New Add-on Therapy for Partial-onset Epilepsy

a report by
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Adequate control of partial-onset epilepsy often requires polypharmacy, either due the to less than ideal efficacy of one antiepileptic drug (AED) (see *Table 1*) or due to side effects caused by the initial AED (see *Table 2*). Up to one-third of patients with partial-onset epilepsy will require treatment with more than one AED.

The ideal medical management of epilepsy is based on tailoring each patient's regimen to his or her seizure type, comorbidities, lifestyle, and history of medication side effects. Therefore, a greater number of potential treatments offers greater options for any given patient to be treated with the best combination of medications. In recent years, many new AEDs have become available for add-on therapy for partial-onset epilepsy.

Of the newer AEDs, those that are US Food and Drug Administration (FDA)-approved for the adjunctive treatment of partial-onset epilepsy include felbamate tigabine, lamotrigine, pregabalin, gabapentin, topiramate, oxcarbazapine, zonisamide, and levetiracetam. An add-on AED should ideally have a clean pharmodynamic and phamcokinetic profile to minimize drug interactions and side effect profile. The newer AEDs are generally safer than the first-generation AEDs and, with the exception of Felbamate, do not require routine blood monitoring. All of the newer AEDs are category C in terms of use in females who want to have children, although a patient who is planning a pregnancy should aim for the lowest number of AEDs given at the lowest dose.

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Rational polypharmacy has long been a goal, but unfortunately this has not been well studied in this age of evidence-based medicine. With so many different possible combinations, one rule of thumb of rational polypharmacy is to use medications with different mechanisms of action. Of the newer AEDs, one combination that would not be 'rational' would be neurontin and pregabalin, as they have exactly the same mechanism of action. One rational combination is valproic acid and lamotrigine, as lamotrigine's half-life is prolonged, resulting in the patient requiring significantly lower doses.

Felbamate

Felbamate is recommended to patients with severe partial epilepsy or Lennox-Gastaut syndrome who fail other treatments. It is a potent blocker of N-methyl D-aspartate (NMDA) receptors and voltage-gated calcium (Ca) channels, and modulates sodium (Na^+)-channel conductance. It is approximately 25% bound to plasma proteins and undergoes hepatic metabolism. In monotherapy, its elimination half-life may be as long as 30 hours, but when given with P450-inducing agents its half-life decreases to roughly 14 hours.[1,2] The co-administration of valproate leads to increased plasma concentrations of felbamate. This medication will notably increase phenytoin levels and decrease carbamazepine levels.[2,3] In both the adult and pediatric population, concomitant AEDs should be reduced by a minimum of 20% when starting felbamate, and may be reduced further if levels are high.[1]

Felbamate is generally well tolerated, with the most common adverse effects being insomnia, dizziness, fatigue, decreased appetite, weight loss, nausea, ataxia, and lethargy.[2–5] In 110,000 patients, there were 10 cases of fatal aplastic anemia and 14 cases of fatal hepatic failure. The labeling was changed to advise that it be utilized in a limited subset of patients along with bi-weekly blood monitoring. Due to the risk for aplastic anemia and hepatic failure, it should be used when the benefits outweigh the risks.

Topiramate

Topiramate is currently approved for partial-onset and secondarily generalized tonic-clonic seizures, primary generalized tonic-clonic seizures, and Lennox-Gastaut syndrome. Topiramate acts via several different mechanisms: the enhancement of Gamma-aminobutyric acid (GABA); the inhibition of Na^+ conductance, thus reducing the duration of spontaneous bursts and the frequency of action potentials; the inhibition of alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA); and weak inhibition of carbonic anhydrase.[6]

