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ORIGINAL RESEARCH

# Levetiracetam for epilepsy: an evidence map of efficacy, safety and economic profiles

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**Objective:** To evaluate the efficacy, safety and economics of levetiracetam (LEV) for epilepsy.
**Materials and methods:** PubMed, Scopus, the Cochrane Library, OpenGrey.eu and ClinicalTrials.gov were searched for systematic reviews (SRs), meta-analyses, randomized controlled trials (RCTs), observational studies, case reports and economic studies published from January 2007 to April 2018. We used a bubble plot to graphically display information of included studies and conducted meta-analyses to quantitatively synthesize the evidence.
**Results:** A total of 14,803 records were obtained. We included 30 SRs/meta-analyses, 34 RCTs, 18 observational studies, 58 case reports and 2 economic studies after the screening process. The included SRs enrolled patients with pediatric epilepsy, epilepsy in pregnancy, focal epilepsy, generalized epilepsy and refractory focal epilepsy. Meta-analysis of the included RCTs indicated that LEV was as effective as carbamazepine (CBZ; treatment for 6 months: 58.9% vs 64.8%, OR=0.76, 95% CI: 0.50–1.16; 12 months: 54.9% vs 55.5%, OR=1.24, 95% CI: 0.79–1.93), oxcarbazepine (57.7% vs 59.8%, OR=1.34, 95% CI: 0.34–5.23), phenobarbital (50.0% vs 50.9%, OR=1.20, 95% CI: 0.51–2.82) and lamotrigine (LTG; 61.5% vs 57.7%, OR=1.22, 95% CI: 0.90–1.66). SRs and observational studies indicated a low malformation rate and intrauterine death rate for pregnant women, as well as low risk of cognitive side effects. But psychiatric and behavioral side effects could not be ruled out. LEV decreased discontinuation due to adverse events compared with CBZ (OR=0.52, 95% CI: 0.41–0.65), while no difference was found when LEV was compared with placebo and LTG. Two cost-effectiveness evaluations for refractory epilepsy with decision-tree model showed US$ 76.18 per seizure-free day gained in Canada and US$ 44 per seizure-free day gained in Korea.
**Conclusion:** LEV is as effective as CBZ, oxcarbazepine, phenobarbital and LTG and has an advantage for pregnant women and in cognitive functions. Limited evidence supports its cost-effectiveness.
**Registered number:** PROSPERO (No CRD 42017069367).

**Keywords:** seizure freedom, responder rate, quality of life, malformations, neurological development, psychiatric side effects, cost-effectiveness

## Background

Epilepsy ranks fourth after tension-type headache, migraine and Alzheimer disease in the world's neurological disorders burden.[1] A systematic review (SR) and meta-analysis of international studies reported that the point prevalence of active epilepsy was 6.38 per 1,000 people, while the lifetime prevalence was 7.60 per 1,000 people. The annual cumulative incidence of epilepsy was 67.77 per 100,000 people, while the incidence rate was 61.44 per 100,000 person-years.[2] As a fairly common clinical condition affecting all ages and requiring long-term, sometimes lifelong, treatment, epilepsy incurs high health care costs for the society.[1] In 2010, the total annual cost for

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epilepsy was 13.8 billion and the total cost per patient was €5,221 in Europe.[3] Meanwhile, in the USA, epilepsy-related costs ranged from $1,022 to $19,749 per person annually.[4] What is more, drug-refractory epilepsy was a major cost driver,[5] with main costs from anticonvulsants, hospitalization and early retirement.[6]

Currently, antiepileptic drugs (AEDs) are the main treatment method for epilepsy patients, and it was reported that approximately two-thirds of epileptic seizures were controlled by AEDs.[7] Conventional AEDs such as carbamazepine (CBZ) and sodium valproate (VPA) have been proven to have good therapeutic effects and low treatment cost. However, some adverse events (AEs) related to these drugs, such as Stevens–Johnson syndrome, menstrual disorder and memory deterioration seriously affect the tolerance and compliance of patients. Compared with conventional AEDs, new AEDs have the potential to be safer, but also more expensive.[8]

Levetiracetam (LEV) is a novel AED that has been approved as an adjunctive therapy for adults with focal epilepsy since 1999 in the US. In 2006, it was licensed as monotherapy for adults and adolescents above 16 years of age with newly diagnosed focal-onset seizures with or without secondary generalization in Europe. Also, it has been indicated as an adjunctive therapy for partial-onset seizures in patients above 4 years of age in China since 2007. Although the precise mechanism of LEV is still unclear, current researches suggest that its pharmacological mechanism is different from those of other AEDs. It may bind to the synaptic vesicle protein 2A (SV2A), which presents on the synaptic vesicles and some neuroendocrine cells. SV2A may participate in the exocytosis of synaptic vesicles and regulate the release of neurotransmitters, especially the release of excitatory amino acids, and thus depress the epilepsy discharge.[9,10] Other possible mechanisms of LEV include the following: selective inhibition of voltage-dependent N-type calcium channels in hippocampal pyramidal cells and reduction of the negative allosteric agents' inhibition, such as zinc ions and B-carbolines, on glycine and γ-aminobutyric acid neurons, which results in indirectly increasing central nervous system inhibition.[11]

LEV is almost completely absorbed after oral administration and the absorption is unaffected by food. The bioavailability is nearly 100% and the steady-state concentrations are achieved in 2 days if LEV is taken twice daily. Sixty-six percent of LEV is renally excreted unchanged and its major metabolic pathway is enzymatic hydrolysis of the acetamide group, which is independent of liver CYP/CYP450; so, no clinically meaningful drug–drug interactions with other AEDs were found.[12] One published SR of LEV suggested LEV has an equal efficacy compared with conventional AEDs and it is well tolerated for long-term therapy without significant effect on the immune system.[13] But in recent years, apart from the most frequent AEs of LEV, such as nausea, gastrointestinal symptoms, dizziness, irritability and aggressive behavior, some rare AEs of LEV have been reported, including eosinophilic pneumonia, rhabdomyolysis, thrombocytopenia, elevated kinase and reduced sperm quality.[14–17]

Thus, we conducted a mapping review to evaluate the efficacy, safety and economic profiles of LEV compared with all other AEDs for epilepsy, to provide evidence-based information for the rational use of LEV and research agendas.

## Materials and methods

### Search strategy

We searched PubMed, Scopus, Cochrane Central Register of Controlled Trials, ClinicalTrials.gov and OpenGrey.eu from Jan 1, 2007 to April 30, 2017 and updated the search results till April 23, 2018. The following keywords were used in search terms: "anticonvulsant*", "anticonvulsive", "antiepileptic*", "antiepilepsirin*", "epileps*", "epileptic*", "seizure*", "convulsion*", "trial", "comparative effectiveness research", "cohort study", "case-control study", "case report*", "case series", "cost-benefit analysis", "cost-effectiveness analysis", "cost-utility analysis", "cost-minimization analysis", "systematic review", "meta-analysis" and "health technology assessment". The search terms "Keppra", "Levetiracetam", "Desitrend", "Spritam", "Kepcet", "Kevtam" and "Levitam" were used to search relevant literature to LEV. The study was registered on PROSPERO (No CRD 42017069367).

### Study selection and outcome measures

Four independent investigators manually screened the references of all retrieved records for potentially eligible studies through the title and abstract screening in the first stage and the full-text screening in the second. For the title and abstract screening, studies appearing to meet the inclusion criteria or with insufficient information to make a clear judgment, judged by either authors or both, were included in the full-text screening process. We obtained full texts of all these studies for the full-text screening. We included studies if they 1) enrolled patients diagnosed with epilepsy, 2) compared the efficacy, safety or economic profiles of LEV, without restricting to dosage and duration and 3) SR, meta-analysis, randomized controlled trials (RCTs), observational

studies, case reports and economic studies were considered. We resolved the disagreements through discussion, and if necessary, a third party was consulted and discussed.

The primary efficacy outcomes focused on seizure freedom. The secondary efficacy outcomes included 50% responder rate, quality of life (QoL), discontinuation due to AEs, serious AEs, total AEs, single AEs and cost-effectiveness.

## Data extraction and quality assessment

Data extraction was performed by two independent investigators according to a predesigned data collection form. Extracted information included authors, publication year, search time frame, number of LEV trials, participant characteristic (seizure type, gender and age), intervention information (the dosage and duration), treatment duration, outcome of interest and dropout rate.

Two investigators independently assessed the methodological quality of included studies. We assessed the quality of included SRs using the Assessment of Multiple Systematic Reviews tool (range, 0–11).[18] We assessed the risk of bias in the eligible RCTs with the Cochrane risk of bias assessment tool.[19] The methodological quality of eligible observational studies was evaluated with the Newcastle–Ottawa Scale.[20] We evaluated the quality of the eligible pharmacoeconomic study with consolidated health economic evaluation reporting standard.[21] We did not conduct quality assessment of case reports. In the case of missing data, we contacted the authors of eligible studies for clarifications. All disagreements about data extraction and quality assessment were resolved through discussion among all authors.

## Statistical analysis

We compared the treatment effect through meta-analyses in an intention-to-treat manner (following the allocation of participants in studies) of newly included RCTs. Results of RCTs evaluating similar interventions in similar participants were pooled. We calculated the OR for categorical outcomes. We performed meta-analyses of newly included RCTs with RevMan 5.3 software using random-effect model. Statistical heterogeneity was assessed with the Mantel–Haenszel chi-squared test and quantified with the $I^2$ test. $P<0.05$ was considered statistically significant. Analyses of evidence mapping were conducted in R version 3.4.3. We used a bubble plot to graphically display the evidence regarding seizure type, control vs LEV and outcome measures. Seizure type was classified based on the type of patients and type of epilepsy. Controls were classified based on the class of antiepileptic drug. Outcomes were classified into efficacy and safety outcomes. The number of included studies in SRs and the number of included patients in RCTs were presented as the size of the circles. We described the safety outcomes of observational studies and pooled the numbers of case reports by classification of diseases.

