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Exposure to rufinamide and risks of CNS adverse events in drug-resistant epilepsy: a meta-analysis of randomized, placebo-controlled trials

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WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- Epilepsy is a complex disease necessitating continuous development of therapeutic strategies to encounter drug-resistant cases.
- Among new adjuvant antiepileptic drugs, rufinamide is used to treat partial-onset seizures and seizures associated with Lennox-Gastaut syndrome (LGS) in adult and children.
- To date, there has been no attempt to evaluate systematically the risks of adverse events with rufinamide.

WHAT THIS STUDY ADDS

- This study systematically quantifies the risks of adverse central nervous system events based on rufinamide randomized, double-blind, add-on, placebo-controlled trials.

AIM

Epilepsy is a complex disease necessitating continuous development of new therapeutic strategies to encounter drug-resistant cases. Among new adjuvant antiepileptic drugs, rufinamide is structurally distinct from other antiepileptic drugs. It is used to treat partial-onset seizures and seizures associated with Lennox-Gastaut syndrome (LGS) in adult and children. To date, there has been no attempt to evaluate systematically the risks of adverse events with rufinamide.

METHODS

We performed a quantitative risk analysis of central nervous system (CNS) adverse events of rufinamide from all randomized, double-blind, add-on, placebo-controlled trials. The meta-analysis was undertaken with fixed effects models.

RESULTS

Of the 886 publications reviewed, 99 papers were retrieved and five articles met the inclusion criteria. One thousand two hundred and fifty-two patients were included. Our study showed that exposure to rufinamide was associated with a significant increase in risk of somnolence [relative ratio (RR) 1.87; 95% confidence interval (CI) 1.33, 2.62; $P = 0.0003$], dizziness (RR 2.66; 95% CI 2.00, 3.55; $P = 0.00001$), fatigue (RR 2.14; 95% CI 1.57, 2.91; $P = 0.01$) and headache (RR 1.28; 95% CI 1.02, 1.59, $P = 0.03$). In addition, exposure to rufinamide was associated with higher treatment discontinuation rates as compared with placebo (RR 2.65; 95% CI 1.74, 4.03; $P = 0.00001$).

CONCLUSIONS

The risk of CNS adverse events appears to be increased in patients exposed to rufinamide as well as the treatment discontinuation rates. However, although statistical associations were significant, additional long term safety studies are required to confirm the clinical significance of these findings, as most reports described only mild and moderate adverse events.

Introduction

Epilepsy is a complex disease necessitating continuous development of new therapeutic strategies to encounter drug-resistant cases. It is estimated that 30% of epileptic cases are refractory to the antiepileptic medications [1, 2]. In addition, epilepsy is more challenging in patients with Lennox–Gastaut syndrome (LGS) where more than 75% of seizures resist multiple antiepileptic drugs [3]. Thus, efforts are currently devoted to discover adjuvant medications that could help in the management of epilepsy in these patients. Among the new adjuvant drugs, rufinamide is structurally distinct from other antiepileptic drugs [4]. Rufinamide is used as an adjuvant anticonvulsant against partial-onset seizures and seizures associated with LGS in adults and children [5, 6]. Desirably, rufinamide has low plasma protein binding and is metabolized by hydrolysis without contribution of the cytochrome P450 system leading to uncommon drug interactions [7, 8].

Moreover, several randomized controlled studies have confirmed the efficacy of rufinamide in the management of LGS and other drug-resistant epilepsies with limited effects on cognitive function [9]. However, although the effectiveness of rufinamide has been confirmed [6], to date, there has been no attempt to evaluate systematically the risks of rufinamide-induced adverse effects. Usually, in clinical practice, decisions regarding the use of new adjuvant therapies to treat refractory epilepsy are quite complex and require careful weighing of different variables. Both safety and tolerability of rufinamide are considered among these determinants in defining the whole clinical effectiveness. Of interest, it has been reported that the incidence of drug-induced adverse events was higher in the rufinamide-treated group (around 5–10% higher than placebo) [10, 11]. Also, the drug was associated with higher withdrawal rates as compared with placebo. Of interest, the CNS adverse events were also reported among the most frequent reasons for treatment discontinuation during randomized clinical trials of rufinamide [10, 11]. Although some studies discussed tolerability of rufinamide [12], these studies were limited in their findings due to small sample size, few randomized trials and potential publication bias.

