Meta-Analysis of Randomized Trials on First Line and Adjunctive Levetiracetam

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ABSTRACT: *Context:* New evidence suggests that levetiracetam may be as effective as traditional agents, with better safety profile. *Objective:* To synthesize evidence regarding efficacy and tolerability of levetiracetam as first line, adjunctive or prophylactic antiepileptic agent. *Study Selection & Data Extraction:* Eligible studies were randomized controlled trials (RCTs) of levetiracetam used in adults with epilepsy. MEDLINE, EMBASE, CENTRAL, CINHAL, PAPERSFIRST, PROCEEDINGSFIRST, PROQUEST and conference proceedings identified studies (to September 30, 2010). Two investigators independently selected, appraised studies, collected and analyzed data. *Results:* Of ten eligible randomized trials, eight investigated adjunctive levetiracetam for refractory seizures, one as monotherapy for newly diagnosed seizures, one as monotherapy for prophylaxis. Eight RCTs of adjunctive levetiracetam were of moderate quality (GRADE criteria), with two showing lack of allocation concealment. Meta-analyses showed adjunctive levetiracetam was more effective than placebo in achieving at least 50% reduction of seizure frequency, when added to baseline antiepileptic regimen (pooled RR 2.15 [1.65,2.82], $I^2 = 45\%$, p value (heterogeneity) = 0.08, p value (overall effect) < 0.01). Likelihood of serious adverse events necessitating withdrawal from study was not significantly different between levetiracetam and control (pooled RR 1.37 [0.88,2.13], $I^2 = 0\%$, p value (heterogeneity) = 0.84, p value (overall effect) = 0.17). Subgroup analyses suggested similar effects across different dosages. Sensitivity analysis of studies with adequate concealment showed similar effects. *Conclusions:* Levetiracetam is an effective adjunctive agent for refractory epilepsy. More studies are needed to establish whether it is effective as monotherapy for newly diagnosed seizures, and for prophylaxis in traumatic brain injury.

RÉSUMÉ: Méta-analyse d'essais randomisés évaluant le lévétiracétam comme traitement de première intention ou d'appoint. *Contexte :* Selon des données récentes, le lévétiracétam serait aussi efficace que les agents traditionnels et bénéficierait d'un meilleur profil de sécurité. *Objectif :* Le but de cette étude était de faire la synthèse des données concernant l'efficacité et la tolérance du lévétiracétam comme traitement de première intention, comme médicament d'appoint ou comme agent antiépileptique prophylactique. *Choix des études et recueil des données :* Nous avons choisi les essais cliniques contrôlés randomisés évaluant le lévétiracétam chez des adultes épileptiques ainsi que les comptes rendus de conférences, publiés avant le 30 septembre 2010 dans les bases de données MEDLINE, EMBASE, CENTRAL, CINHAL, PAPERSFIRST, PROCEEDINGSFIRST et PROQUEST. Deux chercheurs ont choisi les essais cliniques de façon indépendante, les ont évalués et ont colligé et analysé les données. *Résultats :* Parmi les 10 essais cliniques randomisés éligibles, 8 portaient sur le lévétiracétam comme médicament d'appoint pour traiter l'épilepsie réfractaire au traitement, 1 comme médicament de première intention chez des patients au moment du diagnostic de l'épilepsie et 1 comme monothérapie en prophylaxie. Huit des essais cliniques randomisés évaluant le lévétiracétam comme médicament d'appoint étaient de qualité moyenne (critères GRADE), dont 2 où le traitement n'était pas en aveugle. Les méta-analyses ont montré que le lévétiracétam comme traitement d'appoint était plus efficace que le placebo pour diminuer d'au moins 50% la fréquence des crises quand il était ajouté au régime posologique de base (RR global 2,15 [1,65 - 2,82] ; 12 = 45%, p (hétérogénéité) = 0,08 ; p effet global < 0,01). La probabilité que des incidents thérapeutiques sérieux entraînent le retrait du patient de l'étude n'était pas significativement différente entre le groupe recevant le lévétiracétam et le groupe témoin (RR global 1,37 [0,88 - 2,13] ; 12 = 0% ; p (hétérogénéité) = 0,84 ; p effet global = 0,17). Selon les analyses de sous-groupes, les effets seraient les mêmes, quelle que soit la posologie. Les analyses de sensibilité des études bien menées à l'insu ont montré des effets similaires. *Conclusions :* Le lévétiracétam est un médicament d'appoint efficace dans l'épilepsie réfractaire au traitement. Il devra faire l'objet de nouvelles études pour établir son efficacité en monothérapie chez les patients dont le diagnostic est récent et en prophylaxie chez les patients qui ont subi un traumatisme crânien.

Levetiracetam, a pyrrolidine, the racemically pure S-enantiomer of pyrrolidineacetamide, is an antiepileptic medication with a novel mechanism, related to a specific binding site in the brain for the synaptic vesicle protein 2A[1]. In contrast to the mechanism of traditional antiepileptics, there is no evidence for action on voltage-gated sodium channel, gamma-amino butyric acid, or glutamate-mediated synaptic transmission[2]. Levetiracetam has a linear pharmacokinetic profile, high oral bioavailability (close to 100%), and is not bound to proteins, with 95% being metabolized and excreted in urine[3]. Plasma concentrations peak within one hour, with steady-state concentrations at 48 hours with repeated dosing[4]. Its half life is between six to eight hours, with dosing between 1000-3000 mg, with minimal drug-drug interactions[4]. The most

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common side effects of levetiracetam include somnolence, asthenia and dizziness[5]. Meta-analysis suggests that the extended release version of this medication, when compared to placebo, may be associated with lower incidence of nervous system, psychiatric, nutritional and metabolic adverse effects[2-5]. So far, only four systematic reviews[2-5] have been conducted verifying its efficacy as a sole agent in refractory partial-onset seizures, as well as adjunctive agent in epilepsy. These studies were limited by lack of clarity in selection criteria, exclusion of potentially relevant trials, lack of critical appraisal of primary studies, and for-profit funding of most trials.

OBJECTIVES

The purpose of this review and meta-analysis is to systematically collect, critically appraise, and synthesize current evidence regarding the efficacy and tolerability of levetiracetam as a first line or adjunctive agent for adults suffering from idiopathic and secondary epilepsy, or those at risk.

