



Prescription of Valproate-Containing Medicines in Women of Childbearing Potential who have Psychiatric Disorders: Is It Worth the Risk?

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Abstract

Valproate-containing medicines have long been used in psychiatric practice, principally in the treatment of acute manic episodes, as augmentation agents in the treatment of bipolar and unipolar depressive episodes, and in the prophylaxis of bipolar affective disorder. Many babies are still being born with the adverse consequences of valproate exposure in utero, which include congenital malformations, neurodevelopmental delay, and increased risks of attention-deficit hyperactivity disorder and autism spectrum disorder. Previous measures designed to better inform women about the risks associated with valproate have not been sufficiently effective. This review highlights recent recommendations from influential regulatory and advisory bodies, summarises the relative efficacy and tolerability of valproate preparations in the psychiatric conditions for which they have often been prescribed, and offers practical guidance for the withdrawal and replacement of valproate-containing medicines in women with psychiatric disorders.

Key Points

Previous attempts to inform women about the risks associated with valproate have not been sufficiently robust.

We review regulatory recommendations regarding valproate in women of childbearing potential and offer guidance for the withdrawal and replacement of valproate-containing medicines in women with mental disorders.

1 Background

Despite long-standing awareness of the potential teratogenicity of valproate-containing medicines, and repeated and widespread regulatory guidance regarding such hazards, many babies are still being born with the adverse consequences of valproate exposure in utero. Legal class actions have been brought against the manufacturers of valproate-based medicines in France and the UK. Within Europe, revised guidance regarding valproate preparations from the European Medicines Agency (EMA) and the UK Medicines and Healthcare products Regulatory Agency (MHRA) was published in 2018. In the UK, the Department of Health and Social Care has convened an implementation group to guide the incorporation of this guidance into professional practice, and an Independent Medicines and Medical Devices Safety Review is reviewing how previous professional clinical practice seemed to have been unaffected by knowledge of potential hazards associated with valproate. The Royal College of Psychiatrists published a Position Statement on the use of valproate in psychiatric practice in December 2018 and multiple Royal Colleges and other professional bodies published a statement on valproate in other aspects of clinical practice in March 2019. This narrative structured review summarises the features and epidemiology of foetal valproate syndrome,

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considers the evidence for the effectiveness and tolerability of valproate-containing medicines in the major psychiatric conditions in which it is often used, and offers practical guidance for the withdrawal and replacement of valproate in women with psychiatric disorders.

2 Foetal Valproate Syndrome

The potential teratogenic effects of valproate-containing medicines had been described within 2 years of their first becoming available for widespread clinical use [1], and a broad syndrome of abnormalities associated with exposure to valproate in utero (comprising unusual facial features, hypospadias and psychomotor delay) was soon recognised [2]. A reliable syndrome of malformations (including spina bifida, craniosynostosis, facial dysmorphism, cleft lip/palate, hypospadias, atrial septal defect, bilateral radial aplasia and polydactyly) was established through careful epidemiological cohort studies [3]. Further investigations raised awareness of a range of neurodevelopmental problems associated with valproate, including developmental delay and lower than expected intelligence quotient [4], and increased risks of attention-deficit/hyperactivity disorder [5] and autism spectrum disorder (including childhood autism, 'Asperger syndrome', atypical autism and unspecified pervasive developmental disorders) [6]. Identified risk factors for foetal valproate syndrome include the prescribed daily dosage (although valproate kinetics are highly variable in women of childbearing age), a history of parental congenital malformations and a congenital malformation in an earlier pregnancy [7]. Potential mechanisms underlying teratogenicity are uncertain, although valproate exerts epigenetic effects via potent histone deacetylase inhibition, and the balance of acetylation/deacetylation is known to be crucial in brain development [8].