Therefore, as additional randomized placebo-controlled studies have been published, the overall sample size has increased and allows a more precise estimation of potential risks of rufinamide's adverse effects. The objective of the present study was to perform quantitative analysis of adverse CNS events of rufinamide including all randomized, double-blind, add-on, placebo-controlled trials.

Methods

Search strategy

We carried out literature searches of MEDLINE, EMBASE, Web of Science and the Cochrane Central Register for Controlled Trials database from their inception until 30 March 2014. The terms rufinamide and epilepsy were used in the systematic search with no language restrictions. We also searched for additional articles through review of the reference lists of published reviews.

Inclusion and exclusion criteria

Clinical trials were selected based on the following inclusion criteria: randomized controlled trials, double-blinded with placebo, conducted in patients with drug-resistant partial or generalized epilepsies, with the experimental drug or placebo added to a traditional antiepileptic drug therapy, in either adults or children. The primary outcome of interest in this meta-analysis was risks of CNS adverse events associated with exposure to rufinamide as defined by the authors of the original studies. We excluded reviews, case reports, editorials, and studies without placebo controls.

Statistical analyses

We calculated the relative risks of the different adverse CNS events by the ratio of their occurrence in the active *vs.* the placebo groups. Using a fixed effect model, Mantel–Haenszel analysis was utilized to calculate the risk ratios (RR) with 95% confidence interval (CI). The fixed effects model was used because the test for heterogeneity was negative. To assess for publication bias, we visually inspected the funnel plot of the study estimates on the log scale for relative ratios against their standard error. We also conducted sensitivity analyses to determine the influence of any individual study by excluding each study one by one and recalculating the pooled effect. To detect heterogeneity of studies and consistency of evidence, we used the χ^2 and I^2 tests. The benchmarks for I^2 are 25%, 50%, and 75% representing low, moderate and high degrees of heterogeneity, respectively. All analyses were performed using Review Manager 5 [13].

Results

The literature search resulted in 886 publications (Figure 1). After screening of titles and abstracts, 99 full articles were reviewed. Thereafter, 93 publications were excluded based on a carful review of the full texts, which did not include relevant information or were not controlled trials as defined in our inclusion criteria. Six studies met the inclusion criteria [5, 10, 11, 14–16]; however, after a careful analysis, we excluded one study by Kluger *et al.* [16] since it represents findings of the same group of subjects in Glauser *et al.*'s paper [5] with additional results from an open label follow-up, open label extension study. The remaining papers were five studies [5, 10, 11, 14, 15], which were included in the meta-analysis. In these clinical trials, the doses were titrated weekly based on weight, to a

