

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

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## Endorsements

The following organisations have endorsed this document:



## Contents

Endorsements .....	2
Executive Summary .....	5
List of Abbreviations.....	6
Introduction.....	7
1. Girls with epilepsy.....	9
1.1 Females under 10 years.....	10
1.2 Females aged 10-12 years.....	10
1.3 Females aged 13-15 years.....	10
1.4 Females aged 16 years and over.....	11
2. Girls with bipolar disorder .....	11
3. Girls under 16: sexual activity, capacity, confidentiality and safeguarding .....	11
3.1 Communicate the decision .....	11
4. GMC principles on Decision-making, consent and capacity .....	12
5. Transition of care from childrens' services or CAMHS to adult services .....	13
6. Women of childbearing potential.....	13
6.1 Contraception for the PPP.....	13
6.2 Drug interactions .....	15
6.3 Contraceptive choice in young women.....	15
6.4 Contraception choice in older women .....	15
6.5 Emergency contraception .....	16
6.6 Adverse effects of contraception.....	16
6.7 Discontinuation or exchanging of valproate.....	16
6.8 Women choosing to remain on valproate, but without a PPP .....	17
6.9 Women who fail to attend their specialist appointment or who refuse to engage with specialist referral .....	18
6.10 Intellectual Disability (ID) .....	18
6.11 Non face to face consultations.....	20
6.12 Prescribing responsibility: consider shared care.....	20
6.13 Particular situations that may arise .....	21
6.14 Pharmacies and supply of valproate .....	22
7. Women not at risk of pregnancy for other reasons .....	22
8. Pregnancy in women on valproate .....	22
9. Other issues .....	23
9.1 Which healthcare professionals can be considered as specialists? .....	23
9.2 Epilepsy Specialist Nurses (ESN) and specialist midwives.....	23
9.3 GPs with an extended role in epilepsy (GPwERs).....	24

9.4 Independent Prescribing Pharmacists with scope in neurology/mental health (Pharmacist IP).....	24
9.5 Mental Health.....	25
9.6 Adoption and surrogacy.....	25
10. Babies born to women who have taken valproate during pregnancy .....	25
11. Concluding remarks .....	26
12. Patient support networks.....	27
Contributors.....	28
References .....	29

## Executive Summary

Valproate (Epilim, Depakote, Convulex, Episenta, Epival, Kentlim, Orlept, Syonell, Valpal and Belvo) is associated with a significant risk of birth defects and developmental disorders in children born to women who take valproate during pregnancy. The catastrophic harm of historic prescribing of valproate in pregnant women has recently been publicly reviewed. The MHRA has strengthened regulations governing its use: the pregnancy prevention programme, PPP, is a key element of these regulations.

In the UK valproate is licensed for use in the treatment of epilepsy and for some women, it may be the only drug that controls their condition. It is also licensed for the treatment of bipolar disorder, but there are other drugs that have been shown to be at least as effective. For 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 nineteen 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 child to adult 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 carefully. However, the circumstances of each individual patient are unique and require individualised management. This guidance cannot cover every scenario and will require on-going updating as regulations, circumstances and knowledge evolve, and clinicians should pay attention to new information as it is made available.

This document has been updated to reflect changes since its initial publication in 2019. The advice it contains is applicable across the four nations comprising the United Kingdom (UK).

## 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

ARAF, Annual Risk Acknowledgement Form  
CQC, Care Quality Commission  
CAMHS, Child and Adolescent Mental Health Services  
CHC, Combined Hormonal Contraception  
Cu-IuD, Copper Intrauterine Device  
DMPA, Depot Medroxyprogesterone Acetate  
ECT, Electro-convulsive therapy  
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  
IMMDSR, Independent Medicines and Medical Devices Safety Review  
ICD, International Classification of Diseases  
ID, Intellectual Disability  
iHV, Institute of Health Visiting  
IMP, Progestogen-only Implant  
IUC, Intrauterine Contraception  
LARC, Long Acting Reversible Contraceptive  
LNG-IUS, Levonorgestrel-releasing Intrauterine System  
MHA, Mental Health Act  
MHRA, Medicines and Healthcare Products Regulatory Agency  
NHS, National Health Service  
NICE, National Institute for Health and Care Excellence  
NMC, Nursing and Midwifery Council  
POP, Progestogen-only Pill  
PPP, Pregnancy Prevention Programme  
PREVENT, Pregnancy Prevention Programme  
QOF, Qualities and Outcomes Framework  
RCOG, Royal College of Obstetricians and Gynaecologists  
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  
UKTIS, UK Teratology Information Service

