

## Newly available treatments for epilepsy: review of clinical studies of lacosamide, ezogabine, perampanel and eslicarbazepine acetate

Despite that many different treatment options are available for epilepsy, approximately 30% of epilepsy patients still remain refractory. Among patients who are refractory to medical treatment, only small percentage of patients may be candidates for epilepsy surgery. For the remaining majority of refractory seizure patients, combination treatment of different medications, especially with new or novel medications, can be an appropriate therapeutic option. The most recent antiepileptic medications may offer new mechanisms of action and more favorable safety profiles than the previous-generation medications. The purpose of this review article is to review clinical studies of newly approved medications for partial epilepsy such as lacosamide, ezogabine, perampanel and eslicarbazepine acetate.

**Keywords:** eslicarbazepine acetate • ezogabine • lacosamide • perampanel • rufinamide

Epilepsy affects 1–2% of the world population [1], and majority of them are treated with antiepileptic drugs (AEDs) for many years, if not lifetime. Despite many new available AEDs, more than a third of them still experience recurrent seizures and undesirable side effects [2,3]. The main interests in new AED development are providing these unmet needs of superior treatment efficacy and tolerability without compromising short- and long-term patient safety. For the majority of patients with medically refractory epilepsy, adjunctive therapy with two or more AEDs could be the most appropriate therapeutic options. There are many new AEDs approved by US FDA and other agencies since 2008 for the treatment of partial-onset seizures and many other new AEDs are still under current development. The main purpose of this article is to provide useful information for clinicians and to review new AEDs' clinical studies which include pharmacokinetic properties, proposed mechanisms of actions, efficacy and tolerability.

### Lacosamide

Lacosamide (Vimpat®) was approved as an adjunctive treatment for partial-onset seizures

for adult patients by the European Medicines Agency (EMA) in August 2008 and by the US FDA in October 2008. It is available in oral tablet, intravenous solution and oral solution.

### Pharmacokinetics & mechanisms of action

Lacosamide has a linear pharmacokinetic profile [4,5] and reaches the peak serum concentration within 1–2 h after oral administration. The elimination half-life of lacosamide is about 13 h and the steady-state plasma concentrations are reached after 3 days with twice daily dosing [6]. Lacosamide has low plasma protein binding ( $\leq 15\%$ ) and the volume of distribution is similar to body water [7].

Lacosamide is partially metabolized by the hepatic isoenzyme 2C19 (<30%), but primarily eliminated as unchanged form through kidney (>40%) [4,6]. Lacosamide has low potential for drug–drug interactions and co-administration of CYP2C19 inducers or inhibitors did not cause significant lacosamide serum level changes [7].

Lacosamide appears to enhance slow inactivation phase of voltage-dependent sodium channels, which is different from other

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existing sodium channel acting AEDs since they tend to affect fast inactivation phase of voltage-dependent sodium channels [8,9].

#### Clinical studies: efficacy & tolerability

Three pivotal studies were completed to establish the efficacy and tolerability of lacosamide. All three studies were randomized, double-blind, placebo-controlled trials (SP667, SP754 and SP755) examining three different doses of lacosamide (200, 400 and 600 mg/day), which were administered as adjunctive therapy for patients with partial-onset seizures [10–12]. The starting dosage was 50 mg twice daily, followed by weekly increase of 100 mg until it reached the target doses. The intent-to-treat (ITT) population was used for the primary efficacy analysis. A total of 1294 patients comprised the ITT population. Of these, 1116 patients completed titration and entered the maintenance phase. The percentages of patients completing the trial were 88% (placebo), 83% (lacosamide 200 mg/day) and 78% (lacosamide 400 mg/day) [13].

All three clinical studies revealed significant seizure reduction compare to the baseline. For the pooled analysis, the median percent reduction in seizure frequency was 18.4% for placebo, 33.3% for lacosamide 200 mg/day and 36.8% for lacosamide 400 mg/day. The 50% responder rates ( $\geq 50\%$  reduction in baseline seizure frequency) were 22.6% for placebo, 34.1% for lacosamide 200 mg/day and 39.7% for lacosamide 400 mg/day [13]. During the study period, seizure freedom was achieved in 2.7, 3.3 and 0.9% of patients who received lacosamide 200 and 600 mg/day, and placebo, respectively [13].

