Abstract. – OBJECTIVE: The aim of the study was to summarize the findings of the studies documenting the efficacy and safety of perampanel when used in children/adolescents or adults, either as add-on therapy or as monotherapy.

MATERIALS AND METHODS: A systematic search was conducted using PubMed, EMBASE and Scopus. Only studies with a cohort-based approach (either prospective or retrospective) were included. We were interested in real-world studies and therefore, studies with a highly regulated environment, such as randomized controlled trials, were excluded. The primary outcomes of interest were retention rates, response rates and seizure-free rates. Random effects model was used for the analysis. Effect sizes were reported as pooled prevalence along with 95% confidence intervals.

RESULTS: A total of 34 studies were included. The retention rates, within 24 months from initiation of treatment as an add-on therapy, ranged between 65% to 77% among children and adolescents. For adults, the retention rate varied between 56% to 77% within 24 months from initiation of treatment. The response rate was around 70% in children/adolescents and 52% in adults at 24 months of follow-up. Around 25% of children and adolescents and 37% of adults were seizure-free at 24 months follow-up period. The proportion of children/adolescents and adults reporting any treatment-related adverse effects was 29% and 41%, respectively. The commonly reported adverse effects were dizziness/drowsiness, somnolence, behavioral problems (irritability, aggression, anxiety, mood changes), postural instability/gait problems, fatigue and weight gain.

CONCLUSIONS: Perampanel might be an effective anti-epileptic drug in both children/adolescents and adults when used as an adjunct therapy. More data is required to comment on its use as monotherapy. Careful monitoring for psychiatric problems and behavioral disturbances is required, both prior to initiating treatment as well as during the course of management. Studies with long-term follow-up may are needed to confirm the findings of this meta-analysis.

Key Words: Perampanel, Fycompa, Focal epilepsy, Children and adolescents, Adults, add-on therapy, Monotherapy, Systematic review, Meta-analysis.

Introduction

Epilepsy is a common neurological disease and globally, around 46 million people are estimated to be affected by this disease condition1. The age-standardized prevalence is around 622 per 1,00,000 population1. The causes and pathophysiology of epilepsy is diverse and therefore, various types of epileptic and seizure disorders are often found in clinical practice. However, there is one common feature among these different forms of seizure disorders and that is the deranged balance between the excitatory and inhibitory drive at synapse2. Antiepileptic drugs (AEDs) form the mainstay of treatment and intend to achieve a complete remission of seizures or reduce the frequency to the maximum extent, while keeping the adverse effects to the minimum and overall, improving the overall quality of life of the patients3,4. In this respect, it is important that the efficacy is high and adverse effects are less so that the highest desirable compliance is achieved.

There has been an increase in the number of new-generation anti-epileptic medications that were approved by the Food and Drug Administration (FDA) in the last decade5. One such drug is perampanel (PER) which works as a non-competitive antagonist at post-synaptic α-aminooxy-3-hydroxy-5-methyl-4-isoxazole-propionate receptors6. It has been approved for use in treat-
ment of focal (partial) seizures and as an add-on treatment for generalized tonic-clonic seizures\(^7\). Currently, it is indicated to be used either as monotherapy or as an adjunct treatment for focal-onset seizures, without or without generalized seizures, in subjects aged 4 years or more\(^8,9\). It is also used as an add-on therapy for primary generalized tonic-clonic seizures in those aged 7 years and older\(^10\).

Much of the data on the efficacy and adverse event profile of perampanel comes from well conducted clinical and regulatory trials (RCTs). The approvals for use are also based on data from these regulatory trials, which is a standard practice. While RCTs are useful, there are some key differences between doses and titration schedules when used as a “potential” therapy in clinical trials designed for regulatory approval compared with real-world use in patients. Therefore, evidence from real world studies (RWS) is needed to complement the findings from RCTs. Real-world studies (RWS) are those that aim to assess the effectiveness, safety, and utilization of health interventions, such as medications, medical devices, or healthcare services, in real-world settings. Unlike randomized controlled trials (RCTs) that are conducted in highly controlled conditions with strict inclusion and exclusion criteria, RWS are designed to evaluate the interventions in diverse patient populations and clinical settings that are more representative of routine clinical practice. In the recent past, several studies from the real-world have presented evidence on the efficacy and safety of perampanel for epilepsy. To date, there has been one attempt by Fong et al to summarize the findings from these studies\(^11\). However, the authors conducted a systematic review and not a meta-analysis and the focus of the review was primarily on the safety profile related to cognition, behaviour and psychological status. Further to this review, many new studies have been published and there is a need to conduct a meta-analysis to provide reliable pooled evidence on the efficacy and safety of use of perampanel.

