

## Retigabine (Ezogabine) for management of partial onset seizures: A mini review

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### ABSTRACT

Epilepsy, a neurological disorder is currently the target of many drug research companies who are constantly involved in the development of new therapies with novel mechanism of actions as the current plethora of anti epileptics have not been successful in achieving full control of the seizures. Retigabine (Ezogabine) is a new paradigm in the treatment of epilepsy, as it is first of its kind of a drug that targets neuronal voltage gated potassium channels (Kv7) and facilitates them, thus decreasing the repetitive firing of neurons. It has been approved by European Medicine Agency and USA Food and Drug Administration as an add on therapy for use in patients 18 years and above suffering from partial onset seizures with or without secondary generalization.

**Key words:** Retigabine, Ezogabine, Kv7 channels, partial onset seizures

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### INTRODUCTION

Epilepsy is the second most common neurological disease of humans after stroke affecting around 50 million people across the world. The estimated incidence is 20-70 new cases/10,000 individuals<sup>[1]</sup> and it is associated with significant morbidity and mortality. By definition, epilepsy is a brain disorder characterized predominantly by recurrent and unpredictable interruptions of normal brain function, called epileptic seizures.<sup>[2]</sup> The term seizure refers to a transient alteration of behavior due to the disordered, synchronous and rhythmic firing of brain neurons. Seizures can be non epileptic (with provocative cause) or epileptic (without provocative cause).<sup>[3]</sup>

Currently, a plethora of anti-epileptic drugs is available with distinct mechanism of actions. They act predominantly by targeting voltage gated sodium channels (phenytoin, carbamazepine, topiramate, valproic acid); gamma amino butyric acid A (GABA<sub>A</sub>) channels (benzodiazepines, tiagabine & vigabatrine); calcium channels (ethosuximide) and synaptic vesicle protein SV<sub>2</sub>A (levetiracetam, brivaracetam).<sup>[3]</sup>

Despite such an armamentarium of antiepileptics being available, complete seizure

control is not achieved in many patients as they fail to respond completely to the pharmacotherapy while others suffer from intolerable side effects of these drugs which many a times leads to discontinuation of the treatment. Hence clinical research continues in this field to come up with novel antiepileptics with new targets and mechanisms of actions which have improved activity and/or reduced side effects. One such potential target is neuronal voltage gated K<sup>+</sup> channels.<sup>[4]</sup>

Potassium channel is a tetramer of a subunit and has several families out of which six transmembrane helix voltage gated (Kv) channels are of importance in epilepsy.<sup>[4]</sup> Potentiation of these channels by synthetic chemical ligands is believed to be useful in treatment of diseases with hyperexcitability like epilepsy. The Kv channels conduct various voltage gated K<sup>+</sup> currents including A current (by Kv1, Kv3, Kv4) and M current (by Kv7/ KCNQ).<sup>[5,6]</sup>

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These currents play an important role in stabilizing hyper-excitable neurons in brain areas like neocortex and hippocampus.<sup>[4]</sup> KCNQ channels are widely expressed in various tissues and it has five isoforms. The neuronal isoforms are KCNQ2-5 while KCNQ1 is present in cardiac myocytes.<sup>[7]</sup> The mutations in KCNQ2 and KCNQ3 were seen in benign familial neonatal convulsions, linking them to human epilepsy.<sup>[8]</sup> In neurons, KCNQ2 and KCNQ3 are responsible for the bulk of M current which determines the neuronal firing threshold and firing rate thus taking care of the neuronal hyperexcitability.<sup>[9,10]</sup> Many new molecules targeting KCNQ K<sup>+</sup> channels are being developed and retigabine (ezogabine in USA) among them has shown both preclinical and clinical efficacy and it is shown to facilitate the neuronal K<sup>+</sup> channels Kv7.2 and Kv7.3 (encoded by genes KCNQ2 and KCNQ3) thus potentiating the M current. Retigabine as is known in Europe was approved for use in March 2011 under the trade name of 'Trobalt' while in USA, its non proprietary name is ezogabine and trade name is 'Potiga' which got the FDA approval in June 2011. This drug has been developed and manufactured jointly by Canada based Valeant Pharmaceuticals and UK based GlaxoSmithKline.<sup>[11,12,13]</sup>

