Ezogabine is a new drug for adjunctive therapy of partial-onset seizures with a novel mechanism of action. As a potassium-channel facilitator, it promotes membrane repolarization and thus opposes rapid repetitive discharges. Side effects are typical for antiepileptic drugs and the safety profile is good. Occasional instances of urinary difficulty may require surveillance.

**Mechanism of Action**

Ezogabine is often referred to as a “potassium channel opener”, but this is a simplified description. EZG does not directly open a potassium channel. The channels at which it acts are voltage-gated, not ligand-gated. This is demonstrated by its efficacy in the low-magnesium seizure model, which does not depend upon synaptic transmission (7). The principal mechanism by which membrane repolarization occurs after an action potential is an outward potassium current, termed the M-current (muscarinically-modulated). This current flows at subthreshold voltages and is enhanced as depolarization further opens the Kv7.2 and Kv7.3 species of voltage-gated potassium channels, allowing potassium to flow outward driven by its concentration gradient (8). EZG facilitates the action of the neuronal Kv7.2 and Kv7.3 channels (encoded by genes KCNQ 2 and KCNQ 3) by shifting the channels’ activation potentials 20-30mV toward hyperpolarization (9). This has the following physiological consequences: 1) a lesser degree of depolarization is needed to open the channel; 2) the channel, which usually opens rather slowly, opens faster, and 3) the channel stays open longer—perhaps as much as two to four times longer(10). This presumably has the effect of slowing repetitive firing, and thus underlies the compounds’ antiseizure effect.

At the stereocchemical level, EZG seems to act as a sort of prop or doorknob, binding into a hydrophobic pocket within the “gate” region of the Kv7.2 and 3 channels which is the site of a molecular “hinge”(11). To extend the analogy, once EZG has lodged within this pocket, it bends the hinge slightly open, decreasing the angle through which the gate must swing to open fully. Therefore less energy is required to open the channel and to keep it open. It should be noted that the gate must be slightly open for EZG to act, suggesting that its most important effect is to stabilize the channel in the open state— in a sense, propping it open at a more favorable angle (12). EZG does not affect cardiac potassium channels, possibly because those channels (e.g.Kv7.1: coded by gene KCNQ1) are missing a glycine component which is essential for EZG to fit within its target (11).
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There were early reports that EZG increases GABA action and decreases glutamate release (13), but it now seems likely that these are epiphenomena.

Pharmacokinetics
EZG is rapidly absorbed, with a T_{max} of 1.5 hours, and absorption is delayed but not reduced by food (14). Serum concentrations are linear through 1200 mg/day. The elimination half-life is 8 hours, so in clinical trials it was given three times per day. EZG is mostly glucuronidated rather than being metabolized by cytochrome P450 enzymes; therefore no significant age or sex effects on metabolism are expected. No clinically significant drug interactions have been identified. Phenytoin and carbamazepine increase the metabolic rate of EZG modestly but phenobarbital does not (15). Both the parent drug and metabolites are renally cleared.

Efficacy
Results of two multinational, randomized, controlled trials of EZG in patients with refractory partial-onset seizures have been published (16,17). A third trial, enrolling mostly in the US, was recently reported (18). All three multicenter trials had a classical add-on design. The three most common concomitant drugs were carbamazepine (about half of patients), lamotrigine and valproic acid (about one-quarter each). Over 70% of patients were on polytherapy when EZG was added, so no conclusions were possible concerning the best combinations.

To sum up the efficacy results from these trials, there was a reduction in seizures in the tested dose range 600 to 1200 mg/day.

All data that follow are presented as the result for each dosage cohort with the result for the parallel placebo cohort subtracted. The key primary endpoint aimed at FDA approval was the responder rate for the intent-to-treat population (50% seizure reduction from baseline, calculated from baseline, including the titration period. For the 600 mg/day dose, this reduction exceeded the placebo reduction by 7% (16) and 12% (17), for 900 mg/day by 16% (16) and 28% (17), and for 1200 mg/day, 17% (16) and 27% (18). The key primary endpoint aimed at European Medicines Agency approval was the responder rate in the intent-to-treat (ITT) population during the maintenance (stable dose) period. This was, for the 600 mg/day dose with the placebo rate subtracted, 1% (16) and 2% (17), for the 900 mg/day dose 9% (16) and 14.5% (17), and for the 1200 mg/day dose 15.2% (16) and 33% (18). In the first study, these figures were lowered by the unusually high placebo responder rate of 26% during the maintenance period (16).

The secondary endpoint in these studies was the median percent seizure reduction over baseline. The median percent reductions over placebo for the FDA ITT population were: 600 mg/day 10% (16) and 12% (17); 900 mg/day 16 (16) and 24% (17), and 1200 mg/day 22% (17) and 27% (18). In pairwise comparisons, the 600 mg dose was not statistically better than placebo but the 900 mg (16,17) and 1200 mg (16,18) doses were (p < .001).

The results of maintenance-phase data for patients reaching their target dose were superior, as expected, to the ITT populations: the median percent reduction in seizure number over the baseline number for the 600 mg/day dose was 20% (16); for the 900 mg/day dose the reduction was 26% better than placebo (17), and for the 1200 mg day dose 37% (18). Seizure-free rates counted from the time of randomization were low, as expected in a refractory population: 3.2% at 600 mg/day and 4.7% at 900 mg/day, not statistically different from the 1.2% placebo rate (17).