**Materials and Methods**

**Data Sources Searched and Strategy Used**

We registered the review in PROSPERO (registration number CRD42023410653). For conducting this meta-analysis, we followed the standard PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines\(^2\). An electronic search strategy was developed for each of the three databases i.e., PubMed, Scopus and EMBASE. The search strategy included the following terms: (Perampanel OR anti-epileptic OR anti-seizure medication OR Fycompa) AND (efficacy OR retention rate OR effectiveness OR response rate OR seizure cure rate OR seizure-free rate OR adverse effect OR real world) AND (monotherapy OR concomitant therapy OR adjuvant therapy OR add on therapy). The search was aimed at identifying studies published until 15\(^{th}\) March 2023. We only considered studies published in English language.

**Study Selection Criteria**

We were interested in real-world studies and not in studies with a highly regulated environment, such as randomized controlled trials. The included studies should have primarily examined and documented the efficacy of perampanel. We preferred that the included studies should have adopted a cohort design (either prospective or retrospective) wherein follow-up data was available after the initiation of treatment. Therefore, we excluded case-control and cross-sectional design-based studies. The primary outcomes of interest were retention rates, response rates and seizure-free rates. Additionally, we also documented proportion of subjects reporting treatment related adverse effects. We reported retention rates as a percentage and this represented the number of study subjects that continued to remain on perampanel at any given follow-up time, out of the total number of subjects who were initially started on treatment. Response rate (%) was defined as the proportion of patients with ≥50% reduction in seizure frequency per 28 days from baseline. As a continuation of this, seizure-free rate (%) was defined as the proportion of patients with 100% reduction in seizure frequency per 28 days from baseline.

Figure 1 presents the process of selection of studies. Two review authors independently screened the titles and abstracts to identify the relevant citations. This was followed by full text review of studies that had the potential to be included. There were further exclusions based on the full text review and among the final set of selected studies, data was extracted using a pre-tested sheet. In case of any disagreements between the two review authors, resolution was achieved through discussion with a third senior
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Statistical Analysis

Analysis was performed using STATA 16 software (College Station, TX, USA). We reported the pooled effect sizes as proportion with 95% confidence intervals (CI). We decided to use the random effects model as the included studies differed in their subject characteristics, dose and duration of perampanel use, age of the subjects and were conducted in different geographical settings. We considered these differences to be substantial enough to create significant heterogeneity. Assessment of the risk of bias was done using the Newcastle-Ottawa Scale\(^13\). Publication bias was statistically assessed using Egger’s test\(^14\). We conducted subgroup analysis based on the age of the subjects, i.e., children and adolescents, and adults, and whether perampanel was used as an add-on therapy or monotherapy. A \(p\)-value lower than 0.05 was considered to denote statistical significance.

Results

We obtained a total of 1,592 studies through the search strategy in the three databases. After removal of the 431 duplicates, 1,161 unique studies remained. This was followed by screening based on the title and abstract. This step led to further exclusion of 1,090 studies. The full text of the remaining 71 studies was reviewed and 37 studies were further excluded (Figure 1). Finally, a total of 34 studies were included in this meta-analysis\(^15\text{-}48\).

