

Valproate in the treatment of epilepsy in girls and women of childbearing potential

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SUMMARY

This document provides guidance on the use of valproate in girls and women of childbearing age from a joint Task Force of the Commission on European Affairs of the International League Against Epilepsy (CEA-ILAE) and the European Academy of Neurology (EAN), following strengthened warnings from the Coordination Group for Mutual Recognition and Decentralised Procedures-Human (CMDh) of the European Medicines Agency (EMA), which highlight the risk of malformations and developmental problems in infants who are exposed to valproate in the womb. To produce these recommendations, the Task Force has considered teratogenic risks associated with use of valproate and treatment alternatives, the importance of seizure control and of patient and fetal risks with seizures, and the effectiveness of valproate and treatment alternatives in the treatment of different epilepsies. The Task Force's recommendations include the following: (1) Where possible, valproate should be avoided in women of childbearing potential. (2) The choice of treatment for girls and women of childbearing potential should be based on a shared decision between clinician and patient, and where appropriate, the patient's representatives. Discussions should include a careful risk–benefit assessment of reasonable treatment options for the patient's seizure or epilepsy type. (3) For seizure (or epilepsy) types where valproate is the most effective treatment, the risks and benefits of valproate and other treatment alternatives should be discussed. (4) Valproate should not be prescribed as a first-line treatment for focal epilepsy. (5) Valproate may be offered as a first-line treatment for epilepsy syndromes where it is the most effective treatment, including idiopathic (genetic) generalized syndromes associated with tonic–clonic seizures. (6) Valproate may be offered as a first-line treatment in situations where pregnancy is highly unlikely (e.g., significant intellectual or physical disability). (7) Women and girls taking valproate require regular follow-up for ongoing consideration of the most appropriate treatment regimen.

KEY WORDS: Valproate, Valproic acid, Anticonvulsants, Teratogenicity, Epilepsy, Pregnancy.



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^{1,2}Recommendations from a joint Task Force of the Commission on European Affairs of the International League Against Epilepsy (CEA-ILAE) (1) and European Academy of Neurology (EAN) (2).

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KEY POINTS

Recommendations for the Use of Valproate in the Treatment of Epilepsy in Girls and Women of Childbearing Potential

- The choice of treatment for girls and women of childbearing potential should be that of a shared decision between clinician and patient, and be based on a careful risk–benefit assessment of reasonable treatment options for the patient’s seizure or epilepsy type.
- Given the risks associated with exposure in utero, valproate should be avoided wherever possible as initial treatment of epilepsy in girls and women of childbearing potential.
- Valproate should thus generally not be used for treatment of focal epilepsies, and withdrawal of valproate or switch to treatment alternatives should be considered for women of childbearing potential who are established on treatment with valproate for focal seizures and who are considering pregnancy.
- In cases where valproate is considered the most appropriate option (e.g., some idiopathic/genetic generalized epilepsies), every female patient and the parents of a female child must be fully informed of the risks associated with valproate use during pregnancy as well as of the risks and benefits of treatment alternatives.
- When used in girls and women of childbearing potential, valproate should be prescribed at the lowest effective dose, when possible aiming at doses not exceeding 500–600 mg/day, although, at times, higher doses may be necessary to attain seizure control.
- Women of childbearing potential who are not planning pregnancy and who continue treatment with valproate should utilize effective contraception methods or otherwise ensure that unplanned pregnancies can be avoided.
- It is generally not advisable to switch from valproate to another treatment in women who discover that they are pregnant while on valproate.
- Women should be informed about the possibilities and limitations of prenatal screening, which may detect major malformations but cannot identify children whose neurodevelopment will be affected.

The Coordination Group for Mutual Recognition and Decentralised Procedures–Human (CMDh) of the European Medicines Agency (EMA) has recently strengthened warnings on the use of valproate in girls and women.¹ The Summary of Product Characteristics (SmPC), therefore, now states that valproate “should not be used in female children, in female adolescents, in women of childbearing potential and pregnant women unless alternative treatments are inef-

fective or not tolerated.” This should, however, not be interpreted to suggest that every individual female patient needs to try and fail all alternative treatments before being prescribed valproate if that is the most appropriate treatment for her epilepsy. Given the importance of these treatment decisions and the challenges in making a risk–benefit assessments, the Commission on European Affairs of the International League Against Epilepsy (CEA-ILAE) and the European Academy of Neurology (EAN) considered it important to issue recommendations for clinical use of valproate in girls and women with epilepsy in the context of these new warnings and restrictions.

The objective of this document is to provide guidance on the use of valproate (valproic acid, sodium valproate, and divalproex sodium), taking into account the risks of malformations and developmental problems in infants who are exposed to valproate in the womb as well as the benefits of a higher probability of seizure control with valproate in some seizure and epilepsy types. The first part of this article presents the Task Force’s consensus recommendations for the use of valproate in specific clinical situations along with risk–benefit assessments of different treatment alternatives. This is followed by an overview of the information that informs these recommendations, which includes a brief review of the teratogenic effects of valproate and other antiepileptic drugs (AEDs), an overview of the efficacy of valproate and treatment alternatives in different seizure types and epilepsies, and of data on risks associated with withdrawal of valproate or switches from valproate to other AEDs.

RECOMMENDATIONS FOR THE USE OF VALPROATE FOR TREATMENT OF EPILEPSY IN GIRLS AND WOMEN OF CHILDBEARING POTENTIAL

Given the risks associated with exposure in utero, valproate should be avoided, wherever possible, in the treatment of epilepsy in girls and women of childbearing potential. For focal epilepsies, there are a number of alternatives to valproate with either superior or similar efficacy, and valproate should not be initiated as a first-line treatment. For girls and women of childbearing potential who are already established on valproate for focal epilepsy, withdrawal of valproate or a switch to treatment alternatives should be considered following a discussion of likely benefits and risks. A similar approach should be used for women with unclassified seizures or epilepsy who are taking valproate, unless there is a strong suspicion of an epilepsy syndrome where AEDs for focal epilepsies might exacerbate seizures.

