NHS Greater Glasgow & Clyde
Mental Health Services
Prescribing Management Group

Use of valproate within Mental Health Services

In 2018 the Medicines and Healthcare products Regulatory Authority (MHRA) introduced the valproate pregnancy prevention programme (PREVENT) for all valproate products in response to increasing evidence of the teratogenic effects of valproate. The programme is to ensure that women of childbearing potential who are currently prescribed valproate or who may be considered for valproate treatment are fully informed of the potential risks of valproate to the unborn child and are provided with highly effective contraception to prevent an unplanned pregnancy.

From January 2024 restrictions on valproate prescribing have been extended to include males aged under 55 following recent evidence indicating that the use of valproate in males can cause infertility (which can last up to 3 months after discontinuing treatment) and testicular toxicity. In September 2024, a further drug safety update was issued by the MHRA, advising of a possible association between valproate use by men around the time of conception and an increased risk of neurodevelopmental disorders in their children. Currently, 1258 men are prescribed valproate within GGC, this figure has not been filtered for those open to other specialities. This is a larger population than women, where evidence from audits have shown use has been declining in recent years.

Valproate is contraindicated in the following circumstances:

- In pregnancy
- In women of childbearing potential unless the conditions of the pregnancy prevention programme are fulfilled.
- In males aged under 55 without second opinion

This means the use of valproate in women of childbearing potential without meeting the conditions of the pregnancy prevention programme or in males without completed risk acknowledgement form is contraindicated and therefore is an unlicensed use.

This document describes how valproate restrictions in female and male patients aged under 55 will be implemented within mental health services in NHS Greater Glasgow & Clyde.

Process for obtaining second opinion

One of the main changes to the guidance is the requirement for two independent specialists (prescriber and countersignature) to review treatment and document that there is no other effective or tolerated treatment. Both must complete and sign relevant sections in the annual risk acknowledgment form. There is no requirement for the counter signatory to see the patient face to face as part of this process.

Countersigning specialist can be:

- Consultant psychiatrist
- Speciality doctor in mental health
- Independent Psychiatric nurse prescriber
- Specialist mental health independent pharmacist prescriber

The counter signatory cannot be directly line managed by the prescribing specialist.

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If the counter signatory disagrees with the decision to prescribe valproate the case should be escalated to the appropriate clinical director.

For NEW patients, both male and female, this is required before treatment can be initiated.

For EXISTING FEMALE patients this is required to be carried out at their next annual review.

At subsequent annual reviews for females, only the prescribing specialist is required to complete the risk acknowledgement form unless the patients' circumstances change. Each CMHT should create and keep up to date a valproate register and develop a local process for reminder and recall of women for annual review.

Minimum information to be provided by prescribing specialist using the form set out in appendix 1:

- Diagnosis
- List of medication previously trialled for bipolar disorder with summary of why they are or were unsuitable.
- If standard treatments have not been trialled a reason must be given as to why.
- For women, an indication of their contraceptive status or childbearing potential and for new female patients' pregnancy status

Outpatient: Each CMHT should work with clinical director to establish a robust system for obtaining and recording second opinion.

Inpatient: Before starting valproate, a discussion should be had at a multidisciplinary team meeting to determine the appropriateness of treatment and the second signature should be a named prescribing specialist.

Designated Medical Practitioners (DMP) providing a second opinion under the Mental Health Act CANNOT be used as the countersigning specialist. When a DMP has the discussion with the prescribing specialist about the treatment plan, they should confirm if the MHRA requirements have been met. If the DMP chooses to authorise valproate, it should be stated on the T3B as a condition that the MHRA requirements need to be met.

Appropriate clinical director should be informed of ALL initiations of valproate.

The MHRA have produced three infographics to help support prescribers and clarify in which situations review by two specialists may be required:

Female patients under 55 years old
Male patients under 55 years old
Male and female patients 55 years and older

Support materials

The MHRA have produced a set of information resources to enable clinicians to undertake appropriate conversations with patients. These resources maybe found at the following link: valproate safety measures materials.

The most relevant documents for psychiatrists are:

- Guide for Healthcare professionals (HCP)
- Patient guide- women and men
- Risk acknowledgement forms (available as a document template on EMIS)

An easy read patient leaflet and decision making tool for people taking Valproate who could become pregnant are also available on the Right Decision Service:

Valproate - easy read | Right Decisions

Use of valproate in women- the valproate pregnancy prevention programme

Evidence shows that 1 in 10 children born to women who took valproate during pregnancy will have a physical birth defect and up to 40% will have early developmental problems that can lead to significant learning disabilities. Epidemiological studies have also reported a decrease in mean birth weight, and a higher risk of being born with a low birth weight or small for gestational age.

