EXPERT OPINION

Safety profile of two novel antiepileptic agents approved for the treatment of refractory partial seizures: ezogabine (retigabine) and perampanel

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Introduction: Complex-partial seizures are frequently resistant to antiepileptic therapy. Two new medications with mechanisms of action novel within the antiepileptic class have recently received approval for the adjunctive treatment of partial (focal) seizures.
Areas covered: A Medline search was conducted to identify preclinical and clinical studies of ezogabine and perampanel. This was supplemented with additional articles obtained from online sources and information provided by the FDA and the manufacturers. The focus of this review is on the safety profiles of ezogabine (retigabine), a novel antiepileptic that targets voltage-gated potassium channels, and perampanel, a noncompetitive α-amino-3-hydroxyl-5-methyl-4-isoxazole-propionate glutamate receptor antagonist.
Expert opinion: Central nervous system effects are predominant within the adverse event profiles of both ezogabine and perampanel. In addition, ezogabine exerts its inhibitory effects on potassium channels in the urogenital tract potentially resulting in urinary retention and related outcomes. Recent reports of blue discoloration of the skin and in the retinas of long-term ezogabine users have surfaced. Both drugs have demonstrated the ability to induce neuropsychiatric symptoms. Though both are welcome additions to the antiepileptic drug class, additional monitoring, appropriate counseling, and careful selection of patients are warranted to minimize adverse events.

Keywords: AMPA, ezogabine, glutamate, partial seizures, perampanel, potassium channels, retigabine, urinary retention

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1. Introduction

Of all seizure types, partial (focal) seizures are the most common among patients with epilepsy. Worldwide, approximately 50 million persons have epilepsy, and, of those, approximately 60% experience partial seizures [1]. Because of the often refractory nature of partial seizures despite trials of multiple medications, developing new drugs with novel mechanisms of action is a current aim of epilepsy research. At present, the FDA has approved eight medications as monotherapeutic options for partial seizures. They include carbamazepine, phenytoin, phenobarbital, and valproic acid, which are among the older antiepileptic medications. Second-generation agents approved for monotherapy include lamotrigine, felbamate, oxcarbazepine, and topiramate. All approved monotherapeutic agents demonstrate similar rates of efficacy (approximately 20 – 50% decrease in seizure frequency) [2].

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Article highlights.

- Ezogabine and perampanel are newly approved antiepileptic agents for the adjunctive treatment of partial seizures.
- Ezogabine is a first-in-class modulator of Kv7 potassium channels.
- Perampanel is a first-in-class, selective, noncompetitive antagonist of AMPA glutamate receptors.
- The adverse event profiles of both medications are primarily related to CNS effects.
- Urinary retention, blue discoloration of skin and retinas, and neuropsychiatric changes have been observed with ezogabine.
- Perampanel labeling includes a warning about neuropsychiatric adverse events including aggression and homicidal ideation.

This box summarizes key points contained in the article.

Most medications recently approved for the treatment of partial seizures have been given the designation 'adjunctive therapy' owing to difficulties associated with satisfying requirements for clinical trials of new entities demonstrating monotherapeutic efficacy. These second-generation agents include gabapentin, lacosamide, levetiracetam, pregabalin, tiagabine, vigabatrin, and zonisamide. The majority of approved antiepileptics either modulate voltage-gated sodium or calcium channels, or facilitate the enhancement of the inhibitory neurotransmitter gamma-aminobutyric acid). Exceptions include gabapentin and pregabalin which act upon the α2δ-subunit of L-type voltage-regulated calcium channels, lamotrigine which acts upon the H-current, and levetiracetam which exerts activity via synaptic vesicle protein 2A. Two of the newest additions to the partial seizure medication arsenal are ezogabine (Potiga®, GlaxoSmithKline) and perampanel (Fycompa®, Eisai, Inc.). Both agents have novel mechanisms of action, and each has been approved as adjunctive therapy for refractory partial seizures (**Table 1**).

