Rational Polytherapy: Current status:

- No Class I/II evidence supporting its clinical value
- Clinical evidence (class III/IV) for specific mechanistic combinations
  - Better efficacy by combination of Na-channel blockers
  - (CBZ, LTG) vs multiple actions (VPA, TPM)
  - Treated refractory TLE (74% vs 7%, p<0.02; Norman & Brodie, 2002)
  - VPA/ESM in absence epilepsy (Yossi, 1983)
  - VPA/LTG: 56% vs CBZ/LT = 71%, 84% (91%); Brodie et al., 1997
  - VPA/LTG: SF in 30% of pts failed to mono- and polytherapy (Raber et al., 1990)
- Experimental evidence of synergism (isobolographic analysis)
  - LTG/TMP ALEV/TMP: most effective combination (Lusardi et al., 2002, 2006)

Rational Polytherapy: Pharmacokinetic:

- Useful interaction: VPA + LTG
- No relevant interaction: LEV + VPA + OXC
- Negative interaction: VPA + CBZ
  - LTG + PHB
  - TPM + PB, PRM

Rational Polytherapy: Pharmacodynamic:

- Problem: very little evidence in humans
  - Probably synergy: VPA + LTG
    - VPA + ESM (in absence)
  - No synergy: VPA + CBZ
  - Increased toxicity: Barbiturates + Benzodiazepines
  - VPA + TPM?
  - LEV + TPM?

Rational Polytherapy: Summary:

- Theoretically attractive and rational mode therapy
- Major mode of AEDs therapy for refractory epilepsy
- Available experimental and clinical evidence of synergistic pharmacodynamic interactions support the concept of (i) mechanistic combination approach, (ii) avoiding combination of drugs having similar AE-profile and pharmacokinetic interactions
- No class I/II evidence for differences in efficacy and safety between monotherapy and polytherapy -> Need future controlled trial

Adjunctive therapy for Refractory Level A evidence seizures:

<table>
<thead>
<tr>
<th>Drug</th>
<th>Adult</th>
<th>Pediatric</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gabapentin</td>
<td>YES</td>
<td>YES</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>YES</td>
<td>YES</td>
</tr>
<tr>
<td>Topiramate</td>
<td>YES</td>
<td>YES</td>
</tr>
<tr>
<td>Tiagabine</td>
<td>YES</td>
<td>?</td>
</tr>
<tr>
<td>Oxcarbazepine</td>
<td>YES</td>
<td>YES</td>
</tr>
<tr>
<td>Levetiracetam</td>
<td>YES</td>
<td>?</td>
</tr>
<tr>
<td>Zonisamide</td>
<td>YES</td>
<td>?</td>
</tr>
</tbody>
</table>

Refactory seizures:

Adjunctive therapy in adults with partial seizures:
- Gabapentin, lamotrigine, topiramate, tiagabine, oxcarbazepine, levetiracetam, zonisamide, and pregabalin (all have level A recommendations)
- For children with partial seizures, gabapentin, lamotrigine, topiramate, and oxcarbazepine can be used (recommendation A)
- Insufficient evidence in children to recommend tiagabine, or zonisamide for the aforementioned conditions.
**Adjunctive therapy for Refractory generalized seizures:**

<table>
<thead>
<tr>
<th>Idiopathic</th>
<th>Symptomatic (Lennox-Gastaut)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gabapentin</td>
<td>NO (1200 mg)</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>yes</td>
</tr>
<tr>
<td>Topiramate</td>
<td>YES (GTCC)</td>
</tr>
<tr>
<td>Tiagabine</td>
<td>?</td>
</tr>
<tr>
<td>Oxcarbazepine</td>
<td>?</td>
</tr>
<tr>
<td>Levetiracetam</td>
<td>?</td>
</tr>
<tr>
<td>Zonisamide</td>
<td>?</td>
</tr>
</tbody>
</table>

**Sequential AEDs therapy:***

1. **Initial AEDs Therapy**
   - Monotherapy, based on the concept of optimized individual patient-oriented therapy
   - Advantages of choosing broad-spectrum AEDs
     - Allow single-drug treatment in epilepsy syndrome with multiple Sz types
     - Allow effective treatment of Szs, if the Dx of Sz types/epilepsy syndromes has not been drawn firmly
     - Low risk of exacerbating seizures

**Aggravation of Seizure by AEDs:***

- Well-known phenomenon occurring in ~10% of AED therapy
- Risk factors:
  - multiple types of seizure
  - polytherpy or overtreatment
  - inappropriate choice of drugs
  - narrow spectrum drugs; GABAergic drugs Na+ channel blockers

**Aggravation of Seizure by AEDs:***

<table>
<thead>
<tr>
<th>AED</th>
<th>Seizure Type Exacerbated</th>
</tr>
</thead>
<tbody>
<tr>
<td>BDZ</td>
<td>Tonic seizures in Lennox–Gastaut syndrome</td>
</tr>
<tr>
<td>CRZ</td>
<td>Absence, atomic, myoclonic</td>
</tr>
<tr>
<td>OCZ</td>
<td>Absence, atomic, myoclonic</td>
</tr>
<tr>
<td>PTZ</td>
<td>Absence, atomic, myoclonic</td>
</tr>
<tr>
<td>LTG</td>
<td>Myoclonic, atypical absence</td>
</tr>
<tr>
<td>TGB</td>
<td>Absence</td>
</tr>
</tbody>
</table>

BDZ = benzodiazepines; CRZ = carbamazepine; OCZ = oxcarbazepine; PTZ = phenytoin; PB = phenobarbital; LTG = lamotrigine; TGB = tiagabine.

