妊娠可能女性に対する抗てんかん薬治療について

Review　BABA　2017/02/14

はじめに

日本てんかん学会より 2007 年に『てんかんを持つ妊娠可能年齢の女性に対する治療ガイドライン』が発表されているが、近年日本でも認可されてきている新規抗てんかん薬に関する情報は皆無である。2010 年以降に報告された新規抗てんかん薬を含む催奇性についてまとめ、International League Against Epilepsy（ILAE）から発表された妊娠可能女性に対するバルプロ酸治療についての提言を解説する。

Rate of major congenital malformations for AED monotherapy

*Major congenital malformations: Cardiovascular, neural tube defects, oro-facial clefts, Hypospadia

	Valproate	Carbamazepine	Phenobarbital	Phenytoin	Topiramate	Lamotorigine	Levetiracetam	*Oxcarbazepine*
EURAP (Lancet Neurol 2011)	9.7%(98/1010)	5.6%(79/1402)	7.4%(16/217)	5.8%(6/103)	6.8%(5/73)	2.9%(37/1280)	1.6%(2/126)	3.3%(6/184)
NAAPR (Neurology 2012)	9.3%(30/323)	3.0%(31/1033)	5.5%(11/199)	2.9%(12/416)	4.2%(15/359)	1.9%(31/1562)	2.4%(11/450)	2.2%(4/182)
UKIre (J Neurol Neurosurg Psychiatr 2014)	6.7%(82/1220)	2.6%(43/1657)		3.7%(3/82)	4.3%(3/70)	2.3%(49/2098)	0.7%(2/304)	
AUS (Epilepsia 2010)	13.8%(35/253)	5.5%(19/346)		2.4%(1/41)	2.4%(1/42)	4.6%(14/307)	2.4%(2/84)	5.9%(1/17)
NMBR (J Neurol 2014)	6.3%(21/333)	2.9%(20/685)	7.4%(2/27)		4.2%(2/48)	3.4%(28/833)	1.7%(2/118)	1.8%(1/57)
SMBR (	4.7%(29/619)	2.7%(38/1430)		6.7%(8/119)	7.7%(4/52)	2.9%(32/1100)	0%(0/61)	3.7%(1/27)

The Task Force's recommendations

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);　Epilepsia 2015

(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.

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	• Delayed seizure control • Increased risk of seizures • Adverse psychosocial impact due to lack of seizure control	• Reduction of risk of teratogenicity and neurodevelopmental delay • Less need to switch when pregnancy planned	The risk associated with seizures varies with the seizure type; GTCS have a higher risk of morbidity and mortality than absence or myoclonic seizures
	Valproate prescribed as initial treatment in selected patients	• Teratogenicity and risk of neurodevelopmental delay in case of pregnancy • Switch if pregnancy is planned or patient reached an age with childbearing potential	• Highest chance of full seizure control in selected syndromes • Avoidance of unnecessary suboptimal seizure control	The magnitude of risk depends on previous family history of birth defects, and the dose of valproate
Female patients with epilepsies for which valproate is particularly effective and who have failed on treatment alternatives	Valproate not prescribed	• Delayed seizure control • Increased risk of seizures • Adverse psychosocial impact due to lack of seizure control	• Reduction of risk of teratogenicity and neurodevelopmental delay • Less need to switch when pregnancy planned	The risk associated with seizures varies with the seizure type; GTCS have a higher risk of morbidity and mortality than absence or myoclonic seizures
	Switch from existing treatment to valproate	• Teratogenicity and risk of neurodevelopmental delay in case of pregnancy • Switch if pregnancy is planned or patient reached an age with childbearing potential	• Highest chance of full seizure control in selected syndromes • Avoidance of unnecessary suboptimal seizure control	The magnitude of risk depends on previous family history of birth defects, and the dose of valproate
Female patient on valproate not considering pregnancy	Withdrawal of valproate in seizure-free patients and in adult patients with focal epilepsy	• Seizure relapse with potential consequences (injury, driving license, etc.)	• Avoidance of unnecessary drug treatment • Elimination of valproate-associated teratogenicity • Elimination of valproate-associated neurodevelopmental delay	The magnitude of risk depends on age, syndrome, seizure type, previous history, and other patient related factors The magnitude of the benefits depends on dose and potentially present adverse effects
	Switch of valproate to an alternative treatment	• 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	• Elimination of valproate-associated teratogenicity • Elimination of valproate-associated neurodevelopmental delay • Chance of improved seizure control if suboptimal on valproate	The magnitude of risk depends on age, syndrome, seizure type, previous history, and other patient related factors The magnitude of the benefits depends on dose and potentially present adverse effects
	Unchanged treatment with valproate	• Risk of teratogenicity and neurodevelopmental delay in case of pregnancy	• Avoidance of unnecessary suboptimal seizure control	Requires a proactive approach with reminders of need to reassess treatment in future
Female patient taking valproate considering pregnancy	Withdrawal of valproate in seizure-free patients and in adult patients with focal epilepsy	• Seizure relapse with potential consequences (injury, driving license, etc.)	• Avoidance of unnecessary drug treatment • Elimination of valproate-associated teratogenicity • Elimination of valproate-associated neurodevelopmental delay	The magnitude of risk depends on age, syndrome, seizure type, previous history, and other patient related factors The magnitude of the benefits depends on dose and potentially present adverse effects
	Switch from valproate to an alternative treatment	• 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	• Elimination of valproate-associated teratogenicity • Elimination of valproate-associated neurodevelopmental delay • Chance of improved seizure control if suboptimal on valproate	The magnitude of risk depends on age, syndrome, seizure type, previous history, and other patient related factors The magnitude of the benefits depends on dose and potentially present adverse effects
	Unchanged treatment with valproate	• Risk of teratogenicity and neurodevelopmental delay	• Avoidance of unnecessary suboptimal seizure control	The magnitude of risk depends on previous family history of birth defects, and the dose of valproate
Woman already on valproate treatment while pregnant	Withdrawal of valproate	• Maternal and fetal risks of uncontrolled seizures	• Possible reduction of the risk of valproate-associated neurodevelopmental delay	Withdrawal of valproate during pregnancy is unlikely to reduce the risk of malformations Risks outweigh possible benefits
	Switch from valproate to an alternative treatment	• 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	• Possible reduction of the risk of valproate-associated neurodevelopmental delay	No data available on pregnancy outcomes after treatment switches during pregnancy Exchange of valproate during pregnancy is unlikely to reduce the risk of malformations Risks outweigh possible benefits
	Reduction of valproate dose	• Maternal and fetal risks of uncontrolled seizures	• Possible reduction of the risk of valproate-associated neurodevelopmental delay	Reduction of valproate dose during pregnancy unlikely to reduce risk of malformations The magnitude of the benefits depends on dose and potentially present adverse effects