# Results

## Study selection

The initial search identified 14,803 relevant records and the updated search identified 694 records. Also, 11,801 records remained after duplicates were removed. Of these, 10,455 records were excluded after LEV search and title/abstract screening and 162 reports were eligible for full-text review. After full-text review, we included 142 reports: 30 SRs/meta-analyses,[22–51] 34 RCTs,[52–85] 18 observational studies,[86–103] 58 case reports[104–161] and 2 economic studies[162,163] (Figure 1).

## Study characteristics and quality assessment

The included SRs were published between 2007 and 2018, enrolling patients with pediatric epilepsy, epilepsy in pregnancy, focal epilepsy, generalized epilepsy and refractory focal epilepsy. Twenty SRs compared LEV with placebo,[22–35,38,40,44,46,49,50] 19 SRs compared LEV with other AEDs[23,24,30,34,36–43,45–51] and 8 SRs were network meta-analyses that compared LEV with other AEDs[23,30,37,45–48,50] as well as placebo.[23,30,46,50] Outcome measures included seizure freedom, 50% responder rate, reduction in seizure frequency, neuropsychological findings, congenital malformation, serious AEs, total AEs, single AEs and other outcomes (Figure 2A).

Among the included RCTs, 12 compared LEV with placebo,[52,55,56,58,60–63,65,66,68,78] 9 compared LEV with CBZ,[53,69,70,73,74,79–82] 4 compared LEV with lamotrigine (LTG),[57,64,71,81] 3 compared LEV with phenobarbital (PB),[64,75,85] 3 compared LEV with VPA,[70,74,82] 2 compared LEV with oxcarbazepine (OXC),[54,83] 2 compared LEV with sulthiame,[72,84] 1 compared LEV with pregabalin,[77] 1 compared LEV with phenytoin[59] and 1 compared LEV with topiramate.[67] Outcome measures included seizure freedom, 50% responder rate, reduction in seizure frequency, QoL, serious AEs, total AEs, single AEs and other outcomes (Figure 2B).

The two economic studies were from Canada and Korea, both of which focus on add-on therapy for refractory epilepsy.[162,163] The two studies used a decision-tree model from the social perspective and payer perspective, respectively.

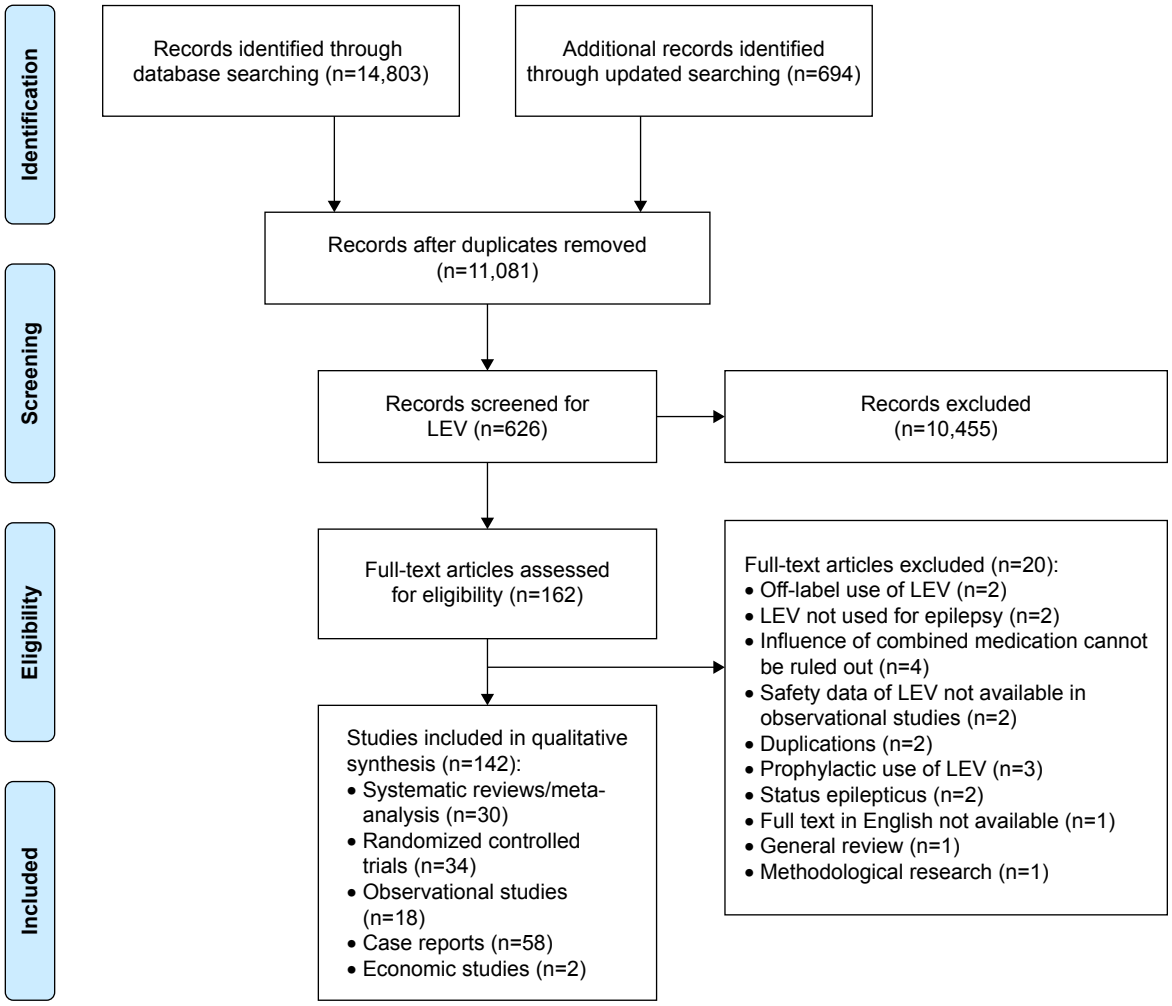


**Figure 1** Flow diagram for literature search and study selection.
**Abbreviation:** LEV, levetiracetam.

Study characteristics of the included observational studies and case reports are shown in Tables 1 and 2, respectively.

In general, the quality of included SRs and economic studies was good. The included RCTs were generally of low risk of bias. Sixteen RCTs used the double-blind design and 24 adopted the intention-to-treat principle to analyze data (Table 3).

## Efficacy

### Seizure freedom

Thirteen SRs evaluated rates of seizure freedom[23,26,31,37,40,41,43–46,49–51] (Figure 2A) and indicated that LEV increased the rates of seizure freedom compared with placebo,[23,26,31,40,44,46,49,50] but there was no difference when LEV was compared with OXC,[41,49] LTG[23,37,45,51] and brivaracetam.[40]

Meta-analysis of newly included RCTs indicated that LEV increased the rates of seizure freedom compared with placebo (19.2% [121/629] vs 3.4% [19/565], OR=5.42, 95% CI: 3.27–8.98). Meta-analyses of newly included RCTs showed that there was no difference when LEV was compared with CBZ (treatment for 6 months: 58.9% [567/963] vs 64.8% [629/970], OR=0.76, 95% CI: 0.50–1.16; treatment for 12 months: 54.9% [538/980] vs 55.5% [560/1,009], OR=1.24, 95% CI: 0.79–1.93), OXC (57.7% [112/194] vs 59.8% [113/189], OR=1.34, 95% CI: 0.34–5.23), PB (50.0% [31/62] vs 50.9% [27/53], OR=1.20, 95% CI: 0.51–2.82) and LTG (61.5% [225/366] vs 57.7% [202/350], OR=1.22, 95% CI: 0.90–1.66). We observed significant heterogeneity across included studies in the subgroup of CBZ ($I^2$=74% for 6 months treatment and $I^2$=76% for 12 months treatment), as shown in Figure 3A.

### ≥50% responder rates

Sixteen SRs evaluated ≥50% responder rates[23,24,26,27,29–31,36,40–43,46,49–51] (Figure 2A) and 12 SRs indicated that LEV increased the rates of ≥50% responder rates compared with