## Introduction

The Medicines and Healthcare Products Regulatory Agency (MHRA) is a regulatory body covering the whole of the UK. New regulations were issued by the 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. The roles of each group of health and social care professionals have been summarised by the Care Quality Commission (CQC) (2). Difficulties with implementation of the regulations were foreseen and have emerged in practice.

The Independent Medicines and Medical Devices Safety Review (IMMDSR) chaired by Baroness Cumberlege was published in July 2020 (3), documenting its investigation of valproate prescription to pregnant women when it was clearly known to cause congenital malformations and neurodevelopmental problems. When the review was announced by the then Secretary of State for Health, Jeremy Hunt, the aim was to build a

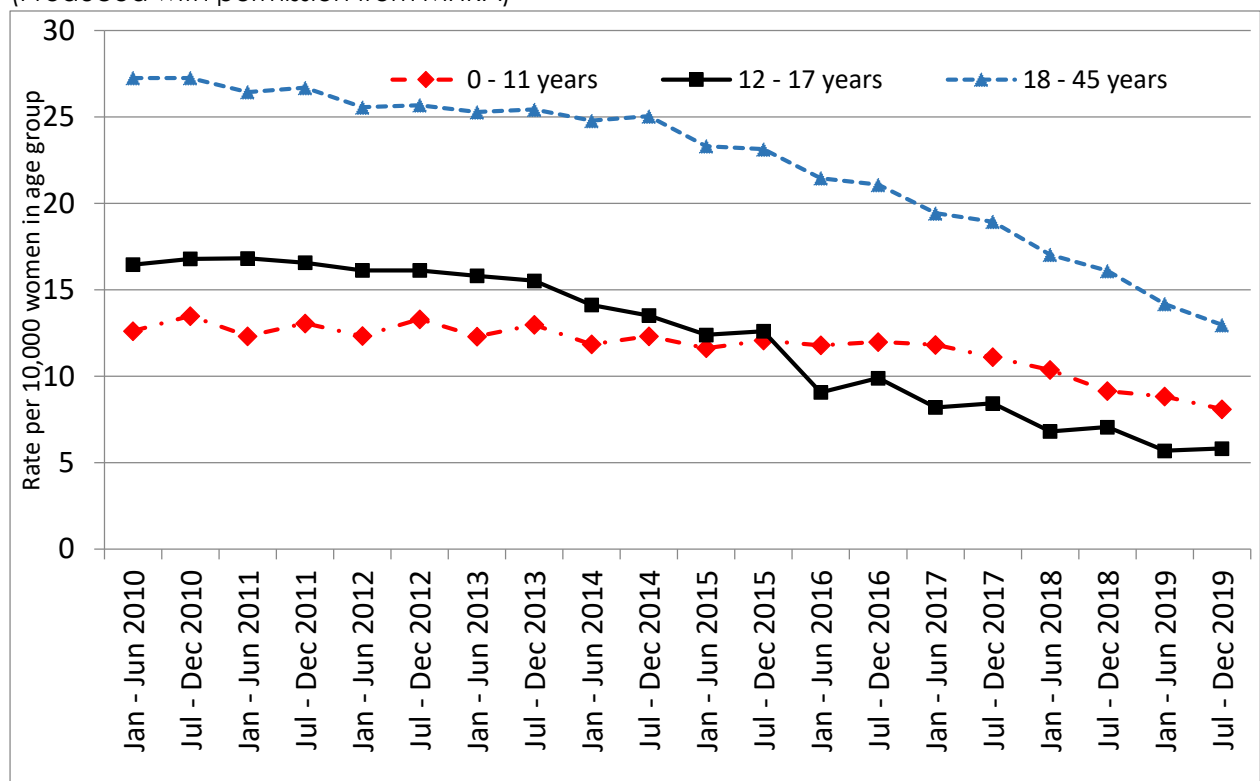
*“system that listens, hears and acts – with speed, compassion and proportionality”* (4)

The report made a number of recommendations, that can be found in the report, (3)

Historically, valproate was used extensively in this population. Although recent practice has changed, with a steep reduction in new prescriptions, there are still a considerable number of girls and women of childbearing potential taking valproate in the UK, as shown in Figure 1.

