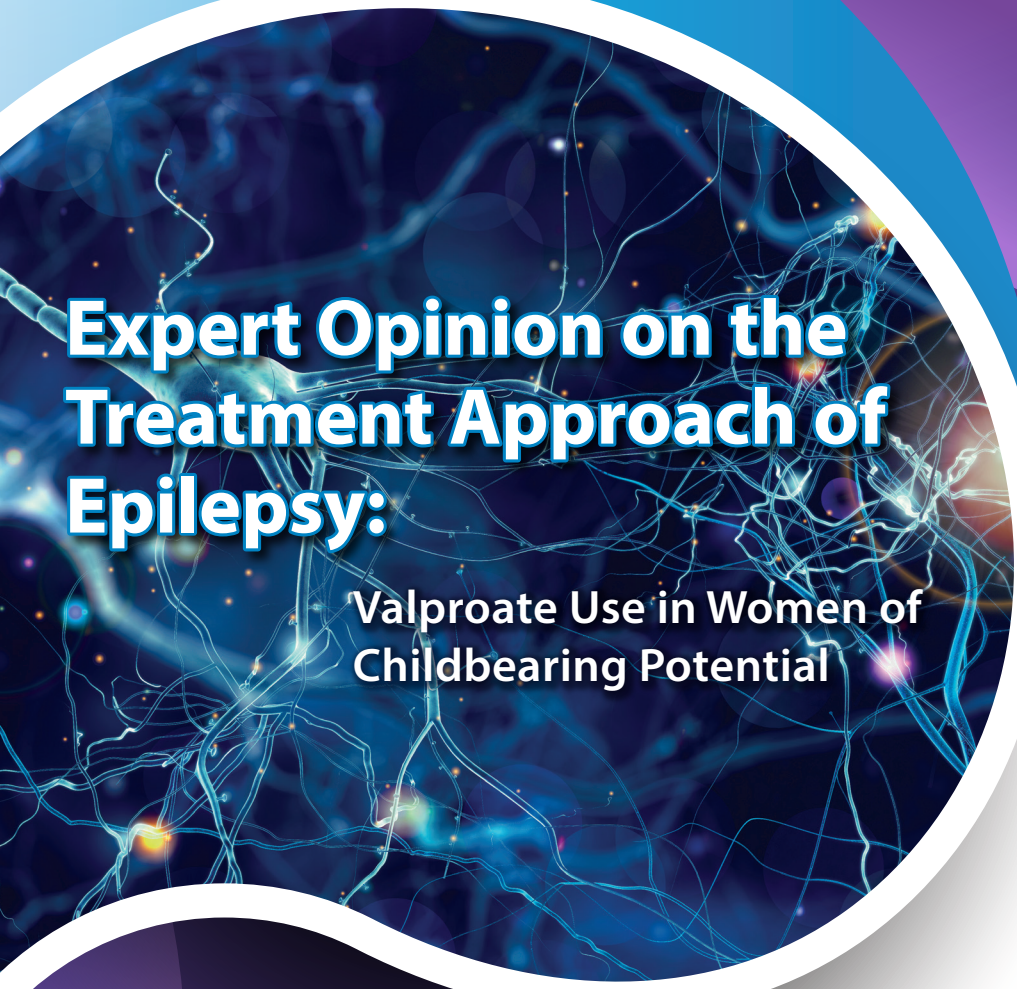

Expert Opinion on the Treatment Approach of Epilepsy:

Valproate Use in Women of Childbearing Potential

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Malaysian Society of Neurosciences
Persatuan Neurosains Malaysia
EPILEPSY COUNCIL

Contents

Abbreviations ▶

HCPs:	healthcare professionals
AEDs:	anti-epileptic drugs
WOCBP:	women of childbearing potential
VPA:	valproate
ILAE:	International League Against Epilepsy
CBZ:	carbamazepine
LTG:	lamotrigine
LEV:	levetiracetam
OXC:	oxcarbazepine
PB:	phenobarbital
PHT:	phenytoin
TPM:	topiramate
MCMs:	major congenital malformations
CI:	confidence interval
PRAC:	Pharmacovigilance Risk Assessment Committee
SUDEP:	sudden unexpected death in epilepsy
GTCS:	generalized tonic-clonic seizures
IGE:	idiopathic generalized epilepsy
O&G:	Obstetrician & Gynaecologist
OD:	once daily

Foreword ▶

The use of VPA is associated with increased teratogenic risks in WOCBP. In 2018, new recommendations have been introduced to strengthen previous restrictions on the use of VPA, along with the introduction of the Pregnancy Prevention Programme.

This booklet serves as a guide to provide an up-to-date information on the teratogenicity risks of AEDs in WOCBP, risk-benefit analysis of AED treatment, treatment algorithms and recommendations on the use of VPA and patient counselling tips. It has been reviewed by a team of local and international Neurologists and is disseminated with the permission of the Malaysian Society of Neurosciences.

I would like to thank all who have contributed to this publication, particularly the reviewers of this booklet. I hope this new booklet will provide clarity for doctors who manage epilepsy in WOCBP and ultimately, improve treatment outcomes in this group of patients.

