

Guidance Document on Valproate Use in Women and Girls of Childbearing Years

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Royal College of Physicians

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Endorsements

The following organisations have endorsed this document:



Royal College of
General Practitioners



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of Physicians



Royal College of
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Foreword

Medicine changes all the time based on new research, evidence and learnings, and as such the way we do things as healthcare professionals is constantly evolving. When best practice changes, in the interests of delivering the safest possible care for our patients, the way it is communicated across the profession is essential – and that we all take it on board.

Use of sodium valproate in pregnancy is associated with a 40% risk of persistent neurodevelopmental disorders and a 10% risk of physical birth defects. In April 2018, I wrote to all healthcare professionals in England advising them of new regulations from the Medical and Healthcare products Regulatory Agency that valproate should not be prescribed to women of childbearing potential unless they meet the conditions of a Pregnancy Prevention Programme.

This is, of course, important for healthcare professionals to know – but it is also important for them to know how to implement this change and work differently.

I am very pleased that the Medical Royal Colleges have come together to produce this important and helpful guidance, so that doctors and other healthcare professionals across primary and secondary care are on the same page regarding the use of sodium valproate - including around instances where its use is still appropriate.

I hope this new guidance will provide clarity for doctors, and ultimately, improve patient care.



Professor Dame Sally Davies
Chief Medical Officer for England

Executive Summary

Valproate (Epilim, Depakote, Convulex, Episenta, Epival, Kentlim, Orlept, Syonell, Valpal) is associated with a significant risk of birth defects and developmental disorders in children born to women who take valproate during pregnancy. Strengthened regulations governing its use have recently been put in place, and received extensive publicity. The pregnancy prevention programme, PPP, is a key element of the new regulations.

Valproate is licensed for use only in the treatment of epilepsy and bipolar disorder. For some women with these conditions, it may be the only drug that controls their condition. In any woman, abrupt cessation of valproate is dangerous and should not be undertaken. For most women of child-bearing potential with bipolar disorder there are other drugs that have been shown to be at least as effective. The implementation of the new regulations is central to reducing the significant harms associated with valproate use. In daily practice, challenging situations may arise when valproate use is being considered, reviewed or discontinued. Clinicians are required to act in the best interests of each individual patient. This document is intended to provide practical information and guidance, and sources of further support, for clinicians involved with valproate: it gathers data, where available, on best practice and summarises consensus opinion from seventeen national bodies across the UK.

The areas covered for girls are: epilepsy; bipolar disorder; competence to consent to treatment, confidentiality in young women and transition from paediatric to adulthood care. In women of childbearing potential, we discuss: contraception for the PPP across the age range and its risks, discontinuation or exchanging of valproate, women remaining on valproate without a PPP, intellectual disability, failure to carry out annual specialist review, prescribing responsibility, special situations such as status epilepticus, women detained in prison or under the Mental Health Act. In addition, we consider: valproate dispensing; women not at risk of pregnancy; healthcare when pregnancy does occur on valproate; competencies across specialties and roles; adoption and surrogacy; peri-menopausal women and babies born following in utero valproate exposure.

The licensed indications for valproate are serious, sometimes life-threatening, conditions. Valproate may be an effective therapy, but the significant risks associated with its use require clinicians to observe the regulations. However, the circumstances of each individual patient are unique and require bespoke management. This guidance cannot cover every scenario and will require updating as regulations, circumstances and knowledge evolve, and clinicians should pay attention to new information as it is made available.

Disclaimer

This guidance should not override the clinical discretion of the prescriber to act in the best interest of their patient and in accordance with their professional duties and within the limits of their expertise

List of Abbreviations

(A)RAF, (Annual) Risk Acknowledgement Form
CAMHS, Child and Adolescent Mental Health Services
CHC, Combined Hormonal Contraception
Cu-ICD, Copper Intrauterine Device
DMPA, Depot MedroxyProgesterone Acetate
ESN, Epilepsy Specialist Nurses
FACS, Fetal Anticonvulsant Syndrome
FSRH, Faculty of Sexual & Reproductive Healthcare
GMC, General Medical Council
GPs, General Practitioners
GPwERS, GPs with an extended role in epilepsy
HCPs, Healthcare Professionals
ICD, International Classification of Diseases
ID, Intellectual Disability
IMP, Progestogen-only Implant
IUC, Intrauterine Contraception
LARC, Long Acting Reversible Contraceptive
LNG-IUS, Levonorgestrel Intrauterine System
MHA, Mental Health Act
MHRA, Medicines and Healthcare products Regulatory Agency
NICE, National Institute for Health and Care Excellence
POP, Progesterone-only Pill
PPP, Pregnancy Prevention Programme
PREVENT, Pregnancy Prevention Programme
QOF, Qualities and Outcomes Framework
RCOG, Royal College of Obstetrics and Gynaecology
RCPsych, Royal College of Psychiatrists
RPS, Royal Pharmaceutical Society
SRH, Sexual and Reproductive Health
SUDEP, Sudden Unexpected Death in Epilepsy
UKMEC, UK Medical Eligibility Criteria for Contraceptive Use

Introduction

New regulations were issued by the Medicines and Healthcare products Regulatory Agency (MHRA) regarding the use of valproate in girls and women of childbearing potential in March 2018 (1). These regulations have been extensively publicised, with periodic updates, and require action by all involved in the recommendation, prescription and dispensing of valproate. Issues around the use of valproate are also part of the Independent Medicines and Medical Devices Safety Review chaired by Baroness Cumberlege (2).

