

RADiANT Psychiatry of Forensic Learning Disability CPD

PHARMACOLOGICAL TREATMENTS IN PEOPLE WHO HAVE INTELLECTUAL OR DEVELOPMENTAL DISABILITIES

Valproate use in women: guidance and regulations

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August 2021

Aims

Overview of the effects of prescribing valproate in pregnancy

Outline of guidance and regulations related to valproate prescribing in women of child bearing potential

Highlight the challenges to the implementation of guidance in people with intellectual disabilities

Shared decision making, informed consent and the development of accessible information

Overview of the effects of prescribing valproate in pregnancy

Children exposed to valproate *in utero* are at high risk of serious **developmental disorders (30–40% risk)** and **congenital malformations (10% risk)**.

- ❖ Major congenital malformations are predominantly neural tube defects, clefting abnormalities, cardiovascular defects, genitourinary defects in males and musculoskeletal defects.
- ❖ Increased risk of developmental delays, includes delays in walking, talking, poor language skills, memory problems and low intellectual ability
- ❖ Increased risk of autism (approximately 3 x) and are also more likely to develop symptoms of attention-deficit/hyperactivity disorder

Outline of guidance and regulations related to valproate prescribing in women of child bearing potential

Assess and review whether valproate is the only suitable treatment for a female of childbearing potential (up to the age of 55)

Need to ensure that pregnancy is excluded by a negative pregnancy test before continuing or commencing treatment on valproate for women of childbearing age.

If treatment is to be continued, the woman or girl must be enrolled on a valproate Pregnancy Prevention Programme (PPP) also known as “Prevent.”

Outline of guidance and regulations related to valproate prescribing in women of child bearing potential

The Pregnancy Prevention Programme is a system of ensuring all female patients taking valproate medicines:

- have been told and understand the risks of use in pregnancy and have signed a Risk Acknowledgement Form annually
- are on highly effective contraception if necessary
- see their specialist at least every year

Annual Risk Acknowledge Form (ARAF)

https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/860762/Risk-acknowledgment.pdf

Three steps in completing the form:

Step 1 – Decide if the patient needs to be on ‘prevent’ – the valproate pregnancy prevention programme

Step 2 – ‘prevent’ applies to this patient- she is of childbearing potential and at risk of pregnancy

Step 3 – Your patient needs to complete this section to confirm they understand the risks of valproate in pregnancy

Prescribing valproate in pregnancy

For **migraine prophylaxis** and **bipolar disorder**, the MHRA advises that valproate must not be used in pregnancy.

For **epilepsy**, the MHRA advises valproate must not be used in pregnancy unless there is no suitable alternative treatment; in such cases, access to counselling about the risks should be provided (see Healthcare Professional Guide for more information) and a Risk Acknowledgement Form signed by both specialist and patient.

If valproate is to be used during pregnancy, the lowest effective dose should be prescribed in divided doses or as modified-release tablets to avoid peaks in plasma-valproate concentrations; doses greater than 1 g daily are associated with an increased risk of teratogenicity. (BNF)

Women not at risk of pregnancy

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, 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 not requiring contraception in such cases can be documented on the ARAF.

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 may not be necessary but may be indicated for the underlying condition.

There may be other individual reasons, 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.

Women with intellectual disabilities lacking capacity (MCA)

Royal College of General Practitioners and Association of British Neurologists and Royal College of Physicians (2019) Guidance Document on Valproate Use in Women and Girls of Childbearing Years recommend:

Discussions with 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.

<https://www.rcgp.org.uk/-/media/Files/CIRC/Epilepsy/Guidance-on-Valproate-use---Dec-2020.ashx?la=en>

Women choosing not to use contraception but remain on valproate

Prescribing valproate without PPP is off label

Examples of these circumstances include:

- Women concerned about switching AEDs and effects on driving license, SUDEP, relapse of epilepsy
- Patients may not consent to a PPP for personal, medical, religious, or cultural reasons.
- Women who wish to avoid side effects associated with some hormonal methods.