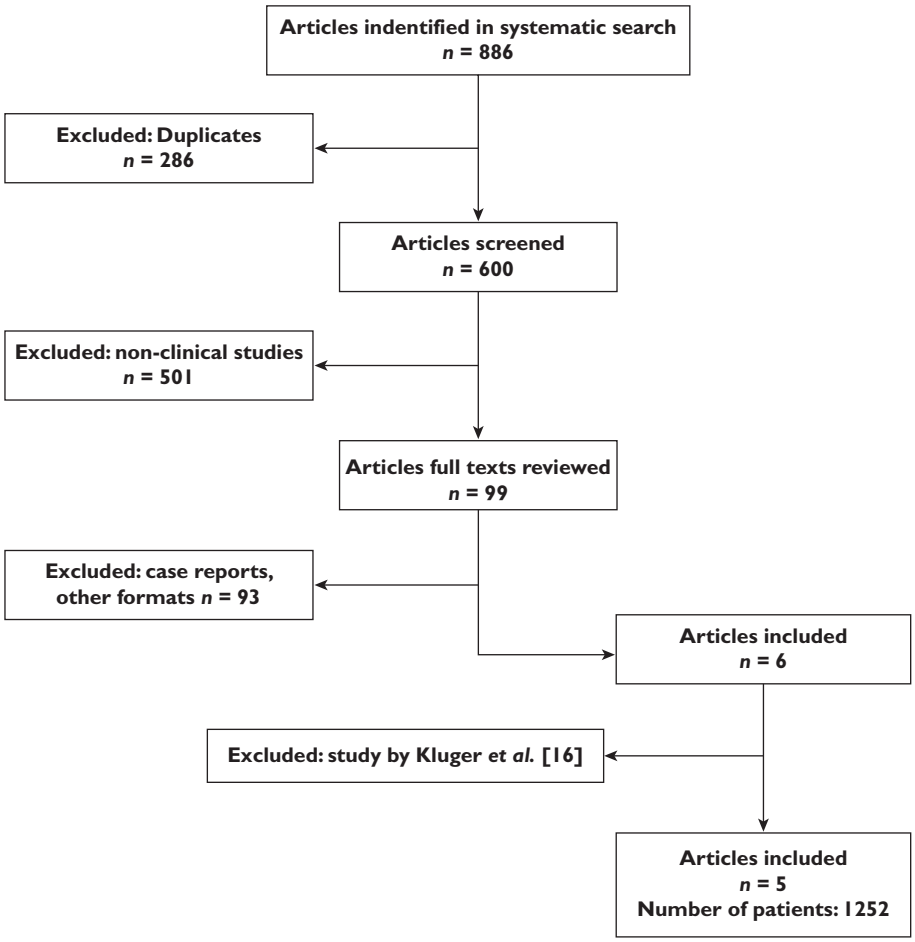

Figure 1
Study flow

Table 1
Characteristics of included studies

Study number	Authors	Year	Study characteristic: Multicentre	Study characteristic: Randomized	Reported adverse events	Rufinamide Patients treated	Placebo Patients treated
1	Palhagen *et al.* [15]	2001	9	1:1 ratio	Fatigue, headache and dizziness	25	25
2	Glauser *et al.* [5]	2008	36	Blocks of four, centre level	Somnolence	74	64
3	Elger *et al.* [14]	2010	Yes*	1:1 ratio	Fatigue, headache, dizziness and somnolence	262	133
4	Biton *et al.* [11]	2011	65	1:1 ratio	Fatigue, headache, dizziness and somnolence	176	180
5	Brodie *et al.* [10]	2009	48	1:1 ratio	Fatigue, headache, dizziness and somnolence	156	157

*Number of centres is not mentioned in the original article.

maximum dose of 45 mg kg^{-1} daily. Thereafter, the target dose was maintained throughout the trial.

A total of 1252 patients were included in the five studies accepted by us, varying from 25 to 262 patients per study (Table 1). In Glauser *et al.*'s study [5], there was a random assignment of patients into blocks of four for each centre [5]. From Elger *et al.*'s paper [14], we included only two dosing groups (800 and 1600 mg/daily) in order to maintain consistency of dosage with the other studies [14]. Also, taking into consideration patients' withdrawal from the trials, some minor differences were observed in patients' numbers within the rufinamide and placebo

Table 2

Exposure to rufinamide and risk of CNS adverse events: meta-analysis of somnolence

Study characteristics			Rufinamide		Placebo		Risk ratio	Weight
Study number	Authors	Year	Events	Total	Events	Total	M-H, Fixed, 95% CI	%
1	Biton *et al.* [11]	2011	22	176	13	180	1.73 [0.90, 3.33]	27.3
2	Brodie *et al.* [10]	2009	32	156	19	157	1.70 [1.01, 2.86]	40.3
3	Elger *et al.* [14]	2010	25	262	5	133	2.54 [0.99, 6.48]	14.1
4	Glauser *et al.* [5]	2008	18	74	8	64	1.95 [0.91, 4.17]	18.3
Total events			97	668	45	534	1.87 [1.33, 2.62]	100

Heterogeneity: $\chi^2 = 0.61$, d.f. = 3 ($P = 0.89$); $I^2 = 0\%$. Test for overall effect: Z = 3.64 ($P = 0.0003$).

groups in some studies. The five studies included children and adults (age 4 to 80 years). However, the published data did not separate adverse events into children vs. adults.

Safety of rufinamide

In the following sections, the meta-analyses of specific adverse CNS events are described.