Prevent requires the patient to see a relevant 'specialist' for an **annual** risk review of her valproate treatment. The risk acknowledgement form must be completed on an annual basis to record the patient's understanding of the risks and her agreement to participate in the Prevent programme and use highly effective contraception without interruption throughout treatment. The MHRA defines highly effective contraception as having a failure rate of less than 1% and includes;

- Copper intra-uterine device
- Levonorgestrel intra-uterine device
- Progestogen only implant
- Male and female sterilisation

If a user-independent method is not used then two complimentary forms of contraception including a barrier method should be used and regular pregnancy testing considered.

Any use of valproate out with these requirements is unlicensed and any deviation needs to be escalated through appropriate governance structures.

Process for initiating highly effective contraception

For out-patients requiring highly effective contraception a referral should made to the patient's GP to discuss and initiate this as defined by the MHRA.

For in-patients already on valproate and any women being considered for valproate treatment referral should be made to local Sandyford Sexual Health Services.

The guidance is clear that valproate treatment should not be initiated for new patients until pregnancy is excluded and highly effective contraception is in place.

Use of valproate in male patients

Valproate use in men may impair fertility; this may be irreversible. For other patients' infertility can last for at least 3 months after discontinuing treatment. Toxicity studies in animals have also shown

testicular toxicity including testicular degeneration/atrophy, spermatogenesis abnormalities and decreased testes weight. A retrospective observational study has also indicated a possible association between valproate use by men around the time of conception and an increased risk of neurodevelopmental disorders in their children.

Before initiation the above risks should be clearly explained to the patient and second opinion obtained as per the process above. New and existing patients, regardless of age, should be advised of the need to use effective contraception (condoms and another form of female contraceptive) throughout valproate treatment and for 3 months after stopping valproate, to allow for one completed sperm cycle not exposed to valproate. They should also be advised not to donate sperm whilst taking valproate and for 3 months after stopping. Full details can be found here and an information leaflet for patients is available.

At initiation the risk acknowledgement form should be discussed and completed.

For those patients with a permanent reason that these risks do not apply e.g. vasectomy then the second opinion is not required. The reasoning should be documented clearly in the patients EMIS records and risk acknowledgement form.

Commission on Human Medicines (CHM) has advised that there will be **NO** required to complete risk acknowledgement form or seek second opinion for those prescribed valproate historically.

Patients moving into GGC already prescribed valproate

On occasion patients already on valproate will move into the area from another health board or country. All patients should be assess for ongoing appropriateness of treatment. If no risk acknowledgement form is available and treatment is to continue then a second opinion should be obtained and paperwork should be completed at the patient's next appointment.

Following completion of paperwork

The annual risk acknowledgement form should uploaded to their EMIS record and a copy shared with GP and the patient or their representative.

A warning should be added to their EMIS record indicating that they are on valproate treatment. For women this should include the date when next annual review is due.

