



## Review

# Retigabine: the newer potential antiepileptic drug

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### Abstract:

Retigabine represents an antiepileptic drug possessing a completely different mechanism of action when compared to the existing classical and newer antiepileptic drugs. In the therapeutic range, retigabine enhances potassium currents, very likely *via* destabilization of a closed conformation or stabilization of the open conformation of the potassium Kv7.2–7.3 channels. There are also data indicating that this drug may be a GABA enhancer. Kainate-induced status epilepticus in rats resulted in massive apoptosis in the pyriform cortex and hippocampal area – retigabine inhibited neurodegeneration only in the former brain structure. The metabolism of retigabine has nothing to do with cytochrome P450 enzymes and the drug undergoes glucuronidation and acetylation. Randomized, placebo-controlled multicenter studies have shown that retigabine produced a considerable improvement as an add-on drug in patients with partial drug-resistant epilepsy. The most prominent adverse effects due to retigabine combined with the existing antiepileptic treatment were dizziness, somnolence and fatigue. The preclinical data indicate that this antiepileptic drug may possibly be applied in patients with neuropathic pain and affective disorders. Initial clinical data suggest that retigabine may be also effective in Alzheimer's disease or stroke.

### Key words:

retigabine, potassium current, Kv7 channels, epilepsy, neuroprotection, neuropathic pain

**Abbreviations:** AED(s) – antiepileptic drug(s), AMPA –  $\alpha$ -amino-3-hydroxyl-5-methyl-4-isoxazole-propionate, CNS – central nervous system, NMDA – N-methyl-D-aspartate, OGD – oxygen and glucose deprivation, UGT – UDP-glucuronosyltransferase

## Introduction

Epilepsy is the most common serious neurologic disorder with approximately 50 million diagnoses world-

wide [8, 10]. There are annually around 20 to 70 new cases per 10,000 individuals, with the lifetime chance of developing epilepsy being 3 to 5%. Patients with epilepsy do not respond to currently available drugs in about 25–30% cases [8], and approximately 65–70% of patients with epilepsy are successfully treated with the generally available classical antiepileptic drugs (AEDs, carbamazepine, ethosuximide, phenobarbital, phenytoin, primidone and valproate) [8]. The intensive pharmacological search for newer AEDs along with clinical trials led to the development of a number of drugs (felbamate, gabapentin, lamotrigine, leveti-

racetam, oxcarbazepine, tiagabine, topiramate, vigabatrin, and zonisamide) that are primarily used in the form of an add-on therapy of patients with refractory epilepsy [8].

So far, a couple of important mechanisms exerted by AEDs have been identified [for review see 7]. Some of AEDs (carbamazepine, gabapentin, lamotrigine, oxcarbazepine, phenytoin, topiramate, and valproate) target voltage-dependent sodium or calcium channels and by their blockade inhibit sustained repetitive firing of neurons. These drugs effectively inhibit seizure activity in human generalized tonic-clonic or partial epilepsies. However, AEDs sharing multiple mechanisms of action (for example, topiramate or valproate) may be effective in other forms of epilepsy [1, 37]. The next group of AEDs is GABA enhancers, and this group comprises benzodiazepines, gabapentin, phenobarbital, tiagabine, topiramate, vigabatrin, and valproate. As with the first group, some of these drugs possess a broad spectrum of antiepileptic activity [7]. Antagonists of T-type calcium channels (ethosuximide, zonisamide) are effective anti-absence drugs, although zonisamide may be also effective in other types of epilepsy due to its multiple mechanisms of action [for review see 38, 46]. There are also AEDs reducing glutamate-induced excitation at the receptor level including felbamate, phenobarbital, and topiramate [7]. Recently, lamotrigine has been documented to reduce glutamate-mediated events by  $\alpha$ -amino-3-hydroxyl-5-methyl-4-isoxazole-propionate (AMPA) receptors [29].

Although the existing AEDs affect various targets in the central nervous system, there are still problems in about 30% of epileptic patients to control sufficiently their seizure activity [43]. Consequently, some novel targets are searched for the better management of refractory epilepsy. Retigabine seems a good example of the drug exerting a completely different mechanism of action unrelated to the mechanisms of action of existing AEDs.