The incidence of valproate exposure-associated problems is high. When unborn babies are exposed to valproate-containing preparations in utero, there is a high risk (approximately 10 in every 100 deliveries) of congenital malformations (including spina bifida, atrial septal defect, cleft lip and palate, renal and urogenital defects, and limb defects) [9]. There is also a very high risk (between 30 and 40 in every 100 deliveries) of neurodevelopmental problems (including lower intellectual ability, poor language skills and memory problems) [10–12]. Measured intelligence quotient at the age of 6 years in valproate-exposed children is on average 7–10 points lower than in children exposed to other antiepileptic drugs [13]. Awareness of these problems led to a recommendation from the British Association for Psychopharmacology that valproate-containing medicines are not used in girls, female adolescents or women of childbearing potential [14].

3 Recent Regulatory and Advisory Measures

Previous health policy measures designed to better inform women about the risks associated with valproate have not been sufficiently effective: many women have not received the right information at the right time. As an example, a recent clinical audit of prescribing practice (across 55 Mental Health Trusts in England) in female patients of childbearing potential with the diagnosis of bipolar disorder found that 24% of women aged younger than 50 years were prescribed valproate-containing medicines: in only half of such women was there documented evidence that information had been provided on risks for the unborn child and the need for adequate contraception [15].

In a 2013 safety communication from the US Food and Drug Administration [16], the use of valproate-based prescriptions was considered to be contraindicated in pregnant women or those of childbearing potential: although medication should not be stopped abruptly in women who become pregnant whilst taking a valproate-containing medicine. The Food and Drug Administration recommended that drug labels for valproate-containing medicines should contain information about the risks of using this medication in pregnant and childbearing women, particularly regarding major structural and functional birth defects. There are also recommendations that health professionals should inform women of childbearing potential of the potential consequences to children exposed in utero to this type of medication, and discuss with patients potential alternatives to treatment with valproate-containing medicines. Women taking valproate-containing medicines are advised to take supplementary dietary folic acid as this may reduce the risk of neural tube defects; and pregnant patients taking valproate-containing medicines are encouraged to enrol in a registry, designed to gather information on the effects of in utero exposure.

The Royal Australian and New Zealand College of Psychiatrists [17] recommends that valproate-containing medicines should be avoided in women of childbearing potential. The guidelines state that in women with severe bipolar disorder, lithium seems to be the safest option among available mood-stabilising drugs: though the use of lithium should be balanced against potential risks to the developing foetus, together with the risk of relapse if lithium is discontinued. Women should have folate supplementation and an ultrasound to determine whether an abnormality is present (along with a plan for next steps should an abnormality be found).

The Canadian Agency for Drugs and Technologies in Health [18] recommends that valproate-containing medicines should be avoided during pregnancy, to reduce the risk of major congenital malformations and 'reduced' (i.e.

adverse) cognitive outcomes. This agency also recommends that folic acid supplementation at a daily dose of 5 mg should be given for women of childbearing potential who are taking antiepileptic drugs from pre-conception through the first trimester, to reduce the risk of neural tube defects. The British Columbia Reproductive Mental Health Program and Perinatal Services [19] recommends that in a woman who has been clinically stable for at least 4–6 months whilst taking a mood stabiliser or an antipsychotic, and the risk of relapse is considered to be low, a trial to gradually discontinue the medication should be considered before an intended pregnancy. However, if the patient has a history of severe illness (with swift relapse after discontinuing medication) and medication needs to be continued, the clinician should prescribe the usual medication unless it is a valproate-containing medicine, in which case the recommendation is it should be replaced by another mood stabiliser or atypical antipsychotic. If during pregnancy a new treatment course is required, valproate-containing medicines, lithium and carbamazepine should all be avoided, but an atypical antipsychotic could be used.

The EMA (in May 2018) and the UK MHRA (in May 2018) therefore issued fresh guidance designed to minimise in utero exposure to valproate-containing medicines. The EMA [20] bans the use of valproate-containing medicines for migraine or bipolar disorder during pregnancy, and bans their use when treating epilepsy during pregnancy unless there is no other effective treatment available. The EMA also states that valproate-containing medicines must not be used in any woman or girl able to have children unless the conditions of a new pregnancy programme are met: the programme being designed to ensure that patients are fully aware of the risks and of the need to avoid becoming pregnant. The EMA also requires that companies who market valproate-containing medicines should perform additional studies on the nature and extent of the risks, and monitor valproate use and the long-term effects from affected pregnancies.