Topiramate has nearly 100% bioavailability. Its elimination half-life is 18–23 hours.[6] The hepatic P450 system metabolizes ~15% of topiramate and the remainder (~85%) is excreted unchanged in urine, and thus in renal failure dosages must be reduced. P450-inducing drugs, such as phenytoin or carbamazepine, may significantly reduce serum topiramate concentrations: levels were found to be reduced by 50% in some studies. Conversely, topiramate has not been found to significantly influence steady-state concentrations of other drugs given in polytherapy, except for an increased phenytoin level observed in a subset of patients. Physicians should be aware that topiramate decreases ethyl estradiol levels, and may therefore inactivate low-dose oral contraceptives at doses greater than 200mg.[6,7]

In adults the most common adverse effects are paresthesia in the extremities, cognitive slowing (including impairment of concentration, confusion, memory disturbance, and slowness of speech), ataxia, dizziness, fatigue, somnolence, depression, and agitation.[8] Weight loss, which appears to be secondary to appetite suppression, may be >10kg, an effect that may lead to discontinuation if the patient is of normal or below ideal weight prior to treatment initiation. This is thought of as a positive side effect by some overweight patients.

Topiramate's carbonic anhydrase inhibition increases the risk for renal calculi. Patients should be encouraged to stay well hydrated. Another potential side effect related to carbonic anhydrase inhibition is the development of hyperchloremic non-anion gap metabolic acidosis; this can be checked by measuring bicarbonate levels. A rare adverse event is acute myopia in closed-angle glaucoma.[9]

Oxcarbazapine

Oxcarbazepine is approved for monotherapy or adjunctive treatment of partial and secondary generalized seizures. Oxcarbazepine is similar to carbamazepine in that it has a tricyclic ring structure and primarily works as an Na-channel blocker, but it has a different effect on the Ca-channel subtype. Oxcarbazepine was produced with the goal of avoiding carbamazepine's auto-induction and drug interactions. The metabolism of oxcarbazepine does not generate the 10,11-epoxide metabolite responsible for many of the adverse effects of carbamazepine. Oxcarbazepine is nearly completely absorbed and broken down into the active metabolite monohydroxy derivative (MHD). Peak plasma levels are reached at approximately four hours. It has a half-life of eight to 10 hours. Hepatic metabolism induces a limited subset of P450 enzymes. Oxcarbazepine in high doses (>1,200mg) significantly affects oral contraceptives and may render them ineffective.[10]

Studies have been performed where oxcarbazepine and carbamazepine were used together successfully with additive benefit. If oxcarbazepine were to be substituted for carbamazepine, a recommended ratio of 3:2 has been studied; dosing is outlined in *Table 1*. As noted above, oxcarbazepine has fewer drug interactions and is better tolerated than carbamazepine. However, some retrospective studies have uncovered the exacerbation of seizures in juvenile idiopathic generalized epilepsies in patients treated with oxcarbazepine.[10–12]

The most commonly reported adverse effects include headache, weight gain, somnolence, dizziness, rash, hyponatremia, alopecia, and gastrointestinal upset. If a patient is allergic to carbamazepine, allergic cross-reactivity to oxcarbamazepine has also been reported, although at a rate of 27% it occurs less frequently. Many of the reported adverse effects are dose-related (fatigue, dizziness, ataxia, and headache). Hyponatremia (uncommon in children <17 years of age, but reported in 2.5% of adults and 7.4% of elderly patients) is generally mild and can usually be easily treated with fluid restriction.[10–14]

Lamotrigine

Lamortigine is approved for adjunctive treatment and for cross-over to monotherapy for partial-onset and secondarily generalized tonic-clonic seizures, for Lennox-Gastaut syndrome, and as add-on therapy for primary generalized tonic clonic seizures in patients ≥2 years of age.

Lamotrigine is believed to work via several mechanisms, the principal one being Na^+-channel blockade, and its bioavailability approaches 100%. It is 55% protein-bound and has an elimination half-life of 24–41 hours. Co-administration with valproate increases lamotrigine levels by increasing its half-life to roughly 70 hours. Lamotrigine is metabolized hepatically and excreted renally. At higher doses, it may cause autoinduction.