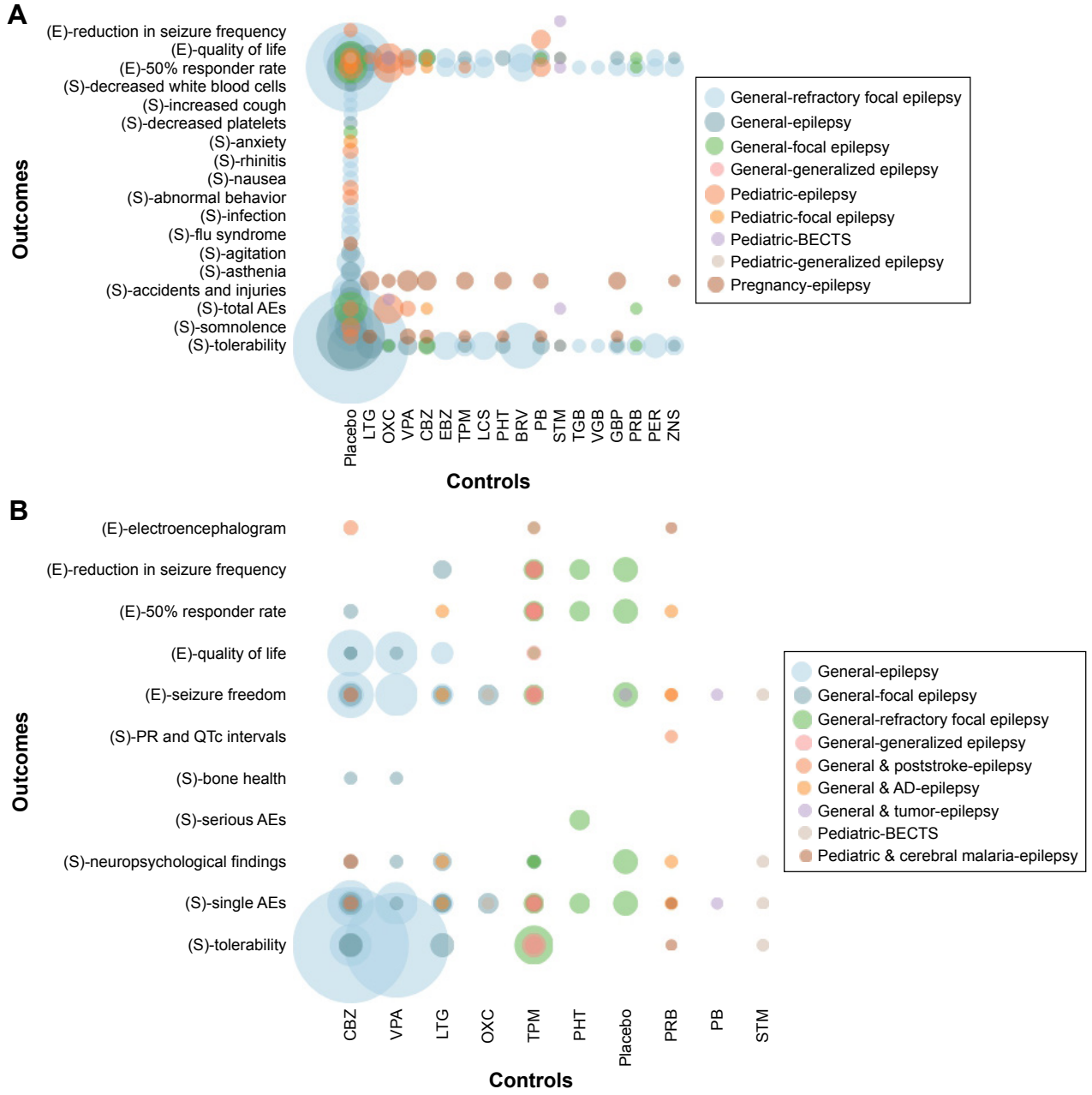


**Figure 2** Evidence mapping of included systematic reviews (**A**) and randomized controlled trials (**B**).
**Abbreviations:** AD, Alzheimer's disease; AEs, adverse events; BECTS, benign childhood epilepsy with centrotemporal spikes; BRV, brivaracetam; CBZ, carbamazepine; E, efficacy outcomes; EBZ, eslicarbazepine; GBP, gabapentin; LCS, lacosamide; LTG, lamotrigine; OXC, oxcarbazepine; PB, phenobarbital; PER, perampanel; PHT, phenytoin; PRB, pregabalin; S, safety outcomes; STM, sulthiame; TGB, tiagabine; TPM, topiramate; VGB, vigabatrin; VPA, sodium valproate; ZNS, zonisamide.

placebo,[23,24,26,27,29–31,36,40,42,46,49] but there was no difference when LEV was compared with brivaracetam.[40]

Meta-analysis of newly included RCTs indicated that LEV increased the rates of ≥50% responder rates compared with placebo (n=1,558, 47.3% [431/912] vs 27.7% [179/646], OR=3.20, 95% CI: 2.27–4.52), as shown in Figure 3B.

### Improvement of QoL

One SR suggested that LEV had a positive effect on some aspects of QoL in adults.[27]

Meta-analysis of newly included RCTs showed that there was no difference between LEV and placebo in improvement of QoL (n=224, OR=2.76, 95% CI: 0.85–8.94). We observed significant heterogeneity ($I^2$=72%) across included studies.

## Safety

### Discontinuation due to AEs

SRs indicated that there was no difference in risk of discontinuation due to AEs when LEV was compared with placebo.[24]

**Table 1** The characteristics of included observational studies

| Study, year | Intervention | | | Duration | Safety outcomes |
|---|---|---|---|---|---|
| | Patients | LEV | Control | | |
| Bootsma et al, 2008[86] | Patients with chronic refractory epilepsies | LEV | TPM | 24 months | Drug discontinuation, adverse events |
| Andersohn et al, 2010[87] | Patients with epilepsy | AEDs including LEV | No AEDs | 5.5 years | Self-harm/suicidal behavior |
| Arif et al, 2010[88] | Above 55 years old with epilepsy | LEV | CBZ/CLB/GBP/LTG/OXC/PHT/TPM/VPA/ZNS | 12 months | Most common intolerable adverse effects |
| Merrell et al, 2010[89] | Patients with glioma and seizures | LEV | PHT | 18 months | Adverse side effects |
| Rauchenzauner et al, 2010[90] | Prepubertal children with idiopathic epilepsy | LEV | VPA | 6 months | Sex steroid hormone |
| Veiby et al, 2014[91] | Children exposed prenatally to AEDs | AEDs including LEV | No AEDs | During pregnancy | Risk of growth restriction, major congenital malformations |
| Xiao et al, 2014[92] | Children with typical BECTS | LEV | VPA | 18 months | Adverse events |
| Javed et al, 2015[93] | Adult outpatients with epilepsy | LEV | CBZ/CLB/FBM/GBP/LCM/LTG/OXC/PB/PGB/PHT/PRM/RFM/TGB/TPM/VGB/VPA/ZNS | 12 years | Cognitive side effects |
| Tinchon et al, 2015[94] | Patients with glioblastoma multiforme and symptomatic seizures | LEV | No AEDs/VPA | 4–8 weeks | Hematological toxicity |
| Tomson et al, 2015[95] | Children exposed prenatally to AEDs | LEV | CBZ/LTG/OXC/PB/polytherapy/VPA | During pregnancy | Intrauterine death rates |
| Bektaş et al, 2017[96] | Children with new-onset partial seizures | LEV | VPA | 3 months | Psychiatric and behavioral side effects |
| Chen et al, 2017[97] | Patients with epilepsy | LEV | CBZ/CLB/FBM/GBP/LCM/LTG/OXC/PB/PGB/PHT/PRM/RFM/TGB/TPM/VGB/VPA/ZNS | At least 1 year | Psychiatric and behavioral side effects |
| Frey et al, 2017[99] | New user of AEDs | LEV | CBZ/CLB/LMG//PB/PHT/PRB/VPA | ≤84 days prior to the index date | Stevens–Johnson syndrome and toxic epidermal necrolysis |
| Maschio et al, 2017[101] | Patients with brain tumor-related epilepsy | LEV | LCM | 6 months | Adverse events |
| Shih et al, 2017[102] | Patients with epilepsy | LEV | CBZ/LTG/OXC/PB/PHT/polytherapy/TPM/VPA | NR | Thyroid function |
| Stephen et al, 2017[103] | Patients with uncontrolled seizures | LEV | ESL/LCM/PER/PRB/RTG/TPM/ZNS | 6–8 weeks | Psychiatric side effects |
| Egunsola et al, 2018[98] | Children receiving AEDs | LEV | CLB/CBZ/ESM/LCM/LTG/PHT/PB/TPM/VGB/VPA/ZNS | 3 months | Adverse drug reactions |
| Lee et al, 2018[100] | Patients with drug-induced seizures | LEV | No control | NR | Adverse events |

**Abbreviations:** AED, antiepileptic drugs; BECTS, benign childhood epilepsy with centrotemporal spikes; CBZ, carbamazepine; CLB, clobazam; ESL, eslicarbazepine acetate; ESM, ethosuximide; FBM, felbamate; GBP, gabapentin; LCM, lacosamide; LEV, levetiracetam; LMG, lamotrigine; LTG, lamotrigine; NR, not reported; OXC, oxcarbazepine; PB, phenobarbital; PER, perampanel; PGB, pregabalin; PHT, phenytoin; PRB, pregabalin; PRM, primidone; RFM, rufinamide; RTG, retigabine; TGB, tiagabine; TPM, topiramate; VGB, vigabatrin; VPA, sodium valproate; ZNS, zonisamide.