Ezogabine was approved by the FDA in June of 2011 (and by the European Medicines Agency (EMA) in May 2011 under the nonproprietary name retigabine). It is the first antiepileptic agent to specifically target potassium channels (**Figure 1**). Perampanel received FDA approval in October 2012 (EMA approval was received in July of the same year). It is a selective antagonist at α-amino-3-hydroxyl-5-methyl-4-isoxazole-propionate (AMPA) receptor sites (**Figure 2**). The early approval of perampanel for patients as young as 12 years of age is unique among the antiepileptic class.

2. Ezogabine

2.1 Pharmacology

Though ezogabine is commonly called a potassium channel opener, that designation is not entirely accurate [3]. The drug has activity at Kv7.2 and Kv7.3, two voltage-gated potassium channel types corresponding to the KCNQ2 and KCNQ3 genes. Binding occurs at the hydrophobic pocket of the activation gate within the pore of the channels [3-7]. Subsequently, enhancement of the outward potassium current that ultimately results in membrane repolarization after an action potential, also known as the M-current, occurs [3]. Ezogabine causes a shift in the action potential resulting in a more hyperpolarized state. The drug causes the gate to remain open slightly resulting in the need for less energy to complete the opening process, and an extension of the time the gate is in the open state (up to fourfold) [8]. Ultimately, this results in inhibition of repetitive neuronal firing.

Because of the preponderance of potassium channels throughout multiple body systems, particular attention has been paid to the possibility that ezogabine's effects may extend beyond the central nervous system (CNS) causing unwanted adverse reactions.

2.2 Safety and tolerability

Three Phase III clinical trials were pivotal to the eventual approval of ezogabine for use to treat seizures. The first was a study by Porter *et al.* during which placebo or ezogabine at daily doses of 600, 900, or 1200 mg was administered [9]. RESTORE 1 compared placebo to ezogabine 1200 mg/day, and RESTORE 2 compared subjects taking 600 or 900 mg of ezogabine daily with those taking placebo [4,10]. As would be expected and consistent with other antiepileptic agents, the most commonly observed adverse effects seen with ezogabine use are CNS-related. At least 10% of study participants in Phase III clinical trials experienced somnolence, fatigue, confusion, dizziness, tremor, abnormal thinking, vertigo, speech disorders, or amnesia [4,9,10]. Adverse effects not of CNS origin that were seen with relative frequency included headaches and asthenia. Most of these adverse effects appear to be related to dose, and are typically reported to be mild or moderate in nature.

Similar information has come from two ongoing extension trials of ezogabine [11]. At the time of interim data publication, 60% of subjects had received at least one year of open-label therapy in these trials allowing for analysis of long-term data. Of 477 reported adverse events, 411 were believed to be possibly related to medication use. As in the Phase III trials, the majority (62%) of adverse events were CNS-related.

In addition, several ezogabine users experienced neuropsychiatric events including hallucinations (2%), confusion (9%), and psychosis (1%) [12]. The majority of these episodes occurred within the first two months of drug exposure in individuals with no documented history of a psychiatric disorder. Approximately half of the patients required medical intervention, including hospitalization. There appears to be a correlation to dose with these events, as well as a correlation with rapid dose titration [13]. In the extension trials, 24% of subjects reported a psychiatric event of some kind [11].

As the cardiac system is replete with potassium channels, the potential for associated adverse events was made an early focus of ezogabine safety evaluations. However, the Kv7.1

Table 1. Summary of ezogabine (retigabine) and perampanel drug properties.