Lamotrigine will neither induce nor inhibit hepatic enzymes, therefore no dosing changes are indicated when given with oral contraceptives or warfarin. However, medications that induce hepatic enzymes may decrease lamotrigine's half-life to 14–16 hours, and dosing must be adjusted accordingly.[10,15] Oral contraceptives decrease lamotrigine half-life, but as combined oral contraceptive monthly packs have seven days with no hormonal placebo pills, lamotrigine levels can rise by as much as 40%, leading to monthly flucutuations and causing side effects. It has been found to be effective in myoclonic seizures, but can cause worsening of myoclonic seizures in some juvenile myoclonic epilepsy. Dosing and titration depends on AED co-administration, with a slower titration required with enzyme-inhibiting AEDs than with enzyme-inducing AEDs.[6,10,15,16]

Lamotrigine is available in several starter packs. These have different titrations depending on the co-administered AEDs to aid in patient compliance with what may otherwise be a complicated initiation of medication. Up to 5% of patients develop a rash, often associated with a rapid titration. A severe rash, most common in children on valproate, may develop and result in the rare but potentially fatal Stevens-Johnson syndrome (0.1%). Other adverse reactions include ataxia, diplopia, headache, tremor, blood dyscrasias, gastrointestinal upset, psychosis, somnolence, insomnia, and hypersensitivity reactions.[15–17]

Zonisamide

Zonisamide is approved by the FDA for adjunctive treatment in patients above 12 years of age with partial seizures. Its major mechanism of action is Na-channel blockade, although it also has been shown to bind and reversibly inactivate T-type Ca channels, making it effective for myoclonus, as found in juvenile myoclonic epilepsy.

Zonisamide is rapidly and completely absorbed. It is partially metabolized by the liver (~70%), and although it utilizes P450, it does not induce the enzymes. Zonisamide has long half-life of about 63 hours, permitting

