RC PSYCH
ROYAL COLLEGE OF PSYCHIATRISTS

PS01/25

Valproate in psychiatry:

Female and male reproductive health risks, pregnancy harms, withdrawal and safer alternatives

September 2025

POSITION STATEMENT

Contents

How to cite this publication:
Royal College of Psychiatrists (2025) College Position Statement PS01/25 – Valproate in psychiatry: Female and male reproductive health risks, pregnancy harms, withdrawal and safer alternatives

About this statement

Valproate carries serious risks for reproductive health and pregnancy.

Recent changes to regulatory requirements (MHRA, 2024) relating to medicines containing valproate have a significant impact on the overall care and management of many patients – both male and female – who suffer from bipolar disorder and other psychiatric disorders.

In response to these changes, the Psychopharmacology Committee of the Royal College of Psychiatrists (with additional input from the Faculty of Perinatal Psychiatry and the British Association for Psychopharmacology) have therefore collaboratively developed this guidance to support prescribing decisions for men and women of childbearing potential.

This statement updates and replaces the College's 2018 statement *PS04/18: Withdrawal of, and alternatives to, valproate-containing medicines in girls and women of childbearing potential who have a psychiatric illness*.

The key updates in this position statement:

- Outline and responds to new regulatory standards (MHRA 2024)
- Extend the scope to include male, as well as female, psychiatric patients
- Strengthen prescribing controls and documentation
- Provide updated clinical guidance on withdrawal and alternatives.

Links to the mandatory risk acknowledgement forms and other new mandatory regulatory materials are also provided.

Authors and acknowledgements

Authors

Updated position statement (2025):

Coordinated by Dr Rupert McShane, Dr Carolina Schneider and Professor Oliver Howes

Original position statement (2018):

Written by Professor David Baldwin and Dr Angelika Wieck, based on contributions from:

The Pharmacology Committee (2018)
Professor Katherine Aitchison, Professor David Baldwin, Professor Thomas Barnes, Professor Rupert McShane, Ms Ellisiv Clarke, Professor Jeremy Hall, Dr Adrian James, Dr Imran Malik, Dr Carolina Schneider, Professor Hamish McAllister-Williams, Dr Ahmed Shoka, Dr Paul Stokes, Professor Allan Young and Professor Oliver Howes.

The Faculty of Perinatal Psychiatry (2018)
Dr Trudi Seneviratne and Dr Angelika Wieck.

British Association for Psychopharmacology (2018)
Professor Ian Jones and Professor Carmine Pariante.

Acknowledgements

Many thanks to Dr June Raine of the MHRA for reviewing this statement, and to Dr Mary Houston of the University of Southampton for secretarial support for the original position statement.

Background

Medicines containing valproate have often been used to treat patients with bipolar disorder or epilepsy. The active ingredient in these medicines can include valproic acid, magnesium valproate, sodium valproate, valproate semi sodium or valpromide (common trade names include 'Depakote', 'Epilim' and 'Epival'). The collective term 'valproate' is used in regulatory materials and in this document.

Unborn babies exposed to valproate in utero are at very high risk (between 30–40 in every 100) of neurodevelopmental problems (including autistic spectrum disorders and lower intelligence) and at high risk (approximately 10 in every 100) of congenital malformations (which include spina bifida, atrial septal defect, cleft palate and hypospadias). A smaller increase in risk of neurodevelopmental disorders may also occur in children of men taking valproate (5 in 100, compared with 3 in 100 in those taking lamotrigine or levetiracetam). There is also an increased risk of infertility in men taking valproate. It is important to note that new evidence is likely to emerge in the next few years, so readers are advised to refer to the MHRA website for any updates.

Previous measures designed to better inform women about risks with valproate have not been sufficiently effective: many women have not received the right information at the right time and babies are still being born with the adverse consequences of valproate exposure during pregnancy. The Medicines and Healthcare products Regulatory Agency [MHRA] (January 2024) have therefore issued fresh guidance designed to minimise in utero valproate exposure and to address the newly recognised risks in men.

Updated regulatory guidance

Full guidance is provided by the MHRA through the following links. Psychiatrists who prescribe valproate should read the guidance for healthcare professionals in full.