METHODS

We included randomized trials of adult patients (older than 18 years) with EEG-documented epilepsy (including primary or refractory partial, complex partial, or generalized epilepsy, including both idiopathic and secondary seizures), comparing levetiracetam with dosing up to 3000 mg/day, as a single agent or as adjuvant therapy, to no therapy, placebo, or existing regimens (usually dilantin, carbamazepine, or valproic acid). We were interested in the following outcomes, where available:

(1) greater than 50% reduction in seizures (≥ 50% responder), and if available from study,
(2) six-month seizure freedom (proportion of patients remaining seizure free for at least six months), and
(3) any adverse effects.

In these trials, refractory epilepsy has been defined as recurrent seizures despite receiving at least one but no more than three concomitant antiepileptic medications. Eligible studies required a minimum follow-up of one year. We excluded studies including pediatric patients (younger than 18 years), pregnant and/or lactating patients, those with status epilepticus, those without electroencephalogram (EEG) confirmation, including patients with pseudo-seizures, and those with multiple organ dysfunction.

Literature Search

Two reviewers (BL, HK) independently searched the following electronic databases (to September 30, 2010) with the assistance of a medical librarian: OVID Medline, OVID EMBASE, the Cochrane Central Register of Controlled Trials (CENTRAL), clinicaltrials.gov, and the cumulative Index to Nursing and Allied Health Literature (CINAHL), without language restrictions. To include grey literature, we also searched PROCEEDINGSFIRST, and PAPERSFIRST. Proceedings of the following meetings were also searched: European *Association of Neurosurgical Societies Annual Meeting* (2003-2009), *American Association of Neurological Surgery Annual Meeting* (2003-2009), *Annual Meeting of the American Epilepsy Society* (2003-2009), *International Epilepsy Congress Annual Meeting* (2003-2009), *American Academy of Neurology Annual Meeting* (2003-2009), and the *Canadian Neurological Sciences Federation Annual Meeting* (2003-2009).

We used the following search terms: levetiracetam, keppra, seizures and epilepsy. Several search strategies were used to maximize the number of citations generated.

Study Selection

Both investigators reviewed all titles and abstracts, and full reports of all potentially relevant trials. Interrater reliability was very high (Kappa 1.0 for citation and abstract screening). BL and HK independently applied the inclusion criteria to the full reports using the aforementioned study eligibility form. Each trial report was examined carefully for its methodologic quality (kappa statistic = 0.87). Excluded studies are listed, with reason for exclusion in the "Characteristics of excluded studies" table. (Table 1). Disagreements were resolved through discussion and consensus discussions.

Data Collection Process

Two reviewers (BL, HK) tested a data extraction form and corresponding explanatory manual on three studies, revised as needed, and then used the final version of the form to independently extract data from each of the 16 studies. Disagreements were resolved by consensus discussions.

We recorded patient demographics, study and control interventions, study design, research ethics board approval, informed consent, study locations, author affiliations, method of randomization, presence of allocation concealment, length and frequency of treatments (including dose changes), duration of follow-ups, early stoppage of trials, as well as adverse events reporting. For each outcome, we noted the number of participants randomized and the number analyzed in each treatment group. For dichotomous outcomes, we noted the number of participants experiencing the outcome, and the number assessed in each treatment group. For continuous outcomes, we recorded means, standard deviations or medians, and interquartile ranges for each treatment group, together with the numbers assessed in each group. Disagreements between reviewers were resolved through consensus discussions.

Risk of Bias in Individual Studies

Both reviewers reviewed for likelihood of bias, including consistency of results, directness of evidence, imprecision and publication bias. In particular, the reviewers noted whether each study used the following methodologic qualities: allocation concealment, intention to treat analysis, adequate blinding, inclusion of all randomized patients in the analysis, completeness of follow-up, early stopping of trial, and selective outcome reporting.

Summary Measures

The primary outcome of interest to this review was 50% reduction in seizure frequency. Secondary measures included serious adverse events necessitating withdrawal from study.

Synthesis of Results

Data were analyzed with Review Manager 5 (RevMan) using relative risk for dichotomous data. It was used to measure for consistency of each meta-analysis. If there was discrepancy between the number randomized and the number analyzed, we noted the number loss to follow-up for each treatment group and reported this information.

We assessed for statistical heterogeneity by inspecting forest plots for overlapping confidence intervals, applying both the p value for heterogeneity, p value for overall effect, and the I^2 test ($I^2 < 30$ %: mild, 30-50%: moderate, >50%: substantial)[6]. We pooled data using random effects model. Pre-specified potential sources of heterogeneity included seizure subtypes, drug dosages and formulations, treatment lengths, number of baseline drugs, severity of disease and causes of seizures, route of administration, allocation concealment, blinding and patient ethnicity.

Assessment of Methodological Quality

Assessment of methodological quality for included studies was performed according to the GRADE criteria, with the addition of a synthesis GRADE Profile Table[6-8]. Assessments included generations of the allocation sequence and concealment classified as a*dequate, inadequate, or unclear* (Juni, Altman, & Egger, 2001)[6]. In generation of allocation sequence, if the method used was described and the resulting sequences were unpredictable, it was classified as *adequate*. If the trial was randomized, but the method was not described, it was classified as *unclear*. If sequences could be predicted, it was classified as

inadequate. Regarding allocation concealment, it was classified as *adequate* if participants and the investigators enrolling participants could not foresee assignment. Allocation concealment was *unclear* if the method used was not described. Concealment was *inadequate* if participants and investigators enrolling participants could foresee upcoming assignment. Inclusion of all randomized participants (proportion of participants included for which an efficacy endpoint is available) was classified as *adequate* (if ≥ 90%), *inadequate* (if < 90%), or *unclear*. Disagreements were resolved by consensus.

Additional Analyses

A funnel plot was constructed to look for evidence of publication bias[9]. Sensitivity analyses were conducted to test for robustness of findings.

