Guidance on prescribing valproate for bipolar disorder in women of child-bearing potential

This Guide provides:-

- Risk minimization measures developed for valproate to inform valproate prescribers of the risks associated with the use of valproate by women of childbearing potential and during pregnancy.

- Up-to-date information about the risk of neurodevelopmental disorders in children of women who have taken valproate during pregnancy in addition to the known risk of congenital malformations in exposed babies.

This guide should be used in conjunction with the Patient information leaflet (appendix 1). To learn more about valproate, please read the complete Summary of Product Characteristics before prescribing valproate. http://www.medicines.org.uk

Background

Valproate contains valproic acid, an active ingredient with known teratogenic effects, which may result in congenital malformation. Available data also show that in utero exposure to valproate can be associated with an increased risk of developmental disorders.

Valproate is prescribed for mood stabilisation in bipolar disorder. The risk of unplanned pregnancy in the general population is approximately 50%. However, women with a diagnosis of bipolar disorder may become sexually disinhibited and therefore the rates of pregnancy may be higher than 50% in this patient group. Therefore the risks of using valproate in women of child-bearing potential must be discussed prior to prescribing.

The 2014 NICE\(^1\) guidance for bipolar disorder recommended that valproate should not be offered to women of child bearing potential for either long-term treatment or to treat an acute episode. NICE\(^1\) guidance also stated that valproate should not be offered to girls and young women of child-bearing potential because of the risk of polycystic ovary syndrome and risks to the unborn child.

A MHRA Drug safety alert\(^2\) in January 2015 stated valproate is associated with a dose-dependent risk of abnormal pregnancy outcomes, whether taken alone or in combination with other medicines.

The main pregnancy outcomes were:-

- The children exposed in utero to valproate are at a high risk of serious of congenital malformations (in approximately 10% of cases).
Studies in preschool children exposed in utero to valproate show that up to 30-40% experience delays in their early development such as talking, and/or walking, have low intellectual abilities, poor language skills and memory problems.

CONGENITAL MALFORMATIONS<sup>2</sup>

Data derived from a meta-analysis (including registries and cohort studies) has shown that 10.73% of children of women with epilepsy exposed to valproate monotherapy during pregnancy suffer from congenital malformations (95% CI: 8.16 -13.29), which represents a greater risk of major malformations than for the general population, for whom the risk is about 2-3%. Available data show the risk is dose dependent. The risk is greatest at higher doses (above 1 g daily). A threshold dose below which no risk exists cannot be established based on available data.

The most common types of malformations include neural tube defects, facial dysmorphism, cleft lip and palate, craniostenosis, cardiac, renal and urogenital defects, limb defects (including bilateral aplasia of the radius), and multiple anomalies involving various body systems.

DEVELOPMENTAL DISORDERS<sup>2</sup>

Exposure to valproate in utero can have adverse effects on mental and physical development of the exposed children. The risk seems to be dose-dependent but a threshold dose below which no risk exists, cannot be established based on available data. The exact gestational period of risk for these effects is uncertain and the possibility of a risk throughout the entire pregnancy cannot be excluded.

Studies in preschool children exposed in utero to valproate show that up to 30-40% experience delays in their early development such as talking and walking later, lower intellectual abilities, poor language skills (speaking and understanding) and memory problems.

Intelligence quotient (IQ) measured in school aged children (age 6) with a history of valproate exposure in utero was on average 7-10 points lower than those children exposed to other antiepileptics. Although the role of confounding cannot be excluded, there is evidence in children exposed to valproate that the risk of intellectual impairment may be independent from maternal IQ.

There are limited data on the long term outcomes.

Available data show that children exposed to valproate in utero are at increased risk of autistic spectrum disorder (approximately three-fold) and childhood autism (approximately five-fold) compared with the general study population.

One study suggests that children exposed to valproate in utero may be more likely to develop symptoms of attention deficit/hyperactivity disorder (ADHD).

