Meta-analysis Evaluating Efficacy and Safety of Levetiracetam for the Management of Seizures in Children.

***Source Citation*:** Zhang L, Wang C, Li W. A meta-analysis of randomized controlled trials on levetiracetam in the treatment of pediatric patients with epilepsy. Neuropsychiatr Dis Treat. 2018;14:769-79.
***Section Editor*:** ABHIJEET SAHA

SUMMARY

This meta-analysis was conducted to evaluate clinical efficacy, safety and tolerability of levetiracetam as mono- or adjunct-therapy in the treatment of children and adolescents with epilepsy. A total of 1,013 patients were included from 13 randomized controlled trials (RCTs). Levetiracetam had a comparable seizure-free rate (RR 1.16, 95% CI 1.03, 1.31; *P*=0.30) compared to other anticonvulsants (oxcarbazepine, valproate, sulthiame, carbamazepine) or placebo. Seizure-frequency reduction of (>50% from baseline) levetiracetam was equivalent (RR 1.08, 95% CI 1.01 to 1.16; *P*=0.35) to other antiepileptic drugs (AEDs) with a comparable side effect profile (RR 0.90, 95% CI 0.77, 1.06). The authors concluded that levetiracetam had comparable efficacy, tolerability and adverse effect profile compared to others AEDs, and advocated more well-designed trials to justify widespread use of levetiracetam.

COMMENTARIES

Evidence-based Medicine Viewpoint

Relevance: In recent years, levetiracetam has gained popularity for treating seizure disorders in adults and children. The National Institute for Health and Clinical Excellence (NICE) guidelines in the United Kingdom recommended it as an add-on medication for certain types of seizures such as partial seizures, myoclonic seizures, and a limited number of other specific causes of childhood seizures [1]. This is probably because the mechanism of anti-convulsant action of levetiracetam is different from other medications. Its other pharmacological properties, including near-complete absorption after oral intake, minimal metabolism, and absence of drug interactions make it attractive for clinical use. A recently published Cochrane review [2] undertook a network meta-analysis to examine the comparative therapeutic efficacy of ten AEDs. Although the review was not targeted to children alone, it concluded that medications like phenobarbitone or phenytoin had greater efficacy than newer agents, but these were also associated with the highest risk of non-compliance compared to lamotrigine or levetiracetam. Overall, the network meta-analysis suggested that valproate is the drug of choice for generalized tonic-clonic seizures, while lamotrigine or levetiracetam are other appropriate options. Similarly, in partial seizures, carbamazepine and lamotrigine are appropriate as initial therapy; although, levetiracetam could be an option. Another systematic review [3] evaluating levetiracetam monotherapy in children included 32 studies with various study designs, but failed to find convincing evidence to support levetiracetam in preference to other medications. A fairly recent systematic review explored the safety profile of levetiracetam in children [4], and identified a higher (but statistically insignificant) prevalence of behavioral problems as well as drowsiness. Another systematic review in adults and children also confirmed that the adverse event profile of levetiracetam affected compliance to treatment [5]. Against this background, this new systematic review focusing on the efficacy and safety of levetiracetam in children has been published [6].

Critical appraisal: ***Table* I** summarizes critical appraisal of the systematic review using one of several tools available for the purpose [7]. However, several additional issues emerged. It appears that the authors were more focused on the meta-analysis component, rather than the systematic review of literature. This is also reflected in the title's emphasis on meta-analysis, instead of the review itself. It should be clarified that meta-analysis is only one component of systematic reviews, and represents a statistical tool for pooling the results across included studies to obtain a summary estimate of effect. Therefore, if the systematic review is not conducted properly, the meta-analysis can be flawed.