In contrast, treatment alternatives are few in idiopathic (genetic) generalized epilepsies. The only AEDs presently approved by the EMA for monotherapy treatment of primary generalized tonic–clonic seizures (GTCS), mainly in

the context of idiopathic (genetic) generalized epilepsies, are lamotrigine, phenobarbital, phenytoin, topiramate, and valproate (treatment indications derived from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/landing/epar_search.jsp&mid=WC0b01ac058001d124 and <https://www.medicines.org.uk/emc/>). Of these, treatment with phenobarbital and phenytoin is nowadays rarely initiated in Europe, and cannot be considered reasonable treatment alternatives to valproate.

There are syndromes, for example, juvenile myoclonic epilepsy (JME), for which valproate is considered the most effective drug. For some of the available treatment alternatives, the teratogenic risks have not yet been adequately assessed, in particular the effects of the agents on cognitive outcomes. For topiramate, preliminary data suggest an increased risk of major congenital malformations (MCMs), but there are no systematic studies of cognitive development. In addition, data on cognitive development are limited for levetiracetam, which is frequently used to treat primary GTCS, although not currently approved by EMA for monotherapy for this indication.

When choosing a treatment, as in general, the principle should be one of shared decision making between clinician and patient. Discussions should also include patient's representatives when the patient lacks capacity to act independently, most likely due to his or her age or learning disability. The clinician has a responsibility to describe the range of reasonable treatment options for the seizure or epilepsy type, and to discuss their risks and benefits. The patient has the right to be given information about reasonable treatment options and to express a treatment preference, taking into account individual priorities and circumstances. The clinician and patient (and his or her representatives) should together make a treatment choice and initiate treatment.

Where valproate is the most appropriate treatment option, the patient and caregiver or guardian must be fully informed of the risks associated with valproate use during pregnancy as well as of the relative risks and benefits of treatment alternatives. This will include discussion of the likely effectiveness of valproate compared to alternatives for the patient's seizure type (e.g., GTCS, absence, myoclonus), and any risk those seizures pose to the patient as well as the fetus should there be diminished or delay in achieving seizure control. Female patients (and their representatives) should also be informed about the limitations of prenatal screening methods, which cannot identify children whose intelligence quotient (IQ) and neurodevelopment will be affected, and some malformations will be missed. Every effort should be made to ensure that the patient and/or caregiver or guardian have truly understood these risks.

Where valproate is the most effective treatment (e.g., JME), a woman with capacity, or her representatives, may state a clear preference for valproate. When this occurs, this preference should be considered seriously when in reaching

a treatment decision. In most such cases it may be appropriate to initiate valproate. For female patients already established on valproate, it is also important to allow the patient to state a preference as to whether to continue the valproate. In most such cases it may be appropriate to continue valproate when the patient prefers to do so.

The following sections discuss the risks and benefits of various treatment options in some specific clinical situations. Some general recommendations are summarized in Box 1 (Key Points). The aim of the specific recommendations is to provide advice for the clinician that will inform discussions with female patients and their caregivers or guardians when making treatment decisions. The risks and benefits of different treatment alternatives are assessed for each of these clinical situations and summarized in Table 1. Given that valproate is not a preferred treatment for focal epilepsies, Table 1 primarily addresses the treatment of other epilepsies.

Newly diagnosed epilepsy—treatment options

Because a substantial proportion of patients with newly diagnosed epilepsy will respond to the first AED and are likely to remain on that treatment long term, selection of the initial treatment has implications for future situations, including the prospect of a future pregnancy.

In many cases of newly diagnosed epilepsy, valproate should not be prescribed to girls and women unless other treatments are likely to fail. However, there are certain generalized epilepsies for which other treatments are less effective than valproate. In such cases, and also under circumstances that make fetal exposure to valproate unlikely, valproate could still be considered as a first-line option. Such circumstances include young girls with self-limiting epilepsy with a very high likelihood of treatment withdrawal before puberty, and girls or women with severe concurrent disabilities that make pregnancy very unlikely.

Consult Table 1 for a risk–benefit analysis of the options below

Clinical option 1: Valproate not prescribed unless other treatments failed

Clinical option 2: Valproate prescribed as initial treatment in selected patients

Recommendations

- Valproate should not be prescribed for focal seizures in girls and women with newly diagnosed epilepsy.
- Valproate as well as alternatives should be considered as appropriate treatment options for generalized epilepsies where these agents are more effective than other drugs (e.g., JME, or juvenile absence epilepsy). If following discussion of risks and benefits, the woman who is not planning pregnancy chooses valproate, it should be initiated.
- When most appropriate for the seizure or epilepsy type, valproate may be considered as initial treatment for girls

Table 1. Risk–benefit analysis of valproate use and alternative treatment strategies in different clinical situations