- Guide for Healthcare Professionals (Information on the risks of valproate use in all patients)
- Guidance: Valproate – reproductive risks
- Comprehensive valproate guidance
  [Valproate (Belvo, Convulex, Depakote, Dyzantil, Epilim, Epilim Chrono or Chronosphere, Episenta, Epival and Syonell): New safety and educational materials to support regulatory measures in men and women under 55 years of age]

Summary of guidance

(The full guidance should be read before prescribing)

Advice for healthcare professionals

- Valproate must not be started in new patients (male or female) younger than 55 years of age, unless two specialists independently consider and document that there is no other effective or tolerated treatment, or there are compelling reasons that the reproductive risks do not apply. For the majority of patients, other effective treatment options are available.
- At their next annual specialist review, women of childbearing potential and girls receiving valproate should be reviewed using the revised valproate annual risk acknowledgement form. A second specialist signature will be needed if the patient is to continue on valproate, however subsequent annual reviews will only require one specialist signature.
- General practice and pharmacy teams should continue to prescribe and dispense valproate and, if required, offer patients a referral to a specialist to discuss their treatment options. Valproate should be dispensed in the manufacturer's original full pack.
- Report suspected adverse drug reactions associated with valproate on a Yellow Card.
- Pregnant women taking antiepileptic drugs in general and valproate in particular should be enrolled in the UK Epilepsy and Pregnancy Register.

Advice for patients – to be provided by healthcare professionals:

- Do not stop taking valproate without advice from a specialist. This is because epilepsy or bipolar disorder may worsen without treatment.
- If you are on valproate, please attend any offered appointments to discuss your treatment plan and talk to a healthcare professional if you are concerned.
- See the College's new resource, Patient information: Valproate in pregnancy and conception, to understand the risks of valproate. Also see the MHRA information page for more resources, including their Patient Guide: What you need to know about valproate.
- As a precaution for male patients planning to have a child within the next year: Speak to a healthcare professional about your treatment options.

Prescribing valproate for females

Valproate preparations must not be prescribed for bipolar disorder in pregnant women. It must not be prescribed for epilepsy in pregnancy unless two specialists independently consider and document that there is no other effective or tolerated treatment.

Where possible, existing patients under 55 years should be switched to another treatment unless two specialists independently consider and document that there is no other effective or tolerated treatment or the risks do not apply.

For girls and women under 55 years of age, valproate in any indication must be prescribed and dispensed according to the Valproate Pregnancy Prevention Programme (also known as 'Prevent').

If the medicine containing valproate is being prescribed on the recommendation of a psychiatrist or for a psychiatric indication, at least one of the specialists should be a psychiatrist.

Valproate pregnancy prevention programme (Prevent)

The details of the Valproate Pregnancy Prevention Programme (Prevent) are on section 4.4 of the SmPC (Clinical Particulars/Special Warnings) for each preparation – accessible from the Electronic Medicines Compendium.

In summary, the specialist must ensure that:

- Individual circumstances affecting risk of pregnancy are evaluated in each case and the patient has received comprehensive information on pregnancy prevention.
- The patient is capable of complying with effective contraception for the entire duration of treatment.

- A pregnancy test is performed before treatment in all women under 55 years of age.
- The patient has received the MHRA Patient Guide and understands:
  - the nature and magnitude of the risks of malformations and neurodevelopmental disorders.
  - that she should ask a GP for a specialist referral as soon as she is planning to become pregnant.
  - the urgent need to consult a GP for a referral if she becomes pregnant.
- The parents/caregivers of female children taking valproate understand the need to contact their GP once the child experiences menarche and, once menarche happens, are provided with comprehensive information about the magnitude of the risks of malformations and neurodevelopmental disorders
- An annual specialist review of bipolar disorder is undertaken
- The patient signs the annual risk acknowledgement form each year
- Annual risk acknowledgement form for female patients

Prescribing valproate for males

In boys and men under 55 years of age, valproate must not be initiated unless two specialists experienced in the management of epilepsy or bipolar disorder independently consider and document that other treatments are not effective or tolerated or the risk of infertility or potential risk of testicular toxicity are not applicable.

Men should be made aware of the increased risk of infertility and of testicular toxicity in animal studies before starting valproate containing medicines.

The patient should sign the risk acknowledgement form for male patients starting valproate.