Historically, valproate was used extensively in this population. Although recent practice has changed, difficulties with implementation of the regulations were foreseen and have emerged in practice. Valproate is an effective drug for certain types of **epilepsy** (3), and epilepsy is a serious neurological condition that carries risks, including of premature mortality. The drug is widely used for the licenced indication of **bipolar disorder**, but there is evidence that there are other treatments with equal or superior efficacy (4). In addition, other treatments present much lower potential risks to fetal development (5). In other mental disorders where valproate is unlicensed there is either no or very limited evidence of efficacy (4). The National Institute for Health and Care Excellence (NICE) recommends that it is not offered to girls and women with mental disorders who are pregnant or have childbearing potential (6).

Women of childbearing potential, whatever their underlying diagnosis, should therefore not be prescribed valproate unless there are exceptional circumstances. During pregnancy, the MHRA regulations also state that valproate should not be prescribed unless a girl or woman suffers from a type of epilepsy that is not responding to other treatments.

In response to these complexities and the serious consequences of valproate use in women during pregnancy, this cross-speciality consensus document has been produced as a practical guide to management, including for particular situations that may present difficulties. There may be separate, additional, risks that are specialty- and disease-specific (e.g. the independent risk of inheritance of the condition for which the mother is prescribed valproate), but such risks will have been present irrespective of valproate use, and are not considered here. The document is based on evidence where available. In many areas there is no evidence base and here the document is based on cross-specialty expert opinion. Additional research is needed in many of these areas. This document seeks to provide support and guidance for the individual healthcare professional facing challenging situations, but it cannot cover every possible clinical scenario.

The MHRA is a regulatory body covering the whole of the UK. The current MHRA regulations (1) state that valproate must no longer be used in any woman or girl able to have children unless she has a pregnancy prevention programme (PPP), also known as PREVENT, in place. The PPP involves:

- Assessing the patient's potential for becoming pregnant
- Explaining the known risks to an unborn child exposed to valproate (30-40% for poor neurodevelopmental outcomes and 10% for major congenital malformations)
- Conducting pregnancy tests before and during treatment as appropriate (<https://www.gov.uk/drug-safety-update/medicines-with-teratogenic-potential-what-is-effective-contraception-and-how-often-is-pregnancy-testing-needed>)

- Explaining the need for highly effective contraception
- Annual (or more frequent) specialist review of treatment
- Specialists using an annual risk acknowledgement form (ARAF) to confirm provision and understanding of the requirements:
<https://www.medicines.org.uk/emc/rmm/1207/Document>

Materials for healthcare professionals (HCPs) and patients are available to support discussions at <https://www.gov.uk/guidance/valproate-use-by-women-and-girls> (1). From April 2019, General Practitioners (GPs) will be encouraged to undertake patient safety quality improvement activities through the Qualities and Outcomes Framework (QOF), including for valproate (7). Changing skills within the NHS mean that many pharmacists, nurses, and midwives are now also Independent Prescribers and the Royal Pharmaceutical Society (RPS) has produced a practical guide for these professionals (8).

The MHRA are currently leading discussions on the creation of a registry of women and girls of childbearing age who are taking valproate. It will be important that such a registry also includes individuals who have stopped valproate as a result of the new regulations, in order to track all significant outcomes related to the changes.

Individual clinicians are required to act in the best interests of each individual patient (9, 10). Each woman or girl of childbearing potential is an individual and, wherever possible, should be fully involved in the choices she makes about her health and fertility (11). The regulations could lead to some situations where the best interests of the patient may not appear to be served. In this situation, clinical judgement should be exercised. When faced with difficult individual circumstances, clinicians should consider making use of additional resources, such as best interest meetings, peer review, consultation with multidisciplinary teams, advice from Trust or Health Board medicines committees or Clinical Director, and speciality support groups. The General Medical Council (GMC) also provides information, for example on prescribing unlicensed drugs (12). Some of the points raised by implementation of the new regulations are complex ethical issues, which we do not attempt to answer in this document. We take a pragmatic approach, considering issues through life stages.

1. Girls with epilepsy

Our consensus is that the current guidance requires clarity with regard to the age and developmental stage of girls/young people as it is not appropriate for all children/young people in the paediatric population. In order to provide a framework for clinical management, the prescribing needs of children/young people should be considered by age and learning ability (13).

The prescribing needs of girls with intellectual disability (ID) are specifically considered further under section 5 of this document.

1.1 Females under 10 years

The current regulations do not advise against the use of valproate in this age group. Girls with epilepsy under the age of 10 years will be managed by specialist services and will be under regular review and must be seen in specialist services at least annually. The choice

of antiepileptic drug in this age group should follow national guidance (13). There is existing information for parents/carers of girls and girls in this age group about the risks of valproate therapy, and that it is not a desirable treatment when they reach adolescence due to the associated risks (14). Information for older girls and their parents is also available (15, 16). This should be discussed and documented in the ARAF on an annual basis. The PPP is not required in this age group.

If a girl less than 10 years has already gone through the menarche (and paediatricians should always ask), they should be managed as for the 10-12 years age category.

