

Valproate and the Pregnancy Prevention Programme: exceptional circumstances

In March 2018 the European Medicines Agency endorsed new measures to avoid in utero valproate exposure. Subsequently, updated valproate regulations published by the Medicines and Healthcare products Regulatory Agency (MHRA)¹ contraindicate the use of valproate medicines in girls or women of childbearing age unless they participate in the Pregnancy Prevention Programme. Participants must be fully informed of the risks of valproate use in pregnancy, sign a Risk Acknowledgement Form each year, have an annual specialist review, and adhere to a highly effective (pregnancy rate of <1%) but invasive contraception. Valproate is widely prescribed in general practice for a range of indications including epilepsy, bipolar affective disorder, and migraine. This article will argue that there are exceptional circumstances, and personal and practical implications, that have not been adequately considered in the MHRA regulations on valproate prescribing.

TERATOGENIC RISK

Valproate is a known serious teratogen associated with a risk of major congenital malformations (MCM). Large observational studies of national pregnancy registers have identified MCM rates between 6.7% and 10.3%.²⁻⁵ Some of the malformations associated with intrauterine valproate exposure include hypospadias, congenital heart defects, neural tube defects, and orofacial clefts. In addition to the MCM risk there is an increased association with neurodevelopmental, cognitive, and behavioural disorders.

Both MCMs and the neurodevelopmental concerns appear to have a clear dose-dependent relationship.^{3,4,6} It is also recognised that a family history of MCMs or neurodevelopmental problems respectively contribute substantially to the risk in an individual. Thus, although the MHRA guidance emphasises a risk of around 10% for MCMs, and ≤40% of adverse neurodevelopmental outcomes, for some women on low doses without additional risk factors the risks may in fact be substantially lower.¹

WHEN VALPROATE MAY STILL BE APPROPRIATE

There is a consensus of opinion (the Royal College of Psychiatrists Faculty of

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Intellectual Disability Psychiatry, the United Kingdom Learning Disability Professional Senate, and 61 signatories) on exceptional circumstances in which valproate prescription may be necessary, and participation in the Pregnancy Prevention Programme may not be appropriate.⁷ The MHRA regulations recognise that for some women stopping valproate prescription in pregnancy may confer considerable risk to both the mother and the fetus, including death. In such circumstances it may be more appropriate to continue treatment in pregnancy under specialist care.¹

EMERGENCY TREATMENT

A specialist may consider valproate the most effective medication to manage uncontrolled seizure activity or status epilepticus. In such scenarios the individual will often be at least temporarily unable to provide informed consent. As applies in many emergency situations, clinicians must make rapid best-interests decisions and document their reasoning. If individuals regain capacity they should be informed about treatment they have already received, and, if valproate is to be continued, informed consent and the Pregnancy Prevention Programme addressed at the earliest opportunity.

INFORMED CONSENT

There will be women of childbearing age in whom valproate is the most effective medication for those individuals, and/or the medication best supporting their seizures, quality of life, or there being no other suitable drug, and who, following a fully informed discussion, choose to continue with valproate prescription and do not wish to participate in the Pregnancy Prevention Programme.⁸ This includes women who are actively looking to conceive with the support of a specialist. For some women the modes of contraception imposed by the MHRA are not acceptable to them because of

personal, moral, religious, or health-related reasons, or because of previous or potential associated adverse events.⁸

WOMEN WHO LACK MENTAL CAPACITY TO PROVIDE INFORMED CONSENT

There are individuals who lack the mental capacity to make informed choices about medication; this includes some women with intellectual disability (ID). People with moderate to profound ID may also lack the mental capacity to consent to sexual relationships and participation in the Pregnancy Prevention Programme. Adherence to invasive contraceptives may put women in this population at unnecessary risk of physical and emotional harm, and be arguably unethical. For these individuals, pregnancy would raise serious safeguarding concerns, possibly implying sexual abuse. It also needs to be appreciated that approaching discussion around this topic itself can be a very distressing process for the individual and their families. There may be other clinical indications for contraceptive use, therefore each case needs to be considered on an individual basis following the best-interests process under the 2005 Mental Capacity Act (MCA).⁹

The prevalence of epilepsy in people with ID is far higher than the general population, and over two-thirds of this population may be treatment resistant.¹⁰ Valproate remains a first-line drug for generalised seizures and people with ID and refractory epilepsy may be more responsive.¹¹ In addition, people with ID and epilepsy commonly suffer psychiatric comorbidities. Valproate is often a good choice given its additional mood-stabilising effects, thus reducing the risks associated with polypharmacy. Valproate remains a mainstay of treatment in this complex vulnerable population, and to exclude it as a treatment option would put many individuals at significant risk of harm.

Impaired mental capacity in this context may include difficulties in understanding benefits and risks, and/or difficulties weighing up relevant information. In making a determination about capacity, as part of a best-interests process, all reasonable adaptations should be made in order to aid the individual's understanding, including the use of tailored communication aids. The principles of the MCA stress taking all practicable steps to engage the individual in the decision process. This may require involvement of other specialist members of the multidisciplinary team, such as speech and language therapists. Family and caregivers are an important asset and key to gaining reliable collateral information. It is fundamental to appreciate the vulnerability of this population. If we do not, then there is a risk of decisions being imposed on individuals without maximising their involvement in the decision-making process.

CONCLUSION

It is essential that in implementing the MHRA regulations we continue to consider cases on an individual basis. A blanket regulation for all, including the necessity to adhere to a Pregnancy Prevention Programme and complete a Risk Acknowledgement Form, neglects the rights of a vulnerable population, such as women who lack capacity to consent to the decision-making process. It would be in contraindication of the MCA for any individual to consent on behalf of another adult, without the necessary legal powers. In these scenarios a Risk Acknowledgement Form will still need to be signed, or documented as part of a best-interests decision-making process.

The MHRA regulation also discriminates against the small number of women making fully informed decisions about choice of contraception and potential pregnancy on valproate, depriving them of the right to self-determination, without feeling they are doing something wrong. A person-centred approach is required with a well-defined rationale for stopping or avoiding valproate, weighing up the risks and benefits, and considering the context of the individual.

An explicit statement from the MHRA recognising the needs of these groups is the aim of all concerned. However, the existing Risk Acknowledgement Form does not provide for these situations, other than by the specialist annotating some sections as 'not applicable', or otherwise amending at the time of completion. There is a clear need for a modified Risk Acknowledgement Form for those scenarios where a best-

interests process is being followed, or in those women where continuing valproate without invasive contraception is agreed on an individual basis.

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