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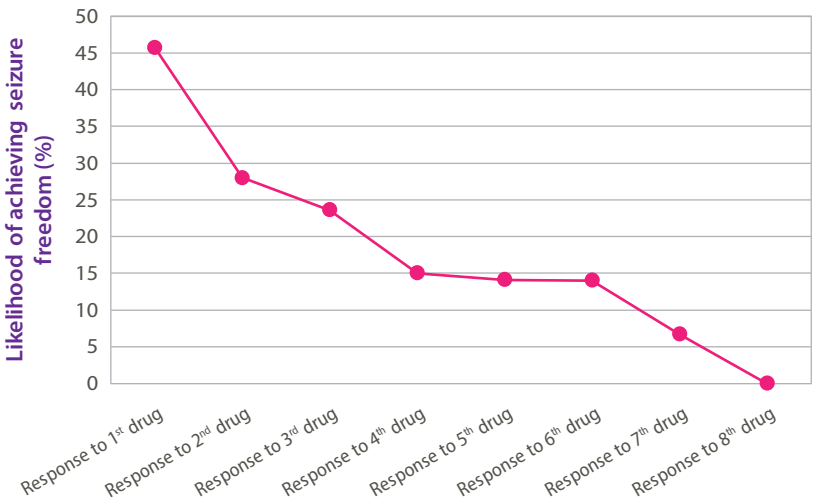
Introduction ▶

- Despite the availability of many new AEDs in the past two decades, the overall outcomes in newly diagnosed epilepsy have not improved[1]
- More than one-third of patients who have epilepsy remain uncontrolled[1]
- The chances of response decrease with each successive AED trial[1,2]

Success rate of AEDs regimen in patients with previously untreated epilepsy



- Patients who have many seizures before therapy or inadequate response to initial therapy with AED are likely to have refractory epilepsy[2]

Current evidence of teratogenicity risks of AEDs in WOCBP ▶

Risks of foetal malformations and long-term cognitive teratogenic effects

- The risk of foetal malformations in general population is 1–3%. If one AED is taken, the risk increases to 4–8%, and 15% if more than one AED is taken[3]
- The risk of foetal malformation is higher in polytherapy than in monotherapy (6% vs. 3.7%), and the risk is even higher if the combination contains VPA[3]
- Teratogenic effects of commonly used AEDs include cleft lip and palate and neural tube defects[3]
- Exposure to some AEDs may lead to long-term cognitive teratogenic effects, such as impaired verbal and non-verbal ability, executive function and memory[3]

Note: The recommended practice would be prescribing single-drug therapy at the lowest possible dose that effectively controls seizures

Current evidence of teratogenicity risks of AEDs in WOCBP ▶

Reported teratogenic effects of AEDs[4]

AEDs								
	CBZ (n=1957)	LTG (n=2514)	LEV (n=599)	OXC (n=333)	PB (N=294)	PHT (n=125)	TPM (n=152)	VPA (n=1381)
Cardiac	28 (1%)	15 (1%)	5 (1%)	4 (1%)	8 (3%)	5 (4%)	3 (2%)	34 (2%)
Cleft lip or palate	2 (<1%)	3 (<1%)	1 (<1%)	1 (<1%)	1 (<1%)	0	0	6 (<1%)
Hypospadias	10 (1%)	6 (<1%)	1 (<1%)	0	1 (<1%)	0	1 (1%)	22 (2%)
Neural tube defects	7 (<1%)	1 (<1%)	0	0	2 (1%)	1 (1%)	0	16 (1%)
Polydactyly	2 (<1%)	0	0	1 (<1%)	2 (1%)	0	0	8 (1%)
Gastrointestinal	7 (<1%)	8 (<1%)	1 (<1%)	0	0	0	0	2 (<1%)
Renal	12 (<1%)	8 (<1%)	1 (<1%)	0	1 (<1%)	0	0	7 (1%)
Other major congenital malformations	31 (<2%)	27 (<1%)	8 (1%)	4 (1%)	4 (1%)	2 (2%)	2 (1%)	30 (2%)
Multiple major congenital malformations	8 (<1%)	6 (<1%)	0	0	0	0	0	17 (1%)
Total number of major congenital malformations	107 (5%)	74 (3%)	17 (3%)	10 (3%)	19 (6%)	8 (6%)	6 (4%)	142 (10%)
No major congenital malformations reported	1850 (95%)	2440 (97%)	582 (97%)	323 (97%)	275 (94%)	117 (94%)	146 (96%)	1239 (90%)
Data are n (%) of affected offspring, unless stated otherwise.								