Table 1: The Administration of Antiepileptic Medications

Medication	Metabolism	Drug Interactions	Adult Dosing	Pediatric Dosing
Felbamate	Hepatic.	Valproate increased levels Increased PHT and CBZ P450 inducers reduce $t_{1/2}$ from 30 to14 hours	Start 1,200mg divided TID-QID, increase by 600 weekly to max of 3,600/day *Reduce other AEDs by ≥20% when starting felbamate	Start 15mg/kg/day, titrate weekly up to 45mg/kg/day *Reduce other AEDs by ≥20% when starting felbamate *Approved for >14 years of age
Topiramate	~15% metabolized by hepatic P450 system, ~85% excreted unchanged in urine.	P450-inducers may significantly reduce levels May inactivate low-dose oral contraceptives	Start 25mg daily or BID, titrate over several weeks to months to typical effective dose of 200–600mg/day divided BID *In renal failure, dosages must be reduced	Start 0.5–1mg/kg/day, titrate by 0.5–1mg/kg/day every 2 weeks to typical effective dose of 9–11mg/kg/day *In renal failure, dosages must be reduced *Approved for >2 years of age
Oxcarbamazepine	Hepatic metabolism with renal excretion.	May inactivate oral contraceptives	Start 600mg/day divided BID, titrate to 400mg/day *May be substituted for carbamazepine with 3:2 oxcarbazepine:carbamazepine ratio	Start 10mg/kg/day divided BID, titrate to 30mg/kg *Approved for >4 years of age
Lamotrigine	Hepatic metabolism with renal excretion.	P450-inducers may significantly reduce $t_{1/2}$ Valproate increases lamotrigine levels by increasing $t_{1/2}$	Administered BID. Slow titration significantly improves tolerability. Dosing/titration depends on AED co-administration, with a slower titration with enzyme-inhibiting AEDs. Starter packs available with specific titrations depending on co-administered medications	Administered BID. Slow titration significantly improves tolerability. Dosing/titration depends on AED co-administration, with a slower titration with enzyme-inhibiting AEDs If given with valproate, start at 0.15mg/kg/day divided BID, with escalations every 1–2 weeks to a maximum of 5mg/kg. If on enzyme inducers, start at 0.6mg/kg/day divided BID, titrate to a maximum of 15mg/kg. *Approved for ≥2 years of age
Zonisamide	~70% hepatic metabolism without P450 induction.	$t_{1/2}$ may decrease (from 63 to 27–46 hours) when co-administered with pheytoin, carbamazepine, phenobarbital, or valproate	Start 100mg/day, titrate every two weeks,by 100mg/day to goal of 100–60mg/day (there is no suggestion of increasing response above 400mg/day). Since zonisamide is metabolized hepatically and excreted renally, patients with renal or hepatic disease may require slower titration and more frequent monitoring. Due to zonisamide's long $t_{1/2}$, up to two weeks may be required to achieve steady state	Start 2mg/kg/day, divided BID, titrate by 2mg/kg/day every two weeks to goal of 8–10mg/kg/day *Approved for ≥12 years of age
Tigabine	Hepatic, P450; metabolism and excretion are reduced in liver patients.	P450-inducers decrease $t_{1/2}$ (from 4–8 to 4–5 hours) and increase clearance by ~⅔	Start 4mg/day, titrate 4–8mg daily each week to a goal of 32–56mg/day	Start 0.1mg/kg/day, divided TID, titrate by 0.1mg/kg/day weekly to goal of 0.4mg/kg/day (max of 32mg/day) *Approved for ≥12 years of age
Gabapentin	Not metabolized and is excreted in unchanged form. In patients with decreased renal function, dosing should be adjusted according to Cr clearance. Gabapentin is removed by hemodialysis.	Antacids may decrease bioavailibility	Start 300mg TID (900mg/day), titrate weekly to a maximum of 4,800mg daily (though often titration stopped at 3,600mg daily, as bioavailability rapidly drops as dosage escalates)	Start 5mg/kg/day, divided TID, titrate by 5mg/kg/day to goal of 15–20 mg/kg/day (max of 60mg/kg/day) *Approved for >3 years of age
Levetiracetam	~ 27% metabolized; cleared by glomerular filtration with partial tubular reabsorption ~⅔ excreted unchanged in urine. In renal insufficiency, elimination half-life prolonged; removed during hemodialysis.		Start 500mg BID, titrate weekly by 500–1,000mg daily to maximum of 3,000mg	Start 5–10mg/kg/day, divided daily or BID, titrate by 5–10mg/kg/day weekly to goal of 30–50mg/kg/day (max of 100mg/kg/day) *Approved for ≥4 years of age
Pregabalin	Not significantly metabolized; excreted unchanged by kidneys. In patients significant renal dysfunction (creatine clearance <60ml/minute), doses must be lowered.		Start 15mg/day divided BID or TID, titrate to maximum dose of 600mg/day	*Approved for adult usage only

TID-QID = three to fours times daily; PHT = pulmonary hypertension; CBZ = carbamazepine; AEDs = aintiepileptic drugs; BID = twice daily.