**Figure 1: Prescribing prevalence in females in England by age**

(Produced with permission from MHRA)



In [England](#) and [Scotland](#) there is detailed and comparative information on prescribing (note that for Scotland the Indicator Group is called “MHRA warning” not valproate). In England a valproate safety dashboard will be introduced in December 2020.

Valproate is an effective drug for certain types of **epilepsy** (5), 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 (6). In addition, other treatments present much lower potential risks to fetal development (5). The MHRA are currently reconsidering the indication for valproate in bipolar disorder. In other mental disorders where valproate is unlicensed there is either no or very limited evidence of efficacy (7). 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 (8). Valproate is not licensed for the treatment of **migraine** and should not be used for this indication.

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 except in rare situations in epilepsy for patients who are resistant or intolerant to other treatments.

In response to these issues 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 current MHRA regulations state that:

“Valproate must not be used in any woman or girl able to have children unless there is a pregnancy prevention programme (PPP) in place”

The PPP programme, also known as “Prevent” carries the following responsibilities: -

#### **General practitioners' role**

- Ensure continuous use of **highly effective contraception** in all women of childbearing potential (consider the need for pregnancy testing if not a highly effective method).
- Check that all patients have an up to date, signed, Annual Risk Acknowledgment Form (ARAF) each time a repeat prescription is issued.
- Ensure the patient is referred back to the specialist for annual review.
- Refer to the specialist urgently (within days) in case of unplanned pregnancy or where a patient wants to plan a pregnancy.



## Specialists' role

- Discuss the risks with the patient (or parent/caregiver/responsible person).
- Exclude pregnancy in women of childbearing potential (by serum pregnancy test) before the first prescription is issued.
- Arrange for highly effective contraception for women of childbearing potential before the first prescription is issued.
- Complete the Annual Risk Acknowledgment Form with the patient (or parent/caregiver/responsible person); give them a copy and send a copy to the GP.
- See the patient urgently (within days) if referred back in case of unplanned pregnancy or if she wants to plan a pregnancy.
- Provide a copy of the Patient Guide to the patient (or parent/caregiver/responsible person).

[Materials for healthcare professionals \(HCPs\) and patients](#) are available to support discussions (1). The patient leaflet is intended for girls and women and it is available in English and Welsh.

It is our **consensus** view that the patient leaflet should be available in other languages, in forms appropriate for girls, including girls with Intellectual Disability (ID) and in an easy read format for adults with ID. [The UK Teratology Service \(UKTIS\)](#) also produces evidence-based leaflets for healthcare professionals and patients

In April 2019, General Practitioners (GPs) were encouraged to undertake patient safety quality improvement activities through the Qualities and Outcomes Framework (QOF), including for valproate (9). This incentive has now been changed to alternative QI activities. 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 (10).

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 regulatory changes.

Individual clinicians are also required to act in the best interests of each individual patient (11, 12). 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 (13). 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, Clinical Director, or specialty support groups. The General Medical Council (GMC) also provides information, for example on prescribing unlicensed drugs (14). 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

Current NICE guidelines on prescribing of valproate for of girls and young people do not cover age and intellectual disability ID in enough detail(15). A BPNA/RCPCH document provides more clarity (15).

The prescribing needs of girls with 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 (15). 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 (17). Information for older girls and their parents is also available (18, 19). This should be discussed and documented in the ARAF on an annual basis. The PPP is not required in this age group, unless a girl under 10 years has already gone through the menarche (and paediatricians should always ask sensitively), when 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 for 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 (16).

### **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).

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. In some individual cases, 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." Contraception information can be provided to young people of this age group without parental knowledge or consent, provided the criteria set out by the GMC are fulfilled (20)

## **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. Young women in this age group receiving valproate must have an annual review in specialist services and a formal transition process to adult services. Every effort should be made by the specialist to switch young women who have the potential for future pregnancy from valproate to an alternative treatment before they reach 18 years of age (16).

