Cognitive Vitality Reports® are reports written by neuroscientists at the Alzheimer's Drug Discovery Foundation (ADDF). These scientific reports include analysis of drugs, drugs-in-development, drug targets, supplements, nutraceuticals, food/drink, non-pharmacologic interventions, and risk factors. Neuroscientists evaluate the potential benefit (or harm) for brain health, as well as for age-related health concerns that can affect brain health (e.g., cardiovascular diseases, cancers, diabetes/metabolic syndrome). In addition, these reports include evaluation of safety data, from clinical trials if available, and from preclinical models.

Retigabine

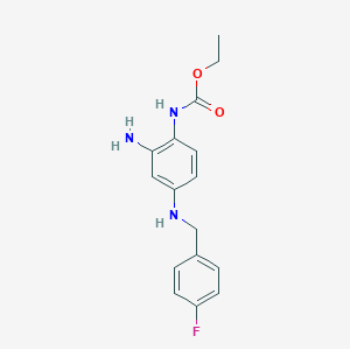
Evidence Summary

Retigabine was FDA-approved for partial-onset seizures but the manufacturer has since withdrawn it from the market. It is associated with cognitive side effects and pigment changes in the eyes and skin.

Neuroprotective Benefit: Retigabine treatment in patients with partial-onset seizures have caused cognitive side effects including somnolence, confusion, memory problems, and speech disturbances, some of which leading to discontinuation of treatment.

Aging and related health concerns: Retigabine protects against ischemia-reperfusion injury and different types of neuropathy in rodent models, but these findings have not been extended to humans.

Safety: Adverse events are common and include dizziness, somnolence, confusion, neuropsychiatric symptoms, tremor, abnormal coordination, memory impairment, speech disorder, blurred vision, gait disturbance, urinary retention, and QT prolongation.

Availability: previously Rx; withdrawn from the market in 2017	**Dose**: The initial dose for seizures in adults was 100 mg orally 3 times a day, and gradually increased to a maintenance dose of 200 mg to 400 mg orally 3 times a day.	**Chemical formula:** $C_{16}H_{18}FN_3O_5$ **MW**: 303.33  Source: PubChem
Half life: 7.5 hours	**BBB**: penetrant	
Clinical trials: A phase 3 randomized double-blind placebo-controlled trial in epilepsy patients included 539 participants.	**Observational studies**: N/A	

What is it? Retigabine (known as ezogabine in the US) was an anticonvulsant used as an adjunctive agent in the treatment of drug-resistant partial-onset seizures (PubChem). It was approved by the European Medicines Agency in March 2011 (under the trade name Trobalt), and in the US by the Food and Drug Administration (FDA) in June 2011 (under the trade name Potiga). However, in 2013, the FDA placed a black boxed warning on the drug label, related to risks of retinal abnormalities, potential vision loss, and blue discoloration of the skin, nail, mucous membrane, and eyes. In 2015, the FDA revised its warning based on safety reports suggesting that the retinal pigment changes did not appear to affect vision, and the skin discoloration appeared to be cosmetic—while requiring GlaxoSmithKline to perform a long-term observational study to evaluate long-term safety. In June 2017, GlaxoSmithKline announced its withdrawal of retigabine/ezogabine from all markets (Neurology Times).

Retigabine selectively activates voltage-activated potassium channels Kv7.2-Kv7.5, which generate the M-current, a subthreshold potassium current that serves to stabilize the membrane potential and control neuronal excitability (DrugBank). Retigabine does not activate cardiac Kv7.1, thereby avoiding cardiac side effects. Retigabine also activates the GABA-A receptor, which is a key inhibitory receptor in the central nervous system and is implicated in epilepsy. Disruption of the GABA-A receptor leads to hyperexcitability in the brain.

Neuroprotective Benefit: Retigabine treatment in patients with partial-onset seizures have caused cognitive side effects including somnolence, confusion, memory problems, and speech disturbances, some of which leading to discontinuation of treatment.

Types of evidence:

- Several meta-analyses in adults with partial-onset seizures
- 1 randomized controlled trial in ALS patients
- 1 retrospective study in epilepsy patients
- Numerous laboratory studies

Human research to suggest prevention of dementia, prevention of decline, or improved cognitive function:

No studies have tested retigabine for the prevention of dementia or age-related cognitive decline. If anything, retigabine may cause cognitive side effects.

