Primary generalized tonic-clonic (PGTC) seizures are the most debilitating seizure type, and treatment options for them are limited. Accurate identification of PGTC seizures is critical, as misdiagnosis can result in inappropriate therapy that could potentially harm the patient.

In this two-part CME activity, I review antiepileptic drugs used to treat PGTC seizures based on their mechanism of action, efficacy, safety, and tolerability. Through a case-based discussion, I explore the development of management plans that are tailored to the needs of each individual patient, highlighting strategies to modify treatment regimens for patients with PGTC seizures when they are experiencing an inadequate response or tolerability issues. I hope you find this educational activity useful in your daily practice.

Sincerely,

Steve Chung, MD
Activity Information

Activity Description and Educational Objectives
In this activity, a renowned expert in neurology discusses the management of patients with primary generalized tonic-clonic seizures.

Upon completion of this activity, participants should be better able to:
• Recognize treatment options for PGTC seizures based on their mechanism of action, efficacy, safety, and tolerability
• Employ approaches to treating PGTC seizures that are tailored to the needs of each individual patient
• Apply strategies to modify treatment regimens for patients with PGTC seizures when they are experiencing an inadequate response or tolerability issues

Target Audience
This activity has been designed to meet the educational needs of neurologists and other clinicians involved in the treatment of patients with primary generalized tonic-clonic seizures.

Requirements for Successful Completion
In order to receive credit, participants must view the activity and complete the post-test and evaluation form. A score of 70% or higher is needed to obtain CME credit. There are no pre-requisites and there is no fee to participate in this activity or to receive CME credit. Statements of Credit are awarded upon successful completion of the post-test and evaluation form.

Media: Enduring Material
Release and Expiration Dates: May 26, 2016 - May 25, 2017
Time to Complete: 30 minutes

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Consultant for Eisai Co., Ltd.; Lundbeck; Sunovion Pharmaceuticals Inc.; UCB, Inc.; and Upsher-Smith Laboratories, Inc.
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Steve Chung, MD, does intend to discuss either non-FDA-approved or investigational use for the following products/devices: Off-label use of antiepileptic drugs for the treatment of primary generalized tonic clonic seizures.

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Improving Outcomes in Patients With Primary Generalized Tonic-Clonic Seizures Through Evidence-Based Treatments and Personalized Approaches

Updates in Treatment Options for Patients With Primary Generalized Tonic-Clonic Seizures

Steve Chung, MD
Banner University Medical Center
Phoenix, Arizona

Dr. Chung: Hello, this is Dr. Steve Chung from the Banner University Medical Center in Phoenix, Arizona. Welcome to this educational activity focused on the management of patients with primary generalized tonic-clonic seizures. After completing the activity, access the post-test and evaluation form by clicking the red “Get Certificate” button. I also encourage you to download the slides, Practice Aids, and any other activity features that may interest you.

Seizure Types1,2

- Generalized Onset
  - Convulsive
  - Nonconvulsive
- Partial Onset
  - Simple
  - Complex
  - Tonic Clonic
  - Tonic-clonic (PGTC)
  - Absence Myoclonic
  - Atonic
  - Secondary Generalized

PGTC: primary generalized tonic-clonic.

Primary generalized tonic-clonic seizures are a very common type of convulsive seizures that occur in a symptomatic generalized or idiopathic generalized epilepsy patient. So primary generalized means that a seizure starts in both sides of the brain at the same time compared to, again, partial-onset seizures, which may spread into both sides of the brain eventually.
Tonic activity is a sudden muscle stiffening often followed by the clonic activity, which is a more rhythmic contraction of the muscles. Some people may have a tonic-clonic or clonic-tonic seizure based on which seizure type happens first.

