Optimizing therapy of seizures in children and adolescents with developmental disabilities

Young Hoon Kim, MD
Department of Pediatrics,
College of Medicine, Catholic University of Korea
Goals in treatment

• No seizures, no adverse effects
• Patients’ QoL can be significantly improved by minimizing both seizures and adverse effects of AEDs.
• Reduction in polypharmacy and restriction of the use of sedative AEDs
• Choice of AED
  - incidence of epilepsy
  - type of seizures
  - common comorbidities (intellectual, motor, psychiatric, social)
  - chronic side effects of AEDs
Mental retardation (MR)

- Disability with significant limitations in both intellectual functioning and adaptive behavior
- Occurring before age 18 years
- About 3% of the general population
- 21% (IQ > 50) vs 50% (IQ < 50)
- 26% of MR have epilepsy
- 38% of active epilepsy have MR
- More severe MR, earlier start of epilepsy
# Epilepsy in children with CP

<table>
<thead>
<tr>
<th>Reference</th>
<th>Class</th>
<th>N</th>
<th>Types of cerebral palsy</th>
<th>% Patients with epilepsy</th>
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<tr>
<td>Murphy et al., 1993</td>
<td>I</td>
<td>204</td>
<td>M</td>
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<td>von Wendt et al., 1985</td>
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<td>Miller and Cala, 1989</td>
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<td>Zafeiriou et al., 1999</td>
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<td>Hadjipanayis et al., 1997</td>
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<td>Al-Sulaiman, 2001</td>
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<td>151</td>
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<td>Kwong et al., 1998</td>
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<td>Taudorf et al., 1984</td>
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<td>Senbil et al., 2002</td>
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<td>M</td>
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<td>Cohen and Duffner, 1981</td>
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<td>52</td>
<td>H</td>
<td>58</td>
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<td>Total</td>
<td></td>
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M = mixed; A = ataxic; H = hemiplegic.
Autistic spectrum disorder

- Multiple etiologies from chromosomal abnormalities to birth injury
- One-third of ASD have epilepsy
- Most commonly MR
- EEG abnormalities more commonly
- Forty percent of ASD live in large residential facilities have epilepsy
Psychiatric and behavioral comorbidities

- Common and often poorly characterized and diagnosed
- Diagnostic challenges in the use of DSM criteria
- Irritability and agitation may be signs of depression
- Seven times more common
- Both underestimations due to lack of recognition and overtreatment
Diagnosis of epilepsy

- Both over- and under- diagnosed
- Generalized seizure usually correctly
- Brief staring spells often overlooked
- Repetitive self-stimulating behaviors as partial seizures
- Inability to self-report and qualifications of multiple observers
- Require a full work-up
- All neuroimaging
- CCTV-EEG
Types of seizures

- No single seizure type
- Most symptomatic epilepsy with partial and/or secondarily generalized seizures
- In Sunder's series of 250 MR and/or I/DD 65%
- Positive correlation between motor disability and severity of epilepsy
- 37% Lennox–Gastaut syndrome
- 26% symptomatic generalized epilepsy
- 23% symptomatic partial epilepsy
- Fractures and/or ongoing head injury
- Mortality of 1/200 per year owing to SUDEP
AEDs

- Helpful without exacerbating seizures are VPA, LTG, TPM, ZS M, and LVT
- FBM is clearly effective in Lennox–Gastaut
- Key is to prevent polypharmacy—two medications and, at the maximum, three AEDs during conversion
- New AED is tried in partially controlled patients
- Taper and remove one of the failed AEDs
- Maximize one established AED and slowly taper one failed AED
- Rectal diazepam or oral lorazepam/midazolam is necessary
- Available in suspension, sprinkle, tablet, extended release, and IV formulations
- In future, other preparations of benzodiazepines, e.g. sublingual or intranasal
Drug-drug interactions

- Drug–drug interactions are a common source of difficulties
- Result of AED polypharmacy and many other medications
- Avoidance of AEDs that have significant P450-inducing properties (PHT, CBZ, PHB, OXC)
- All its attendant medical problems such as hypertension, hypercholesterolemia, vascular disease, type II diabetes, and osteoporosis
- The P450-inducing agents lower serum concentrations of some statins, SSRIs, and some calcium channel blockers
- Age-related osteoporosis, by reducing active vitamin D and calcium absorption.
Therapeutic levels of an AEDs

