University Health System Guidelines for the Management of Epilepsy and the Use of Antiepileptic Medications

Due to the recent introduction of new antiepileptic drugs (AEDs) to the market and rising concerns over the cost of managing patients with epilepsy, we would like to update the UHS Clinical Pathways/Guidelines documents for the management of epilepsy and AED use. The Guidelines are summarized in the slide presentation at the end of this discussion. These Guidelines reflect the general approach taken by most comprehensive epilepsy centers in the United States for treating partial or generalized epilepsy.

New Terminology

Traditionally, the FDA has approved AEDs for specific types of seizures, such as partial or generalized seizures. Partial seizures include simple partial, complex partial, and secondary generalized tonic-clonic seizures (GTCS). Generalized seizure types include absence, myoclonic, tonic, atonic, or GTCS. Chronic AED therapies are indicated primarily for people with repeated unprovoked seizures, or epilepsy. People with epilepsy may have several seizure types. A person with localization-related epilepsy, may have simple, complex and secondary GTCS. A person with generalized epilepsy, specifically juvenile myoclonic epilepsy (JME), may have absence, myoclonic and GTCS. More recently, some antiepileptic medications have been approved for the treatment of specific epilepsy syndromes, such as JME or Lennox-Gastaut syndrome.

First-line Monotherapy Drugs for Partial Seizures

The first-line AEDs for partial seizures are carbamazepine (CBZ), phenytoin (PHT), and oxcarbazepine (OXC). These medications are generally well tolerated and have well-documented efficacy in the treatment of all partial seizures. These medications can be used by primary care physicians for the treatment of newly-diagnosed partial seizures. However, certain restrictions apply to UHS prescriptions:

- Phenytoin (PHT) is an inexpensive medication, which is easy to load, but difficult to maintain. Levels can fluctuate dramatically in a given patient, especially in the very young and the elderly. People with medically refractory epilepsy should be on the brand name Dilantin® in order to assure optimal blood levels.
- Due to carbamazepine’s success, several competing formulations are available. Patients with a good response to CBZ but side effects due to the peak levels or breakthrough seizures with low trough levels may benefit from Carbatrol® (CBT). CBT has proven to be an extremely dependable slow-release formulation of carbamazepine requiring only twice daily dosing. Please note that the type of intolerance to CBZ must be stated on the prescription for CBT.
- OXC also requires that the type of intolerance to CBZ must be stated on the prescription.
Alternate Monotherapy Drugs for Partial Seizures

Some AEDs that were traditionally used as the first-line treatment of partial seizures, have become second-line due to either their lower efficacy in controlling simple partial seizures or to their adverse side effect profile. These medications include phenobarbital (PB), primidone (PRM), valproic acid (VPA), and felbamate (FBM). Currently, these medications are commonly added to the primary agent as an adjunctive therapy, and less frequently used as monotherapy. Other AEDs have been approved by the FDA as alternative monotherapies based upon efficacy studies showing equivalence to the first-line agents. Lamotrigine (LTG) has been recently approved for alternate monotherapy and levetiracetam (LVT) may soon be approved for this purpose.

Common or clinically significant side effects and other considerations are as follows:

- LTG is associated with a high incidence of rash, as well as Stevens-Johnson syndrome, and needs to be titrated slowly.
- Patients may become sedated or depressed on PB/PRM.
- Weight gain on VPA is a major concern in our local indigent population.
- Due to substantial risk of aplastic anemia and/or liver failure with felbamate, national guidelines were drafted for initiation of therapy, including monthly blood counts and metabolic profiles. Use of this drug is restricted to the Neurology Service.
- Initiation of therapy with LVT is restricted to the Neurology Service.

Adjunctive Drugs for Partial Seizures

The next line of AEDs for localization-related epilepsy have been designed to be adjunctive agents for the treatment of partial seizures. These include levetiracetam (LVT), gabapentin (GBP), clonazepam (CLN), topiramate (TPM), zonisamide (ZNS), pregabalin (PRG) and tiagabine (TGB). These medications are added when patients are not controlled by one of the other primary agents in monotherapy. Although these medications have not been compared to each other in double-blinded, randomized trials, PRG, LVT and TPM may be superior in their efficacy compared to the other agents. However, TPM’s use is limited by side effects, such as worsening depression, sedation, or less frequently, nephrolithiasis. PRG can cause weight gain and CNS toxicity. However, because of its biochemical similarity and improved efficacy and bioavailability, PRG is replacing GBP. Levetiracetam is easy to titrate and well-tolerated overall and has become the second-best-selling AED in the U.S. after PHT. TGB also has a relatively low side-effect profile but has limited usefulness because of CNS toxicity and AED interactions. ZNS is one of the better tolerated AEDs with respect to sedation or psychiatric side effects, but can cause nephrolithiasis.