**Tonic activity**
- Sudden muscle stiffening
- Often followed by the clonic activity

**Clonic activity**
- More rhythmic contraction of the muscles
- Some people may have tonic-clonic or clonic-tonic seizures

**Seizure Types**
- Tonic-clonic seizures
- Clonic-tonic seizures

**Complications**
- Head trauma
- Falls and fractures (more common in PGTC seizures than in other epilepsies)
- Oral/tongue trauma
- Aspiration pneumonia
- Sudden unexpected death in epilepsy (SUDEP)

**Frightening experience** for patients and families

**PGTC Seizures: Often the Most Debilitating Seizure Types Within IGE**

**Can lead to potentially serious complications, including increased risk of**
- Head trauma
- Falls and fractures (more common in PGTC seizures than in other epilepsies)
- Oral/tongue trauma
- Aspiration pneumonia
- Sudden unexpected death in epilepsy (SUDEP)

**IGE:** idiopathic generalized epilepsy.

PGTC is the most debilitating seizure type, often involves the head trauma or the body trauma, as well as a fall and fracture. Aspiration pneumonia can occur.

Patients lose their consciousness and are unaware of their surroundings. They won’t be able to respond to the surrounding people, and people develop postictal confusion for a while.

One of the important things we have to recognize here is the sudden unexpected death in epilepsy is more common in those patients who had uncontrolled tonic-clonic or primary generalized tonic-clonic seizures. As you can imagine, this type of seizure is also quite frightening to the observers, even though a patient may not be aware of what’s going on.

**Need for AEDs With Broad Spectrum**

- Limited number of studies in PGTC patients
- No optimized screening tool or animal models
- Often involves children, which further limits clinical studies
- General perception that PGTC seizures are better controlled than partial-onset seizures

**AED:** antiepileptic drug.

When we talk about primary generalized seizures, and specifically primary generalized tonic-clonic seizures, only half of medications [available are] indicated by FDA [US Food and Drug Administration]. One of the main reasons is, we don’t have a good screening tool or animal models to recognize the medication that could be valuable for this type of seizure. Therefore, the clinical studies are also limited. By and large this type of [patient] can do much better compared to the partial-onset seizures. So the choice of medication that is indicated for this type of seizure is quite important.

**Treatment of PGTC Seizures**

**Monotherapy in PGTC Seizures**
- Valproate
- Topiramate
- Lamotrigine

**Adjunctive Therapy in PGTC Seizures**
- Lamotrigine
- Levetiracetam
- Topiramate
- Perampanel
- Zonisamide

*Of-label use.*


So we have several medications listed here. Monotherapy indications are quite difficult to get, but we have topiramate and lamotrigine as a conversion monotherapy. Valproic acid does not have specific clinical studies, but is approved as a monotherapy indication, because it was before the strict regulation of FDA.
On the right side, these are the medications that are approved by FDA for adjunctive therapy in patients with PGTC seizures, which include lamotrigine, levetiracetam, topiramate, perampanel. And I listed zonisamide here even though zonisamide is not approved by FDA. It’s been approved elsewhere in the world, utilized for the PGTC seizures. The following several slides will show those clinical studies.

The first one here is lamotrigine. The left side is regular lamotrigine. And again, a comparison to the placebo effect in patients with PGTC and as an adjunctive treatment. The most common side effects noted with lamotrigine were dizziness, somnolence, and nausea.


The first one here is lamotrigine. The left side is regular lamotrigine, and showing the efficacy compared to the placebo when it’s added on to the existing medication to control PGTC seizures. On the right side, these are the extended-release lamotrigine. And again, a comparison to the placebo effect in patients with PGTC and as an adjunctive treatment. The most common side effects noted with lamotrigine were dizziness, somnolence, and nausea.

LEV: levetiracetam; SV2A: synaptic vesicle glycoprotein 2A; TEAE: treatment-emergent adverse events.

Next one is levetiracetam. Again, this is adult population and pediatric population who has diagnosis of primary generalized tonic-clonic seizures. Most of them are idiopathic generalized epilepsy patients.

Initial target dosage was 3,000 mg/day, but many of them had to be down-titrated to 2,000 mg/day. Nonetheless, it shows a quite robust effect of seizure freedom as well as responder rate and reduction in seizure frequency compared to the placebo effect. The most common side effects from levetiracetam include somnolence and behavioral changes such as irritability.
Improving Outcomes in Patients With Primary Generalized Tonic-Clonic Seizures Through Evidence-Based Treatments and Personalized Approaches

**AEDs as Add-On Therapy in Refractory PGTC Seizures: Topiramate**

- Approved as both monotherapy and adjunctive treatment for PGTC and partial-onset seizures in patients aged ≥2 y
- Also approved as adjunctive treatment for patients aged ≥22 y with LGS
- Broad spectrum of pharmacologic properties

A TPM was titrated to target doses of approximately 6 mg/kg/d over 8 weeks and maintained for another 12 weeks.