**Prescribing of valproate**

Given the risks above, valproate for the treatment of bipolar disorder should not be used during pregnancy and in women of child-bearing potential unless unavoidable necessary i.e. in situations where other treatments are ineffective or not tolerated.
Carefully balance the benefits of valproate treatment against the risks when prescribing valproate for the first time, at routine treatment reviews, when a female child reaches puberty and when a woman plans a pregnancy or becomes pregnant.

When prescribing valproate to a woman of child-bearing potential, she must be strongly advised to use effective contraception during treatment and be fully informed of the risks for the unborn child if she becomes pregnant during treatment with valproate.

Valproate treatment must be started and supervised by a doctor experienced in managing epilepsy or bipolar disorder

Patients (and if necessary relevant family member/care-givers) must be informed of and understand:

- Risks associated with valproate during pregnancy
- Risks related to treatment, including risks related to valproate in case of pregnancy
- Need to use effective contraception to avoid unplanned pregnancy
- Need for regular review of treatment
- Need to contact her doctor if she plans to become pregnant but before any contraception is stopped
- Need to contact her doctor immediately if she becomes pregnant or thinks she might be pregnant.

Folic acid supplementation may decrease the general risk of neural tube defects but the evidence does not suggest that it reduces the risk of birth defects associated with in utero valproate exposure. Folic acid at 5mg daily should be prescribed particularly if there is concern about an unplanned pregnancy.

**Treatment during pregnancy**

If a woman with bipolar disorder who is treated with valproate plans a pregnancy or becomes pregnant, consideration should be given to alternative treatments.

If valproate treatment is continued during the pregnancy:

- The lowest effective dose should be used and the daily dose should be divided into several small doses to be taken throughout the day - the use of a prolonged release formulation may be preferable to other treatment forms

- Initiate specialised prenatal monitoring in order to monitor the development of the foetus, including the possible occurrence of neural tube defects and other malformations

- Folate supplementation before the pregnancy may decrease the risk of neural tube defects common to all pregnancies; however the available evidence does not suggest it prevents the birth defects or malformations due to valproate exposure. 5mg daily is the recommended dose.
Prescriber responsibilities

- A patient information leaflet, incorporating a consent form, on possible valproate side-effects in women of child-bearing potential (appendix 1) is available.

- A completed consent form must be put in the patient’s notes and a copy given to the patient. The leaflet and consent form is available from the Trust’s website: valproate leaflet and consent form.pdf

- All discussions should be clearly documented in the patient’s notes.

- If a pregnancy does occur, advice from a specialist should be sought as soon as possible. The NICE guidance for bipolar disorder should also be referred to.

References


3. Patient information leaflet for Epilim. Sanofi Aventis 04/2008


If you require this document in an alternative format, ie easy read, large text, audio, Braille or a community language please contact the Pharmacy Team on 01243 623349 (Text Relay calls welcome)
Appendix 1

Patient information leaflet on possible valproate side-effects if you become pregnant (incorporating a consent form)

Before you decide to start taking valproate your doctor should discuss with you the possible problems when it is taken in pregnancy.

If you are a woman capable of becoming pregnant your doctor should only prescribe valproate for you if nothing else works for you.

Before prescribing this medicine to you, your doctor will have explained what might happen to your baby if you become pregnant whilst taking valproate. If you decide later you want to have a child you should not stop taking your medicine until you have discussed this with your doctor and agreed a plan for switching you onto another product if this is possible.

Effects of valproate on pregnancy

**Birth defects**
Valproate (including semi-sodium valproate (Depakote®) and sodium valproate (Epilim®, Episenta® and Convulex®)) can be harmful to an unborn child.

The normal risk of an abnormality in women on no medicines is 2-3 per 100 babies born. This increases to 10 abnormalities in 100 babies born when mother is taking valproate when they become pregnant. You therefore have a 3-5 times greater risk of a child born with an abnormality.