## Structure of the drug

Retigabine is an ethyl *N*-{(2-amino-4-[(4-fluorophenyl)methylamino]phenyl) carbamate (Fig. 1). Retigabine in humans and dogs undergoes glucuronidation reactions, which leads to the formation of two distinct *N*-glucuronides – the *N*2-glucuronide, where

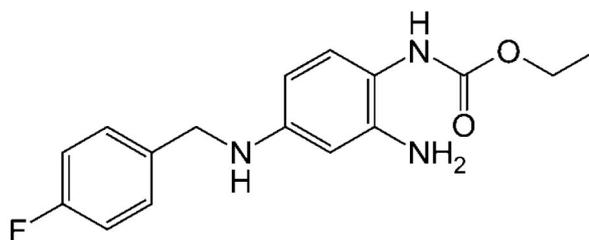


Fig. 1. A chemical structure of retigabine

the primary amino group in the 2 position is the site of glucuronidation. This metabolite exceeds the amount of the *N*4-glucuronide considerably, where the secondary amino group in 4 position is subject to glucuronidation [19, 22].

## Mechanisms of action

Retigabine has been documented to exert its anticonvulsant action *via* multiple mechanisms. There is evidence indicating that retigabine enhances GABAergic transmission in the central nervous system. For instance, the drug has been shown to augment the synthesis of GABA in rat hippocampal slices [26] and to enhance at 10  $\mu$ mol GABA-induced chloride currents in cultured rat cortical neurons [42]. The enhancement by retigabine of GABA-related currents was not sensitive to a benzodiazepine receptor antagonist, flumazenil, which does not suggest the involvement of benzodiazepine receptors in this particular effect [42]. Both, retigabine and GABA allosterically, displace a GABA<sub>A</sub> receptor tracer ligand and they enhance their binding to the GABA<sub>A</sub> receptor complex [48]. Inhibition of kainate-induced currents and blockade of voltage dependent sodium or calcium channels has been evident at a high concentration of retigabine of 100  $\mu$ mol speaking for non-specificity [42]. However, retigabine is effective as a neuronal potassium channel opener, displaying a measurable effect in a concentration as low as 0.1  $\mu$ mol [41]; the classical AEDs, carbamazepine, phenytoin or valproate being completely ineffective in this regard [41]. It is likely that retigabine-induced neuronal hyperpolarization in combined rat hippocampal-entorhinal slices may involve the potassium channels [21].

**Tab. 1.** Mechanism of action of retigabine (RTG) in comparison with that of valproate (VPA), lamotrigine (LTG), and topiramate (TPM)

AED	Enhancement of GABA-mediated inhibition	Blockade of sodium channels	Blockade of calcium channels	Inhibition of glutamate excitation	Enhancement of potassium currents
VPA	+	+	+(T-type)	NE	NE
LTG	NE	+	+(N, P/Q, R, T)	+	NE
TPM	+	+	+(L)	+	NE
RTG	+	NE	NE	NE	+

+ – well documented mechanism of action, NE – not effective. Data derived from supratherapeutic AED concentrations or inconsistent data have not been considered. Data for VPA, LTG, and TPM were taken from refs. 6 and 28 and these for RTG from refs. 19, 22, 30, 31, and 35

Wickenden et al. [49] have confirmed the findings of Rundfeldt [41] on the retigabine produced outward current in neuronal cell preparations and extended their studies to the identification of the molecular nature of the potassium channel affected by the drug. According to their studies conducted with the use of patch-clamp technique and the whole-cell configuration, they reached the conclusion that this AED very potently enhanced Kv7.2–7.3 currents, probably by destabilization of a closed conformation or stabilization of the open conformation of the Kv7.2–7.3 channels [49]. Interestingly, these potassium currents were induced by retigabine in concentrations of 0.1 to 10  $\mu\text{mol}$  and were sensitive to the inhibition caused by the Kv7.2–7.3 blocker, linopridine at 10  $\mu\text{mol}$  [49]. There are five Kv7 potassium channel subunits and all but Kv7.1 are expressed in the nervous system [for review see 6]. Four of these, Kv7.2–Kv7.5, form subunits of the low-threshold voltage-gated potassium channel, so called the “M-channel”. However, in most neurons M-channels consist of mainly Kv7.2 and Kv 7.3 subunits [6].