Highly effective contraception

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),

Male and female sterilisation

Women using the progestogen-only implant should avoid use of any medication that induces hepatic enzyme activity as this could reduce contraceptive effectiveness

If a woman will only accept a user-dependent method like combined hormonal contraceptives (COC), progesterone minipills (POP) or depot medroxyprogesterone acetate (DMPA) contraceptive injection, she should be advised to also use additional barrier contraception.

Challenges of implementing this guidance in women with intellectual disabilities

- ❖ Valproate is a recommended treatment in bipolar disorder.
- ❖ Valproate is a recommended treatment for epilepsy.
- ❖ Increased prevalence of both these conditions in people with intellectual disabilities.
- ❖ Valproate is also an off label treatment for migraine
- ❖ It is also used in the management of challenging behaviour when a mental health diagnosis may be unclear.
- ❖ Need careful consideration of prescribing valproate in female children.
- ❖ Some valproate preparations are licensed only for epilepsy and some only for bipolar – consent required for off label prescribing

❖ These restrictions limit therapeutic options and the alternatives are not risk free in pregnancy

❖ Imperative that patients are informed of the risks associated with alternative drugs

❖ Bipolar Disorder:

- Alternative mood stabilisers e.g. lithium, lamotrigine and carbamazepine are also associated with risk of malformation and perinatal complication, including teratogenesis, impaired neurological development and autism
- Some women may choose to stop all mood stabilisers altogether before pregnancy or after valproate is discontinued during pregnancy.
- Untreated women have double the risk of relapse compared with women who remain on mood stabilisers and increased risk of pregnancy complications and post partum psychosis.
- Switching to lithium - managing monitoring blood levels, interactions, hydration

❖ Epilepsy:

- Valproate remains the best treatment for idiopathic (genetic) generalised epilepsies
- Avoidance of valproate in girls with idiopathic generalised epilepsies, even before they reach childbearing potential, could result in poorly controlled epilepsy.
- Evidence suggests some negative effects of uncontrolled seizures during developmental years, most notably an adverse impact on cognition.
- The risk of death from sudden unexpected death in epilepsy (SUDEP) increases with greater seizure frequency.

Challenges of implementing this guidance in women with intellectual disabilities

Challenges of implementing this guidance in women with intellectual disabilities

Fertility

- ❖ Think about the deprescribing of medicines that cause hyperprolactinaemia e.g. amisulpride and risperidone - STOMP
- ❖ Raised prolactin can cause amenorrhea and reduced fertility in women. As prolactin returns to normal, fertility may be increased.
- ❖ Impact of increased fertility and the prescribing of valproate.
- ❖ NB: PPP is still required in women with amenorrhea

Difficult conversations with families

Safeguarding issues, sexually active or sexual abuse?

Challenges of implementing this guidance in women with intellectual disabilities

Completing the risk acknowledgement form with limited literacy skills

In the absence of capacity to consent to treatment, the valproate risk acknowledgement form can be signed by a relative or a carer

For women with capacity they may not choose to allow a carer or relative to complete the form

Is easy read available? Not on the .gov.uk website.
Quality assurance of this material?

Clinical Practice

The risks of taking valproate should be communicated with care and should not raise undue concern, leading to sudden unplanned discontinuation of valproate and, perhaps, other anti-epileptic medicines in the absence of advice from the responsible clinician.

Switching to carbamazepine - consideration should be given to current prescriptions of combined oral contraception to ensure that the correct strength of oestrogen is prescribed and to avoid inadvertent reduced efficacy of contraception.

Switching to lithium – need to think about more regular blood testing, drug interactions, hydration and toxicity

Clinical Practice

Availability of pregnancy test kits at clinic sites
and for home visits

Linking up with primary care, contraceptive
services

Ethinylestradiol (present in most combined contraceptive pills, the combined transdermal patch and the combined vaginal ring) may reduce valproate levels

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

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

Effectiveness of CHC, POP and IMP may be reduced by coprescribing other medications (including some antiepileptic drugs) that induce hepatic enzymes.