Clinical indication	Scenario	Risks	Benefits	Comments
Newly diagnosed epilepsy where valproate is likely more effective than alternative AEDs	Valproate not prescribed unless other treatments failed	<ul style="list-style-type: none"> Delayed seizure control Increased risk of seizures Adverse psychosocial impact due to lack of seizure control 	<ul style="list-style-type: none"> Reduction of risk of teratogenicity and neurodevelopmental delay Less need to switch when pregnancy planned Highest chance of full seizure control in selected syndromes Avoidance of unnecessary suboptimal seizure control 	<p>The risk associated with seizures varies with the seizure type; GTCS have a higher risk of morbidity and mortality than absence or myoclonic seizures</p> <p>The magnitude of risk depends on previous family history of birth defects, and the dose of valproate</p>
	Valproate prescribed as initial treatment in selected patients	<ul style="list-style-type: none"> Teratogenicity and risk of neurodevelopmental delay in case of pregnancy Switch if pregnancy is planned or patient reached an age with childbearing potential 	<ul style="list-style-type: none"> Avoidance of unnecessary suboptimal seizure control 	
Female patients with epilepsies for which valproate is particularly effective and who have failed on treatment alternatives	Valproate not prescribed	<ul style="list-style-type: none"> Delayed seizure control Increased risk of seizures Adverse psychosocial impact due to lack of seizure control 	<ul style="list-style-type: none"> Reduction of risk of teratogenicity and neurodevelopmental delay Less need to switch when pregnancy planned Highest chance of full seizure control in selected syndromes Avoidance of unnecessary suboptimal seizure control 	<p>The risk associated with seizures varies with the seizure type; GTCS have a higher risk of morbidity and mortality than absence or myoclonic seizures</p> <p>The magnitude of risk depends on previous family history of birth defects, and the dose of valproate</p>
	Switch from existing treatment to valproate	<ul style="list-style-type: none"> Teratogenicity and risk of neurodevelopmental delay in case of pregnancy Switch if pregnancy is planned or patient reached an age with childbearing potential 	<ul style="list-style-type: none"> Avoidance of unnecessary suboptimal seizure control 	
Female patient on valproate not considering pregnancy	Withdrawal of valproate in seizure-free patients and in adult patients with focal epilepsy	<ul style="list-style-type: none"> Seizure relapse with potential consequences (injury, driving license, etc.) 	<ul style="list-style-type: none"> Avoidance of unnecessary drug treatment Elimination of valproate-associated teratogenicity Elimination of valproate-associated neurodevelopmental delay 	<p>The magnitude of risk depends on age, syndrome, seizure type, previous history, and other patient related factors</p> <p>The magnitude of the benefits depends on dose and potentially present adverse effects</p>
	Switch of valproate to an alternative treatment	<ul style="list-style-type: none"> Seizure relapse in seizure-free patients with potential consequences (injury, driving license, etc.) Seizure deterioration in patients who are not seizure free Adverse effects of the new drug Teratogenicity of the new drug Risk of teratogenicity and neurodevelopmental delay in case of pregnancy 	<ul style="list-style-type: none"> Elimination of valproate-associated teratogenicity Elimination of valproate-associated neurodevelopmental delay Chance of improved seizure control if suboptimal on valproate 	<p>The magnitude of risk depends on age, syndrome, seizure type, previous history, and other patient related factors</p> <p>The magnitude of the benefits depends on dose and potentially present adverse effects</p>
Unchanged treatment with valproate	Unchanged treatment with valproate		<ul style="list-style-type: none"> Avoidance of unnecessary suboptimal seizure control 	<p>Requires a proactive approach with reminders of need to reassess treatment in future</p>

Continued

Table 1. Continued.

Clinical indication	Scenario	Risks	Benefits	Comments
Female patient taking valproate considering pregnancy	Withdrawal of valproate in seizure-free patients and in adult patients with focal epilepsy	<ul style="list-style-type: none"> Seizure relapse with potential consequences (injury, driving license, etc.) 	<ul style="list-style-type: none"> Avoidance of unnecessary drug treatment Elimination of valproate-associated teratogenicity Elimination of valproate-associated neurodevelopmental delay 	<p>The magnitude of risk depends on age, syndrome, seizure type, previous history, and other patient related factors</p> <p>The magnitude of the benefits depends on dose and potentially present adverse effects</p>
	Switch from valproate to an alternative treatment	<ul style="list-style-type: none"> Seizure relapse in seizure-free patients with potential consequences (injury, driving license, etc.) Seizure deterioration in patients who are not seizure free Adverse effects of the substituted drug, including its possible teratogenicity 	<ul style="list-style-type: none"> Elimination of valproate-associated teratogenicity Elimination of valproate-associated neurodevelopmental delay Chance of improved seizure control if suboptimal on valproate 	<p>The magnitude of risk depends on age, syndrome, seizure type, previous history, and other patient related factors</p> <p>The magnitude of the benefits depends on dose and potentially present adverse effects</p>
Woman already on valproate treatment while pregnant	Unchanged treatment with valproate	<ul style="list-style-type: none"> Risk of teratogenicity and neurodevelopmental delay 	<ul style="list-style-type: none"> Avoidance of unnecessary suboptimal seizure control 	<p>The magnitude of risk depends on previous family history of birth defects, and the dose of valproate</p>
	Withdrawal of valproate	<ul style="list-style-type: none"> Maternal and fetal risks of uncontrolled seizures 	<ul style="list-style-type: none"> Possible reduction of the risk of valproate-associated neurodevelopmental delay 	<p>Withdrawal of valproate during pregnancy is unlikely to reduce the risk of malformations</p> <p>Risks outweigh possible benefits</p> <p>No data available on pregnancy outcomes after treatment switches during pregnancy</p>
	Switch from valproate to an alternative treatment	<ul style="list-style-type: none"> Maternal and fetal risks of uncontrolled seizures Teratogenicity and risk of valproate-associated neurodevelopmental delay Teratogenicity of substituted drug and its transient combination with valproate Adverse effects of the substituted drug 	<ul style="list-style-type: none"> Possible reduction of the risk of valproate-associated neurodevelopmental delay 	<p>Exchange of valproate during pregnancy is unlikely to reduce the risk of malformations</p> <p>Risks outweigh possible benefits</p>
	Reduction of valproate dose	<ul style="list-style-type: none"> Maternal and fetal risks of uncontrolled seizures 	<ul style="list-style-type: none"> Possible reduction of the risk of valproate-associated neurodevelopmental delay 	<p>Reduction of valproate dose during pregnancy unlikely to reduce risk of malformations</p> <p>The magnitude of the benefits depends on dose and potentially present adverse effects</p>

AED, antiepileptic drug; GTCS, generalized tonic-clonic seizure.

with epilepsies who have a high likelihood of remission and treatment withdrawal before puberty.

- When most appropriate for the seizure or epilepsy type, valproate may be considered as initial treatment when the epilepsy is of such a severe nature, or the patient has concurrent severe disabilities, that future pregnancy is extremely unlikely.
- Ensure effective contraception whenever relevant if valproate is prescribed.