According to Lange et al. [28], retigabine anchors a hydrophobic pocket in between the cytoplasmic parts of transmembrane segments S5 and S6 involving Trp-236 and the Kv7.2 channel’s gate. Binding of this AED to Kv7.3 channels also takes place within segments S5 and S6 and involves Trp-265, Gly-340 as well as Leu-314 in the pore region of Kv7.3 channels. In this context, Trp-265 and Leu-314 are likely to represent the upper and lower margins of the retigabine’s binding site [28]. Interestingly, transfer of the Trp into the Kv7.1 channel structure makes this channel retigabine sensitive [44]. Conversely, when the S5 or S6 segment in Kv7.2 is substituted by the respective segments of Kv7.1, then the Kv7.2 channel does not re-

spond to retigabine [50]. Moreover, two other residues of S5 and S6, respectively, Leu-272 and Leu-338, are also of importance for the binding of retigabine. Leu-338 is required for lining the hydrophobic binding pocket for this AED. Considering that the pocket accompanies only the open state of the Kv7.3 channel, retigabine may be regarded as a stabilizer of an open conformation [28].

Mechanisms of action of retigabine in comparison with other AEDs are listed in Table 1.

## Pharmacokinetics

Retigabine is metabolized primarily by glucuronidation to N-glucuronide metabolites and by acetylation to form its mono-acetylated metabolite AWD21-360 [18, 33]. Retigabine is not metabolized, however, by cytochrome P450 enzymes [16]. In humans and dogs, the metabolism of retigabine mainly occurs by N-glucuronidation, whilst in rats, there are multiple metabolites of this new AED [33].

A constant ratio between retigabine and retigabine N-glucuronide *in vivo* in humans and dogs has been documented [14, 22]. According to Hiller et al. [22], the constant ratio is indicative of a coupling between the concentrations of retigabine and its N-glucuronide *via* enterohepatic circulation and glucuronidation/deglucuronidation reactions. The enterohepatic circulation of retigabine through retigabine N-glucuronide does not seem to occur in rats because the above phenomenon was not observed in this species [22]. Both UDP-glucuronosyltransferase 1 (UGT1) and UGT2 catalyze N-glucuronidation of retigabine in rats, whilst

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in humans this process is carried out by UGT1A1, A3, and A4, the latter enzyme being mainly involved [22].

As already mentioned above, rats produce multiple metabolites of retigabine and this results from acetylation, which accompanies glucuronidation [18]. Glucuronides were found in incubates containing liver microsomes and in plasma, bile or feces as well but remained completely undetected in urine sampled over 24 h since retigabine administration. In contrast, urine contained unmetabolized retigabine (2% of the dose) and more than 20 metabolites because of acetylation (29% of the dose). In dogs, 39% of the retigabine dose was eliminated with feces within 24 h and in the urine with 13% as unchanged drug, retigabine-N-glucuronide (5%), and retigabine-N-glucoside (1%) [18]. In healthy volunteers taking oral 600 mg dose of retigabine, an analysis of plasma and urine indicates that this AED undergoes metabolism *via* two main metabolic pathways: glucuronidation and acetylation [18].

Retigabine (a single oral dose of 200 mg) in young men (18–40 years), following fast absorption, reached its maximum plasma concentration (ca. mean value of 420 ng/ml) within 2 h, an apparent clearance being  $0.67 \text{ L} \times \text{h}^{-1} \times \text{kg}^{-1}$  and mean terminal half-life – 8.5 h. In young women, retigabine reached higher maximum concentration (by 56%), but the clearance did not differ significantly [19].

Ferron et al. [15] have documented that in healthy adult white and black male volunteers taking retigabine orally (the first dose of 100 to 350 mg on day one and subsequently twice daily over a fortnight), the drug's pharmacokinetics was linear and dose-proportional. Following an acute dose of 200 mg, a rapid absorption, with a mean maximum concentration ( $C_{\text{max}}$ ) of 819 ng/ml and a mean time to  $C_{\text{max}}$  ( $t_{\text{max}}$ ) of 1.6 h were observed. A mean apparent terminal half-life ( $t_{1/2}$ ) of 8 h and an apparent clearance of  $0.70 \text{ L} \times \text{h}^{-1} \times \text{kg}^{-1}$  were noted in white subjects whilst in the black volunteers, retigabine's clearance and volume of distribution were 25 and 30% lower, respectively [15].

