

Valproate mhra guidance: limitations and opportunities

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Introduction

The Medicines and Healthcare products Regulatory Agency (MHRA) in the United Kingdom have recently strengthened the regulatory measures for valproate medicines ([1](#)). The new regulations contraindicate the use of valproate medicines in girls or women of child bearing age unless they participate in the Pregnancy Prevention Programme ([Appendix 1](#)).

The MHRA regulations recognize that it is not safe for some women to discontinue valproate prescription in pregnancy and doing so may in fact pose considerable risk to both the mother and the fetus. In such scenarios it may be more appropriate to continue treatment under specialist care ([1](#)). There are however exceptional circumstances and practical implications that have not been fully considered by the MHRA regulations. Notwithstanding the requirement for clear documentation and informed consent, it is important not to lose sight of individual circumstances and the importance of working collaboratively toward providing person center care ([2](#)).

Valproate-evidence of Teratogenic Risk

Valproate is a known serious teratogen associated with a risk of major congenital malformations (MCM) ([Table A1](#)). A MCM is defined as an abnormality of an essential anatomical structure interfering with function or requiring major intervention ([3](#)). The evidence base for valproate teratogenicity is largely based on observational studies of people with epilepsy.

In addition to the MCM risk in children of mothers prescribed valproate there is an increased association with neurodevelopmental, cognitive, and behavioral sequelae. Intelligence Quotient (IQ) assessments have consistently shown lower scores associated with valproate exposure in comparison to other antiepileptic drugs (AEDs). The Neurodevelopmental Effects of Antiepileptic Drugs (NEAD) study was a prospective observational study in which cognitive assessments were completed on children at a 6 year interval. The assessors were unaware of which antiepileptic drug was prescribed for the mother in each case. Valproate exposure was associated with lower IQ scores than other commonly prescribed AEDs (Lamotrigine, Carbamazepine, and Phenytoin). This was evidenced across domains of verbal ability, non-verbal ability, memory, and executive function. Adverse effects on cognition were more prominent in association with high dose valproate prescription which was not observed in the other AEDs investigated ([4](#)). This cohort also demonstrated statistically significant lower scores on a range of adaptive functioning assessments, and a specific increase in association with attention deficit hyperactivity disorder (ADHD) ([5](#)). A population-based study of all live births in Denmark for 1996-2006 compared exposure to valproate to autism spectrum disorder (ASD) diagnosis. The relative risk of ASD diagnosis in this population was over 4% ([6](#)).

Both with respect to the MCMs, and the neurodevelopmental concerns, there appear to be a clear dose dependent relationship ([5](#), [7](#) - [9](#)). A family history of MCMs or neurodevelopmental problems contributes to the risk on an individual basis. Therefore, women prescribed low dose valproate without

additional risk factors may be at lower risk. The totality of the long-term risks associated with valproate remains unknown as regulatory bodies have not followed the trajectory of development and health in all children exposed to this teratogen during pregnancy.

Valproate Prescription in Exceptional Circumstances

For some women of child-bearing age on valproate treatment participation in the Pregnancy Prevention Programme may not be appropriate ([Appendix 2](#)

). In these scenarios there are still situations in which a Risk

Acknowledgment Form will need to be signed by the individual and specialist following informed discussion. However, the current Risk Acknowledgment Form does not allow for these circumstances. For a woman who is trying to conceive, or one who is sexually abstinent the “ Effective contraception is essential while taking valproate,” and specific emphasis on invasive methods (coil, implants or sterilization) is clearly inappropriate and potentially discriminatory. Another vulnerable group of women are those who lack capacity to fully participate in the decision making process. In these scenarios the only option may be for the specialist to amend the form by hand and justify those areas that are not applicable.

Valproate in People With Epilepsy and Intellectual Disability

People with epilepsy and ID require specific consideration. The prevalence of epilepsy in people with ID is far higher than the general population ([10](#)).

The etiological influences are complex and include genetic abnormalities (including epilepsy syndromes), underlying structural changes, and co-

morbid neurological deficits ([11](#)). This complexity contributes to the fact
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that people with epilepsy and ID are refractory to antiepileptic medication. A population-based prevalence study has shown that up to 68% of people with epilepsy and ID may be treatment resistant ([12](#)). Therefore, any change in medication will require careful consideration for those individuals who are stable on monotherapy valproate or a combination of valproate and other AEDs. In addition, people with ID and epilepsy commonly suffer psychiatric co-morbidities ([13](#), [14](#)). Therefore, valproate is often considered a first line treatment for its additional mood stabilizing benefits to help moderate the pharmacological load.

The evidence base for prescribing antiepileptic medication for people with epilepsy and ID is limited and there are no randomized controlled trials or Class I evidence ([15](#)). The prescription of valproate in this population is largely guided by evidence extrapolated from large robust investigations in the general population such as the SANAD study ([16](#)). Valproate remains a first-line drug for generalized seizures, and there is also evidence that people with ID and treatment resistant seizures may be more responsive ([15](#)).