**Epilepsy management: Summary:***

- Dx of Epilepsy tx type, syndrome
- Initial monotherapy
- 2nd drug therapy (austin vs done)
- Sr retention (> 50%)
- Sr retention (< 50%)
- Surgical resection
- Post-op seizure

- Dx of Epilepsy tx type, syndrome
- Initial monotherapy
- 2nd drug therapy (austin vs done)
- Sr retention (> 50%)
- Sr retention (< 50%)
- Surgical resection
- Post-op seizure

- Dx of Epilepsy tx type, syndrome
- Initial monotherapy
- 2nd drug therapy (austin vs done)
- Sr retention (> 50%)
- Sr retention (< 50%)
- Surgical resection
- Post-op seizure

- Dx of Epilepsy tx type, syndrome
- Initial monotherapy
- 2nd drug therapy (austin vs done)
- Sr retention (> 50%)
- Sr retention (< 50%)
- Surgical resection
- Post-op seizure

**Epilepsy and Pregnancy:***

- Most pregnancies in epileptic mothers produce normal children
- Fetal anomalies (up to 10% of pregnancies) are multifactorial
  - Drug effects
  - Consequences of the mother’s underlying diseases
  - Consequence of maternal seizures during pregnancy
- All antiepileptic drugs carry teratogenic risks
Effects on pregnancy on epilepsy
- Risk of increased seizures (low if compliance maintained, doses adjusted upward to maintain free levels)
- Risk of seizures during delivery (impaired absorption, sleep deprivation, exhaustion)
- Effects of epilepsy on pregnancy
  - Genetic factors in some cases
  - Risks of convulsive seizures
  - Risks of AEDs

Effects of epilepsy on pregnancy
- Gene.c factors in some cases
- Risks of convulsive seizures
- Risks of AEDs

Most available data on risk of AEDs comes from pregnancy registries.
Main outcome variable of most registries are major congenital malformations (MCM)
MCM = malformation that affects physiological function or requires surgery
Neural tube defects
Cardiac defects
Genitourinary defects
Drugs
MCMs are more common with AED exposure
MCM risk in general population 1.6-2.1%
MCM risk with AED monotherapy 4.5% (OR 2.6)
MCM risk with Polytherapy 8.6% (OR 5.1)

Risk of fetal malformation is increased two fold to three fold
Prenatal diagnosis should be discussed
Seizures may be deleterious to the fetus
Adequate folate should be ensured (at least 1 mg/day)
Monotherapy should be used if possible, with the lowest effective dose

96% of pregnancies in mothers with epilepsy produce normal children
Spontaneous abortions and pre-term birth more common in women with epilepsy
Increased rate of fetal malformations associated with antiepileptic drug exposure
Seizures during pregnancy may be harmful
Tonic-clonic seizures associated with intracranial hemorrhage, fetal bradycardia and lower IQ in children
Status associated with increased fetal and maternal mortality in some studies
Insufficient data on non-convulsive seizures

Valproate consistently associated with poorer outcomes
MCM rate with valproate monotherapy 6.2-13.2% across 5 registries
Most studies show dose-related increase in risk with doses > 1000mg/day
Polytherapy regimens including valproate also substantially increased risk of MCM
Valproate associated with lower IQ in exposed children
Phenobarbital probably also poses higher risk of MCM
compared with other monotherapy regimens.

MCM rate similar among other studied AEDs in monotherapy, but not enough data to show significant difference between them
Levetiracetam
Early data promising (0% in monotherapy, 2.7% in polytx)
Carbamazepine (2.2-3.9%)
Substantial data available, relatively good track record
Lamotrigine (2.4-4.4%)
Increased risk (1.4%) with doses > 400/day
Gabapentin (0-3.2%)
Topiramate (0-6.8%)
Zonisamide, Phenytoin
No substantial data on monotherapy

MCM rate in early pregnancy and in early second trimester:
Levetiracetam
Early data promising (0% in monotherapy, 2.7% in polytx)
Carbamazepine (2.2-3.9%)
Substantial data available, relatively good track record
Lamotrigine (2.4-4.4%)
Increased risk (1.4%) with doses > 400/day
Gabapentin (0-3.2%)
Topiramate (0-6.8%)
Zonisamide, Phenytoin
No substantial data on monotherapy

MCM rate similar among other studied AEDs in monotherapy, but not enough data to show significant difference between them
Levetiracetam
Early data promising (0% in monotherapy, 2.7% in polytx)
Carbamazepine (2.2-3.9%)
Substantial data available, relatively good track record
Lamotrigine (2.4-4.4%)
Increased risk (1.4%) with doses > 400/day
Gabapentin (0-3.2%)
Topiramate (0-6.8%)
Zonisamide, Phenytoin
No substantial data on monotherapy