There are available data on the pharmacokinetic profile of retigabine when combined with phenobarbital in healthy volunteers. It has been revealed that there was no pharmacokinetic interaction between the two AEDs because probably, phenobarbital had no impact on enzymes metabolizing retigabine and its acetylated metabolite [14]. However, the combined treatment of lamotrigine with retigabine in healthy subjects resulted in modest pharmacokinetic interactions [20]. There was a 13% reduction of retigabine

clearance and its mean half-life and area under the plasma concentration-time curve were elevated by 7.5 and 15%, respectively. This interaction seems to result from competition for renal excretion between both AEDs, competition for glucuronidation being rather unlikely [20]. Retigabine has also simultaneously and significantly affected the pharmacokinetic parameters of lamotrigine, which was reflected by an increase in its apparent clearance (by 22%) and reductions of lamotrigine's mean half-life (by 15%) and area under the plasma concentration-time curve (by 18%). The affected parameters clearly indicate that there was a moderate potentiation of the lamotrigine metabolism, although, according to Hermann et al. [20], the nature of this phenomenon is unclear. Any involvement of the induction of metabolizing enzymes by retigabine does not come into question because this AED has not significantly affected the pharmacokinetics of phenobarbital in healthy subjects [15] and other AEDs (carbamazepine, phenytoin, topiramate, and valproate) in epileptic patients [2].

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### Activity in experimental models of epilepsy

Retigabine displays a broad spectrum of anticonvulsant activity in animal models. The AED is effective against convulsions produced by maximal electroshock, pentetrazol, NMDA, picrotoxin, kainate or audiogenic stimulation in rodents [for review see 30]. Retigabine has also increased afterdischarge threshold and simultaneously shortened afterdischarge duration in fully hippocampal-kindled rats. The protective effects in kindled rats were noted for retigabine given in doses producing no or only mild adverse effects [32]. It is noteworthy that in three age groups of rats (P14, P21, and P35 corresponding to post-neonatal, early childhood, and adolescent stage of development) this AED prevented the evolution of kindling to the highest stage (full kindling), and in P14 rats, it delayed the acquisition of focal seizures. These results indicate that apart from the clear-cut anticonvulsant action, retigabine also exerted antiepileptogenic effects [32]. However, in mutant Sz1 mice whose Kv7.2 channels are deprived of most of the C-terminus, retigabine was found to be less effective in inhibition of partial psychomotor seizures when compared to littermate control [36].

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## Interactions of retigabine with classical AEDs in mice

De Sarro et al. [11] have evaluated a capacity of retigabine, given in a subeffective dose of 0.5 mg/kg, to potentiate the protective effects of AEDs against audiogenic seizures in DBA/2 mice. It was evident that retigabine enhanced the protection offered by carbamazepine, diazepam, felbamate, lamotrigine, phenytoin, phenobarbital and valproate, with the degree of additivity being the highest for diazepam, phenobarbital, phenytoin and valproate. In no case could pharmacokinetic interactions contribute to the final effects of drug combinations because retigabine did not modify total or free plasma concentrations of other AEDs. Remarkably, the protective indices of the combined treatments were better than that for retigabine alone [11]. Another study devoted to the problem of the combination therapy with retigabine and other AEDs has employed an isobolographic analysis, which allows to substantiate synergistic, additive or antagonistic interactions [31]. A clear-cut synergy has been found for the combination of retigabine + valproate at fixed dose ratios of 1:3, 1:1, and 3:1. Because the dose-effect curve for retigabine against maximal electroshock was not parallel to that for carbamazepine or lamotrigine, only the fixed dose ratio of 1:1 was studied for these combinations which proved additive. No studied combinations disturbed motor coordination, long-term memory or muscular strength. An analysis of both free plasma and total brain concentrations of AEDs combined with retigabine has revealed that only the combination with the fixed ratio of 3:1 (retigabine:valproate) resulted in the elevated free plasma and total brain concentrations of valproate [31]. Until today, no more animal data are available on the combinations of retigabine with other AEDs.

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## Toxicity in animal models

Acute toxicity studies in a number of animal species resulted in comparable toxicity, including mainly effects from the central nervous system, including hyper- or hypokinesia, uncoordinated movements, tremor, stilted gait, and convulsions [3]. Retigabine did not affect QTc interval in the isolated guinea-pig heart or the

ECG pattern in monitored by telemetry dogs when given orally up to 38 mg/kg for a week [3].