Dispensing valproate

All packaging for medicines containing valproate must include a visual warning about the risk of valproate in pregnancy. Each time valproate is dispensed, the dispensing pharmacist should check that the patient has a copy of the Patient Guide, discuss its contents, and give them a Patient Card. Manufacturers of medicines containing valproate are required to monitor continuing valproate use and the long-term outcomes of any exposed pregnancies.

Wider responsibilties of health providers

All healthcare professionals who prescribe or dispense medicines containing valproate are required to ensure the following: all girls and women of (or near to) childbearing age who are taking such medicines are identified systematically; local training, procedures, and protocols are reviewed and revised as necessary; and there is a clear understanding of the clinical roles and responsibilities relating to the identification and counselling of girls and women of childbearing age who are taking such medicines.

Alternatives to medicines containing valproate

In psychiatric practice, medicines containing valproate have been prescribed for three main indications: as an alternative to other antimanic treatment (including antipsychotic medication or lithium) in patients experiencing manic episodes; to augment antidepressant treatment in patients with unipolar or bipolar depressive episodes; and to reduce the likelihood of further episodes of illness in patients with bipolar disorder or recurrent unipolar disorder.

Medicines containing valproate have also been prescribed in psychiatric settings:

- To patients with epilepsy, many of whom have comorbid psychiatric illness
- occasionally as an augmentation of antipsychotic medication in patients with schizophrenia and related conditions
- as an alternative to antidepressant or anxiolytic treatment in patients with anxiety disorders
- or as treatment for persistent impulsivity and aggressive behaviour.

The current prevalence of 'off-label' use of valproate in patients with schizophrenia or schizoaffective disorder within mental health services is uncertain, but the findings of prevalence studies conducted in other countries (Israel, United States and multiple Asian countries) suggest that between 14.1% and 35.2% of patients might be prescribed medicines containing valproate, typically combined with antipsychotic medication.

The following paragraphs mention particular medicines in particular indications though in some instances the named medication does not currently (July 2024) have a market authorisation ('license') for that indication. Further guidance on steps to be taken when considering the prescription of a medicine outside the terms of its licensed indications is provided within College Report 210 (Royal College of Psychiatrists Psychopharmacology Committee, 2017).

- **Treatment of manic episodes:** Findings of network meta-analysis indicate that valproate has broadly similar efficacy and tolerability compared with antipsychotic medications (when grouped together) or lithium as monotherapy for acute manic episodes (Yildiz et al., 2014). A previous network meta-analysis indicated that valproate was probably less effective than haloperidol, olanzapine and quetiapine (Cipriani et al., 2011). Although antipsychotic medications are not ideal, they carry low risks of intrauterine malformations (McAllister-Williams et al., 2017), and therefore should be prescribed in preference to medicines containing valproate in women of childbearing age who are experiencing acute manic episodes.

- **Augmentation treatment of depressive episodes:** In bipolar depressive episodes, valproate preparations may be efficacious as an augmentation agent for acute treatment of bipolar depression (Bond et al., 2010; Taylor et al., 2014), but there is stronger evidence for the effectiveness of quetiapine or combination olanzapine plus fluoxetine,

and possibly for olanzapine monotherapy, lamotrigine (Goodwin et al., 2016) and lurasidone (Loebel et al., 2014) for the treatment of bipolar depression. Lamotrigine exposure does not appear to be associated with an increased risk of major congenital abnormalities, but little is known about the safety of lurasidone during pregnancy and the alternatives are probably preferable: current knowledge about the effects of intrauterine exposure to psychotropic medications are summarised in guidelines from the British Association for Psychopharmacology (McAllister-Williams et al., 2017).

There are no randomised controlled trial data supporting the use of valproate as an acute treatment in unipolar depression (Vigo and Baldessarini, 2009). Alternative evidence-based, options such as lithium, quetiapine and aripiprazole should be considered instead (Cleare et al., 2015). Lithium may be associated with risks during pregnancy (including teratogenicity/cardiovascular anomalies in the first trimester and neonatal toxicity), although the evidence base is smaller than for many other established drugs. Concerns and precautions around its use must be carefully discussed with patients who could become pregnant, as summarised in the British Association for Psychopharmacology guidelines (McAllister-Williams et al., 2017). Valproate preparations can be beneficial as augmentation of antidepressant treatment in unipolar depressive episodes, but the evidence is more substantial for other pharmacological augmentation approaches, including lithium and antipsychotic medications. Alternatives to valproate preparations should therefore be strongly considered in women of childbearing age who are experiencing acute depressive (bipolar or unipolar) episodes.