Medication	Approved indication	Mechanism of action	Adverse effects	Dosing
Ezogabine	Adjunctive treatment of partial-onset seizures in patients aged 18 years and older	Modulation of voltage-gated Kv7 potassium channels	Dizziness, somnolence, confusion, fatigue, urinary retention, increased PVR, blue discoloration of skin and eyes, neuropsychiatric events	100 mg p.o. tid (initiation) Maximum recommended dose is 400 mg p.o. tid Dosage adjustment required for patients > 65 years of age, renal dysfunction, and moderate/severe hepatic dysfunction
Perampanel	Adjunctive therapy for the treatment of partial-onset seizures in patients with epilepsy aged 12 years and older	Noncompetitive antagonist of the ionotropic AMPA glutamate receptors on postsynaptic neurons	Dizziness, somnolence, ataxia, fatigue, neuropsychiatric events (including aggression and homicidal ideation)	2 mg p.o. q hs (initiation) or 4 mg p.o. qhs (for patients on enzyme-inducing antiepileptics) Maximum recommended dose is 12 mg po qhs

AMPA: α-amino-3-hydroxy-5-methyl-4-isoxazolepropionicacid; PVR: Post-void residual volume.

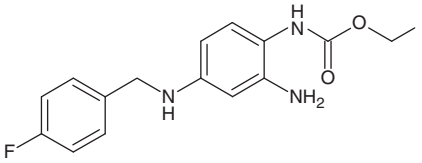

Figure 1. Ezogabine chemical structure.

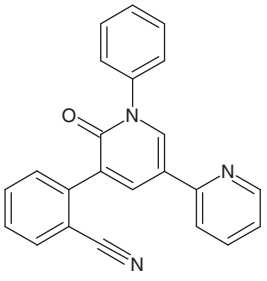

Figure 2. Perampanel chemical structure.

channels found in the cardiac tissue lack the glycine target needed for binding of the drug [3]. In Phase III clinical trials, no notable cardiac effects were demonstrated on ECG or during holter monitor use [13]. However, in healthy volunteers, QT interval prolongation (average 7.7 ms) was observed with ezogabine. In most cases, this reaction has been associated with a 1200 mg/day dose (the high end of the recommended range). There is no specific contraindication for ezogabine use when a patient is already taking a medication known to prolong the QT interval, and no post-marketing reports have been published that would suggest that this is a significant problem in clinical practice. However, monitoring for additive effects leading to ECG changes and cardiac symptoms is advised [13].

Much of the focus on ezogabine safety has been on adverse events involving the urinary system. Potassium channels in the urothelium of the bladder may be affected by ezogabine leading to negative outcomes [14]. Normally, contraction of smooth muscle in the urinary bladder occurs due to spontaneous action potentials [15,16]. Enhanced activity in the Kv7 channels would logically be expected to result in a decrease in contractile response [17]. In early studies performed in rats, bladder tissue demonstrated a reduction in tone and in contractility when exposed to ezogabine, and increased micturition volume and voiding intervals were noted [18,19].

One analysis of 1365 persons receiving ezogabine demonstrated voiding difficulties in 8.6%. Another 3% experienced an increase in post-void residual volume (PVR). Urinary catheterization was necessary for 5 individuals, including one 31-year-old male subject with a history of urinary retention related to anticholinergic medication use who had to continue self-catheterization after drug withdrawal and washout [20]. Phase III studies utilized the American Urological Association Symptom Index (AUA-SI) and PVR measurement to assess effects on the urinary tract. A single subject in the RESTORE 1 trial experienced urinary retention while receiving ezogabine compared with two patients who were given placebo. Increased PVR of ≥ 100 ml was seen in 15 and 6 patients receiving active treatment and placebo, respectively [10]. However, no significant changes were seen in patients enrolled in RESTORE 2 when assessed according to the AUA-SI or PVR. Three subjects withdrew due to nephritis or urinary retention. Individuals enrolled in the extension studies experienced urinary adverse events (retention and hesitation most commonly) at rates of 3% or less [11].