Adapted from Tomson T, et al. *Lancet Neurol* 2018;17:530–538

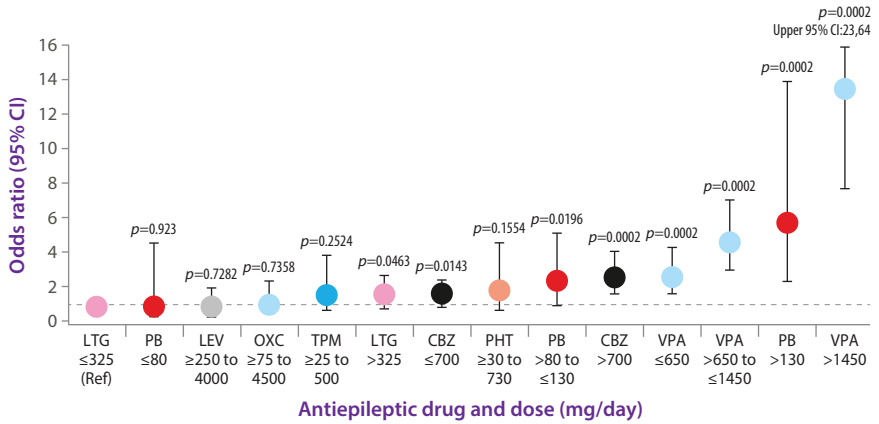
Results from the table above is obtained from a longitudinal, prospective cohort study based on the EURAP international registry. 7,555 women who are pregnant and exposed to AED monotherapy at conception were prospectively identified from 42 countries to compare the risk of MCMs with eight different AEDs assessed at 1 year after birth of offspring[4]

Current evidence of teratogenicity risks of AEDs in WOCBP ▶

Teratogenicity risks of AEDs are dose-dependent

- All AEDs are associated with teratogenicity risks, but higher risk with VPA[4]
- Prospective cohort study based on the EURAP international registry showed that low-dose of VPA (≤650 mg/day) does not increase the odds of MCM, compared with high-dose LTG (>325 mg/day)[4]

Comparisons between the treatment associated with the lowest frequency of MCMs (LTG ≤325 mg/day) and other antiepileptic drug treatments[4]



VPA should be avoided in patients of childbearing age whenever possible unless attempts to control seizures with other AEDs have failed. If VPA is used, lowest possible dose is recommended, viz. ≤700 mg daily[3]

Note: The risk is dose-dependent but a threshold dose below which no risk exists cannot be established based on the available data

Current evidence of teratogenicity risks of AEDs in WOCBP ▶

Prenatal exposure to AEDs is associated with lower IQ

- Children with prenatal exposure to AEDs are associated with lower verbal IQ, compared with no AED exposure[5]
- Among the AEDs, VPA has the strongest data demonstrating poor cognitive outcome, with those exposed to higher VPA dosages faring worse[5]
- Compared to other AEDs, VPA is associated with lower IQ at 3 years of age (no difference in IQ was seen with VPA doses less than 1000 mg per day)[6]

	CBZ	LTG	PHT	VPA
Mean IQ (95% CI)	98 (95–102)	101 (98–104)	99 (94–104)	**92** (88–97)
P-value	0.04	0.009	0.04	

Adapted from Baker GA, et al. *Neurology* 2015;84:382–390

- Higher dose of VPA is associated with poorer IQ while lower dose of VPA (<800 mg daily) is not associated with reduced IQ at 6 years of age[7]

Compared with controls:

IQ	
VPA >800 mg daily	9.7 points lower
VPA ≤800 mg daily	no difference
LTG, CBZ	no difference
Need for educational intervention	
VPA >800 mg daily	8.0-fold
VPA ≤800 mg daily	5.9-fold
Maternal epilepsy on no AED	3.9-fold

Note: The risk seems to be dose-dependent but a threshold dose below which no risk exists cannot be established based on the available data

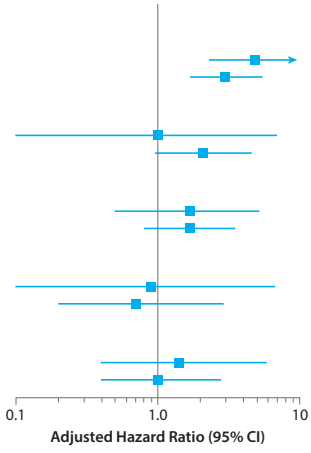
Current evidence of teratogenicity risks of AEDs in WOCBP ▶

Foetal exposure to AEDs is associated with a risk of autism

- Foetal exposure to AEDs has been associated with neurobehavioural problems, particularly autism spectrum disorder (ASD)[8]
- Children whose mothers were exposed to VPA in combination with other AEDs are at greatest risk of autism but the risk is dose-dependent[8]
- Exposure to VPA in utero was shown to increase the risk for ASD by three-fold and childhood autism by five-fold, compared with those not exposed to VPA[9]

ASD and childhood autism in offspring of mother who used AEDs as monotherapy during pregnancy versus offspring of women who did not use the individual AED[9]

	No.		Adjusted Hazard Ratio (95% CI)
	Unexposed	Exposed	
Valproate			
Total	655 107	388	
Childhood autism	2058	7	4.9 (2.3-10.3)
Autism spectrum disorder	5423	12	3.0 (1.7-5.4)
Oxcarbazepine			
Total	655 205	321	
Childhood autism	2064	1	1.0 (0.1-6.9)
Autism spectrum disorder	5427	7	2.1 (0.96-4.6)
Lamotrigine			
Total	654 747	647	
Childhood autism	2062	4	1.7 (0.5-5.2)
Autism spectrum disorder	5426	8	1.7 (0.8-3.5)
Clonazepam			
Total	655 233	269	
Childhood autism	2063	2	0.9 (0.1-6.7)
Autism spectrum disorder	5431	3	0.7 (0.2-2.9)
Carbamazepine			
Total	655 153	386	
Childhood autism	2065	2	1.4 (0.4-5.8)
Autism spectrum disorder	5433	4	1.0 (0.4-2.8)