Retigabine was without effect on reproductive functions in rats and exerted no teratogenic activity in rats and rabbits. In addition, perinatal or postnatal administration of retigabine to rats did not result in any developmental toxicity, some reduced growth being observed when the animals were given the highest dose of this AED [3].

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## Initial clinical data

Individual or combined treatments in fifteen healthy volunteers were generally well-tolerated. In one subject, on day 10, retigabine induced severe abdominal pain and was withdrawn. The most frequent reported adverse event was headache. No relevant disturbances in the electrocardiograms, vital signs or laboratory measurements were observed [14].

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## Trials with the use of retigabine

A phase II multicenter, randomized, placebo-controlled clinical trial has been conducted with retigabine as an adjunctive AED in patients with partial onset seizures [39]. The AED was titrated to daily doses of 600, 900, or 1,200 mg over 2–6 weeks. The responder rates (at least a 50% reduction in seizure frequency) were 23% for retigabine at 600 mg/day, 32% for 900 mg/day ( $p = 0.021$ ), and 33% for 1,200 mg/day ( $p = 0.016$ ), vs. 16% for placebo. The most frequently encountered adverse effects for retigabine as an add-on AED were somnolence, dizziness, confusion, speech disorder, vertigo, tremor, amnesia, abnormal thinking, abnormal gait, paresthesia, and diplopia [39].

So far, two next phase III multicenter and placebo-controlled trials have been completed in patients with refractory partial-onset seizures being treated with 1–3 AEDs [3]. In the first study, officially registered as RESTORE 1 and sponsored by Valeant [23], retigabine given at 1,200 mg/day, titrated over 6 weeks, has resulted in a responder rate of 45.0% vs. 18% for placebo [3]. The most frequently encountered adverse effects associated with retigabine as an adjunctive AED

to the existing antiepileptic therapy were dizziness (in 17, 26, and 40% of patients receiving retigabine at 600, 900, and 1,200 mg/day, respectively – vs. 9% for placebo), somnolence (in 14, 26, and 31% vs. 13% for placebo), and fatigue (17, 15, and 16% vs. placebo of 5%). Other adverse effects, such as confusion, dysarthria, ataxia, tremor, and nausea, were in the range of 11–14% of patients (vs. placebo of 1–5%) for the highest dose of retigabine [3]. The second study, officially registered as RESTORE 2, also sponsored by Valeant [23], (retigabine was titrated to 600 or 900 mg daily over 2–4 weeks) revealed a 50% reduction in baseline seizure frequency in 31.5 and 39.3% of patients for retigabine 600 and 900 mg/day, respectively. The placebo effect was observed in 17.3% of patients. The most prominent adverse effects of retigabine as an add-on AED are given in Table 2.

### Possible non-epilepsy indications for retigabine

Existing evidences indicate that AEDs may be therapeutically applied in conditions other than epilepsy, for instance in neuropathic pain, migraine, affective disorders, spasticity, or restless legs syndrome [for review see 51]. Retigabine has been proven to attenuate nociceptive behaviors in rat models of neuropathic pain – chronic constriction injury and spared nerve models or the formalin test [4, 35]. Interestingly, this AED at 1 mg/kg also significantly inhibited amphetamine + chlordiazepoxide-induced locomotor activity in rats which apparently points to its possible anti-manic activity [12]. The specificity of this effect can be confirmed by the fact that the basal locomotor activity was reduced by retigabine at 4 mg/kg [12].

Other experimental data indicate that retigabine may prove an effective anxiolytic and antidystonic drug [27, 40]. The inhibition by retigabine of the psychostimulatory effects produced by cocaine, methylphenidate and phencyclidine in rats may point to its potential in the treatment of addiction [17]. There is also an isolated report on a possibility of beneficial effects of retigabine in Alzheimer’s disease [16], although a report on the clinical trial is also available [47].