- Preexisting gait and coordination difficulties owing to CP may decompensate with low levels of sodium channel blockers, including PHT, CBZ, LTG, and OXC.
- Pre-existing cognitive dysfunction and/or behavioral problems resulting from their intellectual disability may worsen with those AEDs that effect neuronal excitability, such as PHB, benzodiazepines, TPM, GBP, ZSM, and LVT.
- Concept of total drug load important.
- Two AEDs that potentiate GABA function may produce significant sedative, cognitive, and behavioral effects at a low therapeutic dose.
- Chronic exposure to AEDs effects on bone, connective tissue, and cardiovascular system.
<table>
<thead>
<tr>
<th>AED</th>
<th>Behavioral effects</th>
<th>Psychiatric side effect</th>
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<tr>
<td></td>
<td>Negative B</td>
<td>Positive B</td>
</tr>
<tr>
<td>PHB</td>
<td>+++</td>
<td>-</td>
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<tr>
<td>Benzodiazepine</td>
<td>+++</td>
<td>-</td>
</tr>
<tr>
<td>GBP</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>VGB</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>CBZ</td>
<td>+</td>
<td>+++</td>
</tr>
<tr>
<td>ESX</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>LTG</td>
<td>+</td>
<td>+++</td>
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<tr>
<td>OXC</td>
<td>+</td>
<td>-</td>
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<tr>
<td>PHT</td>
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<tr>
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<td>ZNS</td>
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<tr>
<td>TPM</td>
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<td>+</td>
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<tr>
<td>LVT</td>
<td>+</td>
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</table>
Working mechanism of AEDs and cognitive profile

Still unknown, but it appears that

1. Sodium channel drugs (PHT, CBZ, LTG, and OXC) → less likely associated with cognitive AE

2. Gabergic drugs (PHB, benzodiazepines, TPM, GBP, VGB, and TGB). → higher risk for cognitive AE

3. Anti-glutamatergic drugs (TPM, FBM)
   → more associated with learning and memory

4. LVT → binds to a synaptic vesicle SV2A
   → influences release of some neurotransmitters
Relative cognitive effects of AEDs

CBZ = PHT
PHT = VPA
PB > CBZ, PHT, VPA
GBP < CBZ
LTG < CBZ
TPM >> VPA
### Clinical recommendations

<table>
<thead>
<tr>
<th>Condition</th>
<th>Recommendations</th>
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<tr>
<td>For patients with no active behavioral or psychiatric problems</td>
<td>For patients with behavioral or psychiatric comorbidities under therapy</td>
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<td>Monotherapy</td>
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<td>Consider AEDs without a GABAergic MOA</td>
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<td>Adjunctive therapy</td>
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<tr>
<td>If patient is already on a GABAergic AED, consider AEDs without a GABAergic MOA</td>
<td>Consider AEDs without a GABAergic MOA</td>
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<tr>
<td></td>
<td>Consider AEDs that do not induce P450 enzymes</td>
</tr>
</tbody>
</table>
Adverse effects of AEDs

• Express drug-induced dizziness as resisting activities and increased irritability
• Patient taking CBZ who becomes ataxic, with nausea and vomiting when treated with EM or other mycin derivatives.
• Cosmetic effects, AED-associated bone disease, peripheral neuropathies, connective tissue disorders, and weight gain
• Already predisposed to osteoporosis because of low levels of weight-bearing activity, lack of sun exposure, and inadequate calcium intake
• Calcium and vitamin D supplements, bone density measurements, and appropriate medical management
QoL

- No seizures, no side effects and improved QoL
- QoL includes seizure frequency, severity, post-ictal state and adverse effects
- Aberrant Behavior Checklist (ABC), alertness scale, QoL interview for residents with epilepsy (QOLIE) and the Liverpool Quality of Life questionnaire
- Yearly for a well-controlled patient and at least biannually for a poorly-controlled patient
- Communication among the multidisciplinary team is crucial for success
Quality of life assessment: lamotrigine vs. conventional AEDs

QOLIE-31 Assessment
Polytherapy

• Polytherapy for best treatment results is not true
• Polytherapy should be strongly avoided
• A reduction of three or more AEDs to one or two is successful with improvements in seizure frequency, adverse effects, and measured QoL
• Monotherapy, even in this difficult-to-control population
• Reductions in the use of sedative AEDs, such as PB and benzodiazepines, has positive effects on behavior and alertness without worsening of seizures.
• Complete withdrawal of AEDs is possible in well-controlled patient for a number of years and is worth trying
Safety

- Increased risk for seizure-related morbidity (particularly fractures) and mortality
- Tonic–clonic, myoclonic, and atonic seizures have a two- to threefold risk for death
- Causes of death include seizures, drowning, status epilepticus, pulmonary aspiration, and SUDEP
- Threefold higher mortality rate
- Those with three or more of disabilities were at the highest risk for death
- Epilepsy and psychopathology are independent variables that increase the risk for injury in the MR population.
Conclusions

• Care of the I/DD patient is both challenging and rewarding
• Seizure type, severity, chronicity of epilepsy, comorbidities, susceptibility to adverse effects, drug–drug interactions, and drug formulations
• Reduction in polypharmacy is an achievable goal with a resulting improved QoL
• Our society will be judged by the compassionate care of the least fortunate among us.
Thank you for attention !!!