Table I presents the specific details of the included studies. The majority of the studies were retrospective in design (n=28), five studies had a prospective design\(^17,19,29,37,42\), and one study was a single-arm open label trial\(^34\). Ten studies were conducted in China\(^15,17,19,20,25,26,30,32,36,37\), seven in Italy\(^16,27,28,31,40,41,43\) and three in USA\(^21,33,35\). Two studies each were conducted in Taiwan\(^46,48\) and Spain\(^42,45\). One study each was conducted in the Republic of South Korea\(^18\), Germany\(^47\), Thailand\(^22\), Australia\(^23\), Israel\(^18\), Norway\(^24\) and Japan\(^29\). Three studies were multicentric\(^34,39,44\). A total of 12 studies were conducted among children and adolescents\(^5,17,22,25,27,30,32,36-38,48\) and 20 studies in adults\(^18,20,23,24,28,29,31,33-35,39-47\). There were two studies that had both children and adolescents.
Table I. Demographic characteristics, study descriptions, and design of the investigations selected for our systematic review.

<table>
<thead>
<tr>
<th>Author (year of publication)</th>
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<th>Country</th>
<th>Participant characteristics; mode of perampanel therapy</th>
<th>Newcastl Ottawa quality score</th>
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<tbody>
<tr>
<td>Chu (2022)</td>
<td>Retrospective</td>
<td>China</td>
<td>Children aged 4-12 years; mean age of around 7 years; refractory epilepsy; male (44%); focal epilepsy (35%) and combined epilepsy (65%) Perampanel administered as concomitant therapy</td>
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<tr>
<td>Fernandes (2021)</td>
<td>Observational</td>
<td>Italy</td>
<td>Both children and adolescents and adults; mean age of sample studied was 37 yrs; males (49%); majority with focal epilepsy (64%) Perampanel administered as combination therapy</td>
<td>7</td>
</tr>
<tr>
<td>Zhang (2023)</td>
<td>Prospective</td>
<td>China</td>
<td>Children and adolescent aged ≤18 years; mean age of starting perampanel around 6 years; female (48%); all patients with focal epilepsy Perampanel administered as combination therapy</td>
<td>8</td>
</tr>
<tr>
<td>Im (2021)</td>
<td>Retrospective</td>
<td>Republic of Korea</td>
<td>Adults (mean age of around 43 yrs); males (&gt;40%); all patients with focal epilepsy Perampanel administered as combination therapy</td>
<td>8</td>
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<tr>
<td>Wang (2022)</td>
<td>Prospective</td>
<td>China</td>
<td>Mean age of around 27 yrs; males (56%); all patients with focal epilepsy Perampanel administered as combination therapy</td>
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<tr>
<td>Zhang (2022)</td>
<td>Retrospective</td>
<td>China</td>
<td>Mean age of around 28 yrs; males (57%); majority patients with focal epilepsy (96%) Perampanel administered as combination therapy</td>
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<tr>
<td>Segal (2022)</td>
<td>Retrospective</td>
<td>USA</td>
<td>Both adolescents (12 to &lt;18 years) and adults ≥18 years; females (50%); majority with generalized tonic-clonic (50%), followed by myodonic or absence seizures (around 20-25%) Perampanel administered as combination therapy</td>
<td>7</td>
</tr>
<tr>
<td>Suwanpakdee (2022)</td>
<td>Retrospective</td>
<td>Thailand</td>
<td>Children and adolescents aged 3 to 13 years; mean age of 8.6 years; majority patients with focal epilepsy (&gt;50%) Perampanel administered as combination therapy</td>
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<tr>
<td>Sagar (2021)</td>
<td>Retrospective</td>
<td>Australia</td>
<td>In adults; mean age of 39 years; females (55%); patients with refractory focal and generalized epilepsy Perampanel administered as combination therapy</td>
<td>8</td>
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<tr>
<td>Lossius (2021)</td>
<td>Retrospective</td>
<td>Norway</td>
<td>In adults; mean age of around 32 years; females (52%); majority with focal epilepsy (80%) Perampanel administered as combination therapy</td>
<td>9</td>
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</tbody>
</table>