In this review [6], the authors applied several restrictions to their literature search that have not been

TABLE I CRITICAL APPRAISAL OF THE SYSTEMATIC REVIEW

Parameter	*Comments*
Validity	
1. Is there a clearly focused clinical question?	The authors did not state a focused clinical question in the PICOT format. However, the presumed question is: What is the efficacy and safety (Outcomes) of levetiracetam mono or add-on therapy (Intervention) versus other anti-convulsant medications (Comparison) in children/adolescents with any type of seizures (Population)? However, the time-frame (T of PICOT) for the outcomes is unclear.
2. What are the criteria for selection of studies?	The authors selected randomized controlled trials (RCTs) conducted in children/ adolescents younger than 16 y with diagnosed epilepsy, who were treated with levetiracetam *versus* any other medication or placebo. However, they included only those trials reporting at least two of the three stated outcomes of interest. Further selection was restricted to RCTs with >30 participants, published from 2007 onwards, and those published in English or Chinese only.
3. Is the literature search method specified?	The authors reported a list of databases and a list of search terms. However, they did not specify the search strategy or search terms for each database.
4. Have the identified studies been evaluated	The authors appear to have used the Cochrane Collaboration Risk of Bias tool [8] for for methodological quality? methodological assessment, but not stated the same.
5. Is it appropriate to combine the results from different studies?	The results from the included studies can be combined.
Results	
1. Were the results consistent from one study another?	There was significant heterogeneity for both the outcomes representing efficacy. to However, barring analysis by the (more conservative) random effects model, this was not explored further. There was far less heterogeneity for the adverse events.
2. What were the overall results of the review?	Levetiracetam *vs* another medication/ placebo (13 trials, 1013 participants) • Seizure-free rate: RR 1.09 (95% CI 0.92, 1.30) • Seizure frequency reduction ≥50% from baseline: RR 1.05 (95% CI 0.95, 1.15) • Adverse events: RR 0.90 (95% CI 0.77, 1.06)
3. How precise were the results?	The pooled confidence intervals for the three outcomes are fairly narrow, suggesting reasonable precision.
Applicability	
1. Is the local population similar to the people included in the original studies?	The local population can be considered similar to some of the participants in some of the included trials.
2. Is the intervention feasible in my setting?	Yes
3. Have all the clinically relevant results been taken into consideration?	Unfortunately, only a limited number of outcome measures were considered.
4. Do the benefits outweigh the potential harm?	It is difficult to judge the balance between benefits and harms from the data in this review.

properly justified. For example, trials were included only if they reported two specific outcome measures of therapeutic efficacy *viz* seizure-free rate and >50% frequency reduction from baseline. This restriction limited the scope of considering trials with other outcome measures of efficacy, such as seizure-free period, time to seizure recurrence, time to withdrawal of medication, and ≥75% frequency reduction from baseline. Similarly, adverse events were represented in a single outcome without emphasizing on serious events, and those leading to therapy discontinuation. Thus, coupled with a single outcome measure on adverse events, there were only three outcome measures in this review. Further, the authors included only those RCTs reporting at least two of these three outcomes. This reflects bias.

Although the review was focused on the pediatric age group, only trials including children younger than 16 years of age were included, and no justification for excluding children between 16 to 18 years was provided. Another serious restriction was the exclusion of trials with less than 30 participants. These arbitrary restrictions

TABLE II COMPARISON OF LEVETIRACETAM EFFICACY BY EXPRESSION OF OUTCOME MEASURES (RISK RATIO, RANDOM EFFECTS MODEL)

	Review by Zhang [6] Event: Seizure-free rate	*Re-analysis of data Event: Absence of seizure-free state*	*Review by Zhang [6] Event: Seizure-free reduction ≥50% from baseline*	*Re-analysis of data Event: Absence of seizure-free reduction ≥50% from baseline*
vs Oxcarbazepine	1.09 (0.95, 1.25)	0.93 (0.72, 1.20)	1.00 (0.93, 1.09)	1.06 (0.69, 1.64)
vs Placebo	4.25 (1.92, 9.45)	0.77 (0.61, 0.98)	1.79 (1.26, 2.53)	0.73 (0.62, 0.86)
vs Sulthiame	0.89 (0.70, 1.14)	2.10 (0.43, 10.26)	0.89 (0.70, 1.14)	2.10 (0.43, 10.26)
vs Valproate	1.11 (0.88, 1.40)	0.94 (0.80, 1.11)	1.08 (0.93, 1.25)	0.60 (0.25, 1.44)
vs Carbamazepine	0.64 (0.36, 1.16)	1.49 (0.87, 2.54)	0.76 (0.50, 1.15)	1.65 (0.77, 3.53)
Pooled estimate	1.09 (0.92, 1.30)	0.87 (0.77, 1.00)	1.05 (0.95, 1.15)	0.83 (0.67, 1.02)