The most common treatment-emergent adverse events (TEAEs) at an incidence of  $\geq 10\%$  in the lacosamide-treated group and greater than placebo were dizziness (31 vs 8%), headache (13 vs 9%), nausea (11 vs 4%) and diplopia (11 vs 2%). All of these with the exception of headache appeared to be dose-related and mostly occurred during the titration phase. Other less common TEAEs were vomiting, fatigue, coordination abnormal, blurred vision, tremor, somnolence and nystagmus [13]. The incidence of rash (all were mild to moderate) was low for patients randomized to lacosamide (3%), and was similar to that reported with placebo. Lacosamide appears to have no significant cardiac side effects, but small increase in mean PR interval at the end of maintenance (1.4–6.6 ms increase) was noted, but all of them were symptomatic [14].

#### Ezogabine

Ezogabine (Trobal<sup>®</sup>, Potiga<sup>®</sup>) is a new AED with a novel mechanism of action, and was approved as an adjunctive treatment for partial-onset seizures

for patients  $\geq 18$  years by EMA (Trobal<sup>®</sup>) in March 2011 and by FDA (Potiga) in June 2011. In Europe, ezogabine is known as retigabine.

#### Pharmacokinetics & mechanisms of action

Ezogabine is rapidly absorbed with oral administration, and has a linear pharmacokinetic profile [15]. Peak plasma concentration is reached approximately at 2 h with food, and modestly delayed with a high-fat meal. However, its oral bioavailability is estimated to be only about 60% [15]. The plasma half-life of ezogabine is about 8 h (7.2–9.4 h), with recommended three-times daily dosing. Ezogabine has moderate protein binding of 80% and the volume of distribution at steady-state is about 2–3 l/kg [15].

Ezogabine is metabolized mainly by the hepatic enzymes. The primary metabolites are mono-acetylated form via *N*-acetylation and *N*-glucuronide structure via glucuronidation [16]. The clearance of ezogabine was reduced by 50% in those with moderate or severe renal disease or those who required dialysis [17]. The serum concentration of ezogabine was reduced by about 30% when administered with phenytoin or carbamazepine, but no significant interaction was seen with co-administration of valproate or topiramate [18,19]. Lamotrigine mildly increased the serum level of ezogabine, while ezogabine reduced the serum level of lamotrigine, probably due to the fact that hepatic glucuronidation is the main metabolic pathway for both medications [20].

The anticonvulsant effect of ezogabine is primarily the enhancement of voltage-gated potassium channels through heteromeric KCNQ2/3 channels and KCNQ3/5 channels [21,22]. Therefore, ezogabine promotes inhibition on neuronal excitation and its repetitive firing.

#### Clinical studies: efficacy & tolerability

A double-blind, placebo-controlled, randomized Phase II clinical trial (Study 205) evaluated different doses of ezogabine (600–1200 mg/day) as an adjunctive therapy for adult patients with partial seizures [23]. Patients underwent titration to 600, 900 or 1200 mg/day or to placebo followed by maintenance phase. The median percent changes in seizure frequency of the ITT population were 23.4% for 600 mg, 29.3% for 900 mg ( $p = 0.0387$ ) and 35.2% for 1200 mg ( $p = 0.0024$ ), compared with 13.1% for the placebo group. Two additional Phase III studies (study 301 and 302) confirmed the dose-dependent efficacy of ezogabine in comparison to placebo effects [24,25]. Pooled analysis (integrated analysis) showed that the median percent seizure frequency reduction was 26% with 600 mg ( $p = 0.003$ ), 37% with 900 mg ( $p < 0.001$ ) and 39% with 1200 mg/day ( $p < 0.001$ ), compared to

14–15% with placebo. The 50% responder rates were 35 and 45% for 600 and 900 mg, respectively (placebo = 21%;  $p < 0.001$ ), and 50% for 1200 mg/day (placebo = 24%;  $p < 0.001$ ) [26].

The most commonly reported TEAEs in all ezogabine-treatment groups (pooled analysis) were dizziness 23.2%, somnolence 22.0%, fatigue 14.7%, confusion 9.2%, tremor 8.1%, vertigo 7.5% and blurred vision 5.6%. Among non-CNS TEAEs, bladder-related adverse events were observed with ezogabine, primarily at 1200 mg/day. Bladder ultrasound revealed a modest increase in mean post-void residual volume at the 1200-mg dose, and urinary retention was observed in 0.9% of subjects, along with urinary hesitation in 2.2% and dysuria in 2.3%. In addition, ECG study in healthy volunteers also produced a mean 7.7 ms QT interval prolongation at 400 mg three-times daily dosing [27]. The QT prolongation effect occurred within 3 h after oral administration of ezogabine.