Adapted from Christensen J, et al. *JAMA* 2013;309:1696–1703

There was no statistically significant effect of dose on the risk of ASD or childhood autism

Contraindications and strengthened warnings on VPA use ▶

- In May 2018, the European Commission endorsed the new measures recommended by the European Medicines Agency (EMA) Pharmacovigilance Risk Assessment Committee (PRAC) strengthening previous restrictions on use of VPA along with the set-up of Pregnancy Prevention Programme[10]
- VPA may be initiated in girls and WOCBP only if the conditions of VPA Pregnancy Prevention Program (outlined below) are fulfilled[11]

The prescriber must ensure that:

- Individual circumstances should be evaluated in each case, involving the patient in the discussion, to guarantee her engagement, discuss therapeutic options and ensure her understanding of the risks and the measures needed to minimize the risks
- The potential for pregnancy is assessed for all female patients
- The patient has understood and acknowledged the risks of congenital malformations and neurodevelopmental disorders including the magnitude of these risks for children exposed to VPA in utero
- The patient understands the need to undergo pregnancy testing prior to initiation of treatment and during treatment, as needed
- The patient is counselled regarding contraception, and that the patient is capable of complying with the need to use effective contraception, without interruption during the entire duration of treatment with VPA
- The patient understands the need for regular (at least annual) review of treatment by a specialist experienced in the management of epilepsy
- The patient understands the need to consult her physician as soon as she is planning pregnancy to ensure timely discussion and switching to alternative treatment options prior to conception and before contraception is discontinued
- The patient understands the need to urgently consult her physician in case of pregnancy
- The patient has received the Patient Guide
- The patient has acknowledged that she has understood the hazards and necessary precautions associated with the use of VPA (Annual Risk Acknowledgement Form)

Risk-benefit analysis in treatment considerations ▶

- In general, discontinuation or withdrawal of AEDs during pregnancy may lead to[12]:
  - Increase seizure risk
  - Risk to baby: foetal intracranial haemorrhage, transient foetal bradycardia
  - Miscarriage
  - Trauma
  - SUDEP (dose reduction due to teratogenicity concerns and changes in drug clearance may also increase the risk for SUDEP[13])
- Withdrawal of VPA or switch from VPA to another AED has been shown to have a higher probability of experiencing GTCS during pregnancy, compared with those who continued treatment with VPA[14]

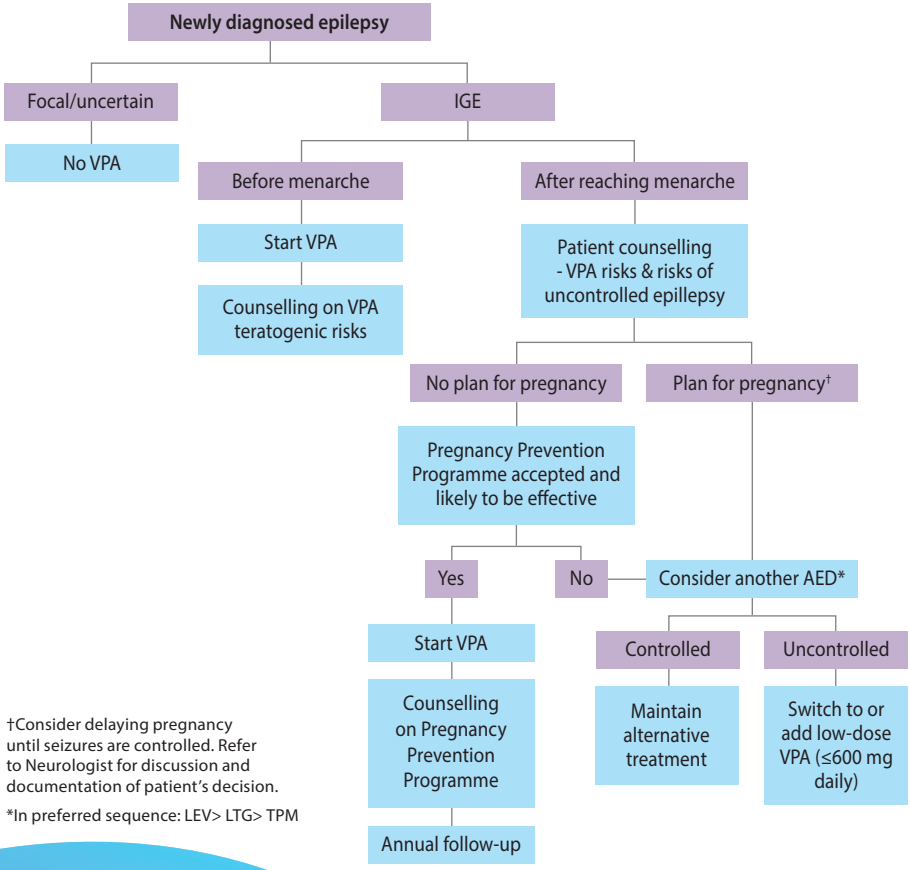
Proportion of women with GTCS during whole pregnancy	
VPA withdrawn	**33.2% [31/93]**
VPA switched	**28.6% [11/38]**
VPA continue	**16.3% [257/1,580]**

