

Systematic Reviews and Metanalyses of Add-on Studies in Epilepsy: Unanswered Questions

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Outline

- ❖ Role of add-on studies in epilepsy and answers provided
- ❖ Limitations of add-on AED studies
- ❖ Role (and limitations) of metanalysis
- ❖ List of unanswered questions

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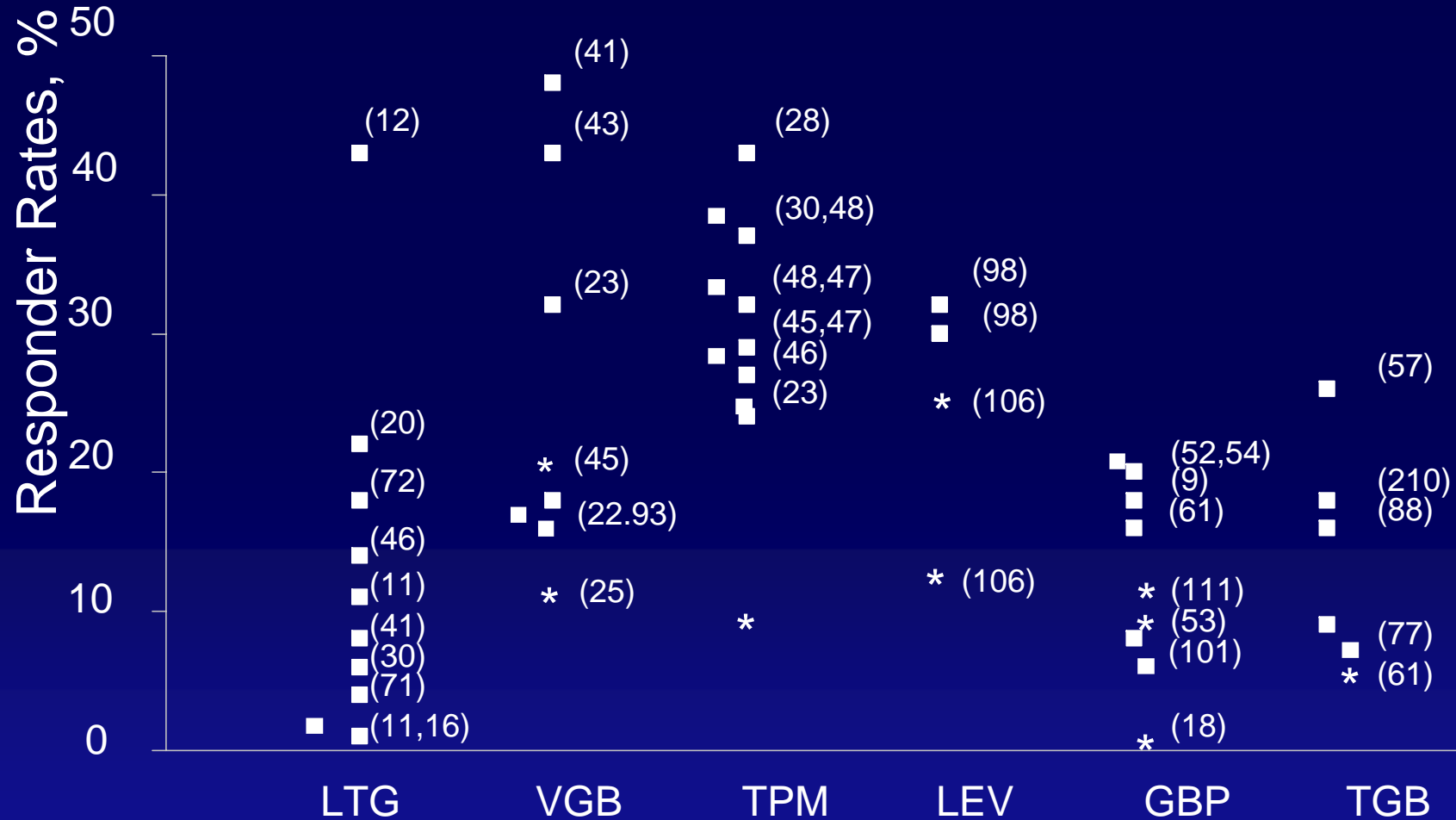
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Add-on Studies in Epilepsy