Long-term extension clinical study also revealed skin discoloration and retinal abnormalities: approximately 10% of patients in long-term clinical trials developed skin discoloration, generally after 2 or more years of treatment and at higher doses ( $\geq 900$  mg) of ezogabine. The retinal abnormalities have been reported in patients who have taken ezogabine for a long period of time. Approximately a third of the patients who had eye examinations performed after approximately 4 years of treatment were found to have retinal pigmentary abnormalities [27].

### Perampanel

Perampanel (Fycompa<sup>®</sup>) is a newly approved AED that has a unique mechanism of action, which was recently approved as an adjunctive treatment for partial-onset seizures for patients  $\geq 12$  years by EMA in July 2012 and by FDA in October 2013.

### Pharmacokinetics & mechanisms of action

Perampanel is rapidly absorbed following oral administration, with peak plasma concentrations reach between 30 min and 2 h under fasted condition. The half-life is estimated to be about 105 h, and the steady-state plasma concentration is achieved in about 14 days. Following oral administration of perampanel, 70% was found as unchanged form in feces and 30% in urine [28,29]. Perampanel has high protein binding of 95%, and the overall estimated volume distribution is about 77 l [28,29]. Perampanel is mainly metabolized by hepatic CYP3A4 pathway and its plasma concentration can be reduced by 50% when used with carbamazepine or phenytoin [28]. Even though the low to medium dose of perampanel (4–8 mg/day) did not affect the effectiveness of oral contraceptives, high dose of perampanel

(12 mg/day) was found to reduce levonorgestrel by 40% [29].

Perampanel is highly selective noncompetitive antagonist of AMPA receptors, which inhibits glutamate-mediated intracellular calcium influx and neuronal excitation [28].

### Clinical studies: efficacy & tolerability

Clinical efficacy and safety data are available from two Phase II and three Phase III studies [30–32]. The Phase II studies evaluated perampanel dose of 4, 6, 8, 10 and 12 mg/day and randomized 153 patients. The 50% responder rates over the maintenance treatment phase were ranged from 31 to 40% on perampanel compare to 20 to 22% on placebo. Subsequent international Phase III studies were conducted in 25 countries to evaluate the efficacy and safety in patients with partial-onset seizures. The starting dosage was 2 mg once daily, followed by weekly increase of 2 mg/day until reaching the target doses 94–12 mg/day). Of the enrolled subjects, 1478 subjects were analyzed in ITT population. In the combined analysis of three Phase III studies, the 50% responder rates were 19.8, 28.5, 35.3 and 35.0% for placebo, 4, 8 and 12 mg of perampanel, respectively. The median treatment effects over placebo (medication–placebo effects) were reported at 15.3, 25.7 and 33.2% for the approved dosages of 4, 8 and 12 mg of perampanel, respectively [29].

In the Phase III studies, the most common adverse events were dizziness (9, 16, 32 and 43% with placebo, 4, 8 and 12 mg/day, respectively), headache (11, 11, 11 and 13% with placebo, 4, 8 and 12 mg/day, respectively), irritability (3, 4, 7 and 12% with placebo, 4, 8 and 12 mg/day, respectively), fatigue (5, 8, 8 and 12% with placebo, 4, 8 and 12 mg/day, respectively) and falls (3, 2, 5 and 10% with placebo, 4, 8 and 12 mg/day, respectively) [28]. Most of the events were mild and the incidence was higher with 12 mg dosing. FDA had issued a boxed warning for potential psychiatric and behavioral adverse effects of perampanel including aggression, hostility irritability, anger, homicidal ideation and threats [28]. Homicidal ideation and/or threats were exhibited in 0.1% of 4368 perampanel-treated patients [28]. There were no significant effects on cardiac symptoms or EKG findings.

