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Meta-analyses of newer antiepileptic drugs as adjunct for treatment of focal epilepsy in children

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ABSTRACT

Aim: This study conducted a systematic review evaluating the effectiveness of newer antiepileptic drugs (AEDs) (namely, lamotrigine, levetiracetam, topiramate, vigabatrin, zonisamide, oxcarbazepine, perampanel, gabapentin, and stiripentol) as add-on for treatment of focal epilepsy in children.
Methods: Articles were retrieved from EMBASE, Medline and Cochrane Library from inception to January 2016. Treatment outcomes were analysed based on responder, seizure-free, withdrawal and adverse event rates. Quality of each study was also assessed.
Results: Twelve articles fulfilled the inclusion criteria. Heterogeneity and quality of the included studies were considered acceptable. Overall, newer AEDs as adjunct therapy in children with inadequate control of focal seizure showed a trend of better seizure outcomes. The pooled ORs for responder, seizure-free and withdrawal rates were 2.15 (95%CI:1.72, 2.69), 1.99 (95%CI:0.72, 5.48) and 0.69 (95%CI:1.13, 2.39) respectively. Adverse events of newer AEDs were comparatively higher than placebo (OR:1.64, 95%CI:1.13, 2.39).
Conclusion: In our updated review, newer AEDs as adjunct therapy for focal epilepsy in children have trends of better effectiveness compared to placebo. Newer AEDs are associated with statistically more children with > 50% seizure reduction, and a trend of better seizure freedom. Their tolerability would also be considered acceptable with the observed low withdrawal rate. However, the relative lack of well-conducted RCTs evaluating their effectiveness against other active AED treatment in children would not facilitate evidence-based practice. This highlights the knowledge gap and the need for more well-conducted RCTs against active treatments to ascertain the long term effectiveness and the role of newer AEDs in managing epilepsy in children.

1. Introduction

Mental and neurologic conditions account for 30.8% of all disability adjusted life years (DALY), with epilepsy among the most encountered disorders in both specialist and primary care settings globally (Leonardi and Ustun, 2002; WHO, 2004). The incidence and prevalence of epilepsy peak in childhood and elderly in developed countries, but children and young adults contribute to a significant proportion of cases in developing countries (Mac et al., 2007). The reported epilepsy prevalence in children up to 15 years old was approximately 5–7 per 1000 population in UK (Connock et al., 2006) and 3.8 per 1000 population in Singapore (Mohamed et al., 2006). In comparison, a wide incidence range between 49.3 and 190 per 100,000 populations were reported in developing countries (WHO, 2005; Mohamed et al., 2006).

Clinically, antiepileptic drugs (AEDs) provide significant benefit in the management of epilepsy as many patients become seizure free within a few years of therapy, and may eventually discontinue treatment (Shinnar and Pellock, 2002). The clinical goal of AED treatment, especially for those with intractable epilepsy, is to find an optimal balance between health benefits and tolerability of AEDs. Hence, the emergence of newer AEDs commonly licensed as add-on therapy in recent years has provided more therapeutic options, especially for focal seizure. With reported better tolerability profile, newer AEDs may be preferable in children with intractable epilepsy after failing to respond to two tolerated and appropriately chosen AEDs (Glauser et al., 2013).

Randomized clinical trials (RCTs) of newer AEDs as adjunct therapy in adults generally reported better tolerability profile and comparable efficacy with older AEDs (Glauser et al., 2013). Likewise, RCTs in children also reported similar health benefits of newer AEDs (Elterman et al., 1999; Glauser et al., 2006; Pina-Garza et al., 2008; Pinea-Garza et al., 2009). However, concerns have been raised about the quality of these RCTs to provide sufficient evidence to properly advice on the

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value of newer AED treatments in children (Glauser et al., 2013). Hence, gathering more robust information of the value of newer AEDs in treating epilepsy in children is necessary. (Connock et al., 2006). With this in mind, our study aimed to systematically review and conduct meta-analyses of the effectiveness of newer AEDs as adjunctive treatment for focal epilepsy in children. Results of the study would provide more accurate and updated evidence of the role of newer AEDs in the pediatric population.

2. Methods

2.1. Data sources and search strategy

Articles were searched electronically from databases including Embase, Medline, and Cochrane Library, from inception to January 2016. The search terms used were seizure(s), or epilepsy, or partial-onset, or localization-onset, or focal-onset, and children, or pediatric(s), and newer antiepileptic drugs (AEDs), or second-generation AEDs, or specific newer AEDs agents (namely, lamotrigine, levetiracetam, topiramate, vigabatrin, zonisamide, oxcarbazepine, perampanel, gabapentin and stiripentol). These were among newer AEDs licensed and mostly recommended for treatment of focal seizure in children.