Female patients with epilepsies for which valproate is particularly effective and who have failed to respond to treatment alternatives

In girls and women with epilepsies (e.g., JME, or juvenile absence epilepsy) for which valproate is likely to be the most effective drug, who have failed to attain acceptable seizure control on reasonable treatment alternatives, and who may or may not wish to become pregnant in the future, it is generally appropriate to consider a treatment attempt with valproate.

Consult Table 1 for a risk–benefit analysis of the options below

Clinical option 1: Valproate not prescribed

Clinical option 2: Switch from existing treatment to valproate

Recommendations

- Valproate should be considered as an appropriate treatment option for girls and women who have failed to respond to other reasonable treatment alternatives and who have generalized epilepsies where valproate is likely to be more effective (e.g., JME, or juvenile absence epilepsy).
- The women and female child's caregiver/guardian must be carefully informed about the teratogenic risks and the limitations of prenatal screening as well as the risks of uncontrolled epilepsy.
- When valproate is selected, the lowest effective dose should be prescribed, ideally not exceeding 500–600 mg/day, although at times, a higher dose may be required to control seizures.

Female patients already established on valproate treatment not considering pregnancy

In this section, we consider advice to female patients who are not currently planning to conceive, but may do so at some future time point. A consultation with the epilepsy specialist should be scheduled to provide patient and caregiver complete information about the risks of valproate in pregnancy.

Consult Table 1 for a risk–benefit analysis of the options below

Clinical option 1: Withdrawal of valproate

Patients with seizures in remission may wish to consider drug withdrawal. The risk of seizure relapse can be esti-

mated (see below), and for some groups with idiopathic (genetic) generalized epilepsies, the risk of relapse is high. Drug withdrawal is usually undertaken gradually over weeks to months, which allows an opportunity to identify the likely minimum required dose should a seizure occur during drug withdrawal.

Clinical option 2: Switch of valproate to an alternative treatment

The switch of valproate to an alternative treatment will commonly occur over at least 2–3 months. The new medication is usually first gradually introduced as add on to valproate. This can take up to 6 weeks to reach a potentially effective dose of the new treatment; thereafter an attempt can be made to gradually withdraw valproate.

Clinical option 3: Unchanged treatment with valproate

Recommendations

- In female patients with focal epilepsies, withdrawal of valproate or a switch to an alternative treatment should be considered.
- Valproate can be continued when the patient and clinician agree that the benefits of staying on valproate outweigh the risks of withdrawal or switch to an alternative.
- For female patients who wish to continue with valproate but are willing to accept the risks associated with a dose reduction, the dose should be reduced to the lowest possible to achieve acceptable seizure control, aiming for doses not exceeding 500–600 mg/day, if possible.
- For female patients whose seizures were controlled only after failing to respond to other appropriate treatment alternatives, and for whom the risks of withdrawal are not acceptable, valproate can be continued.
- For female patients in remission on valproate, withdrawal of treatment should be considered if the likelihood of relapse on withdrawal is acceptable to the patient.
- For women taking valproate with suboptimal seizure control or adverse effects, a switch to another treatment should be considered.
- Women of childbearing potential who continue treatment with valproate should be on effective contraception or otherwise ensure that unplanned pregnancies can be avoided.

Female patients already established on valproate treatment considering future pregnancy

A consultation with the epilepsy specialist should be scheduled well in advance of the planned pregnancy. To allow for possible modifications of treatment and for adequate assessment of the revised treatment, this should ideally be initiated a year or more before planned conception. Reassessment of treatment is mandatory, with a careful risk–benefit analysis of available treatment options. A change in treatment should be considered and discussed with every patient.

Consult Table 1 for a risk–benefit analysis of the options below

Clinical option 1: Withdrawal of valproate in seizure-free patients

See Section C

Clinical option 2: Switch to an alternative AED in patients with suboptimal treatment outcomes with valproate

See Section C

Clinical option 3: Unchanged treatment with valproate

Recommendations

- Treatment should be reassessed and changes carefully considered for every woman on valproate treatment who is considering pregnancy.
- In women with focal epilepsies, withdrawal of valproate or a switch to an alternative treatment should always be considered.
- Treatment changes should be completed and adequately evaluated before conception. For valproate as well as for other treatments, the lowest effective dose should be established before conception.
- Withdrawal of valproate treatment should be considered in women with epilepsy in remission for whom the risk of relapse on withdrawal is acceptable.
- A switch from valproate to alternative treatments should be considered for every woman who is not suitable for, or who has failed to respond to, treatment withdrawal.
- Continued valproate treatment can be considered for women who are well controlled on a low dose of valproate (up to 500–600 mg/day) and who consider the risks associated with attempts to withdrawal or switch of treatment to be unacceptable. These women as well as those who need to continue valproate treatment at higher doses must be carefully informed about the teratogenic risks and the limitations of prenatal screening.

Woman already on valproate treatment while pregnant, unplanned pregnancy

An urgent consultation with the epilepsy specialist is mandatory, and the woman should continue to take her treatment until this consultation has taken place. The purpose is a reassessment of the current epilepsy treatment, and to carefully provide complete information to the pregnant patient about risks and benefits of different treatment strategies as well as of possibilities and limitations of prenatal screening tests. The outcome of this consultation will only rarely result in the withdrawal of valproate or a switch to an alternative treatment. Any decision to attempt to withdraw or reduce the dose of valproate will depend on the type of seizures and the individual patient's willingness to accept the risk of deterioration in seizure control.

Consult Table 1 for a risk–benefit analysis of the options below

Clinical option 1: Withdrawal of valproate

An epilepsy medication is generally withdrawn gradually over weeks to months. Even with such a procedure, AED withdrawal in a seizure-free patient is usually associated with a significant risk of seizure relapse.

Clinical option 2: Change of valproate to an alternative treatment

See Section C

Clinical option 3: Reduction of valproate dose

Recommendations

- The general rule is to continue treatment with valproate in a patient who discovers that she is pregnant.
- Withdrawal of valproate treatment in a pregnant patient with good seizure control should be initiated only if the risks of doing so are acceptable to the patient, and after careful consideration of the risks to both mother and fetus. This is usually only the case when there is agreement that treatment is not needed to maintain acceptable seizure control.
- A reduction in valproate dose can be considered when the risks of doing so are acceptable to the patient. This is usually only the case when prior history suggests that the dose is higher than that needed to maintain acceptable seizure control.
- A switch from valproate to another AED is generally not recommended during pregnancy in a patient with good seizure control while on valproate.

