NHS Greater Glasgow & Clyde
Mental Health Services
Prescribing Management Group

Implementation of Prevent – the Valproate Pregnancy Prevention Programme in Mental Health Services

The Medicines and Healthcare products Regulatory Authority (MHRA) amended the marketing authorisation (or product licence) for all valproate products in April 2018. The MHRA took this action in response to increasing evidence of the teratogenic effects of valproate. Evidence now 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. Valproate is now contraindicated in the following circumstances:

- In pregnancy
- In women of childbearing potential unless the conditions of the pregnancy prevention programme are fulfilled.

This means the use of valproate in women of childbearing potential without meeting the conditions of the pregnancy prevention programme is contraindicated and therefore off-label.

This document describes how Prevent- the valproate pregnancy prevention programme will be implemented within mental health services in NHS Greater Glasgow & Clyde.

What is Prevent- the valproate pregnancy prevention programme?

In essence the programme is a process 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.

To support this, 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 MHRA Prevent- the valproate pregnancy prevention programme materials .

The most relevant documents for psychiatrists are:

- Guide for Healthcare professionals (HCP)
- Patient guide
- Risk acknowledgement form

The process 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. The MHRA defines highly effective contraception as;

- Copper intra-uterine device
- Levonorgestrel intra-uterine device
- Progestogen only implant

The HCP guide was updated in November 2019 and makes the following additional statements about contraception

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Progestogen-only injections e.g. Depo-Provera have a typical-use failure rate of 6%, but this may be due to repeat injections being administered late. Progestogen-only injections may be considered highly effective **if** repeat injections are documented as having been administered on schedule by a healthcare professional.

User dependent methods of contraception are not considered highly effective.

There is an expectation that all patients who are of childbearing potential will agree to participate in the Prevent programme although the guidance does state the following:

'These conditions also concern 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 risk.'

This acknowledges that some existing patients may opt to remain on valproate treatment but having had the risks explained may choose not to participate in the prevent programme. Use of valproate in this circumstance is contraindicated and constitutes high risk off label prescribing. This should be the exception rather than the norm. Clearly documenting an individual's decision to opt out of the Prevent programme at the annual review using the standardised annual risk acknowledgement form is essential. The risk acknowledgement form is part of the MHRA's Prevent programme materials and as such, has been designed with the expectation that affected women will participate in the Prevent programme and be prescribed highly effective contraception. Therefore it is essential that any statements that are not applicable for individuals opting out of the Prevent programme e.g. around the use of highly effective contraception are annotated appropriately. In addition to the completion of the risk acknowledgement form for women opting out of Prevent, it is highly recommended that a clear, unambiguous entry is made within their case/ EMIS record to record their objection, the rationale for opting out and that the prescriber is content with this decision.

The following wording is suggested;

Following a full consultation with the patient discussing the risks of remaining on valproate without the use of highly effective contraception (as described within the MHRA's Prevent programme and risk acknowledgement form), I am of the view that it is appropriate for the patient to remain on valproate without the use of highly effective contraception. I have informed the patient that this is contraindicated and constitutes off label use. This will be subject to regular review.'

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.

What should you do now?

Psychiatrists are asked to familiarise themselves with the contents of Prevent- the MHRA's valproate pregnancy prevention programme and to conduct an annual risk review for all current patients affected by this at their next scheduled appointment or within the next 6 months whichever is sooner.

The annual risk acknowledgement form should be completed for each patient of childbearing potential and a copy uploaded to their EMIS record and another sent to their GP.

A warning should be added to their EMIS record indicating that they are on valproate treatment.

Cohort of affected patients within GGC MHS

Prescribing data suggests there may be up to 800 women between the ages of 13 and 55 currently receiving valproate. eHealth data suggests approximately 300 of these are open mental health patients (EMIS data), 230 patients are open to neurology, 57 to both but for the remaining approximate 350 it is not clear which specialty initiated their valproate treatment. GPs will review these patients in line with their responsibilities under the Prevent programme but services should be aware that some of these patients may be referred to the relevant specialty for their annual risk acknowledgement review.

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Valproate Risk Management Process for female patients already established on valproate[1]

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

Is the patient of child-bearing potential[2]?

No

Record details in case notes and EMIS and prescribe as normal. Ensure system in place for annual recall and review where appropriate[2]

Yes

Review the ongoing need for valproate.

Perform pregnancy test if necessary[3]. If pregnant **refer to Perinatal MH Service and consider discontinuing valproate.** Use the Prevent Patient Booklet to explain risks of valproate treatment and the requirement to enrol in the Prevent Programme if not already prescribed highly effective contraception[4].