Epilepsy/seizure: In a meta-analysis of 3 double-blind randomized controlled trials in adults with partial-onset seizures, retigabine treatment (600, 900, or 1200 mg/day) for 16-18 weeks improved responder rate (odds ratio [OR]=2.79; 95 % CI, 2.08 to 3.76) and rate of seizure freedom (OR =2.54; 95 % CI, 0.92 to 6.98)(Craig et al., 2013). When compared in a network meta-analysis with comparator antiepileptic drugs (eslicarbazepine acetate, lacosamide, pregabalin, tiagabine and zonisamide), retigabine offered similar efficacy in terms of responder rate and freedom from seizure. This study was published in 2013 before retigabine was withdrawn from the market in 2017, but at the time, additional analyses led the Evidence Review Group to conclude that the use of retigabine was not cost effective for the National Institute for Health and Clinical Excellence. Its appraisal committee recommended that retigabine be offered as an option for the adjunctive treatment of partial-onset seizures with or without secondary generalization in adults aged 18 years and older with epilepsy, only when previous treatment with carbamazepine, clobazam, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, sodium valproate and topiramate failed to provid an adequate response, or was not been tolerated.

In a review of antiepileptic medications and their impact on cognition, authors concluded that retigabine may be more problematic than other antiepileptics and that low starting doses and slow titration rates are required to improve cognitive tolerability (Mula et al., 2012). Across the 3 double-blind randomized controlled trials, retigabine treatment-emergent cognitive problems appeared to have a dose-response relationship and occurred during the titration phase, with prevalence rates up to 22% for somnolence, 9.2% for confusion, 5.7% for memory problems, and 4.6% for speech disturbances. Adverse events led

to discontinuation in 17.4, 25.3, and 31.3% of patients for retigabine at doses of 600, 900, and 1200 mg/day, respectively, compared with 10.5% for placebo. The adverse events that most frequently led to discontinuation in retigabine-treated patients included dizziness (5.7%), confusional state (3.9%), somnolence (3.4%), and fatigue (3.3%).

In a retrospective study of 20 patients with drug-resistant epilepsy and cognitive impairment, retigabine treatment (initial dose, 50 mg/day; increased until seizure control; added to preexisting medications) led to many discontinuations (Huber and Bocchicchio, 2015). Retention rates were 60% after 6 months, 35% after 12 months, and 20% after 24 months. At 12 months, there were 2 responders (10%): one had a >90% seizure reduction and the other had a >50% seizure reduction. Another 5 patients remained on retigabine because of minor improvements. Notably, cognitive or emotional changes were the side effects that most frequently led to discontinuation.

Amyotrophic lateral sclerosis (ALS): Increased excitability of motor neurons in patients with ALS may contribute to motor neuron damage. In a double-blind randomized controlled crossover trial of 18 ALS patients, a single dose of retigabine (300 mg) showed significant decreases in peripheral motor nerve excitability measures, including strength-duration time-constant (by 9.2%) and refractoriness at 2 ms (by 10.2%) compared to placebo (Kovalchuk et al., 2018). Other observed significant treatment effects (compared to placebo) were: increases in hyperpolarizing I/V-slope (by 21.7%), resting I/V-slope (by 6.1%), minimum I/V-slope (by 8.5%), rheobase (by 28.0%), threshold for a target compound muscle action potential of 50% (by 25.0%), accommodation half-time (by 3.15 ms), and a decrease in refractory period (by 0.17 ms). However, no correlation between the ALS Functional Rating Scale-Revised and excitability variables was found. Retigabine did not normalize any of the parameters that were found to be significantly different from healthy controls in the study. But retigabine did change strength-duration time constant in the direction of normalization, a variable that has previously been shown to be abnormally increased in patients with ALS. These findings need to be confirmed in longer-term studies to evaluate whether retigabine can impact disease progression and survival. Notably, no significant effects on peripheral motor nerve excitability measures were seen with riluzole treatment, an approved ALS medication.

Human research to suggest benefits to patients with dementia: None available.

Mechanisms of action for neuroprotection identified from laboratory and clinical research: Retigabine's mechanism of action involves reduction of neuronal excitability by enhancing the activity of KCNQ (Kv7) potassium channels (Mula et al., 2012).