The best results were from the third trial, which enrolled 306 patients, mostly from the US, randomized to only one dose of EZG, 1200 mg/day, or to placebo as adjunctive therapy (18).

Tolerability
Effectiveness is a balance between efficacy and tolerability. A good measure of tolerability is the total dropout rate, which is more objective than the dropout rate attributed to adverse effects by the investigators. Most dropouts were during the titration period. During the first randomized clinical trial, dropouts during dose titration were 25% for the 600 mg/day arm, 38% for the 900 mg/day arm, and 50% for the 1200 mg/day arm (16). Because of the high dropout rate in the 1200 mg/day cohort, doses were limited to 900 mg/day for a later study: dropouts during titration were placebo 9%, 600 mg/day 13%, and 900 mg/day 16% (17). However, when the 1200 mg dose was tried again in the third trial, the dropout rate was only 27% compared to 9% for placebo (18). When data from clinical trials with this design are published, the statement is often made that the titration was forced, with the implication that slower titrations would increase tolerability. However, this does not completely explain the differences in dropout rates between the three EZG studies. The first trial permitted a rather leisurely 8-week titration to the target dose (16), but recorded more dropouts than the second trial, which provided for only a 4-week titration (17). The forced titration period for the third trial was 6 weeks, but it had the fewest dropouts (18).

The most common reasons for dropouts attributed to adverse effects were somnolence, dizziness, and fatigue or asthenia (16,17,18). Adverse effects with a definite dose-relationship were dizziness and somnolence (17). The dizziness was not usually associated with ataxia. There were also some instances of blurred vision, confusion, dysarthria, and – unusually for an antiepileptic drug- urinary tract infection (18).

Bladder epithelium contains voltage-gated potassium channel isoforms K_{V} 7.2 and 3, and EZG causes urodynamic effects in rats (19). Accordingly, most participants in clinical trials had systematic measurements of post-voiding residual volumes and were administered a standard urological questionnaire designed to detect symptoms of prostatic hypertrophy (20). Among 1365 patients from 7 clinical trials, symptoms related to voiding difficulty or urinary retention occurred in 8.6%, slight increases in post-voiding residual volumes were recorded in 3.0%, and 5 of these 1365 patients required urinary catheterization (21). Symptoms resolved when EZG was discontinued. EZG can cause a reddish or orange discoloration of the urine, which is harmless and unrelated to bladder function.

Safety
So far, EZG therapy appears relatively safe. Concerns about possible cardiac effects of potassium-channel actions have
been allayed by the normal results of ECGs in human trials, including a 24-hour Holter monitor in the first trial (16). In contrast to other antiepileptic drugs, EZG-treated subjects were virtually rash-free (16,17,18), had no visual field effects with formal testing (16), and had no clinically significant changes in hepatic enzymes or hematological parameters (16,17,18). In clinical trials, there were single reported cases of suicidal ideation and of psychosis (16). Sudden death rates are not caused by something unrelated to EZG therapy, such as hemoconcentration, and patients should be informed that urinary discoloration may occur. Although patients certainly should be advised that urinary discoloration may occur. Although peak-dose dizziness occurs, taking EZG with food may help. Patients certainly should be informed that urinary discoloration may occur. Although this effect appears to be harmless, if a patient reports this it may be useful to do a urinalysis to be sure the discoloration is not caused by something unrelated to EZG therapy, such as blood.

Urinary hesitation may occur, and patients should be told this as well. A relative contraindication to EZG use may be prostatism or other pre-existing voiding difficulty. Formal screening and followup with the American Urological Association questionnaire (20) (AUA-SI) may be worthwhile in that circumstance, but is probably unnecessary in most patients. In the absence of evidence of cardiac effects, and with a good biological explanation of why EZG should not affect cardiac function (9), electrocardiographic surveillance should not be required.

Place in therapy
It is to be expected that EZG will tried for patients with refractory partial-onset seizures who have failed other drugs. Most of the interest in this drug derives from its unique mechanism of action. It is tempting to say that we ought to try it in patients who have failed drugs with other mechanisms, but that hardly narrows the field of potential candidates. Will EZG be a path toward rational polytherapy of epilepsy? Theoretically, it should be complementary to both sodium-channel blocking drugs or GABA-facilitating drugs. A critical question is whether EZG displays synergism with other drugs, or merely another “broad-spectrum” antiepileptic drug. EZG holds some promise for having a broad spectrum of activity based on animal data, but it has not been tested for generalized-onset seizures. EZG may also prove useful for conditions other than epilepsy, because its target channels are ubiquitous in the nervous system.

Conclusion
Ezogabine is the first antiepileptic drug with a very specific effect on central nervous system potassium channels. It changes the angle of a critical hinge in two isoforms of voltage-gated potassium channels, facilitating the open state of the channels. Thus it opens a new avenue for therapy of refractory epilepsies. It is also a tool to sort out which syndromes are modifiable by this mechanism. It has advantages of minimal drug interactions and mostly renal excretion. There are few safety concerns and most side effects are those typically seen with antiepileptic agents. The exception is urinary retention, which may rule out its use in populations susceptible to this problem.

References
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