- **Prophylaxis in bipolar disorder or recurrent unipolar depressive disorder:** Valproate preparations have limited evidence of efficacy in maintenance treatment of bipolar disorder (Cipriani et al., 2013), but lithium is preferable as it has both a larger evidence base and efficacy in the prevention of manic and depressive episodes (Miura et al., 2014). There is little evidence to support the use of medicines containing valproate in maintenance treatment in unipolar depression, in contrast to the substantial evidence for antidepressants.

- **Augmentation treatment in schizophrenia:** There is little high-quality evidence to support the use of medicines containing valproate to augment antipsychotic treatment in patients with schizophrenia or related conditions (Wang et al., 2016). Valproate preparations are sometimes used to augment the effectiveness of clozapine treatment, but there is better evidence for augmentation of clozapine with aripiprazole or fluoxetine (Siskind et al., 2018).

- **Augmentation treatment in anxiety disorders***:* Pooled analyses provide no evidence to support the use of valproate preparations in post-traumatic stress disorder (Wang et al., 2014) although there is some evidence of efficacy in generalised anxiety disorder (Aliyev and Aliyev, 2008). There are many alternative antidepressant or anxiolytic treatments, including selective serotonin reuptake inhibitors and serotonin-noradrenaline reuptake inhibitors (Baldwin et al., 2014).

- **Treatment for persistent impulsivity and aggression:** Findings of a systematic review suggest that medicines containing valproate are superior to placebo in male outpatients with persistent aggression, for impulsively aggressive adults with certain ('cluster B') personality disorders, and for youths with conduct disorder,

though not superior to placebo in children or adolescents with pervasive developmental disorder: however, the reviewers consider that firm conclusions about the potential value of valproate cannot be made (Huband et al., 2010).

There are many recognised side effects of valproate-containing medicines, other than risks associated with pregnancy, including hepatotoxicity (family history of liver disease represents a contra-indication), hair loss and thrombocytopenia, and these and other potential problems also need to be considered and discussed with patients when making treatment decisions.

Switching patients from valproate-containing preparations to alternatives

- **All pregnant women** taking valproate for bipolar disorder, or for any other psychiatric indications, should be withdrawn from valproate. The only exception would be if they also have epilepsy, and two specialists have attested that there are no alternatives. Pregnant patients taking valproate should be seen by a specialist within days of the recognition of pregnancy.

- **Most women of childbearing potential and men under the age of 55 years old** who are undergoing psychiatric care should be withdrawn from continued treatment with valproate.

- **Men taking valproate** should be made aware of the risks of infertility and of testicular toxicity in animal studies.

Patients should not stop taking valproate without advice from a specialist. Abrupt discontinuation can lead to a significant deterioration in their condition.

Some patients (probably only a few in each local service) may have poor experience of alternative treatments and a reluctance to try other options and so wish to continue with valproate preparations, whilst being aware of potential hazards should they become pregnant. Completion of the annual risk acknowledgement form formalises the process which must now be followed in such circumstances.

Guidance on the withdrawal of medicines containing valproate

- **For women who are not pregnant or for men:** When medicines containing valproate need to be withdrawn in a patient who is currently well, the dose should be tapered gradually in order to reduce the risk of relapse.
  - In a patient who is not pregnant but is psychiatrically unwell whilst taking a valproate preparation, much faster cross-tapering while introducing the alternative is needed.
  - In patients experiencing an acute manic episode, haloperidol, olanzapine or quetiapine should be considered.
  - In patients experiencing an acute depressive episode, combination olanzapine and fluoxetine or olanzapine monotherapy or lithium or quetiapine (or possibly lurasidone) should be considered – however, avoid introducing an antidepressant without concomitant treatment with a mood-stabilising medication in people with bipolar disorder.