In a rat model of acute stress-induced cognitive impairment, a single injection of retigabine (8 mg/kg, i.p.) alleviated spatial memory retrieval impairment by preventing the downregulation of the deubiquitinating enzyme USP2 (Li et al., 2018). Retigabine also restored USP2's upstream regulators (PGC-1α, E4BP4 and β-catenin) and its downstream targets (mTOR, autophagy and GluA1) to normal levels.

APOE4 interactions: Unknown.

Aging and related health concerns: Retigabine protects against ischemia-reperfusion injury and different types of neuropathy in rodent models, but these findings have not been extended to humans.

Types of evidence:

- Several laboratory studies

Ischemia: In a rat model of cerebral ischemia-reperfusion (middle cerebral artery occlusion), retigabine treatment (10 mg/kg, i.p.) one hour after ischemia reduced cerebral infarction volume and decreased the permeability of the blood-brain barrier (Zhao et al., 2018). Retigabine treatment also increased the expressions of tight junction proteins (claudin-5, occludin, and ZO-1) in the blood-brain barrier of the ischemic brain tissue along the microvessels. Retigabine also inhibited the increased expressions of MMP2 and MMP9, proteins that regulate inflammation-related pathological remodeling, at 3, 24, 48, and 96 hours after cerebral ischemia-reperfusion.

Peripheral neuropathy: Retigabine treatment showed efficacy in a rat model of diabetic neuropathy (Djouhri et al., 2019), a rat model of paclitaxel-induced peripheral neuropathy (Li et al., 2019), and an *in vitro* experimental model of partial damage to the saphenous nerve (Bernal et al., 2016). In a rat model of diabetic neuropathy, retigabine treatment (15 mg/kg, i.p.) significantly attenuated mechanical, but not heat hypersensitivity, and was as effective as the positive control gabapentin (Djouhri et al., 2019). In a rat model of paclitaxel (chemotherapy)-induced peripheral neuropathy, retigabine treatment (10 mg/kg, i.p., twice daily) for 10 days attenuated the development of neuropathy without altering the chemosensitivity of breast cancer cells to paclitaxel (Li et al., 2019).

Spontaneous pain is the most devastating positive symptom in neuropathic pain patients. Partial damage to a peripheral nerve may increase the incidence of spontaneous activity in C-fibers, and recent data show a direct relationship between spontaneous discharges in C-fibers and spontaneous pain in

neuropathic patients. In an *in vitro* experimental model of partial damage to the saphenous nerve, retigabine exposure depressed spontaneous discharges by 70% in 15/18 units tested without altering physiological responses in primary afferents (Bernal et al., 2016).

Safety: Adverse events are common and include dizziness, somnolence, confusion, neuropsychiatric symptoms, tremor, abnormal coordination, memory impairment, speech disorder, blurred vision, gait disturbance, urinary retention, and QT prolongation.

Types of evidence:

- 3 meta-analyses or systematic reviews
- 1 double-blind randomized controlled trial in ALS
- 1 retrospective study in epilepsy patients
- 1 review of antiepileptic medications

In 2013, the FDA placed a black boxed warning on the retigabine drug label, related to risks of retinal abnormalities, potential vision loss, and blue discoloration of the skin, nail, mucous membrane, and eyes. In 2015, the FDA revised its warning based on safety reports suggesting that the retinal pigment changes did not appear to affect vision, and the skin discoloration appeared to be cosmetic—while requiring GlaxoSmithKline to perform a long-term observational study to evaluate long-term safety. GlaxoSmithKline has since withdrawn retigabine from the market.

In a meta-analysis of 3 double-blind randomized controlled trials in adults with partial-onset seizures, retigabine treatment (600, 900, or 1200 mg/day) for 16-18 weeks was associated with adverse events at a frequency of 73.7 % in the 600 mg/day group, 81.7 % in the 900 mg/day group, 87.6 % in the 1200 mg/day group, and 74.5 % in the placebo group (n = 427)(Craig et al., 2013). Rates of serious adverse events were 5.9 % in the placebo group and 8.2 % in the 600 mg group, 6.6 % in the 900 mg group, and 11.2 % in the 1200 mg group. The manufacturer reported that the most common adverse events observed during treatment were dizziness (23 %), somnolence (22 %), confusional state (9 %), tremor (8 %), abnormal coordination (7 %), memory impairment (6 %), speech disorder (5 %), blurred vision (5 %), gait disturbance (4 %), aphasia (4 %), balance disorder (4 %), and constipation (3 %). Across the 3 double-blind randomized controlled trials, retigabine treatment-emergent cognitive problems appeared to have a dose-response relationship and occurred during the titration phase.