Table 1: Characteristics of excluded studies

| Study	Reasons for exclusion.
Berkovic, *et al.* 2007[10]	Inclusion of pediatric population.
Jones, *et al.* 2008[11]	Prospective cohort study.
Lim, *et al.* 2009[12]	Pilot feasibility study, no appropriate control group.
Milligan, *et al.* 2008[13]	Retrospective cohort study.
Noachtar, *et al.* 2008[14]	Inclusion of pediatric population.
Steinhoff, *et al.* 2007[15]	Open label study, no appropriate control group.
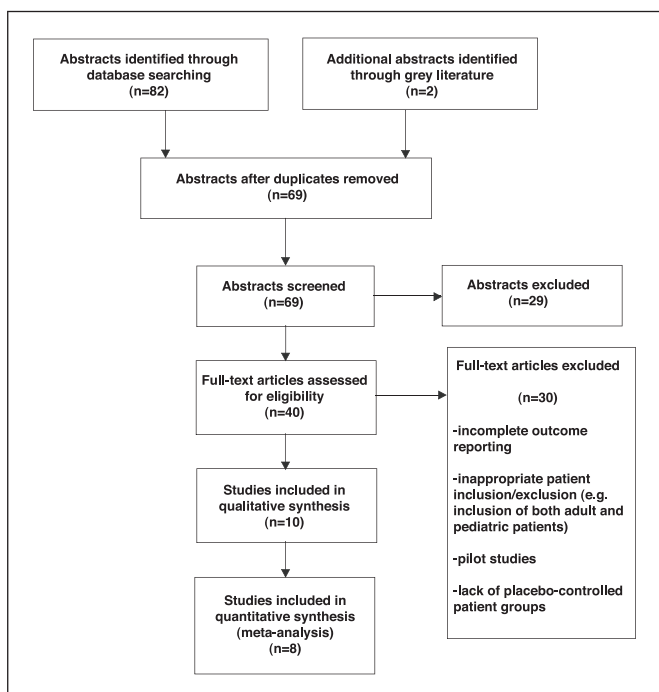
Figure 1: Flow Diagram of Study Selection.

RESULTS

Study Selection

There were 82 citations originally identified in our literature search (Figure 1). Abstract screening yielded 40 full text articles for assessment, with ten meeting our inclusion criteria. Reasons for exclusion included: incomplete/inappropriate outcome reporting, inappropriate patient groups, as well as pilot studies also reported in full. Eight studies, investigating the effects of

add-on levetiracetam, were included in our meta-analyses. Two other studies were included in our qualitative synthesis, one using levetiracetam as prophylactic agent, and the other as monotherapy agent. These two studies were not included in our quantitative meta-analysis because of differences in trial administrations, time to dose escalations, and intervals of outcome assessments.

Results of Individual Studies

Results and critique, using GRADE[7] criteria, of each study are as included in the "Characteristics of included studies," and "Characteristics of excluded studies" tables.

Study Characteristics

The eight included randomized controlled trials (RCTs) investigating adjunctive levetiracetam included patients with seizure types including simple partial seizures, complex partial seizures, partial seizures with secondary generalization, as well as primary generalized tonic-clonic seizures. These randomized trials investigated the effects of levetiracetam across multiple dosages and formulations, namely, 1000 mg/day, 2000 mg/day, 3000 mg/day, 4000 mg/day; as well as extended release formulations.

While not included in the quantitative synthesis, the single RCT investigating monotherapy levetiracetam as prophylactic agent (Szaflarski 2010[16]) points to its potential role for seizure prevention post traumatic brain injury. In this study, levetiracetam seems to be as effective as phenytoin for seizure prophylaxis (p value for difference in efficacy = 0.85), with fewer side effects (p = 0.02).

Similarly, the single RCT investigating monotherapy levetiracetam treatment agent (Brodie 2007[17]) points to its potential role for newly diagnosed, rather than treatment-resistant, epilepsy. In this study, levetiracetam seems to be as effective as carbamazepine CR for treatment of newly diagnosed seizures (p value for difference in efficacy = 1.00), with non-significant difference in side effect profile of the two medications (p = 0.12). This latter study had clear randomization techniques, blinding, as well as allocation concealment.

Table 2: Assessment of methodological quality for included studies

| Trial	Randomization	Concealment	Blinding	Percentage of randomized patients included in trial
Ben-Menachem 2000[18]	Likely done	Unclear	Double blind	95%
Shorvon 2000[19]	Likely done	Adequate	Double blind	100%
Cereghino 2000[1]	Adequate	Adequate	Double blind	100%
Peltola 2009[20]	Adequate	Adequate	Double blind	100%
Xiao 2009[21]	Adequate	Adequate	Double blind	100%
Wu 2009[22]	Likely done	Unclear	Double blind	100%
Tsai 2006[23]	Adequate	Adequate	Double blind	100%
Betts 2000[24]	Adequate	Adequate	Double blind	100%
Brodie 2007[17]	Adequate	Adequate	Double blind	100%
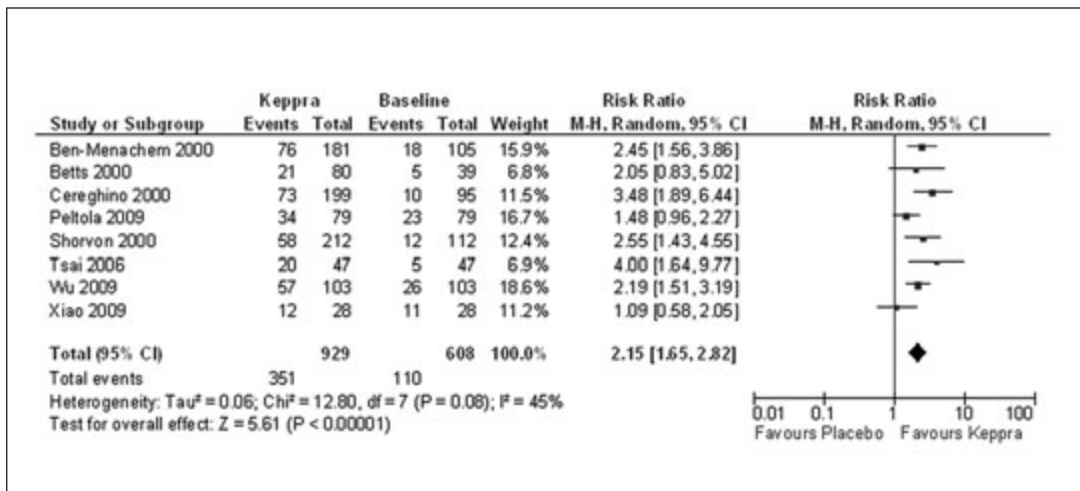
Figure 2: Forest plot combining eight RCTs using levetiracetam as adjunctive agent in achieving at least 50% seizure reduction. Here, various dosages have been combined. Subsequent meta-analyses performed using each dosing regimen.

