

PS04/I8

Withdrawal of, and alternatives to, valproate-containing medicines in girls and women of childbearing potential who have a psychiatric illness

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POSITION STATEMENT

New regulatory requirements relating to valproate-containing medicines necessarily have a significant impact on the overall care and management of many pregnant women, and girls and women of childbearing potential, who suffer from bipolar disorder or other psychiatric disorders.

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 the following guidance relating to prescribing decisions regarding valproate preparations in women of childbearing potential.

We describe recent regulatory statements regarding valproate prescriptions, summarise evidence for alternatives to valproate, provide advice on how women who are currently undergoing treatment with valproate-containing preparations can be switched to alternative treatments, and provide a link to the recommended annual risk acknowledgment form to facilitate discussions with patients about hazards associated with valproate-containing medicines.

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1. Recent regulatory guidance

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 semisodium or valpromide (common trade names include 'Depakote', 'Epilim' and 'Epival').

Unborn babies exposed to valproate preparations *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).

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 European Medicines Agency [EMA] (February 2018) and the Medicines and Healthcare products Regulatory Agency [MHRA] (April 2018) have therefore issued fresh guidance designed to minimise *in utero* valproate exposure (summarised below).

Valproate preparations must not be used in pregnant women.

In girls and women of childbearing age, valproate preparations must not be used unless the patient meets the conditions of a '**pregnancy prevention programme**', which comprises the following features:

- assessing patients for the potential of becoming pregnant
- conducting pregnancy tests before starting and during treatment with valproate preparations
- counselling patients about the risks of valproate preparations
- explaining the need for **effective contraception** throughout treatment
- annual (or more frequent) reviews of treatment
- using a risk acknowledgement form to confirm the provision and understanding of relevant information.

Effective contraception must continue without interruption during the entire duration of treatment with valproate. Patients must be provided with comprehensive information on pregnancy prevention and should be referred for contraceptive advice if they are not using effective contraception. At least one effective method of contraception (preferably a user independent form such as an intra-uterine device

or implant) or two complementary forms of contraception including a barrier method should be used. Individual circumstances should be evaluated in each case when choosing the contraception method, involving the patient in the discussions. Even if she has amenorrhea she must follow all the advice on effective contraception.

EMA and MHRA guidance also stipulates that all packaging for valproate-containing medicines must include a visual warning about the risk of valproate in pregnancy: in addition, pharmacists should ensure that each prescription is accompanied by a patient reminder card to be discussed with each patient, each time a valproate-containing medicine is dispensed. Furthermore, manufacturers of valproate-containing medicines are required to monitor on-going valproate use and the long-term outcomes of any exposed pregnancies.

All healthcare professionals who prescribe or dispense valproate-containing medicines are required to ensure that all girls and women of (or near to) childbearing age who are taking valproate are identified systematically; to review and if necessary revise local training, procedures and protocols; and to ensure staff understand their roles and responsibilities in identifying and counselling girls and women of childbearing age who are taking valproate-containing medicines.

2. Alternatives to valproate-containing medicines

In psychiatric practice, valproate-containing medicines have been prescribed for three main indications: for patients experiencing manic episodes, as an alternative to other anti-manic drugs including antipsychotics or lithium; in patients with unipolar or bipolar depressive episodes, as an augmentation of antidepressant drug treatment; and in patients with bipolar disorder or recurrent unipolar disorder, as prophylaxis designed to reduce the likelihood of further episodes of illness.

A recent clinical audit of prescribing practice across 55 Mental Health Trusts in female patients of childbearing potential and with the diagnosis of bipolar disorder (conducted by the Prescribing Observatory for Mental Health of the Royal College of Psychiatrists) found that 24% of women aged younger than 50 years were prescribed valproate-containing medicines: for only half of these women was there documented evidence that information had been provided on the risks for the unborn child and the need for adequate contraception (Paton *et al.*, 2018).

Valproate-containing medicines have also been prescribed:

- to patients with epilepsy, many of whom have comorbid psychiatric illness;

- occasionally as an augmentation of antipsychotic drugs 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 valproate-containing medicines, typically combined with antipsychotic medication.