### Eslicarbazepine acetate

Eslicarbazepine acetate (Zebinix<sup>®</sup>, Aptiom<sup>®</sup>) is a prodrug of eslicarbazepine, which shares structural similarity with carbamazepine and oxcarbazepine (dibenz/b,f/azepine) [33]. Eslicarbazepine acetate was approved as an adjunctive treatment for partial-onset seizures for patients  $> 18$  years by EMA (Zebinix) in April 2009 and by FDA (Aptiom) in November 2013 [34].

### Pharmacokinetics & mechanisms of action

Eslicarbazepine acetate is rapidly metabolized to eslicarbazepine within 1–4 h following oral uptake [35], which is responsible for antiepileptic pharmacological activity [36]. While oxcarbazepine is a prodrug to both eslicarbazepine (also called S-licarbazepine or S-MHD) and R-licarbazepine (also called R-MHD), eslicarbazepine acetate is a prodrug of only for eslicarbazepine.

Eslicarbazepine acetate is completely absorbed with or without food and has estimated protein binding of 40% [35,37]. Its half-life is 13–20 h and the steady-state concentration is reached within 4–5 days with once daily dosing [35]. The metabolites of eslicarbazepine are excreted unchanged through kidney or by hepatic glucuronidation. Dosage adjustment is recommended for patients with renal impairment [38].

Eslicarbazepine acetate poses a moderate inhibitory effect on CYP2C19 [17]. It may also have a mild inducing effect on CYP2C9 and co-administration of eslicarbazepine acetate with warfarin may cause decrease in exposure to (S)-warfarin [17]. Pharmacokinetics analysis from the Phase III studies showed no relevant effect on the clearance of carbamazepine, clobazam, gabapentin, levetiracetam, phenobarbital, phenytoin, topiramate or valproic acid [39]. However, the plasma concentrations of oral contraceptives (both ethinyl-estradiol and levonorgestrel) are reduced by 32% after eslicarbazepine acetate 1200 mg/day [35].

Previous *in vitro* studies suggest that eslicarbazepine acetate acts similarly to carbamazepine and oxcarbazepine by inhibiting sodium channels, but displayed higher affinity toward the inactivated state rather than resting state of sodium channels [40].

### Clinical studies: efficacy & tolerability

A Phase II placebo-controlled study initially showed significantly higher 50% responder rates compare to placebo (54 vs 28%;  $p = 0.008$ ) [41]. In the subsequent Phase III trials, patients were randomized to receive placebo or once-daily eslicarbazepine acetate 400, 800 or 1200 mg ( $n = 102$ ) in the double-blind treatment phase [34]. The starting dose was 400 mg once daily with weekly increase of 400 mg to reach target doses. Pooled analysis from the three Phase III studies (Bia 2093–301, BIA 2093–302 and BIA 2093–304) included data obtained from 1049 patients enrolled by 125 centers, in 23 countries [41]. The 50% responder rate was significantly higher in the eslicarbazepine acetate groups than in the placebo group: 36% with 800 mg and 44% with 1200 mg, compared to 22% with placebo. The median percent reduction in seizure frequency was 15% with placebo, 35% with eslicarbazepine acetate 800 mg and 39% with 1200 mg/day.

When the drug was co-administered with carbamazepine, which reduced the serum concentration of eslicarbazepine acetate by 20–30%, the median relative reduction in seizure frequency was 14.3% in placebo, 33.3% in 800-mg and 44.3% 1200-mg groups; in patients not taking carbamazepine, the relative reduction was 14.8, 38.9 and 37.8%, respectively [42].