Guidance from the MHRA stipulates that valproate preparations must not be used in pregnant women; and in girls and women of childbearing age, valproate preparations must not be used unless the patient meets the conditions of a ‘pregnancy prevention programme’. Such a programme 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; and using a risk acknowledgement form to confirm the provision and understanding of relevant information [21].

The MHRA also stipulates that 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 intrauterine device or implant) or two complementary forms of contraception including a barrier method should be used; all packaging for valproate-containing medicines must include a visual warning about the risk of valproate in pregnancy; and 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 [21]. In addition, manufacturers of valproate-containing medicines are required to monitor ongoing valproate use and the long-term outcomes of any exposed pregnancies; and 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 that staff understand their roles and responsibilities in identifying and counselling girls and women of childbearing age who are taking valproate-containing medicines [21].

4 Use of Valproate-Containing Medicines in Psychiatric Practice

Given the increased concern about hazards associated with valproate prescriptions in women of childbearing potential, it seems timely to review the current evidence of the benefits and risks of valproate in these conditions. The Royal College of Psychiatrists therefore published its Position Statement in December 2018 [22]. In psychiatric practice, valproate-containing medicines have been prescribed for three main indications: in 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 treatment; and in patients with bipolar disorder or recurrent unipolar disorder as a prophylaxis designed to reduce the likelihood of further episodes of illness. Valproate-containing medicines have also been prescribed as an augmentation approach with antipsychotics in patients with psychotic illnesses; as an alternative to antidepressants or anxiolytics in patients with anxiety disorders; as treatment for patients with persistent impulsivity or aggressive behaviour; and in patients with epilepsy, many of whom have comorbid psychiatric conditions [23]. The current prevalence of ‘off-label’ prescriptions of valproate in patients with schizophrenia or schizoaffective disorder within mental health services in the UK is uncertain, although findings of previous prevalence studies

conducted in other countries (China, Israel, USA) suggest that between 12.6% and 28% of patients with schizophrenia are prescribed valproate-containing medicines, typically combined with antipsychotic medication [24–26].

4.1 Treatment of Manic Episodes

A systematic review and network meta-analysis of randomised controlled trials indicated that valproate was probably less effective than the comparators haloperidol, olanzapine and quetiapine [27], though a more recent network meta-analysis indicates that valproate has broadly similar efficacy and tolerability when compared to antipsychotics (when grouped together) or lithium, as monotherapy in patients experiencing acute manic episodes [28]. Neither analysis found evidence of an advantage for valproate.

It is estimated that between 3000 and 4000 pregnancies each year are exposed to antipsychotics, in the UK alone [29]. An early systematic review of adverse events associated with antipsychotics indicated that there was insufficient evidence to draw definite conclusions about potential teratogenic effects of antipsychotics [30], though a subsequent meta-analysis indicates that antipsychotic exposure in utero is associated with increased risks of major malformations and cardiac defects [31]. A carefully designed controlled study, which addressed potential confounding factors, suggests that the risks of adverse events are more associated with factors with the patient population than with antipsychotic treatment [32]. British Association for Psychopharmacology guidance therefore notes that although antipsychotics are not ideal, they carry relatively lower risks of intrauterine malformations and therefore should be prescribed in preference to valproate-containing medicines in women of childbearing age who are experiencing acute manic episodes [14].

4.2 Treatment of Bipolar Depressive Episodes

Valproate preparations may be efficacious as augmentation agents in patients experiencing an acute treatment of bipolar depression [33, 34]. In a systematic review and meta-analysis of 29 placebo-controlled studies involving a total of 8331 patients, the highest effect sizes (for a reduction in depression) were seen for olanzapine (alone or combined with fluoxetine): valproate was effective, as were quetiapine, lurasidone, lithium and selective serotonin reuptake inhibitors, but monoamine oxidase inhibitors, aripiprazole, risperidone and ziprasidone were all ineffective [34]. Although valproate can be effective, there is stronger evidence for the effectiveness of quetiapine or the combination of olanzapine plus fluoxetine, and possibly for olanzapine monotherapy, lamotrigine and lurasidone [35, 36]. Lamotrigine exposure during pregnancy does not

appear to be associated with an increased risk of major congenital abnormalities, but little is known about the safety of lurasidone, and alternatives are probably preferable [14].