**Table 2** The characteristics of included case reports

| Psychiatric and behavioral side effects (n=17) | Hematological side effects (n=10) | Skin (n=10) | Kidney (n=4) | Liver (n=4) | Seizure aggravation (n=3) | Others (n=10) |
|---|---|---|---|---|---|---|
| Tamarelle et al, 2009[109] | Gallerani et al, 2009[105] | Gómez-Zorrilla et al, 2012[123] | Hurwitz et al, 2009[107] | Broli et al, 2010[111] | Caraballo et al, 2010[112] | Newsome et al, 2007[104] |
| vande Griend et al, 2009[110] | Hacquard et al, 2009[106] | Zou et al, 2012[125] | Chau et al, 2012[122] | Xiong et al, 2012[124] | Babtain, 2012[118] | Alkhotani and Mclachlan, 2012[117] |
| Givon et al, 2011[116] | Peer Mohamed et al, 2009[108] | Karadag et al, 2013[127] | Isaacson et al, 2014[136] | Sethi et al, 2013[130] | Makke et al, 2015[149] | Akiyama et al, 2014[131] |
| Bishop-Freeman et al, 2012[119] | Oghlakian et al, 2010[113] | Zou et al, 2014[142] | Spengler et al, 2014[140] | Azar and Aune, 2014[133] | | Aksoy et al, 2014[132] |
| Calabrò et al, 2012[120] | Sahaya et al, 2010[114] | Eleni, 2015[144] | | | | Koklu et al, 2014[137] |
| Camacho et al, 2012[121] | Bachmann et al, 2011[115] | Gencler et al, 2015[147] | | | | Arı et al, 2015[143] |
| Hommet et al, 2013[126] | Flannery et al, 2015[145] | Bayram et al, 2016[153] | | | | Ju et al, 2016[157] |
| Kaufman et al, 2013[128] | Peyrl et al, 2015[151] | Dar et al, 2016[154] | | | | Turati et al, 2017[158] |
| Metin et al, 2013[129] | Taberner Bonastre et al, 2015[152] | Jones et al, 2016[156] | | | | Kubota et al, 2017[159] |
| Bui et al, 2014[134] | García et al, 2016[155] | Sereflican et al, 2017[161] | | | | Ozdemir et al, 2018[160] |
| Hwang et al, 2014[135] | | | | | | |
| Kumar et al, 2014[138] | | | | | | |
| Park et al, 2014[139] | | | | | | |
| Zaki and Gupta, 2014[141] | | | | | | |
| Fujikawa et al, 2015[146] | | | | | | |
| Kawakami et al, 2015[148] | | | | | | |
| Molokwu et al, 2015[150] | | | | | | |

Meta-analysis of newly included RCTs indicated that LEV decreased discontinuation due to AEs compared with CBZ (OR=0.52, 95% CI: 0.41–0.65), while there was no difference when LEV was compared with placebo (OR=1.16, 95% CI: 0.92–1.46) and LTG (OR=1.24, 95% CI: 0.55–2.83). We observed significant heterogeneity ($I^2$=74%) across included studies in the subgroup of LTG.

## Serious AEs

Meta-analysis of newly included RCTs showed that there was no difference when LEV was compared with placebo (OR=1.10, 95% CI: 0.59–2.05), CBZ (OR=0.83, 95% CI: 0.35–1.95) and LTG (OR=1.40, 95% CI: 0.74–2.62) in the rates of serious AEs.

## Total AEs

SRs indicated that AEs were not significantly different between the LEV group and the placebo group.[31]

Meta-analysis of newly included RCTs showed that there was no difference when LEV was compared with placebo (OR=1.16, 95% CI: 0.92–1.46) and OXC (OR=0.73, 95% CI: 0.47–1.15) in the rates of total AEs.

## Single AEs

### Malformations and prenatal outcomes

Two SRs reported the safety of AEDs during pregnancy, both of which indicated that LEV was not associated with a higher risk compared to control (RR=0.32, 95% CI: 0.10–1.07 and OR=0.72, 95% CI: 0.43–1.16, respectively).[39,47]

Two observational studies used data from deliveries recorded in the compulsory Medical Birth Registry of Norway 1999–2011 and International Registry of Antiepileptic Drugs and Pregnancy (EURAP) registry, respectively.[91,95] While data in the Norway registry showed LEV had a low malformation rate for pregnant women (OR=0.63, 95% CI: 0.16–2.55 for monotherapy and OR=1.08, 95% CI: 0.27–4.43 for polytherapy), data in the EURAP registry indicated low intrauterine death rates (8.6%, 95% CI: 5.8%–12.3%).

### Neurological development

One SR showed that LEV did not increase the risk for delayed development of children (cognitive development delay: OR=3.42, 95% Credible Interval: 0.65–16.40; psychomotor development delay: OR=0.27, 95% Credible Interval: 0.00–4.65).[48]

An observational study by Javed et al[93] indicated a low risk of cognitive side effects of LEV (OR=0.68, 95% CI: 0.48–0.99 in patients newly started on polypharmacy).

**Table 3** Risk of bias of included randomized controlled trials

| Study, year | Random sequence generation | Allocation concealment | Blinding | Incomplete outcome data | Selecting reporting | Other source of bias |
|---|---|---|---|---|---|---|
| Berkovic et al, 2007[52] | Low | Low | Low | Low | Low | High |
| Borggraefe et al, 2013[72] | Low | Low | Low | Low | Unclear | Unclear |
| Brodie et al, 2007[53] | Unclear | Unclear | Low | Low | Low | Unclear |
| Consoli et al, 2012[69] | Low | High | High | Low | Unclear | Low |
| Coppola et al, 2007[54] | Low | High | High | Low | Unclear | Unclear |
| Cumbo and Ligori, 2010[64] | Unclear | Unclear | Low | Low | Unclear | Low |
| de La Loge et al, 2010[65] | Unclear | Unclear | Low | Low | Low | High |
| Fattore et al, 2011[68] | Low | Unclear | Low | Low | Unclear | Unclear |
| Hakami et al, 2016[82] | Low | Unclear | High | Low | Low | Low |
| Hakami et al, 2012[70] | Low | Unclear | High | Low | Low | Low |
| Inoue et al, 2015[78] | Unclear | Unclear | Low | Low | Low | Unclear |
| Labiner et al, 2009[57] | Unclear | Unclear | Low | Low | Unclear | Low |
| Jung et al, 2015[79] | Low | Low | High | Unclear | Low | Low |
| Kim et al, 2017[83] | Unclear | Unclear | High | Unclear | Low | Unclear |
| Levisohn et al, 2009[58] | Low | Unclear | Low | Low | Low | High |
| Lim et al, 2009[59] | Low | Unclear | Unclear | Low | Unclear | Unclear |
| Peltola et al, 2009[60] | Unclear | Unclear | Low | Low | Low | High |
| Piña-Garza et al, 2009[61] | Unclear | Unclear | High | Unclear | Low | Unclear |
| Rosenow et al, 2012[71] | Low | Unclear | High | Low | Low | Low |
| Rossetti et al, 2014[76] | Low | Low | High | Low | Low | Unclear |
| Siniscalchi et al, 2014[85] | Unclear | Unclear | High | Low | Unclear | Low |
| Suresh et al, 2015[80] | Unclear | Unclear | High | Unclear | Low | Low |
| Tacke et al, 2017[84] | Low | Low | Low | Unclear | Low | Unclear |
| Trinka et al, 2013[74] | Low | Low | High | Unclear | Low | High |
| Werhahn et al, 2015[81] | Low | Low | Low | Low | Low | Low |
| Wu et al, 2009[62] | Unclear | Unclear | Low | Low | Low | Low |
| Xiao et al, 2009[63] | Low | Low | Low | Low | Unclear | Unclear |
| Zaccara et al, 2014[77] | Low | Unclear | Low | Low | Low | Unclear |
| Zhou et al, 2008[56] | Low | Unclear | High | Unclear | Unclear | Unclear |
| Noachtar et al, 2008[55] | Low | Low | Low | Low | Low | Unclear |
| NCT01228747[66] | Unclear | Unclear | Low | Low | Low | Unclear |
| NCT01982812[75] | Unclear | Unclear | High | Low | Low | Low |
| NCT01954121[73] | Unclear | Unclear | High | Low | Low | Unclear |
| NCT01229735[67] | Unclear | Unclear | High | Low | Low | Unclear |

### Psychiatric and behavioral side effects (PBSEs)

One SR showed from various types of studies that LEV administration was associated primarily with adverse psychotropic effects including anxiety, irritability and depression.[28] One SR[32] indicated that LEV increased the risk of developing several behavioral side effects (RR=2.18, 95% CI: 1.42–3.37) such as aggression, hostility and nervousness, while the other SR reported lower rates of behavioral effects.[33] Another SR indicated that LEV may have a relationship with suicidality in epilepsy (Figure 2A).[34]

Meta-analysis of newly included RCTs indicated that LEV increased the risk of irritability compared with placebo (n=328, OR=11.55, 95% CI: 2.12–62.90; Figure 4A) and the risk of depression compared with CBZ (n=1,564, OR=2.18, 95% CI: 1.24–3.82; Figure 4B). But no difference was found in the risk of depression when LEV was compared with LTG (n=673, OR=1.80, 95% CI: 0.82–3.97).

For observational studies, Bootsma et al[86] indicated the most prevalent AEs for LEV were activating mood disorders (8.1% for 6 months, 5.2% for 12 months and 10.6% for 18 months), Arif et al[88] indicated psychiatric AEs were the most common adverse effects leading to intolerability and Andersohn et al[87] indicated LEV was associated with an increased risk of self-harm or suicidal behavior. Chen et al[97]