Continued
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<tr>
<td>Qu (2021)</td>
<td>Retrospective</td>
<td>China</td>
<td>Children and adolescents aged 2-14 years; mean age of 7.9 years; females (45%); majority with focal (66%) followed by generalized epilepsy (21%) Used as combination therapy</td>
<td>8</td>
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<tr>
<td>Yu (2022)</td>
<td>Retrospective</td>
<td>China</td>
<td>Children with mean age of around 9.7 years; males (61%); subjects with focal epilepsy Combination therapy</td>
<td>8</td>
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<tr>
<td>Operto (2022)</td>
<td>Retrospective</td>
<td>Italy</td>
<td>Children aged 8-10 years with absence epilepsy Combination therapy as well as second line monotherapy</td>
<td>7</td>
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<tr>
<td>Lattanzi (2021)</td>
<td>Retrospective</td>
<td>Italy</td>
<td>In adults; mean age of around 69 years; Majority with focal (80%) or focal to bilateral tonic-clonic seizures (24%) Perampanel administered as combination therapy</td>
<td>8</td>
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<tr>
<td>Inoue (2022)</td>
<td>Prospective</td>
<td>Japan</td>
<td>Older adults; mean age of around 45 years; females (47%); focal seizures (68%) Perampanel administered as combination therapy</td>
<td>8</td>
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<tr>
<td>Li (2022)</td>
<td>Retrospective</td>
<td>China</td>
<td>Children; median age of 7.8 years; focal epilepsy (67%) Concomitant use of Perampanel</td>
<td>9</td>
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<tr>
<td>Gasparini (2022)</td>
<td>Retrospective</td>
<td>Italy</td>
<td>Adults with mean age of around 32 yrs; males (41%); majority with focal (78%) epilepsy Concomitant use of Perampanel</td>
<td>9</td>
</tr>
<tr>
<td>Gao (2022)</td>
<td>Retrospective</td>
<td>China</td>
<td>Among children with mean age of around 8.6 years; males (65.4%); majority of the subjects with generalized onset (52%) followed by focal onset (21%) epilepsy Concomitant use of Perampanel</td>
<td>7</td>
</tr>
<tr>
<td>Wheless (2020)</td>
<td>Retrospective</td>
<td>USA</td>
<td>Adults with mean age of around 29 yrs; females (54%); focal epilepsy in 51% and idiopathic generalized epilepsy in 20% Perampanel used predominantly as concomitant (98.8%) therapy</td>
<td>8</td>
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<tr>
<td>Husni (2022)</td>
<td>Uncontrolled, single-arm, open-label, trial</td>
<td>Japan and South Korea</td>
<td>Adults with mean age of around 40 yrs; females (48%); all with focal onset epilepsy Perampanel used as monotherapy</td>
<td>8</td>
</tr>
<tr>
<td>Wechsler (2022)</td>
<td>Retrospective</td>
<td>USA</td>
<td>Adults with mean age of around 29 yrs; females (52%); majority with generalized tonic clonic (51%) followed by focal to bilateral tonic-clonic (36%) Perampanel used predominantly as concomitant therapy</td>
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Table I (continued). Demographic characteristics, study descriptions, and design of the investigations selected for our systematic review.