- The most common AEs were somnolence, fatigue, weight loss, difficulty with memory, and nervousness

[Graph showing reduction in seizure frequency and responder rate]

**AEDs as Add-On Therapy in Refractory PGTC Seizures: Perampanel**

- The first FDA-approved, noncompetitive AMPA glutamate receptor antagonist
- Approved in 2015 as adjunctive therapy for PGTC seizures in pts aged ≥12 y
- Approved in 2012 as adjunctive therapy for partial-onset seizures w/ or w/o secondarily generalized seizures in pts aged ≥12 y

The next one is topiramate, also showing quite an improvement compared to the placebo effect in a similar population. Topiramate is indicated for specifically pediatric population age 2 and above, as well as adult population. The most common side effects from topiramate include somnolence, fatigue, weight loss, and difficulty with memory as well as nervousness.

LGS: Lennox-Gastaut syndrome; TPM: topiramate.

The next one is the most recent one. Perampanel has also approved indication for adjunctive therapy for the PGTC seizures in patients age 12 and above. The left one shows a median seizure reduction, and the right-side column is a 50% responder rate. Seizure freedom rate was reportedly above 30% with perampanel, which is comparable to the other studies shown earlier. Even though there’s no clinically relevant changes in hepatic, cardiac, and renal parameters, the most frequent side effects included dizziness and fatigue.

AMPA: α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; FDA: US Food and Drug Administration; PER: perampanel.
Improving Outcomes in Patients With Primary Generalized Tonic-Clonic Seizures Through Evidence-Based Treatments and Personalized Approaches

**Clinical Experience**
- Extensive clinical experience in Japan, where 22%-66% of adults and children experiencing tonic-clonic, tonic, clonic, myoclonic, or absence seizures responded to treatment.

**Monotherapy**
- Even greater responder rates have been reported when ZNS was used as monotherapy in patients refractory to other AEDs or with newly diagnosed epilepsy.

**Retrospective Study in IGE Patients**
- Mo 6: Response achieved in 8 of 12 patients (66.6%), 7 of which were seizure-free (58.3%).
- Mo 12: 8 of the 11 patients were responders (72.7%) and 6 were seizure-free (54.5%).

Well tolerated, with a low incidence of AEs, which are generally mild and CNS-related.

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CNS: central nervous system; ZNS: zonisamide.

So zonisamide, again, is not approved by FDA for the PGTC use, but it has been quite widely utilized since the year 2000 worldwide for this type of [seizure]. Overall, zonisamide is a well-tolerated medication with a low incidence of side effects. Patients had dizziness, some irritability, as well as paresthesias.

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The Future of PGTC Treatment

- **Neurostimulation**
- **Immunomodulation and anti-inflammatory treatment**
- **Natural herbs**
- **New PGTC studies of newer generation AEDs**

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**Case 1: Patient Presentation**

**Patient Profile**
- 18-year-old male
- Freshman in college
- Heavily involved in school activities

**Clinical Presentation**
- Has had two seizures in the past month
- Both occurred shortly after waking
- Observers noted muscle contractions, followed by a rhythmic shaking
- Was unresponsive for about 5 minutes

**Evaluation**
- Thorough history, physical, and neurological examination revealed no evidence of any localized, regional, or diffuse brain abnormality
- Clinical labs and imaging studies unremarkable; awake EEG normal

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**Dr. Chung:** I'd like to discuss two cases. The first case is an 18-year-old man who is a freshman in college. He's heavily involved in school activities, which is good news. But he had two seizures in the past month. Having two seizures established him to have epilepsy. So we don't have any trigger factors for him at this point.

Both seizures occurred shortly after waking up in the morning, which is actually a common feature for the primary generalized tonic-clonic seizures, and the seizures were described as tonic-clonic activities—the muscle contractions followed by the rhythmic shaking of the body. He became then unresponsive for about 5 minutes.

