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# Cognitive and fatigue side effects of anti-epileptic drugs: an analysis of phase III add-on trials

Rani A. Sarkis[1] · Yazel Goksen[1] · Yi Mu[2] · Bernard Rosner[2] · Jong Woo Lee[1]

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## Abstract

We aimed to investigate the terms used to refer to cognitive and fatigue related side effects and their prevalence in phase III add-on clinical trials of anti-epileptic drugs (AEDs). We extracted data from publicly available FDA documents as well as the published literature. Target drug doses were then calculated as drug loads and divided into three categories (low, average, high). The odds ratio of developing the side effects was calculated for each drug load, and the presence of a dose–response effect was also assessed. We found that the cognitive terms used across trials were very variable, and data on discontinuation rates were limited. Placebo rates for cognitive side effects ranged from 0 to 10.6% while those for fatigue ranged from 2.5 to 37.7%. Keeping in mind the variable placebo rates and terminology, the majority of AEDs exhibited a clear dose response effect and significant odds ratios at high doses except brivaracetam and zonisamide for the cognitive side effects and tiagabine, topiramate, and zonisamide for the fatigue side effects. Due to their clinical relevance and impact on quality of life, new trials should make data related to the prevalence and discontinuation rates of these side effects publicly available. Given the clear dose response effect, physicians should consider aiming for lower drug loads and adjusting doses to improve tolerability.

**Keywords** Side effects · Cognitive · Memory · Fatigue · Regulatory trials · Antiepileptic drugs

## Introduction

People with epilepsy rank cognitive and fatigue side effects as one of their main concerns when taking AEDs (Anti-epileptic drugs) [1, 2]. Memory complaints are commonly reported by people with epilepsy [3] while up to 38% also report that they are dissatisfied with their energy level [4] and both of these factors can have a significant adverse impact on quality of life. The literature focusing on cognitive related AED side effects is quite variable given patient heterogeneity and the different tasks used for assessment [5]. On the other hand, the exact frequency of both cognitive and fatigue side effects is difficult to ascertain from clinical trials due to the use of different terminology (concentration difficulties vs. memory problems vs. mental slowness, fatigue vs. asthenia vs. somnolence). The goal of the current study is to assess the terms used to refer to cognitive and fatigue related side effects in phase III clinical trials submitted to the FDA and their incidence.

## Methods

We analyzed publicly available phase III data on second and third generation AEDs. For each drug the sources included (1) publicly available FDA submission documents, (2) individual trial publications, (3) published pooled analyses for each individual drug. Trials not submitted to the FDA were not analyzed. Trial inclusion criteria included (1) patient population consisting of adult patients with focal epilepsy, (2) the study design was an add-on study drug design, (3) there were fixed target doses for the drug, (4) presence of a placebo arm (5) use of at least one cognitive or fatigue side effect term. Conversion to monotherapy trials were

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✉ Rani A. Sarkis
rsarkis@bwh.harvard.edu

[1] Division of Epilepsy and EEG, Department of Neurology, Brigham and Women's Hospital, Harvard Medical School, 60 Fenwood Road - 4036, Boston, MA 02115, USA

[2] Channing Division of Network Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA

excluded. When there was a discrepancy between FDA data and peer reviewed data, the FDA data were favored. Trials including ages older than 12 or 16 were still included if the majority of the cohort were adults older than 18.

After a review of the studies and medical dictionary for regulatory activities (medDRA) terms used, a list of terms considered to be associated with cognitive related and fatigue related side effects was generated (Supplementary material) and then used to extract the data. Discontinuation rates were also extracted for the side effects of interest when present. The drug load was calculated for each target dose as (prescribed daily dose/defined daily dose) per the World Health organization [6]. Drug doses were then divided into 3 categories: Low (drug load $\leq 0.66$), average ($> 0.66$ to $\leq 1.33$), and high ($> 1.33$). If two drug doses belonged to the same category they were combined.

### Statistical analysis

We conducted two logistic regression analyses to assess the relationship between dose of epilepsy drug and side effects. The first analysis used dose as a categorical variable (low, average, high, placebo), with placebo as reference group to generate odds ratios for each dose category as compared to placebo. The second analysis was performed to determine whether there was a dose–response effect and the dose was analyzed as a numeric variable. The false discovery rate (FDR) correction was applied to correct for multiple comparisons and generate adjusted $p$ values. A cut-off of $< 0.05$ was used for significance. We also calculated the overall percentage of side effects for the placebo group and drug loads using a random effects model.