1.2 Females aged 10-12 years

Unless there are pressing clinical needs, no female patient aged over 10 years should be commenced on treatment with valproate, if there is potential for future pregnancy. Existing patients should undergo formal evaluation to see if the valproate can be discontinued or substituted with an alternative therapy. Existing patients must remain under specialist care and be seen at least annually. Additionally, the prescriber must ensure that:

- The parents/caregivers of female children and girls understand the need to contact the specialist once the female child using valproate experiences menarche.
- The parents/caregivers and girls who have experienced menarche are provided with the valproate guidance and managed as girls aged 13-15 years (1).
- The ARAF should be completed by the specialist and the responsible person documenting that they are aware of the risks of teratogenicity, but no PPP intervention is required.

1.3 Females aged 13-15 years

Females in this age group who have potential for future pregnancy should only be prescribed valproate if other treatments are ineffective. They must be kept under at least annual review by specialists.

The young woman herself is the most important person in the discussion about the importance of avoiding pregnancy during use of valproate. Therefore, the person that needs to be informed (in language that she can understand and with age-appropriate written/digital information) is the young woman. Discussing the contents of the ARAF could be very sensitive if the parents or carers are present (see Section 3 below). If there are "*compelling reasons to indicate that there is no risk of pregnancy*" (1), information about pregnancy risk should be given, but the full PPP may not be required.

In girls who are known to be, or are likely to become, sexually active in the near future the full PPP should be implemented as for an adult woman. MHRA are currently developing an ARAF more appropriate to this age group which will soon be available on the MHRA website.

1.4 Females aged 16 years and over

These young women should be managed as adult women in line with PPP. Females over 16 with ID should be managed as outlined in section 5.

2. Girls with bipolar disorder

Bipolar disorder is a condition that can be highly disruptive to the development of young people and frequently requires treatment with medication. As in adults, valproate should rarely be used in girls who could get pregnant: for example, when the illness is very severe and there is no effective alternative option. A girl receiving treatment with valproate should be under the close supervision of a specialist Child and Adolescent Mental Health Service (CAMHS).

3. Competence to consent to treatment and confidentiality in young women

Many young women do not wish to discuss their sex lives with their parents or carers. The median age for first heterosexual sexual experience is 14 years (17). Those under age 13 are not considered competent legally to consent to sexual activity (18-20). If a girl under 16 years has mental capacity, her competence to consent to treatment needs to be assessed (21). This applies to valproate as well as contraception. However, having the capacity to consent to sexual activity may be different from the capacity to consent to a high risk treatment, such as valproate. Competence to consent to treatment is demonstrated (22) if she can:

- understand the treatment, its purpose and nature, and why it is being proposed
- understand its benefits, risks and alternatives
- understand in broader terms what the consequences of the treatment will be
- retain the information for long enough to use it and weigh it up in order to arrive at a decision

In young women who are assessed as being competent to consent to sexual activity, the conversation about sexual activity and contraception should take place without the parents and respect the principles of confidentiality (23). These discussions should take place in paediatric services and CAMHS, with onward referral to primary care or sexual health services for contraceptive provision if required. A subsequent discussion in the presence of the parents/carers can *also* take place (but must respect confidentiality) and discussion between the girl and her parents/carers should be actively encouraged.

We consider that if competence has been demonstrated, then after discussion regarding the risks associated with use of valproate in pregnancy and in line with GMC guidance, it follows that contraceptive advice, provision of contraception and signing of the valproate ARAF is entirely appropriate for young women aged 13-15; parental consent would *not* be required, but should be encouraged.

Where ID is also present, there will be additional issues to consider (see below, main section 5).

4. Transition of care from paediatric services or CAMHS to adult services

The transition of girls from paediatric epilepsy care or CAMHS to adult care is a time requiring particular care across the spectrum of health conditions. Anecdotal evidence suggests this is when a girl can fall between the gaps and local services should have clear policies about when the transition happens. It is essential to proactively ensure continuity

of care, including for use of valproate and the PPP, at a time when behavioural and compliance issues may be particularly acute, whilst conversely seizure or mood control on valproate may be good. Vigilant, seamless prescribing support is imperative in this cohort of young women due to lifestyle issues, increased risk of sudden unexpected death in epilepsy (SUDEP), potential interactions with contraception, balancing future risk of teratogenicity versus seizure control, and associated cognitive, hormonal, and psychiatric adverse effects of alternative antiepileptic drugs prescribed instead of valproate. For girls with moderate to severe ID, this transition process can be protracted as they often attend specialist schools until the age of 19 years or later.

All young people with **epilepsy**, with or without significant ID, should ideally participate in a transition process from the age of 12 years to specifically address the needs of this age group and plan for handover to adult services. This is essential for young women who remain on valproate treatment. In girls with **mental illness** the transition to adult services will normally occur around 18 years.

5. Women of childbearing potential

The MHRA regulations apply to both **epilepsy** and **bipolar disorder** and state:

"In girls and women of childbearing potential (a pre-menopausal female who is capable of becoming pregnant) valproate must be initiated and supervised by a specialist experienced in the management of epilepsy or bipolar disorder. Valproate should not be used in girls and women of childbearing potential unless other treatments are ineffective or not tolerated. Valproate may be initiated in girls and women of childbearing potential only if the conditions of PREVENT – the valproate pregnancy prevention programme (PPP) are fulfilled."