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Table 3: GRADE evidence profile for levetiracetam and epilepsy

Quality assessment							Summary of findings					
							No of patients		Effect			
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	levetiracetam (as adjunctive or monotherapy)	placebo or baseline antiepileptics	Relative (95% CI)	Absolute	Quality	Importance
Adequate response (≥ 50% responder rate; follow-up median 26 weeks)												
8	randomized trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	reporting bias[2] strong association[3]	351/929 (37.8%)	110/608 (18.1%)	RR 2.15 (1.65 to 2.82)	208 more per 1000 (from 118 more to 329 more)	MODERATE	CRITICAL
Serious Adverse Events Requiring Withdrawal from Study (follow-up mean 26 weeks)												
8	randomized trials	serious[4]	no serious inconsistency	no serious indirectness	no serious imprecision	reporting bias[5] strong association[6]	47/687 (6.8%)	29/607 (4.8%)	RR 1.37 (0.88 to 2.13)	18 more per 1000 (from 6 fewer to 54 more)	MODERATE	IMPORTANT

Question: Should adjunctive levetiracetam versus placebo be used for epilepsy? **Settings:** urgent and non-urgent care. **Bibliography:** Ben-Menachem 2000, Betts 2000, Cereghino 2000, Peltola 2009, Shorvon 2000, Tsai 2006, Wu 2009, Xiao 2009; [1] lack of allocation concealment in two of eight studies (Ben-Menachem 2000, Wu 2009); [2] all studies were funded by drug manufacturer; [3] Overall RR = 2.15, with 95% CI of 1.65, 2.82; overall effect Z = 5.61, p < 0.00001; [4] lack of allocation concealment in two of eight studies (Ben-Menachem 2000, Wu 2009); [5] all studies were funded by drug manufacturer; [6] Overall RR = 1.37 (0.88, 2.13), I-squared = 0%, p value for heterogeneity = 0.84, p value for overall effect = 0.17; indicating lack of difference in side effects from keppra versus placebo

Assessment of Methodological Quality for Included Studies

For the eight included RCTs, five had clear descriptions of randomization techniques, and two had unclear concealment. They were all double-blind studies. All, except one, included all randomized patients in the trials (Table 2). Table 3 shows the GRADE Evidence Profile for levetiracetam.

Synthesis of Results

Meta-analysis of the included eight RCTs (intention-to-treat principle) showed that adjunctive levetiracetam was more effective than placebo in achieving at least 50% reduction of seizures, when added to baseline regimen of antiepileptics. With combination of these eight studies, the I^2 value was 45% (moderate heterogeneity) (Figure 2). One study (Xiao 2009[21]), however, contributed to much of the heterogeneity. We note that this study included post-surgical patients with refractory epilepsy, as well as patients with much lower mean body weight. One notes that patient's pharmacokinetic profile, and thus, his or her response to the medication, may differ, if less than 50 kilograms[21]. Sensitivity analysis with exclusion of this study yields an I^2 of 24%, noting mild heterogeneity in the remaining seven RCTs (with p value for heterogeneity = 0.25, and p value for overall effect size < 0.01) (Figure 3).

Different dosages (1000 mg/day, 2000 mg/day, 3000 mg/day, and 4000 mg/day) and formulations (traditional and extended release) are amenable to quantitative combination in our meta-analysis. Subgroup analyses (specified *a priori*) were performed across the different dosages. Similar 95% confidence intervals, favouring levetiracetam, were demonstrated (Figures 4-6).

Treatment-emergent adverse events include somnolence, irritability, headaches, dizziness, respiratory tract infections, and nausea. Incidences of these adverse events are not significantly more frequent than those seen in patients with baseline regimen of several antiepileptic agents. Likelihood of serious adverse events from adjunctive levetiracetam necessitating withdrawal from study was not significantly different those on adjunctive placebo (pooled RR 1.37 [0.88, 2.13], I^2 = 0%, p value for heterogeneity – 0.84, p value for overall effect = 0.17) (Figure 7). These serious adverse events included rash, worsening of seizure frequency, and blood dyscrasias.

Additional Analysis

Sensitivity analysis was done to include randomized trials that had adequate allocation concealment. The resultant relative risk, 95% confidence interval, I^2 value for heterogeneity are similar to meta-analysis completed with all eight randomized trials (Figure 8).