MANAGEMENT OF FEMALE PATIENTS WITH EPILEPSY WHO CONTINUE TREATMENT WITH VALPROATE AND WHO PLAN TO OR MIGHT BECOME PREGNANT

The most important recommendation is to strive for the lowest effective dose of valproate before conception. It is also frequently recommended to divide the daily dose into several small doses to be taken throughout the day, and suggested that the use of a prolonged-release formulation of valproate may be preferable. This recommendation is included in the Summary of Product Characteristics (SmPC) and is based on the assumption that the teratogenic risk is related to the peak plasma concentration of valproate.² However, it is important to be aware that the assumption is based solely on data from studies in mice, and that there is no support from clinical studies that use of divided daily doses or prolonged-release formulations reduce the risk of congenital malformations.³ In addition, the risk of poorer adherence to treatment with more frequent dosing needs to be considered.

Folate supplementation is also frequently recommended and known to decrease the general risk of malformations such as neural tube defects. However, there is no evidence of a reduction of the risks associated with valproate exposure.^{4,5}

CURRENT EVIDENCE OF RISKS: TERATOGENICITY INCLUDING ADVERSE COGNITIVE AND BEHAVIORAL DEVELOPMENT

Teratogenicity

Data derived from a meta-analysis (including English-language studies published from 1966 through 18 May 2007) found an MCM prevalence of 10.7% among children of women with epilepsy who were exposed to valproate monotherapy, compared with a prevalence of 7.1% among children of women with epilepsy in general (of which 83% were on AEDs), and 2.3% among children of healthy mothers.⁶ More recently, a number of important studies have been published that strengthen the evidence for these risks. In three large prospective AED and pregnancy registries, the frequency of MCMs in offspring exposed to valproate monotherapy ranged from 6.7% to 9.7%.^{4,7,8} Similarly, population-based medical birth registries estimate risks associated with exposure to valproate monotherapy ranging from 4.7% to 6.3%, compared to 2.1% to 2.9% in the general population.^{9,10} Frequencies of MCMs associated with other drugs as monotherapy as reported in major prospective registries are summarized in Table 2. MCM frequencies with carbamazepine and lamotrigine are in general similar, and consistently lower than with valproate. The risk with levetiracetam also appears comparatively low, but confidence in estimates is low given the relatively small number of exposures reported. There are even fewer reported monotherapy exposures to topiramate, but the available data indicate an increased risk of MCMs (Table 2).

Although the estimated frequency of MCMs varies among studies, studies have consistently reported that higher valproate dose exposure in early pregnancy is associated with higher MCM risk.^{4,7,8,13–16} The lowest MCM frequencies associated with valproate were reported at doses of 500 mg/day and below in the North American AED Pregnancy Registry (4.3% of exposed to valproate monotherapy with MCMs),⁷ and 600 mg/day and below in the United Kingdom and Ireland Register (5.0% of exposed to

valproate monotherapy with MCMs),⁸ and below 700 mg/day in the European and International Registry of Antiepileptic Drugs in Pregnancy (EURAP; 5.6% of exposed to valproate monotherapy with MCMs).⁴ Estimated frequencies of MCMs at dose levels different from the EURAP, the United Kingdom and Irish Registers, and the North American AED Pregnancy Registry are presented in Table 3.

Adverse effects on cognitive and behavioral development

Exposure to valproate can adversely affect the development of the exposed child. A recent Cochrane Review reported a significant reduction in IQ in valproate-exposed children compared to children of mothers treated with carbamazepine, children of mothers with untreated epilepsy, and children of mothers without epilepsy.¹⁷ In the prospective “Neurodevelopmental Effects of Antiepileptic Drugs” (NEAD) study, IQ at age 6 was on average 8–11 points lower in valproate-exposed children compared with children exposed to other AEDs (carbamazepine, lamotrigine, phenytoin).⁵ These IQ reductions were considered sufficient to affect education and occupational outcomes in later life. A dose dependence was reported in six studies included in the review.¹⁷ When considering lower doses of valproate, in the two largest prospective studies, IQ at age 6 among children exposed to valproate at doses below 1,000 mg daily⁵ or 800 mg daily¹⁸ was comparable to the IQ of children exposed to other AEDs. In the latter study, however, children exposed to valproate <800 mg daily had significantly increased need for extra educational help relative to controls.¹⁸ A further conclusion of the Cochrane Review was that we have insufficient data about newer AEDs. For example, there are no systematic data on the cognitive development of children exposed to topiramate in utero, and only one study assessing development of children exposed to levetiracetam at 3 years of age.¹⁹ The latter reported that children exposed to levetiracetam did not differ from unexposed control children, and scored higher in language and motor development than children exposed to valproate. However, the results must be interpreted with caution given

Table 2. Overall frequencies (%) of major congenital malformations (malformed/exposed) for different monotherapies

Source	Valproate	Carbamazepine	Lamotrigine	Phenobarbital	Phenytoin	Levetiracetam	Oxcarbazepine	Topiramate
EURAP ⁴	9.7% (98/1,010)	5.6% (79/1,402)	2.9% (37/1,280)	7.4% (16/217)	5.8% (6/103)	1.6% (2/126)	3.3% (6/184)	6.8% (5/73)
NAAPR ⁷	9.3% (30/323)	3.0% (31/1,033)	1.9% (31/1,562)	5.5% (11/199)	2.9% (12/416)	2.4% (11/450)	2.2% (4/182)	4.2% (15/359)
UKIre ^{8,11,12}	6.7% (82/1,220)	2.6% (43/1,657)	2.3% (49/2,098)		3.7% (3/82)	0.7% (2/304)		4.3% (3/70)
NMBR ⁹	6.3% (21/333)	2.9% (20/685)	3.4% (28/833)	7.4% (2/27)		1.7% (2/118)	1.8% (1/57)	4.2% (2/48)
SMBR ⁹	4.7% (29/619)	2.7% (38/1,430)	2.9% (32/1,100)		6.7% (8/119)	(0/61)	3.7% (1/27)	7.7% (4/52)

Data from different prospective registers: EURAP, European and International Registry of Antiepileptic Drugs in Pregnancy; NAAPR, North American Antiepileptic Drug and Pregnancy Registry; UKIre, UK and Irish Epilepsy and Pregnancy Registers; Medical Birth Registry of Norway; SMBR, Swedish Medical Birth Register.