"This includes women who are not currently sexually active unless the prescriber considers that there are compelling reasons to indicate that there is no risk of pregnancy. Individual circumstances should be evaluated in each case, involving the patient in the discussion, to guarantee her engagement, discuss therapeutic options and ensure her understanding of the risks and the measures needed to minimise the risks."

The regulations do not refer to specific age ranges.

5.1 Contraception for the PPP

When discussing the PPP, the information voluntarily provided by women and girls about their contraceptive choices should generally be taken in good faith to be accurate.

Prior to provision of contraception, appropriate valid consent must be obtained by the provider. For consent to be valid, the woman must (24):

- Have the mental capacity to make the decision
- Have enough information and opportunity for discussion prior to making a decision
- Be free from duress

Valid consent is obtained by the woman being informed of the nature and purpose of any proposed treatment and the likely outcome(s)—including any significant possible adverse outcomes and the likely result of not proceeding with the proposed treatment—so that she

can make an informed decision. Women must be treated as individuals and their wishes respected at all times (24).

Women of reproductive age who are using valproate are advised to use highly effective contraception to avoid pregnancy. Women should be made aware that no method of contraception is 100% effective (25).

Methods of contraception which are considered '*highly effective*' (1) include the long-acting reversible contraceptive (LARC) methods: copper intrauterine device (Cu-IUD), levonorgestrel 13.5mg/19.5mg/52mg intrauterine system and progestogen-only implant (IMP), as well as male and female sterilisation (with male sterilisation, the possibility of a new partner needs to be kept in mind). These methods all have a failure rate of less than 1% with typical use (Table 1) (26). Women using the progestogen-only implant should avoid use of any medication that induces hepatic enzyme activity as this could reduce contraceptive effectiveness (27).

Table 1: Percentage of women experiencing an unintended pregnancy within the first year of use with typical use and perfect use (modified from Trussell et al. (26))

Method	Typical use (%)	Perfect use (%)
No method	85	85
Fertility awareness-based methods	24	0.4–5
Female diaphragm	12	6
Male condom	18	2
Combined hormonal contraception (CHC) including combined contraceptive pill, transdermal patch and vaginal ring	9	0.3
Progestogen-only pill (POP)	9	0.3
Progestogen-only injectable depot medroxyprogesterone acetate (DMPA)	6	0.2
Copper intrauterine device (Cu-IUD)	0.8	0.6
Levonorgestrel 13.5mg/19.5mg/52mg intrauterine system (LNG- IUS)	0.2	0.2
Progestogen-only implant (IMP)	0.05	0.05
Female sterilisation	0.5	0.5
Vasectomy	0.15	0.1

The estimated typical use failure rate of combined hormonal contraception (CHC; the combined contraceptive pill, transdermal patch and vaginal ring) and progesterone-only pill (POP) is 9%; for the progestogen-only injectable intramuscular and subcutaneous depot medroxyprogesterone acetate (DMPA) it is 6%. Given the importance of avoiding pregnancy during use of known teratogenic drugs, the Faculty of Sexual & Reproductive Healthcare (FSRH) recommends that during use of valproate, women using CHC, POP or DMPA should be advised to use additional contraceptive precautions (e.g. condoms) (25).

It is important to note that ethinylestradiol (present in most combined contraceptive pills, the combined transdermal patch and the combined vaginal ring) may modestly reduce valproate levels (27). The contraceptive effectiveness of CHC, POP and IMP is not reduced by valproate, but may be reduced by use of other medications that induce liver enzymes; intrauterine contraception (IUC) (28) and the DMPA are not affected (29).

5.2 Contraceptive choice in young women

Young age alone does not limit contraceptive choice. From menarche, the benefits of use of all effective reversible methods of contraception generally outweigh potential risks (22, 30). Young age and nulliparity do not contraindicate use of IUC (28). Despite concerns about achieving peak bone mineral density, use of DMPA by women under age 18 is acceptable if other methods have been discussed and considered unsuitable or unacceptable (22, 30). The UK Medical Eligibility Criteria for Contraceptive Use (UKMEC 2016) should be used to assist clinicians in determining which contraceptive methods can be used safely in young people with particular medical conditions/characteristics (30).

5.3 Contraception choice in older women

Women aged 50 and over should be advised to avoid CHC due to associated cardiovascular and breast cancer risk (31). DMPA is generally avoided for women over 50 and for women over 40 with additional risk factors for osteoporosis (of which long term valproate use is one) because of concern regarding bone health. The Cu-IUD, LNG-IUS, IMP (and POP plus condoms) can all be used for contraception by a woman using valproate until age 55 years. The UKMEC 2016 should be used to determine safety of contraceptive use by women with other medical conditions (30).

In general, contraception is required until age 55 unless a clinical diagnosis of menopause is made before this time; spontaneous conception after age 55 is exceptionally rare. FSRH guidelines recommend that, *"women should be informed that although a natural decline in fertility occurs with age and spontaneous pregnancy is rare after age 50, effective contraception is required until menopause to prevent an unintended pregnancy"* (31).

