Valproate and Carbamazepine: still the go to first line agents

Neurology update

18th Nov 2015
Treatment of Epilepsy

- Counselling patient and family e.g. factual information, emergency management of seizures
- Treatment of underlying cause e.g. infection, cerebral tumour
- Avoid precipitating factors e.g. sleep deprivation, flashing lights
- Lifestyle constraints e.g. bathing, swimming, alcohol, driving, vocational
- Management of comorbidities e.g. educational, psychological, psychiatric, behavioural
- Antiepileptic drug therapy if indicated
- Special treatments for refractory epilepsies e.g. surgery, ketogenic diet, VNS
PHARMACOTHERAPY OF EPILEPSY:
The issues

• Is treatment justified? (likelihood of further seizures and its risks including SUDEP) vs (consequences, inconvenience, and risks of taking regular medication)

• **Which AED/what to start?**

• Risks associated AED treatment?

• How long should treatment be continued/When to stop?
Ideal AED

• Achieve complete seizure remission
• No adverse effects
Older AEDs

• Performance qualities
• Drug-drug interactions, and idiosyncrasies
• Side effect profiles, though undesirable, are more or less predictable, and physicians and patients face few surprises.
Older AEDs in infants

- CBZ & Phenytoin have unfavourable kinetics
  - CBZ dose is higher & should be given tid dosage
- Phenytoin –difficult to determine adequate dose
  - Slight change in dose may produce toxicity/subtherapeutic level
- Valproate hepatotoxicity
  - Increased below the age of 2 yrs
  - Polytherapy
  - Presence of associated psychomotor delay
  - Look for undiagnosed inherited metabolic diseases
Results: Patients carrying HLA-B*15:02 are at strongly increased risk for CBZ-induced Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN) in populations where HLA-B*15:02 is common, but not CBZ-induced hypersensitivity syndrome (HSS) or maculopapular exanthema (MPE). HLA-B*15:02-positive patients with CBZ-SJS/TEN have been reported from Asian countries only, including China, Thailand, Malaysia, and India. HLA-B*15:02 is rare among Caucasians or Japanese; no HLA-B*15:02-positive patients with CBZ-SJS/TEN have been reported so far in these groups. HLA-A*31:01-positive patients are at increased risk for CBZ-induced HSS and MPE, and possibly SJS/TEN and acute generalized exanthematous pustulosis (AGEP). This association has been shown in Caucasian, Japanese, Korean, Chinese, and patients of mixed origin; however, HLA-A*31:01 is common in most ethnic groups. Not all patients carrying either risk variant develop an HSR, resulting in a relatively low positive predictive value of the genetic tests.
Need for new AEDs

- 30% of patients continue to have seizures despite pharmacological treatment.
- The probability of seizure freedom declines rapidly after the failure of the first monotherapy.
- 14% seizure-free during treatment with a second or third drug.

Sillanpää M, Schmidt D. Brain. 2006;129:617–24
Kwan and Brodie. NEJM 2000
Properties of New AEDs

- Efficacious as monotherapy
- Adjunctive treatment of seizures
- Allow synergistic combination therapy
- Fewer adverse events (including idiosyncratic, teratogenic, and cognitive ones)
- Fewer pharmacokinetic drug interactions,
Efficacy of new AEDs

• The relative efficacy has not been established.
• New AED approvals are achieved by add-on trials of patients with refractory epilepsy.
• Most RCT’s on new drugs have been compared to placebo
• Long term adverse effects ??
• Severe persistent visual field constriction associated with vigabatrin. BMJ 1997
• Bluish discoloration with Retigabine
Vigabatrin White Matter Changes
Variables that affect initial AED selection