Brickel and colleagues assessed all urinary adverse event data available from Phase II and III trials through early October 2009 [17]. Considering the entire subject pool, 8.6% of subjects experienced symptoms consistent with urinary retention and dysfunctional voiding. Overall, the rate of discontinuation considering both Phase II and Phase III

studies due to urinary retention was 0.4%. The majority of AUA-SI scores were reported as consistent with mild dysfunction. In the Phase III trials, the relative risk of reporting a urinary adverse event in ezogabine users was 1.32 (95% confidence interval, 0.986 – 1.761). Urinary tract infections that occurred in study subjects enrolled in the Phase III trials are difficult to link to drug therapy as none were preceded by urinary retention, and few were confirmed by urine culture. Crystals described as 'bilirubin-like' were noted in 15.1% of subjects in the Phase III trials, but, upon analysis, none were found to be composed of bilirubin. Of 10 individuals developing nephrolithiasis while receiving ezogabine, 5 were noted to be receiving topirimate concurrently, and 3 had a positive history. Stone formation is a known side effect associated with topiramate use presumably due to its weak carbonic anhydrase inhibiting activity. Ezogabine does not inhibit carbonic anhydrase, and the incidents of nephrolithiasis that occurred during use are not believed to have been a consequence of drug exposure. Neither nephrolithiasis nor nephrotoxicity has been associated with ezogabine therapy to date. There was no demonstrable difference between subjects of either sex in terms of frequency of adverse urinary events in Phase II or Phase III trials. Differences by age group were not possible due to small numbers of subjects (i.e., the elderly). It should be noted that reddish-orange discoloration of the urine is a known side effect of ezogabine. However, there is no evidence that this change in urine color affects bladder function in any way [3].

There have been isolated cases of urinary retention in patients receiving other second-generation antiepileptic drugs, but it is not considered a common occurrence for any. However, ezogabine is unique in that its mechanism of action predisposes users to this adverse event. In response to the discovery of substantial urinary-related adverse events with ezogabine use, a risk evaluation and mitigation strategy (REMS) has been put in place. The stated goal of the REMS is to inform healthcare providers of the potential for urinary retention. Data submission from the manufacturer is required for the first three years the drug is available on the US market, and again seven years from the date of the REMS approval. A medication guide instructing patients on how to self-monitor for potential changes in urinary function (including difficulty with initiation, bladder emptying, weak stream, and dysuria) must be dispensed with all ezogabine prescriptions and samples.

On April 26, 2013, a Drug Safety Communication was disseminated to healthcare professionals by the FDA [21]. Newly identified changes in the retinas of patients receiving long-term ezogabine have been reported, as have occurrences of blue skin discoloration. Only subjects who were enrolled in clinical trials have been affected substantiating that the appearance of these adverse events is linked to extended medication use. The earliest reported event occurred after three years of drug exposure. Retinal pigment changes have been linked to impaired vision, but at present the FDA is stopping short of declaring that visual acuity may be reduced in ezogabine users who experience this adverse event. Reports of impaired vision have been noted in ezogabine recipients, and retinal dystrophy has been identified in a single patient who has undergone a full panel of retinal studies. Eleven of 36 subjects remaining in ongoing trials who underwent funduscopic and corrected visual acuity examinations demonstrated pigment changes. How quickly the abnormalities progress and the optimal detection method are yet to be identified. However, baseline ophthalmologic exams are suggested, with periodic follow-up exams to continue indefinitely while the patient remains on medication. Discontinuation of the drug if abnormalities are found is recommended. The blue skin changes are most commonly isolated to the nail beds, but some patients have experienced discoloration of the face, lips, or legs. Scleral and conjunctival discoloration has been observed in some patients as well. The mean exposure to drug in these patients is 4.04 years, with a range of 0.8 – 7 years. Of the patients who have been examined, 6.3% (of an estimated 605 total individuals) have evidence of skin discoloration. Overall, one in three patients has been found to have evidence of retinal pigment changes, and two of three of those patients also exhibited blue skin discoloration. The significance and the permanence of these adverse effects are yet to be determined. These adverse events have not been observed with other antiepileptic drugs.

