

Valproate MHRA guidance: limitations and opportunities

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Abstract

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Recent publication of the Medicines and Healthcare products Regulatory Agency (MHRA) in the United Kingdom has strengthened the regulatory measures for valproate medicines. It highlights the importance of making women of childbearing age with epilepsy aware of the teratogenic risks of valproate and encourages the withdrawal of it from those currently prescribed. While a significant directive, it raises concerns of not having considered the impact on special populations such as women with Intellectual Disability (ID). While it is important that women with ID are not excluded from such safety initiatives, due caution needs to be taken on a case by case basis preferably, to ensure their best interests are central to the decision making. Many women with moderate to profound ID cannot have informed consented sexual relationships not to mention cognitive incapability to make informed choices on medication suitability. These women are at potential risk of having their epilepsy control undermined due to the MHRA directives. Around 30% of people with moderate to profound ID have seizures of which 60% are considered treatment resistant. In this vulnerable population changes to medication without clear clinical and social insights could lead to increased harm levels. This paper enumerates the challenges of application of the new directive to these special populations and proposes a pathway based on individual cognitive ability to provide informed consent to facilitate the continuation or removal of valproate.

It is important not to lose sight of individual circumstances and the importance of working collaboratively towards providing person centre care.

Ethics statements

(Authors are required to state the ethical considerations of their study in the manuscript, including for cases where the study was exempt from ethical approval procedures)

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Ethical publication statement

We confirm that we have read the journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines. No ethical approval was needed as this is a perspective piece which does not involve any patient related data or information.

Key Words:-

Valproate, pregnancy, communication, risk assessment, Intellectual Disability

Abstract

Recent publication of the Medicines and Healthcare products Regulatory Agency (MHRA) in the United Kingdom has strengthened the regulatory measures for valproate medicines. It highlights the importance of making women of childbearing age with epilepsy aware of the teratogenic risks of valproate and encourages the withdrawal of it from those currently prescribed. While a significant directive, it raises concerns of not having considered the impact on special populations such as women with Intellectual Disability (ID). While it is important that women with ID are not excluded from such safety initiatives, due caution needs to be taken on a case by case basis preferably, to ensure their best interests are central to the decision making. Many women with moderate to profound ID cannot have informed consented sexual relationships not to mention cognitive incapability to make informed choices on medication suitability. These women are at potential risk of having their epilepsy control undermined due to the MHRA directives. Around 30% of people with moderate to profound ID have seizures of which 60% are considered treatment resistant. In this vulnerable population changes to medication without clear clinical and social insights could lead to increased harm levels. This paper enumerates the challenges of application of the new directive to these special populations and proposes a pathway based on individual cognitive ability to provide informed consent to facilitate the continuation or removal of valproate. It is important not to lose sight of individual circumstances and the importance of working collaboratively towards providing person centre care.

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 I).

The MHRA regulations recognise 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 foetus. 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 towards providing person centre care [2].

Valproate-evidence of teratogenic risk

Valproate is a known serious teratogen associated with a risk of major congenital malformations (MCM) (Table I). 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 behavioural 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 to 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, 8, 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 Acknowledgement Form will need to be signed by the individual and specialist following informed discussion. However, the current Risk Acknowledgement 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 aetiological 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 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]. Therefore valproate is often considered a first line treatment for its additional mood stabilising 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 randomised controlled trials or Class I evidence [14]. 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 [15]. Valproate remains a first-line drug for generalised seizures, and there is also evidence that people with ID and treatment resistant seizures may be more responsive [14].

Consent

Where an individual lacks capacity to make informed decisions around their antiepileptic medication a formal best interest's process should be followed (Pathway I). 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 trialled 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 counselling and decision making, are now being referred back into already pressured secondary care services to complete a Risk Acknowledgement 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 Acknowledgement Form it is challenging to deliver person centre 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.

Declarations:

Lance V Watkins, No declarations of interest.

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Heather Angus-Leppan 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).

Kim Morley, No declarations of interest.