Results above were obtained from the EURAP observational international registry of AEDs and pregnancy to assess changes in seizure control and subsequent AED changes in women who underwent attempts to withdraw VPA during pregnancy[14]

Expert opinion on the use of VPA for epilepsy treatment in WOCBP ▶

Newly diagnosed epilepsy where VPA is likely more effective than alternative AEDs

- Epilepsy types most likely to benefit from VPA: IGE (juvenile myoclonic epilepsy, childhood absence epilepsy, juvenile absence epilepsy or other epilepsy syndromes, GTCS alone), Dravet syndrome and Lennox-Gastaut syndrome



†Consider delaying pregnancy until seizures are controlled. Refer to Neurologist for discussion and documentation of patient's decision.

*In preferred sequence: LEV> LTG> TPM

Expert opinion on the use of VPA for epilepsy treatment in WOCBP ▶

Newly diagnosed epilepsy where VPA is likely more effective than alternative AEDs (continued)

Patient counselling tips:

- VPA should generally not be used for treatment of focal epilepsies
- Counsel patients on the risk of VPA treatment (teratogenicity, autism, lower IQ) and the risk of uncontrolled epilepsy (trauma, SUDEP, psychosocial impact)
- WOCBP who continue treatment with VPA should be on effective contraception or otherwise ensure that unplanned pregnancies are avoided
- Refer to specialist (physicians [optional], O&G) for follow-up

General rules when prescribing VPA[11]

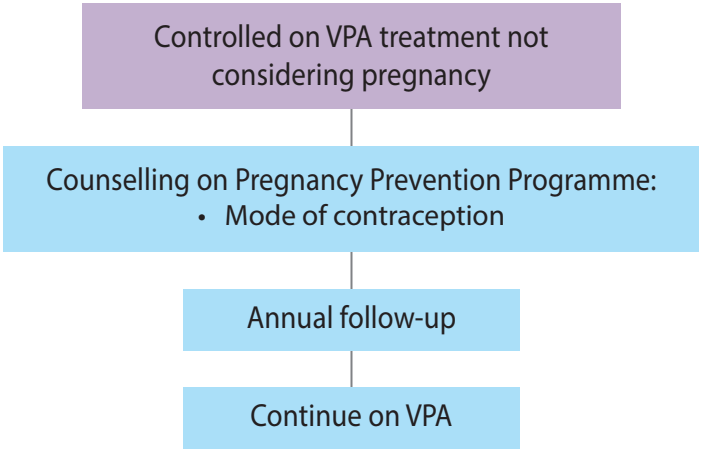
- Initiate VPA only if there is no suitable alternative treatment
- Explain to your patient the risks related to VPA when used in pregnancy
- Explain to your patient that the use of effective contraception without interruption during the entire duration of treatment with VPA is mandatory
- Tell your patient to contact you immediately if she thinks she might be pregnant or becomes pregnant

What is IGE?[15]

- IGE constitutes one-third of all epilepsies
- IGE manifests with typical absences, myoclonic jerks and generalized tonic-clonic seizures, alone or in varying combinations and severity
- Most syndromes of IGE start in childhood or adolescence, but some have an adult onset
- Seizures often precipitated by hyperventilation, sleep deprivation and/or intermittent photic stimulation

Expert opinion on the use of VPA for epilepsy treatment in WOCBP ▶

Patients controlled on VPA treatment not considering pregnancy



Patient counselling tips:

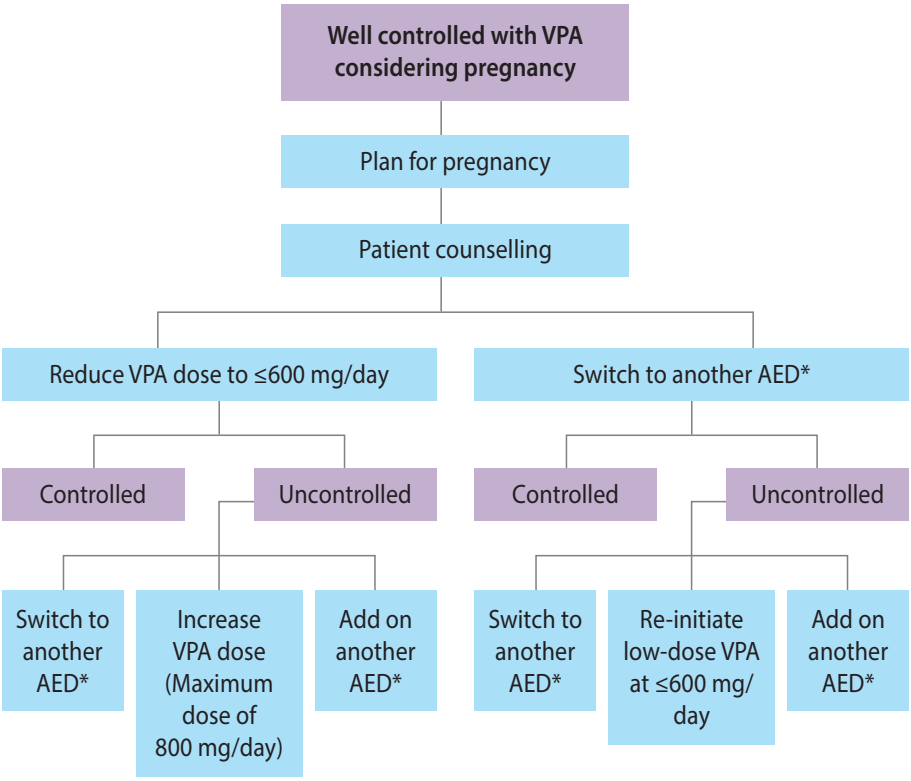
- Counsel patients on the risk of VPA
- WOCBP who continue treatment with VPA should be on effective contraception or otherwise ensure that unplanned pregnancies are avoided
- Refer to specialist (physicians [optional], O&G) for annual follow-up