Menopause can be diagnosed in a woman aged over 50 after one year of amenorrhoea (this applies only if the woman is not using hormonal contraception) (31). If a woman aged over 50 is very keen to stop contraception and has a follicle stimulating hormone level >30iU/L, she may consider stopping contraception a year later. However, this would not absolutely exclude future ovulation and risk of pregnancy, as hormone levels fluctuate widely in the peri-menopause. Post-menopausal women do not need to be referred for specialist advice for the PPP; however, it would be helpful to document their status on the ARAF.

5.4 Emergency contraception

If a woman or girl is not compliant with the PPP, she should also be advised to seek emergency contraception, if appropriate, to prevent a pregnancy. If a woman using valproate has had unprotected intercourse, if all recent unprotected intercourse was within the last 5 days or she is within 5 days of the earliest likely date of ovulation, she should be offered a Cu-IUD, the most effective method of emergency contraception. If a Cu-IUD is not suitable or acceptable, she should be offered oral emergency contraception with effective contraception "quick started" immediately after levonorgestrel oral emergency contraception or 5 days after ulipristal acetate oral emergency contraception (32).

5.5 Adverse effects of contraception

When prescribing any medicine, the potential risks as well as the intended benefits of the medication(s) in question need to be considered. In this instance, the potential benefits of valproate, as well as the potential harms to the patient and to any future offspring, are well described. However, it is also important to consider that the contraception required as part of the PPP may also have potential adverse effects associated with its use e.g. irregular bleeding. The risk/benefit assessment and potential adverse effect profile is therefore more complex than for most other medications and may require coordinated specialist input. By consensus, most neurologists and psychiatrists responsible for recommending valproate use lack the knowledge, experience and communications skills about contraception needed for this aspect of the discussion. Healthcare professionals must recognise and work within the limits of their competence: appropriate referral is essential for implementation of the PPP. In some areas of the UK there are limitations in services for contraception provision. Each specialist clinic should foster relations with their local sexual and reproductive health (SRH) services so that there are special access pathways for these patients, who may be less able than other women to access SRH services directly without help from healthcare professionals.

5.6 Discontinuation or exchanging of valproate

Any fully informed discussion about the use of valproate must also present the risks of withdrawing or exchanging valproate for another agent.

In the context of **epilepsy**, the discussion will include the limited information available on the comparative effectiveness of different antiepileptic drugs in particular types of epilepsy (3, 33); additional data will be emerging from further comparative trials (e.g. SANAD2). Discussions should include the risk of unintended consequences of not taking valproate when this might be the best therapeutic option – such as the risks of loss of seizure control on its withdrawal (34, 35), or lack of control when its use may not even have been considered (36). The potential accompanying increased risk of SUDEP with lack of seizure control needs consideration. The proportion of maternal deaths related to epilepsy is estimated at between 4-7%; SUDEP is an important contributor to these deaths (37). Whilst overall maternal deaths fell over the 30 year period from 1979-2008, the proportion attributed to epilepsy has risen (38). Clinical experience also shows that in a proportion of individuals who recommence an antiepileptic drug that has been withdrawn, the previous degree of seizure control cannot be regained (39). Women who are in the process of gradually switching from valproate to alternative treatments should be counselled to continue using effective contraception, if they wish to avoid unintended pregnancy. Valproate has a mood-stabilising effect, and, separately, unintended consequences on mood need to be explained, as these can affect quality of life and seizure control.

In the context of **bipolar disorder**, if a non-pregnant woman wishes to withdraw her valproate she should be referred for specialist assessment. Under specialist care, valproate should be tapered down gradually (4).

5.7 Women choosing to remain on valproate, but without a PPP

This is a very contentious issue. Prescription and use of valproate in a woman of childbearing potential without a PPP would be outside its licence. The General Medical Council prescribing guideline outlines the roles and responsibilities of the prescriber (typically the GP) under these circumstances (12).

There will be women who wish to remain on valproate but do not want to comply with a PPP. This document does not take a position on such use, but seeks to provide guidance for healthcare professionals faced with this situation. Examples of these circumstances include: in the context of epilepsy, with its attendant risk of SUDEP and other impacts on quality of life (such as for driving privileges) (40), concern about the risks of changing to a different antiepileptic drug with either proven lack of, or unknown, efficacy in the individual patient. Patients may not consent to a PPP for personal, medical, religious or cultural reasons. In addition, there may be women who wish to avoid bleeding problems or side effects associated with some hormonal methods. The GMC consent process (currently under consultation) (41), states that:

*You **should** do your best to make sure that such patients have considered the available options and reached their own decision (clause 42).*

*You **must** respect a patient's decision to refuse an investigation or treatment, even if you think their decision is wrong or irrational (clause 43).*

It is essential that the discussion is fully documented, so that it is clear how it has been made, and following best practice all parties involved should be included in correspondence. Even if a woman is non-compliant with a PPP, it is unsafe to withhold the prescription of valproate.

In this situation the requirement for decisions to be fully informed must be followed. Patient support groups for families affected by in utero valproate exposure can offer information on the undesirable outcomes that can follow such exposure and relevant information and links are provided at the end of the document. Whilst the risks may be known, the actual outcomes may not be within the direct experience of healthcare professionals discussing valproate usage with women and girls of childbearing potential. A second professional opinion (e.g. another neurologist, psychiatrist, fetal medicine specialist, clinical geneticist) may be helpful for women choosing to remain on valproate without a PPP, though the reality of service provision issues need to be recognised. The discussion and decision need to be fully documented, revisited at least annually, with a mechanism for rapid review in case of changes, including pregnancy.