<table>
<thead>
<tr>
<th>AED-specific variables</th>
<th>Patient-specific variables</th>
<th>Nation-specific variables</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Seizure type or epilepsy syndrome specific efficacy or effectiveness</td>
<td>• Genetic background</td>
<td>• AED availability</td>
</tr>
<tr>
<td>• Dose-dependent adverse effects</td>
<td>• Age</td>
<td>• AED cost</td>
</tr>
<tr>
<td>• Idiosyncratic reactions</td>
<td>• Gender</td>
<td>• Insurance coverage</td>
</tr>
<tr>
<td>• Chronic toxicities</td>
<td>• Comedications</td>
<td></td>
</tr>
<tr>
<td>• Teratogenicity</td>
<td>• Comorbidities</td>
<td></td>
</tr>
<tr>
<td>• Carcinogenicity</td>
<td>• Insurance coverage</td>
<td></td>
</tr>
<tr>
<td>• Pharmacokinetcs</td>
<td>• Ability to swallow pills/tablets</td>
<td></td>
</tr>
<tr>
<td>• Interaction potential</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Formulations</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Major considerations in choosing an AED

- Type of seizure
- Type of epileptic syndrome
- Adverse effect profile
- Age & genetic background (pharmacogenomics)
- Ease of use (fast and easy dose titration)
- Specific co-morbidities
<table>
<thead>
<tr>
<th>Epilepsy syndrome</th>
<th>First-line AEDs</th>
<th>Adjunctive AEDs</th>
<th>Other AEDs that may be considered on referral to tertiary care</th>
<th>Do not offer AEDs (may worsen seizures)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Childhood absence epilepsy or other absence syndromes</td>
<td>Ethosuximide, Lamotrigine, Sodium valproate</td>
<td>Ethosuximide, Lamotrigine, Sodium valproate</td>
<td>Clobazam, Clonazepam, Levetiracetam, Topiramate, Zonisamide</td>
<td>Carbamazepine, Gabapentin, Oxcarbazepine, Phenytoin, Pregabalin, Tiagabine, Vigabatrin</td>
</tr>
<tr>
<td>Juvenile absence epilepsy or other absence syndromes</td>
<td>Ethosuximide, Lamotrigine, Sodium valproate</td>
<td>Ethosuximide, Lamotrigine, Sodium valproate</td>
<td>Clobazam, Clonazepam, Levetiracetam, Topiramate, Zonisamide</td>
<td>Carbamazepine, Gabapentin, Oxcarbazepine, Phenytoin, Pregabalin, Tiagabine, Vigabatrin</td>
</tr>
<tr>
<td>NICE</td>
<td>Lamotrigine\textsuperscript{a}</td>
<td>Lamotrigine\textsuperscript{a}</td>
<td>Clobazam\textsuperscript{a}</td>
<td>Carbamazepine</td>
</tr>
<tr>
<td>-------------------------------</td>
<td>---------------------------------</td>
<td>---------------------------------</td>
<td>------------------------------</td>
<td>-----------------</td>
</tr>
<tr>
<td>Juvenile myoclonic epilepsy</td>
<td>Levetiracetam\textsuperscript{a}</td>
<td>Levetiracetam</td>
<td>Clonazepam</td>
<td>Gabapentin</td>
</tr>
<tr>
<td></td>
<td>Sodium valproate</td>
<td>Sodium valproate</td>
<td>Zonisamide\textsuperscript{a}</td>
<td>Oxcarbazepine</td>
</tr>
<tr>
<td></td>
<td>Topiramate\textsuperscript{a}</td>
<td>Topiramate\textsuperscript{a}</td>
<td></td>
<td>Phenytoin</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Pregabalin</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Tiagabine</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Vigabatrin</td>
</tr>
<tr>
<td>Benign epilepsy with centrotemporal spikes</td>
<td>Carbamazepine\textsuperscript{a}</td>
<td>Carbamazepine\textsuperscript{a}</td>
<td>Eslicarbazepine acetate\textsuperscript{a}</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Lamotrigine\textsuperscript{a}</td>
<td>Clobazam\textsuperscript{a}</td>
<td>Lacosamide\textsuperscript{a}</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Levetiracetam\textsuperscript{a}</td>
<td>Gabapentin\textsuperscript{a}</td>
<td>Phenobarbital</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Oxcarbazepine\textsuperscript{a}</td>
<td>Lamotrigine\textsuperscript{a}</td>
<td>Phenytoin</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sodium valproate</td>
<td>Levetiracetam\textsuperscript{a}</td>
<td>Pregabalin\textsuperscript{a}</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Oxcarbazepine\textsuperscript{a}</td>
<td>Tiagabine\textsuperscript{a}</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sodium valproate</td>
<td>Vigabatrin\textsuperscript{a}</td>
<td></td>
</tr>
</tbody>
</table>
# AED options by seizure type

