QUESTION 35

A 22yo woman with primary generalised epilepsy presents for advice regarding a planned pregnancy. At age 16 years, she presented with a seizure following sleep deprivation and alcohol excess. She was commenced on phenytoin, but after two further seizures in similar circumstances she was changed to sodium valproate and has been seizure-free for three years. She seeks pre-conception advice regarding ongoing anticonvulsant therapy.

To have the best probability of a successful pregnancy, the patient should be advised to minimise provoking factors, take folate and:

A. Continue sodium valproate therapy  
B. Stop anticonvulsant therapy  
C. Change to carbamazepine therapy  
D. Change to topiramate therapy  
E. Change to clonazepam therapy

From therapeutic guidelines…

Types of epileptic seizures (Table 7.3)

<table>
<thead>
<tr>
<th>Generalised seizures</th>
<th>Partial seizures</th>
</tr>
</thead>
<tbody>
<tr>
<td>absence</td>
<td>simple partial</td>
</tr>
<tr>
<td>myoclonic</td>
<td>complex partial</td>
</tr>
<tr>
<td>tonic-clonic</td>
<td>secondarily generalised</td>
</tr>
<tr>
<td>tonic</td>
<td></td>
</tr>
<tr>
<td>atonic</td>
<td></td>
</tr>
</tbody>
</table>

Based on the International League Against Epilepsy classification of epileptic seizures.

Classification of epileptic syndromes (Box 7.1)

Generalised epilepsies

*Primary generalised (ie presumed genetic basis)*

- childhood absence epilepsy  
- juvenile absence epilepsy  
- juvenile myoclonic epilepsy  
- epilepsy with tonic-clonic seizures on awakening

*Symptomatic generalised (ie mostly associated with other neurological conditions)*

- West syndrome (infantile spasms)  
- Lennox-Gastaut syndrome

Partial epilepsies

- symptomatic (eg mesial temporal lobe epilepsy)  
- idiopathic (eg benign childhood epilepsy with centrotemporal spikes)
Epilepsies undetermined whether partial or generalised

- neonatal seizures
- tonic-clonic seizures (clinical and EEG findings do not permit classification as generalised or partial onset)

Special syndromes

- febrile seizures
- isolated seizure or status epilepticus
- metabolic and toxic induced seizures

Based on the International League Against Epilepsy classification of epileptic syndromes.

TREATMENT OF EPILEPSY

- Exclude non-epileptic causes such as breath-holding attacks, arrhythmias, pseudoseizures
- Classify type of epilepsy based on history, neurological exam, EEG and imaging
- Identify and avoid precipitants if possible (eg: drugs, sleep deprivation, alcohol withdrawal)

Single Seizure

- After a single seizure, only 30-50% of patients will have a recurrence
- Consider:
  - Symptoms (previous unrecognised seizures)
  - Signs (EEG or neuro abnormalities increase the risk of recurrence)
  - Seizure type (certain syndromes are more likely to be recurrent – eg: juvenile myoclonic epilepsy, partial seizures)
  - Age (elderly have higher risk of recurrence)
  - Patient wishes

- Lowest recurrence rates associated with normal EEG and examination, no identifiable cause for SZ or clear avoidable precipitant

Second Seizure

- Treatment usually indicated after 2 or more SZ in 6-12 month period
- About 80% of these pts will have recurrence
- Exception is if there is a clear avoidable precipitant
**Drug Choice**

<table>
<thead>
<tr>
<th>First Line</th>
<th>Second Line</th>
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</thead>
<tbody>
<tr>
<td><strong>Partial</strong></td>
<td></td>
</tr>
<tr>
<td>Carbamazepine &gt; valproate</td>
<td>Gabapentin, lamotrigine, levetiracetam, oxcarbazepine, phenobarbitone, phenytoin, pregabalin, tiagabine, topiramate</td>
</tr>
<tr>
<td><strong>Generalised tonic-clonic</strong></td>
<td></td>
</tr>
<tr>
<td>Valproate, lamotrigine</td>
<td>Carbamazepine, oxcarbazepine, phenobarbitone, phenytoin, topiramate</td>
</tr>
<tr>
<td><strong>Absence</strong></td>
<td></td>
</tr>
<tr>
<td>Valproate, ethosuximide</td>
<td>Clobazam, clonazepam, lamotrigine</td>
</tr>
<tr>
<td><strong>Myoclonic</strong></td>
<td></td>
</tr>
<tr>
<td>Valproate</td>
<td>Clobazam, clonazepam, phenobarbitone</td>
</tr>
<tr>
<td><strong>Infantile spasms</strong></td>
<td></td>
</tr>
<tr>
<td>Tetracosactrin (ACTH analogue), prednisolone</td>
<td>Clonazepam, nitrazepam, vigabatrin, valproate</td>
</tr>
<tr>
<td>Lennox-Gastaut syndrome</td>
<td></td>
</tr>
<tr>
<td>Valproate</td>
<td>Lamotrigine, topiramate, clonazepam</td>
</tr>
</tbody>
</table>