## Results

Cognitive related side effect data were available for 12 drugs, and fatigue related side effect data were available for 15 drugs (Fig. 1). Immediate release lamotrigine was excluded due to the use of valproic acid as a comparator, and gabapentin and felbamate were excluded due to the absence of data per individual daily dosing. Three drug trials had a lower age cut-off of 12 (Lamotrigine XR, Levetiracetam XR, Perampanel). Brivaracetam doses of 5 and 20 mg were excluded as these are not considered therapeutic doses.

Side effect data were extracted from the FDA in all the drugs except 3: levetiracetam [7–9], levetiracetam XR [10], and lacosamide [11]. For lacosamide, the discontinuation data extracted were based on FDA submitted documents rather than the published articles. The terms used are listed in Supplementary Table 1, and were very variable across trials. Drugs with a difference of at least 5% when compared to placebo included: eslicarbazepine (high load), perampanel (high load), Pregabalin (average and high load), tiagabine (high load), topiramate (average and high load), and vigabatrin (high load). Data for discontinuation rates were less available (Fig. 2), with only four drugs with cognitive related side effects (Fig. 2a). The placebo rates across studies ranged from 0 to 10.6%. The overall percent of patients across all trials with cognitive side effects were 2.7% for the placebo group, 2.8% low, 5.8% average, and 8.7% high drug loads, respectively, using a random effects model.

With regards to fatigue related side effects, a difference higher than 10% as compared to placebo was present in: Brivaracetam (low and high load), Eslicarbazepine (high load), levetiracetam (low load) Oxcarbazepine (low, average and high load), Oxcarbazepine XR (high load), perampanel (average and high load), and pregabalin (average and high load), tiagabine (high load), topiramate (average load), topiramate XR (average load), vigabatrin (high load). The placebo rates across studies ranged from 2.5 to 37.7%. Discontinuation rates were more available with a very high rate of 25.85% for oxcarbazepine at high loads (Fig. 2b). When analyzing the odds ratio of developing the side effects and the presence of a dose response to side effects, all AEDs clearly showed a dose response effect except for brivaracetam for the cognitive side effects and tiagabine for the fatigue side effects (Table 1). The overall percent of patients across all trials with fatigue side effects were 13.4% for the placebo group, 19.8% low, 23.2% average, and 27.8% high drug loads, respectively, using a random effects model.

## Discussion

In a review of publicly available phase III add-on trial data of second and third generation AEDs in focal epilepsy, we found cognitive and fatigue side effects to be common with most medications showing a clear dose response effect. Whether these side effects lead to a discontinuation of the drugs is unclear given the limited data published.

Although cognitive side effects are of interest to patients and physicians, studies do not routinely comment on their prevalence. The side effects tend to be diluted due to the use of different terminology, and changes in the MedRA over time. Since fatigue is also a common side effect and can adversely affect cognition we chose to analyze its prevalence as well. In addition, a certain subset of patients complaining of fatigue may in fact be referring to mental fatigue in the setting of executive difficulties. All of the patients enrolled in the trials were on polytherapy by default given the add-on nature of the trials. In general, the use of polytherapy in epilepsy is prevalent, challenging, and associated with higher risks of side effects especially when fixed rather than flexible dosing is targeted [12]. The rates can also be underestimated if a passive rather than active inquiry is performed [13] and