- ❖ The cornerstone of the registration dossier
- ❖ RCTs available for all AEDs licensed in the last 20 years (and some of the older AEDs)
- ❖ Trial design relatively similar for all AEDs
- ❖ Inclusion criteria relatively similar for all AEDs
- ❖ Almost invariably, placebo-controlled parallel-group comparisons

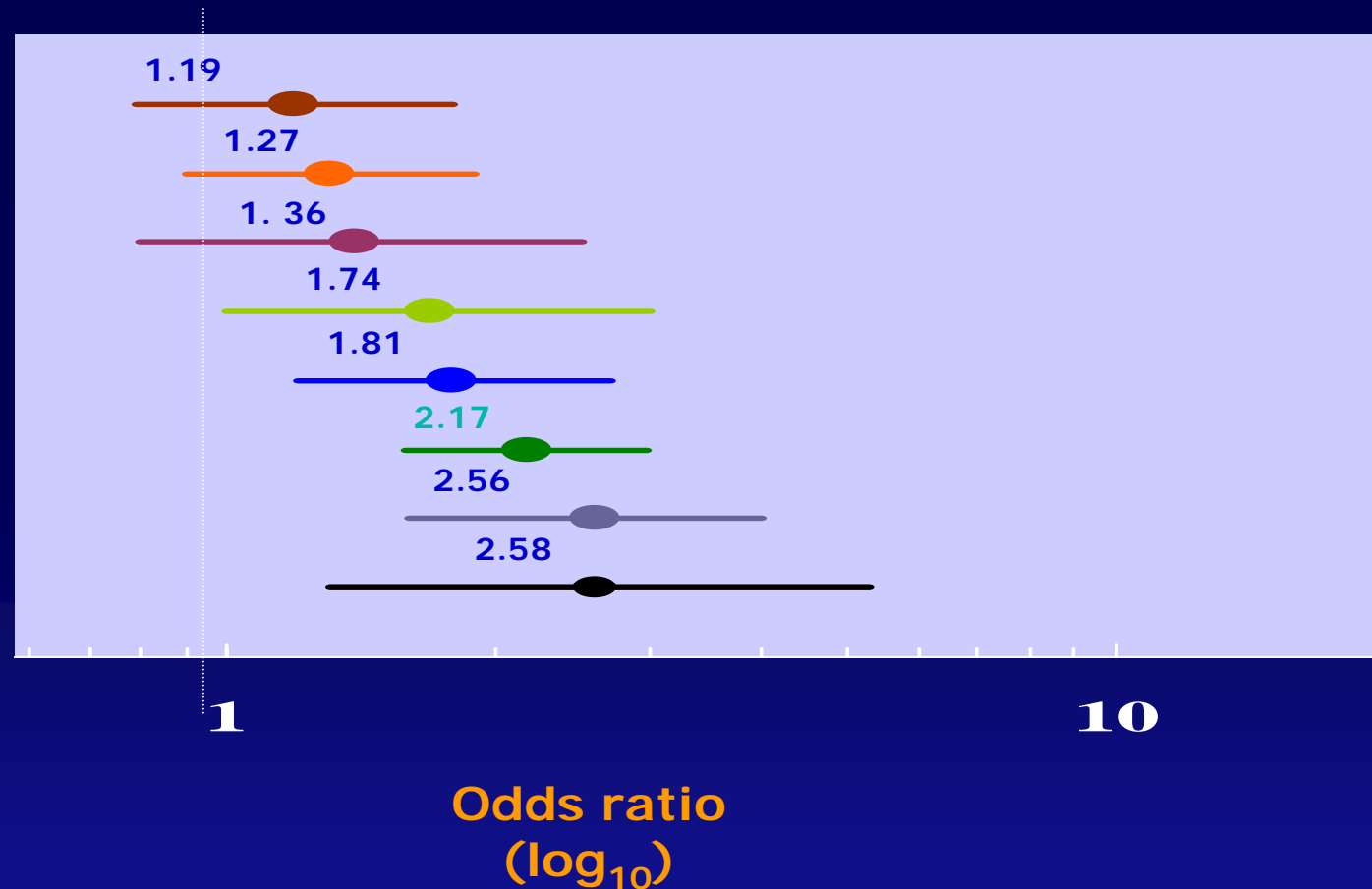
Efficacy of New AEDs in Placebo-Controlled RCTs in Refractory Partial Epilepsy