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<tr>
<td>Dan Li (2022)</td>
<td>Retrospective</td>
<td>China</td>
<td>Children with mean age of 10.2 years; male (64%); with focal and/or generalized epilepsy Perampanel used as concomitant therapy</td>
<td>9</td>
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<tr>
<td>Inoue Y (2022)</td>
<td>Prospective</td>
<td>China</td>
<td>Adolescents with mean age of 14.4 years; male (59%); majority with focal epilepsy (77%) Perampanel used as concomitant therapy</td>
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<tr>
<td>Heyman (2017)</td>
<td>Retrospective</td>
<td>Israel</td>
<td>Children with mean age of around 10 years; females (63%); majority with focal and/or generalized epilepsy (67%) Perampanel used predominantly as concomitant therapy</td>
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<tr>
<td>Gil-Nagel (2018)</td>
<td>Retrospective</td>
<td>Multicentric</td>
<td>Adults ≥18 years; 76%; females (63%); majority with focal epilepsy (80%) Perampanel used as monotherapy</td>
<td>8</td>
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<tr>
<td>Delgado (2020)</td>
<td>Retrospective</td>
<td>Italy</td>
<td>Adults with mean age of 49.6 years; majority with focal (73%) and generalized tonic-clonic epilepsy (25%) Perampanel used as monotherapy</td>
<td>8</td>
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<tr>
<td>Nilo (2021)</td>
<td>Retrospective</td>
<td>Italy</td>
<td>Adults with mean age of 46 years; majority with focal lesion epilepsy (77%) Perampanel used as concomitant therapy</td>
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<tr>
<td>Jaramillo (2020)</td>
<td>Prospective</td>
<td>Spain</td>
<td>Adults with mean age of 40.3 years; males (51%); all with focal epilepsy Perampanel used as an add-on therapy</td>
<td>8</td>
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<tr>
<td>Santamarina (2020)</td>
<td>Retrospective</td>
<td>Italy</td>
<td>Adults with mean age of 41 years; males (55%); majority with focal epilepsy (78%) Perampanel used as an add-on therapy</td>
<td>8</td>
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<tr>
<td>Rohracher (2018)</td>
<td>Retrospective</td>
<td>Multicentric</td>
<td>Adults with median age of 40 years; females (51%); majority with focal epilepsy (79%) Perampanel used as an add-on therapy</td>
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<tr>
<td>Villanueva (2018)</td>
<td>Retrospective</td>
<td>Spain</td>
<td>Adults with mean age of 36 years; females (51%); subjects with idiopathic generalized epilepsy Perampanel used as an add-on therapy</td>
<td>7</td>
</tr>
<tr>
<td>Lin (2019)</td>
<td>Retrospective</td>
<td>Taiwan</td>
<td>Adults with mean age of 42 years; females (54%); all with mesial temporal lobe epilepsy Perampanel used as adjunct therapy</td>
<td>7</td>
</tr>
<tr>
<td>Huber (2017)</td>
<td>Retrospective</td>
<td>Germany</td>
<td>Adults with age range of 21-55 years; mean age of 30 years; females (58%); majority with structural or metabolic cause for epilepsy (81%) Perampanel used as adjunct therapy</td>
<td>8</td>
</tr>
<tr>
<td>Lin KL (2018)</td>
<td>Retrospective</td>
<td>Taiwan</td>
<td>Children and adolescents; mean age of 15 years; females (46%); Majority with focal or focal to bilateral tonic-clonic seizures (76%) Perampanel used as adjunct therapy</td>
<td>8</td>
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</table>
as well as adults as their subjects. 16,21

The majority of the studies (n=30) had examined the effect of perampanel when used as an add-on or adjuvant therapy along with other anti-epileptic drugs (AEDs). Three studies had perampanel as monotherapy 4,39,40 and in one study, the efficacy was examined both as a combination therapy and second line monotherapy 27. In the majority of the included studies, the subjects had focal epilepsy and/or generalized epilepsy (n=30). Other types of epilepsy included generalized tonic-clonic, absence seizures, focal to bilateral tonic-clonic, mesial temporal lobe epilepsy and myoclonic seizures. The quality assessment has been presented in Table I. Quality assessment was done using the Newcastle Ottawa Scale where the maximum score that can be obtained is 9. The studies included in our meta-analysis were of good quality and had score ranging between 7 to 9.

Findings on Retention Rate

Among children and adolescents with PER used as concomitant therapy

The pooled analysis suggests the retention rates at 3 months (73%; 95% CI: 66-80%; n=2), 6 months (77%; 95% CI: 62-91%; n=4), 12 months (65%; 95% CI: 50-80%; n=6) and 24 months (67%; 95% CI: 39-94%; n=3) from the start of the treatment were at an acceptable level (Figure 2). The proportion of subjects continuing on PER was higher in the first six months from the start of the treatment and thereafter lowered a bit. There was no evidence of publication bias upon egger’s test (p=0.41).

Among adults with PER used as concomitant therapy

The retention rates at 6, 12, 24 and 36 months from start of therapy were 77% (95% CI: 68-87%; n=3), 66% (95% CI: 57-76%; n=13), 56% (95% CI: 42-70%; n=6) and 51% (95% CI: 41-61%; n=1) respectively (Figure 3). From the pooled findings, it appeared that the rates tended to decrease over time. Egger’s test did not suggest presence of publication bias (p=0.28).