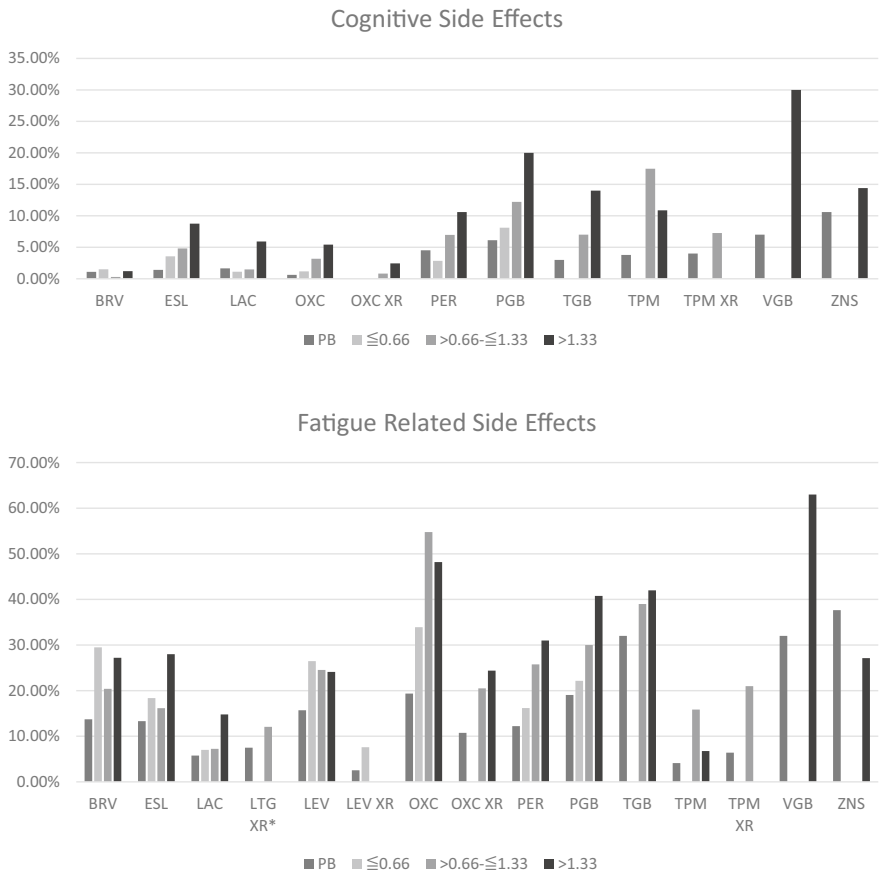


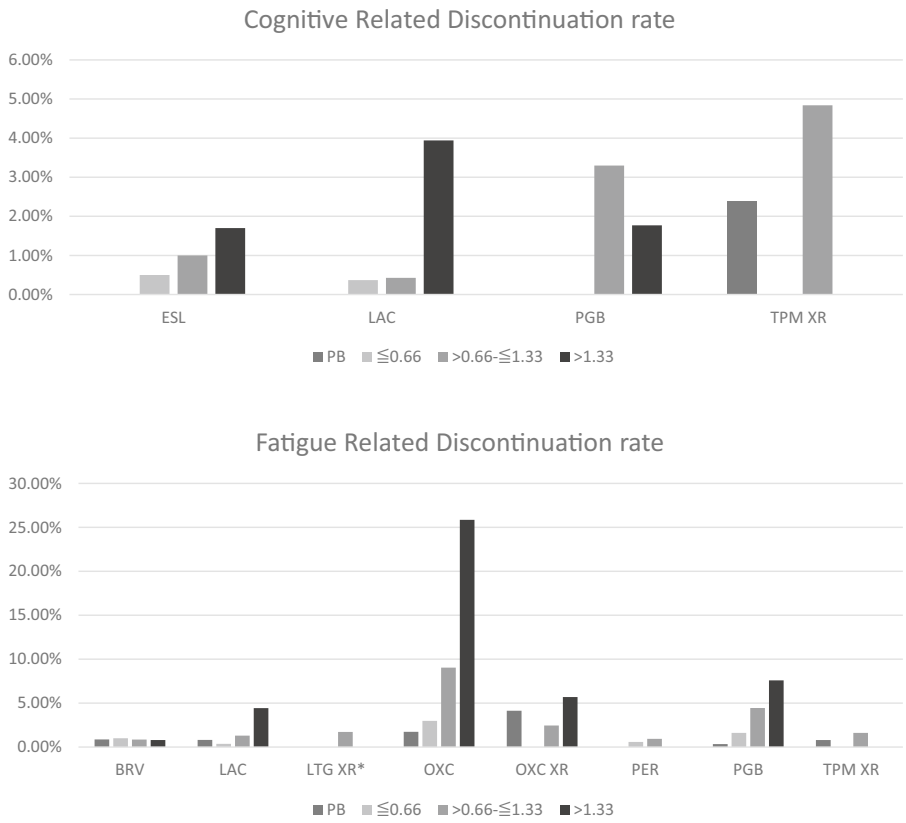

**Fig. 1** Cognitive and fatigue related side effects categorized by drug load. Asterisk denotes lamotrigine XR load range was 0.7–1.7. *BRV* Brivaracetam, *ESL* Eslicarbazepine, *LAC* Lacosamide, *LTG* Lamotrigine, *OXC* Oxcarbazepine, *PER* Perampanel, *PGB* Pregabalin, *TGB* Tiagabine, *TPM* Topiramate, *VGB* Vigabatrin, *XR* extended release, *ZNS* Zonisamide