Neurologic examination was normal, and other personal and family history was not revealing. The labs were normal, as well, and brain imaging studies and EEG were both normal.
Improving Outcomes in Patients With Primary Generalized Tonic-Clonic Seizures Through Evidence-Based Treatments and Personalized Approaches

Teenage onset suggests that this person probably has generalized-onset seizures rather than partial-onset seizures. A person can have partial-onset seizures in this age due to head trauma and infection. But without those triggering brain damage, more likely this person has generalized-onset seizures.

Secondly, juvenile myoclonic epilepsy is very common in this age, so you want to ask about other types of seizures that he’s not reporting to you. Patients usually do not volunteer saying that they have absence seizures and myoclonic jerks. For absence seizures, we may have to ask, “Have you experienced staring off or your friends are telling you in the middle of the conversation you would not respond for a few seconds?”

Myoclonic jerks usually occur in the morning, so ask them, “Have you noticed that you become a little jerky and drop things, holding the objects and then the next second you have a little jolt of jerks, and then you drop things on the floor?”

AED: antiepileptic drug; IGE: idiopathic generalized epilepsy; PGTC: primary generalized tonic-clonic.

Finding or diagnosing proper type of seizures is very important, again. You do not want to use a medication that can potentially harm the person, such as causing more seizures, and causing even status epilepticus that was reported when carbamazepine was utilized for JME population or primary generalized tonic-clonic seizure type.

AEDs with a broad spectrum of activity that are effective for both partial-onset and generalized epilepsy are the most appropriate treatment.
Improving Outcomes in Patients With Primary Generalized Tonic-Clonic Seizures Through Evidence-Based Treatments and Personalized Approaches

So you’ve got to start with the one medication that has good supporting data. Here are the class III and class IV evidence that supports the valproic acid, lamotrigine, and topiramate as the initial monotherapy. If the first medication doesn’t work or cannot [be tolerated] by the patient, you may want to try a second monotherapy, or [think] about polytherapy or combination therapy shortly after that.

<table>
<thead>
<tr>
<th>Patient Factors</th>
<th>AED Characteristics</th>
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<tbody>
<tr>
<td>Seizure type and syndrome</td>
<td>Spectrum of efficacy</td>
</tr>
<tr>
<td>Personal preference</td>
<td>Mechanism of action</td>
</tr>
<tr>
<td>Age</td>
<td>Indications (eg, monotherapy, children, etc)</td>
</tr>
<tr>
<td>Pregnancy potential</td>
<td>Tolerability/safety</td>
</tr>
<tr>
<td>Comorbidities</td>
<td>– Neuropsychological implications</td>
</tr>
<tr>
<td>Comedications</td>
<td>– Dosing frequency, titration complexity, simplicity of use</td>
</tr>
<tr>
<td>Individual lifestyle (once-daily dosing, etc)</td>
<td>– Drug–drug interaction profile</td>
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<tr>
<td></td>
<td>– Teratogenic potential</td>
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<tr>
<td></td>
<td>– Availability, cost, reimbursement</td>
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</table>


And here are some of the guidelines. First of all, seizure type—very, very important. How about the age? If a woman, then you may consider the medication does not cause a lot of teratogenic side effects, and the pregnancy potential as well.

You may want to avoid some of the side effects that can worsen their underlying comorbid condition, or sometimes you can provide some medication that can actually help. One example would be using the seizure medication that can help towards a migraine headache.

When you talk about the seizure medication itself, there is a lot more to think about, especially when you combine the medication, then we talk about mechanism of action, understanding about how medication works in the body. Safety, tolerability, that goes without saying. Especially those patients who are taking more than two or three medications, drug interactions are very common. Cost and frequency of dosing is also a very important aspect.

So this patient, with some conversation, was placed on the monotherapy of the valproic acid. The patient appears to be tolerating it very well, but he had breakthrough seizures. And because this medication was given as a twice-daily, he often forgets to take the medication, which is a very important issue in younger patients.

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When you use a combination therapy, again, one thing I want you to think about is the mechanism of action. It might not be a good idea to add in another medication with a similar mechanism of action. Since we have a lot of options of medication, we can just choose a medication that has a quite different mechanism of action.