The following paragraphs mention particular medicines in particular indications though in some instances the named drug does not currently (December 2018) have a market authorisation ('licence') 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 to antipsychotic drugs (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 drugs are not ideal, they carry low risks of intrauterine malformations (McAllister-Williams *et al.*, 2017), and therefore should be prescribed in preference to valproate-containing medicines 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

drugs 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). 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 drugs. Alternatives to valproate preparations should therefore be strongly considered in women of childbearing age who are experiencing acute depressive (bipolar or unipolar) episodes.

- c *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 valproate-containing medicines in **maintenance treatment in unipolar depression**, in contrast to the substantial evidence for antidepressants.
- d *Augmentation treatment in schizophrenia.* There is little evidence to support the use of valproate-containing medicines as augmentation of 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).
- e *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 generalized 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).
- f *Treatment for persistent impulsivity and aggression.* Findings of a systematic review suggest that valproate-containing medicines are superior to placebo in male out-patients 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.

3. Switching patients from valproate-containing preparations to alternative medicines

Psychiatrists should consider the possibility of a potential pregnancy when assessing and managing all women of child bearing potential. The new regulatory requirements will necessarily have a significant impact on the overall management of many pregnant women and of women with childbearing potential who suffer from epilepsy, or bipolar disorder or other psychiatric disorders (Wieck and Jones, 2018).

Psychiatrists must review patients who are currently prescribed valproate-containing medicines at least once a year. This review must include detailed consideration of the alternatives to valproate preparations, and their replacement whenever possible. Some clinicians may occasionally have a few patients who do not tolerate and do not wish to take alternative medicines: in these exceptional patients, an effective pregnancy prevention programme must be followed.

Taken together, these measures should minimise the chance that a woman with a psychiatric disorder becomes pregnant whilst taking valproate: but if a pregnancy should nevertheless occur, the drug should be stopped and if continued pharmacological treatment is needed, an alternative medicine should be prescribed.

The following paragraphs provide guidance on the withdrawal of valproate-containing medicines, in women of childbearing potential who are not currently pregnant, and in women who are currently pregnant.

- a *Withdrawal of valproate-containing medicines in women who are not pregnant.* When valproate-containing medicines need to be withdrawn in a **patient who is currently well**, the dose should be tapered gradually (over at least 4 weeks) 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+fluoxetine or olanzapine monotherapy or lithium or quetiapine (or possibly lurasidone) should be considered, but avoid introducing an antidepressant drug without concomitant treatment with a mood-stabilising medication.

- b *Withdrawal of valproate-containing medicines in 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 valproate-containing medicine 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 valproate-containing medicine until they are seen by this service. They should also be referred urgently to a specialist experienced in fetal medicine who provides scanning and counselling for women with a valproate-exposed pregnancy. Patients should be asked to continue with the valproate-containing medicine until they are seen by that service.

Patients who are currently psychiatrically unwell, pregnant and taking valproate-containing medicines should be managed with urgent referral to a specialist perinatal community mental health team. 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.

- c Women and their clinicians may want to withdraw valproate-containing medicines as soon as possible. There is limited evidence to guide the duration of withdrawal, but experience gained from studies of lithium withdrawal may be relevant. On the basis of these data, current guidelines on bipolar disorder from the British Association for Psychopharmacology (Goodwin, 2016) suggest a withdrawal period of at least 4 weeks. There is some relationship between valproate dosage and risk of its harmful effects, so risks for the fetus are declining during these 4 weeks.
- d Should a woman experience a relapse in pregnancy and develop a manic episode, treatment with antimanic drugs (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)

4. Checklist to guide discussions about valproate-containing medicines

Most women of childbearing potential who are undergoing psychiatric care should be withdrawn from continued treatment with valproate-containing medicines. 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. The sometimes difficult clinical issues related to capacity and consent, or in women who are not currently active in a heterosexual relationship will be discussed in a separate paper.

The MHRA has produced an annual risk acknowledgement form, which provides the framework to guide and record discussions with patients about valproate-containing medicines. This form may be updated periodically, based on stakeholder feedback: it should therefore be accessed whenever needed through this link to the MHRA website:

https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/708856/2018_05_17_FINAL_4.0a_Sodium_Valproate_Annual_Risk_Acknowledgement_Form.docx

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