4.3 Treatment of Unipolar Depressive Episodes

There are no randomised controlled trial data supporting the use of valproate as a short-term treatment in unipolar depression [37], in contrast to the strong evidence for antidepressants, lithium, quetiapine and aripiprazole, which should be considered instead [38]. Valproate preparations can sometimes be beneficial as augmentation agents in antidepressant treatment in patients experiencing unipolar depressive episodes, but the evidence is more substantial for other pharmacological augmentation approaches, including lithium and antipsychotics. Alternatives to valproate preparations should therefore be strongly considered in women of childbearing potential who are experiencing acute depressive (either bipolar or unipolar) episodes.

4.4 Prophylaxis in Patients with Affective Disorders

There is negligible evidence to support the use of valproate-containing medicines in the maintenance treatment of patients with recurrent unipolar depression, in contrast to the substantial evidence of benefit with antidepressants. However, there is evidence of the efficacy of valproate preparations (in monotherapy) in the maintenance treatment of patients with bipolar disorder [39]. A network meta-analysis of 33 randomised controlled trials involving 17 treatments and a total of 6846 patients found that aripiprazole, carbamazepine, imipramine and paliperidone were not superior to placebo, but all other treatments (including valproate) were efficacious in preventing a mood relapse or recurrence. Only lithium and quetiapine prevented depressive and manic episodes, whereas valproate did not prevent either depression or mania, when each condition was considered alone [40].

Lithium is preferable to valproate, as it has both a larger evidence base and established efficacy in the prevention of both manic and depressive episodes [40], although there is some uncertainty about the safety of lithium in pregnancy [41]. Early retrospective studies had indicated that exposure to lithium in utero is associated with a considerable increase in the risk of Ebstein's cardiac abnormality [42, 43], but a systematic review and meta-analysis of 385 studies reporting safety data with lithium found only weak evidence for an increased risk of congenital malformations [44]. The combination of valproate-containing medicines with lithium may offer some advantages over lithium monotherapy for 'postmania treatment' [45].

4.5 Augmentation Treatment in Other Psychiatric Conditions

There is little evidence to support the use of valproate-containing medicines as augmentation of antipsychotic treatment in patients with schizophrenia or related conditions [46]. Valproate preparations are sometimes used to augment the effectiveness of clozapine treatment, although there is better evidence for the augmentation of clozapine with either aripiprazole or fluoxetine [47]. In the treatment of patients with anxiety and anxiety-related disorders, there is some evidence of efficacy in generalised anxiety disorder [48]. There are many alternative antidepressant or anxiolytic treatments with a more substantial evidence base, including selective serotonin reuptake inhibitors and serotonin-noradrenaline reuptake inhibitors [49]. Exposure to antidepressants in utero is associated with an increased risk of congenital malformations, though meta-analyses indicate that this increased risk is around 1–2% above the background incidence of 2–4% in the general population [50]. Antidepressant exposure has also been associated with increased risks of ‘poor neonatal adaptation syndrome’ (with its more severe features of poor temperature control, hypoglycaemia, respiratory distress and seizures) [51] and persistent pulmonary hypertension of the newborn [52]. The findings of a systematic review suggest that valproate-containing medicines are superior to placebo in male outpatients with persistent aggression, impulsively aggressive adults with certain (‘cluster B’) personality disorders and youths with conduct disorder (but not in children or adolescents with pervasive developmental disorder): however, the reviewers considered that firm conclusions about the potential value of valproate could not be made [53].