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In review

References

1. Medicines and Healthcare Products regulatory Agency. New measures to avoid valproate exposure in pregnancy, 2018. <https://www.gov.uk/drug-safety-update/valproate-medicines-epilim-depakote-contraindicated-in-women-and-girls-of-childbearing-potential-unless-conditions-of-pregnancy-prevention-programme-are-met>.
2. Angus-Leppan H, Shankar R, Cock H. Valproate, women, and exceptional circumstances. *BMJ*. 2018 Aug 28;362:k3625.
3. Pennell PB. Use of antiepileptic drugs during pregnancy: evolving concepts. *Neurotherapeutics*. 2016 Oct 1;13(4):811-20.
4. Meador KJ, Baker GA, Browning N, Cohen MJ, Bromley RL, Clayton-Smith J, Kalayjian LA, Kanner A, Liporace JD, Pennell PB, Privitera M. Fetal antiepileptic drug exposure and cognitive outcomes at age 6 years (NEAD study): a prospective observational study. *The Lancet Neurology*. 2013 Mar 1;12(3):244-52.
5. Cohen MJ, Meador KJ, Browning N, May R, Baker GA, Clayton-Smith J, Kalayjian LA, Kanner A, Liporace JD, Pennell PB, Privitera M. Fetal antiepileptic drug exposure: adaptive and emotional/behavioral functioning at age 6 years. *Epilepsy & Behavior*. 2013 Nov 1;29(2):308-15.
6. Christensen J, Grønborg TK, Sørensen MJ, Schendel D, Parner ET, Pedersen LH, Vestergaard M. Prenatal valproate exposure and risk of autism spectrum disorders and childhood autism. *Jama*. 2013 Apr 24;309(16):1696-703.
7. 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
8. 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.
9. 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.
10. Robertson J, Hatton C, Emerson E, Baines S. Prevalence of epilepsy among people with intellectual disabilities: a systematic review. *Seizure*. 2015 Jul 1;29:46-62.
11. Busch RM, Najm I, Hermann BP, Eng C. Genetics of cognition in epilepsy. *Epilepsy & Behavior*. 2014 Dec 1;41:297-306.
12. 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.
13. Turky A, Felce D, Jones G, Kerr M. A prospective case control study of psychiatric disorders in adults with epilepsy and intellectual disability. *Epilepsia*. 2011 Jul;52(7):1223-30. Beavis J, Kerr M, Marson AG. Pharmacological interventions for

epilepsy in people with intellectual disabilities. *Cochrane Database of Systematic Reviews*. 2005(3).

14. 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.
15. Marson AG, Al-Kharusi AM, Alwaidh M, Appleton R, Baker GA, Chadwick DW, Cramp C, Cockerell OC, Cooper PN, Doughty J, Eaton B. The SANAD study of effectiveness of valproate, lamotrigine, or topiramate for generalised and unclassifiable epilepsy: an unblinded randomised controlled trial. *The Lancet*. 2007 Mar 24;369(9566):1016-26.
16. Angus-Leppan H, Liu RS. Weighing the risks of valproate in women who could become pregnant. *BMJ*. 2018 Apr 18;361:k1596.
17. 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.
18. Vajda FJ, O'Brien TJ, Hitchcock A, Graham J, Cook M, Lander C, Eadie MJ. Critical relationship between sodium valproate dose and human teratogenicity: results of the Australian register of anti-epileptic drugs in pregnancy. *Journal of Clinical Neuroscience*. 2004 Nov 1;11(8):854-8.
19. Vajda FJ, O'Brien TJ, Lander CM, Graham J, Eadie MJ. The teratogenicity of the newer antiepileptic drugs—an update. *Acta Neurologica Scandinavica*. 2014 Oct;130(4):234-8.
20. 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.
21. Shankar R, Bradley M, Jory C, Olotu V. Consent to contraceptive treatment among clients with epilepsy. *Learning Disability Practice*. 2013 Dec 1;16(10).

Appendix I Participation in the Pregnancy Prevention Programme for women of child-bearing age prescribed valproate [1].

1. The individual being informed of and understanding the risks of valproate use in pregnancy, and signing a Risk Acknowledgement Form along with a specialist.
2. Annual review with a specialist.
3. Adherence to a highly effective but invasive contraception, with a pregnancy rate of less than 1%.