Infantile spasm (West syndrome) – usual onset 4 to 12 months. Brief sudden contractions of the head, neck and trunk. Characteristically spasms occur in runs and last several minutes. Hypsarrhythmia is typically seen on EEG but not essential for diagnosis.

Lennox-Gastaut syndrome – usually onset is 18 months to 3 years. Difficult to control. Characterised by multiple seizure types including tonic (especially nocturnal), myoclonic, atypical absence and tonic-clonic seizures.

Absence – Usual onset 4 to 9 years (childhood) or 10 to 15 years (juvenile). If infrequent, may not require treatment. 50% of patients will also have GTCS. Ethosuximide and valproate are equally effective for absence SZ but ethosuximide does not protect against GTCS. Continue treatment until EEG ceases to show 3 per second spike wave activity and no seizures have occurred for 2 years.

Myoclonic – avoid carbamazepine as it can worsen myoclonic and absence seizures. Also avoid gabapentin, pregabalin, oxcarbazepine and tiagabine.

**Treatment Withdrawal**

- May be considered after 2-3 years without SZ
- Slowly wean dose (over weeks to months)
- Good prognosis to remain SZ-free if history of few seizures, absence seizures only, younger age when SZ control achieved, normal neuro exam, no brain lesion

**Contraception**

- Several antiepileptics induce hepatic enzymes and increase metabolism of OCP
- High risk of contraceptive failure
- Carbamazepine, phenytoin, oxcarbazepine, barbiturates and topiramate

**Pregnancy**

- Consider withdrawal of treatment if SZ-free for >2 years
- Risk of congenital malformation, even if antiepileptics stopped once pregnancy confirmed
- All antiepileptics are potentially teratogenic, no one is safe
- If antiepileptics need to be continued, generally the choice is the agent that best controls the epilepsy at the lowest possible dose
- Should be offered counselling and pre-natal screening (AFP and U/S)
- Folic acid may have role in preventing neural tube defects (5mg daily for 3/12 before and after conception)
- Valproate = ADEC D
- Carbamazepine = ADEC D
- Topiramate = ADEC B3
- Clonazepam = ADEC C

This patient has not had a seizure for more than 3 years. Previous seizures were provoked. Treatment withdrawal prior to pregnancy is the best option for her.

Answer is B – stop anticonvulsant therapy
Category A
Drugs which have been taken by a large number of pregnant women and women of childbearing age without any proven increase in the frequency of malformations or other direct or indirect harmful effects on the fetus having been observed.

Category B1
Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals have not shown evidence of an increased occurrence of fetal damage. (Animal studies submitted in support of new drug applications must conform to the Australian Guidelines on the Registration of Drugs - Volume 1, Prescription and Other Specified Drug Products, 2nd edition.)

Category B2
Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals are inadequate or may be lacking, but available data show no evidence of an increased occurrence of fetal damage. (Animal studies submitted in support of new drug applications must conform to the Australian Guidelines on the Registration of Drugs - Volume 1, Prescription and Other Specified Drug Products, 2nd edition.)

Category B3
Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals have shown evidence of an increased occurrence of fetal damage, the significance of which is considered uncertain in humans. (Animal studies submitted in support of new drug applications must conform to the Australian Guidelines on the Registration of Drugs - Volume 1, Prescription and Other Specified Drug Products, 2nd edition.)

Category C
Drugs which, owing to their pharmacological effects, have caused or may be suspected of causing, harmful effects on the human fetus or neonate without causing malformations. These effects may be reversible. Accompanying texts should be consulted for further details.

Note that Category C in the Australian and Swedish Categorisations of Risk is a pharmacological effect category and differs from that in the FDA Categorization (where Category C indicates greater likelihood of risk than in B on the basis of adverse effects of any type in animal studies).

Category D
Drugs which have caused, are suspected to have caused or may be expected to cause, an increased incidence of human fetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects. Accompanying texts should be consulted for further details.

Category X
Drugs which have such a high risk of causing permanent damage to the fetus that they should not be used in pregnancy or when there is a possibility of pregnancy.