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A New Antiepileptic Agent with Novel Mechanism of Action

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Epilepsy is one of the most common neurological disorders estimated to affect about 1% of the general population [1]. Until 1992, there were 4 main antiepileptic medications primarily utilized for the treatment of epilepsy and they included phenobarbital, phenytoin, carbamazepine, and valproic acid. After 1992, there was an explosion of medications approved for the treatment of seizures. The most recent agent to be approved by the Food and Drug Administration (FDA) was perampanel marketed under the brand name Fycompa®. Perampanel is approved for use in patients 12 years of age and older for the adjunctive treatment of partial-onset seizures with or without secondary generalized seizures [2]. Perampanel has a novel mechanism of action and is the first agent approved in the AMPA receptor antagonists class of antiepileptic medications [3]. By targeting the AMPA receptor, perampanel decreases neuronal excitatory thereby decreasing seizure activity.

Perampanel has been shown to be an effective adjunctive treatment option when compared to placebo. A phase III randomized, placebo-controlled, double-blind trial known as study 306 was conducted by GL Krauss and colleagues [4]. Patients were enrolled into this study if they experienced persistent seizures while taking 1 to 3 antiepileptic medications. Patients were randomized to receive 1 of 3 perampanel doses including 2 mg/day, 4 mg/day, 8 mg/day, or to receive placebo. Doses of perampanel were titrated by 2 mg each week and maintained at the desired dose for a total of 13 weeks. The results of the study showed a statistically significant median percent change in seizure frequency from placebofor perampanel 4 mg/day and 8 mg/day of -10.7%, 23.3% (p=0.0026), and -30.8% (p=<0.0001), respectfully. Additionally, two other phase III, randomized, placebo-controlled,double blind trials, study 304 and study 305, evaluated perampanel doses up to 12 mg/day compared to placebo. However, 12 mg/day did not consistently show an increase in efficacy when compared to 8 mg/day in study 304 and study 305 [3]. The increase in dosage up to the 12 mg/day did show an increase in side effects which is an important point for prescribers to consider when evaluating titrations of doses above 8 mg/day.

Perampanel is available as an oral tablet and is administered once daily. Therapy should be initiated with 2 mg per day taken at bedtime and titrated to an effective daily dose of 4 to 12 mg per day. Patients with mild to moderated renal or hepatic impairment will require reduced dosages and monitoring [5]. Patients with renal or hepatic failure are not recommended to receive perampanel. Perampanel is 95% protein bound and extensively hepatically metabolized via the cytochrome P450 system 3A4 and/or 3A5 [3]. Dizziness, drowsiness, weight gain, falls, and excessive sleep were among the most common side efforts reported during clinical trials [2]. A box warning has been placed on the label of perampanel for serious neuropsychiatric events which may lead to life threatening events. Events include anger, aggression, irritability, mental status changes, paranoia, agitation, euphoric mood and anxiety. Patients should be monitored closely especially during the initial titration of doses and when prescribed higher doses.

While Perampanel was approved by the FDA in October of 2012, it has yet to be released into the United States market. Currently the medication is awaiting the Drug Enforcement Administration's (DEA) classification as a controlled substance due to the concern for abuse potential during the initial approval process [6]. Perampanel's place in therapy is still to be determined.

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