Prescribing Management Group – Mental Health

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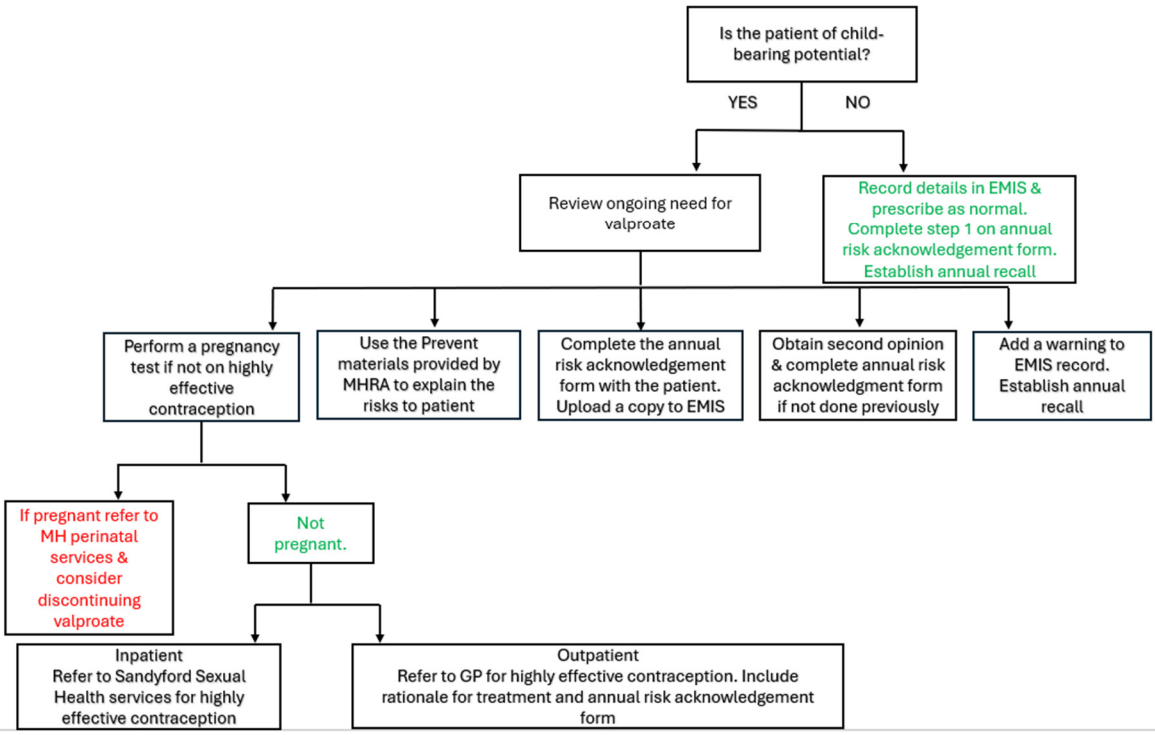
Valproate Risk Management Process for EXISTING FEMALE patients

Valproate is contraindicated in women of childbearing potential unless the conditions of the Prevent programme are fulfilled



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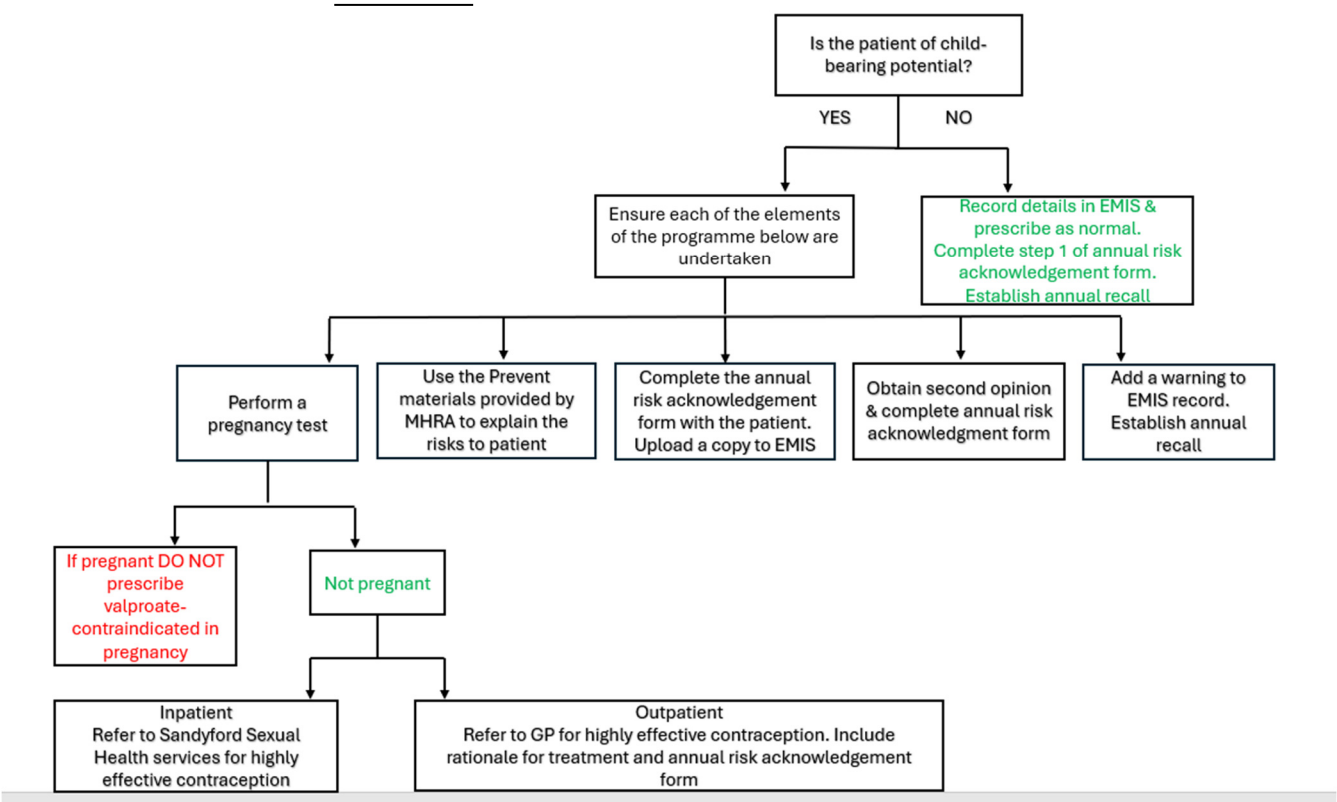
Valproate Risk Management Process for NEW FEMALE patients