Use the Prevent Annual Risk Acknowledgement form to record the patients understanding of the risks and agreement to participate in the Prevent Programme.

File a copy of the Annual Risk Acknowledgement Form in the case notes and upload to EMIS.

Add a warning to EMIS to indicate the patient is prescribed valproate and subject to the Prevent Programme

Ensure system in place for annual recall for review and recordin[illegible]isk acknowledgement.

Out-patient

Refer patient to GP if required for prescription of highly effective contraception[4,5] and ongoing valproate. Include rationale for valproate and copy of annual risk acknowledgment form with referral.

In-patient

Arrange for initiation of highly effective contraception and prescribe valproate.[4,5]

On discharge ensure GP has a copy of the risk acknowledgement form.

If a patient refuses to participate in the Prevent Programme and valproate remains the only viable treatment; record their understanding of the risks and their refusal to enrol in the Prevent Programme in their case record and review on at least and annual basis. The risk acknowledgement form must be used for this purpose. [6]

Valproate Risk Management Process for new female patients[1]

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

Is the patient of child-bearing potential[2]?

No

Record details in case notes or EMIS and prescribe as normal. Ensure system in place for annual recall and review where appropriate[2]

Yes

Perform pregnancy test if necessary[3]. If pregnant **DO NOT prescribe valproate.**

Use the Prevent Patient Booklet to explain risks of valproate treatment and the requirement to enrol in the Prevent Programme if not already prescribed highly effective contraception.[4]

Use the Prevent Annual Risk Acknowledgement form to record the patients understanding of the risks and agreement to participate in the Prevent Programme.

File a copy of the Annual Risk Acknowledgment Form in the case notes and upload to EMIS.

Add a warning to EMIS to indicate the patient is prescribed valproate and subject to the Prevent Programme. Ensure system in place for annual

Out-patient

Refer patient to GP for prescription of highly effective contraception and valproate[4, 5]. Include rationale for valproate and copy of annual risk acknowledgment form with referral.

Using valproate in a woman of childbearing potential without enrolment in the Prevent programme would be outwith the marketing authorisation. Women prescribed valproate should be encouraged to enrol.

In-patient

Arrange for initiation of highly effective contraception and prescribe and valproate.[4,5]

On discharge ensure GP has a copy of the risk acknowledgement form.

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

Notes:

1. These flowcharts should be used in conjunction with the Prevent Programme Guide for Healthcare Professionals

2. Valproate should not be used in female children or women of childbearing potential unless other treatments are ineffective or not tolerated. In other words it should be viewed as a treatment of last resort.
   A young female or woman may be considered **not** to be of child-bearing potential in the following circumstances (**n.b. This may not be an exhaustive list**)
   - Before puberty*
   - Post menopause
   - Confirmed infertility
   - Confirmed sterilisation
   - Confirmed hysterectomy

   * Where patients fertility status changes, e.g. post-puberty, the patient should be recalled for an annual review as required by the Prevent Programme.

3. Valproate preparations are contraindicated in pregnancy. If there has been unprotected sexual intercourse in the previous 3 weeks it is not possible to exclude pregnancy by means of a negative pregnancy test. In new patients, valproate treatment must be delayed until pregnancy can be excluded.

4. The MHRA defines 'highly effective contraception' to be those user independent methods such as the long acting reversible contraceptives (LARC); copper intrauterine device (Cu-IUD), levonorgestrel intrauterine system (LNG-IUS) and progestogen only implant (IMP) and female sterilisation, all of which have a failure rate of less than 1% with typical use.

5. For new patients, the guidance from the MHRA recommends highly effective contraception should be in place before the first valproate prescription is issued. Referral to Sandyford sexual health services will be required for inpatients to established on highly effective contraception. For outpatients, it is expected that GPs will make the onward referral to Sandyford services.

6. The presumption is that the majority of women will agree to be enrolled in the Prevent Programme and receive highly effective contraception. It is acknowledged however that some women after a full explanation of the risks may wish to remain on valproate treatment but decline highly effective contraception due to their specific circumstances. If the prescriber concurs with this position and agrees to continue valproate, full details of this must be recorded in the case record and within the risk acknowledgement form. This decision must be revisited on an annual basis for as long as the patient continues to take valproate and is of childbearing potential. Use of valproate without participation in the prevent programme is contraindicated and hence an off label use of the drug. The link below contains all the documentation relating to the Prevent Programme

   MHRA Valproate Prevent Programme Materials

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