^aAs reported in.¹⁰

Table 3. Frequencies of major congenital malformations (95% CI) with monotherapy with valproate, carbamazepine, and lamotrigine at different dose levels in EURAP, UKIre, and NAAPR

Drug	EURAP ⁴			UKIre ⁸			NAAPR ⁷		
	Dose range (mg/day)	No. exposed	MCM % (95% CI)	Dose range (mg/day)	Number of exposed	MCM % (95% CI)	Dose range (mg/day)	Number of exposed	MCM % (95% CI)
Valproate	<700	431	5.6 (3.6–8.2)	<600	476	5.0 (3.4–7.4)	1–500	NA	4.3 (0.2–8.3)
	≥700	480	10.4 (7.8–13.5)	>600 to <1,000	426	6.1 (4.2–8.8)	501–999	NA	6.8 (1.6–12.1)
	<1,500			>1,000	297	10.4 (7.4–14.4)	1,000–1,500	NA	10.7 (5.2–16.1)
	≥1,500	99	24.2 (16.2–33.9)				>1,500	NA	26.1 (8.1–44.0)
Carbamazepine	<400	148	3.4 (1.1–7.7)	<500	721	1.9 (1.2–3.2)			
	≥400	1,047	5.3 (4.1–6.9)	>500 to <1,000	739	2.7 (1.8–4.1)			
	≥1,000	207	8.7 (5.2–13.4)	>1,000	170	5.3 (2.7–9.5)			
Lamotrigine	<300	836	2.0 (1.2–3.2)	<200	1,143	2.1 (1.4–3.1)			
	≥300	444	4.5 (2.77–6.87)	>200 to <400	665	2.4 (1.5–4.0)			
				>400	267	3.4 (1.9–6.5)			

NA, not available; MCM, major congenital malformation; EURAP, European and International Registry of Antiepileptic Drugs in Pregnancy; NAAPR, North American Antiepileptic Drug and Pregnancy Registry; UKIre, UK and Irish Epilepsy and Pregnancy Registers.

the low and varied age at assessment, and that compared to levetiracetam a much smaller proportion of children exposed to valproate participated in the assessment.

In addition to developmental delay, there is growing evidence of prenatal exposure to valproate being associated with an increased risk of attention-deficit/hyperactivity disorder (ADHD),^{20,21} autism, and autistic spectrum disorder.²² A subset of the children included in the NEAD study were also assessed for adaptive and behavioral functioning at ages 3 and 6.^{20,21} These limited data suggested a dose-dependent decrease in adaptive scores and greater risk for a diagnosis of ADHD in children exposed to valproate.

Limited data from a population-based Danish national register suggest that children exposed to valproate are at a 1.7-fold increased risk of autism spectrum disorder, which corresponds to an absolute risk of 4.2% and 2.9-fold increased risk for autism, corresponding to an absolute risk of 3%.²²

CURRENT EVIDENCE OF THE EFFICACY OF VALPROATE AND TREATMENT ALTERNATIVES

Shortly after its introduction in the 1970s and 1980s, the efficacy of valproate against seizures associated with the idiopathic (genetic) generalized epilepsies was recognized and it soon was widely accepted into routine practice. This was primarily an era that predates the current approach to assessing the efficacy and safety of AEDs. The following text summarizes current evidence, focusing on randomized controlled trials of valproate in various seizure types associated with idiopathic (genetic) generalized epilepsies, or other epileptic syndromes.

Absence seizures

Absence seizures can occur in the context of a number of epilepsy syndromes with onset ranging from infancy to adolescence, the most common idiopathic (genetic) generalized epilepsies being childhood and juvenile absence epilepsy. A systematic review identified four small randomized trials of poor methodologic quality assessing valproate, ethosuximide, or lamotrigine as therapy for absence seizures.²³ Three studies compared valproate with ethosuximide. No significant difference between valproate and ethosuximide was found for seizure control. The fourth study²⁴ compared valproate and lamotrigine and found that seizure freedom rates were significantly higher with valproate (53% vs. 5%, respectively, at 1 month and 68% vs. 53% at 12 months).

The largest randomized trial comparing these drugs²⁵ recruited 452 participants with childhood absence epilepsy. This was a well-designed double-blind trial. At 16–20 weeks, participants were significantly more likely to be retained on valproate (53%) and ethosuximide (58%) than lamotrigine (29%), with a tolerability advantage for ethosuximide over valproate in terms of a lesser impact on cognitive (attentional) function. Similar results were seen at 12-month follow-up.

Another randomized trial compared valproate with lamotrigine and topiramate^{26,27} and recruited a heterogeneous population with idiopathic (genetic) generalized epilepsies. Achieving 12-month remission was significantly more likely on valproate than lamotrigine, both overall and in the subgroup with absence seizures.