DISCUSSION

Summary of Evidence, with Implications for Clinical Practice and Research

Levetiracetam is an antiepileptic medication with a novel mechanism, with a favourable pharmacokinetic profile, and minimal drug-drug interactions. Prior systematic reviews established its role as an adjunctive agent for treatment of refractory partial seizures. In this systematic review and meta-analyses, levetiracetam is established as an effective adjunctive agent for control of refractory epilepsy. It seems to be effective at doses from 1000 mg per day to 3000 mg per day, titrated to effect. Clinically, one notes that the converse is also possible, in that a patient not responding to a medium dose of levetiracetam
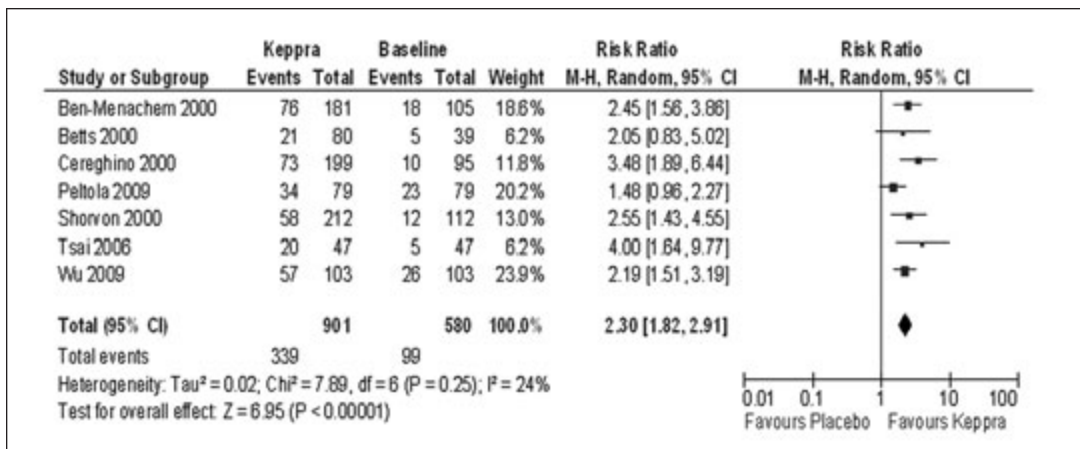
Figure 3: *Forest plot, excluding Xiao study[21], which contributed to overall study heterogeneity. Seven RCTs using levetiracetam as adjunctive agent in achieving at least 50% seizure reduction.*
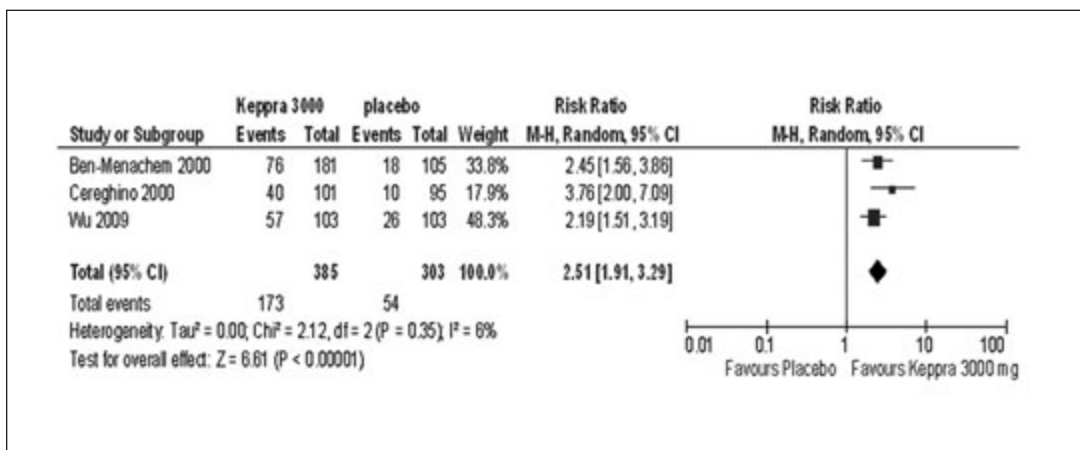

Figure 4: *Forest plot, of adjunctive levetiracetam at 3000 mg/d in achieving at least 50% seizure reduction.*
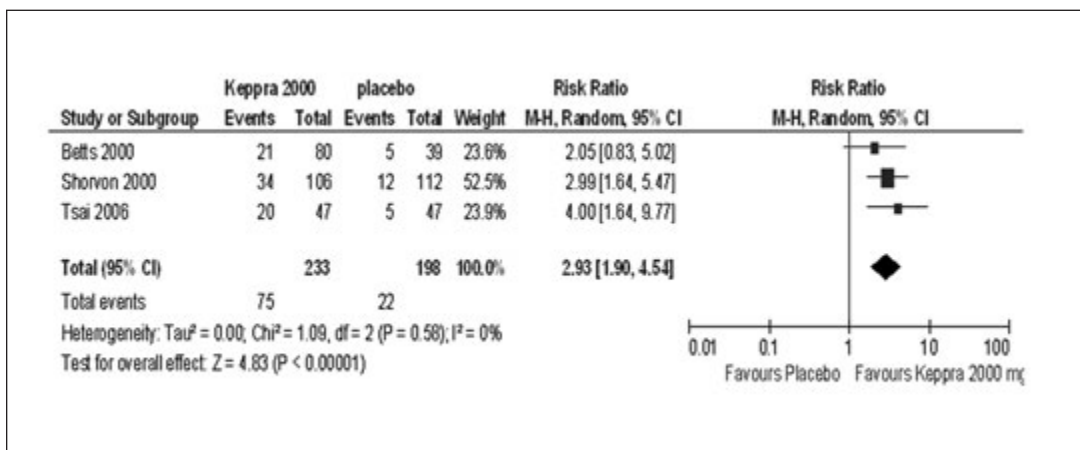

Figure 5: *Forest plot, of adjunctive levetiracetam at 2000 mg/d in achieving at least 50% seizure reduction.*
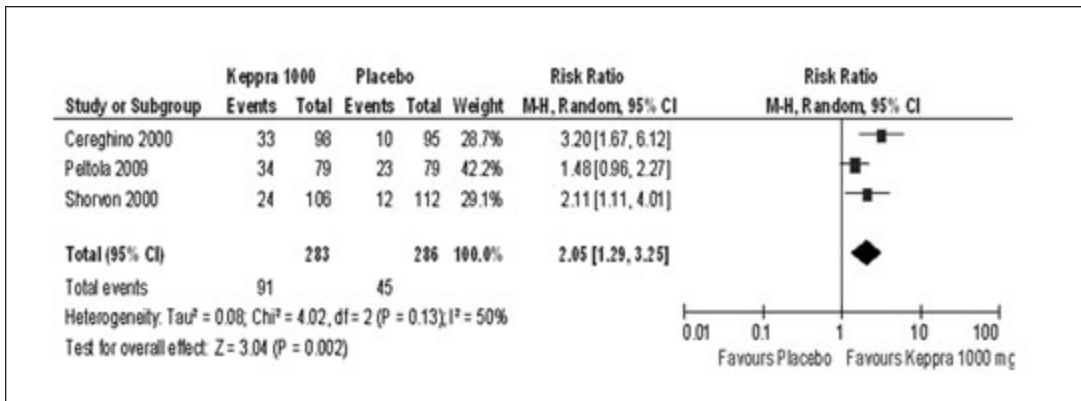
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Figure 6: Forest plot, of adjunctive levetiracetam at 1000 mg/d in achieving at least 50% seizure reduction.
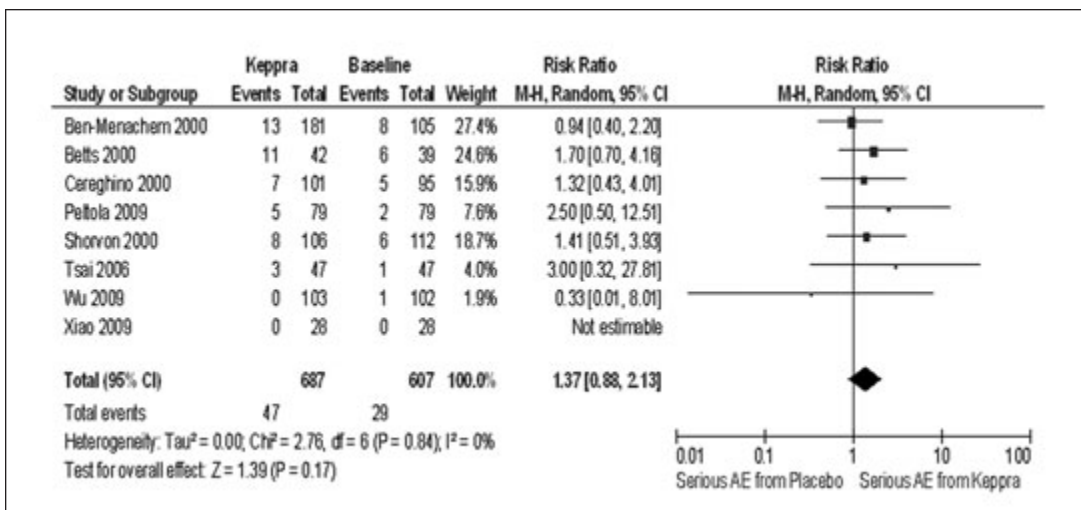