Consent

Where an individual lacks capacity to make informed decisions around their antiepileptic medication a formal best interest's process should be followed ([Pathway A1](#)). If lack of capacity is temporary (emergency situation) the individual should be notified of treatment and if treatment continues, informed consent should be obtained at the earliest opportunity.

A proportion of women with ID and epilepsy will permanently lack capacity to make informed decisions about their medical care including the prescription

of AEDs. Capacity should be assessed formally for each decision as set out in the guidance from the Mental Capacity Act (MCA) (2005). In accordance with the principles of the MCA, all practicable steps should be taken to engage the individual in the decision making process. This includes making reasonable adjustments and the use of communication aids and/or assistance from specialist speech and language therapists. Impaired capacity may include difficulty understanding the risk and benefits of the medication; difficulties in retaining relevant information for long enough to make a decision; difficulties in weighing up relevant information; difficulties in communicating any decision.

Where individuals are assessed and deemed to lack capacity to make an informed decision, it is important to attempt to understand their views and involve the individual in decision making process where possible and appropriate. This could be facilitated through purposely designed valproate resources for the ID community, and the opportunity for advocacy support to help the individual make their voice heard and challenge decisions. Family and caregivers are an important source of information, however, it is essential to appreciate the vulnerability of this population. There is an inherent risk of decisions being imposed on individuals without any involvement in the decision making process.

In the MHRA regulations there are two clear decisions that require informed consent-valproate treatment, and participation in the Pregnancy Prevention Programme. Capacity to provide informed consent should be assessed for these two decisions individually. Many women with more moderate to

profound ID will not only lack capacity to consent to medical treatment but also lack capacity to consent to sexual relationships. Participation in the Pregnancy Prevention Programme includes adherence to invasive contraceptive methods. These contraceptive methods are associated with their own risks and therefore participation may not be in an individual's best interest. For individuals who lack capacity to consent to sexual relationships pregnancy would raise serious safeguarding concerns, implying sexual abuse. Approaching discussion around this topic unnecessarily can potentially be very distressing for the individual, their families, and caregivers.

Conclusion

The regulatory measures for valproate prescription from the MHRA are based on a weight of evidence that has guided clinical practice for some time. However, there are individuals and scenarios that have not been fully considered in the regulation. There are women who may consider the contraceptive methods advised by the MHRA unacceptable for personal, religious, or health reasons. In such circumstances the regulations discriminate against these women who are in a position to make fully informed decisions around treatment choice. The MHRA guidance to only prescribe valproate in rare cases for patients who are resistant or intolerant of other treatments does not consider the complex reality of clinical practice including:

1. Women who have not trialed an alternative antiepileptic drug nor do they wish to for fear of potential life threatening consequences of uncontrolled seizures, therefore their response to other treatment is unknown.
2. Women under-going a valproate treatment change in pregnancy-a slow titration process where the consequences of polytherapy and impact on teratogenicity and seizure control are largely unknown.

The regulations neglect to consider women who lack capacity to make informed decisions around medical care. This includes some women with ID who are more likely to have treatment resistant seizures and multiple physical and psychiatric co-morbidities. There are also practical considerations that will impact on primary care services, community pharmacists and secondary services. People on stable doses of valproate, with and without capacity, and even where there is recent and comprehensive documentation about counseling and decision making, are now being referred back into already pressured secondary care services to complete a Risk Acknowledgment Form. All now require annual specialist review purely for this purpose. Once the form is completed (including following a best interest's process for individuals who lack capacity) where prescription of valproate continues, there should be no need to change existing arrangements for prescribing undertaken in primary care. For those who lack capacity, where a best interest decision is established and discussions with the community pharmacist completed- this should be placed on an individual's patient medication record to prevent further unnecessary questioning every time valproate is dispensed which could cause

inappropriate distress. In adhering to the MHRA guidelines with the current Risk Acknowledgment Form it is challenging to deliver person center care. Without modification, the current Risk Acknowledgment Form does not recognize scenarios where enforced invasive contraception maybe inappropriate, and in which individuals lack capacity to consent to treatment where a Best Interest process is required. In fact it is in contradiction to the MCA (2005) as no individual has the authority to sign the form to consent on behalf of another adult, unless there are formal legal powers in place.

Author Contributions

LW: preliminary draft. HC, HA-L, KM, and MW: conceptualization, editing, and redrafting. RS: supervision, process management, editing, proofreading, and submission.

Conflict of Interest Statement

HC 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. HA-L 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) and UCB (2016). RS is a principal stakeholder of the “ SUDEP and Seizure Safety Checklist,” a developer of

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The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Supplementary Material

The Supplementary Material for this article can be found online at:

<https://www.frontiersin.org/articles/10.3389/fneur.2019.00139/full#supplementary-material>

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