## **2. Girls with bipolar disorder**

Bipolar disorder is a mental health 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). If she has childbearing potential the PPP should be followed.

## **3. Girls under 16: sexual activity, capacity, confidentiality and safeguarding**

Many young women do not wish to discuss their sex lives with their parents or carers. The median age for first heterosexual sexual experience in the UK is 14 years (21). Those under age 13 are not considered legally competent to consent to sexual activity (22-24).

Girls under 16 may have the capacity to consent to treatment, depending on their ability to understand and weigh up the information about the available options (20). This applies to prescribing valproate as well as contraception. It is important to assess capacity to consent in relation to a specific decision – i.e. a specific treatment - bearing in mind the complexity and importance of the decision to be made.

Competence to consent to a specific treatment is demonstrated (25) if a girl 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

Child protection issues may also be raised and appropriate safeguarding action may need to be taken (20)

### **3.1 Communicate the decision**

In young women who have the maturity and ability to understand what is involved, the conversation about sexual activity and contraception can take place without the parents if the patient prefers, and confidentiality should be respected (20). On the other hand some young women may want their parent(s) present for the discussion. In any case a doctor should encourage the young person to tell their parents or to allow the doctor to do this (20). These discussions should take place in childrens' services and CAMHS, with onward referral to primary care or sexual health services for contraceptive provision if required.

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. GMC principles on Decision-making, consent and capacity

The principles of decision-making and consent in the GMC's guidance are important in making decisions with women on valproate (25). Nursing principles are equally important (11, 26)

### The seven principles of decision making and consent

Principle one	All patients have the right to be involved in decisions about their treatment and care and be supported to make informed decisions if they are able.
Principle two	Decision making is an ongoing process focused on meaningful dialogue: the exchange of relevant information specific to the individual patient.
Principle three	All patients have the right to be listened to, and to be given the information they need to make a decision and the time and support they need to understand it.
Principle four	Doctors must try to find out what matters to patients so they can share relevant information about the benefits and harms of proposed options and reasonable alternatives, including the option to take no action.
Principle five	Doctors must start from the presumption that all adult patients have capacity to make decisions about their treatment and care. A patient can only be judged to lack capacity to make a specific decision at a specific time, and only after assessment in line with legal requirements.
Principle six	The choice of treatment or care for patients who lack capacity must be of overall benefit to them, and decisions should be made in consultation with those who are close to them or advocating for them.
Principle seven	Patients whose right to consent is affected by law should be supported to be involved in the decision-making process, and to exercise choice if possible.

(Reproduced with permission from the GMC)

Decision making with patients on valproate is challenging. There are no appropriate evidence-based decision aids. One paper has suggested using the "talk model" (27, 28).

## 5. Transition of care from childrens' services or CAMHS to adult services

The transition of girls from childrens' 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 the valproate and the PPP, at a time when behavioural and adherence 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 psychological 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 demonstrated in the national ["Ready, Steady, Go" programme](#). 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.

## 6. Women of childbearing potential

The MHRA regulations apply to valproate prescribing, irrespective of the medical indication. They 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. While women and girls are waiting for their specialist appointment to complete the ARAF, GPs should continue to prescribe valproate.

### 6.1 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.

Women must be treated as individuals and their wishes respected at all times (29). They should be made aware that no method of contraception is 100% effective (30).

Women of reproductive age who are using valproate are advised to use at least one "highly effective" method of contraception (preferably a user-independent form) or two

complementary forms of contraception, including a barrier method. Even if a woman has amenorrhoea, she must follow all the advice on highly effective contraception. Methods of contraception which are considered 'highly effective' (1) include the long-acting reversible contraceptive (LARC) methods: copper intrauterine device (Cu-IUD), levonorgestrel-releasing 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 (see Table 1) (31). However, women using the progestogen-only implant should avoid use of any medication that induces hepatic enzyme activity as this could reduce contraceptive effectiveness (32)