5 Practical Considerations in Withdrawing and Replacing Valproate-Containing Medicines

The following paragraphs reflect guidance within the recent Position Statement published by the Royal College of Psychiatrists [22]. Psychiatrists should consider the possibility of potential pregnancy when assessing and managing all women of childbearing potential. They must review all patients who are currently prescribed valproate-containing medicines at least once a year, with detailed consideration of the alternatives to valproate preparations and their replacement whenever possible. The MHRA has produced an annual risk acknowledgement form, which provides a framework to guide and record discussions with patients about valproate-containing medicines.

5.1 Withdrawal of Valproate-Containing Medicines

Most women of childbearing potential who are undergoing psychiatric care should be withdrawn from valproate-containing medicines. Some clinicians may have a few patients who do not tolerate and do not wish to take alternative medicines, and in these exceptional patients, an effective pregnancy prevention programme must be followed.

Many women and their clinicians may want to withdraw valproate-containing medicines as soon as possible: there is limited evidence to guide the rate and duration of treatment withdrawal, though experience gained from studies of lithium withdrawal may be relevant, and current British Association for Psychopharmacology guidelines suggest a withdrawal period of at least 4 weeks. A recent clinical scenario-based consensus statement recommends tapered withdrawal of valproate-containing medicines over up to 2 weeks in later pregnancy (with slower tapering in women who are planning pregnancy) [54].

5.2 Women Who are Not Pregnant

When valproate-containing medicines need to be withdrawn in a patient who is currently psychiatrically well, the dose should be tapered gradually (over a few weeks) to reduce the risk of relapse. Should a woman experience a relapse and develop a manic episode, treatment with anti-manic drugs (haloperidol, olanzapine, quetiapine) could be started, augmented by benzodiazepine anxiolytics if necessary: if these treatments prove insufficient, electroconvulsive therapy could be considered [55]. In patients who are currently psychiatrically unwell and taking a valproate preparation, much faster cross-tapering while introducing an alternative is usually needed. In patients experiencing an acute manic episode, haloperidol, olanzapine or quetiapine may be beneficial. In patients experiencing an acute depressive episode, combination olanzapine plus fluoxetine, or olanzapine monotherapy, lithium or quetiapine (or possibly lurasidone) should be considered. It is best to avoid introducing an antidepressant without concomitant treatment with a mood-stabilising medication.

5.3 Women Who are Pregnant

Patients who are currently psychiatrically well, but discover they are pregnant (or who are discovered by a health professional to be pregnant) whilst taking a valproate-containing medicine should be informed not to stop it abruptly. Rather, 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 that service: they should also be referred urgently to a specialist experienced in foetal medicine who provides scanning and counselling for women with a valproate-exposed pregnancy. By contrast, pregnant patients who are currently psychiatrically unwell and taking valproate-containing medicines should be managed with urgent referral to a specialist 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, and the team would also undertake close monitoring of the mental state, further antenatal care planning and formulate a relapse prevention plan.

A number of teratogen information services gather and provide up-to-date information about the risks of medications (and also chemicals, alcohol and other substances) during pregnancy. For example, patients and health professionals based in the UK can contact the UK Teratology Information Service (<http://www.UKTIS.org>): and a European network of similar services provides information in the Dutch, English, French and German languages (<http://www.entis-org.eu>).

6 Conclusions

Health professionals should be aware of the wide range of serious hazards associated with the prescription of valproate-containing medicines to pregnant women. In girls and women of childbearing potential who have a psychiatric illness and for whom psychotropic drug treatment is indicated, there are a broad range of options, which have often included the prescription of a valproate-containing medicine. However, there is no convincing published evidence that valproate-based medicines have an advantage over comparator treatments in terms of effectiveness or acceptability, and the risk of congenital malformations and neurodevelopmental problems associated with in utero exposure is higher with valproate than with alternative treatment options. For this reason, alternatives to valproate should always be considered when making treatment decisions in women of childbearing potential. Women with psychiatric illness who choose to remain on valproate-based medicines should participate in a pregnancy prevention programme involving reliable effective contraception, and provide consent to be followed up carefully for as long as they continue with valproate-based treatment.

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Compliance with Ethical Standards

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