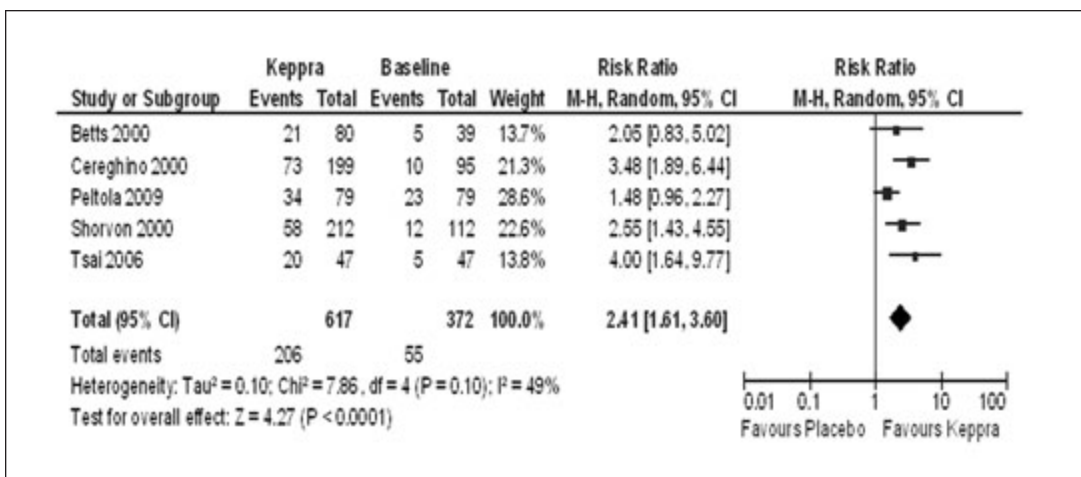*Figure 7:* Forest plot of serious adverse events from adjunctive levetiracetam requiring withdrawal from study.

Figure 8: Sensitivity analysis – forest plot of studies with adequate allocation concealment.
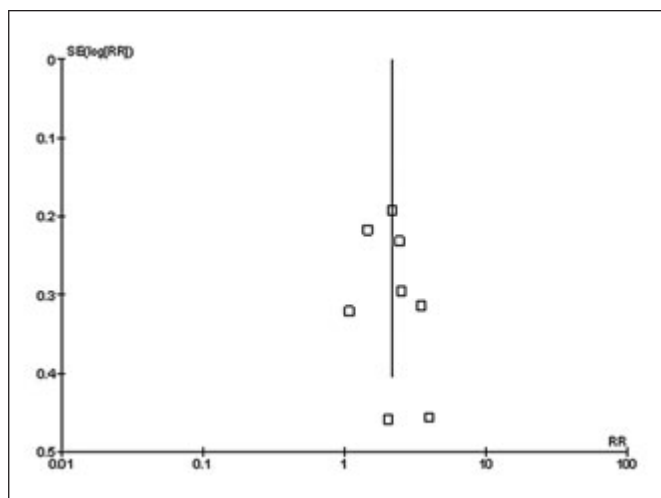
Figure 9: Funnel plot of eight included RCTs.

may not exhibit seizure reduction with dose escalation. More importantly, our study shows that it is effective across multiple seizure types, including simple partial, complex partial, partial seizure with secondary generalization, as well as generalized tonic-clonic seizures. Patients, when taking this medication as an adjunctive agent to baseline regimen of antiepileptic medications, do not seem to have increased side effects attributable to levetiracetam. Because of lack of allocation concealment in two of eight studies, as well as publication bias, the overall quality of evidence is moderate. Yet, the results of this study are of high level of importance for patient management. The robustness of meta-analysis results remained intact when studies with adequate allocation concealment were entered into the sensitivity analyses.

Overall, the quantitative synthesis showed mild to moderate heterogeneity, depending on whether all studies were included. Causes of heterogeneity may include: drug-drug interactions from baseline antiepileptics, different seizure subtypes, varying duration and severity of disease, length and rate of drug titration, and different week number for evaluation. One study (Xiao 2009[21]), in particular, contributed to much of the heterogeneity. We note that the mean body weights in this study was significantly lower that those form other studies, noting a possible different pharmacokinetic profile of the drug in those who weigh less than 50 kilograms. In addition, the Xiao study included patients who underwent epilepsy surgery. When compared to the non-surgical patient population, the surgical group with refractory epilepsy may exhibit different response profiles to re-introduction and dose adjustments of multiple anti-epileptics, including levetiracetam, after resection of epileptic foci. Confounding factors in the surgical group include hemosiderin deposition, cortical scarring and occurrence of the rekindling phenomenon.

Although not sufficient for quantitative synthesis, two stand alone trials investigating the role of levetiracetam as monotherapy agents point to its possible efficacy in treating newly diagnosed epilepsy of all types, as well as its role in preventing seizures in those with post-traumatic brain injury. Further studies are currently underway to further investigate these roles. In addition, further studies are needed to investigate the long-term efficacy and safety of the use of this medication.