Placebo-corrected 50% Responder Rates in Individual RCTs



Add-on Trials of New AEDs: Odds Ratios for Withdrawals

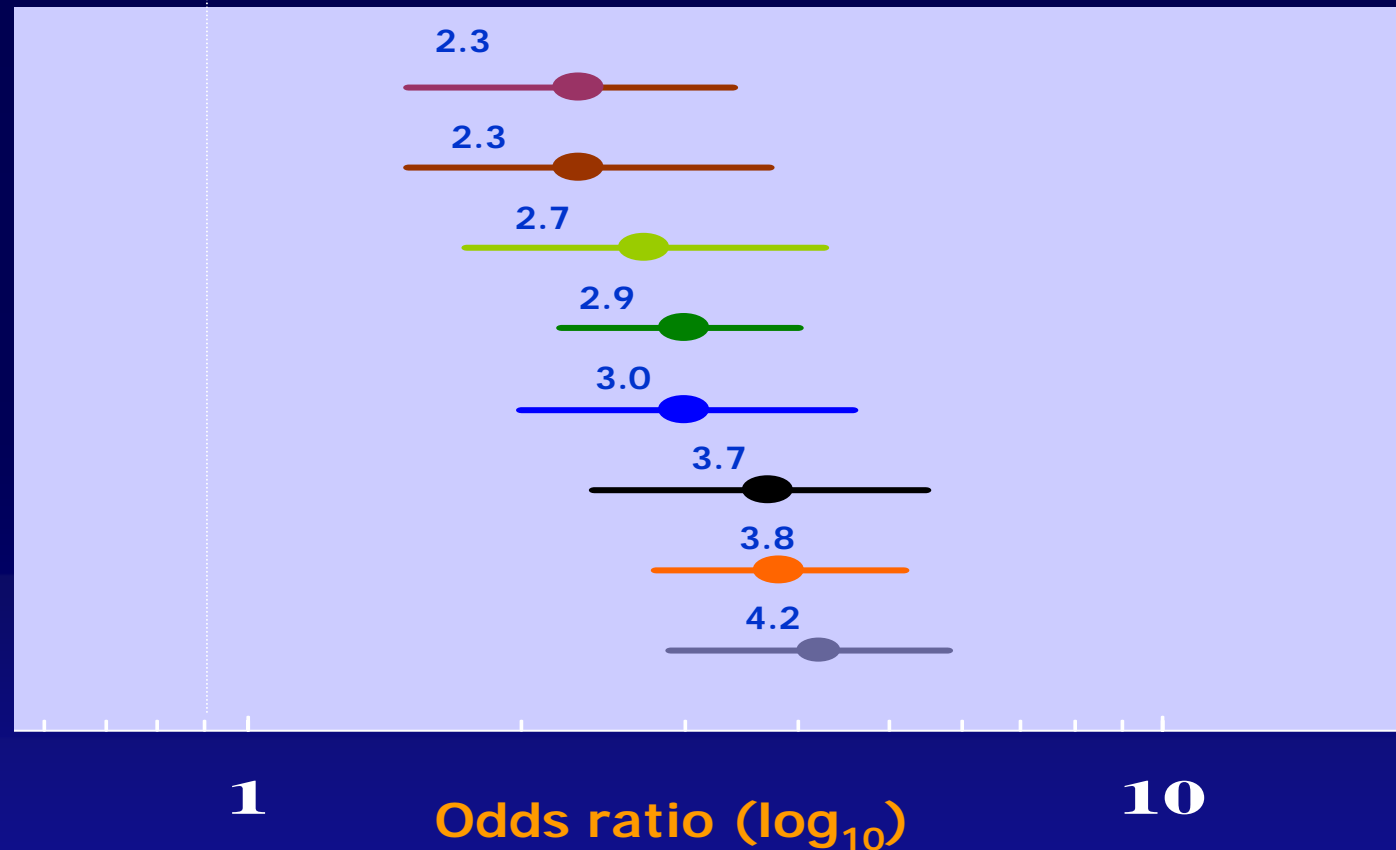
Lamotrigine
Levetiracetam
Gabapentin
Zonisamide
Tiagabine
Oxcarbazepine
Topiramate
Vigabatrin



Modified from Marson et al, *Epilepsia*, 1997; 38, 859-880

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Limitations of Existing Add-on RCTs of AEDs

