Clinical pearls for chronic use of antiepileptic drugs

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ABSTRACT

Patients with various forms of epilepsy rely on antiepileptic medications to control and prevent seizures. This article describes some of the "clinical pearls" that should be considered when initiating, combining, or transitioning patients on epileptic medication therapy.

KEYWORDS

antiepileptic medication, seizure, epilepsy, monitoring, combination therapy

INTRODUCTION

Antiepileptic medications are extremely useful in controlling and preventing seizures in patients with various forms of epilepsy. However, these medications are not benign and require special considerations during use that may not be obvious to practitioners without much experience prescribing them. There are several "Clinical Pearls" that should be remembered when initiating, combining or transitioning patients on antiepileptic drug therapy that are common to most medications in the class.

Antiepileptic drugs (AEDs) can be divided into 2 generations based on differences in timing of development, metabolism and side effect profiles. The majority of the first generation AEDs are inducers, inhibitors and/or substrates of hepatic enzymes and lead to many significant drug interactions. In general, the second-generation antiepileptics are approved as add-on therapy for seizure control because it is unethical to do primary placebo-controlled trials in the United States when there are known effective medications. A few exceptions include oxcarbazepine and topiramate, which are both indicated for monotherapy, as well as lamotrigine which is indicated for conversion to monotherapy. Please see Table 1 for a list of approved agents.

TREAMENT INITIATION

Treatment initiation for patients with epilepsy should be patient specific and practitioners should consider an analysis of the risks and benefits associated with not treating epilepsy as well as with the drugs used for treatment. Adherence to AEDs is crucial to reduce the risk of morbidity and mortality from breakthrough seizures. If medications are deemed appropriate, there are certain strategies that have proven beneficial to reduce the risks of side effects and therefore improve adherence.

Table 1: Current, as of 2012, FDA Approved Antiepileptic Drugs (AEDs).

First Generation AEDs	Second Generation AEDs
Phenobarbital (Luminal ®)	Ezogabine (Potiga ®)
Primidone (Mysoline ®)	Felbamate (Felbatol ®)
Phenytoin (Dilantin ®, Phenytek ®)	Lamotrigine (Lamictal ®)
Fosphenytoin (Cerebex ®)	Gabapentin (Neurontin ®)
Ethosuximide (Zarontin ®)	Topiramate (Topamax ®)
Carbamazepine (Tegretol ®, Carbatrol ®)	Tiagabine (Gabitril ®)
Valproate (Depakote ®, Depacon ®)	Levetiracetam (Keppra ®)
	Oxcarbazepine (Trileptal ®)
	Zonisamide (Zonegran ®)
	Pregabalin (Lyrica ®)
	Vigabatrin (Sabril ®)
	Lacosamide (Vimpat ®)
	Rufinamide (Banzel ®)
	Clobazam (Onfi ®)
	Perampanel (Fycompa®)

Side effects common to all AEDs include central nervous system depression (dizziness, drowsiness, loss of coordination, etc.) and risk of hypersensitivity, mainly in the form of a maculopapular rash. Slow initial titration of AEDs may reduce the incidence and severity of both of these adverse effects and many others. Unless the patient is in an emergent situation, such as status epilepticus, rapid dose escalations of AEDs are unsafe and often cause more harm than benefit. Therefore, AEDs should be initiated one at a time with doses increased at intervals of 1 to 2 weeks. The optimal dose will vary in every patient and should be based on effective seizure control with minimal side effects. If adequate seizure control cannot be attained without precipitation of unmanageable side effects, then combination therapy should be considered.

COMBINATION AED THERAPY

The main idea for optimal use of multiple antiepileptics is to promote combination of complimentary mechanisms of action to elicit antiseizure activity. Often lower doses of each medication can be used to achieve seizure control

while simultaneously reducing side effects from each drug that could occur with higher doses. One example of a positive AED combination is lacosamide and levetiracetam. Lacosamide acts on sodium channels to enhance slow inactivation while levetiracetam's main mechanism is thought to involve binding SV2A proteins on synaptic vesicles of the brain.

Combination therapy is most often initiated due to the occurrence of adverse events or lack of seizure control on maximally tolerated doses of monotherapy. A second AED should be added at a low dose prior to any adjustments of the original AED and then slowly titrated up while simultaneously decreasing the dose of the original AED every 1 to 2 weeks. Along with reducing the risk of adverse effects and minimizing the frequency and severity of seizures, the slow titration helps to determine the optimal doses of the combination therapies at which patients are seizure-free and minimally affected by adverse events. However, the first combination of AED therapy does not always work. After a sufficient trial of 3 to 4 months, a different combination should be attempted with slow up-titration of the third drug and slow dose decreases of one or both of the other agents in play. In some instances, a faster escalation or taper of the dose is warranted to avert severe side effects without reducing seizure control.

Use of more than one AED can increase the risk of some side effects that are common to all AEDs. If a new side effect appears upon combination therapy that is known to be characteristic for only one of the agents, then decreasing or discontinuing that culprit is appropriate. However, if the side effect is anticipated from either drug, then it is often warranted to maintain the second agent added and decrease the original. Reasons for this strategy are based on previously mentioned ideas that the addition of the second drug only occurs when the first drug does not achieve adequate seizure control. For example, when lacosamide is added to other sodium channel-depressing agents, the incidence of CNS side effects such as dizziness is much more pronounced. Intuitively, the reaction of most clinicians is to decrease the lacosamide as the offending agent. However, in this case, the best management for the side effect, to prevent loss of seizure control, is to maintain the lacosamide and decrease the other sodium channel-blocking agent and the dizziness should remit.

