Strategies for studying cognitive and behavioral effects of antiepileptic drugs

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Disclaimer

The opinions expressed in this presentation are my own and not necessarily those of the Agency. They are based on my experience as a clinical reviewer with the Division of Neurology Products (DNP), CDER, FDA.
What is Epilepsy?

• Not a specific disease

• Heterogeneous group of disorders (the epilepsies) which each produce a tendency to have recurrent seizures
What is a seizure?

A seizure is an occasional, sudden, excessive discharge of cortical neurons that disrupts ongoing cortical function.

The clinical manifestation may be convulsive or nonconvulsive.
Seizure types

I. Partial (Focal, Local) Seizures

II. Generalized Seizures (Primarily Generalized)
Seizure Types

I. Partial (Focal, Local) Seizures
   - Simple partial (no alteration of consciousness)
   - Complex partial (alteration of consciousness)
   - Secondarily generalized

II. Generalized Seizures (Primarily Generalized)
   - Absence
   - Myoclonic
   - Tonic Clonic
Seizure Etiologies

- In general, the partial (focal, local) seizures and secondarily generalized seizures are caused by hypoxic/ischemic injury, brain malformation or focal cortical dysplasia, tumor, infection, trauma.

- In general, the (primarily) generalized seizures are genetically determined.
Epileptic Patients and Neurocognitive/Behavioral Assessment

- A heterogeneous population
- Most epileptic patients have normal intelligence and many have above normal intelligence.
- As a total population, epileptic patients have impaired cognitive abilities compared to a population of age-matched, education-matched healthy subjects even if the epileptic patients are not treated with antiepileptic drugs.
Why do epileptic patients have neurocognitive impairments?

- Underlying etiology of the seizures causes both seizures and neurocognitive impairments
- Seizures cause neurocognitive impairments
- Psychosocial effects of having epilepsy
- Effects of antiepileptic drugs (AEDs)
Seizures causing neurocognitive impairment

- Age of onset of the seizures: critical age-dependent neurodevelopmental stages disrupted?
- Frequency of seizures
- Duration of seizures
- Severity of the seizures
- Mechanism of the seizure: interictal, intraictal, and postictal neurophysiologic dysfunction
- Cumulative cortical damage caused by seizures
Goal of Antiepileptic Drug Therapy

Eliminate the seizures with the fewest adverse effects from the antiepileptic drugs.
AEDs produce neurocognitive adverse effects

- Antiepileptic drugs work by a variety of mechanisms.
- All AEDs reduce “neuronal irritability” and thus will likely also interfere with the physiologic neuronal excitability involved in developmental synaptic growth and connectivity during infancy/childhood and in ongoing cognitive function at any age.
AEDs produce neurocognitive adverse effects

- Usually the neurocognitive adverse effects are slight as detectable by neuropsychological testing when AEDS are used as monotherapy in standard therapeutic range
- The reduction in seizure frequency and severity produced by the AEDs may improve cognition more than the AEDs impair cognition
AEDs produce neurocognitive adverse effects

- Many patients require dosage/blood levels of antiepileptic drugs above the “standard” therapeutic levels
- Many patients require multiple AEDs
- Balance of risk vs. benefit for the individual patient
How do we currently study the neurocognitive adverse effects of antiepileptic drugs?

- Nonclinical studies
- Clinical trials for short-term adverse effects
- Clinical open-label studies for long-term adverse effects
Studying neurocognitive adverse effects of the AEDs

Nonclinical Studies (pre- and postnatal development)

• Conducted to assess potential developmental neurotoxicity including the pre- and postnatal development study

• Usually conducted in rats which are exposed to a drug throughout gestation and lactation, then evaluated as adults in a battery of neurobehavioral screening tests that assess long-term effects on various measures of sensory-motor and cognitive function.
Studying neurocognitive adverse effects of the AEDs

Nonclinical Studies (Juvenile animal studies)
When a drug is being developed for a pediatric patient population, juvenile animal studies are conducted in which animals are directly dosed during a developmental period corresponding to that during which pediatric patients would be treated and a number of neurological and neurobehavioral endpoints are assessed.
Nonclinical: Juvenile animal studies (continued)

These juvenile animal studies include the same kinds of measures of sensory-motor and cognitive function as used in the pre- and postnatal development study and, in addition, a detailed neurohistopathology examination focused on alterations indicative of developmental insult such as, for example, neuronal apoptotic changes.
Nonclinical Studies (continued)

These studies can provide important information about the potential for long-term effects of drugs on neurobehavioral development, since such assessment cannot be obtained in clinical trials.
Studying short-term neurocognitive adverse effects of the AEDs: Clinical trials

Most Phase 3 AED clinical trials for efficacy and safety have some measures of cognitive function and behavior as secondary endpoints.

Randomized, double-blind, placebo-controlled

No agreement as to which specific assessment tools to use these trials.
Studying long-term neurocognitive adverse effects of the AEDs: Clinical trials

- Open-label long-term observational studies of neurocognitive adverse effects of the AEDs

- Typically 6 months to 12 months of observations
Many published clinical studies of cognitive effects of marketed AEDs

Shortcomings reviewed by Kimford Meador
Chapter 92: Cognitive effects of epilepsy and antiepileptic medications
Experimental design problems

• Subject selection bias: not randomly assigned to treatment groups or adequately matched

• Nonequivalence of clinical variables: not controlling for AED blood levels or seizure frequency

• Nonequivalence of dependent measures: did treatment groups perform similarly on dependent measures prior to treatment?
Shortcomings studies of cognitive effects of AEDs reviewed by Kimford Meador

Other Design Issues:

• Sample size: often not based on any statistical power calculation
• Selecting the meaningful test assessment: (e.g., verbal memory, attention, performance)
• Test-retest effects
• Statistical analysis and interpretation issues
• Determining the clinical significance of a statistically significant finding
Neurocognitive Adverse Effects are Likely Most Important in Childhood

- Even slight adverse cognitive effects of AEDs may have a more severe cumulative effect when given over many years of therapy.
- The developing nervous system may be more vulnerable to adverse neurodevelopmental effects from modification of neuronal excitability by AEDs.
Possible future approaches to neurocognitive adverse event assessment

- Agreement on certain assessments tools to be used in all studies to allow some cross-study comparisons
- More enlightened choice of other assessments tools tailored to the specific AED or epileptic syndrome being studied
- To be discussed this afternoon
Back up