#### METHODS FOR DATA COLLECTION

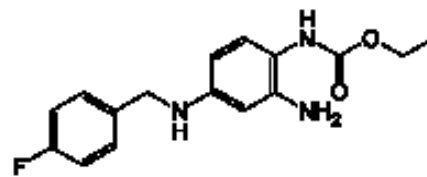
For this review article, resources which were relevant to the topic were searched in the months of July, August and September from online papers (pubmed) using the key words retigabine, ezogabine, partial onset epilepsy, new antiepileptic drugs, novel antiepileptic drug targets. Apart from introductory text selection from text book (Goodman and Gillman's The pharmacological basis of therapeutics), about 40 articles from pubmed were retrieved (including abstracts) and 25 out of them were used for preparation of the review which have been mentioned in the reference list. The articles were studied and the ones (especially the full length available articles) in which the information regarding the role of neuronal voltage gated K<sup>+</sup> currents in epilepsy, chemistry and mechanism of action of retigabine, preclinical and clinical

efficacy and safety studies for retigabine, pharmacokinetics and dosage were presented and discussed in details were considered. All the data gathered was then used to draft a comprehensive review article about the new antiepileptic retigabine, by the authors, with an aim to cover all its important aspects.

#### DRUG REVIEW

##### Chemical structure

Retigabine is ethyl *N*-(2-amino-4-(4-fluorobenzyl amino)-phenyl) carbamic acid ethyl ester.<sup>[11,14]</sup>



##### Mechanism of action

Retigabine (Ezogabine) acts on neuronal KCNQ2-5 (Kv7.2-7.5) K<sup>+</sup> channels leading to hyper polarization of membrane potential and decreased neuronal excitability. Retigabine binds to a hydrophobic pocket at the cytoplasmic ends of the S5-S6 domains of the K<sup>+</sup> channel protein and stabilizes the open form of KCNQ2-5 and causes a hyperpolarization of neuronal resting membrane potential by activation of neuronal K<sup>+</sup> currents (I<sub>KM</sub>) thus reducing spontaneous or synaptically triggered neuronal activity.<sup>[1,4,10,15,16]</sup> Among these subunits, Kv7.2 and Kv7.3 show higher sensitivity to the drug and seem to be the major molecular targets for retigabine.<sup>[17]</sup>

The potentiation of K<sup>+</sup> channel opening by retigabine causing hyperpolarization in hippocampal-entorhinal slices of rat tissue has been demonstrated experimentally.<sup>[17]</sup> A study on Chinese hamster ovary cells showed inhibition of retigabine induced currents on giving linopridine, a blocker of Kv7.2-7.3 channels, further strengthening the fact that the anticonvulsant action of retigabine occurred mainly by action on Kv7.2-7.3 channels.<sup>[18]</sup>

Retigabine does not affect cardiac K<sup>+</sup> channels because Kv7.1 do not contain glycine

component which is important for retigabine to bind to its target.<sup>[11,15,17]</sup> Other mechanism of actions which have been suggested are action on voltage gated sodium and calcium channels and interaction with GABA<sub>A</sub> receptors to potentiate GABA-mediated chloride currents as studied in rat cortical neurons, and these effects occurred at concentrations of 10 μmol/L.<sup>[10,16,17]</sup>

### Pharmacokinetics

Retigabine when orally administered is rapidly absorbed and has a bioavailability of 60%. Food delays its absorption by 2 hours. It has a T<sub>max</sub> of 1.5 hours and elimination half life of 8 hours. Retigabine is widely distributed in the body and is 80% plasma protein bound. It gets metabolized in the liver by acetylation and significantly by glucuronidation to N-glucuronide. Mild hepatic impairment does not require dose reduction. Renal excretion is the main route of elimination of the drug. Patients with creatinine clearance < 50 ml/min require 50% reduction in the dosing of retigabine. In elderly patients of age > 65 years, reduction in dose is recommended and upto a maximum of 900 mg/day can be administered. Retigabine does not influence CYP450 enzymes and exhibits no clinically significant drug interactions with other drugs like valproate, lamotrigine or imipramine *in vitro* assays on human liver microsomal preparations.<sup>[1,19,20]</sup> But in a study on 29 healthy human volunteers where the pharmacokinetic interaction between retigabine and lamotrigine was studied (as both undergo predominantly N-glucuronidation and renal clearance), it was seen that clearance of retigabine was decreased due to both the drugs competing for renal clearance while clearance of lamotrigine was slightly increased.<sup>[21,22]</sup> Whether retigabine causes induction of glucuronidation leading to increase in lamotrigine levels still needs further evaluation. It was seen that in patients already on phenytoin and carbamazepine (inducers of glucuronidation), there was an increase in retigabine clearance by 36% and 27% respectively while administration of topiramate and valproate did not have any interaction with retigabine. Retigabine did not alter pharmacokinetics of phenytoin, carbamazepine, valproic acid, phenobarbital and topiramate.<sup>[1]</sup>

