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Treating women of reproductive age with valproate

PERSPECTIVES

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The question of valproate use by women of reproductive age is important, complicated and timely. The drug can be extremely harmful to the fetus, but some pregnant women with epilepsy will continue to have seizures if they don't take it.

Illustration: Espen Friberg

Valproate came on the market in France in 1967. It is one of the most effective drugs for treating generalised epilepsy, bipolar disorder and migraine. As these are common conditions in women of reproductive age, valproate has been the third most used antiepileptic drug in pregnant women in the Nordic countries for the last 10–20 years.

Valproate and fetal development

One in ten children exposed to prenatal valproate develop malformations such as neural tube defects, cardiac malformations and urinary tract anomalies. In cases where the mother has used more than 1000–1500 mg daily, more than one in four will be affected (1, 2). In 2013, Danish researchers found that children of mothers who had bought valproate during pregnancy were five times more likely to be diagnosed with autism than other children (3). Meanwhile, two large-scale studies showed that the IQ of children exposed to prenatal valproate was 10 points lower than that of other children (4). The results could not be explained by maternal IQ or epilepsy type and were not seen for other epilepsy drugs.

Prenatal exposure to valproate is subsequently associated with delayed language development (5), ADHD (6) and poor school performance (7). It is not clear whether it is safer to use valproate in late pregnancy compared to early pregnancy. Organogenesis takes place during the first trimester, but cognitive development continues until birth.

The term 'Fetal Valproate Spectrum Disorder' (FVSD) has recently been introduced to describe the composite clinical picture of malformations, cognitive impairments, neuropsychiatric conditions and dysmorphic features that can be seen in children who have been exposed to valproate (1).

The Depakote scandal

Due to the findings above, the European Medicines Agency and the Norwegian Medicines Agency published a warning in 2014 against the use of valproate in women of reproductive age (8). In the years that followed, many French patients with prenatal exposure to valproate sought compensation from Sanofi. The situation was described as a national health scandal. In Norway, patients and the Norwegian Epilepsy Association expressed concern (9).

> ***«For some patients with generalised epilepsy, valproate is the only drug that prevents seizures»***

Parallel to the introduction of other antiepileptic drugs that successfully treat generalised epilepsy, such as lamotrigine and levetiracetam, the use of valproate in women of reproductive age in Norway has been slowly declining (Figure 1). However, neither the warning issued by the medicines agencies in 2014 nor the Depakote scandal in France triggered any sudden drop in the use of valproate.