These terms were searched in the abstracts, keywords and titles field. The search was limited to English language articles; and humans. Manual search from bibliography of the identified articles was conducted to retrieve other related studies.

2.2. Inclusion and exclusion criteria

Articles published as position papers, reviews, letters, and case reports or series were excluded; the inclusion criteria were as follows:

- Study must specifically report the seizure outcome in children aged less than 18 years old.
- Diagnosis and seizure outcome of focal seizure, as defined by the International League against Epilepsy (ILAE), must be explicitly reported in the study. ILAE defined focal as “originating within networks limited to one hemisphere. They may be discretely localized or more widely distributed. Focal seizures may originate in subcortical structures” (Berg et al., 2010). Over the years, this terminology for type of seizure is changing, to avoid missing relevant publications, we also used both partial- and localization-onset epilepsy in our search term (Fisher et al., 2017).
- The outcome must at least report the responder rate (more than 50% seizure reduction from baseline) or seizure free events and number of total patient involved. A seizure free event was described as absence of seizure during the period of trial.
- The outcome of newer AEDs must be compared to either placebo or older AEDs treatment.
- Newer AEDs was used as adjunct treatment for focal epilepsy in children.

2.3. Data extraction

Information such as authorship, study design and duration, numbers of participants, age of children, and outcomes of AEDs treatment, were extracted from individual study.

The process of searching, selection and extraction of articles was undertaken by the first investigator (i.e., NAMT). If there were uncertainty for inclusion or rejection of a selected article, the first reviewer (i.e., NAMT) would refer to the second reviewer (i.e., SCL). Articles were included or rejected in the review with mutual agreement of both reviewers. Outcomes were reported following the statement of preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines (Moher et al., 2009) (Supplementary Table S1).

2.4. Outcomes measured

Primary outcomes were responder and seizure-free rates, withdrawal rate due to adverse events and ineffective treatment, and total numbers of treatment-emergent adverse events (TEAE). Adverse events of somnolence, nausea and/or vomiting, aggressive behaviour, dizziness, headache, rhinitis and rash were reported as secondary outcomes. These were among the most reported specific adverse events in the clinical trials. Subgroup analysis of the outcomes for individual newer AED agents, whenever possible, was also performed.

Throughout this study, we used the term efficacy to describe the therapeutic performance of AEDs to produce seizure freedom and responder rate. Tolerability represented incidence, severity and impact of AED-related adverse events. Combination of both outcomes of efficacy and tolerability was described as effectiveness; while withdrawal rate would also reflect the effectiveness of AEDs.

2.5. Quality assessment

Quality of the included studies were assessed by the reviewers for selection bias (random sequence generation and allocation concealment), performance bias (blinding of participants and personnel), detection bias (blinding of outcome assessment), attrition bias (incomplete outcome data), and reporting bias (selective reporting). These judgements were divided into three levels of high risk, unclear risk and low risk based on the recommendations from the Cochrane review to describe the quality of individual studies.

Quality assessment was first assessed by the first reviewer (i.e NAMT) then refer to the second reviewer (i.e, SCL) for confirmation. At final assessment, both reviewers must have mutual agreement on the quality of the included studies.

2.6. Data analysis

The analysis to compare the effectiveness of newer AEDs with placebo or older AEDs were performed using Review Manager 5.3 software, a software designed for systematic review (Review Manager (RevMan) Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). Estimation of the pooled Odds Ratios (ORs) and 95% Confidence Interval (CI) of the included studies were analysed using the random-effects weighted Mantel-Haenszel method. Statistically significant results is described as the value of 95%CI not overlapping the null value (i.e., OR = 1). Variation across studies were assessed using I^2 test, with percentage of 25%, 50% and 75% indicating low, medium and high heterogeneity (Deeks et al., 2001).

3. Results

3.1. Identified articles & study selection

A total of 6658 articles was identified using the search terms. Duplicate titles were deleted using EndNote citation manager, producing 1323 articles. Further screening excluded 663 articles with irrelevant titles. Another 447 articles were excluded, with 34 being non-English articles, 83 abstract-only articles, and 8 series of case reports. Another 322 articles consisting of 188 review articles and 134 articles discussing only the safety data of AEDs were further excluded. After reviewing the abstracts, 117 out of the remaining 213 studies were retrieved for further review. Exclusion reasons of these 96 articles included non-comparative trials (N = 85), comparison of two newer AEDs (N = 2), and studies in mixed population without specifying outcomes in children (N = 9).

Finally, another 105 full-text articles were excluded due to several reasons including: articles not specific to children less than 18 years, not specific to focal epilepsy, no comparative trials with placebo or older AEDs, not reported either responder rate or seizure free events,