### Efficacy studies

#### *Preclinical studies*

Retigabine (Ezogabine) has been found to be effective in various animal experimental models of epilepsy as it reduced convulsions induced by maximal electroshock and by pentylentetrazole, NMDA and picrotoxin which are predictive of the efficacy of a drug in humans against generalized tonic clonic seizures, absence seizures and myoclonic epilepsy.<sup>[1,17,22]</sup> It has also shown efficacy against sound induced seizures in genetic epilepsy prone rats (GEPR-3s and GEPR-9s) where in low dose, retigabine produced anticonvulsant effect in moderate seizure GEPR-3s than in severe seizure GEPR-9s.<sup>[23]</sup> When retigabine was administered to amygdala-kindled rats (model for complex partial seizures), it increased threshold for induction of after-discharges in amygdala at low dose (0.01 mg/kg intraperitoneally or orally) and also reduced severity and duration of the seizures and after discharge duration at high dose of 5 mg/kg intraperitoneally or 15 mg/kg orally.<sup>[1]</sup>

In other models of pharmaco-resistant epilepsy, which were resistant to antiepileptics like lamotrigine, phenytoin, carbamazepine, topiramate and tiagabine, retigabine inhibited seizures and reduced duration of after discharge caused due to amygdala stimulation.<sup>[1]</sup> Therefore it shows that retigabine can prove to be effective in cases of epilepsy resistant to other anti epileptics.

#### *Clinical studies*

The demonstration of antiepileptic potential of retigabine in preclinical models paved way for further efficacy studies in humans. A 16 week phase II study of retigabine was carried out in 396 patients suffering from uncontrolled partial onset epilepsy and already on one or two antiepileptics. Dosages of 600, 900 and 1200 mg per day each of which were divided in three daily doses versus placebo as an add on/ adjunctive therapy were studied. It was seen that retigabine caused a significant and dose dependent reduction in frequency of monthly seizures in patients (-23.4% with 600 mg/day, -29.3% with 900 mg/day and -35.2%

with 1200 mg/day) as compared to placebo group where a reduction of 13% in seizure frequency was observed. Number of patients who showed  $\geq 50\%$  reduction in seizure frequency was also higher among retigabine group ranging from 23 - 33% (higher with increased dose) while it was 16% in patients who received placebo.<sup>[1,12,15,17]</sup>

Two phase III multicenter, randomized, double blind, placebo controlled short term trials were then conducted with retigabine, known as Retigabine (adjunctive therapy) Efficacy and Safety Study for Partial Onset Refractory Seizures in Epilepsy (RESTORE 1 and RESTORE 2). Both the trials were conducted on patients of 18 - 75 years of age, suffering from refractory partial seizures with or without secondary generalization and on 1 - 3 approved antiepileptics among which carbamazepine was the most commonly received antiepileptic drug, followed by lamotrigine, sodium valproate, topiramate and phenytoin. The dose of retigabine in RESTORE 1 trial was 1200 mg/day (in three divided doses) titrated over 6 weeks. There was significant median percentage reduction in seizure frequency from baseline in retigabine group (44.3%) as compared to placebo group (17.5%) ( $p = 0.001$ ). Also the patients showing  $\geq 50\%$  reductions in seizure frequency were 44.4% with retigabine and 17.8% with placebo ( $p = 0.001$ ).