2.3 Serious adverse events and study withdrawals

Serious adverse events with ezogabine in the Phase III trials were uncommon. In the study by Porter *et al.*, 21 subjects experienced adverse events considered serious compared to 8 who were taking placebo [9]. Suicidal ideation and psychosis were included among the events experienced. Seventy-nine patients withdrew from the study, 62 of whom were receiving ezogabine. Withdrawals occurring in ≥ 5% of subjects in any treatment group were attributed to confusion, dizziness, speech disorder (not otherwise specified), and asthenia. In the RESTORE 1 trial, 8 and 19 serious events occurred in the placebo and active treatment arms, respectively [10]. These events were categorized as related to the nervous system, as being psychiatric in nature, or metabolic/nutritional. Events occurred in the ezogabine treatment groups at rates of 2 – 4 times those seen in the placebo group. Of 71 withdrawals, 11 involved subjects receiving placebo. Discontinuation rates for subjects in the RESTORE 2 trial were 8% for the placebo group, 17% for the 600 mg/day group, and 26% for the 900 mg/day group. Serious adverse events were reported by 4 and 8% of the placebo and active treatment groups, respectively [4]. No negative laboratory, ECG, or vital sign events were documented during the Phase III trials.

In the ongoing extension trials of ezogabine, 104 of 334 individuals ceased study participation due to adverse events as of the time of data cutoff for the report [11]. Eighty-eight subjects (16%) claimed a serious adverse event, 7% of

which were epilepsy-related. Psychiatric adverse events, including confusional state and conversion disorder, each of which occurred in more than one individual, were seen in 3% of study participants. Six deaths have occurred in the extension studies as well. Two of them were classified as SUDEP, one was probable SUDEP, and the remaining three cases were not believed to be related to the medication or to the diagnosis of epilepsy.

2.4 Drug interactions

Ezogabine has minimal potential for significant interactions with other antiepileptic agents [22]. However, ezogabine labeling does mention the possible need for dose increases when the drug is given simultaneously with carbamazepine or phenytoin, both known to be potent enzyme-inducing medications (primarily CYP3A4 and CYP2C9) [12].

A study evaluating 29 healthy male subjects who received ezogabine with concomitant lamotrigine demonstrated an increase in the half-life of ezogabine of 15%, and an increase in the area under the curve (AUC) of 7.5%, both of which reached statistical significance [23]. Alternately, lamotrigine AUC and half-life were decreased by 18 and 15%, respectively (also significant). The results regarding lamotrigine remain unexplained as ezogabine is not known to have significant effects on hepatic enzymes. At this time, no specific changes in prescribing of either drug are recommended when they are to be used together. Significant interactions with other medications (including a combination oral contraceptive, imipramine, phenobarbital, propofol, and valproic acid) have not been identified [24-26].

2.5 Abuse potential

Ezogabine was approved as a schedule-V drug under the FDA's Controlled Substances Act [27]. The drug has been shown to exhibit CNS depressant properties similar to medications classified as sedative-hypnotics. Euphoria was reported in Phase I trials at a similar rate that is reported by users of the benzodiazepine alprazolam given at doses of 1.5 to 3 mg (6 – 9%). In particular, patients with a history of recreational use of sedative-hypnotic agents reported higher ratings on visual analog scales created to detect likeability of drug effects. Euphoria rates were more common in this group (18 – 33%). To date, no accounts of ezogabine diversion for the purpose of abuse have been described.

3. Perampanel

3.1 Pharmacology

Increased levels of glutamate in the CNS have long been a suspected seizure trigger, and elevated hippocampal levels have been observed during and immediately prior to seizure activity [28,29]. Previous attempts at targeting N-Methyl-D Aspartate glutamate receptors have been disappointing, and were associated with frequent neuropsychiatric adverse effects [30,31]. However, the AMPA glutamate receptors, which are the principal mediators of excitatory neurotransmission in the brain, have been identified as playing a significant role in the development of seizure activity [31]. These receptors serve as both binding sites for glutamate and as ligand-gated cation channels [32]. Excessive stimulation of these receptors by glutamate has the potential to induce calcium overload in cells, and, subsequently, excitotoxicity [33,34]. Perampanel was created to inhibit this excessive stimulation by acting as a selective, noncompetitive antagonist at excitatory postsynaptic AMPA receptors. Binding of the drug to its receptor site allows for simultaneous binding of glutamate, but the receptor is inhibited from responding to the latter resulting in inhibition of seizure activity. The drug is also unique due to its extensive half-life (66 – 90 h at steady state in healthy volunteers).