These abnormalities can include:

- Head and face deformities including cleft palate (a gap or depression in the lip)
- Deformities of the bones, including hip dislocation
- Malformations of the arms and legs
- Deformities of the tube from the bladder to the penis, where the opening is formed in a different place
- Heart and blood vessel malformations, including heart defects
- Defects of the lining of the spinal cord
- An abnormality of the spinal cord called ‘Spina bifida’
- Malformations of the urethra (tube urine passes down)
Pregnant mothers who take valproate may have babies with:

- Blood clotting problems (such as blood not clotting or not clotting very well). This may appear as bruising or bleeding which takes a long time to stop.
- Hypoglycaemia (low blood sugar)
- Hypothyroidism (underactive thyroid gland, which can cause tiredness or weight gain).

Ask your doctor about taking 5mg of folic acid each day as it may lower the risk of having a baby with spina bifida and early miscarriage that exists with all pregnancies. However it is unlikely to reduce the risk of birth defects associated with valproate.

Problems with childhood development

It is estimated that up to 30-40% of preschool children whose mothers took valproate during pregnancy may have problems with early childhood development. Children can be slow to talk, and/or walk, be intellectually less able than other children, and have difficulty with language and memory.

Autistic spectrum disorders and childhood autism are more often diagnosed in children exposed to valproate and there is some evidence children may be more likely to be at risk of developing symptoms of attention deficit hyperactivity disorder (ADHD).

If you decide to take valproate you should use an effective method of contraception and talk to your doctor before stopping your contraception and trying for a baby. When getting advice on which is the best contraceptive for you, explain how important it is not to get pregnant because you are taking valproate. Valproate has no effect on how well the oral contraceptive pill works and they can safely be taken together.

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If you are think you may be pregnant or become pregnant, you must tell your doctor straight away. If you plan to have a baby, speak to your doctor before stopping your contraceptive.

- Your doctor will give you appropriate counselling and may suggest changes to your treatment or the dose of your medication.
- He or she will also want to regularly check your progress while you are pregnant.

It is extremely important that you discuss your treatment with your doctor well before you become pregnant.

Please read and complete the attached consent form below. If you would like more time to think about the information given to you today or would like to discuss it with a partner, relative or friend before making a decision, please let your doctor know.
Consent given/wthheld form for use when considering the use of valproate in women of child-bearing potential

Initial each box if you agree with the statement.

I confirm that:

☐ Doctor ………………. has explained the benefits and possible side-effects, including the risks to an unborn baby, of using valproate to treat bipolar disorder and I have understood the explanation.

☐ Doctor ………………. has discussed the need for me to use effective contraception (e.g. the pill or coil) while taking valproate. I understand that if I wish to get pregnant I need to discuss this with my doctor before I stop using contraception.

☐ I have been given a patient medication leaflet on valproate.

☐ Doctor ………………. has discussed other treatment options with me, and also the consequences of not using this medication.

Treatment options discussed include:

1. ................................................................................................................

2. ................................................................................................................

3. ................................................................................................................

☐ I have had enough time to consider my decision and to ask questions.

☐ I understand that the valproate is being prescribed within its licence (semi-sodium valproate) but there are risks to the unborn baby if I become pregnant/outside its licensed indication (sodium valproate) and there are risks to the unborn child if I become pregnant*. 
☐ I consent to being treated with valproate*.

or

☐ I do not consent to be treated with valproate*.

☐ I understand I can withdraw my consent at any time and I will inform my doctor if I wish to stop taking valproate and this will not affect my treatment in any other way.

Signed: .......................... (patient) ............................... (printed name)

Date: ..............................

Signed: .......................... (doctor) ................................. (printed name)

Date: .............................. .......................... (title)

*Delete as appropriate

Once completed the original should go in the patient’s notes and a copy provided for the patient.

**If you require this document in an alternative format, ie easy read, large text, audio, Braille or a community language please contact the Pharmacy Team on 01243 623349 (Text Relay calls welcome)**

Published: April 2015

Review date: April 2018 (or sooner if relevant national advice is published)