**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. (32))

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
<b>Copper intra-uterine device (Cu-IUD)</b>	<b>0.8</b>	<b>0.6</b>
<b>Levonorgestrel 13.5mg/19.5mg/52mg intrauterine system (LNG- IUS)</b>	<b>0.2</b>	<b>0.2</b>
<b>Progestogen-only implant (IMP)</b>	<b>0.05</b>	<b>0.05</b>
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 progestogen-only pill (POP) is 9%; for the progestogen-only injectable intramuscular and subcutaneous depot medroxyprogesterone acetate (DMPA) it is 6%. For this reason, if a woman will only accept a user-dependent method like CHC, POP or DMPA, she should be advised to also use additional barrier contraception. The MHRA also recommends regular pregnancy tests, as a matter of clinical judgement; this [table](#) may be helpful in deciding whether pregnancy tests are needed (33).

## 6.2 Drug interactions

### Oestrogens and valproate

Ethinylestradiol (present in most combined contraceptive pills, the combined transdermal patch and the combined vaginal ring) may reduce valproate levels (34). Oestrogens are inducers of the UDP-glucuronosyl transferase (UGT) isoforms involved in valproate glucuronidation and may increase the clearance of valproate, which could result in decreased serum concentration of valproate and potentially decreased valproate efficacy (35). Prescribers should monitor clinical response (seizure control or mood control) when initiating or discontinuing oestrogen-containing products.

Valproate has no enzyme inducing effect; as a consequence, valproate does not reduce the contraceptive effectiveness of CHC, POP and IMP, but effectiveness be reduced by co-prescribing other medications (including some antiepileptic drugs) that induce hepatic enzymes. Relevant interactions are listed [here](#) (36) The intrauterine contraception (IUC) (37) and the DMPA are not affected (38).

### 6.3 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 (29, 39). Young age and nulliparity do not contraindicate use of IUC (37). 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 (29, 38). 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 by young people with particular medical conditions/characteristics (39).

### 6.4 Contraception choice in older women

Women aged 50 and over should be advised to avoid CHC due to associated cardiovascular and breast cancer risk (40). 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 (39).

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”* (40).

Women on valproate should be recommended to continue to use highly effective contraception until the age of 55 years. The possibility of pregnancy cannot be ruled out before this age. Trying to diagnose the menopause is fraught with difficulties, even using a follicle stimulating hormone level >30iU/L because this does not absolutely exclude future ovulation and risk of pregnancy.

After the age of 55 years women do not require to sign the ARAF, but they may need specialist advice for their care if they are taking valproate.

## 6.5 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. After unprotected intercourse during use of valproate: -

- If all recent unprotected intercourse was within the last 5 days or the individual is within 5 days of the earliest likely date of ovulation, a Cu-IUD, the most effective method of emergency contraception, should be offered.
- If a Cu-IUD is not suitable or acceptable, oral emergency contraception should be offered, with effective contraception "quick started" immediately after levonorgestrel oral emergency contraception or 5 days after ulipristal acetate oral emergency contraception (41).
- Additional contraceptive precautions should be used until the quick started contraception becomes effective and a follow up pregnancy test taken 21 days after the last unprotected sex. (42)

The MHRA booklet for healthcare professionals (1) also states

*"Pregnancy tests may not detect an early pregnancy that has occurred after unprotected sex in the preceding 3 weeks. Therefore, women should have a repeat pregnancy test 3 weeks after starting a new contraceptive method if there was any risk of pregnancy at the start of the contraceptive method, even if the first test was negative"*

## 6.6 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.

The provision of contraception for patients on valproate is considered a priority service by the FSRH. 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.

## 6.7 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. The MHRA review of the safety in pregnancy of other antiepileptics is about to be published. (43)

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 (5, 44); 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 (45, 46), or lack of control when its use may not even have been considered (47). 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 (48). Whilst overall maternal deaths fell over the 30-year period from 1979-2008, the proportion attributed to epilepsy has risen (49). 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 (50). 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.

Drug interaction between the new treatment and contraception should always be considered and managed as needed. Valproate may have mood-stabilising effects in some patients with epilepsy and, separately, potential unintended consequences of valproate withdrawal on mood need to be mentioned, as these might affect quality of life and seizure control.