Important issues concerning the right to autonomy and societal values are beyond the scope of this document.

5.8 Intellectual Disability (ID)

The prevalence of epilepsy is high in patients with ID: they constitute nearly 25% of the total population with epilepsy and 60% of the total population with treatment-resistant epilepsy (42). General considerations about capacity must always be borne in mind, including the possibility that capacity may fluctuate and should be considered with regard to the issue in hand (43).

Apart from epilepsy and bipolar disorder, valproate is sometimes prescribed to people with ID for the management of challenging behaviours: these include acts of aggression towards people or property, self-neglect, and self-harm and occur in 5–15% of people with ID (44). Scientific support for the efficacy of valproate in this area is very limited (45) and the most commonly prescribed drugs for challenging behaviour are antipsychotics. In clinical practice, valproate is also sometimes used in people with ID to manage mood

instability and fluctuations of arousal in the absence of a psychiatric diagnosis, but again the evidence base here is very limited.

Because of the lack of supporting evidence and valproate's unlicensed status for these problems, alternative management strategies should be pursued in girls and women with ID and childbearing potential. Discussions of the research evidence and detailed management guidance can be found in NICE (44) and RCPsych reports (4, 42, 45)

5.8.1 With lack of mental capacity

There are women of childbearing potential in whom lack of mental capacity means that discussion with the woman herself cannot take place and in whom consent to sexual activity would be unlikely to be given, or impossible. This will include most girls and women with some specific epilepsy syndromes, such as Dravet Syndrome or Lennox-Gastaut Syndrome, for which valproate is the recommended first-line treatment (13). Valproate is typically also the first-line treatment for many other severe epilepsies ('developmental and epileptic encephalopathies') which are typically associated with ID.

The following statement from the MHRA guide needs consideration: *"For children or for patients without the capacity to make an informed decision, provide the information and advice on highly effective methods of contraception and on the use of valproate during pregnancy to their parents/caregiver/responsible person and make sure they clearly understand the content."* For women in this category, we recommend discussion with the family and the care providers to evaluate whether sexual activity is likely to occur or not. If it is agreed that there is no risk of pregnancy, the ARAF should be completed on at least one occasion. The discussion should be clearly documented in medical records and relevant correspondence, and the position should be reviewed at least annually in case of changes in circumstances. It is important to recognise that these discussions in themselves are difficult and can cause psychological distress for any party involved.

5.8.2 With mental capacity

Girls and women with mild ID and mental capacity should be involved in the discussion wherever possible. Careful evaluation will be required in this setting: the PPP and ARAF will be necessary if there is judged to be childbearing potential. Capacity needs to be considered in each individual situation e.g. consent to have sex is not the same as consenting to use contraception. Women with ID have the right to be sexually active if this is consensual, but healthcare professionals also need to be alert to the possibility of sexual abuse.

Involvement and use of best interest meetings, adult safeguarding, Mental Health Capacity Advocacy, Court of Protection, community ID services, hospital leads for people with ID, and others involved in supporting the individual woman may be required, in order to balance working in their best interests, sexual human rights and least invasive therapy. Many of these issues are discussed in a useful paper (46).

5.9 Women who fail to attend their specialist appointment

Some women who are on valproate and have childbearing potential may miss their appointment for specialist assessment and may be at risk of a valproate-affected pregnancy. In this situation, the specialist needs to follow up, by re-inviting the woman, attempting a telephone discussion and by contacting the GP. Good communication

between service providers and the patient is clearly very important: the letter from the specialist needs to explicitly identify the risks of a valproate-affected pregnancy and to request the GP to proactively contact the woman to discuss. The onus and responsibility then lies with the prescriber to decide how to manage this situation, which would involve prescribing outside the licence. Taking advice and scrupulous documentation are clearly very important, but the GP needs to carefully consider the risks of failing to prescribe.

5.10 Prescribing responsibility: consider shared care

Most specialist services will request the GP to issue valproate prescriptions for their patients. As far as the GMC is concerned, the prescriber takes the responsibility and must be competent to do so (12). Not all GPs can be expected to accept this responsibility if they feel this involves them practising beyond their level of competence. Shared care is another way for the responsibility of prescribing to be distributed between specialist and GP. However, the doctor who signs a prescription will still be responsible, even in shared care (47).

In addition, all parties, including the patient, must be willing to accept this arrangement. Shared responsibility, education, communication and support in getting rapid advice may reassure the GP and it is our consensus view that all those involved consider moving towards this as the usual way in which valproate prescribing should be arranged.

5.11 Particular situations that may arise

5.11.1 Status epilepticus

Although NICE protocols for the management of this acute medical emergency do not include valproate, its intravenous formulation (and those of other antiepileptic drugs) is not uncommonly used for status epilepticus (48). Best interest considerations will apply in the acute setting. Whilst an urgent pregnancy test is not always part of protocols for treatment of status, it would be prudent for this to be included, and should be undertaken if valproate is to be used, but should not delay treatment of this life-threatening emergency. Antiepileptic drugs introduced for seizure control in status may or may not be continued on recovery, and discussion will need to include following the usual PPP if valproate continuation is being considered.