### Is retigabine a neuroprotectant?

The first report on the possible neuroprotective activity of retigabine has revealed that the drug prevented L-glutamate-induced toxicity in the rat pheochromocytoma PC 12 cells [45]. Retigabine has been also evaluated in another *in vitro* study in terms of its possible neuroprotective activity in rat organotypic hippocampal slice cultures exposed to N-methyl-D-aspartate (NMDA), oxygen and glucose deprivation (OGD), or serum withdrawal. The hippocampal CA1 field was the most vulnerable one to neurodegeneration induced by NMDA or OGD, whilst selective lesion to the dentate gyrus was observed upon the culture exposure to serum withdrawal. Retigabine potently inhibited neurodegeneration in the dentate gyrus with an IC<sub>50</sub> value of 0.4 μM but was less effective against lesions to the CA1 region [45]. Interestingly, the neuroprotective activity of retigabine in the dentate gyrus was not dependent upon the activation of potassium current because two potassium Kv7 channel blockers did not affect the degree of retigabine-induced neuroprotection [5].

**Tab. 2.** Relative prevalence\* of adverse effects induced by retigabine (RTG) as an add-on AED in patients with partial drug-resistant seizures

Treatment (mg/24 h)	Adverse effects					
	Dizziness	Somnolence	Fatigue	Confusion	Dysarthria	Nausea
RTG (600)	8	1	12	1	4	1
RTG (900)	17	13	10	4	1	2
RTG (1200)	31	18	11	13	11	6

\* These are net percent effects calculated based on observed effects minus placebo. The percentages were calculated from the data taken from ref. 3

Kainate-induced status epilepticus in rats produced massive neurodegeneration in the hippocampus and pyriform cortex and the peak expression of apoptosis was evident at 24–48 h following the status [13]. Retigabine, administered 90, 150, and 210 h after the status terminated with diazepam, evidently protected the pyriform cortex against the lesion but, in contrast to dizocilpine, was ineffective against the lesion to the hippocampal area [13].

The potassium channel blocker, 4-aminopyridine, has been documented to produce seizure activity and neurodegeneration upon microdialysis perfusion of the rat hippocampus [34]. When retigabine was co-administered to the perfusate, it considerably diminished 4-aminopyridine-induced stimulation of glutamate release and exerted a protective effect against the hippocampal cell death observed following 4-aminopyridine alone. Strikingly, retigabine failed to affect the EEG discharges [34].

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## Conclusions

At present, retigabine undergoes phase III clinical evaluation, and compared to the existing AEDs, it offers a unique mechanism of action [25]. From the pre-clinical point of view, this AED interacts synergistically with valproate against maximal electroshock-induced convulsions in mice and in only one of three evaluated dose ratios was associated with a pharmacokinetic interaction. The interaction profile of retigabine seems much better than that of stiripentol, which is another AED evaluated in phase III clinical trials [9]. Stiripentol displayed a complex interaction with carbamazepine, with both synergy and antagonism being observed depending upon the dose ratio. With regard to other classical AEDs (ethosuximide, phenobarbital, and valproate), additive interactions were noted. All combinations of stiripentol with the aforementioned drugs resulted in distinct pharmacokinetic interactions [9].

In patients with partial epilepsy resistant to pharmacotherapy, retigabine as an adjunctive drug, produced a distinct improvement, reflected by a 50% reduction in seizure frequency in a significant number of patients. As already mentioned, this AED offers a unique mechanism of action, which renders retigabine a potential and exciting novel AED for the man-

agement of drug-resistant seizures. A possibility arises that the adverse effects observed in retigabine phase II or III trials may result from pharmacodynamic interactions of retigabine with the existing antiepileptic treatment. At present, however, data on the efficacy and tolerability of retigabine in the form of monotherapy are lacking. Probably, retigabine will be marketed in late 2010 or early 2011 because the data for the approval submission have not yet been disclosed [24].

It is remarkable that retigabine possesses neuroprotective properties both, in various *in vitro* and *in vivo* models of neurodegeneration. However, the significance of this effect may be not that high in terms of epileptogenesis. Ebert et al. [13] have clearly demonstrated that dizocilpine (an uncompetitive NMDA receptor antagonist) exhibited a potent neuroprotective activity in the hippocampus and pyriform cortex of rats challenged with kainate-induced status epilepticus and yet this neuroprotection failed to prevent the development of recurrent spontaneous seizures.

A possibility of other non-antiepileptic treatment applications for retigabine needs to be carefully considered. These other illnesses include neuropathic pain, mania (possibly bipolar disorder), or even Alzheimer's disease. Clinical trials for the use of retigabine in Alzheimer's disease and stroke have been conducted and indicate that this AED may possess a broad clinical spectrum of activity [47].

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