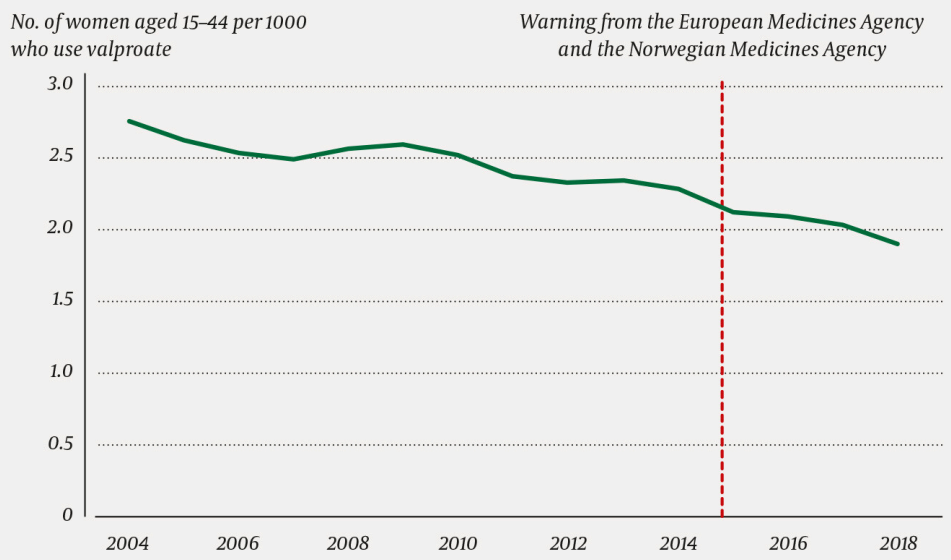

Figure 1 Use of valproate in Norway. Source: Norwegian Prescription Database

In 2018, the medicines agencies supplemented the 2014 warnings with a detailed pregnancy prevention programme to prevent women becoming pregnant while using valproate (10, 11) Box 1). The programme prohibits the use of valproate in pregnant psychiatric patients. In epilepsy patients, it must only be used if other drugs cannot be taken or have no effect ((11). The doctor and the patient must confirm in writing that safety information has been provided and that other drugs have failed.

Box 1 Norwegian Pharmaceutical Compendium's guidelines for healthcare personnel (12)

Women with epilepsy: valproate is contraindicated in pregnancy unless there are no other suitable alternatives. Valproate is contraindicated in women of reproductive age unless the conditions of the pregnancy prevention programme have been met.

Women with bipolar disorder: valproate is contraindicated during pregnancy. Valproate is contraindicated in women of reproductive age unless the conditions of the pregnancy prevention programme have been met.

Use of valproate in pregnancy prevention programme

Specialists in neurology/psychiatry with experience in epilepsy treatment/bipolar disorder must only initiate the use of valproate in girls and women of reproductive age if other treatment has no effect or causes adverse reactions.

Prior to start-up, pregnancy must be ruled out through a blood pregnancy test. The result must be confirmed by medical personnel.

The specialist must review the indication for treatment at least once a year.

The specialist must complete the form on the risk of fetal damage together with the patient at the start of treatment, at the annual check-up, at pre-pregnancy planning appointments and upon confirmation of the pregnancy. Doctors who meet female users of valproate must inform the patient/parents/guardians/carers about the risk of fetal damage when using valproate, the need for reliable contraception, and tell them to consult a doctor in the event of pregnancy. The information must be provided at all appointments with doctors as well as health visitors and midwives. Pharmacists in chemists must also provide information.

The doctor must provide patient guidelines to all female patients/parents/guardians/carers treated with valproate.

Women who are trying to conceive must switch to another suitable treatment. For patients with epilepsy, the specialist must 'do everything possible to switch to an appropriate alternative treatment' before discontinuing contraception.

The lowest effective dose must be used, and total and free serum concentrations must be measured before, during and after pregnancy.

Women exposed to valproate during pregnancy and their partners must be referred to a specialist with experience in assessing fetal damage from medicines so that they can be given information on the significance of the exposure.

In the case of unplanned pregnancies, the woman must see a doctor without delay, and following the consultation must switch to another suitable treatment, if possible.

The above conditions also apply to sexually inactive patients if future pregnancy cannot be completely ruled out.

The programme has sparked debate due to the lack of emphasis on the individual situation and medical needs of the women (12). The medical profession in Norway has argued that valproate is the right treatment for many women.

When is it right for fertile and pregnant women to use valproate?

Valproate is one of our most potent antiepileptic medicines for use in generalised epilepsy. For this type of epilepsy, valproate is better than lamotrigine and topiramate (13) and generally as good as levetiracetam (14). However, many patients experience psychiatric side effects from levetiracetam (14). For some patients with generalised epilepsy, valproate is the only medicine that prevents seizures. Reducing the valproate dose or switching medication will increase the risk of exacerbating seizures (15, 16). An individual assessment is therefore needed of the dangers that seizures can entail for the mother and child versus the risk of fetal damage. Frequent generalised seizures are the greatest risk factor for Sudden Unexpected Death in Epilepsy (SUDEP), and uncontrolled epilepsy can therefore have life-threatening consequences for the mother. It is important that women do not become so anxious about the warnings against the use of valproate that they stop taking the medicine or reduce the dose on their own initiative. In England, there has been an increase in deaths since 2013 among pregnant women with epilepsy who unilaterally decided to stop using antiepileptic medication. Four per cent of maternal deaths during this period were due to epilepsy. All of the women who died had uncontrolled epilepsy in pregnancy. Eight out of nine died from SUDEP, and one drowned in the bath. Two out of nine had recently stopped taking valproate (17).