Similarly, a review of antiepileptic medications and their impact on cognition reported that retigabine is particularly associated with cognitive side effects and low starting doses and slow titration rates are required to improve cognitive tolerability (Mula et al., 2012). Adverse events led to discontinuation in 17.4, 25.3, and 31.3% of patients for retigabine doses of 600, 900, and 1200 mg/day, respectively, compared with 10.5% for placebo. The adverse events that most frequently led to discontinuation in retigabine-treated patients included dizziness (5.7%), confusional state (3.9%), somnolence (3.4%), and fatigue (3.3%).

Retigabine can also cause urinary retention (Neurology Times). Close monitoring is required in patients with benign prostatic hypertrophy or cognitive impairment, and also in patients taking anticholinergic medications. Other adverse effects may include QT prolongation, fatigue, and neuropsychiatric symptoms, including confusion, psychotic symptoms, and hallucinations.

In a meta-analysis examining the risk of infection with antiepileptic drugs based on 127 randomized controlled trials in epilepsy patients, a slight but significantly increased risk of infection was seen when all antiepileptic drugs were pooled; however, retigabine when analyzed alone only showed a nonsignificant trend for an increased risk for infection (Zaccara et al., 2017).

Retigabine has also been categorized as a Schedule V substance, which has comparatively low potential for abuse.

***Drug interactions**:* Retigabine has 60 major drug interactions and 350 moderate drug interactions (Drugs.com). Retigabine may interact with orlistat (WebMD.com). You should tell your doctor or pharmacist if you are taking other medications that cause drowsiness, including alcohol, antihistamines (diphenhydramine or cetirizine), sleep aids/anti-anxiety mediations (e.g., alprazolam, diazepam, zolpidem), muscle relaxants, and opioid pain relievers. Retigabine can also inhibit digoxin clearance, and additional monitoring of digoxin levels may be necessary (Neurology Times).

Sources and dosing: Retigabine/ezogabine was a prescription anticonvulsant used as an adjunctive agent in the treatment of drug-resistant partial-onset seizures (PubChem) under the trade name Trobalt (Europe) and Potiga (US), but GlaxoSmithKline announced its withdrawal of retigabine/ezogabine from all markets in June 2017 (Neurology Times).

The initial dose for seizures in adults was 100 mg orally 3 times a day for 1 week, then increased by no more than 50 mg orally 3 times a day at weekly intervals (Drugs.com). Maintenance dose was 200 mg to 400 mg orally 3 times a day; maximum dose was 400 mg orally 3 times a day.

Research underway: There are no ongoing clinical trials testing retigabine based on ClinicalTrials.gov. To date, 28 clinical trials have been completed, withdrawn, or terminated. There are currently 3 NIH-funded studies involving retigabine—one in ALS, one in heavy alcohol drinking, and one in peripheral neuropathy (NIH RePORT).

Search terms:

Pubmed, Google: retigabine or ezogabine

- + Alzheimer, + ApoE, + dementia, + cognitive, + meta-analysis, + clinical trial, + atherosclerosis, + cardiovascular, + cancer, + neuropathy, + lifespan, + mortality

Websites visited for retigabine or ezogabine:

- Clinicaltrials.gov (0 ongoing, 28 completed/terminated)
- DrugAge (0)
- Geroprotectors (0)
- Drugs.com (ezogabine)
- WebMD.com (ezogabine)
- PubChem
- DrugBank.ca
- Cafepharma
- Pharmapro.com (0)

***Disclaimer**: Cognitive Vitality Reports® do not provide, and should not be used for, medical advice, diagnosis, or treatment. You should consult with your healthcare providers when making decisions regarding your health. Your use of these reports constitutes your agreement to the **Terms & Conditions**.*

If you have suggestions for drugs, drugs-in-development, supplements, nutraceuticals, or food/drink with neuroprotective properties that warrant in-depth reviews by ADDF's Aging and Alzheimer's Prevention Program, please contact INFO@alzdiscovery.org. To view our official ratings, visit Cognitive Vitality's Rating page.