Table 2: Adverse Effects of Antiepileptic Medications

Medication	Common Adverse Events	Serious Adverse Events
Felbamate		Aplastic anemia, hepatic failure.
Topiramate	Adult: Extremity paresthesia, weight loss, cognitive slowing, ataxia, dizziness, fatigue, somnolence, depression, and agitation. Pediatric: fatigue, somnolence, anorexia, and anxiety.	Renal calculi. Rarely: acute myopia in closed-angle glaucoma.
Oxcarbamazepine	Headache, weight gain, somnolence, dizziness, rash, hyponatremia, alopecia, gastrointestinal upset, allergic rash. Hyponatremia (uncommon in patients <17 years of age but reported in 2.5% of adults and 7.4% of elderly people). Exacerbation of seizures in juvenile idiopathic generalized epilepsies.	
Lamotrigine	Ataxia, diplopia, headache, tremor, blood dyscrasias, gastrointestinal upset, psychosis, somnolence, insomnia and hypersensitivity reactions. Exacerbation of seizures in juvenile myoclonic epilepsy	Rash often associated with rapid titration. Severe rash, more common in children on valproate, may lead to rare but potentially-fatal Stevens-Johnson syndrome (0.1%).
Zonisamide	Somnolence, fatigue, headache, weight gain, dizziness, anorexia, ataxia, tremor, confusion, speech abnormalities, mental slowing, and irritability	Spontaneous abortions/ congenital abnormalities rate of 7%, ~2x that of general population. Renal calculi in 1.5% of patients, oligohidrosis in some children. Allergic reactions in patients with sensitivity to sulfonamides.
Tigabine	Diarrhea, somnolence, asthenia, depressed mood, emotional lability, nervousness, tremor, dizziness, ataxia, abnormal thinking, abdominal pain, pharyngitis, confusion, psychosis, and skin rash. Children have a reduced clearance of tigabine.	Reports of convulsive and nonconvulsive status epilepticus with tigabine—use with caution in a patient with a history of status epilepticus. Contraindicated in absence or partial epilepsies with generalized spike wave on electrocardiogram and in severe hepatic impairment, pregnancy, and lactation.
Gabapentin	Somnolence, ataxia, dizziness, nystagmus, tremor, fatigue, diplopia, rhinitis, headache, nausea, or vomiting. Rash in 0.5%, neutropenia in 0.2%.	
Levetiracetam	Headache, accidental injury, convulsion, infection, asthenia, somnolence, dizziness, pain, pharyngitis, and flu-like syndrome.	
Pregabalin	Dizziness, somnolence, ataxia, weight gain. May increase creatinine kinase, decrease platelet count and increase PR interval.	

once-daily administration and lack of drug interactions with other AEDs. The half-life of zonisamide may be decreased from 63 to 27–46 hours when co-administered with pheytoin, carbamazepine, phenobarbital, or valproic acid, although zonisamide has no effect on the levels of these medications.[10,19]

Although generally well-tolerated, the most commonly reported adverse reactions with zonisamide were somnolence, fatigue, headache, weight gain, dizziness, anorexia, ataxia, tremor, confusion, speech abnormalities, mental slowing, and irritability. Zonisamide has been associated with renal calculi in 1.5% of patients, and its carbonic anhydrase-inhibiting effects may produce oligohidrosis in some children. Zonisamide should not be used in patients with known allergies to sulfonamides, as it may produce allergic reactions in these individuals.

Tigabine

Tigabine is used as add-on therapy in patients with partial or secondarily generalized seizures. Tigabine, a derivative of the GABA uptake inhibitor nipecotic acid, reversibly inhibits GABA transporter-1.[20,21] It binds 96% to plasma proteins and is metabolized by the hepatic P450 system. In a patient co-medicated with enzyme-inducing drugs, tigabine's plasma half-life of four to eight hours may be reduced slightly to four to five hours. Its metabolism and removal from the body is reduced in liver patients. Tigabine induces a minor decrease in valproate levels (valproate has no effect on tigabine levels), but does not alter the efficacy of oral contraceptives. P450-inducing drugs increase the clearance of tigabine by roughly two-thirds.[10,20–22]

There have been reports of both convulsive and non-convulsive status epilepticus with tigabine usage, and therefore it should be used with caution in a patient with a history of status epilepticus. It is contraindicated in absence epilepsy and in partial epilepsies with generalized spike wave on electrocardiogram (EEG), where it may worsen seizure control.[21]

Gabapentin

Gabapentin is approved for the treatment of partial and secondarily generalized tonic-clonic seizures. It binds the alpha-2 delta subunit of Ca channels in the cerebral cortex, hippocampus, and spinal cord, reducing the influx of Ca at nerve terminals, in turn reducing excitatory neurotransmitters release.[3,6,19,16,23,24]