Risk of Bias Within Studies

Within each study, patients kept their own seizure diaries. Thus, self reporting bias is inherent within each trial, as there is no standardized system for reporting, except in the Wu study[22]. In addition, one study (Xiao study[21]) had observers to verify seizures. In the patients' follow-up visits, only semi-structured interviews were used, with no standardized questionnaires to ensure the accuracy of both seizure numbers, types and durations.

Contamination bias is also possible, as the number and types of baseline agents vary for each patient. Although levetiracetam is not known to have drug-drug interactions with other antiepileptics, these interactions exist between baseline agents used. It is, therefore, very difficult to design a study to measure the pure effects of levetiracetam.

Self-reporting bias also comes into play with reporting of adverse events. Entities such as asthenia, as reported by patients themselves, are subjective and not amenable to objective grading.

Publication Bias

Presence of asymmetric funnel plot was noted. This asymmetry can be a chance finding when there are fewer than ten studies included in the scatter plot (Daya 2006[9]), (Figure 9).

Limitations

The major limitations of this systematic review and meta-analysis include potential publication bias, patient self-reporting bias from lack of standardized seizure diaries and follow-up interviews, contamination from multiple drug-drug interactions, and differing durations of evaluation periods from included studies. One also notes that treatment of each epileptic patient is individualized, depending on the patient's age, duration and severity of disease, response to various medications and surgical interventions, tolerance to medication side effects, and compliance to treatment. Long-term follow-up is needed to investigate the medication's safety and efficacy, as single or adjunctive agent.

CONCLUSIONS

Our systematic review and meta-analyses establish levetiracetam as an effective add-on agent for refractory epilepsy, across all seizure types. More studies are needed to establish whether levetiracetam is an effective agent for monotherapy for treatment of newly diagnosed seizures and for prophylaxis of seizures in the traumatic brain injury population. Long-term studies will be useful in elucidating its continued safety and efficacy.

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(See Appendix on following page)

APPENDIX

Characteristics of Included Studies

Study 1	Ben-Menachem 2000[18]
Methods	Multi-center, randomized, double-blind, parallel-group, responder-selected study. Double blinding during add-on therapy phase. Loss to follow up: 2 patients.
Participants	Patients recruited between June1995 and March 1997 in 47 European institutions. Seizure types included: simple partial seizures, complex partial seizures, and secondarily generalized seizures. Mean body mass index = 24.5 kg/m^2 (SD = 4). At up-titration phase – placebo (N = 105), treatment (N = 181).
Interventions	12 week baseline. Then, randomization. Up-titration for 4 weeks, to one baseline antiepileptic plus Keppra 3000 mg/d or placebo. Add-on evaluation for 14 weeks. If possible, down titration to monotherapy.
Outcomes	Median percentage seizure reduction, > 50% responder rate, number reaching seizure freedom, adverse events.
Randomization	Likely done
Allocation Concealment	Unclear
Blinding	Double-blind (patients, outcome assessors)

Study 2	Shorvon 2000[19]
Methods	Multi-center, randomized, double-blind, placebo-controlled parallel group. Loss to follow-up: none.
Participants	Patients recruited from 61 sites from Europe and the UK. Seizure types included: simple partial seizures, complex partial seizures, partial seizures with secondary generalization. Mean weight = 71.5 kg. At up-titration phase – placebo (N = 112), treatment (N = 106 in Keppra 1000 mg/d; N = 106 in Keppra 2000 mg/d).
Interventions	12 week baseline. Then, randomization. 4-week up-titration, with 12-week treatment period (baseline antiepileptics, and placebo, or Keppra 1000 mg/d, or Keppra 2000 mg/d)
Outcomes	Primary – mean number o f partial seizures per week during evaluation period (seizure frequency); secondary – > 50% responder rate, incidence of seizure-free patients, adverse events.
Randomization	Likely done
Allocation Concealment	Adequate (identical packaging, identical looking drug and placebo)
Blinding	Double-blind (patients, outcome assessors)

Study 3	Cereghino 2000[1]
Methods	Multi-center, randomized, add-on, double-blind, placebo-controlled, parallel-group trial. Double blind titration and treatment period. Loss to follow-up: 3 patients.
Participants	Patients recruited between September 1994 and March 1996 in 41 institutions. Seizure types included: partial seizures with or without secondary generalization. Mean weight = 78.5 kg. At up-titration phase – placebo (N = 95), treatment (N = 98 in Keppra 1000 mg/d; N = 101 in Keppra 3000 mg/d).
Interventions	12 week baseline. Then, randomization. 4-week up-titration to 14-week treatment. Treatment groups: baseline antiepileptics + placebo, or Keppra 500 mg BID, or Keppra 1500 mg BID. Then, withdrawal or entry into follow-up study at week 30.
Outcomes	Primary – mean number of partial seizures per week (over 14-week evaluation period); secondary – mean percent reduction, > 50% responder rate, number of seizure-free patients, adverse events.
Randomization	Adequate (block randomization)
Allocation Concealment	Adequate (identical looking and tasting tablets, identical packaging)
Blinding	Double-blind (patients, investigators)

Study 4	Peltola 2009[20]
Methods	Multi-center, randomized (1:1), placebo-controlled, double-blind, trial. Double blind titration and treatment period. Loss to follow-up: 1 patient.
Participants	Patients recruited from August 2006 to May 2007 from seven countries. Seizure types included: partial seizures with or without secondary generalization. Mean weight = 68.5 kg. At up-titration phase – placebo (N = 79), treatment (N = 79 in Keppra XR 1000 mg/d).
Interventions	8 week baseline, 12 weeks treatment with add-on Keppra XR 500 twice daily versus placebo, 2 weeks evaluation.
Outcomes	Primary –frequency of partial onset seizure per week over treatment period; secondary – 50% reduction in seizure frequency per week, absolute and percentage reduction in seizure frequency per week from baseline, adverse events.
Randomization	Adequate (interactive voice response system)
Allocation Concealment	Adequate (identical shape, size, taste, colour, packaging of placebo and treatment)
Blinding	Double-blind (all study personnel, participants)

Characteristics of Included Studies (continued)

