Valproate and the Pregnancy Prevention Programme- exceptional circumstances

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Introduction

In March 2018 the European Medicines Agency (EMA) endorsed new measures to avoid in-utero Valproate exposure. Subsequently, updated Valproate regulations published by the Medicines and Healthcare products Regulatory Agency (MHRA) contraindicate the use of valproate medicines in girls or women of child bearing 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 less than 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 there are exceptional circumstances, 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% (Hernandez-Diaz *et al,* 2012; Vajda *et al,* 2013; Campbell *et al,* 2014; Tomson *et al,* 2018). 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.

MCMs, and the neurodevelopmental concerns appears to have a clear dose dependent relationship (Vajda 2013; Campbell *et al,* 2014; Bromley *et al,* 2014;). It is also recognized that a family history of MCMs, or neurodevelopmental problems respectively contribute substantially to the risk in an individual. Thus whilst the MHRA guidance emphasises a risk of around 10% for MCMs, and up to 40% of adverse neurodevelopmental outcomes, for some women on low doses without additional risk factors, the risks may in fact be substantially lower (MHRA, 2018).

When Valproate may still be appropriate

There is a consensus of opinion (The Royal College of Psychiatrists Faculty of 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 (Angus-Leppan *et al,* 2018). The MHRA regulations recognise that for some women stopping valproate prescription in pregnancy may confer considerable risk to both the mother and the foetus- including death. In such circumstances it may be more appropriate to continue treatment in pregnancy under specialist care (MHRA, 2018).

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 Program addressed at the earliest opportunity.

Informed consent

There will be women of a childbearing age in whom valproate is the most effective medication for that individual, and who following a fully informed discussion choose to continue with valproate prescription and do not wish to participate in the Pregnancy Prevention Programme (Angus-Leppan and Liu, 2018). 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 (Angus-Leppan and Liu, 2018).

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 Interest process under the Mental Capacity Act (MCA) (2005) (Rowlands, 2011).

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 (McGrother *et al,* 2006). Valproate remains a first-line drug for generalised seizures and people with ID and refractory epilepsy may be more responsive (Doran *et al,* 2016). In addition, people with ID and epilepsy commonly suffer psychiatric co-morbidities. 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 risk, and/or difficulties weighing up relevant information. In making a determination about capacity, as part of a best interest's process all reasonable adaptations should be made in order to aid the individuals understanding including the use of tailored communication aids. The principles of the MCA (2005) 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-The Risk Acknowledgment Form

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 Acknowledgment Form neglects the rights of a vulnerable population - women who lack capacity to consent to the decision making process. It would be in contraindication of the MCA (2005) for any individual to consent of 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 well-defined rational for stopping or avoiding valproate weighing up the risk and benefits, and the context of the individual.

An explicit statement from the MHRA recognizing 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 Interest’s process is being followed, or in whom continuing valproate without invasive contraception is agreed on an individual basis.

References

1. Hernández-Díaz S, Smith CR, Shen A, Mittendorf R, Hauser WA, Yerby M, Holmes LB. for the North American AED Pregnancy Registry, North American AED (Antiepileptic Drug) Pregnancy Registry, Scientific Advisory Committee, and North American AED Pregnancy Registry. Comparative safety of antiepileptic drugs during pregnancy. Neurology. 2012 May 22;78(21):1692-9.
2. Vajda FJ, O'brien TJ, Graham JE, Lander CM, Eadie MJ. Dose dependence of fetal malformations associated with valproate. Neurology. 2013 Aug 2:10-212.
3. Campbell E, Kennedy F, Russell A, Smithson WH, Parsons L, Morrison PJ, Liggan B, Irwin B, Delanty N, Hunt SJ, Craig J. Malformation risks of antiepileptic drug monotherapies in pregnancy: updated results from the UK and Ireland Epilepsy and Pregnancy Registers. J Neurol Neurosurg Psychiatry. 2014 Jan 18:jnnp-2013.
4. Tomson T, Battino D, Bonizzoni E, Craig J, Lindhout D, Perucca E, Sabers A, Thomas SV, Vajda F, Faravelli F, Pantaleoni C. Comparative risk of major congenital malformations with

eight different antiepileptic drugs: a prospective cohort study of the EURAP registry. The Lancet Neurology. 2018 Jun 1;17(6):530-8.

5. Bromley R, Weston J, Adab N, Greenhalgh J, Sanniti A, McKay AJ, Tudur Smith C, Marson AG. Treatment for epilepsy in pregnancy: neurodevelopmental outcomes in the child. The Cochrane Library. 2014 Jan 1.
6. Angus-Leppan H, Shankar R, Cock H. Valproate, women, and exceptional circumstances. BMJ. 2018 Aug 28;362:k3625.
7. Angus-Leppan H, Liu RS. Weighing the risks of valproate in women who could become pregnant. BMJ. 2018 Apr 18;361:k1596.
8. Rowlands S. Learning disability and contraceptive decision-making. BMJ Sexual & Reproductive Health. 2011 Jul 1;37(3):173-8.
9. McGrother CW, Bhaumik S, Thorp CF, Hauck A, Branford D, Watson JM. Epilepsy in adults with intellectual disabilities: prevalence, associations and service implications. Seizure. 2006 Sep 1;15(6):376-86.
10. Doran Z, Shankar R, Keezer MR, Dale C, McLean B, Kerr MP, Devapriam J, Craig J, Sander JW. Managing anti-epileptic drug treatment in adult patients with intellectual disability: a serious conundrum. European journal of neurology. 2016 Jul;23(7):1152-7.