Somnolence Ninety-seven cases of somnolence were reported out of 668 patients treated with rufinamide, as compared with 45 of 534 patients treated with placebo, yielding a RR 1.87 (95% CI 1.33 to 2.62) (Table 2, Figure 2). There was no heterogeneity among the studies ($\chi^2 = 0.61$; d.f. = 3; $P = 0.89$; $I^2 = 0\%$).

Dizziness One hundred and fifty-eight cases presented with dizziness out of 619 patients treated with rufinamide as compared with 50 of 495 patients treated with placebo. The RR was 2.66 (95% CI 2.00 to 3.55) (Table 3, Figure 3). The studies were homogenous ($\chi^2 = 3.34$; d.f. = 3; $P = 0.34$; $I^2 = 10\%$).

Fatigue/lethargy Eighty-eight cases experienced fatigue/lethargy out of 619 patients treated with rufinamide as compared to 38 of 495 patients treated with placebo, yielding RR of 2.14 (95% CI 1.57 to 2.91) (Table 4, Figure 4). There was no heterogeneity among the studies ($\chi^2 = 2.28$; d.f. = 3; $P = 0.52$; $I^2 = 0\%$).

Headache One hundred and sixty cases exhibited headache out of 619 patients treated with rufinamide, vs. 98 of 495 patients treated with placebo. The RR was 1.28 (95% CI 1.02 to 1.59) (Table 5, Figure 5). The studies were homogenous ($\chi^2 = 3.29$; d.f. = 3; $P = 0.35$; $I^2 = 9\%$).

Overall treatment withdrawal rates due to overall adverse events Eighty-five subjects receiving rufinamide were withdrawn from the studies due to overall adverse effects out of 693 as compared with 25 out of 559 patients receiving placebo [RR was 2.65 (95% CI 1.74 to 4.03)] (Table 6, Figure 6). The data was homogeneous ($\chi^2 = 3.85$; d.f. = 4; $P = 0.43$; $I^2 = 0\%$).

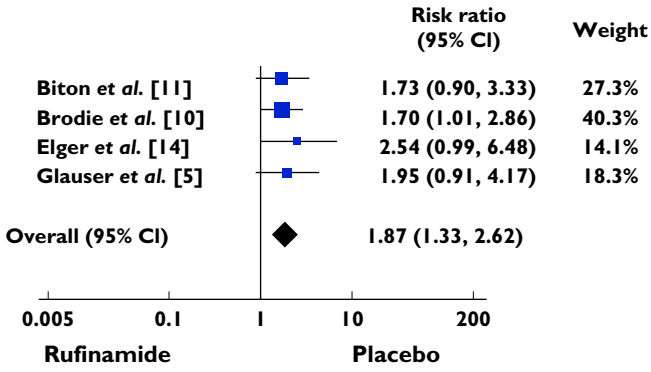

Figure 2

Forest plot showing the risk ratio with 95% confidence interval for somnolence in treatment *vs.* placebo

Influential studies and sensitivity analysis

Potential publication bias was assessed and ruled out by the symmetry of the funnel plot and sensitivity analysis. In the meta-analysis of somnolence, the studies by Biton *et al.* [11] and Brodie *et al.* [10] accounted for most of the relative weight of the analysis for exposure to rufinamide (27.3% and 40.3%, respectively). In the meta-analysis for dizziness, the studies by Elger *et al.* [14] and Brodie *et al.* [10] accounted for most of the relative weight of the analysis for exposure to rufinamide (31.6% and 40.2%, respectively), as was the case in the meta-analyses of fatigue and lethargy (62.2% and 28.9%, respectively) and headache (39.3% and 35%, respectively). Finally, in the meta-analysis of treatment discontinuation rate, the studies by Biton *et al.* [11] and Elger *et al.* [14] accounted for most of the relative weight of the analysis for exposure to rufinamide (37.7% and 41.4%, respectively).