<table>
<thead>
<tr>
<th>Seizure type</th>
<th>First-line AEDs</th>
<th>Adjunctive AEDs</th>
<th>Other AEDs that may be considered on referral to tertiary care</th>
<th>Do not offer AEDs (may worsen seizures)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Generalised tonic–clonic</td>
<td>Carbamazepine</td>
<td></td>
<td>(If there are absence or myoclonic seizures, or if JME suspected)</td>
<td>Carbamazepine, Gabapentin, Oxcarbazepine, Phenytoin, Pregabalin, Tiagabine, Vigabatrin</td>
</tr>
<tr>
<td></td>
<td>Lamotrigine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Oxcarbazepine(^a)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sodium valproate</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tonic or atonic</td>
<td>Sodium valproate</td>
<td>Lamotrigine(^a)</td>
<td>Rufinamide(^a)</td>
<td>Carbamazepine, Gabapentin, Oxcarbazepine, Pregabalin, Tiagabine, Vigabatrin</td>
</tr>
</tbody>
</table>

\(^a\): Available in pediatric doses.
<table>
<thead>
<tr>
<th>Absence</th>
<th>Ethosuximide Lamotrigine&lt;br&gt;Sodium valproate</th>
<th>Ethosuximide Lamotrigine&lt;br&gt;Sodium valproate</th>
<th>Clobazam&lt;br&gt;Clonazepam&lt;br&gt;Levetiracetam&lt;br&gt;Topiramate&lt;br&gt;Zonisamide</th>
<th>Carbamazepine&lt;br&gt;Gabapentin&lt;br&gt;Oxcarbazepine&lt;br&gt;Phenytoin&lt;br&gt;Pregabalin&lt;br&gt;Tiagabine&lt;br&gt;Vigabatrin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myoclonic</td>
<td>Levetiracetam&lt;br&gt;Sodium valproate&lt;br&gt;Topiramate</td>
<td>Levetiracetam&lt;br&gt;Sodium valproate&lt;br&gt;Topiramate</td>
<td>Clobazam&lt;br&gt;Clonazepam&lt;br&gt;Piracetam&lt;br&gt;Zonisamide</td>
<td>Carbamazepine&lt;br&gt;Gabapentin&lt;br&gt;Oxcarbazepine&lt;br&gt;Phenytoin&lt;br&gt;Pregabalin&lt;br&gt;Tiagabine&lt;br&gt;Vigabatrin</td>
</tr>
<tr>
<td>Focal</td>
<td>Carbamazepine&lt;br&gt;Lamotrigine&lt;br&gt;Levetiracetam&lt;br&gt;Oxcarbazepine&lt;br&gt;Sodium valproate</td>
<td>Carbamazepine&lt;br&gt;Clobazam&lt;br&gt;Gabapentin&lt;br&gt;Lamotrigine&lt;br&gt;Levetiracetam&lt;br&gt;Oxcarbazepine&lt;br&gt;Sodium valproate&lt;br&gt;Topiramate</td>
<td>Eslicarbazepine acetate&lt;br&gt;Lacosamide&lt;br&gt;Phenobarbital&lt;br&gt;Phenytoin&lt;br&gt;Pregabalin&lt;br&gt;Tiagabine&lt;br&gt;Vigabatrin&lt;br&gt;Zonisamide</td>
<td></td>
</tr>
</tbody>
</table>
UK NICE guidelines for the use of new AED