The sodium channel is one of the main mechanisms to activate the neuronal cells. GABAergic medications is one good example to increase the inhibition of the neuron activities.

Some medication actually works on the calcium channels, and some of them [work] on the synaptic vesicle binding protein SV2A. Levetiracetam is listed here. And then the benzodiazepines and barbiturates for the GABAergic medications. Tiagabine, there was an increased synaptic GABA concentration.

Refractory seizure disorder patients tend to have increased glutamate, and one of the important mechanisms is to block the glutamate action. And we do now have a medication that blocks the AMPA receptors, which is perampanel.
Now, we're going to turn to a second case. This is a 51-year-old female this time. She started having seizures at age 15, and indeed she was diagnosed with PGTC seizures.

So she was placed on valproic acid. Typically these days, valproic acid would not be the first choice in a 15-year-old woman or girl due to the pregnancy potential, and valproic acid showing higher risk in terms of teratogenicity. But at the time, valproic acid was used quite frequently.

Seizures are very well controlled, and that’s one of the reasons that she continues to take the medication. But two things are happening gradually over time. She noted weight gain and developing severe headaches. Now, weight gain can be very common, and may not be even related to medication. But definitely, valproic acid would not help to control the weight. She also has a family history of cardiovascular disease and diabetes.

Again, you have a question whether weight gain is entirely due to valproic acid or not. But at this point, it is valuable to review what kind of medication might be causing weight gain and weight loss.

So valproic acid and perampanel tend to cause some weight gain. And topiramate and zonisamide cause weight loss. Lamotrigine is weight neutral. Levetiracetam is typically known as a weight-neutral medication, as well, too. Some people actually reported some weight loss or weight gain, too.

Another factor that is important for her is developing now severe headaches. It could be migraine headache. Without having details, we don’t know yet. So your choice is really finding a medication that does not cause weight gain, or at least weight neutral, and hopefully, and somewhat beneficial to control her headaches.

Factors Influencing AED Monotherapy Selection in PGTC Seizures: Metabolic Effects1-3

<table>
<thead>
<tr>
<th>AED</th>
<th>Effects on Weight</th>
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<tbody>
<tr>
<td>VPA</td>
<td>Weight gain</td>
</tr>
<tr>
<td>TPM</td>
<td>Weight loss</td>
</tr>
<tr>
<td>LTG</td>
<td>Weight neutral</td>
</tr>
<tr>
<td>ZNS*</td>
<td>Weight loss</td>
</tr>
<tr>
<td>LEV</td>
<td>Weight neutral</td>
</tr>
<tr>
<td>PER</td>
<td>Weight gain</td>
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</tbody>
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Goal: Identify a medication that may also help to control her headaches and does not cause weight gain

Case 2: Additional Considerations

- Evidence supports VPA, TPM, and LTG as monotherapy
- Adherence has not been an issue for patient

Conversion to TPM initiated
- Patient appears to be doing well and seizures remain controlled
- Patient continues to be monitored for seizure control, effects on weight, and any other potential side effects


So for this patient, the decision was made to convert into topiramate monotherapy. And she then did very well, and seizures remained controlled, and hopefully the headache controlled better than before. Obviously, the weight has to be monitored as you switch the medication.
## Conclusions

- Treatment options for PGTC seizures are limited, but have expanded recently
- Accurate diagnosis of PGTC seizures is critical for determining appropriate therapy
- Treatment selection for patients experiencing PGTC seizures is dependent on a variety of factors
- Treatment plans should be personalized for each individual patient

So overall, only a handful of medications are available and approved for use for the PGTC seizure type. But it is very important to make the diagnosis of PGTC, because certain medications are known for worsening of the seizure type.

Selection of seizure medication is a combination between art and science. You have to know the mechanism of action. You have to know the pharmacokinetics and drug interactions, but at the same time you have to know the patient very well to avoid their existing conditions, problems, or foresee some of the side effects they may not be able to tolerate.

So the treatment plan has to be personalized for each individual patient. You have to know the patient very well—and you have to know the medication choices very well, and then you can make a proper selection for that specific patient.
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