In general, only two AEDs are implemented at any given time. Occasionally, while patients are undergoing changes of primary or adjuvant agents, they may be on three medications simultaneously. Side effects are more severe with every additional agent, whereas there is little improvement of efficacy.
**Drugs for Generalized Seizures**

Primary generalized seizures tend to be more responsive to AEDs than partial seizures. Ethosuximide (ETS) is indicated for the treatment of people with absence seizures without generalized tonic-clonic seizures, whereas CLN is approved for the treatment of myoclonic seizures and LVT for the treatment of myoclonic seizures in JME. Both TPM and LVT are approved for the treatment of primary GTCS. While VPA was never FDA-approved for generalized seizure types, it is still widely used as a primary agent. FBM and LTG were approved as adjunctive agents for symptomatic generalized epilepsy, while ZNS is frequently used off-label as an adjunctive agent.

While almost all medications useful for the treatment of secondary or partial-onset GTCS can be used for primary GTCS, many of these medications (PHT, CBZ, OXC) may not control other seizure types and even aggravate absence and myoclonic seizures.

These guidelines reflect the current standard of care for epilepsy patients in comprehensive epilepsy centers in the United States.

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Strategies for Managing Newly Diagnosed Epilepsy

- Newly Diagnosed Epilepsy
  - First Monotherapy
    - Seizure Free
  - Second Monotherapy
    - Seizure Free
  - Refractory
    - Rational Polypharmacy
    - Surgical Assessment*

*For partial seizures.
Adapted from Brodie, Kwan. CNS Drugs. 2001;15:1-12.
1<sup>st</sup> & 2<sup>nd</sup> Line Monotherapy for Partial Seizures

- **Carbamazepine** (200-2000 mg/day)
  - Generic
  - Tegretol
  - Carbatrol
  - Tegretol XR (Not on UHS formulary)
- **Phenytoin** (100-800 mg/day)
- **Oxcarbazepine** (300 – 3000 mg/day)
Alternate Monotherapies

- Lamotrigine (50-800 mg/day)
- Valproic Acid (500-3000 mg/day)
- Phenobarbital (30-300 mg/day)
- Primidone (100-2000 mg/day)
- Felbamate (300-3600 mg/day)
- Levetiracetam (soon to be approved, 500-4000 mg/day)
Adjunctive agents for Partial Seizures

- Topiramate (50-800 mg/day)
- Tiagabine (4-48 mg/day)
- Pregabalin (150-600 mg/day)
- Clonazepam (0.5-8 mg/day)
- Zonisamide (100-800 mg/day)
- Gabapentin (300-3600 mg/day)
1st & 2nd Line Monotherapies for Generalized Seizures

- Valproic Acid (GTCS, 500-3000 mg/day)
- Clonazepam (Myoclonic seizures, 0.5-8 mg/day)
- Ethosuximide (Absence seizures, 250-1500 mg/day)
Adjunctive or Alternate Therapies for Generalized Seizures

- Lamotrigine (Primary GTCS, 25-800 mg/day)
- Topiramate (Primary GTCS, 25-800 mg/day)
- Levetiracetam (Juvenile Myoclonic Epilepsy, 500-4000 mg/day)
- Felbamate (Lennox-Gastaut Syndrome, 300-3600 mg/day)
Rational Polypharmacy

- Combines medications with different mechanisms and pharmacokinetics
  - E.g. PHT and PRG, CBZ and LVT, LTG and ZNS
  - Maximize efficacy
  - Minimize side effects

- Avoid medications which may aggravate seizure types
  - CBZ, PHT, OXC, GBP and TGB may aggravate myoclonic and absence seizures
Primary Therapies for *Status Epilepticus*

- **Benzodiazepines**
  - Lorazepam (up to 0.05 - 0.1 mg/kg)
  - Diazepam (up to 20 mg)
  - Diazepam suppository (up to 20 mg)

- **Intravenous**
  - Fosphenytoin (“20 mg/kg”, 150 mg/min)

- **Alternates**
  - Valproate (20 mg/kg, <20 mg/min)
  - Phenobarbital (20 mg/kg, <150 mg/min)
Secondary Therapies for Medically Refractory Status Epilepticus

- Phenobarbital (LD 20 mg/kg, <100 mg/min)
- Pentobarbital (LD 5 mg/kg, MD 1-3 mg/kg/hr)
- Midazolam (LD 0.15mg/kg, MD 1-20 µg/kg/min)
- Propofol (LD 1-2 mg, MD 5 µg/kg/min)
**Intravenous Formulations**

- Effective in patients without oral access
- IV and oral doses “bioequivalent”
  - Lorazepam
  - Fosphenytoin
    - Oral phenytoin loads can be attempted in awake patients
  - Phenobarbital
  - Valproate
  - Levetiracetam (particularly in patients with liver damage)