5.11.2 Women on valproate who are detained in prison

There may be additional confounding factors, such as mental illness or substance abuse. Healthcare services in prison are commissioned separately by NHS England (49). However, medical management still needs to follow MHRA regulations, and women should have access to specialist epilepsy, mental health and contraceptive services, including access to valproate if its use is considered best: the principles of care remain unchanged.

5.11.3 Women detained under the Mental Health Act (MHA)

An acute and severe episode of mania is the most likely clinical scenario where reproductive safety issues of valproate could arise in a girl or woman detained under the MHA. Valproate should only be considered in patients who have had an insufficient treatment response to other medications and for whom there are good reasons not to use electroconvulsive therapy (ECT). Sexual disinhibition and impaired judgement are common in acutely ill manic patients, so that a girl or woman with childbearing potential is at an elevated risk of unintended pregnancy. It would be unlikely that she has the mental capacity to consent to sexual activity, so that it becomes the responsibility of the clinical team to prevent her from having intercourse and to put appropriate measures in place.

Her mental capacity needs to be assessed repeatedly to permit discussions with the patient or carer according to the PPP as soon as her mental state has sufficiently improved.

Once the patient's mood has stabilized it may be possible to cautiously rationalise medication ideally withdrawing valproate and replacing it with an alternative drug if necessary. It is essential that plans for treatment, need for contraception and proactive follow up are discussed with the community mental health team to whom the patient's care is transferred on discharge from hospital. It is the responsibility of the mental health team to communicate actions clearly with the GP and agree which professional is responsible for ensuring that they are followed up. Clinical experience shows that transition between services can be a time when a patient 'falls through the gap'.

In a pregnant woman with a mental disorder detained under the Mental Health Act, valproate should not be initiated, and other drug treatments or ECT should be used (4, 50).

5.12 Pharmacies and valproate dispensation

Pharmacists have been advised that they need, on presentation of a prescription for valproate, to discuss the warnings about its use with the patient, and through doing so should be able to determine if there is a PPP in place or not. If not, the patient should be referred back to their GP, but the prescription should still be dispensed. The pharmacy pathway is available from the RPS (51). Dispensing GPs need to ensure that their pharmacy technicians are aware of this guidance.

6. Women not at risk of pregnancy for other reasons

There will be women who are not at risk of pregnancy for health-related, physical or personal reasons. Examples include women who have had a hysterectomy or tubal ligation, a woman in a long term monogamous relationship with a vasectomised male partner, women in same sex relationships not planning pregnancy or a transgender woman who does not have a uterus. The reason for no contraception being needed in such cases can be documented on the ARAF and wherever appropriate reviewed annually. In addition, it is recommended that such information is documented in the patient records and relevant clinical correspondence. If the reason for not being at risk of pregnancy is permanent, annual specialist review from the perspective of the regulations per se should not be necessary, but may be indicated for the underlying condition. There may be other compelling reasons that will need to be considered on an individual basis, such as religious convictions.

If the reason for not being at risk of pregnancy is not considered permanent, the woman needs to be fully aware of the high likelihood of serious harm to the child if she should conceive, and attend for annual specialist review and completion of the ARAF, in line with the PPP. For women detained under the MHA, see above.

7. Pregnancy in women on valproate

Despite the change in the prescribing regulations for valproate, some women will still become pregnant whilst taking valproate. Whatever their diagnosis, they should be

referred for an urgent appointment with an appropriate specialist and advised to continue their medication until seen, because of the high risks of stopping abruptly.

There will be some women who understand the issues, and after consideration, decide that continuing valproate during a pregnancy is a better option for them than the consequences of stopping valproate.

In the **context of a pregnancy in a woman with epilepsy**, detailed discussion will be necessary between the woman, her obstetrician and neurologist, especially to attempt to minimise risk (52).

Valproate is contraindicated in bipolar disorder in pregnancy. In the **context of a pregnancy in a girl or woman with bipolar disorder** a referral for an urgent appointment with a psychiatrist and obstetrician should be made. She should be advised to continue the medication until seen because she would be at a high risk of rapid deterioration if valproate is abruptly stopped. To avoid this, valproate should be tapered down gradually (4). All treatment options to reduce the risk of recurrence and optimize the woman's mental health in pregnancy should be offered and discussed with her. Services should work with the woman to develop a comprehensive care plan for the perinatal period that is appropriate for her individual needs. It is important that the community or specialist mental health midwife works closely with the team and that the obstetrician, GP and all other involved agencies know about the care plan. This is particularly important around the time of delivery and the early postnatal period when the woman is most likely to relapse. Perinatal mental health services can also provide assessment, consultation and management advice for pregnant girls whilst their main care remains with services for child and adolescent mental health and intellectual disabilities.

The woman may decide that she wishes to consider termination of the pregnancy, and in such cases she would meet the relevant criteria under [Section 1.1.d of the Abortion Act 1967](#) ("that there is a substantial risk that if the child were born it would suffer from such physical or mental abnormalities as to be seriously handicapped").

If the woman decides to continue with the pregnancy, this should be managed as described in Royal College of Obstetrics and Gynaecology (RCOG) guidelines (53). Women should receive timely and non-judgmental support and advice throughout their pregnancy, and be encouraged to engage with their obstetric and specialist care. There is a risk that if the woman perceives the care as judgemental she may disengage from all care.