When a switch to a different antiepileptic drug is under consideration, it is important to note that the risks of major congenital malformation, neurodevelopmental disorders or delay, and other reproductive toxic effects on the fetus or neonate with other antiepileptic drugs vary according to the drug in question, and sometimes show dose dependency (43). Robust data are available for some antiepileptic drugs, whilst information for other antiepileptic drugs remains limited. It is incumbent upon the prescriber to consult the most recent sources of data and discuss the most up-to-date information with each individual when a switch to another antiepileptic drug is under consideration. The general principles of caution, advance planning, evaluation of the ratio of benefit to the woman and risk to the fetus, and minimisation of the number and doses of drugs where safe and possible, should be kept in mind.

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 (6).

### **6.8 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 GMC prescribing guideline outlines the roles and responsibilities of the prescriber (typically the GP) under these circumstances (14).

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) (49), 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's guidance on decision making and consent should be consulted and carefully followed in this situation (25). Particular attention should be paid to:

- making sure the information you share is objective and not pressuring a patient to accept advice (paragraph 11)
- exploring what risks a patient would and wouldn't be prepared to take, and how the likelihood of a particular outcome might influence their choice (paragraph 20)
- providing clear, accurate and up-to-date information, based on the best available evidence, about the potential benefits and risks of harm of each available option (paragraph 21)
- using visual or other explanatory aids to support patients to understand their personalised risk (paragraphs 23-24)
- supporting patients to understand and retain relevant information and use it to make a decision, e.g. by being accompanied to the consultation (paragraphs 27-30)
- checking the patient's understanding of relevant information and their expectations about the likely outcome of each option (paragraphs 27-30)
- respecting a patient's right to decide (paragraphs 48-49)

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 would 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.

### **6.9 Women who fail to attend their specialist appointment or who refuse to engage with specialist referral**

Some women who are on valproate and have childbearing potential may miss their appointment for specialist assessment or refuse to engage with specialist referral and may be at risk of a valproate-affected pregnancy. For a missed appointment, 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 lie with the prescriber to decide how to manage this situation, which might involve prescribing outside the licence.

If a woman fails to engage with referral to a specialist the GP will be in the same position. Taking advice from colleagues, specialists and defence organisations, and scrupulous documentation are clearly very important, but the GP should usually prescribe, despite it being outside the licence, as otherwise the woman is put at serious risk of seizures and related harms, including possible death.

### **6.10 Intellectual Disability (ID)**

The prevalence of epilepsy is high in patients with ID: they constitute nearly 25% of the total population of people with epilepsy and 60% of the total population with treatment-resistant

epilepsy (52). There is a general lack of clarity on how best to advise this vulnerable group and the role of guidelines (53).

Mental illness in people with ID is more than twice as common as in the general population (54). When compared to the general population, bipolar disorder exists at double the rate in those diagnosed with ID (55). This is because “Intellectual Disability” has a range of severity, influencing various domains of cognition and social functioning. General considerations about capacity must always be borne in mind, including the possibility that capacity may fluctuate influenced by a range of physiological, physical or mental health factors and should be considered with regard to the issue in hand (56).

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 which occur in 5–15% of people with ID (57). Scientific support for the efficacy of valproate in this area is very limited (58). 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. Although specific prescribing data for valproate in women is not available, the overall prevalence of prescribing some type of antiepileptic drug for adults with ID was 23.3% (59). In the ID population in England, in 2019, 20.4% of antiepileptic drug prescribing was recognised to be without a licensed indication (60). It is highly likely that such prescribing commonly involves valproate for its supposed anxiety, mood stability, impulsivity and aggression management properties (61).

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 (62) and RCPsych reports (6, 52, and 58). Where necessary, person-centred social stories and “easy read” explanatory documents should be used in order to facilitate improved communication and informed feedback.

#### **6.10.1 With lack of mental capacity**

Girls and women with epilepsy and ID, or bipolar disorder, and of childbearing potential may lack the capacity to consent to sexual activity or to treatment (each decision needs to be considered separately). Even where patients do not have capacity to consent to treatment, they should still be involved in the dialogue leading to a decision (25)

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 (15), will fall into this group. Valproate is typically also the first-line treatment for many other severe epilepsies ('developmental and epileptic encephalopathies') which are typically associated with ID.