General rules when prescribing VPA[11]

- Reassess at each visit whether treatment with VPA is still appropriate for your patient
- Remind the patient at each visit of the risks related to VPA when used in pregnancy
- Remind your patient at each visit that effective contraception without interruption during the entire duration of treatment with VPA is mandatory
- Remind your patient at each visit to contact you immediately if she thinks she might be pregnant or becomes pregnant

Expert opinion on the use of VPA for epilepsy treatment in WOCBP ▶

Patients controlled on VPA treatment considering future pregnancy



*In preferred sequence: LEV> LTG> TPM

Expert opinion on the use of VPA for epilepsy treatment in WOCBP ▶

Patients controlled on VPA treatment considering future pregnancy

Patient counselling tips:

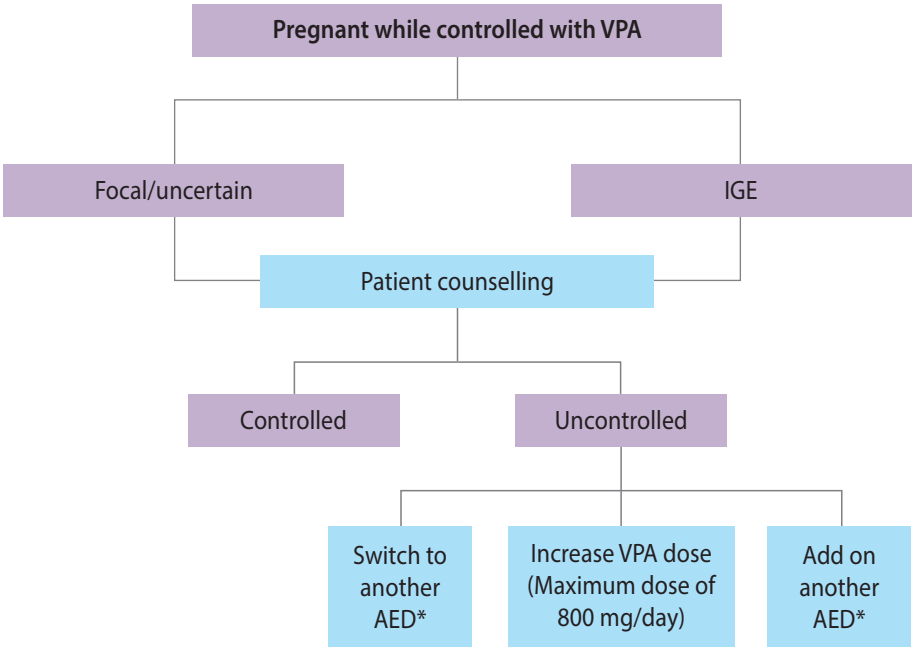
- Counsel patients on the risk of VPA treatment (teratogenicity, autism, lower IQ) and the risk of uncontrolled epilepsy (trauma, SUDEP, psychosocial impact)
- VPA can be continued when the patient and clinician agree that the benefits of staying on VPA outweigh the risks of withdrawal or switch to an alternative
- Take folic acid (5mg/day) pre-conception
- Refer to specialist (physicians [optional], O&G) for follow-up
- Discuss the importance of medication adherence
- Inform patients that majority of pregnancies have normal outcome regardless of drug therapy

General rules when prescribing VPA[11]

- Remind your patient of the risks related to VPA when used in pregnancy
- Remind your patient that switching takes time
- Explain to your patient that contraception should only be stopped after complete cessation of VPA

Expert opinion on the use of VPA for epilepsy treatment in WOCBP ▶

Patients well controlled on VPA treatment with unplanned pregnancy



*In preferred sequence: LEV> LTG> TPM

Expert opinion on the use of VPA for epilepsy treatment in WOCBP ▶

Patients well controlled on VPA treatment with unplanned pregnancy

General rules when prescribing VPA[11]

- Arrange an urgent consultation with your patient
- Explain why she should continue with her treatment until the date of the appointment
- Make sure your patient and her partner have understood the risks related to VPA and refer them to a specialist for further counselling

Patient counselling tips:

- Counsel patients on the risk of VPA treatment (teratogenicity, autism, lower IQ) and the risk of uncontrolled epilepsy (trauma, SUDEP, psychosocial impact)
- VPA can be continued when the patient and clinician agree that the benefits of staying on VPA outweigh the risks of withdrawal or switch to an alternative
- VPA should be prescribed at the lowest effective dose, when possible aiming at doses not exceeding 600 mg/day, although, at times, higher doses may be necessary to attain seizure control
- Take folic acid (5mg/day)
- Refer to specialist (physicians [optional], fetomaternal specialists, O&G) for follow-up
- Discuss the importance of medication adherence
- Inform patients that majority of pregnancies have normal outcome regardless of drug therapy

Postpartum counselling points:

- Advise the patient to continue AED postnatally
- It is safe to breastfeed while on VPA treatment
- Ensure mothers are well supported in the postnatal period to ensure triggers of seizure deterioration such as sleep deprivation, stress and pain are minimized
- Encourage mothers who are taking AEDs during pregnancy to breastfeed
- Discuss with the mother on postpartum safety advice and strategies
  - Nurse baby on the floor
  - Use very shallow baby baths
  - Lay the baby down if there is a warning (aura)
  - Bath baby with supervision
  - Avoid sleep deprivation and alcohol if possible

Contraception methods for women with epilepsy ▶

- WOCBP who are prescribed VPA must use effective contraception without interruption during the entire duration of treatment with VPA[11]
- During the entire duration of treatment with VPA, it is important that patients comply to an effective contraception – at least one effective method of contraception (preferably a user independent form, such as intra-uterine or implant) or two complementary forms of contraception including a barrier method[11]
- Contraception methods which are not user-dependent are preferred. For eg, Cu-IUD, levonorgestrel intra-uterine system or progesterone-only implant
- Individual circumstances should be evaluated in each case, when choosing contraception method involving patient in the discussion, to guarantee her engagement and compliance with the chosen measures[11]
- Even if she has amenorrhoea, she must follow all the advice on effective contraception[11]

Contraception methods for women with epilepsy ▶

Contraception methods	Example(s)	Failure rate* (%)	Note(s)
Copper intra-uterine device (Cu-IUD)[16,17]	Nova T® Cu 200 Ag	0.8	• Considered as a 'highly effective' method • If a woman using VPA has had unprotected intercourse, if all recent unprotected intercourse was within the last 5 days or she is within 5 days of the earliest likely date of ovulation, she should be offered a Cu-IUD, the most effective method of emergency contraception (if Cu-IUD is not suitable or acceptable, oral emergency contraception can be offered)
Levonorgestrel intra-uterine system[16,18]	Mirena® (levonogestrel)	0.2	• Considered as a 'highly effective' method • Can be used by women using VPA until age 55 years
Progesterone-only implant[16,19]	Implanon® NXT (etonogestrel)	0.5	• Contraceptive effectiveness not reduced by VPA • Avoid use of any medication that induces hepatic enzyme activity as this could reduce contraceptive effectiveness
Female sterilization[16]	-	0.5	Considered as a 'highly effective' method
Vasectomy[16]	-	0.15	-
Progestogen-only injectable depot medroxyprogesterone (DMPA)[3,16,20]	Depo-Provera® (medroxyprogesterone acetate)	6	• Despite concerns about achieving peak bone mineral density, use of DMPA by women under age 18 is acceptable if other methods have been discussed and considered unsuitable or unacceptable • IM Depo-Provera® at a dose of 150 mg should be given at a shorter interval (every 10 weeks instead of 12 weeks) if she is on enzyme-inducing AED • DMPA is generally avoided for women over 50 and for women over 40 with additional risk factors for osteoporosis • Use of additional contraceptive precautions such as condoms is recommended

*Percentage of women experiencing an unintended pregnancy within first year of typical use

Contraception methods for women with epilepsy ▶

Contraception methods	Example(s)	Failure rate* (%)	Note(s)
Combined hormonal contraception (CHC) including combined contraceptive pill, transdermal patch and vaginal ring[3,16,21–23]	*Combined contraceptive pill:* Mercilon® (desogestrel 150 mcg, ethinylestradiol 20 mcg), Loette® (levonorgestrel 100 mcg, ethinylestradiol 20 mcg) *Transdermal patch:* Evra® (norelgestromin 6 mg, ethinylestradiol 600 mcg) *Vaginal ring:* NuvaRing® (etonogestrel 11.7 mg, ethinylestradiol 2.7 mg)	9	• Ethinylestradiol (present in most combined contraceptive pills, combined transdermal patch and combined vaginal ring) may modestly reduce VPA levels • Use of additional contraceptive precautions such as condoms is recommended • There is an increased risk of oral contraceptive pill (OCP) failure with AEDs that induce hepatic microsomal enzymes • AEDs that are liver enzyme inducers which reduce the concentration of OCP include CBZ, PHT, phenobarbitone, OXC and TPM • AEDs that are safe to be used with OCP include gabapentin, LEV, LTG, tiagabine, VPA and zonisamide • If patient prefers to rely on OCP alone, at least 50 µg of oestradiol is recommended, as opposed to commonly available OCP that contains ≤35 µg of oestradiol
Progesterone-only pill (POP)[3,16,24,25]	Cerazette® (desogestrel), Escapelle® (levonorgestrel)	9	• Contraceptive effectiveness not reduced by VPA • The POP is not recommended as a reliable contraceptive in women taking enzyme-inducing AEDs • Use of additional contraceptive precautions such as condoms is recommended
Male condom[16]	-	18	-
Female diaphragm[16,26]	Caya® SILCS diaphragm	12	-
Fertility awareness-based methods[16]	-	24	-

*Percentage of women experiencing an unintended pregnancy within first year of typical use

Case scenario 1 ▶

WOCBP with unplanned pregnancy

YT is a 28-year-old woman with generalized epilepsy that is currently well controlled with VPA 800 mg daily for 4 years. She has just found out that she is at 8 weeks of gestation. She wants to know if VPA is safe during pregnancy. She has no other medical conditions and is not taking any other medication or supplement except folic acid 5 mg OD.