There is currently no evidence from randomized controlled trials to indicate that levetiracetam has efficacy against absence seizures. One small placebo-controlled trial of 2 weeks' duration did not find a significant difference between levetiracetam and placebo.²⁸

Primary generalized tonic–clonic seizures

This section refers to GTCS occurring in the context of generalized epilepsies, most commonly idiopathic (genetic) generalized epilepsies. Trials assessing valproate for GTCS have included participants with tonic–clonic seizures alone or in combination with other generalized seizure types. A systematic review and meta-analysis²⁹ comparing valproate and carbamazepine found no difference between the two drugs for time to 12-month remission. It may be that misclassification of patients, particularly adults with focal epilepsy, confounded results and masked a superior effect of valproate. Valproate was significantly more effective in younger participants who were more likely to have truly “primary” generalized seizures. A further systematic review³⁰ compared phenytoin with valproate; no significant difference was found, and it is again likely that misclassification of patients confounded results. In a large open-label randomized trial²⁶ that recruited participants with generalized or unclassified epilepsy, valproate was superior to topiramate for time to treatment failure (retention on treatment), and superior to lamotrigine for time to 12-month remission. Prognostic modeling of these data²⁷ indicated that these treatment effects were consistent across seizure types including tonic–clonic seizures. A further meta-analysis used a network approach,³¹ and for time to 12-month remission, estimates suggested superiority of valproate over topiramate, oxcarbazepine, phenobarbital, and lamotrigine, although only the comparison with lamotrigine was statistically significant. A more recent open-label randomized trial including 696 patients with newly diagnosed unclassified or generalized epilepsy found levetiracetam not superior to extended-release valproate in terms of time to treatment failure, 12-month remission rates, and time to first seizure.³²

Myoclonic seizures

Myoclonic seizures occur predominantly in the context of JME, but also in other forms of idiopathic (genetic) generalized epilepsies and other generalized epilepsies that have onset ranging from infancy to adolescence. Few randomized trials have assessed the efficacy of valproate for myoclonic seizures. Results from the Standard and New Antiepileptic Drugs (SANAD) trial suggest superior efficacy of valproate compared to lamotrigine or topiramate.^{26,27} Two small randomized controlled trials comparing valproate and topiramate in JME have been reported.^{33,34} Neither found a significant difference, but they were not powered to do so, and hence the results do not inform treatment choices. Adjunctive (add-on) levetiracetam has been shown to have efficacy against myoclonic seizures associated with idiopathic (genetic) generalized epilepsies,³⁵ but we have no randomized controlled trial evidence to support efficacy as monotherapy. In addition, there are data from observational studies supporting efficacy of valproate in the treatment of myoclonic seizures in the context of idiopathic (genetic) generalized epilepsies.^{36,37}

Specific idiopathic (genetic) generalized epilepsy syndromes

As highlighted, except for the absence epilepsies, trials have not provided robust evidence about comparative efficacy of AEDs in specific idiopathic (genetic) generalized epilepsy syndromes, primarily those that include GTCS; epilepsy with GTCS alone, and JME are the most frequently seen. The latter in particular is believed more likely to respond to valproate. Observational studies provide further evidence about likely effectiveness, the largest of which focused on idiopathic (genetic) generalized epilepsies and assessed outcomes in 962 patients attending a regional epilepsy clinic in the United Kingdom from point of diagnosis.³⁸ Accepting likely selection biases, 52% of patients achieved remission on valproate, 17% on lamotrigine, and 35% on topiramate. Results were similar across different idiopathic (genetic) generalized epilepsy subgroups.

Efficacy, limitations, and risks of alternatives to valproate as initial monotherapy in genetic (idiopathic) generalized epilepsy

The preceding text highlights current evidence about the comparative efficacy of valproate. In this section, we consider the risks and limitations of alternatives as initial monotherapy.

For absence seizures associated with childhood or juvenile absence epilepsy, current evidence suggests that ethosuximide has efficacy similar to that of valproate, and should be considered a first-line option for most cases. There are no data from randomized trials to inform treatment choice for absence seizures presenting in infancy. Ethosuximide does not have efficacy against GTCS or myoclonic seizures, and where these occur in combination with absence seizures, valproate is recommended. Lamotrigine and topiramate are inferior to valproate for treatment of absence seizures and their use as first-line therapy will likely result in delay in seizure control with a potential negative impact on education and psychosocial development. There is also concern that alternatives to valproate might exacerbate certain seizure types in idiopathic (genetic) generalized epilepsies; for example, lamotrigine can exacerbate myoclonic seizures.³⁹

Tonic–clonic seizures pose the greatest risk, as they are associated with a higher risk of injury and epilepsy-related death than other seizure types.⁴⁰ As highlighted earlier, GTCS may occur in isolation, or be one of a number of seizure types experienced in epilepsy syndromes such as in JME. Most recent evidence supports greater efficacy of valproate compared to alternatives. Use of drugs other than valproate as first-line treatments can result in diminished or delayed seizure control and increase the risk of injury epilepsy-related death, as well as increase psychological and social disadvantage.^{41–44} In addition to the maternal risks associated with seizures, uncontrolled GTCS may be harmful to the fetus.¹⁰ Frequent GTCS during pregnancy have,

for example, been associated with poorer neurodevelopment of offspring.⁴⁵

Epilepsies and syndromes with focal seizures

A meta-analysis of randomized trials comparing valproate and carbamazepine monotherapy²⁹ found that carbamazepine was superior to valproate for treatment of focal seizures. A second meta-analysis comparing valproate with phenytoin monotherapy³⁰ found no significant difference for time to 12-month remission, although confidence intervals were wide and the possibility of an important difference could not be excluded. A network meta-analysis³¹ found that valproate was significantly inferior to carbamazepine for time to 12-month remission.

Current evidence therefore does not support the use of valproate as a first-line treatment for focal seizures. However, valproate may be indicated for focal seizures associated with childhood epilepsy syndromes such as epilepsy with continuous spike-waves during sleep (CSWS or electric status epilepticus in sleep [ESES] syndrome), atypical benign focal epilepsy,^{46,47} and Dravet syndrome because sodium channel blockers, such as carbamazepine or oxcarbazepine, may exacerbate seizures and cognitive dysfunction in these conditions.³⁹

Efficacy in specific epilepsy syndromes

Few randomized trials have been undertaken to assess the efficacy of valproate in the treatment of epilepsy syndromes

with onset in infancy or childhood.⁴⁸ The best-studied syndrome is childhood absence epilepsy, for which valproate can be used as a first-line treatment. The majority of the patients become seizure free several years before puberty, and can discontinue drug therapy without relapsing.⁴⁹ Continued treatment beyond puberty may be needed in one third of the patients who relapse with absences or GTCS after attempted drug withdrawal.^{50,51} For other specific epilepsy syndromes, data on drug treatment are observational. The syndromes in which valproate may be considered as initial treatment are listed in Table 4.