In women with bipolar disorder, using lithium as an alternative to valproate in the moderately–profoundly affected group would involve major complexities around monitoring lithium levels (consent for blood tests) and managing drug interactions.

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 (59): the individual's best interests must be formally addressed.

#### **6.10.2. 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 for each separate decision e.g. consenting to take valproate 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 (62).

#### **6.11 Non face to face consultations**

In response to COVID-19 and increased use of telephone/video clinics, the MHRA has issued [advice](#) on how to meet the requirements of the PPP remotely (63). Ideally, initiation of valproate in women and children of child-bearing potential should be done face to face unless the patient is shielding, with annual reviews being undertaken virtually. Clinical information resources, such as the patient information booklet and the ARAF should be sent via email or WhatsApp (or another method to receive electronic files). The discussion and risk assessment should follow GMC guidance and should be clearly documented in the medical notes. Where possible the prescriber should ask the patient to confirm (via email/WhatsApp/other messaging service; if possible) receiving the ARAF and whether it reflects the discussion undertaken. Pregnancy testing may be challenging, however home pregnancy testing kits can be used (minimum required sensitivity 25 mIU/mL), with the results ideally been shown by video call /picture.

#### **6.12 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 (14). 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 (14).

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.

### **6.13 Particular situations that may arise**

#### **6.13.1 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 (64). 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.

#### **6.13.2 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 (65). However, medical management still needs to follow MHRA regulations; 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.

#### **6.13.3 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 safeguarding 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 (6, 66).

### **6.14 Pharmacies and supply of valproate**

The role of pharmacists in supplying valproate are described by MHRA and CQC (2). They are tasked with providing a [Patient Card](#) every time valproate is dispensed and to have a conversation about the warnings. In addition, valproate medicines should be supplied in original packaging wherever possible. When generating a prescription for valproate, where possible, patients should be prescribed whole packs (multiples of 30) to ensure warning stickers are available. Details of when the last annual review was completed should be endorsed on the prescription where possible to streamline the dispensing pathway.

The above checks should also be performed by pharmacists even if a supply is not made (for example during medication reconciliation or medication review).

If it seems the patient has not been seen by her GP or specialist, the prescription should still be dispensed, but the patient should also be referred to their GP.

Dispensing GPs need to ensure that their pharmacy technicians are aware of this guidance.

## **7. 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 are women who have had a hysterectomy, bilateral oophorectomy 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 may 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.

## **8. 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 valproate abruptly (loss of seizure control, death, deterioration of mental health).

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**, a detailed discussion will be necessary between the woman, her obstetrician and neurologist, especially to attempt to minimise risk (67).

Valproate is contraindicated in bipolar disorder during 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 (6). 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 relapse is most likely. 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 Obstetricians and Gynaecologists (RCOG) guidelines (68). 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.

## **9. Other issues**

### **9.1 Which healthcare professionals can be considered as specialists?**

The MHRA defines a specialist prescriber as

*“A specialist prescriber, who initiates treatment, is a consultant neurologist, psychiatrist or paediatrician who regularly manages complex epilepsy or bipolar disorder”.*

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.

### **9.2 Epilepsy Specialist Nurses (ESN) and specialist midwives**

Epilepsy specialist nurses (and specialist midwives during planning for pregnancy, pregnancy and postnatally) 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 or midwife 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 assessment. Nurses without an independent prescribing qualification would not be able to recommend the initiation of valproate without referral to a consultant neurologist.

### **9.3 GPs with an extended role in epilepsy (GPwERs)**

GPwERs exist in some areas of the country 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. They can initiate valproate for women who satisfy the terms of the PPP and for whom alternative treatment is unsuitable.

#### **Good practice example from Bradford**

In Bradford, the local CCG commission a community-based epilepsy service offering review and on-going management of patients with an established diagnosis of epilepsy using various clinic venues across the district, as well as psychological therapy and support for patients with both epilepsy and non-epileptic seizures. The clinical staff in the service include four GPwERs, three epilepsy nurse specialists and a clinical psychologist. Clinical support is provided through the neurology department at Bradford Hospitals NHS Trust. The epilepsy service uses the same electronic records system as that used by all the local GPs which facilitates communication between the service and primary care, and also by sharing the records when the patient agrees, it is possible to see the entire GP record during a consultation improving clinical effectiveness and safety.