Drug interactions

18

Shared decision
making,
informed
consent and
the
development of
accessible
information

<https://www.hpft.nhs.uk/media/3814/2019-04-17-annual-risk-acknowledgement-form-for-users-of-valproate.pdf>

<https://www.hpft.nhs.uk/media/3789/2019-04-01-sodium-valporate-patient-guide-easyread.pdf>


<https://www.choiceandmedication.org/hertfordshire/generate/handyfactsheetperinatalhcbipolar.pdf>

<https://www.choiceandmedication.org/hertfordshire/generate/handyfactsheetperinatalvalproate.pdf>

<https://www.choiceandmedication.org/hertfordshire/generate/verahandyfactsheetperinatalvalproateuk.pdf>

<https://www.choiceandmedication.org/hertfordshire/generate/quillvalproate.pdf>

Annual Risk Acknowledgement Form

	<p>Valproate has risks in pregnancy</p> <p>If a woman uses valproate while she is pregnant, her child can be harmed.</p> <p>Valproate is not to be used in women of childbearing age unless the conditions of the pregnancy prevention programme are fulfilled.</p>
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Name of person using valproate:

Date of birth:

NHS Number:

Name of responsible person (if applicable):

Relationship of the responsible person to the patient:

Name, role and signature of specialist:

Name of valproate user's GP:

Date:

This form expires 12 months from this date
A new form should be completed at each annual review.



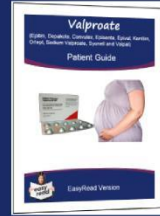
Valproate

(Epilim, Depakote, Convulex, Episenta, Epival, Kentlim, Orlept, Sodium Valproate, Syonell and Valpal)

Patient Guide



EasyRead Version



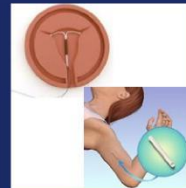
About this guide

Page 3



What are the risks of taking valproate when pregnant?

Page 4



Contraceptives for girls and women who are old enough to get pregnant

Page 6



I am starting treatment with valproate

Page 7



I am taking valproate and I don't want to get pregnant

Page 9



I am taking valproate and I want to have a baby

Page 11



I am taking valproate and I think I am pregnant

Page 13



Things to remember

Page 15

About this guide



This guide is for girls and women who are old enough to get pregnant and who are taking medicine that has valproate in it.



Valproate is also called Epilim, Depakote, Convulex, Episenta, Epival, Kentlim, Orlept, Sodium Valproate, Syonell or Valpal.

You may see one of these names on your prescription or on the box of your medicine.



Valproate is used to treat conditions such as epilepsy or bipolar disorder.



You will need to take contraception while using valproate

What are the risks of taking valproate when pregnant?



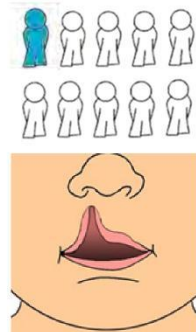
If you take valproate when you are pregnant it can seriously harm your baby.



If you take valproate the risks are higher than if you take other medicines for epilepsy or bipolar disorder.



There is a risk even if you only take a small dose of valproate. The higher the dose, the bigger the risk.



1 in 10 babies have a **birth defect** if a mother takes valproate when she is pregnant. A **birth defect** is where the baby didn't develop properly in the womb. Cleft lip is an example of a birth defect.

What are the risks of taking valproate when pregnant?



If a mother takes valproate when she is pregnant 4 in 10 children have development problems as they grow up



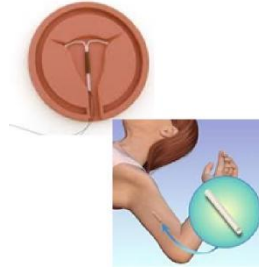
If a mother takes valproate when she is pregnant her child could have the following development problems:

- Late learning to walk and talk.
- Lower intelligence
- Poor speech and language
- Memory problems

If a mother takes valproate while she is pregnant her baby is more likely to have Autism Spectrum Disorder



Contraceptives For girls and
boys who are old enough to
get pregnant



You must use **effective**
contraceptives while you are
taking valproate.

The doctor explained to me that
effective contraceptive includes:
using

a coil and contraceptive implant.
You must use contraceptives even if
you are not sexually
active at the moment.



You should talk to your doctor about
the best type of contraceptive for you.