In the sensitivity analyses, we excluded the studies one by one in order to recalculate the pooled risk. With the exception of Brodie *et al.*'s study [10], the relative ratios

Table 3

Exposure to rufinamide and risk of CNS adverse events: meta-analysis of dizziness

Study characteristics			Rufinamide		Placebo		Risk ratio	Weight
Study No.	Authors	Year	Events	Total	Events	Total	M-H, Fixed, 95% CI	%
1	Biton *et al.* [11]	2011	47	176	15	180	3.20 [1.86, 5.51]	27.2
2	Brodie *et al.* [10]	2009	66	156	22	157	3.02 [1.97, 4.63]	40.2
3	Elger *et al.* [14]	2010	43	262	13	133	1.68 [0.94, 3.01]	31.6
4	Palhagen *et al.* [15]	2001	2	25	0	25	5.00 [0.25, 99.16]	0.9
Total events			158	619	50	495	2.66 [2.00, 3.55]	100

Heterogeneity: $\chi^2 = 3.34$, d.f. = 3 ($P = 0.34$); $I^2 = 10\%$. Test for overall effect: Z = 6.67 ($P < 0.00001$).

Table 4

Exposure to rufinamide and risk of CNS adverse events: meta-analysis of fatigue/lethargy

Study characteristics			Rufinamide		Placebo		Risk ratio	Weight
Studynumber	Authors	Year	Events	Total	Events	Total	M-H, Fixed, 95% CI	%
1	Biton *et al.* [11]	2011	4	176	3	180	1.36 [0.31, 6.01]	6.6
2	Brodie *et al.* [10]	2009	25	156	13	157	1.94 [1.03, 3.64]	28.9
3	Elger *et al.* [14]	2010	54	262	21	133	1.31 [0.83, 2.07]	62.2
4	Palhagen *et al.* [15]	2001	5	25	1	25	5.00 [0.63, 39.79]	2.2
Total events			88	619	38	495	1.57 [1.11, 2.24]	100

Heterogeneity: $\chi^2 = 2.28$, d.f. = 3 ($P = 0.52$); $I^2 = 0\%$. Test for overall effect: Z = 2.53 ($P = 0.01$).

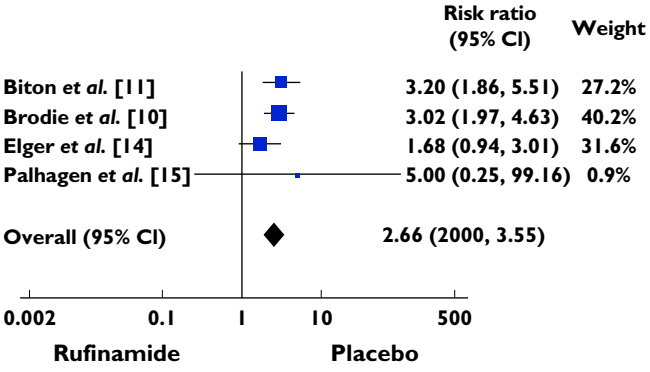

Figure 3

Forest plot showing the risk ratio with 95% confidence interval for dizziness in treatment *vs.* placebo

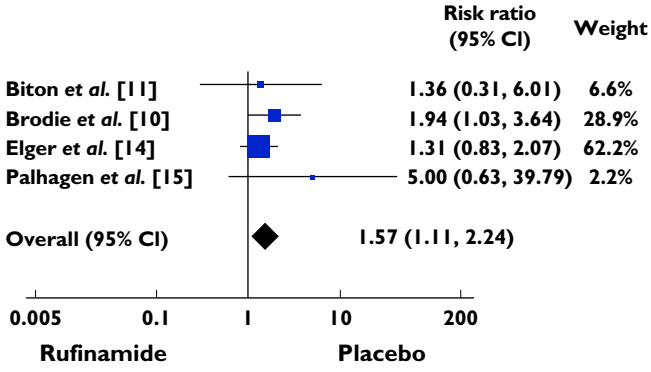

Figure 4

Forest plot showing the risk ratio with 95% confidence interval for fatigue/lethergy in treatment *vs.* placebo

remained significant when each study was excluded in the meta-analysis of somnolence, dizziness, fatigue/lethargy, headache and treatment discontinuation rate. However, in the meta-analysis of fatigue/lethargy, when we excluded Brodie *et al.*'s study [10], the RR was 1.43, which was not significant ($P = 0.10$). Similarly, when we excluded Brodie *et al.*'s study [10], the RR of headache was 1.12, which was not significant ($P = 0.43$).