### **9.4 Independent Prescribing Pharmacists with scope in neurology/mental health (Pharmacist IP).**

Pharmacists have a unique and in-depth knowledge in all aspects of medicines, essential to the safe on-going monitoring, support and treatment of patients. As a result, numbers of specialist pharmacist prescribers with a scope of practice of within epilepsy services are increasing.

Pharmacist specialist prescribing clinics exist within epilepsy services in which girls and women prescribed valproate are reviewed, ensuring they meet the conditions of the PPP and the annual PPP risk assessment is completed. However, details of practice may differ depending on local agreements.

The decision to initiate females of child-bearing potential must be made by a multidisciplinary team, including a consultant neurologist.

Specialist mental health pharmacists are integral to ensuring girls and women in mental health services prescribed valproate are compliant with the MHRA guidance. The roles for mental health specialist pharmacists managing these patients and completing annual PPP risk assessments are currently being developed in many Trusts.



### **Good practice example**

#### **Epilepsy Specialist Pharmacist working across Medway Maritime Hospital and Medway and Swale Clinical Commissioning Group – Kent**

In the Medway and Swale region of Kent, an epilepsy specialist pharmacist (ESP) independent prescriber works across both primary and secondary care. Working across the interface has enabled use of GP practice data to identify women and girls taking valproate. All individuals are reviewed by the ESP regardless of the clinical indication for the valproate prescription to ensure the ARAF has been completed and if appropriate the conditions of the PPP are in place. This process involves close liaison with the local mental health trust and the practice-based and Primary Care Network pharmacists.

For adults with epilepsy under the Medway Maritime neurology department, the ESP will undertake the annual risk acknowledgement consultation with the patient, completing the ARAF. As part of this consultation, the need for, and benefit of, continued valproate use is determined with neurologist oversight as appropriate. Once the annual risk acknowledgment consultation is complete, the ESP will liaise with GP and nurse colleagues to advise and facilitate PPP implementation if needed and to ensure records are correct and follow-up planned. If required, the ESP will work with the consultant neurologist to facilitate initiation of alternative antiepileptic medication and ultimate withdrawal of the valproate. The ESP can follow up the patient in primary care if this is deemed helpful.

The Medway and Swale service is currently focused on adults over 16 years of age, but involvement of a childrens' services specialist pharmacist is being explored to cover girls aged 10-15 with both pharmacists working together to facilitate transition to adult services.

### **9.5 Mental Health**

Most areas in the UK have specialist perinatal community mental health teams in place who will see women for medication advice, preconception consultations and management before, during and after childbirth. Mood-stabilizing medication in patients with bipolar disorder will typically be reviewed by senior psychiatrists who can do this urgently in case of pregnancy. If a specialist perinatal psychiatry team is not available, a referral can be made to adult psychiatry services. If the patient is a young female, CAMHS may work together with perinatal or general adult psychiatrists and their teams.

### **9.6 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 for England and Wales was updated in November 2019 (69). 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 exploration of the option of surrogacy on the NHS for appropriate women on valproate should be considered by NICE for cost-effectiveness.

## **10. 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 should 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 to standardise 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. This has also been recommended in the IMMDS review (3). The details of how this should happen and how it will be funded need to be developed. A training package and resources should be available for midwives, health visitors and GPs. 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.

## **11. Concluding remarks**

Valproate use is under strict regulation, but the regulatory requirements are not always fulfilled. It was one of the subjects of the pivotal IMMDS review that produced important recommendations and actions for improvement. (3) 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 and listen to each individual girl or woman, taking into account their individual preferences and circumstances and facilitating informed shared decision making.

## 12. Patient support networks

[Bipolar UK](#)

[Connate Support](#)

[Epilepsy Action](#)

[Epilepsy Society](#)

[FACS-aware](#)

[Mind](#)

[OACS](#)

[SUDEP Action](#)

[UK Epilepsy and Pregnancy Register](#)

[Bumps](#)

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