I am not old enough to get pregnant and starting treatment with valproate



If you are too young to get pregnant your doctor will explain the risks of valproate to your parents or carers.



Your doctor should only give you valproate if other medicines do not work.



You should talk to your doctor as soon as you have your first period to make sure that valproate is still the best medicine for you.

I am old enough to get pregnant starting treatment with valproate



If you are old enough to get pregnant your doctor will ask you to take a pregnancy test before giving you valproate.

You will need to do regular pregnancy tests while you are taking valproate.



While you are taking valproate you will need to see your doctor every year to make sure that it is still the best medicine for you.

This is called an **annual review meeting**.

At your annual review meeting your doctor will ask you to sign an Annual Risk Acknowledgement Form to make sure that you understand the risks of taking valproate.

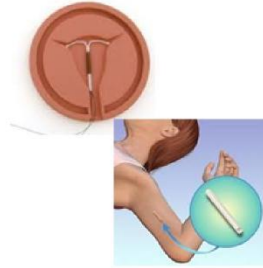
Annual Risk Acknowledgement form for users of Sodium Valproate

	If you use valproate while you are pregnant, your child has a high risk of serious harm.
	This form confirms that you or your (GPs), parent or responsible person understands the risks of using valproate.

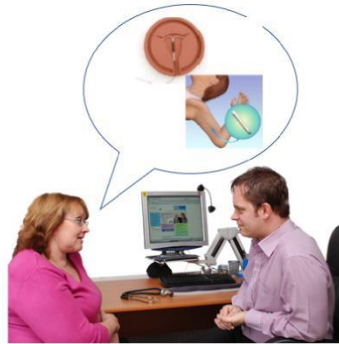
Please complete Part A of this form (below)
Please tick to say that you understand.

This form expires 12 months from this date.
A new form should be completed at each annual review.

I am taking valproate and I don't want to get pregnant



If you are taking valproate and you do not plan to have a baby you must use contraceptives all the time.



You should talk to your doctor about the best type of contraceptive for you.



You will need to do regular pregnancy tests while you are taking valproate.

This is to make sure you are not pregnant.

I am taking valproate and I don't want to get pregnant



While you are taking valproate you will need to see your doctor every year to make sure that it is still the best medicine for you.

This is called an **annual review meeting**.

Annual Risk Acknowledgement form for users of Sodium Valproate

	If you use valproate while you are pregnant, your child has a high risk of serious harm.
	This form confirms that you or your GPC, parent or responsible person understands the risks of using valproate.

(Please complete Part A of this form (below))
Please fill to say that you understand

This form expires 12 months from issue date
A new form should be completed at each annual review

At your annual review meeting your doctor will ask you to sign an Annual Risk Acknowledgement Form to make sure that you understand the risks of taking valproate.

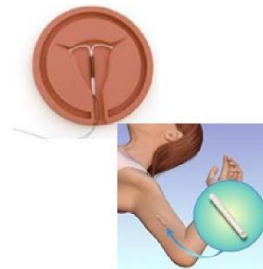
I am taking valproate and I want to have a baby



If you want to have a baby you **must** talk to your doctor **first**. You must keep using contraceptives.



You **must** keep taking valproate until you speak with your doctor.



You **must** keep using contraceptives until you speak with your doctor.

I am taking valproate and I want to have a baby



Valproate can harm babies at any time in your pregnancy.



Your doctor will need to change your medicine a long time before you get pregnant.



This is to make sure that your new medicine is working properly.

I a& taking valproate and I think I a& pregnant



You must talk to your doctor as soon as you think you are pregnant.



You **must** keep taking valproate until you speak with your doctor.



Your doctor will talk to you about changing to another medicine.

I am taking valproate and I think I am pregnant



Sometimes it is not possible to change to a different medicine.



If this happens your doctor will talk to you about your options.

Annual Risk Acknowledgement form for users of Sodium Valproate

	If you use valproate while you are pregnant, your child has a high risk of serious harm.
	This form confirms that you or your doctor, parent or responsible person understands the risks of using valproate.

Please complete Part A of this form (below)
Please tick to say that you understand

This form expires 12 months from the date
A new form should be completed at each annual review.



