| Recommendation of acceptable forms of contraception | 45/63 | 21/25 | 23/37 | 0.06 |
| Mandatory regulation in place | 44/62 | 22/25 | 22/37 | 0.015* |
| Guidance followed in clinical practice | 47/63 | 21/25 | 26/38 | 0.164 |
| Applied to women and girls with ID | 54/61 | 24/24 | 30/37 | 0.024* |
| Specific guidance for women with ID who are not sexually active | 18/63 | 9/25 | 9/38 | 0.29 |
| Patient information resources available | 56/70 | 25/27 | 31/43 | 0.037* |
| Patient information available in Easy Read Format | 37/68 | 17/25 | 23/43 | 0.24 |

*Significance at 0.05

**Number of total respondents may differ as not all questions were answered

Table 2 Comparison between EMA recommendations and exceptional circumstances and prescribing restrictions pooled from European responses

| **Pooled European respondents views from experience** | **EMA recommendations** |
|---|---|
| *Exceptional Circumstances* | *Exceptional Circumstances* |
| • Life threatening situations E.g. Status Epilepticus.<br>• Patient choice with valid informed consent with pregnancy prevention.<br>• Patient choice with valid informed consent without pregnancy prevention.<br>• Women who lack the capacity to consent to sexual relationships<br>• Treatment failure with other AEDs.<br>• Intolerable side effects from other AEDs.<br>• Specialist choice-as most appropriate treatment given clinical scenario balancing risk and outcomes. | • Alternative treatments are not suitable, specialist consultation required |
| *Restrictions* | *Restrictions* |
| • Teratogenic risk must be discussed<br>• Pregnancy test prior to prescribing<br>• Adherence to appropriate contraceptive regime (user independent)<br>• Do not consider VPA for anything other | • **Pregnancy Prevention Programme**<br>-assessment of pregnancy potential<br>-pregnancy tests before and during treatment as needed<br>-Counselling on risks of VPA and need for |

| | |
|---|---|
| than epilepsy (E.g. Bipolar affective disorder)<br>• Any women prescribed to be placed on a register | effective contraception during treatment<br>-annual review with specialist<br>-risk acknowledgment form<br>• Educational materials<br>• Alert card<br>• No prescribing for migraine or bipolar during pregnancy |

## Table 3. Valproate shared-decision making tool-Girls/women with ID

| **Level of ID** | **Mild (Pathway 1)** | **Moderate to Profound (Pathway 2)** |
|---|---|---|
| **Valproate prescribing** | Assessment of capacity to provide informed consent to AED treatment | Unable to provide informed consent to AED treatment. Therefore prescribed in best interests, potentially involving patient advocate / representative. |
| **Information sharing** | Risks and benefits of VPA prescription for individual and unborn child.<br><br>Unborn child: 10% risk of MCM's, up to 40% risk of neurodevelopmental and cognitive sequalae of varying degree. Risks dose dependent and increased with polypharmacy.<br><br>Risk to individual: Common side effects include weight gain, tremor, and rarely polycystic ovary syndrome. Risk is higher with | Information should be shared as suitable to the cognitive and communication needs of the individual to help support understanding. This will be guided by the person and those close to them (family/carers).<br><br>Support may include longer appointments, easy-read documentation, or involvement from other healthcare professionals with specialist ID expertise. |

| | | |
|---|---|---|
| | higher dose.<br><br>Risk of stopping medication: increased seizure frequency, injury, hospitalisation, SUDEP, and serious harm to unborn child if pregnant. | |
| **Contraceptive advice** | Capacity to consent to sexual relationships and sexually active/or the possibility of becoming sexually active<br><br>If yes, for further discussion around the 'Prevent' programme.<br><br>User independent contraception, some of which are invasive<br><br>If no, move to follow Pathway 2. | Unable to provide informed consent to sexual relationship<br><br>No need for further discussion around contraception and sexual relationships which could cause distress. |
| **Outcome** | Risk acknowledgement form to be signed by epilepsy service and individual, enrolment in 'Prevent', minimum annual review with a specialist | Risk Acknowledgment form to be completed, opting out of 'Prevent' programme |

Figure 1 Comparison between the UK and Europe