SEIZURE-ASSOCIATED RISKS OF SWITCHING FROM VALPROATE TO AN ALTERNATIVE

Women with idiopathic (genetic) generalized epilepsies whose seizures are controlled by valproate may wish to consider switching to an alternative AED before conceiving. Given the superior efficacy of valproate to licensed monotherapy alternatives for some idiopathic (genetic) generalized epilepsies, in particular JME, a treatment switch will be associated with a risk of seizure recurrence and even status epilepticus in a small minority of cases.⁶¹ The precise risk is difficult to quantify, as this scenario has not been investigated in randomized controlled trials or other prospective study designs. Recurrence of GTCS is associated with risk of injury and also with a small risk of epilepsy-related death.

Table 4. Specific epilepsy syndromes where valproate may be considered the most appropriate initial treatment

Syndrome	Evidence	Childbearing potential	Comment
Childhood absence epilepsy	Randomized controlled studies ²⁵	Not affected	Ethosuximide equally effective and better tolerated ²⁵ Self-limiting in childhood in the majority
Juvenile myoclonic epilepsy	Randomized controlled studies	Not affected	Data derived from studies addressing seizure types, not syndromes (see text)
Juvenile absence epilepsy	Randomized controlled studies	Not affected	Data derived from studies addressing absence seizures, not syndromes (see text)
Epilepsy with generalized tonic-clonic seizures alone	Randomized controlled studies	Not affected	Data derived from studies addressing seizure types, not syndromes (see text)
Myoclonic epilepsy in infancy	Observational ⁵²	Not affected	Self-limiting in childhood
Atypical benign focal epilepsy (atypical evolution of BECTS)	Observational ⁴⁷	Not affected	Self-limiting around puberty
Eyelid myoclonia and absences (Jeavons syndrome)	Observational ⁵³	Not affected	
Epilepsy with myoclonic absences	Observational ^{47,54}	Reduced	
Epilepsy with myoclonic atonic seizures	Observational ⁵⁵	Reduced	Variable course
Epileptic encephalopathy with continuous spike-and-wave waves in sleep (ESES/CSWS), including Landau-Kleffner syndrome	Observational ⁵⁶	Reduced	ESES self-limiting around puberty
Progressive myoclonic epilepsies	Observational ⁵⁷	Reduced	Valproate contraindicated for some mitochondrial disorders, especially with <i>POLG</i> mutation ⁵⁸
Dravet syndrome	Observational ⁵⁹	Very rare	RCT evidence for stiripentol added to the combination of valproate and clobazam ⁶⁰
Lennox-Gastaut syndrome	Observational ⁴⁷	Very rare	

BECTS, benign epilepsy with centrotemporal spikes; ESES, electric status epilepticus in sleep; CSWS, continuous spike-waves during sleep; RCT, randomized controlled trial.

For women with idiopathic (genetic) generalized epilepsies whose seizures are not controlled by valproate, a switch will be associated with a possibility for improvement but also likely a risk of worsening seizure control and any associated risk of morbidity and mortality.

WITHDRAWAL OF VALPROATE

Female patients with epilepsy who are in remission on valproate may wish to consider AED withdrawal. For women with absence epilepsy this poses the least risk. Many will enter spontaneous remission, especially those with childhood absence epilepsy.

For women with idiopathic (genetic) generalized epilepsies associated with GTCS, the risks associated with seizure recurrence are higher. The largest randomized controlled trial to assess this is the Medical Research Council (MRC) antiepileptic drug withdrawal study.⁶² This study was undertaken before the availability of newer AEDs, and the majority of patients with what would now be classified as idiopathic (genetic) generalized epilepsies were taking valproate. The trial recruited a heterogeneous group of patients with focal or generalized epilepsy with a seizure remission of at least 2 years. The 2-year recurrence rate was 41% with AED withdrawal and 22% with continued AED treatments. Prognostic modeling showed that factors including myoclonic seizures, GTCS, and abnormal electroencephalography (EEG) studies increased the risk of recurrence after withdrawal. A prognostic index generated⁶³ from this study estimates that for a patient with JME taking valproate monotherapy, AED withdrawal is associated with a 79% risk of recurrence by 2 years. A large observational study found a relapse rate of 80% across idiopathic (genetic) generalized epilepsies and 94% for JME.³⁸

CONCLUDING REMARKS

Valproate is clearly associated with particular dose-dependent teratogenic risks including adverse effects on cognitive and behavioral development of the exposed child, and should when possible be avoided in the treatment of female patients of childbearing potential. It is, however, also clear that there are epilepsies for which treatment alternatives are few and generally less effective than valproate, and thus situations where it is appropriate to prescribe valproate also to female patients of childbearing potential. The Task Force has here made recommendations for the use of valproate in different clinical situations based on risk–benefit assessments of different treatment options. Treatment decisions should be a shared decision between clinicians and patients, and, where appropriate, patients' representatives. The clinician has a responsibility to explain the benefits and risks of reasonable treatment options for the epilepsy or seizure type, and the patient or the patient's guardian has a right to express a preference for a specific treatment, which

must be taken into account when making a treatment choice.

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The current recommendations in this manuscript have been reviewed by EMA to ensure that they are not in conflict with the revised valproate SmPC. It is not within the Agency's remit to discuss the implementation in clinical practice of product-specific regulatory recommendations. Although the Agency can identify some areas where consistency may be improved, it is not possible to unequivocally confirm full regulatory consistency due to the nature of the recommendations and the fact that their implementation in clinical practice will remain, ultimately, with those exercising their clinical judgment on the basis of their experience and the individual patient circumstances.

DISCLOSURE OF CONFLICTS OF INTEREST

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