• If established drugs have failed
  • Typically carbamazepine or valproate
• If most appropriate older drug is contraindicated
• If older drugs could interact with other medications
• If older drugs are already known to be poorly tolerated by the patient
• If patient is a woman of child bearing potential
SANAD study
Standard and New antiepileptic Drugs

- Unblinded RCT in hospital-based outpatient clinics in the UK
- Effectiveness of carbamazepine, gabapentin, lamotrigine, oxcarbazepine, or topiramate for treatment of partial epilepsy
SANAD STUDY

• Lamotrigine is clinically better than carbamazepine for time to treatment failure outcomes (better tolerated with similar efficacy)
SANAD STUDY

• Study of effectiveness of valproate, lamotrigine, or topiramate for generalised and unclassifiable epilepsy
SANAD STUDY

• Valproate is better tolerated than topiramate and more efficacious than lamotrigine, and should remain the drug of first choice for many patients with generalised and unclassified epilepsies.
Levetiracetam

- Compare the efficacy of levetiracetam and controlled-release carbamazepine (carbamazepine CR) in patients with newly diagnosed epilepsy.
- The 6-month seizure-freedom rate (73%) was almost the same for both drugs. Time to withdrawal was also almost identical.
- Fewer patients on levetiracetam (14.4%) discontinued treatment because of adverse events compared with carbamazepine CR (19.2%), although this difference did not reach statistical significance.

Levetiracetam

• KOMET study compared the efficacy of carbamazepine CR and extended-release sodium valproate (val-proate ER), as well as levetiracetam in patients with newly diagnosed epilepsy.

• Levetiracetam was not superior to either valproate ER or carbamazepine CR regarding the time to treatment withdrawal or time to first seizure.

Lamotrigine (Lamictal)

ADVANTAGES
- Minimal effect on other medications
- Works for all types of seizures
- Well tolerated
- Minimal sedation
- Probably safe in pregnancy
- Monotherapy
- Synergistic action with Valproate

DISADVANTAGES
- Rash if started quickly
  Must start slowly (~2 months to full dose)
- May worsen myoclonic seizures
- Insomnia, depression (rare)
Topiramate (Topamax)

ADVANTAGES

- Minimal interactions with other medications
- Probably works for all seizure types
- Sprinkle form
- Approved for monotherapy
- Weight loss
- Approved for migraine prevention

DISADVANTAGES

- Cognitive side effects
- 1-2% renal stones
- Hyperthermia
- Loss of appetite
- Glaucoma
Levetiracetam (Keppra)

**ADVANTAGES**
- No interactions
- Minimal liver metabolism
- Works for most seizure types
- Can start quickly-status epilepticus
- Well tolerated
- Neonatal seizures

**DISADVANTAGES**
- Behavioral/psych side effects
Oxcarbazepine (Trileptal)

As effective and better tolerated than Tegretol
Fewer interactions than Tegretol
Approved for first-line monotherapy (USA)

Not for all seizure types
Low sodium, esp if on diuretics also
Lessens effectiveness of birth control pill
Clobazam (Frisium)

• Advantages
  – Effective
  – Well tolerated
  – Once or twice daily
  – Dose-0.5-1mg/kg/day

• Disadvantages
  – Drowsiness
  – Unsteadiness
  – Rare
    • Behavior changes
Vigabatrin

**Advantages**
- High effectiveness for TSC infantile spasms
- Few significant drug interactions; exception is phenytoin
- Infrequent need for serum drug levels
- Low protein binding