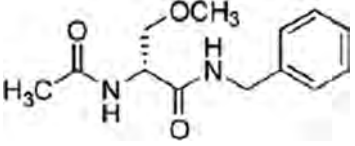
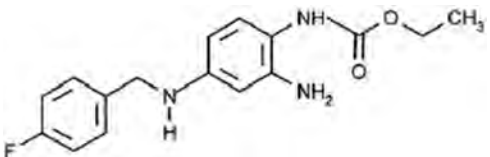
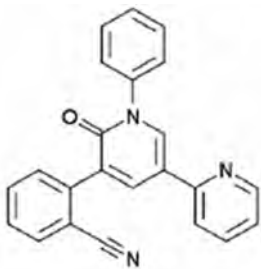
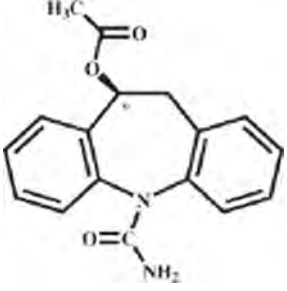
During the Phase II study, the most commonly reported TEAEs were dizziness (19%), somnolence (11%), nausea (7%), diplopia (6%), headache (5.5%) and vomiting (4.8%) [37]. In the pooled analysis, the most common adverse events included dizziness (7, 12 and 29% with placebo, 800, and 1200 mg/day, respectively), somnolence (9, 13 and 15% with placebo, 800 and 1200 mg/day, respectively), headache (9, 10 and 14% with placebo, 800 and 1200 mg/day, respectively) and nausea (2, 7 and 10% with placebo, 800 and 1200 mg/day, respectively) [42]. Less frequent TEAEs included vomiting, abnormal coordination, blurred vision, vertigo and fatigue. Overall, TEAEs were mild to moderate and appeared to be dose-dependent. The incidence of psychiatric complications, rash or hyponatremia was quite low (<1% of patients) [34]. There were no significant changes in the laboratory parameters or electrocardiogram parameters.

### Discussion

In addition to these four new AEDs since 2008 for the treatment of partial-onset seizures, there are still more AEDs in pipeline. However, it is difficult to assess whether overall epilepsy treatment had improved compare to the previous decade when far less AEDs were available. Although the refractory epilepsy patients are still estimated to be 25–30% of all seizure patients [43], many people had benefitted from new medications in terms of better tolerability and/or improved efficacy. When a new AED is introduced, treating clinicians and patients tend to ask the same question: What is better or different with the new medication? Since differences among AEDs mainly lie in their pharmacokinetics, mechanisms of action, potential drug-to-drug interactions and tolerability, it is very important to acquire adequate understanding of these main properties when choosing a new AED (Tables 1 & 2). Favored AEDs should have 100% bioavailability, linear kinetics, low or no drug-to-drug interactions, low protein binding, longer half-life, convenient dosing and preferably a novel way of preventing seizures [44]. Although not all compounds display such favorable properties, some new AEDs display notable advantages over existing AEDs.

Although these new AEDs may provide unique and novel mechanisms of action in controlling seizures, it is not clear whether they can provide synergistic or

Table 1. Chemical structure and mode of action of the newly approved antiepileptic drugs.

AEDs	Chemical structure	Mode of action
Lacosamide (Vimpat®)		Selective enhancement of slow inactivation of sodium channels
Ezogabine (Trobal®, Potiga®)		Enhancement of voltage-gated potassium channels
Perampanel (Fycompa®)		Noncompetitive AMPA receptor antagonist
Eslicarbazepine acetate (Zebinix®, Aptiom®)		Inhibition of voltage-gated sodium channels

AED: Antiepileptic drug.

supra-additive effects with existing AEDs. It is even less clear which combinations of medications can provide the maximal benefit for patients since most of clinical studies had not been designed to answer the question. More recently, isobolographic analysis of lacosamide was performed in order to evaluate pharmacodynamic interactions (synergistic, additive or antagonistic) with other AEDs [45]. The study demonstrated a synergistic effect of lacosamide when combined with levetiracetam or carbamazepine at fixed ratios of 1:3, 1:1 and 3:1 in the mouse 6-Hz psychomotor seizure model. A similar study of isobolographic analysis was done with ezogabine utilizing the mouse MES model [46]. This study found that the combination of ezogabine with valproate at fixed ratios of 1:3, 1:1 and 3:1 exerted synergistic interactions, while combinations with carbamazepine and lamotrigine produced additive interactions. However, the benefit of such combination therapy is not yet clear in actual clinical practices. To date, there are no sys-

tematic clinical studies examining the pharmacodynamic interactions or combined efficacies of specific AEDs to see if certain AED combinations should be preferred. Such future studies would enable clinicians in choosing the right adjunctive medications as most of refractory patients are currently being treated with combination therapy. In addition, better understanding of epileptogenesis from various etiologies, neurobiological effects of seizure provoking factors and the exact reasons for pharmacoresistance would greatly improve the treatment of epilepsy in all ages.

### Conclusion

The safety and efficacy of recently approved lacosamide, ezogabine, perampanel and eslicarbazepine acetate had been established through multiple clinical trials. Although each new medication has pros and cons, availability of new AEDs further expands the treatment options and may provide a significant benefit to those individuals with refractory epilepsy.