Estimates of absolute risk difference and number needed to harm

The absolute risks for the exposure groups were determined for rufinamide-induced CNS adverse events and treatment discontinuation rates. Our analysis revealed an absolute risk of 0.07, 0.16, 0.06, 0.06 and 0.07 for somnolence, dizziness, fatigue, headache and the treatment discontinuation rates, respectively. Accordingly, the number

Table 5

Exposure to rufinamide and risk of CNS adverse events: meta-analysis of headache

Study characteristics			Rufinamide		Placebo		Risk ratio	Weight
Study number	Authors	Year	Events	Total	Events	Total	M-H, Fixed, 95% CI	%
1	Biton et al. [11]	2011	29	176	23	180	1.29 [0.78, 2.14]	21
2	Brodie et al. [10]	2009	59	156	38	157	1.56 [1.11, 2.20]	35
3	Elger et al. [14]	2010	69	262	32	133	1.09 [0.76, 1.57]	39.3
4	Palhagen et al. [15]	2001	3	25	5	25	0.60 [0.16, 2.25]	4.6
Total events			160	619	98	495	1.28 [1.02, 1.59]	100

Heterogeneity: $\chi^2 = 3.29$, d.f. = 3 ($P = 0.35$); $I^2 = 9\%$. Test for overall effect: Z = 2.18 ($P = 0.03$).

Table 6

Exposure to rufinamide and treatment withdrawal due to overall adverse events: Meta-analysis

Study characteristics			Rufinamide		Placebo		Risk ratio	Weight
Study No.	Authors	Year	Events	Total	Events	Total	M-H, Fixed, 95% CI	%
1	Biton *et al.* [11]	2011	27	176	11	180	2.51 [1.29, 4.90]	37.7
2	Brodie *et al.* [10]	2009	21	156	5	157	4.23 [1.64, 10.93]	17.3
3	Elger *et al.* [14]	2010	29	262	9	133	1.64 [0.80, 3.35]	41.4
4	Glauser *et al.* [5]	2008	6	74	0	64	11.27 [0.65, 196.18]	1.9
5	Palhagen *et al.* [15]	2001	2	25	0	25	5.00 [0.25, 99.16]	1.7
Total events			85	693	25	559	2.65 [1.74, 4.03]	100

Heterogeneity: $\chi^2 = 3.85$, d.f. = 4 ($P = 0.43$); $I^2 = 0\%$. Test for overall effect: Z = 4.57 ($P < 0.00001$).

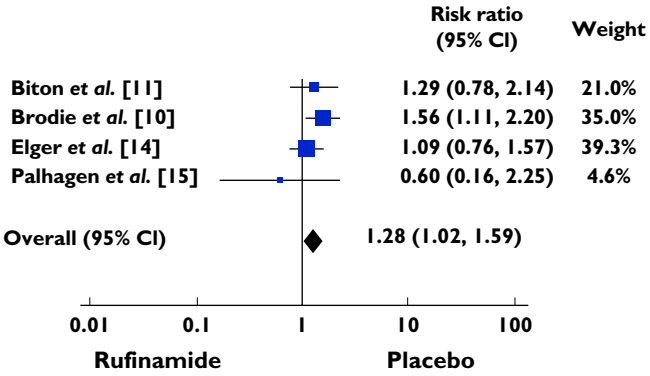

Figure 5

Forest plot showing the risk ratio with 95% confidence interval for headache in treatment *vs*. placebo

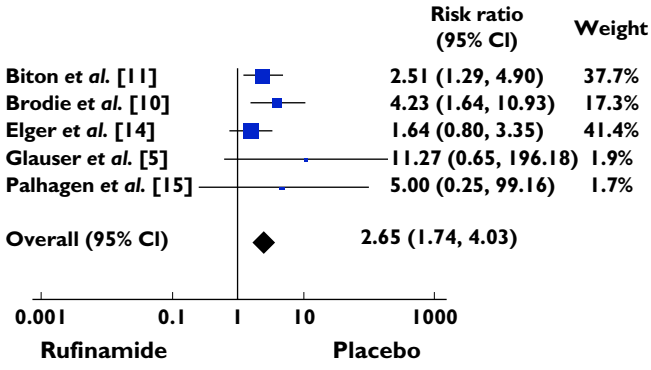

Figure 6

Forest plot showing the risk ratio with 95% confidence interval for treatment withdrawal in treatment *vs.* placebo

needed to harm was 14, 6, 16, 16 and 14 patients for somnolence, dizziness, fatigue, headache and the treatment discontinuation rates, respectively.