*Lamotrigine XR load range was 0.7 to 1.7

BRV: Brivaracetam, ESL: Eslicarbazepine, LAC: Lacosamide, LTG: Lamotrigine, OXC: Oxcarbazepine, PER: Perampanel, PGB: Pregabalin, TGB: Tiagabine, TPM: Topiramate, VGB: vigabatrin, XR: Extended realease, ZNS: Zonisamide,

have a significant economic impact when polytherapy is used instead of monotherapy [14]. The cognitive domain most affected by AEDs is that of executive functioning especially in the setting of high drug loads and polytherapy [15, 16]. The placebo rates across studies ranged from 0 to 10.6% (for zonisamide). The medications with the highest cognitive rates as compared to placebo (using a difference cut-off of 5%) were eslicarbazepine (high load), perampanel (high load), Pregabalin (average and high load), tiagabine (high load), topiramate (average and high load), and vigabatrin (high load). Zonisamide did not reach significance due to the high placebo rate. Pregabalin at high doses has been shown to impact healthy volunteers [17] while topiramate is known to commonly affect cognition [18] leading to a significant limitation of its use. In a flexible dosing study of perampanel in adolescents, small negative effects were seen on continuity of attention and speed of memory, however, data in adults are currently not available [19]. In healthy volunteers, a high load of eslicarbazepine was shown to affect reaction time and category fluency although the differences were not felt to be clinically significant [20]. On the other hand, medications that modulate GABA (tiagabine and vigabatrin) would also be expected to have such a profile. The majority of the data that are publicly available are present within FDA documents, but it is encouraging that recent pooled analyses publications of some drugs specifically commented on cognitive related side effects [21] and this practice should be encouraged given the clinical relevance of the information. On the other hand, data related to discontinuation rates were only available for four drugs. Only polytherapy trials were analyzed, and one would expect different and most likely lower adverse event rates with monotherapy trials.

Fatigue related side effects are some of the most common with AEDs. The exact pathophysiology is unclear but likely involves central effects due to enhanced inhibitory and diminished excitatory neurotransmission as well as peripheral effects such as a decrease in oxygen carrying capacity [22]. The side effects were more commonly reported as compared to the cognitive ones, and the terms used were more limited across studies. The majority of




*Lamotrigine XR load range was 0.7 to 1.7

**Fig. 2** Cognitive and fatigue related side effects leading to discontinuation categorized by drug load. Asterisk denotes lamotrigine XR load range was 0.7–1.7

the drugs had significant differences compared to placebo, with lamotrigine XR and Lacosamide showing the least difference as compared to placebo. Oxcarbazepine immediate release at high doses showed the highest rates of discontinuation compared to the other drugs [23], and dosing instructions now caution physicians about its poor tolerability at doses greater than 1500 mg. Similar to other AED-related side effects, dose reductions are recommended [24, 25] given the clear dose response exhibited by the majority of medications.

Several factors preclude an analysis comparing AEDs to each other, these include patient related factors such as the number and drug load of concomitant AEDs, age, seizure frequency and co-morbid neuropsychiatric disorders. Patients enrolled in older trials are more likely to have older drugs as concomitant AEDs and these tend to have a worse adverse effect profile. Trial-related limitations include the speed of titration, the use of different terminology, and variable reporting approaches (not reporting side effects different from placebo, or prevalent in less than 2 or 5% of cases).

In summary, cognitive and fatigue related side effects are common in AED polytherapy treatment. New trials should make data related to their prevalence and discontinuation rates publicly available. Given the clear dose response effect, physicians should consider aiming for lower drug loads and adjusting doses to improve tolerability.