Table 2. Summary of main properties of the newest antiepileptic drugs for partial-onset seizures.

AED properties	Lacosamide	Ezogabine	Perampanel	Eslicarbazepine acetate
Approval status (year)	EMA, US FDA (2008)	EMA, FDA (2011)	EMA, FDA (2012, 2013)	EMA, FDA (2009, 2013)
Age (years)	16 or older	12 or older	18 or older	Older than 18
Starting dose	50 mg b.i.d.	100 mg t.i.d.	2 mg q.d.	400 mg q.d.
Approved doses (per day), mg	200–400	600–1200	4–12	800–1200
Dosing schedule	b.i.d.	t.i.d.	q.d.	q.d.
Half-life (h)	13	8–9	105	13–20
T <sub>max</sub> (h)	1–4	1–2	0.5–2	2–3
Protein binding (%)	<15	<80	95	<40
DEA scheduling	V	V	III	Not scheduled

AED: Antiepileptic drug; b.i.d.: Two-times a day; C<sub>max</sub>: Time to reach maximal plasma concentrations; DEA: Drug Enforcement Administration (I: Highest potential for abuse; V: Least potential for abuse); EMA: European Medicines Agency; q.d.: Once a day; t.i.d.: Three-times a day.

### Future perspective

There are several new medications with favorable pharmacokinetics and novel mechanisms of action for the treatment of refractory partial-onset seizures within last 5 years. However, the challenge still remains: Would these new AEDs improve clinical outcome and seizure freedom? As the previous studies had pointed out [2,43], it is not yet clear whether these new medications or their combinations would provide greater efficacy. More recently, new approaches of seizure treatment apart from AEDs had emerged

and found to be beneficial when used adjunctively with AEDs. A few examples include recently approved responsive neurostimulation that utilizes a closed-loop circuit electrical stimulation for the treatment of refractory epilepsy, and deep brain stimulation which targets the bilateral anterior nuclei of thalami. In addition, patients had developed keen interests in natural or herbal remedies for epilepsy treatment such as medical marijuana, cannabidiol, other supplements and changes in habitual diet (i.e., ketogenic or low-carbohydrate diet). While neuromodulation methods

### Executive summary

The key points of each antiepileptic drug are listed below.

- Lacosamide
  - Lacosamide promotes slow inactivation phase of sodium channels and provides a favorable pharmacokinetic profile that includes low protein binding, renal excretion and low potential for drug-to-drug interactions.
  - Lacosamide provides fast onset of anticonvulsant effects and significant reduction of partial-onset seizures at 200 and 400 mg/day even in a severely refractory population.
- Ezogabine (Reigabine)
  - Ezogabine activates voltage-gated potassium channels. Three pivotal clinical studies showed that doses of 600–1200 mg/day (200–400 mg three-times daily) were associated with significant reduction in seizure frequency.
  - Potential urinary retention, skin discoloration and retinopathy should be monitored when ezogabine is used.
- Perampanel
  - Perampanel is noncompetitive inhibitor of AMPA receptors. Although it has very long half-life (~105 h), the serum level is reduced by 50% when combined with liver enzyme inducing antiepileptic drugs. Significant efficacy was observed with 4–12 mg per day.
  - Perampanel has boxed warning for behavioral side effects and aggression, which are dose-dependent.
- Eslicarbazepine acetate
  - Although eslicarbazepine acetate does not display a novel mechanism of action, efficacy and long-term safety profiles at 800 and 1200 mg had been well established.
  - Despite the fact that it is derived from oxcarbazepine, unlike its patient drug, the incidence of rash, hyponatremia or weight gain is uncommon.

are fueled by the rapidly advancing technology and better understanding of epileptogenesis, the surged interests in natural remedies are probably propelled by the preconceived notion that these may not cause untoward adverse effects unlike conventional AEDs. Therefore, it is no surprise that even the new development of AEDs tends to focus on novel mechanisms based on the recently acquired understanding of epileptogenesis and seizure propagation that can be tied to better tolerability. Immunomodulation therapy could be one example of them, but there will be more development in regional modulation of epileptogenic foci either by targeted medication delivery or electromagnetic stimulation. On the other hand, more dedicated research should be performed to find out the

actual safety and efficacy values of natural substances or herbal supplements.

#### Financial & competing interests disclosure

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