8. Other issues

8.1 Which healthcare professionals can be considered as specialists?

The latest guide for HCPs (54) from the MHRA notes:

"Specialist prescriber is defined as a consultant psychiatrist or a consultant neurologist who regularly manages bipolar disorder or complex epilepsy".

However, there is an expectation that some functions to support the PPP may be carried out by other healthcare professionals as part of a consultant-led team.

8.2 Epilepsy Specialist Nurses (ESN) and specialist midwives

Epilepsy specialist nurses (and specialist midwives during planning for pregnancy, pregnancy and post-natally) are in an excellent position to support girls and women with epilepsy taking valproate. For the purposes of this guidance, they should be regarded as specialists and are integral to the process. There would be different levels of responsibility depending on whether the nurse held an independent prescribing qualification or not.

Epilepsy specialist nurses with an independent prescribing qualification will be able to see women and girls taking valproate, advise on an appropriate alternative drug, or on appropriate contraception in line with the PPP, and complete the ARAF. They would also be in a position to initiate valproate for women who satisfy the terms of the PPP and for whom alternative treatment is unsuitable. This decision should be taken as part of a multidisciplinary team, involving a consultant neurologist.

Epilepsy specialist nurses who do not hold an independent prescribing qualification will have local governance arrangements, whereby recommendations they make would be ratified by a consultant neurologist. This would be the same process used by nurses without a prescribing qualification when changing medication for other reasons. Following a decision from the multidisciplinary team, which would include a consultant neurologist, an epilepsy specialist nurse without a prescribing qualification would be able to provide ongoing management and support for a woman continuing to take valproate, and complete the annual PPP risk assessment. Nurses without an independent prescribing qualification would not be able to recommend the initiation of valproate without referral to a consultant neurologist.

8.3 GPs with an extended role in epilepsy (GPwERs)

GPwERs exist in some areas of the country (e.g. Bradford) and have the necessary skills to undertake the specialist role described by the MHRA. They are in a particularly good position to provide long-term continuity of care, to see women closer to home and to advise women about appropriate contraception. The competencies required have been described (55). They can initiate valproate for women who satisfy the terms of the PPP and for whom alternative treatment is unsuitable. It would be good practice for this decision to be taken as part of a multidisciplinary team, involving a consultant neurologist. In Bradford, where the service is commissioned, GPwERs are ideally placed to deal with the vast majority of this work, with the support of local neurologists.

8.4 Adoption and surrogacy

Women on valproate may need support and encouragement to approach adoption. However, uncontrolled seizures may in some circumstances be considered a safeguarding risk and as a result adoption may be declined. Another option may be surrogacy. Surrogacy is legal in the UK and a pathway was published in February 2018 (56). Currently, it is only available privately, and would be financially prohibitive for many women. It is unknown if surrogacy protects from all risks: it is not known if there is a potential risk through an ovum exposed to valproate before ovarian retrieval in the in vitro fertilisation process. However, women in these difficult circumstances need support and exploring the option of surrogacy on the NHS for appropriate women on valproate should be considered by NICE for cost-effectiveness.

9. Babies born to women who have taken valproate during pregnancy

At the moment there is no standard follow up pathway for babies born to mothers who have taken valproate during pregnancy. If no abnormalities are obvious at birth the baby is usually discharged with instructions to be referred back if problems develop. However neurodevelopmental issues may be subtle and overlooked by generalist healthcare professionals. Moreover, some neurodevelopmental issues, especially if mild, cannot be diagnosed until much later in childhood, at which point maternal medication history in pregnancy may either not be available or not considered. In addition, fetal valproate syndrome is not recognised yet by the International Classification of Diseases (ICD); the closest classification is fetal anticonvulsant syndrome (FACS). Families may be reluctant or less able to seek help. All harm to these babies can be documented on a [Yellow Card](#) and they should be referred to the Valproate Register when it is operational.

There are some simple steps that could be taken. Midwives could notify the GP and Health Visitor on discharge from hospital that the baby has been exposed to valproate (or other antiepileptic drugs) in utero. This should be coded on medical records and entered into the baby's "Red Book". The best way for standardised coding across settings will need to be defined. Health visitors should be competent to monitor for FACS during child development checks, so that they are able to identify and refer early. In order to fulfil this role, they need access to training and resources.

It is our consensus view that specialist routine follow up of all babies at risk of FACS should be recommended, so that health, education and social care services can optimise the care of these children and help their families. The details of how this should happen and how it will be funded need to be developed. The Valproate Register could be a means of facilitating this. The UK Epilepsy and Pregnancy Register, which has provided important evidence on valproate risks, should also be considered.

Concluding remarks

Valproate use is now under strict regulation. Complicated situations can arise that require careful thought and may need referral for specialist management. We recognise that not all scenarios are covered in this document, and that regulations and associated guidance may change over the coming period of time. Most importantly, clinicians must pay close attention to each particular girl or woman's circumstances, and always act in their best interests.

Patient Support Networks

Bipolar UK	0333 323 3880
Epilepsy Action	0808 800 5050
Epilepsy Society	0149 460 1400
FACSaware	0116 220 0486
Meds and Birth Defects	0208 386 9271
Mind	0300 123 3393
OACS	0790 420 0364
SUDEP Action	0123 577 2850
UK Epilepsy and Pregnancy Register	0800 389 1248

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