Gabapentin, unlike many other newer AEDs, has a relatively poor bioavailability of less than 60%, which is altered primarily by variable absorption via an L-amino acid transporter. At doses greater than 1,200mg, bioavailability further drops off to ~35%. Gabapentin neither binds to plasma proteins nor is metabolized (and does not induce hepatic enzymes), and it is excreted entirely unchanged. Gabapentin has an elimination half-life of five to nine hours. In patients with compromised renal function, dosing must be adjusted according to creatinine clearance.[3,6,16,19] Owing to its lack of drug interactions, lack of plasma protein-binding, and renal excretion, gabapentin is particularly useful in patients with hepatic or renal disease, or in patients on complex drug regimens.[3,10,23–25] It is typically well tolerated, with common adverse effects being somnolence, ataxia, and dizziness. No significant serious idiosyncratic or systemic adverse effects of gabapentin have been reported.[23,25]

Pregabalin

Pregabalin is approved for adjunctive therapy for adult patients with partial-onset seizures. Like gabapentin, pregabalin binds the alpha-2-delta subunit of Ca channels, reducing the influx of calcium at nerve terminals, in turn reducing the release of excitatory neurotransmitters (glutamate, noradrenaline, substance P), but it does not block the Ca channel. Pregabalin is more potent than gabapentin, with a higher binding affinity for the Ca channel subunit, which is a modulator of Ca.

Pregbalin has a high (>90%) oral bioavailability that distinguishes it from gabapentin. Its elimination half-life is roughly six hours. Pregabalin is not significantly metabolized, has no effect on liver enzymes, and is excreted unchanged by the kidneys. Pregabalin does not significantly bind plasma proteins. No significant drug interactions with pregabalin have been identified.[32,33]

Pregabalin's efficacy as add-on therapy in partial-onset seizures was established in three studies, which showed a 43–51% decrease in seizure frequency from baseline versus a 1–10% decrease with placebo.[34–36] Adverse effects were dizziness, somnolence, ataxia, and asthenia. Weight gain >7% from baseline was dose-related and reported in 18% of patients. No significant, serious toxicity related to pregabalin was reported. In patients with significant renal dysfunction (creatinine clearance <60 minutes), doses must be lowered.[36]

Levetiracetam

Levetiracetam is approved as adjunctive therapy in the treatment of partial-onset seizures, myoclonic seizures in juvenile myoclonic epilepsy, and primary generalized tonic-clonic seizures in adults and children ≥6 years of age. There is now an intravenous form of leveitracetam available. Its mechanism of action has not yet been fully identified, but levetiracetam binds a brain-specific binding site presynatpic vesicle protein SV2A, and has been shown to inhibit Ca^{2+} release and other possible neurotransmitters.[27,28]

Levetiracetam has a bioavailability of nearly 100%. It does not bind plasma proteins, is minimally metabolized (~27%), and does not induce P450 enzymes, with two-thirds of the drug excreted unchanged in urine. It has an elimination half-life of six to eight hours, although it appears to have a significantly longer pharmacodynamic half-life. In renal insufficiency, its elimination half-life may approach 24 hours.[27]

Levetiracetam has no known significant drug interactions. It is an AED that is generally well tolerated. Dosing is outlined in *Table 1*. The most significant adverse effects are somnolence, asthenia, and dizziness. A drug-specific adverse effect is irritability, which seems to be more common in patients with underlying behavioral issues and may be dose-related. No serious acute idiosyncratic reactions were reported.[29–31]

Summary

The physician's armamentarium to treat epilepsy has been significantly improved by the increasing number of new AEDs, all of which can be used as add-on therapy. In treating a patient, one must consider not only efficacy, but also comorbidities, potential adverse effects, and dosing schedules. The real-world dosing of AEDs as add-on therapy does not need to follow the package insert dosing recommendation derived from clinical trial titration schedule because the mantra of starting with a lower dose and slowly increasing it will lead to better tolerability and higher retention in most cases, especially in the elderly. With a greater understanding of the strengths and weaknesses of each AED, physicians can use each medication optimally for each patient. ■

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