Discussion

During management of refractory epilepsy, rufinamide confers desirable benefits such as fewer drug-drug interactions, a lower cognitive adverse event profile and correlation of plasma concentrations with clinical efficacy [4, 7, 8]. However, several randomized placebo-controlled studies have revealed mild to moderate risks of CNS and gastrointestinal adverse events. These adverse events were reported previously with an onset during the titration period and continuing throughout the maintenance period. Among different adverse events, rufinamide has specifically been associated with adverse CNS events including somnolence, dizziness, fatigue, and headache, which probably can explain the higher treatment discontinuation rates. To the best of our knowledge, the current

study is the first meta-analysis to examine the association between exposure to rufinamide and risks of adverse CNS events. Our analysis revealed that exposure to the drug is associated with 2–3 fold increase above those reported with placebo. These data are important when rufinamide is added as adjuvant antiepileptic drug with a special focus on increased CNS adverse effects.

Of importance, it is necessary to acknowledge limitations within the current meta-analysis. While the meta-analytical techniques pool all the available data, limitations of the original articles are still exist as potential confounders and methodological limitations. Our study was based on five studies where the removal of studies that did account for the most weight was not associated with a change in statistical significance. The only exception was in meta-analysis of headache and fatigue where the removal of the study by Brodie *et al*. resulted in non-significant results [10]. However, the lack of significance is probably secondary to reduced power. Moreover, existing randomized placebo-controlled studies did not separate adverse events into children vs. adults. Thus, it is possible that the rates of rufinomide's adverse CNS effects might be age-dependent. Early pharmacokinetic/pharmacodynamic analysis of rufinamide has suggested that the probability of adverse events is significantly affected by the patient's age with toxicity being more frequently encountered in adults than in children [17]. Thus, further investigations are required to address this potential source of variability.

Another potential limitation of the current study might be attributed to differences in the methods of reporting drug-induced adverse events among different randomized studies with some adverse effects not being consistently reported in all trials including tremor, ataxia, nausea, vomiting and loss of appetite. Recently, there have been several case series and reports of weight loss that could be attributed to the nausea, vomiting and constipation associated with use of rufinamide [18, 19]. Furthermore, it is quite possible that the adverse events of rufinamide might be dose-dependent. Several studies have reported that the adverse events of this drug are more frequent during titration than during the maintenance phase. In pediatric trials, at a fixed titration dose of 45 mg kg^{-1} day^{-1}, it has been shown that somnolence and headache were more common in the rufinamide-treated groups [5, 20]. In addition, several studies have suggested that drug adverse events occur more frequently at higher levels [21]. However, to date, there are insufficient data to define a reference range for rufinamide [8]. Therefore, further research is needed to determine the dose dependence of rufinamide toxicity.

In summary, rufinamide is associated with a 2–3 fold increased risk of adverse CNS events as compared with placebo. These effects were consistent among studies included in our meta-analysis and were rated as mild to moderate in severity. These data are important when rufinamide is added as an adjuvant antiepileptic drug with special focus on increased CNS adverse effects. Future randomized placebo-controlled studies should be designed to confirm the clinical significance of our findings and to compare the incidence of adverse CNS events in children *vs*. adults.

Competing Interests

Both authors have completed the Unified Competing Interest form at http://www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare no support from any organization for the submitted work, no financial relationships with any organizations that might have an interest in the submitted work in the previous 3 years and no other relationships or activities that could appear to have influenced the submitted work. AMSA was supported by an active scholarship from the Ministry of Higher Education and KSU. The sponsor had no role in the study design or data collection, analysis or interpretation.

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