**A**

| Study or subgroup | LEV Events | Total | Control Events | Total | Weight (%) | OR M–H, random, 95% CI |
|---|---|---|---|---|---|---|
| **LEV vs placebo** | | | | | | |
| Brodie 2007 | 12 | 79 | 5 | 84 | 21.4 | 2.83 (0.95, 8.44) |
| Fattore 2011 | 7 | 38 | 0 | 21 | 3.0 | 10.24 (0.56, 188.83) |
| Levisohn 2009 | 30 | 64 | 3 | 34 | 15.5 | 9.12 (2.53, 32.88) |
| NCT01228747 | 8 | 60 | 0 | 60 | 3.1 | 19.59 (1.10, 347.61) |
| Noachtar 2008 | 32 | 108 | 3 | 97 | 17.1 | 13.19 (3.89, 44.75) |
| Peltola 2009 | 8 | 79 | 1 | 79 | 5.8 | 8.79 (1.07, 72.03) |
| Pina-Garza 2009 | 9 | 58 | 3 | 51 | 13.7 | 2.94 (0.75, 11.52) |
| Wu 2009 | 11 | 102 | 2 | 100 | 10.9 | 5.92 (1.28, 27.45) |
| Xiao 2009 | 3 | 28 | 2 | 28 | 7.3 | 1.56 (0.24, 10.14) |
| Zhou 2008 | 1 | 13 | 0 | 11 | 2.3 | 2.76 (0.10, 74.78) |
| **Subtotal (95% CI)** | | **629** | | **565** | **100** | **5.42 (3.27, 8.98)** |
| Total events | 121 | | 19 | | | |
| Heterogeneity: $\tau^2$=0.00; $\chi^2$=8.05, *df*=9 (*P*=0.53); $I^2$=0% | | | | | | |
| Test for overall effect: *Z*=6.56 (*P*<0.00001) | | | | | | |
| **LEV vs CBZ (6 months)** | | | | | | |
| Brodie 2007 | 190 | 285 | 194 | 291 | 30.4 | 1.00 (0.71, 1.41) |
| NCT01954121 | 88 | 186 | 117 | 171 | 27.2 | 0.41 (0.27, 0.64) |
| Suresh 2015 | 22 | 28 | 20 | 28 | 9.1 | 1.47 (0.43, 4.97) |
| Trinka 2013 | 267 | 464 | 298 | 480 | 33.3 | 0.83 (0.64, 1.07) |
| **Subtotal (95% CI)** | | **963** | | **970** | **100** | **0.76 (0.50, 1.16)** |
| Total events | 567 | | 629 | | | |
| Heterogeneity: $\tau^2$=0.12; $\chi^2$=11.43, *df*=3 (*P*=0.010); $I^2$=74% | | | | | | |
| Test for overall effect: *Z*=1.25 (*P*=0.21) | | | | | | |
| **LEV vs CBZ (12 months)** | | | | | | |
| Brodie 2007 | 142 | 285 | 155 | 291 | 26.2 | 0.87 (0.63, 1.21) |
| Consoli 2012 | 49 | 52 | 46 | 54 | 7.7 | 2.84 (0.71, 11.37) |
| Jung 2015 | 38 | 57 | 37 | 64 | 16.6 | 1.46 (0.70, 3.06) |
| Trinka 2013 | 234 | 464 | 272 | 480 | 27.7 | 0.78 (0.60, 1.01) |
| Werhahn 2015 | 75 | 122 | 50 | 120 | 21.7 | 2.23 (1.34, 3.74) |
| **Subtotal (95% CI)** | | **980** | | **1,009** | **100** | **1.24 (0.79, 1.93)** |
| Total events | 538 | | 560 | | | |
| Heterogeneity: $\tau^2$=0.17; $\chi^2$=16.84, *df*=4 (*P*=0.002); $I^2$=76% | | | | | | |
| Test for overall effect: *Z*=0.93 (*P*=0.35) | | | | | | |
| **LEV vs OXC** | | | | | | |
| Coppola 2007 | 19 | 21 | 13 | 18 | 32.3 | 3.65 (0.61, 21.78) |
| Kim 2017 | 93 | 173 | 100 | 171 | 67.7 | 0.83 (0.54, 1.26) |
| **Subtotal (95% CI)** | | **194** | | **189** | **100** | **1.34 (0.34, 5.23)** |
| Total events | 112 | | 113 | | | |
| Heterogeneity: $\tau^2$=0.67; $\chi^2$=2.53, *df*=1 (*P*=0.11); $I^2$=60% | | | | | | |
| Test for overall effect: *Z*=0.42 (*P*=0.68) | | | | | | |
| **LEV vs PB** | | | | | | |
| Cumbo 2010 | 11 | 38 | 8 | 28 | 63.2 | 1.02 (0.35, 3.00) |
| Siniscalchi 2014 | 20 | 24 | 19 | 25 | 36.8 | 1.58 (0.38, 6.48) |
| **Subtotal (95% CI)** | | **62** | | **53** | **100** | **1.20 (0.51, 2.82)** |
| Total events | 31 | | 27 | | | |
| Heterogeneity: $\tau^2$=0.00; $\chi^2$=0.23, *df*=1 (*P*=0.63); $I^2$=0% | | | | | | |
| Test for overall effect: *Z*=0.41 (*P*=0.68) | | | | | | |
| **LEV vs LTG** | | | | | | |
| Cumbo 2010 | 11 | 38 | 7 | 29 | 7.8 | 1.28 (0.43, 3.86) |
| Rosenow 2012 | 139 | 206 | 130 | 203 | 56.5 | 1.16 (0.77, 1.75) |
| Werhahn 2015 | 75 | 122 | 65 | 118 | 35.7 | 1.30 (0.78, 2.18) |
| **Subtotal (95% CI)** | | **366** | | **350** | **100** | **1.22 (0.90, 1.66)** |
| Total events | 225 | | 202 | | | |
| Heterogeneity: $\tau^2$=0.00; $\chi^2$=0.12, *df*=2 (*P*=0.94); $I^2$=0% | | | | | | |
| Test for overall effect: *Z*=1.27 (*P*=0.20) | | | | | | |

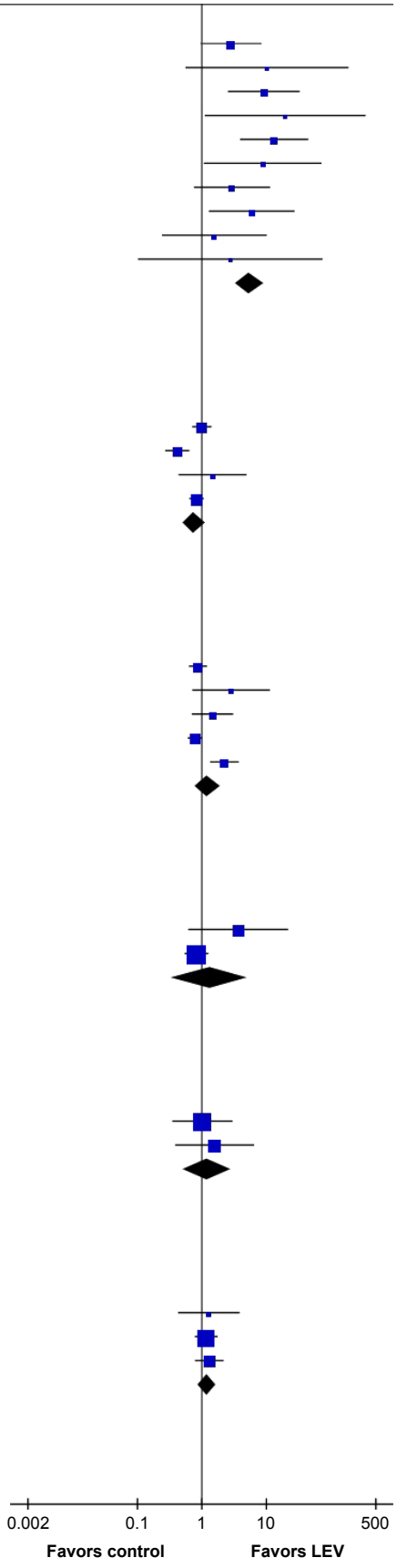


**Figure 3** (*Continued*)

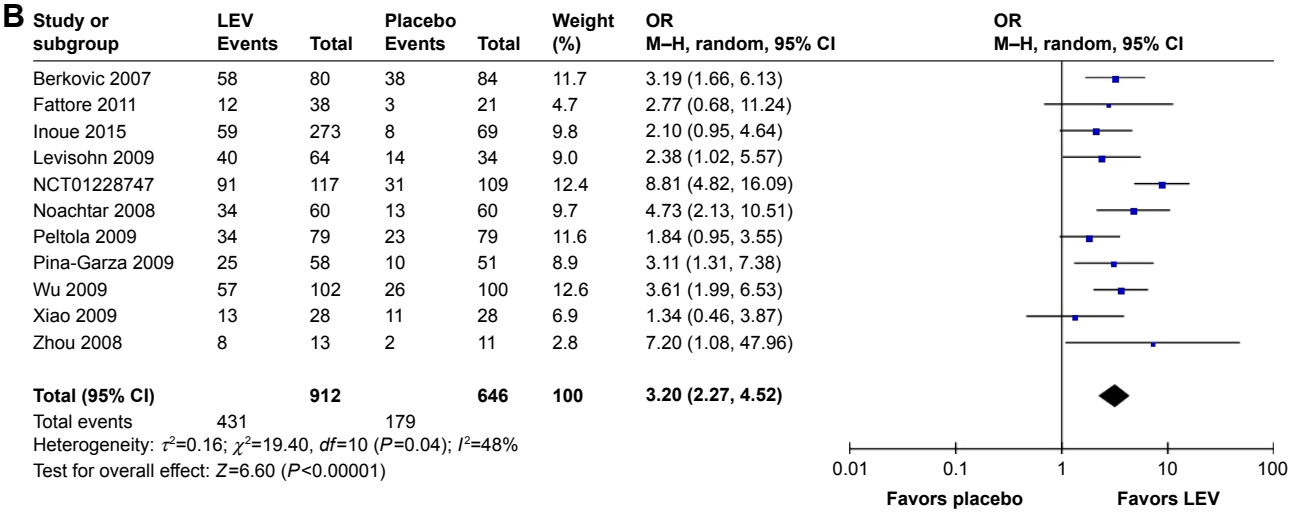


**Figure 3** Rate of seizure freedom of included randomized controlled trials (**A**) and ≥50% responder rates of included randomized controlled trials (**B**).
**Abbreviations:** CBZ, carbamazepine; *df*, degrees of freedom; LEV, levetiracetam; LTG, lamotrigine; M–H, Mantel–Haenszel; OXC, oxcarbazepine; PB, phenobarbital; random, random-effect model.

indicated that LEV had the greatest PBSE rate in adults with epilepsy. However, Bektaş et al[96] indicated that psychosocial and behavioral side effects of LEV treatment are not frequent and they do not emerge in most of the children at lower doses, and Stephen et al[103] indicated a lower rate of psychiatric side effects for LEV than sodium channel blocking AEDs.