resulted in the exclusion of a trial by Rosenow, *et al.* [9] comparing levetiracetam *versus* lamotrigine. The fact that this trial included 33 children upto 17 years of age makes one wonder whether arbitrary restrictions in this review [6] were designed to exclude this trial [9]. Unfortunately, the authors did not present a 'Table of excluded studies' for readers to judge whether any other eligible trials were unfairly excluded. The 'Table of Included studies' [6] lacks information on whether levetiracetam was used as mono- or polytherapy, and whether it was the initial treatment or add-on treatment. Similarly, the duration of therapy was also not described. These are important to judge the clinical utility of levetiracetam.

Conference abstracts were completely excluded from the review without providing a justification. Similarly, the language restriction in the review without specifying reasons is also arbitrary; although, this could be related to resource constraints and the focus on applicability in the local population.

On the other hand, the authors decided not to restrict inclusion of RCTs based on duration of treatment and/or follow-up. This permitted the inclusion of three trials with very short follow-up periods ranging from 5 days to 12 weeks. It is interesting that all three were placebo-controlled, and together showed statistically significant benefit with levetiracetam.

The authors did not explore heterogeneity observed in the meta-analyses. It is essential to understand whether the efficacy of levetiracetam differed on the basis of duration of treatment, baseline clinical diagnosis, compliance to therapy, mono- or polytherapy, initial or add-on agent, *etc*. The table showing quality assessment of the included RCTs reported 'very serious limitations' for all three outcomes despite the absence of any serious inconsistency, indirectness or imprecision. However, no explanation was provided for this. Although publication bias was assessed, the results were not presented.

The overall presentation of the systematic review [6] has considerable room for improvement. For example, the text stated that levetiracetam was superior to placebo for both the outcome measures reflecting therapeutic efficacy. However, the two forest plots reflect the exact opposite result, showing that placebo was superior to levetiracetam. The Discussion section is heavily loaded with a repetition of the results, without alluding to the existing systematic reviews on the topic or the additional value of this review. On a lighter note, data extraction was done in an 'electric' rather than 'electronic' format – a minor point that probably escaped the attention of the editorial process.

Usually, events in RCTs are counted in terms of the unfavorable outcome (*i.e*., treatment failure), rather than favorable outcome (*i.e*., treatment success). Thus, in this review [6], failure of seizure control and failure to achieve >50% reduction in seizure frequency would be the conventional expression of the outcome measures. Reversing the convention affects calculation of relative risks as shown in ***Table* II**. Further, the dramatic efficacy compared to placebo was considerably blunted.

Extendibility: The clinical problem, type of patients, therapeutic options and choice of medication administered, are all extendible to our settings. Therefore, had this review been free from the bias(es) highlighted, the results could have been considered for application.

Conclusion: This systematic review [6] has several methodological limitations that limit the confidence in the reported results that levetiracetam has comparable efficacy and safety with respect to other AEDs in children.

Funding: None; *Competing interests*: None stated.

JOSEPH L MATHEW
Department of Pediatrics,
PGIMER, Chandigarh, India.
dr.joseph.l.mathew@gmail.com