**Disadvantages**
- Irreversible visual field defects
- White matter lesions
- High cost
Lacosamide (Vimpat)

- Licensed use: Focal onset seizures with or without secondary generalization (>16 years)
- ↑Slow inactivation of voltage gated sodium channels
- Pharmacodynamic interaction with CBZ, OXC and Phenytoin
- Adverse effects - dizziness, headache, balance and coordination disorder
- Increases PR interval, caution in patients with heart block
- Dosing <16yrs: 1.5mg/kg twice daily for a week followed by increments of 3mg/kg/day weekly intervals; max dose 12mg/kg/day
Perampanel

- Licensed use: Focal onset seizures with or without secondary generalization; must be in combination with two or more anti-epileptic drugs which includes one second-line adjunctive agent
- Non competitive antagonist of AMPA-type glutamate receptor; long half life
- Adverse effects: Somnolence, dizziness, ataxia, dysarthria, aggression, anxiety, weight gain
- Dosing >12 years: 2 mg once a day, at intervals of 2 weeks increase by 2mg, maintenance dose 4-8mg daily
Relative Efficacy and Tolerability of AEDs

- Levetiracetam
- Topiramate
- Vigabatrin
- Tiagabine
- Oxcarbazepine
- Lamotrigine
- Gabapentin
- Zonisamide

- Panayiotopoulos CP. Epileptic Syndromes and their Treatment, 2007
Case 1

• 10 month old with history of 3 vaccine proximate prolonged focal seizure referred to Neurologist
• Commenced on Levetiracetam by Paediatrician after the 2\textsuperscript{nd} seizure; didn’t stop the 3\textsuperscript{rd} seizure.
• Normal birth and development
• Normal MRI and EEG
• ? Next vaccination ?plan to prevent further seizures
Progress

• Intermittent prophylaxis with Clobazam for next vaccination
• 12 month vaccination-no seizures
• Further seizures triggered by intercurrent illness; Levetiracetam weaned off
• Regular Clobazam
• CGH array and EE gene panel requested
• VEEG- Commenced Valproate
Vaccinations in Dravet Syndrome

• *Effect of vaccination on onset and outcome of Dravet syndrome: a retrospective study*  
  [McIntosh, Lancet Neurology, 2010]
  
  – 40 patients with DS: Vaccine proximate (n=12), vaccine distant (n=28)
  – No difference in intellectual outcome, subsequent seizure type, or SCN1A mutation
  – Early seizure onset in vaccine proximate group (7.8 weeks)
Case 2

- 8 year old girl referred to specialist with staring spells
- EEG: number of episode captured with 3 Hz spike and wave pattern
Ethosuximide, Valproic Acid, and Lamotrigine in Childhood Absence Epilepsy

CONCLUSIONS
Ethosuximide and valproic acid are more effective than lamotrigine in the treatment of childhood absence epilepsy. Ethosuximide is associated with fewer adverse attentional effects. (ClinicalTrials.gov number, NCT00088452.)
Progress

- Ethosuximide: stomach upset and vomiting, whiny and sometimes aggressive
- Valproate: initial some improvement but then seizures recurred. Did not tolerate high doses (mood and behaviour).
- Lamotrigine- partially effective
- Lamotrigine+Valproate- effective
- Other options: Ketogenic diet, Topiramate, Acetazolamide
- Testing for glucose transporter gene mutation
<table>
<thead>
<tr>
<th>Combination</th>
</tr>
</thead>
<tbody>
<tr>
<td>VPA + LTG</td>
</tr>
<tr>
<td>GPN + VGB</td>
</tr>
<tr>
<td>OXC + LEV</td>
</tr>
<tr>
<td>OXC + GPN</td>
</tr>
<tr>
<td>OXC + TGB</td>
</tr>
<tr>
<td>LEV + TPM</td>
</tr>
<tr>
<td>LEV + CBZ</td>
</tr>
<tr>
<td>LTG + TPM</td>
</tr>
<tr>
<td>TGB + GPN</td>
</tr>
<tr>
<td>VPA + PHT</td>
</tr>
<tr>
<td>VPA + ESX</td>
</tr>
<tr>
<td>VPA + GPN</td>
</tr>
<tr>
<td>VPA + TPM</td>
</tr>
<tr>
<td>VPA + VGB</td>
</tr>
<tr>
<td>CBZ + GPN</td>
</tr>
<tr>
<td>CBZ + TPM</td>
</tr>
<tr>
<td>OXC + TPM</td>
</tr>
<tr>
<td>PHB + TPM</td>
</tr>
<tr>
<td>TPM + FBM</td>
</tr>
</tbody>
</table>