Among the 58 case reports, 17 reported PBSEs, including depression, suicidality and hypersexuality.

### Other AEs

SRs indicated that LEV did not increase the risk of imbalance,[22] but increased the risk of diplopia (Figure 2A).[25]

Meta-analysis of newly included RCTs indicated LEV had a lower risk of leukopenia (OR=0.13, 95% CI: 0.02–0.72), rash (OR=0.42, 95% CI: 0.25–0.73), increased liver parameters (OR=0.19, 95% CI: 0.08–0.46) and nausea (OR=0.69, 95% CI: 0.49–0.97) compared with CBZ (Figure 4B). LEV had a lower risk of nausea (OR=0.62, 95% CI: 0.39–0.98) and a higher risk of fatigue (OR=1.87, 95% CI: 1.26–2.77) compared with LTG. Meta-analyses of newly included RCTs showed that there was no difference when LEV was compared with placebo, CBZ, LTG and OXC in headache (Figure 4A). No difference was found in somnolence and dizziness when LEV was compared with placebo, CBZ and LTG (Figure 4A).

Among the observational studies, Merrell et al indicated LEV had fewer side effects than phenytoin.[89] Rauchenzauner et al indicated LEV did not seem to induce changes in reproductive endocrine functions and clinically relevant endocrine side effects in prepubertal children.[90] Tinchon et al indicated LEV has no additional impact on medium-term hematological toxicity in glioblastoma multiforme patients.[94] Xiao et al reported all AEs of LEV were either mild or transient and thus did not lead to withdrawal from drug treatment.[92]

Other case reports were related to side effects in the hematological system, skin, kidney, liver and other systems (Table 2).

## Cost-effectiveness

Two cost-effectiveness evaluations for refractory epilepsy with the decision-tree model were conducted in Canada and Korea, respectively.

The Canadian study showed the incremental cost-effectiveness ratio (ICER) was US$ 76.18 per seizure-free day (SFD) gained for the base-case scenario; when the cost of surgical investigation and surgery was included in the model, the ICERs decreased to US$ 39.18, which was the most cost-effective situation.[162]

The Korean study showed that LEV add-on therapy gained 18.3 SFDs per patient per year and the ICERs were US$ 44 per SFD per patient and US$ 11,084 per quality-adjusted life year gained from the third-party payer perspective.[163]

# Discussion

In our evidence map, the included SRs and newly conducted meta-analyses showed consistent results regarding clinical benefits and potential harms of LEV. Our evidence map indicated that LEV had similar efficacy in seizure freedom compared with conventional AEDs and was superior to placebo in seizure freedom and ≥50% responder rates. What is more, LEV had a lower risk of discontinuation due to AEs compared with CBZ and did not increase the risk of malformations and prenatal outcomes as well as neurological

**A**

| Study or subgroup | LEV Events | Total | Placebo Events | Total | Weight (%) | OR M–H, random, 95% CI |
|---|---|---|---|---|---|---|
| **Nasopharyngitis** | | | | | | |
| Berkovic 2007 | 11 | 79 | 4 | 84 | 11.7 | 3.24 (0.99, 10.63) |
| Inoue 2015 | 49 | 281 | 8 | 70 | 26.0 | 1.64 (0.74, 3.64) |
| Levisohn 2009 | 11 | 64 | 3 | 34 | 9.1 | 2.14 (0.56, 8.28) |
| NCT01228747 | 24 | 126 | 20 | 125 | 38.8 | 1.24 (0.64, 2.37) |
| Noachtar 2008 | 2 | 60 | 4 | 60 | 5.5 | 0.48 (0.09, 2.74) |
| Peltola 2009 | 5 | 77 | 4 | 79 | 9.0 | 1.30 (0.34, 5.04) |
| **Subtotal (95% CI)** | | **687** | | **452** | **100** | **1.49 (0.99, 2.24)** |
| Total events | 102 | | 43 | | | |
| Heterogeneity: $\tau^2$=0.00; $\chi^2$=3.94, *df*=5 (*P*=0.56); $I^2$=0% | | | | | | |
| Test for overall effect: *Z*=1.93 (*P*=0.05) | | | | | | |
| **Dizziness** | | | | | | |
| Berkovic 2007 | 6 | 79 | 8 | 84 | 17.7 | 0.78 (0.26, 2.36) |
| Inoue 2015 | 14 | 281 | 3 | 70 | 13.3 | 1.17 (0.33, 4.19) |
| Levisohn 2009 | 6 | 64 | 4 | 34 | 12.1 | 0.78 (0.20, 2.96) |
| NCT01228747 | 4 | 126 | 9 | 125 | 14.9 | 0.42 (0.13, 1.41) |
| Noachtar 2008 | 2 | 60 | 3 | 60 | 6.5 | 0.66 (0.11, 4.07) |
| Peltola 2009 | 4 | 77 | 2 | 79 | 7.3 | 2.11 (0.38, 11.87) |
| Wu 2009 | 8 | 103 | 14 | 103 | 25.8 | 0.54 (0.21, 1.34) |
| Xiao 2009 | 3 | 28 | 0 | 28 | 2.4 | 7.82 (0.39, 158.87) |
| **Subtotal (95% CI)** | | **818** | | **583** | **100** | **0.77 (0.48, 1.22)** |
| Total events | 47 | | 43 | | | |
| Heterogeneity: $\tau^2$=0.00; $\chi^2$=5.62, *df*=7 (*P*=0.59); $I^2$=0% | | | | | | |
| Test for overall effect: *Z*=1.13 (*P*=0.26) | | | | | | |
| **Somnolence** | | | | | | |
| Berkovic 2007 | 5 | 79 | 7 | 84 | 13.7 | 0.74 (0.23, 2.45) |
| Fattore 2011 | 1 | 38 | 0 | 21 | 2.3 | 1.72 (0.07, 44.10) |
| Inoue 2015 | 36 | 281 | 5 | 70 | 18.5 | 1.91 (0.72, 5.06) |
| Levisohn 2009 | 9 | 64 | 3 | 34 | 10.9 | 1.69 (0.43, 6.71) |
| Noachtar 2008 | 6 | 60 | 1 | 60 | 5.0 | 6.56 (0.76, 56.22) |
| Peltola 2009 | 6 | 77 | 2 | 79 | 8.1 | 3.25 (0.64, 16.65) |
| Pina-Garza 2009 | 8 | 60 | 1 | 56 | 5.1 | 8.46 (1.02, 70.01) |
| Wu 2009 | 18 | 103 | 18 | 103 | 27.3 | 1.00 (0.49, 2.05) |
| Xiao 2009 | 3 | 28 | 5 | 28 | 9.0 | 0.55 (0.12, 2.57) |
| **Subtotal (95% CI)** | | **790** | | **535** | **100** | **1.48 (0.90, 2.44)** |
| Total events | 92 | | 42 | | | |
| Heterogeneity: $\tau^2$=0.10; $\chi^2$=9.76, *df*=8 (*P*=0.28); $I^2$=18% | | | | | | |
| Test for overall effect: *Z*=1.55 (*P*=0.12) | | | | | | |
| **Headache** | | | | | | |
| Berkovic 2007 | 8 | 79 | 10 | 84 | 17.4 | 0.83 (0.31, 2.23) |
| Inoue 2015 | 10 | 281 | 9 | 70 | 18.1 | 0.25 (0.10, 0.64) |
| Levisohn 2009 | 17 | 64 | 5 | 34 | 15.6 | 2.10 (0.70, 6.30) |
| Noachtar 2008 | 13 | 60 | 14 | 60 | 19.6 | 0.91 (0.39, 2.14) |
| Peltola 2009 | 5 | 77 | 11 | 79 | 15.4 | 0.43 (0.14, 1.30) |
| Wu 2009 | 4 | 103 | 9 | 103 | 14.0 | 0.42 (0.13, 1.42) |
| **Subtotal (95% CI)** | | **664** | | **430** | **100** | **0.65 (0.36, 1.17)** |
| Total events | 57 | | 58 | | | |
| Heterogeneity: $\tau^2$=0.28; $\chi^2$=10.22, *df*=5 (*P*=0.07); $I^2$=51% | | | | | | |
| Test for overall effect: *Z*=1.43 (*P*=0.15) | | | | | | |
| **Fatigue** | | | | | | |
| Berkovic 2007 | 8 | 79 | 7 | 84 | 44.2 | 1.24 (0.43, 3.59) |
| Levisohn 2009 | 9 | 64 | 4 | 34 | 31.6 | 1.23 (0.35, 4.32) |
| Noachtar 2008 | 3 | 60 | 6 | 60 | 24.3 | 0.47 (0.11, 1.99) |
| **Subtotal (95% CI)** | | **203** | | **178** | **100** | **0.98 (0.48, 1.98)** |
| Total events | 20 | | 17 | | | |
| Heterogeneity: $\tau^2$=0.00; $\chi^2$=1.30, *df*=2 (*P*=0.52); $I^2$=0% | | | | | | |
| Test for overall effect: *Z*=0.06 (*P*=0.95) | | | | | | |
| **Irritability** | | | | | | |
| Peltola 2009 | 5 | 77 | 0 | 79 | 33.9 | 12.06 (0.66, 221.98) |
| Pina-Garza 2009 | 7 | 60 | 0 | 56 | 34.5 | 15.84 (0.88, 284.19) |
| Xiao 2009 | 3 | 28 | 0 | 28 | 31.7 | 7.82 (0.39, 158.87) |
| **Subtotal (95% CI)** | | **165** | | **163** | **100** | **11.55 (2.12, 62.90)** |
| Total events | 15 | | 0 | | | |
| Heterogeneity: $\tau^2$=0.00; $\chi^2$=0.11, *df*=2 (*P*=0.95); $I^2$=0% | | | | | | |
| Test for overall effect: *Z*=2.83 (*P*=0.005) | | | | | | |