In general, combination therapy is preferred for patients who experience side effects or do not achieve adequate seizure control on a single agent. However, in select patients that experience severe idiosyncratic reactions with a medication, such as a Stevens-Johnson Syndrome (SJS) with lamotrigine, the offending AED should be removed immediately, and a new agent should be initiated as monotherapy following the same gradual dose titration as previously described. Depending on the AED removed, a benzodiazepine may be useful as bridge therapy. Characteristic hypersensitivity reactions of AEDs include SJS and Toxic Epidermal Necrolysis (TEN), which usually present as an exfoliative rash with mouth sores, problems swallowing along with systemic complications (lymphadenopathy, nausea, vomiting, diarrhea and/or fever). These reactions are a medical emergency usually treated with immediate discontinuation of the offending agent and supportive care. Life threatening rash is seen more commonly with AEDs containing an aromatic ring. Cross-reactivity can potentially occur with phenobarbital, primidone, phenytoin, fosphenytoin, lamotrigine, carbamazepine, oxcarbazepine, zonisamide, lacosamide and rufinamide, but has not been reported for all of these drugs.

DRUG INTERACTIONS

Many antiepileptics have the risk of hepatic enzyme induction and/or inhibition that can result in altered drug activity for concomitant medications. As previously stated, the risks are more pronounced with first generation AEDs. Therefore, use of newer antiepileptics is warranted in patients with comorbid conditions that require other chronic drug therapy, but should be monitored for decreased efficacy of the AED and the other medications.

Since many AEDs have been associated with teratogenicity, it is important for women to be aware of these risks and how to manage their epilepsy during pregnancy. Valproic acid is often considered to have the highest teratogenic risk by association with neural tube defects and low IQs in the infant. Women who experience high peak concentrations or are using multiple AEDs simultaneously are likely to increase the risk of minor or major malformations in the developing fetus. Alternatively, experiencing a breakthrough seizure while pregnant poses a risk to the growing fetus. Women who become pregnant on an AED should continue epilepsy treatment, but follow up regularly with their neurologist or health care practitioner. Breast-feeding is encouraged for women on AEDs, but the newborn should be monitored for signs and symptoms of excessive sedation and failure to thrive.

It is often necessary for women of childbearing age to regularly engage in contraceptive practices. Oral contraceptives should be avoided in most women on

AEDs, especially first generation AEDs. This drug interaction has a significant risk for oral contraceptive failure and other options of birth control, such as medroxyprogesterone, intrauterine devices, diaphragms or condoms, should be considered. One caveat to use of medroxyprogesterone is that there is still a potential drug interaction with AEDs that can lead to decreased serum concentrations of medroxyprogesterone. Therefore, some clinicians have started to administer the intramuscular dose every 2 months as opposed to every 3 to override this potential interaction.

Other special populations to consider with respect to drug interactions are patients with HIV, solid organ transplants and the elderly.

AED DRUG MONITORING

Drug levels for antiepileptic medications are difficult to assess because efficacy and side effects are patient specific and often do not necessarily correspond to proposed ranges. One benefit of monitoring a plasma drug level is to document the serum concentration when patients are doing well on a stable dose. It can be helpful to determine if patients with ineffective doses are not adherent. Serum concentrations can also elucidate the occurrence of drug-drug interactions. An exception to this general principle is phenytoin, which should be monitored regularly due to its nonlinear saturation kinetics.

TOLERANCE

As with almost all medications, the human body is capable of developing tolerance to their effects. In the realm of antiseizure medications, tolerance can be beneficial in reducing the body's perceived severity of side effects or detrimental in increasing the frequency and severity of seizures. There are two types of tolerance: pharmacokinetic and pharmacodynamic. Pharmacokinetic tolerance is based on induction of metabolism and can be averted by periodic dose escalations as necessary. Pharmacodynamic tolerance is also called functional tolerance because it is due to the body losing receptor activity. In this instance, dose escalations are typically ineffective at overcoming the tolerance and creation of cross-tolerance with other AEDs of similar mechanisms is possible.

DISCONTINUATION OF AEDS

Discontinuing a patient's antiepileptic medication(s) is much more difficult than initiation. It is necessary in patients experiencing serious adverse events, but discontinuation is dangerous due to increased risks of seizure recurrence, which occurs in 1/3 of patients following discontinuation of AED treatment. A longer duration of seizure-free time usually corresponds to more success in discontinuation. There are no specific rules for when to consider AED discontinuation; however, patients that have been in remission for at least 3 years can be considered, but should be discontinued gradually over several months by slowly decreasing one drug at a time.

CONCLUSION

Treatment of epilepsy is complicated due to patient specific factors and cannot be outlined by a black and white algorithm. Achieving adequate seizure control is difficult while minimizing unpredictable side effects. If slow titration and testing multiple single and combination drug regimens does not achieve adequate seizure control in a patient, then reevaluation of the seizure diagnosis is necessary. Additionally, proper lifestyle modifications can play a significant role in seizure control and should always be implemented in conjunction with drug therapy instead of replaced by medications.

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