REFERENCES

1. National Institute for Health and Clinical Excellence. The epilepsies: the diagnosis and management of the epilepsies in adults and children in primary and secondary care 2012. Available from: *guidance.nice.org.uk/cg137*. Accessed October 15, 2018.
2. Nevitt SJ, Sudell M, Weston J, Tudur Smith C, Marson AG. Antiepileptic drug monotherapy for epilepsy: a network meta-analysis of individual participant data. Cochrane Database Syst Rev. 2017;6:CD011412.
3. Weijenberg A, Brouwer OF, Callenbach PM. Levetiracetam monotherapy in children with epilepsy: A systematic review. CNS Drugs 2015;29:371-82.
4. Egunsola O, Choonara I, Sammons HM. Safety of levetiracetam in paediatrics: A systematic review. PLoS One. 2016;11:e0149686.
5. Verrotti A, Prezioso G, Di Sabatino F, Franco V, Chiarelli F, Zaccara G. The adverse event profile of levetiracetam: A meta-analysis on children and adults. Seizure. 2015;31: 49-55.
6. Zhang L, Wang C, Li W. A meta-analysis of randomized controlled trials on levetiracetam in the treatment of pediatric patients with epilepsy. Neuropsychiatr Dis Treat. 2018;14:769-79.
7. Abalos E, Carroli G, Mackey ME, Bergel E. Critical appraisal of systematic reviews Available from: *http://apps.who.int/rhl/Critical%20appraisal%20of%20systematic%20reviews.pdf.* Accessed December 14, 2016.
8. Cochrane Risk of Bias Tool (modified) for Quality Assessment of Randomized Controlled Trials. Available from: *http://www.tc.umn.edu/~msrg/caseCATdoc/rct.crit.pdf*. Accessed November 20, 2017.
9. Rosenow F, Schade-Brittinger C, Burchardi N, Bauer S, Klein KM, Weber Y, *et al.* The La Li Mo Trial: lamotrigine compared with levetiracetam in the initial 26 weeks of monotherapy for focal and generalized epilepsy- an open-label, prospective, randomised controlled multicenter study. J Neurol Neurosurg Psychiatry. 2012;83:1093-8.

Pediatric Neurologist's Viewpoint

Levetiracetam (LEV) has been the drug most widely used off-label in pediatric population for past decade and half. Initially FDA-approved as an adjunctive anti-epileptic drug (AED) for adults with partial epilepsy, it was later approved for children with partial-onset seizures (above 4 years of age), myoclonic seizures (6 years and older) and generalized tonic-clonic seizures (12 years and older) [1]. In 2012, it was approved for usage in infants from 1 month of age. It was welcomed with open arms by Neurologists caring for infants and children, with hopes of efficacious seizure control with novel mechanism of action and minimal adverse effects. The meta-analysis by Zhang, *et al.* [2] brings out many pertinent issues to light – good and bad – with Levetiracetam usage in children. The vast number of studies/publications excluded (over 1000) in the meta-analysis highlights its widespread use. On the flip side, only13 eligible studies (8 from China) also points to lack of good quality evidence on its efficacy and adverse events. Although LEV was more effective than placebo, and equally effective as other AEDs (Valproate, Carbamazepine, Sulthiame, Oxcarbazepine), in reducing seizures by >50%, it has not shown superiority over other AEDs or placebo in terms of 100% seizure-free rate. In the subgroups, LEV was slightly better in children with Rolandic epilepsy than other partial epilepsies, but this was not statistically significant. The adverse events were also similar to other AEDs. There are lot of limitations in interpreting this data: large heterogeneity of studies with differing sample sizes, variable intervals for efficacy estimation, heterogeneity of epilepsies studied *etc*. With the available studies, it is difficult to make any meaningful conclusions about the efficacy of LEV from this review. As epilepsies in infants and children are diverse, it is hoped that homogenous populations (*e.g.*, epileptic spasms, benign focal epilepsies, primary generalized epilepsies, infantile-onset epilepsies of unknown etiology, focal epilepsies of structural etiology) are studied in future, with clinically meaningful intervals for end-point estimation. For now, it's a long way before LEV can be accorded prime position in pediatric AED armamentarium based on current evidence.

Funding: None; *Competing interests*: None stated.

RAMESH KONANKI
Consultant Pediatric Neurologist
Rainbow Hospital for Women and Children,
Hyderabad, India.
*rameshkonanki@gma*il.com

REFERENCES

1. Weijenberg A, Brouwer OF, Callenbach PM. Levetiracetam monotherapy in children with epilepsy: a systematic review. CNS Drugs. 2015;29 :371–82.
2. Zhang L, Wang C, Li W. A meta-analysis of randomized controlled trials on levetiracetam in the treatment of pediatric patients with epilepsy. Neuropsychiatr Dis Treat. 2018;14:769-79.