Valproate is contraindicated in women of childbearing potential unless the conditions of the Prevent programme are fulfilled



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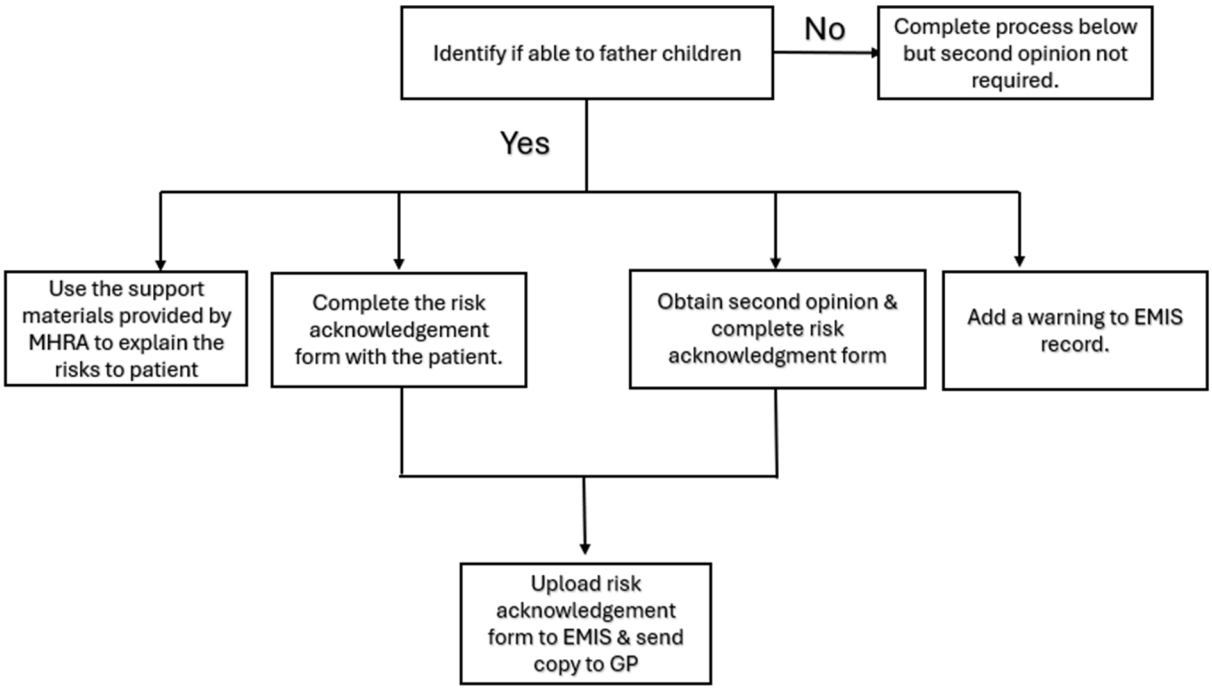
Valproate Risk Management Process for NEW MALE patients



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Appendix 1- Referral form for second opinion.

Name: CHI: Consultant:

Diagnosis:

Medication	Previously tried (yes/no)	Reason treatment discontinued or not appropriate.
Lithium		
Olanzapine		
Quetiapine		
Lamotrigine		
Other (provide details):		

For Women: Contraceptive status (select as appropriate):

Progesterone only implant

Copper intra-uterine device

Levonorgestrel intra-uterine device

Female sterilisation

Male sterilisation

User dependent method- 2 complimentary forms of contraception including a barrier method (provide details):

Other (provide details):

Countersignatory approval (delete as appropriate): YES/NO

Signed: Date:

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