3.2 Safety and tolerability

Two completed Phase II studies included doses of perampanel ranging from 4 to 12 mg/day compared with placebo [35]. Reported rates of adverse events were similar between subjects taking the active drug and those receiving placebo (66.7% for patients receiving 4 mg/day compared with 62.7% of patients receiving placebo in the first study, and 84.2% of active medication recipients vs 80% of patients in the placebo arm for those enrolled in the second study who were given doses up to 12 mg/day). Withdrawal rates were low, and similar among all groups as well [35]. Dizziness and somnolence were both experienced by > 10% of enrolled subjects, but given the fact that patients were allowed to use additional antiepileptic therapy, it is difficult to determine if perampanel was the responsible agent. No significant findings with regard to laboratory testing occurred or were noted during the Phase II trials. An ongoing extension study of the Phase II trials has produced data demonstrating a high rate of adverse events (93.5%), the majority of which are described as mild or moderate in severity [36].

Three Phase III perampanel trials have been completed, and one extension trial is continuing [37-40]. Of the adverse events experienced by subjects enrolled in any of these four trials, 78.2% experienced adverse events that were suspected to be related to perampanel use, while 9.2% were not purported to be drug-related. As with the Phase II trials, intensity was described as mild to moderate for the majority of events. There appeared to be a dose relationship with the emergence of adverse events, as well as a relationship with the speed of drug titration. Dose reduction during the titration phase of a study or interruption in administration of the medication was necessary for 36.1 and 3.3% of study subjects, respectively, most of which resulted from dizziness (> 20%). Other adverse events leading to dose reduction or interruption that occurred in fewer than 10% of enrollees included somnolence, ataxia, fatigue, headache, and disturbances of gait.

Reports of weight gain have been generated from Phase III trials as well. The threshold for weight gain was set at a change from baseline of 7% or greater. Perampanel users

exhibited weight gain at a rate of 14.6% compared to 7.1% for the placebo recipients [41]. The mean weight gain in all users of perampanel was 0.8 kg. Unlike most of the other side effects related to perampanel use, weight gain did not appear to show a correlation to the dose administered. Larger changes in weight were seen in the patients receiving perampanel versus placebo (14.6 vs 7.1%) [41].

Limited occurrences of laboratory changes possibly, but not conclusively, related to perampanel use had been noted in the extension trial at the time of data reporting [40]. Liver function tests (specifically alanine aminotransferase and aspartate aminotransferase) greater than three times the upper limit of the normal range were observed in < 1% of users, and creatine phosphokinase levels higher than five times normal were seen in 1.7%. No ECG changes were noted to be of clinical significance, and blood pressure changes were rare (< 2% of study subjects).

3.3 Serious adverse events and study withdrawal

No deaths occurred during the Phase II trials. Serious adverse events noted in the Phase II extension trial have all been related to the diagnosis of epilepsy (convulsions, status epilepticus, or tonic-clonic seizures) with the exception of a single patient who was diagnosed with schizophrenia [36]. This finding was consistent with the subsequent Phase III trials during which serious adverse events were nearly exclusively related to seizure activity [40]. A single death that occurred during the Phase II trials was due to cardiac arrest, and was not believed to be related to the consumption of the study drug. Withdrawals were infrequent in the Phase II trials, and were not significantly different between placebo and active treatment groups. In the study where patients received only 4 mg of perampanel daily, there were three subjects in both groups who withdrew due to adverse events [35]. Of the subjects in the second trial who had the potential to receive doses as high as 12 mg/day, one withdrawal related to adverse events was reported in the placebo arm compared with two in the perampanel arm [35].

The Phase III trials did not include any subjects who may have experienced SUDEP, though there was one such report in the extension trial [40]. Suicidality was noted in two patients receiving active drug in the Phase III trials (at doses of 2 and 8 mg/day), and in an additional two subjects receiving placebo [37-39]. The withdrawal rate across all of the Phase III studies, including the extension trial, was 13.2% [37-40]. The most common adverse events resulting in withdrawal were dizziness, irritability, and aggression.