> *«Uncontrolled epilepsy can have life-threatening repercussions for the mother»*

Reduced control of seizures in pregnancy can also lead to anxiety and worry, sleeping problems, loss of driver's licence, problems at work and other social issues.

Seizures in pregnancy can also have an effect on the fetus. In addition to physical damage due to falls or blows, status epilepticus can cause prolonged hypoxia and in rare cases fetal death (18). Some clinical studies also indicate that short-term generalised seizures can have adverse effects such as premature birth and low birth weight (19). One study showed that five or more generalised seizures in pregnancy were an independent risk factor for the child having a low IQ and requiring extra educational support (20). Intracranial haemorrhage and fetal death have been reported in case studies (21). Animal studies have shown that offspring of rats with frequent generalised seizures during pregnancy experienced poorer growth, problems with motor skills and coordination, and changes in neuronal networks of the hippocampus (22, 23).

Whether it is appropriate to reduce valproate or switch to another medicine during pregnancy will depend on the frequency and severity of pre-pregnancy seizures, previous effects of other antiepileptic medicines and the woman's own preferences.

Provision for children exposed to valproate

Diagnosing children with FVSD is complicated. The diagnosis is made by clinical and neuropsychological evaluation. Cognitive and behavioural challenges often occur, even if there are no malformations or dysmorphic features. In most cases, the problems will persist into adulthood (1). Neurocognitive issues affecting verbal and auditory skills are a key feature of the FVSD phenotype. In much the same way as for children with Fetal Alcohol Spectrum Disorders (FASD), these complex problems require highly specialised and interdisciplinary health care (24).

According to international recommendations, children with FVSD should be offered specialist follow-up and treatment (1). Assessments are made of children with FASD, but there is no such provision for children exposed to prenatal valproate. The Norwegian clinical guidelines for treating epilepsy do not recommend any specific follow-up (25). Nor are there any Norwegian guidelines for making such diagnoses. The fact that this is a small group with whom few clinicians have sufficient experience is also a challenge. In our experience, there is no specialised assessment and follow-up provision for families with children exposed to prenatal valproate, and no dedicated service for them to contact. The experiences with children with fetal damage due to alcohol and drugs show that it is possible to develop such a provision.

> ***«The choice of medication must be considered on an individual basis for women of reproductive age with epilepsy»***

Diagnosis is important. Clarification and successful assessment and follow-up of the at-risk patients in childhood and adolescence could prevent secondary problems in adulthood. A clear diagnosis can also be important for patient injury compensation cases.

What should be done?

The choice of medication must be considered on an individual basis for women of reproductive age with epilepsy, and this should be reflected in the guidelines.

Valproate must not be abruptly discontinued when a woman becomes pregnant, even though she is not having seizures, as prolonged seizure freedom may be due to the use of the medicine. The benefits and disadvantages must be discussed in detail with the patient. These women should be monitored by a neurologist and obstetrician in close collaboration with their general practitioner (GP). GPs should not initiate valproate in women of reproductive age without consulting a specialist. The pregnancy prevention programme should be simplified so that it can be carried out in clinical practice. The

purpose must be to prevent unnecessary use of valproate and to provide information, not to prevent legal proceedings from exposed patients or to transfer the responsibility to the patient and doctor.

Furthermore, the Norwegian Directorate of Health should, in collaboration with healthcare unions and patient associations, ensure that specialised expertise and guidelines are in place for the assessment and follow-up of children who have or may have FVSD in Norway.

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