**Table 1** Odds ratios of developing cognitive (a) and fatigue (b) related side effects

| Drug | Low drug load OR (CI) | Average drug load OR (CI) | High drug load OR (CI) | Dose response OR (CI) |
|---|---|---|---|---|
| Cognitive related side effects | | | | |
| BRV | 1.38 (0.33–5.84) | 0.26 (0.03–2.22) | 1.10 (0.26–4.65) | 0.90 (0.54–1.47) |
| ESLI | 1.70 (0.57–5.12) | 3.56 (1.42–8.96)[a] | 6.75 (2.81–16.2)[a] | 1.92 (1.49–2.47)[a] |
| LAC | 0.67 (0.17–2.70) | 0.90 (0.30–2.71) | 3.75 (1.39–10.15)[a] | 1.63 (1.11–2.41)[a] |
| OXC | 1.92 (0.17–21.34) | 5.31 (0.59–48.11) | 9.29 (1.16–74.14)[a] | 2.11 (1.24–3.58)[a] |
| PER | 0.62 (0.29–1.34) | 1.58 (0.88–2.83) | 2.50 (1.37–4.55)[a] | 1.44 (1.18–1.77)[a] |
| PGB | 1.34 (0.66–2.76) | 2.14 (0.97–4.71) | 3.83 (2.24–6.56)[a] | 1.59 (1.35–1.88)[a] |
| TGB | | 2.15 (0.52–8.86) | 4.79 (1.21–18.88)[a] | 1.70 (1.05–2.75)[a] |
| TPM | | 5.39 (2.64–11.01)[a] | 3.10 (1.58–6.11)[a] | 1.39 (1.14–1.68)[a] |
| TPM XR | | 1.96 (0.84–4.54) | | |
| VGB | | | 5.98 (2.83–12.65)[a] | |
| ZNS | | | 1.42 (0.60–3.36) | |
| Fatigue related side effects | | | | |
| BRV | 2.63 (1.76–3.94)[a] | 1.61 (1.11–2.33)[a] | 2.35 (1.60–3.45)[a] | 1.26 (1.12–1.41)[a] |
| ESLI | 1.46 (0.93–2.31) | 1.25 (0.86–1.84) | 2.53 (1.78–3.60)[a] | 1.33 (1.19–1.50)[a] |
| LAC | 1.23 (0.65–2.34) | 1.27 (0.73–2.23) | 2.83 (1.58–5.09)[a] | 1.37 (1.12–1.67)[a] |
| LEV | 1.93 (1.25–2.99)[a] | 1.74 (1.02–2.99) | 1.71 (1.13–2.57)[a] | 1.16 (1.02–1.31)[a] |
| LEV XR | 3.16 (0.62–16.18) | | | |
| OXC | 2.1 (1.28–3.46)[a] | 4.96 (2.94–8.35)[a] | 3.81 (2.33–6.23)[a] | 1.57 (1.36–1.83)[a] |
| OXC XR | | 2.14 (1.04–4.42) | 2.68 (1.32–5.44)[a] | 1.39 (1.10–1.75)[a] |
| PER | 1.39 (0.93–2.08) | 2.49 (1.74–3.56)[a] | 3.23 (2.19–4.76)[a] | 1.51 (1.34–1.71)[a] |
| PGB | 1.21 (0.77–1.90) | 1.82 (1.07–3.12) | 2.92 (2.05–4.16)[a] | 1.45 (1.30–1.63)[a] |
| TGB | | 1.35 (0.73–2.49) | 1.56 (0.78–3.09) | 1.16 (0.93–1.44) |
| TPM | | 4.38 (2.17–8.83)[a] | 1.69 (0.84–3.37) | 1.97 (1.30–2.99)[a] |
| TPM XR | | 3.88 (1.68–8.96)[a] | | |
| VGB | | | 3.69 (2.3–5.92)[a] | |
| ZNS | | | 0.62 (0.34–1.12) | |

[a]Adjusted $p$ value $< 0.05$

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## Compliance with ethical standards

**Conflicts of interest** This study was investigator initiated and no sponsors were involved. Dr. Sarkis reports the following disclosures: has received research support from Biogen, Empatica SRL, UCB Pharma and he has received compensation for activities with DigiTrace/SleepMed. Dr. Lee reports the following disclosures: he reads EEGs in his clinical practice (25% effort) and bills for this, performs contract work with SleepMed/DigiTrace and Advance Medical, and has received funding from the NIH (NINDS R03NS091864 02, PI, 2015–2018).

**Ethical standard** This article does not contain any studies with human participants performed by any of the authors.

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