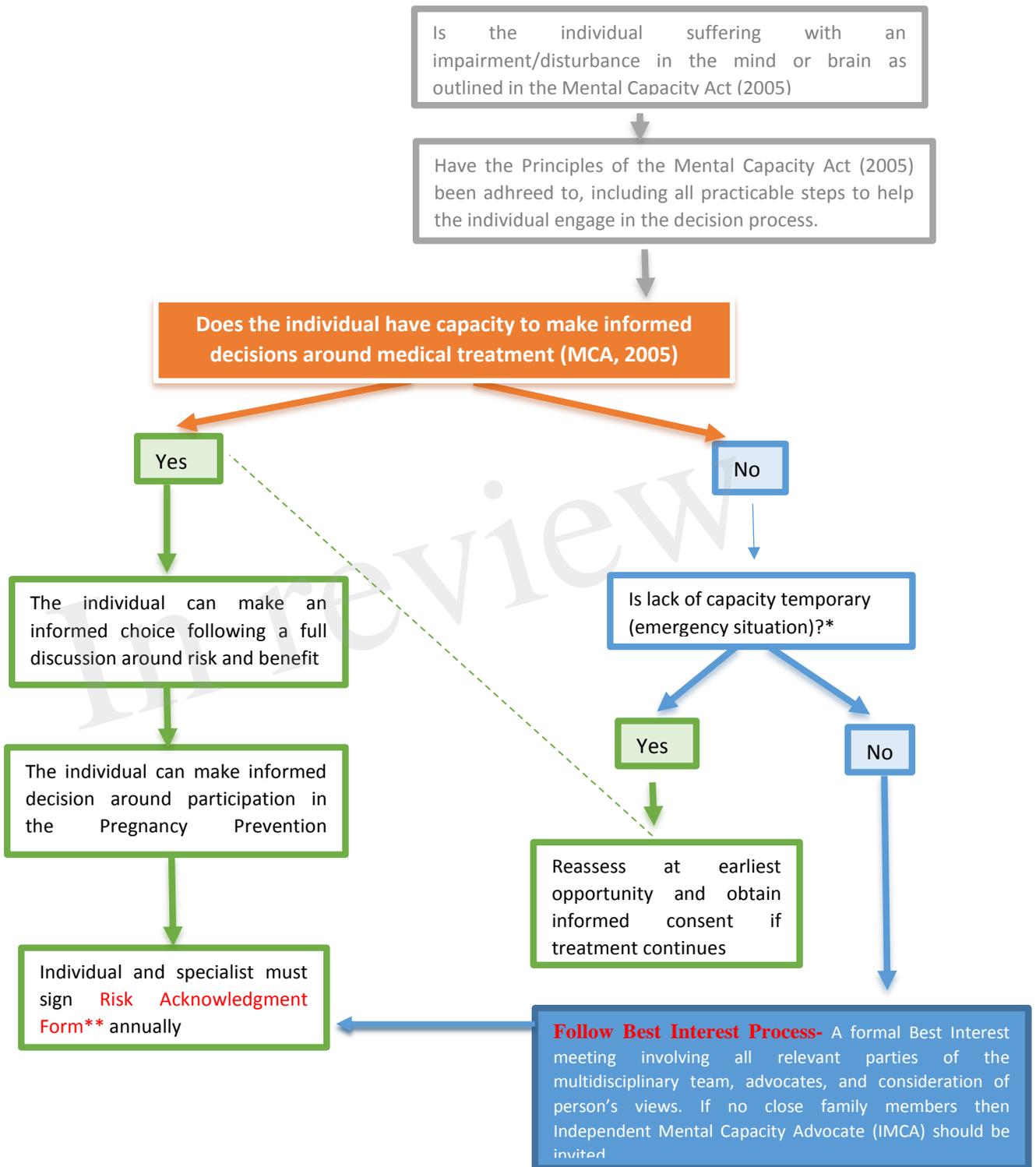
Appendix 2 Consensus opinion of exceptional circumstances for valproate prescription in women of childbearing age [2]

1. *Emergency treatment*- A specialist may consider valproate the most effective medication to manage uncontrolled seizure activity or status epilepticus. In emergency situations it may not be possible to obtain informed consent. Best interest decisions are made rapidly by treating clinicians based on evidence and need. On retaining capacity individuals should be informed of the treatment given and if valproate treatment continues informed consent with participation in the Pregnancy Prevention Programme should be attained at the earliest opportunity.
2. *Informed consent*- There will be women of a childbearing age in whom after a fully informed discussion choose to continue with valproate prescription and do not wish to participate in the Pregnancy Prevention Programme [16]. This includes women who are actively looking to conceive with that decision supported by a specialist.
3. *Lack of capacity*- There will be a population of individuals who lack capacity to make informed choices around medication; this may include a proportion of women with intellectual disability (ID). People with moderate to profound ID may also lack 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 to physical and emotional wellbeing, and be arguably unethical.

Table I. Major malformation rates associated with valproate in prospective observational studies of National/International pregnancy registries

International pregnancy register	Time period (valproate sample)	Major malformation rate	Daily valproate dose (mg)- with malformation vs without malformation
North American AED pregnancy register [17]	1997-2011 (323)	9.3%	1000 vs 750
Australian pregnancy registry [18, 8, 19]	1998-2013 (253)	13.8%	1975 vs 1128 P<0.01
UK and Ireland pregnancy register [9]	1996-2012 (1290)	6.7%	1031.2 vs 897.9 P=0.02
International registry of Antiepileptic drugs and Pregnancy (EURAP) [20]	1999-2016 (1381)	10.3%	Dose dependent relationship with malformation rate (95% CI) P=0.0006 ≤650mg daily 6.3% (4.5-8.6) >650mg to ≤1450mg daily 11.3% (9.0-13.9) >1450mg daily 25.2% (17.6-34.2)

Pathway I. Flow chart for valproate prescription where individuals lack capacity to provide informed consent [21].



*In an emergency situation a formal best interest process may not be possible see Appendix 2

** annotated by clinician as required to suit individual circumstances if indicated