Recommendations

- YT should be carefully informed about the risk of teratogenicity
- Switching from VPA to another AED is generally not recommended during pregnancy since YT has good seizure control while on VPA
- YT should be advised to take 5 mg folic acid once daily until at least the end of first trimester to reduce the incidence of major congenital malformation

Rationale for recommendations

- Major congenital malformations occur between 4 and 8 weeks of gestation. Hence, at 8 weeks, if her baby were to develop any congenital malformation, it would have already taken place
- At a dose of 800 mg per day, the risk of major congenital malformations is low in any case. She is already well controlled on the current dose, so there is no need to change this dose or to add another drug
- A risk of lowered intelligence has not been found at doses or 800 mg or less

Summary

- If patient is well controlled, switching from VPA to another AED is generally not recommended during pregnancy in women of childbearing potential with unplanned pregnancy
- Normal vaginal delivery can be allowed as majority of women with epilepsy who are well controlled with VPA will proceed with uncomplicated labour and delivery

Case scenario 2 ▶

WOCBP not planning for pregnancy

JG, a 12-year-old girl diagnosed with idiopathic generalized epilepsy after she presented with absence seizures was started on VPA. She was well controlled on her current medication for the past year. During follow-up session, you informed her mother on the risks of VPA.

Recommendation

- JG should maintain on current medication if her epilepsy is well controlled

Rationale for recommendation

- The efficacy of VPA is superior to all other AEDs for the treatment of absence seizure

How would you inform JG and her mother on the risk of VPA?

Recommendations

- Assuming that JG has achieved menarche, both JG and her mother must be made aware of the risk of teratogenicity and developmental abnormalities to the baby in case she gets pregnant
- VPA also causes weight gain. Both JG and her mother should be made aware of the risks of other medical conditions as a result of obesity, such as hypertension, diabetes, hyperlipidaemia and polycystic ovarian syndrome

After several years, she is in a stable relationship and planning to get married but no plan for pregnancy yet.

Recommendations on how to counsel JG

- Both her mother and partner must be made aware of the risks of VPA
- If JG is going to be sexually active, a highly effective contraceptive method should be used or otherwise ensure that unplanned pregnancy can be avoided
- JG should not get pregnant until she is completely seizure-free and her AED is discontinued by her neurologist for at least 6 months
- If JG is worried about the risks of VPA intake on her baby in the future, this would be the best time to discuss a change to a 'safer' AED, such as LTG, TPM or LEV. However, she must be made aware of the lower efficacy of these alternatives, compared to VPA
- These alternatives are also not free of side effects. JG and her partner must be made aware of these side effects. For instance, patients on LEV may become moody and suffer from behavioural problems, while patients on TPM may complain of difficulty finding words when holding a conversation
- If she is happy to continue with the VPA, then all the precautions as mentioned above must be adhered to

Summary

- If patient is well controlled, maintaining VPA is generally recommended in WOCBP not planning for pregnancy
- Both WOCBP with epilepsy and her mother must be made aware of the risks of VPA should there be a plan to get pregnant
- If a WOCBP with epilepsy is planning to get pregnant in the future, she must be made aware that switching from VPA to a 'safer' AED with lower efficacy is also not free of risk

General considerations when switching or discontinuing VPA ▶

Issued by Task Force of Commission of European Affairs of International League Against Epilepsy (CEA-ILAE) and European Academy of Neurology (EAN)[11]:

- 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
- The switch of VPA 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 VPA. 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 VPA
- If, despite the known risks of VPA in pregnancy and after careful consideration of alternative treatment, in exceptional circumstances a pregnant woman (or a woman planning to become pregnant) must receive VPA for epilepsy:
  - There is no dose threshold considered to be without any risk. However, the risk of birth defects and developmental disorders is higher at greater doses
  - Use the lowest effective dose and divide the daily dose of VPA into several small doses to be taken throughout the day
  - The use of a prolonged release formulation may be preferable to other treatment formulations in order to avoid high peak plasma concentrations
  - All patients with a VPA exposed pregnancy and their partners should be referred to a Specialist

Conclusion ▶

- Despite the availability of many new AEDs in the past two decades, the overall outcomes in newly diagnosed epilepsy have not improved
- The goal of epilepsy treatment is freedom from seizures with as few treatment adverse effects as possible
- Initiate VPA only if there is no suitable alternative treatment
- VPA may be initiated at lowest effective dose possible (not exceeding 600 mg/day) in girls and WOCBP who are not considering pregnancy
- VPA can be continued when the patient and clinician agree that the benefits of staying on VPA outweigh the risks of withdrawal or switch to an alternative

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