Study 5	Xiao 2009[21]
Methods	Randomized, double-blind, placebo-controlled, trial. Double blind titration and treatment period. Loss to follow-up: none.
Participants	Patients recruited from single center over 4 months. Those with prior epilepsy surgery who failed to reduce seizure frequency included in trial. Seizure types included: partial seizures with or without secondary generalization. Mean weight = 58 kg *(note: significantly lower than other trials)*. At up-titration phase – placebo (N = 27), treatment (N = 28 in Keppra 3000 mg/d).
Interventions	Baseline: 8 weeks. Then randomization, with 4 weeks of treatment, 12 weeks of maintenance. Up-titration to 1000 mg/d, 2000 mg/d, 3000 mg/d, each over 2 weeks. After 24 weeks, open label extension or 4-week withdrawal.
Outcomes	Primary – logarithmically transformed weekly frequency of partial seizures over 16 weeks; secondary – absolute and percentage reduction from baseline; 50% responder rate, percentage change from baseline in weekly frequency of partial seizures, adverse events.
Randomization	Adequate (randomization codes generated by study sponsor)
Allocation Concealment	Adequate (numbered opaque containers used, with identical looking placebo and treatment)
Blinding	Double-blind (patients, outcome assessors)

Study 6	Wu 2009[22]
Methods	Multi-center, randomized, double-blind, placebo-controlled, parallel-group trial. Double blind titration and treatment period. Loss to follow-up: 3 patients.
Participants	Patients recruited between July 2004 and May 2005 in 6 centers. Seizure types included: simple partial, complex partial, partial seizures with generalization, primary generalized. Mean weight = 62 kg. At up-titration phase – placebo (N = 103), treatment (N = 103 in Keppra 1000 mg/d; N = 101 in Keppra 3000 mg/d).
Interventions	8 week baseline. Then, randomization. 4-week up-titration, with 12-week maintenance. Treatment groups: add-on placebo, or Keppra 3000 mg/d (with option of fall back to 2000 mg/d). At 16 weeks, down-titration or conversion to open-label long term Keppra treatment.
Outcomes	Primary – weekly frequency of partial-onset seizures over 16-week treatment period; secondary – weekly frequency of all seizures, absolute and percentage reduction from baseline in weekly frequency of partial onset and all seizures, responder rate, seizure freedom rate, adverse events.
Randomization	Likely done
Allocation Concealment	Unclear
Blinding	Double-blind (patients, outcome assessors)

Study 7	Tsai 2006[23]
Methods	Multi-center, randomized, double-blind, placebo-controlled, parallel-group trial. Double blind titration and treatment period. Loss to follow-up: none.
Participants	Patients recruited from five centers, beginning May 22, 2000. Seizure types included: partial onset seizure, with or without secondary generalization. Mean weight = 64 kg. At up-titration phase – placebo (N = 47), treatment (N = 47 in Keppra 2000 mg/d).
Interventions	8-week baseline. Then, randomization. 2-week up-titration, then 12-week maintenance period. Treatment groups: adjunctive placebo, or Keppra 1000 mg BID. Then, 2-week conversion to long-term, open-label Keppra therapy, or 4-week withdrawal phase.
Outcomes	Primary – logarithmically transformed weekly frequency of partial-onset seizures over 14-week evaluation; secondary – absolute and percentage reduction from baseline in weekly frequency of partial-onset seizures, weekly frequency of total seizures, > 50% responder rate, number of seizure free days per 4 weeks, percentage change from baseline in weekly frequency of partial onset seizures, adverse events.
Randomization	Adequate (block randomization)
Allocation Concealment	Adequate (identical containers, with identical looking placebo and treatment)
Blinding	Double-blind (patients, outcome assessors)

Characteristics of Included Studies (continued)

Study 8	Betts 2000[24]
Methods	Multi-center, randomized, double-blind, placebo-controlled, parallel-group trial. Double blind titration and treatment period. Loss to follow-up: none.
Participants	Seizure types included: partial or secondarily generalized, primary generalized tonic-clonic seizures Mean weight = not reported. At up-titration phase – placebo (N = 39), treatment (N = 42 in Keppra 2000 mg/d, N = 38 in Keppra 4000 mg/d).
Interventions	4-week baseline. Then, randomization. 24-week treatment period, with groups: antiepileptic + placebo, or Keppra 2000 mg/d, or Keppra 4000 mg/d. Then, open-label treatment period for 24 weeks, followed by 4-week run-out down-titration period, or open follow-up study.
Outcomes	Primary – > 50% responder after 24 weeks of treatment; secondary - > 50% responder rate after 4 weeks of treatment, seizure frequency by seizure type, number of seizure free patients, adverse events.
Randomization	Adequate (block randomization, randomization sequence)
Allocation Concealment	Adequate (identical containers, with identical looking, tasting placebo and treatment)
Blinding	Double-blind (patients, outcome assessors)

Study 9	Brodie 2007[17]
Methods	Randomized, double-blind, parallel, group, positive-controlled monotherapy, non-inferiority trial. Double blind titration and treatment period. Loss to follow-up: 10 patients.
Participants	Seizures included newly diagnosed partial or generalized seizures with clear focal origin or generalized tonic-clonic seizures without clear focal origin. Mean weight = 73.7 kg. At up-titration phase – Keppra (N=288), Tegretol CR (N = 291).
Interventions	Baseline of 1 week, 2-week titration (Keppra at 500 mg/d, versus Tegretol at 200 mg/d), 1-week stabilization, then 26-week evaluation. If seizures, can dose escalate to Keppra 2000 mg/d, then 3000 mg/d; Tegretol CR 800 mg/d, then 1200 mg/d.
Outcomes	Primary – 6 month seizure freedom; secondary – 1 year seizure freedom rates, 6-month and 1-year seizure freedom rates by dose level, adverse events.
Randomization	Adequate (block randomization, central 1:1)
Allocation Concealment	Adequate (identical encapsulated, tasting placebo and treatment)
Blinding	Double-blind (patients, outcome assessors)

Characteristics of Study for Seizure Prophylaxis

Study	Szaflarski 2009[16]
Methods	Single center, randomized, single-blinded comparative trial of IV levetiracetam to IV phenytoin for seizure prevention in severe traumatic brain injury or traumatic subarachnoid hemorrhage.
Participants, Interventions	52 patients randomized (34 to Keppra, 18 to Dilantin), each treated for 7 days, with continuous EEG monitoring. Those included: traumatic brain injury or subarachnoid hemorrhage; with GCS 3-8.
Outcomes	Primary – Disability Rating Scale score, Glasgow Outcomes Scales score at 6 months; secondary – seizure occurrence at 1 week, 6 months
Randomization	Likely done
Allocation Concealment	Unclear
Blinding	Single (patient) blind