- ❖ Designed to meet regulatory requirements, not clinical needs
- ❖ Only questions asked: seizure reduction and tolerability vs placebo
- ❖ Strict inclusion criteria (artificial population)
- ❖ Rigid dosing schemes
- ❖ Unchanged underlying AED therapy
- ❖ Short duration (usually, 8 to 16 weeks)

Important Issues which are not Addressed in Add-on RCTs of AEDs (i)

- ❖ Optimal dosages and titration rates
- ❖ Pharmacodynamic interactions (optimal AED combinations)
- ❖ Spectrum of efficacy beyond partial seizures (most AEDs)
- ❖ Special populations (comorbidities, elderly,..)
- ❖ Long-term response
- ❖ Head-to-head comparisons

Important Issues which can not be Addressed in Randomized AED Trials

- ❖ Chronic or delayed adverse effects
- ❖ Second-generation effects (including teratogenicity)
- ❖ Rare adverse effects
- ❖ Effects mimicking condition with a high background incidence (e.g., myocardial infarction)
- ❖ Certain drug interactions

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Can Metanalysis Help in Addressing Questions not Answered by Individual RCTs?

Limitations of Metanalysis of Add-on AED Trials

- ❖ RCTs are generally very few
- ❖ Often, a specific dosage is investigated in only one trial
- ❖ Information from metanalysis may not add much to what is already apparent from reading the single trial publications

Gabapentin as add-on for drug resistant partial epilepsy

“Gabapentin has efficacy as an add-on treatment in patients with for drug resistant partial epilepsy. However, trials were of relatively short duration, and provide no evidence for the long-term efficacy of gabapentin.”

Marson et al, Cochrane Database System Rev 2000, CD001415

Levetiracetam as add-on for drug resistant localization-related (partial) epilepsy

“Levetiracetam reduces seizure frequency when used as add-on treatment for patients with drug resistant localization-related (partial) epilepsy and seems well tolerated... The trials reviewed were of 16-24 weeks duration and results cannot be used to confirm longer-term effects.”

Chaisewikul et al, Cochrane Database System Rev 2001, CD1901

Topiramate as add-on for drug resistant partial epilepsy

“Topiramate had add-on efficacy as an add-on treatment for drug resistant partial epilepsy . However, trials reviewed were of relatively short duration and provide no evidence for the long-term effects of topiramate.”

Jette et al, Cochrane Database System Rev 2002, CD001417

Tiagabine as add-on for drug resistant localization-related (partial) epilepsy

“Tiagabine reduces seizure frequency but is associated with some side effects when used as an add-on for people with drug resistant localization-related seizures.”

Pereira et al, Cochrane Database System Rev 2002, CD001908

Lamotrigine add-on for drug resistant partial epilepsy

“Lamotrigine add-on therapy is effective in reducing seizure frequency in patients with drug resistant partial epilepsy. Further trials are needed to assess the long-term effects of lamotrigine, and to compare it with other add-on drugs”

Ramaratnam et al, Cochrane Database System Rev 2001, CD1909

Suboptimal Metanalyses

- ❖ Metanalyses on every aspect of medicine flood editors' desk each day
- ❖ Most are “technically” well done – but few provide really novel contributions (“template” approach)
- ❖ Flaws are difficult to spot by reviewers – unless reviewer repeats the entire work from scratch
- ❖ Many lack good critical insight: authorship problem?

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Systematic Reviews and Metanalyses of Add-on AED Trials: Unanswered (or not fully answered) questions (i)

- ❖ What is the optimal starting dosage in relation to the characteristics of the patient?
- ❖ What are the optimal titration rate and initial maintenance dose?
- ❖ What is the nature of dose-response relationship for different AEDs?
- ❖ How do therapeutic and adverse effects evolve over time? Does tolerance develop to AED efficacy?
- ❖ How does underlying treatment affect response? What are the relative risk/benefit ratios of specific AED combinations?

Systematic Reviews and Metanalyses of Add-on AED Trials: Unanswered (or not fully answered) questions (ii)

- ❖ How do AEDs compare when used optimally in specific patients groups?
- ❖ What are the best treatment choices in syndromes not investigated in RCTs?
- ❖ What are the best treatment choices in special subgroups (e.g. by age, comorbidity?)
- ❖ What are relative risks for rare but important adverse effects (most notably, second generation effects?)
- ❖ What is the long-term cost-effectiveness of different add-on AEDs?