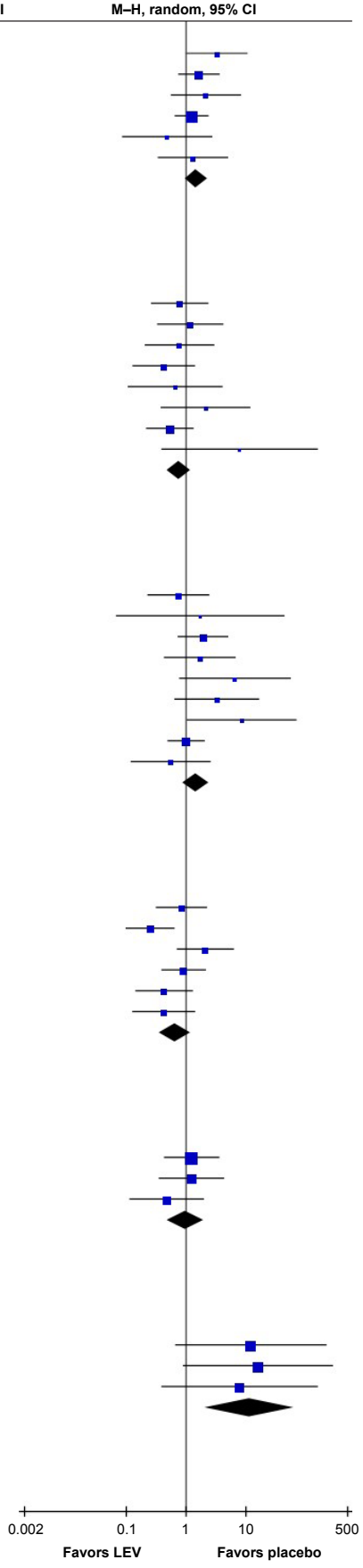


**Figure 4** (*Continued*)

**B**

| Study or subgroup | LEV Events | Total | CBZ Events | Total | Weight (%) | OR M–H, random, 95% CI |
|---|---|---|---|---|---|---|
| **Headache** | | | | | | |
| Brodie 2007 | 59 | 285 | 74 | 291 | 29.1 | 0.77 (0.52, 1.13) |
| Consoli 2012 | 2 | 52 | 1 | 54 | 0.7 | 2.12 (0.19, 24.11) |
| NCT01954121 | 19 | 218 | 16 | 215 | 9.2 | 1.19 (0.59, 2.38) |
| Trinka 2013 | 101 | 489 | 112 | 499 | 48.0 | 0.90 (0.66, 1.22) |
| Werhahn 2015 | 31 | 122 | 29 | 121 | 13.0 | 1.08 (0.60, 1.94) |
| **Subtotal (95% CI)** | | **1,166** | | **1,180** | **100** | **0.91 (0.74, 1.12)** |
| Total events | 212 | | 232 | | | |
| Heterogeneity: $\tau^2$=0.00; $\chi^2$=2.13, *df*=4 (*P*=0.71); $I^2$=0% | | | | | | |
| Test for overall effect: *Z*=0.91 (*P*=0.37) | | | | | | |
| **Somnolence** | | | | | | |
| Brodie 2007 | 32 | 285 | 27 | 291 | 31.4 | 1.24 (0.72, 2.12) |
| Consoli 2012 | 6 | 52 | 5 | 54 | 9.4 | 1.28 (0.37, 4.48) |
| NCT01954121 | 20 | 218 | 7 | 215 | 16.6 | 3.00 (1.24, 7.25) |
| Suresh 2015 | 3 | 28 | 6 | 28 | 6.8 | 0.44 (0.10, 1.97) |
| Trinka 2013 | 39 | 489 | 35 | 499 | 35.8 | 1.15 (0.71, 1.85) |
| **Subtotal (95% CI)** | | **1,072** | | **1,087** | **100** | **1.30 (0.86, 1.97)** |
| Total events | 100 | | 80 | | | |
| Heterogeneity: $\tau^2$=0.07; $\chi^2$=5.75, *df*=4 (*P*=0.22); $I^2$=30% | | | | | | |
| Test for overall effect: *Z*=1.26 (*P*=0.21) | | | | | | |
| **Dizziness** | | | | | | |
| Brodie 2007 | 31 | 285 | 40 | 291 | 25.3 | 0.77 (0.46, 1.26) |
| NCT01954121 | 33 | 218 | 18 | 215 | 21.4 | 1.95 (1.06, 3.59) |
| Suresh 2015 | 0 | 28 | 4 | 28 | 1.8 | 0.10 (0.00, 1.86) |
| Trinka 2013 | 45 | 489 | 52 | 499 | 28.4 | 0.87 (0.57, 1.33) |
| Werhahn 2015 | 36 | 122 | 33 | 121 | 23.1 | 1.12 (0.64, 1.95) |
| **Subtotal (95% CI)** | | **1,142** | | **1,154** | **100** | **1.02 (0.68, 1.53)** |
| Total events | 145 | | 147 | | | |
| Heterogeneity: $\tau^2$=0.11; $\chi^2$=8.71, *df*=4 (*P*=0.07); $I^2$=54% | | | | | | |
| Test for overall effect: *Z*=0.09 (*P*=0.93) | | | | | | |
| **Nasopharyngitis** | | | | | | |
| Brodie 2007 | 26 | 285 | 28 | 291 | 26.1 | 0.94 (0.54, 1.65) |
| NCT01954121 | 40 | 218 | 32 | 215 | 30.8 | 1.29 (0.77, 2.14) |
| Trinka 2013 | 24 | 489 | 32 | 499 | 27.4 | 0.75 (0.44, 1.30) |
| Werhahn 2015 | 20 | 122 | 13 | 121 | 15.7 | 1.63 (0.77, 3.44) |
| **Subtotal (95% CI)** | | **1,114** | | **1,126** | **100** | **1.06 (0.78, 1.45)** |
| Total events | 110 | | 105 | | | |
| Heterogeneity: $\tau^2$=0.01; $\chi^2$=3.49, *df*=3 (*P*=0.32); $I^2$=14% | | | | | | |
| Test for overall effect: *Z*=0.38 (*P*=0.70) | | | | | | |
| **Fatigue** | | | | | | |
| Brodie 2007 | 47 | 285 | 41 | 291 | 31.4 | 1.20 (0.76, 1.90) |
| Consoli 2012 | 7 | 52 | 1 | 54 | 4.9 | 8.24 (0.98, 65.56) |
| Trinka 2013 | 74 | 489 | 95 | 499 | 35.6 | 0.76 (0.54, 1.06) |
| Werhahn 2015 | 31 | 122 | 46 | 121 | 28.1 | 0.56 (0.32, 0.96) |
| **Subtotal (95% CI)** | | **948** | | **965** | **100** | **0.90 (0.55, 1.49)** |
| Total events | 159 | | 183 | | | |
| Heterogeneity: $\tau^2$=0.15; $\chi^2$=9.39, *df*=3 (*P*=0.02); $I^2$=68% | | | | | | |
| Test for overall effect: *Z*=0.40 (*P*=0.69) | | | | | | |
| **Diarrhea** | | | | | | |
| Brodie 2007 | 21 | 285 | 19 | 291 | 38.2 | 1.14 (0.60, 2.17) |
| Consoli 2012 | 0 | 52 | 2 | 54 | 1.7 | 0.20 (0.01, 4.27) |
| Trinka 2013 | 19 | 489 | 20 | 499 | 38.5 | 0.97 (0.51, 1.84) |
| Werhahn 2015 | 9 | 122 | 16 | 121 | 21.6 | 0.52 (0.22, 1.23) |
| **Subtotal (95% CI)** | | **948** | | **965** | **100** | **0.88 (0.59, 1.31)** |
| Total events | 49 | | 57 | | | |
| Heterogeneity: $\tau^2$=0.00; $\chi^2$=3.02, *df*=3 (*P*=0.39); $I^2$=1% | | | | | | |
| Test for overall effect: *Z*=0.64 (*P*=0.52) | | | | | | |
| **Rash** | | | | | | |
| Brodie 2007 | 10 | 285 | 16 | 291 | 45.5 | 0.63 (0.28, 1.40) |
| NCT01954121 | 0 | 218 | 1 | 215 | 2.9 | 0.33 (0.01, 8.08) |
| Trinka 2013 | 9 | 489 | 29 | 499 | 51.6 | 0.30 (0.14, 0.65) |
| **Subtotal (95% CI)** | | **992** | | **1,005** | **100** | **0.42 (0.25, 0.73)** |
| Total events | 19 | | 46 | | | |
| Heterogeneity: $\tau^2$=0.00; $\chi^2$=1.66, *df*=2 (*P*=0.44); $I^2$=0% | | | | | | |
| Test for overall effect: *Z*=3.10 (*P*=0.002) | | | | | | |