Your doctor will ask you to sign an Annual Risk Acknowledgement Form to make sure that you understand the risks of taking valproate.

Κεψ ινφορματιον το ρεμεμβερ



Valproate is also called Epilim, Depakote, Convulex, Episenta, Epival, Kentlim, Orlept, Sodium Valproate, Syonell or Valpal.

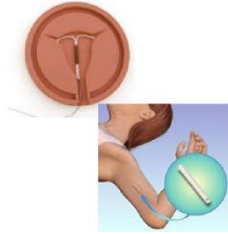
You may see one of these names on your prescription or on the box of your medicine.



Valproate is used to treat conditions such as epilepsy or bipolar disorder.



Valproate can seriously harm an unborn baby.



Always use an effective contraceptive while you are taking valproate



Talk to your doctor as soon as possible if you think you are pregnant.



Talk to your doctor if you are thinking about having a baby.

Don't stop taking valproate or stop contraception until you have talked to your doctor.

Key things to remember



Remember to see your doctor every year to talk about whether valproate is still the best medicine for you.

Annual Risk Acknowledgement form for users of Sodium Valproate

	If you use valproate while you are pregnant, your child has a high risk of serious harm.
	This form confirms that you or your carer, parent or responsible person understands the risks of using valproate.

Please complete Part A of this form (below)
Please tick to say that you understand.

This form expires 12 months from the date.
A new form should be completed at each annual review.

Sign the Annual Risk Acknowledgement Form to say that you understand the risks of taking valproate.

You can find more information
about epilepsy from the following
organisations:



Epilepsy Action

www.epilepsy.org.uk

0808 800 5050

Young Epilepsy

www.epilepsysociety.org.uk

01342 831 342

www.epilepsysociety.org.uk

01494 601 400



You can find more information about
bipolar disorder from the following
organisations:

Bipolar UK

www.bipolaruk.org

0333 323 3880

Mind

www.mind.org.uk

0300 123 3393

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).

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.

Take home messages

In women of child bearing potential, if valproate treatment is to be initiated or continued, the woman or girl must be enrolled on a valproate Pregnancy Prevention Programme (PPP) also known as “Prevent.”

Sudden stopping of valproate can cause relapse

Alternatives to valproate are not free of risk in pregnancy

Some antiepileptic medicines can reduced efficacy of the contraceptive pill

Oestrogens can reduce valproate levels, leading to potential relapse

Women with intellectual disabilities, with literacy difficulties who have capacity, may not choose to allow a carer or relative to complete the Annual Risk Acknowledgment Form

For **migraine prophylaxis** and **bipolar disorder**, the MHRA advises **that valproate must not be used in pregnancy.**

For **epilepsy**, the MHRA advises **valproate must not be used in pregnancy unless there is no suitable alternative treatment**

References

1. Valproate guidance and resources

<https://www.gov.uk/guidance/valproate-use-by-women-and-girls>

2. Sawhney I, Zia A, Adams D, Gates B. Use of valproate: Implications for women with intellectual disabilities and the wider interdisciplinary healthcare team. Br J Learn Disabil. 2019;47:195–200.

<https://onlinelibrary.wiley.com/doi/abs/10.1111/bld.12274>

3. Adams D, Sawhney I. Prescribing and deprescribing sodium valproate: implications for pharmacy practice. Clinical Pharmacist, CP, November 2018, Vol 10, No 11;10(11):DOI:10.1211/PJ.2018.20205542

<https://pharmaceutical-journal.com/article/letters/prescribing-and-deprescribing-sodium-valproate-implications-for-pharmacy-practice>

4. Royal College of General Practitioners and Association of British Neurologists and Royal College of Physicians (2019) Guidance Document on Valproate Use in Women and Girls of Childbearing Years

<https://www.rcgp.org.uk/-/media/Files/CIRC/Epilepsy/Guidance-on-Valproate-use---Dec-2020.ashx?la=en>

Thank you to Dr Regi Alexander and Verity Chester for inviting me to speak today.
Thank you to my co author Dr Inder Sawhney for developing the easy read resources