In RESTORE 2 study, dose of retigabine given was 600 mg/day and 900 mg/day both in divided doses and titrated over 4 weeks versus placebo group. The median percentage reduction in seizure frequency was 27.9% ( $p = 0.007$ ) with the dose of 600 mg/day, 39.9% with 900 mg/day and 15.9% with placebo treatment ( $p = 0.001$ ). Significant reduction in  $\geq 50\%$  seizure frequency was seen with retigabine in the dose of 600 mg/day (38.6%), 900 mg/day (47.0%) while it was 18.9% with placebo ( $p = 0.001$ ).<sup>[11,12,15,17,24]</sup>

Though all these trials were of good quality and used appropriate outcome measures, the use of fixed forced titration and maintenance dose regimens were the cause of increased dropout rates due to intolerable side effects. Therefore lower dose may be useful in epileptic patients. The dosing frequency is

thrice a day for retigabine which may be less favorable for patients who are concurrently on other antiepileptics. Also studies comparing retigabine to other antiepileptics in the market are lacking.

### Safety and tolerability

The potential toxicity of retigabine was investigated in various rodent models of seizures.<sup>[25]</sup> Acute toxicity studies revealed neurological toxicities like hypo or hyperkinesias, disturbed coordination, tremors and convulsions.<sup>[17]</sup> It induced urinary retention which could be due to action on Kv7 channels present in smooth muscles of the bladder along with inhibition of afferent nerve activity.<sup>[28]</sup> No harmful effects on reproductive function of rats were noted and neither did it demonstrate teratogenic or carcinogenic potential.<sup>[17]</sup>

Phase II and Phase III studies in humans where retigabine was used as an adjunct to older antiepileptics, reported adverse events among which the common ones were central nervous system disturbances like dizziness (23%), somnolence (22%), confusion (9%), tremors (8%), abnormal coordination (7%), memory impairment (6%), speech disorder (5%), blurred vision (5%), gait disturbance (4%), aphasia (4%) and balance disorder (4%).<sup>[1,11,12]</sup> These adverse events were dose dependent (more with dose of 1200 mg/day) and rarely serious. They occurred mainly during forced titration phase where many patients withdrew due to dizziness, confusion, somnolence and asthenia. About 26% patients withdrew in retigabine arm as compared to 8.6% patients receiving placebo in RESTORE 1 trial. In RESTORE 2 study, the percentage of patients who left the clinical trial was higher in retigabine group (26% with 900 mg/day and 17% with 600 mg/day) as compared to placebo group (8%). Additionally, in RESTORE 1 trial, 12% patients reported urinary and renal disorders (urinary hesitancy, urinary tract infection and increased post void-residual urine volume).<sup>[11,15,17]</sup> These findings warrant cautious use in patients with cognitive impairment, benign prostatic hyperplasia, neurogenic bladder and patients already on anticholinergics.

A study of cardiac conduction in healthy volunteers showed that retigabine in a dose of 1200 mg/day produced a slight and

transient QT prolongation in ECG tracings within 3 hours of dosing. Hence retigabine needs to be cautiously used in patients with known prolonged QT interval, congestive cardiac failure, ventricular hypertrophy, hypokalemia, hypomagnesaemia, elderly patients of age 65 years and above.<sup>[1]</sup>

### Dosage and precautions

Retigabine is marketed for use in patients of age 18 years or above suffering from partial onset seizures with or without generalization as an adjunctive treatment. The dose can be started at 300 mg/day and gradually increased to 600 - 1200 mg/day in three divided daily doses depending upon the response and tolerability of the drug in the patient. Safety and efficacy of retigabine in children below 18 years of age have not been established yet. It is also not recommended in pregnancy while safety of its use during breast feeding is unknown.<sup>[19]</sup>

### Non epileptic uses of retigabine

Some experimental data suggest other clinical uses of retigabine apart from epilepsy. It may be helpful in treatment of peripheral nerve

hyperexcitability where the role of K<sup>+</sup> channels has been found. Retigabine may have a potential to treat neuropathic pain, mania, dystonia, anxiety disorders, detrusor overactivity and as an anti addictive drug against psychostimulants.<sup>[11]</sup>

### CONCLUSION

Epilepsy significantly alters the quality of life of the patients and although a wide armamentarium of drugs is available for its control, still one third of the patients continue to be resistant to the available pharmacotherapies. As a result of continuous search for new treatment options, retigabine with its novel anti epileptic mechanism of K<sup>+</sup> channel activation has been found to be a good adjunctive measure which has caused considerable reduction of seizure frequency among patients as is observed in the clinical studies. Although it has minimal drug interactions but safety parameters like urological and central nervous system adverse effects need further evaluation which can be clearly understood only when long term studies are carried out. In the meanwhile, further studies are being undertaken to establish its role in other non-epileptic conditions.

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