MCM rate similar among other studied AEDs in monotherapy, but not enough data to show significant difference between them
Levetiracetam
Early data promising (0% in monotherapy, 2.7% in polytx)
Carbamazepine (2.2-3.9%)
Substantial data available, relatively good track record
Lamotrigine (2.4-4.4%)
Increased risk (1.4%) with doses > 400/day
Gabapentin (0-3.2%)
Topiramate (0-6.8%)
Zonisamide, Phenytoin
No substantial data on monotherapy
Epilepsy and Pregnancy

Guideline

- Education
  - Most women with epilepsy have normal children
  - Risk of fetal malformations is increased
  - AED teratogenicity is related to exposure in the first trimester of pregnancy
  - Planning should begin well before pregnancy
  - Seizures may be deleterious to the fetus
  - Compliance with AED treatment is important
  - Prenatal diagnosis of fetal malformations is possible

- Before pregnancy
  - Attempt AED monotherapy with lowest effective dose
  - Consider switching AEDs prior to pregnancy, particularly if on valproate
  - Establish baseline therapeutic levels
  - Folate supplementation
    - At least 1mg/day for women of childbearing age
    - 4mg/day if planning pregnancy or at risk for pregnancy

- During pregnancy
  - Monitor AED dose requirements to maximize seizure control
  - Particularly with lamotrigine (levels fall > 50% and az increase)
  - Also increased clearance of levetiracetam, oxcarbazepine, phenobarbital and phenytoin
  - Continue folate supplementation
  - High-risk OB care, consider prenatal diagnosis of malformations
  - Vit K (10 mg/day orally) starting at 36 weeks

- Breast feeding
  - Breastfeeding should be encouraged unless clear risk posed
  - Probably safe:
    - Carbamazepine
    - Phenytoin
    - Valproate
    - Lamotrigine
  - “Use with caution” in lactating women:
    - Primidone
    - Phenytoin
    - Phenobarbital
    - Ethosuximide

Epilepsy in Elderly

Considering in choosing AEDs

- Milder epilepsy
- More adverse effects
  - More susceptible to cognitive side effects
  - More susceptible to ataxia and falls
  - More prone to hyponatremia
  - Drug/Drug interactions

- Seizure freedom at 2 years
  - <40 years old: 32%
  - 40-65 years old: 22%
  - >65 years old: 62%

VA Co-op 2003
Epilepsy in Elderly
ADR: (PHT, CBZ, PB, FRM)

- Withdrawal rate due to adverse effects
  - <40 years old 33%
  - 40-65 years old 49%
  - > 65 years old 64%

VA Co-op 2003

Epilepsy in Elderly
Pharmacologic problem

- Reduced hepatic clearance
- Reduced renal clearance
- Reduced protein binding
- Increased pharmacodynamic sensitivity
- Taking multiple medications

Epilepsy in Elderly
Pharmacologic problem

- 80% with epilepsy ≥65 years old prescribed phenytoin

Veterans Administration database
Fiscal Year 1999

Epilepsy in Elderly
Expert consensus guide: Treatment

- "Medically stable elderly man or woman"
- How would you rate these drugs? (scored 1-9)
  - Lamotrigine 8.5 ± 0.9
  - Levetiracetam 8.0 ± 0.9
  - Gabapentin 6.9 ± 2.0
  - Carbamazepine 6.8 ± 1.4
  - Ocarbazepine 6.7 ± 1.6
  - Topiramate 5.9 ± 1.5
  - Valproate 5.9 ± 1.6
  - Zonisamide 5.9 ± 1.7
  - Pregabalin 5.7 ± 1.9
  - Phenytoin 5.4 ± 1.9

Survey done 2004
Karceski et al 2005

Epilepsy in Elderly
Lamotrigine and Carbazamoxepine

Newly diagnosed elderly
  - Retention at 168 days
    - LTG 71%
  - CBZ 45%
  - p < 0.001

Brodin, Epilepsy Research 1999

Epilepsy in Elderly
New Onset Epilepsy in the Elderly

- retention at 1 year
  - Carbamazepine 36.6% *
  - Gabapentin 49.2%
  - Lamotrigine 57.9%

- CBZ vs LMG 0.0003
- CBZ vs GPN 0.01
- GPN vs LMG 0.10

VA Co-op. 2003
<table>
<thead>
<tr>
<th>Epilepsy in Elderly</th>
<th>Recommendation AEDs</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>First Line</strong></td>
<td><strong>Second Line</strong></td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>Phenytoin</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>Carbamazepine</td>
</tr>
<tr>
<td>Levetiracetam</td>
<td>Oxcarbazepine</td>
</tr>
<tr>
<td>Topiramate</td>
<td>Valproate</td>
</tr>
<tr>
<td>Zonisamide</td>
<td>Phenobarbital</td>
</tr>
</tbody>
</table>