Although a warning addressing suicidality is standard within the labeling of all antiepileptic drugs, and neuropsychiatric side effects are not unexpected among some drugs within the class, the FDA-approved labeling for perampanel includes a boxed warning indicating the need to monitor for serious life-threatening neuropsychiatric reactions including aggression, hostility, irritability, anger, and homicidal ideation and threats [42]. One subject in the Phase III studies who was receiving 12 mg of perampanel per day exhibited homicidal ideation. The patient was positive for a medical history that included depression and a personality disorder (not otherwise specified). The issue resolved approximately a month after perampanel discontinuation. Similarly, a single individual in the extension trial (also with a history of depression) demonstrated homicidal thoughts, while another patient (with a history of aggression) exhibited aggressive behavior [40,41]. A third patient in the same study with a reported history of antipsychotic use that had been discontinued due to what was described as 'economic' reasons developed an impulse control disorder while receiving perampanel. Suicidality was noted in three subjects in the Phase III trials receiving perampanel as compared to two who were being given placebo.

3.4 Drug interactions

Several antiepileptic drugs are known to be potent inducers of the cytochrome P450 hepatic enzymes. Of these, carbamazepine, oxcarbazepine, and phenytoin have demonstrated the ability to decrease perampanel serum concentrations by as much as 67% [42]. Interestingly, phenobarbital, another potent enzyme-inducing antiepileptic drug, has not shown the same tendency. The manufacturer suggests increasing the initial dose of perampanel by 100% (from 2 to 4 mg daily) when strong enzyme inducers are being administered simultaneously. There is also a general recommendation to consider dose increases with enzyme-inducing drugs in other classes, such as St. John's Wort and rifampin [42].

Though the effect of perampanel on the effectiveness of combination oral contraceptives has not been established, the drug has been shown to decrease levonorgestrel serum concentrations [42]. Backup birth-control methods are recommended if the combination is necessary. Other interactions have been identified including a 14% decrease in midazolam concentrations when coadministered with perampanel, and a decrease in perampanel concentrations of 20% when given simultaneously with the antifungal agent ketoconazole. The significance of these interactions on the effectiveness of any of the drugs involved remains to be determined.

3.5 Abuse potential

At the time of this writing, perampanel remains under review by the DEA for determination of schedule [42]. Perampanel has been studied for its abuse potential. When compared to the benzodiazepine alprazolam (1.5 or 3 mg) and 100 mg of oral ketamine in recreational drug users, higher than normal doses of perampanel (24 or 36 mg) produced euphoric effects similar to both ketamine and the larger dose of alprazolam. On a visual analog scale used to test for dissociative phenomena ('floating', 'spaced out,' or 'detached'), responses for perampanel recipients matched those of ketamine users, and were greater than those observed with alprazolam. Overall, the incidence of euphoria with perampanel ranged from 37% with an 8-mg dose to 46% with a supra-therapeutic dose of 36 mg. This was higher than what was reported with the higher

alprazolam dose, but lower than that seen with ketamine. Perampanel's propensity to result in significant withdrawal symptoms secondary to physical dependence has not been reported [42].

4. Conclusion

Phase II and III trials suggest perampanel to be a safe addition to the antiepileptic drug arsenal for adjunctive therapy of partial seizures. Ezogabine is also well tolerated by most patients. However, a new safety signal (blue discoloration of the eyes and skin) has emerged, and its significance remains to be determined.

5. Expert opinion

Ezogabine and perampanel represent new, novel antiepileptic agents for use in the treatment of partial seizures as add-on therapy. As complex-partial seizures are among the most difficult to control, the arrival of drugs with mechanisms of action distinct from drugs currently available in the marketplace is a welcome occurrence. Both medications claim CNS-related adverse events as the most commonly reported issues with therapy. This is to be expected given the sites of action of these medications, and is consistent with the side-effect profile of other antiepileptic drugs. To offset the frequency with which these adverse events occur and to minimize their effect on the patient, perampanel is recommended to be dosed at bedtime, and both medications should be up-titrated slowly.