"Table 2 Possible synergistic antiepileptic drug combinations (based on preclinical data, mainly from studies using isobolography)"

Mechanisms of action of antiepileptic drugs: the search for synergy
Carl E. Stafstrom
Conclusion

• “Review seizure type/syndrome, age, ethnicity, gender, other meds. All of the AEDs are pretty much the same in efficacy, but how effective a particular drug is going to be for a particular patient has to be evaluated in terms of side-effect issues such as cognitive issues, behaviour, organ toxicity and weight”

• I still prefer Carbamazepine/Valproate as the first line drugs
Which Drug Next? My Approach

• CBZ failure in structural focal epilepsy - swap to OXC if some benefit from CBZ or LEV or add LEV or TPM or CLB depending on patient factors and urgency
• for CBZ failure in genetic focal epilepsy - change to VPA or LEV - add CLB or LEV if still problematic
• for VPA failure in genetic generalised epilepsy – consider ESM if absences or add LTG,
  - add LTG, then CLB (if tonic clonic seizures)
  - if overweight, change VPA to LTG or TPM or LEV
• for VPA failure in structural generalised epilepsy
  - add LTG, TPM, CLB, PHT
Referral to tertiary centre-NICE

- the epilepsy is not controlled with medication within 2 years
- Management is unsuccessful after 2 drugs
- The child is aged under 2 years
- Child experiences unacceptable side effects from medication
- There is a unilateral structural lesion
- There is psychological and/or psychiatric comorbidity
- There is diagnostic doubt as to the nature of the seizures and/or seizure syndrome.
Other resources

• The Epilepsy Prescriber's guide to AEDs - P. Patsalos and B Bourgeois
• MIMS
• PENNSW
• BNF Children
Case 3

• 4 year old Asian girl presented with a long lasting afebrile seizure in the night followed by transient weakness of the right arm and leg.
• Parents recollect a similar but brief seizure 1 month back.
• Awake EEG: consistent with BCECTS
• Would you commence treatment?
• Which AED?
Valproate was considered but declined by parents. Commenced Levetiracteam.

No seizures but parents noted worsening of language abilities.

Lack of speech, poor comprehension and no expression.

Retrospectively, during the child’s third year of life, the parents had been noticing insidious regression of speech abilities with aggressive behaviour.
• Hearing test was normal
• Sleep EEG: focal spike-wave activity in bilateral centro-temporal region becoming diffuse and continuous in sleep.
• MRI Brain: Normal
• Next medication?
• Course of steroids

• Within 3 months, EEG tracing was back to normal and child showed major improvement in speech (both comprehension and expressive).
AEDs: Teratogenesis

- increased risk of most types of birth defects with all AEDs (greatest risk with VPA ~10% and polytherapy)
- small risk increase with epilepsy and no AEDs (1%)
- VPA risk reduced to other AEDs if <800mg/day
- specific associations reported:
  - neural tube defects and hypospadius (VPA, CBZ)
  - congenital heart defects (PHT, VPA, PB)
  - craniofacial abnormalities (PHT, VPA, PB, PRM)
  - genitourinary defects (PHT, VPA, PB)
  - skeletal defects (VPA)
- effects of AEDs (esp. VPA) in pregnancy on cognition in later childhood
- later childhood effects of AEDs on apoptosis and neuroreceptor expression in developing brain
  (Vinten J, Neurology 2005; Meador KJ, NEJM 2009)