- **For pregnant women:** Patients who are currently well but discover they are pregnant (or are discovered by a health professional to be pregnant) whilst taking a medicine containing valproate should be informed not to stop it abruptly. They should be referred urgently for a specialist review, preferably by a consultant in perinatal psychiatry, and asked to continue with the medicine containing valproate until they are seen by this service. The specialist review should occur within days to ensure the risks to the developing child can be addressed promptly. They should also be referred urgently to a specialist experienced in fetal medicine who provides scanning and counselling for women exposed to valproate during pregnancy. Patients should be asked to continue with the medicine containing valproate until they are seen by that service.

- **For patients who are currently psychiatrically unwell, pregnant and taking medicines containing valproate:** Such individuals should be managed with urgent referral to a specialist perinatal community mental health team. They should be seen by this specialist within days. Careful consideration and discussion of the relative risks of malformations and other intra-uterine and post-partum complications is needed before alternative pharmacological treatments are introduced. The team would also undertake close monitoring of the mental state, further antenatal care planning, and would formulate a relapse prevention plan.

- Women and their clinicians may want to withdraw medicines containing valproate as soon as possible. The MHRA states that withdrawal should occur within a 'few weeks' (e.g. over 2–3 weeks). This is faster than is generally recommended (e.g. BAP guidance recommends withdrawal over at least 4 weeks in the absence of immediate risk from valproate (Goodwin et al 2016)) but these recommendations are based on limited evidence and in the absence of an immediate risk from valproate. It is recommended that a relapse prevention plan is agreed. There is some relationship between valproate dosage and risk of its harmful effects, so risks for the fetus are declining during these few weeks.

- Should a woman experience a relapse during pregnancy and develop a manic episode, treatment with anti-manic medications (haloperidol, olanzapine, quetiapine) could be started, augmented by benzodiazepine anxiolytics if necessary. If these treatments prove to be insufficient, electroconvulsive therapy could also be considered if indicated (McAllister-Williams et al., 2017).

Risk acknowledgement forms: Guiding discussions about valproate

Psychiatrists prescribing valproate must be fully cognisant of the details of the Guidance for Healthcare Professionals as described in the previous section.

The MHRA has produced separate risk acknowledgement forms for female and male patients. These provide the framework to guide and record discussions with patients about medicines containing valproate.

For females taking valproate, the form must be completed for all patients under 55 years at least once, irrespective of risk, and annually thereafter while valproate is being prescribed if there is any risk whatsoever of pregnancy. For males under 55 years, the form must be completed when starting valproate.

Both forms require countersigning by a specialist prescriber following an independent review. This review can be of clinical information rather than an independent interview with the patient, though the latter may be helpful. If the medicine containing valproate is being prescribed on the recommendation of a psychiatrist or for a psychiatric indication, at least one of the specialist signatories should be a psychiatrist.

The second specialist signatory should not be line managed by the first signatory, but it is permissible for them to work in the same multidisciplinary team. The specialist should be experienced in the management of epilepsy and or bipolar disorder.

The MHRA has indicated that mental health pharmacists or specialist, associate specialist and specialty doctors could act as countersigning specialists or prescribing specialists respectively as long as they have an appropriate level of competency. The competencies for prescribing specialists and countersigning specialists should be clearly defined either through guidance issued by clinical bodies or at a local level.

If the countersigning specialist does not physically sign the form (which is permissible), the primary specialist prescriber must detail the countersigning specialist's name, role, unique professional identifier and the date of discussion.

The specialist prescriber must also initial to confirm the countersignatory's view of the following on their behalf:

- The patient should be treated with valproate
- The patient's condition does not respond to other treatments or other treatments are not tolerated
- The patient has been informed of the risks, and confirmation of the countersignatory specialist's view that balance of benefits and risks is favourable
- The patient is in the process of changing away from valproate (if applicable).

Following completion of the initial form, a specialist countersignature is not required for each annual review unless the patient's situation changes.

The forms **may be updated periodically**, based on stakeholder feedback. Therefore, they should be accessed by searching for the current versions on the MHRA website.

At the time of writing, the current versions are dated June 2024 and available from MHRA's guidance: Valproate – reproductive risks, listed under 'Materials and resources – Safety and educational materials' as follows:

- Females: Annual risk acknowledgement form
- Males: Risk acknowledgement form for starting valproate

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