The primary concern with perampanel use is the emergence of neuropsychiatric symptoms. Though they appear to be rare, patients have developed aggressive and even homicidal thoughts and behaviors leading to the inclusion of a black-box warning on the proposed labeling of the drug. The limited number of reports to date suggests that individuals with a history of psychiatric diagnoses, including but not limited to depression, may be predisposed to psychiatric adverse events while receiving perampanel therapy. For this reason, patients should be counseled on the need to monitor for symptoms, and additional monitoring by healthcare providers is advisable. Despite this warning, no REMS has been developed for perampanel. Considering ease of use and the potential for drug interactions, perampanel is known to interact significantly with inducers of the cytochrome P450 enzymes. However, given that the drug has such a long half-life, it is unlikely that subtherapeutic levels will result, and once-daily dosing should continue to be adequate. Initiation of therapy should be more aggressive in terms of dose when the drug is given with known inducers, though titration should remain slow so as to minimize the onset of adverse events that may affect adherence.

Ezogabine requires additional monitoring by patients and caregivers for several reasons. The early focus on ezogabine adverse events was on the drug's ability to induce urinary symptoms. Patients must be explicitly told how to monitor for changes in urinary function, and instructed to contact the prescriber if symptoms occur. It is also logical that the drug is best avoided in patients who are predisposed to urinary retention such as those receiving a significant anticholinergic load, those with benign prostatic hyperplasia, and those with cognitive impairment that would impede self-monitoring and regular toileting. All healthcare providers associated with ezogabine use should become familiar with the REMS that has been developed to address the urinary symptom associated with ezogabine use.

The finding that the QT interval is prolonged even in healthy volunteers has led to the recommendation that additional monitoring be undertaken when ezogabine is administered with other drugs that affect the QT interval. In addition, caution should be exercised when prescribing the drug for persons with diagnoses that may predispose them to cardiac events (congestive heart failure, ventricular hypertrophy, and low levels of electrolytes such as potassium and magnesium) [42]. It should be noted that to date, no case reports of negative cardiac outcomes related to the effect of ezogabine on the QT interval have been reported in the literature, and the real-life significance of this finding appears to be small.

Like perampanel, ezogabine has been associated with neuropsychiatric adverse events. However, most of these episodes occurred in patients without a known psychiatric history. These events appear to correlate with the need for higher doses, and have been significant necessitating intervention including hospitalization of a number of patients. Because of the unpredictable nature of these events, patients should be cautioned to look for associated signs, particularly those that are taking doses near the upper end of the dosing spectrum.

Blue discoloration of the skin and eyes in patients taking ezogabine for an extended period of time has recently been identified as a concern with the use of the drug. Currently, there are no recommendations for immediate discontinuation. However, since it is currently not known if the effects are either partially or totally reversible, and because the effect on visual acuity remains in question, all patients currently receiving ezogabine should be evaluated by an ophthalmology professional as soon as possible, and periodically while therapy continues. Until more is known about the significance of the discoloration, it is prudent to discontinue the medication with a slow downward titration in the case that blue deposits in the eyes are identified unless the patient's seizures have proven refractory to most other antiepileptic medications suggesting a positive benefit-to-risk ratio.

Both perampanel and ezogabine represent significant and welcome advances for the treatment of resistant partial seizures, though their efficacy in comparison to other drugs with this indication is unknown. Perampanel appears to be a relatively safe medication, but should be used with caution

in patients with a history of neuropsychiatric diagnoses. Significant adverse events associated with ezogabine appear to be relatively infrequent, but are common enough to warrant consideration of alternative medications in patients who have a predisposition to any of the known reactions. At this time, because the significance of the color changes in the skin and eyes of long-term users is in question, additional consideration should be given to the use of other medications when possible.

Declaration of interest

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