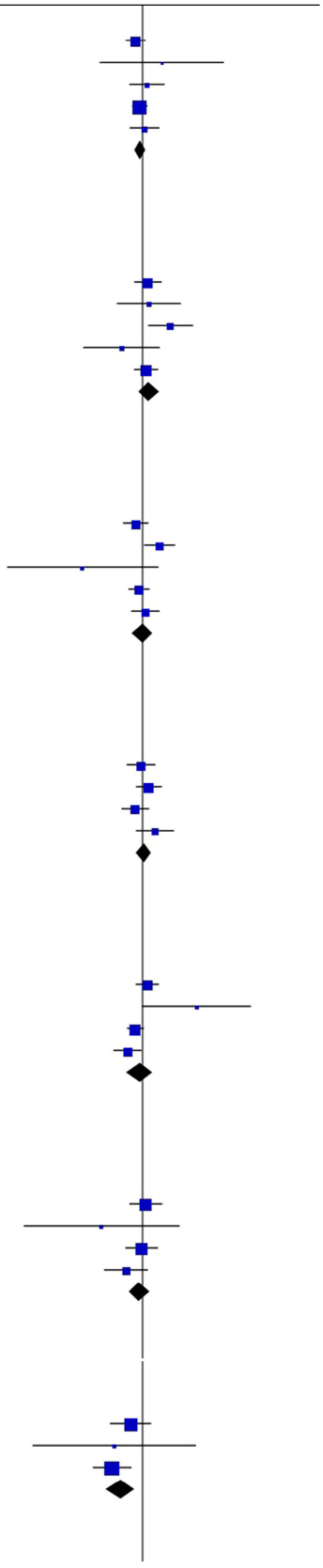


**Figure 4** (*Continued*)

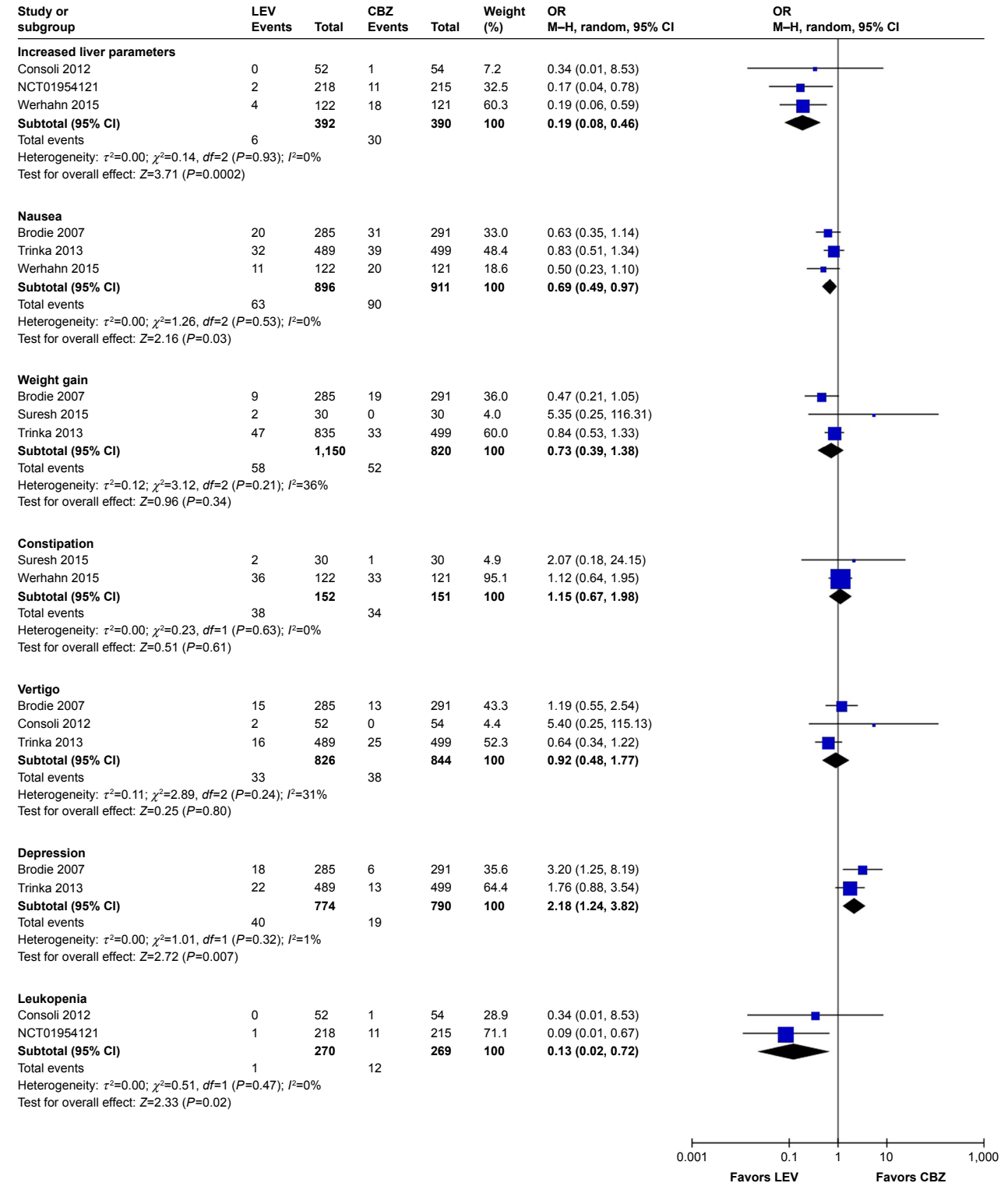


**Figure 4** Risk of single adverse events (LEV vs placebo, **A**; LEV vs CBZ, **B**).
**Abbreviations:** CBZ, carbamazepine; *df*, degrees of freedom; LEV, levetiracetam; M–H, Mantel–Haenszel; random, random-effect model.

development. Limited evidence suggested it was cost-effective in certain settings.

LEV has been classified by the US Food and Drug Administration as a category C drug, with the caution that it should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. A Cochrane review included in our study analyzed the incidence of congenital malformations in pregnant women during AED treatment and

reported that LEV and LTG exposure carried the lowest risk of overall malformation.[39] A recently published prospective cohort study based on the EURAP international registry reported the lowest prevalence of major congenital malformations of LEV (2.8%, 17/599 pregnancies) compared with other seven commonly used AEDs.[164] Two observational studies[91,95] included in this evidence map drew similar conclusions. A published study found that compared with VPA, LEV did not cause apoptosis in immature rat brain neurons, which may be the reason of its safety for pregnant women.[165] Neurologists are also concerned with the effect of AEDs on cognitive function, which significantly affects the QoL of patients, especially children and the elderly. No AEs of LEV on cognitive function were found in our study, which was consistent with the guidelines. However, there are some RCTs, observational studies and case reports indicating the AEs of mood disorders of LEV. We should monitor these AEs during the course of medication.

A number of guidelines included LEV as a main drug for antiepileptic treatment. The National Institute for Health and Care Excellence (NICE; 2017) recommended that LEV could be used as a monotherapy and in the adjunctive treatment of focal epilepsy (with or without secondary generalization) and adjunctive therapy of myoclonic seizures in patients with juvenile myoclonic epilepsy and generalized tonic clonic seizures.[7] The Scottish Intercollegiate Guidelines Network gave a similar recommendation and further suggested that LEV or LTG may be a reasonable alternative for women of childbearing age. Moreover, the guideline also suggested that LEV was better tolerated than sustained-release CBZ in poststroke seizures and produced fewer cognitive AEs than LTG or PB in the elderly with epilepsy and Alzheimer disease.[166] The Biopharmaceutics Drug Disposition Classification System predicted that the risk of skin rash by LEV is not as high as by CBZ or LTG,[167] and that human leukocyte antigen testing is not necessary. With the increasing number of studies on LEV, guideline recommendations need to update the evidence for LEV.[168] Our research provides supplements for evidence update in future guidelines.

The economic evaluation of LEV showed that LEV appeared to be cost-effective when the costs of surgical investigation were discounted. Besides, when LEV is added to the usual treatment of patients with refractory epilepsy, the increase in drug costs may at least be partially offset by savings in other medical costs due to an increase in SFDs and improvement of QoL.[169] But until now, the NICE guideline still has suggested LEV monotherapy as a second-line drug and LEV is considered when the standard first-line drugs such as CBZ and LTG are unsuitable or develop intolerance in the newly diagnosed focal seizure. The economic profiles of our research can help with the cost-effectiveness decision making in certain conditions.

To the best of our knowledge, this study is the most comprehensive evidence of LEV in the following aspects. First, we included various types of studies, such as high-quality RCTs, cohort studies, observational studies, case reports and economic studies. The literature included was comprehensive and involved a large number of patients. Second, we evaluated the clinical application of LEV from three dimensions: efficacy, safety and economy, while the three aspects were studied respectively or the evaluation of LEV was among the overall evaluation of a variety of AEDs in the previous published studies.[30,36,163,170] Thus, our study can provide comprehensive evidence of LEV for physicians or policymakers.

Our study still had some limitations. First, only English language studies were included. We tried to include important conference abstracts found in the databases, but failed to find relevant studies. Moreover, the literature included in this study was published after 2007, although previously published studies were included in the SRs of the evidence map. Third, some special types of seizures such as status epilepticus (SE) were excluded and data of LEV in special populations were not assessed separately. Fourth, no subgroup analysis of different types of seizures and/or epilepsy syndromes was conducted.

The NICE guideline suggested that LEV is potentially as effective as PB and safer for SE. Currently available intravenous AEDs are limited, and intravenous LEV may have advantages for patients who cannot be administered orally with SE or in the perioperative period.[171,172] A chart review in Germany showed LEV was the first choice for intravenous treatment of SE compared with valproate, phenytoin and lacosamide.[173] We can evaluate the role of LEV for SE in future studies.

## Conclusion

LEV has been applied for diverse epilepsies, and the evidence map shows that it increases the rates of seizure freedom and ≥50% responder rates compared with placebo, has similar efficacy with CBZ, OXC, PB and LTG, and also has an advantage for pregnant women as well as in cognitive functions. LEV does not increase the risks of serious AEs and discontinuation from studies due to AEs. Limited evidence supports its cost-effectiveness.

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## Disclosure

The authors report no conflicts of interest in this work.

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