Retention rate when PER used as a monotherapy

There were no studies that examined the retention rate among children and adolescents where PER was used as a monotherapy. In adults, the retention rates were 94% (95% CI: 90-98%; n=2) at 3 months, 87% (95% CI: 81-92%; n=2) at 6 months and 81% (95% CI: 71-88%; n=1) at 12 months from start of therapy. We did not find any evidence of publication bias (egger’s p-value

![Figure 2. Retention rates in children and adolescents with PER as concomitant therapy.](image)

![Figure 3. Retention rates in adults with PER as concomitant therapy.](image)
Among children and adolescents with PER used as concomitant therapy

The pooled findings indicate that the response rate improved with time. A total of 42% (95% CI: 33-50%; n=2) of children and adolescents responded to the treatment at 3 months of follow-up (Figure 4). The proportion responding to treatment increased to 54% (95% CI: 45-64%; n=7) at 6 months, 59% (95% CI: 49-68%; n=7) at 12 months and 69% (95% CI: 57-81%; n=3) at 24 months of follow up (Figure 4). We did not find any evidence of publication bias (egger’s p-value 0.34).

Among adults with PER used as concomitant therapy

Similar to the findings of the analysis in children and adolescents, the pooled findings from adults also suggests that the response rate largely improved with the duration of treatment. A total of 39% (95% CI: 20-57%; n=4) of adult subjects responded to the treatment at 6 months of follow-up (Figure 5). The proportion responding to treatment was 59% (95% CI: 48-69%; n=14) at 12 months, 52% (95% CI: 27-78%; n=6) at 24 months and 85% (95% CI: 72-92%; n=1) at 36 months of follow-up (Figure 5). We did not find any evidence of publication bias (egger’s p-value 0.34).

Findings on Seizure-Free Rate

Among children and adolescents with PER used as concomitant therapy

The pooled analysis suggested that the seizure-free rate increased with the duration of treatment. The proportion of children and adolescents who were free of seizure at 3 months was 12% (95% CI: 7-18%, n=2). This proportion increased to 26% (95% CI: 14-37%, n=6) at 6 months and to 37% (95% CI: 23-51%, n=6) at 12 months of follow up. At 24 months of follow up, 4% (95% CI: 15-33%, n=2) of the subjects were free of seizure. We did not find any
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Among adults with PER used as concomitant therapy

Similar to the findings among children and adolescents, the pooled findings among adults suggested that the seizure-free rate increased with the duration of treatment. The proportion of adults who were free of seizure at 6 months was 21% (95% CI: 15-26%, n=3). This proportion increased to 31% (95% CI: 15-46%, n=14) at 12 months and to 37% (95% CI: 30-44%, n=4) at 24 months of follow-up. At 36 months of follow up, 59% (95% CI: 44-72%, n=1) of the subjects were free of seizure. We did not find any evidence of publication bias (Egger’s p-value 0.52).

Seizure-free rate when PER used as a monotherapy

There were no studies that examined the seizure-free rate among children and adolescents where PER was used as a monotherapy. In adults, the rates were 56% (95% CI: 46-65%; n=2) at 3 months, 52% (95% CI: 44-59%; n=3) at 6 months and 42% (95% CI: 29-55%; n=1) at 12 months of follow-up. We did not find any evidence of publication bias (Egger’s p-value >0.05).

Findings Related to Treatment Related Adverse Effects

Among subjects undergoing treatment with PER as concomitant therapy, the proportion of children and adolescents reporting any treatment related adverse effects was 29% (95% CI: 21-37%; n=12) whereas this proportion was 41% (95% CI: 33-50%; n=18) among adults (Figure 6). We did not note the presence of publication bias (Egger’s p-value >0.05). The common reported adverse effects were dizziness/drowsiness, somnolence, behavioral problems (irritability, aggression, anxiety, mood changes), postural instability/gait problems, fatigue and weight gain. Most of the reported adverse effects were seen in the first few months of starting the treatment.

Discussion

The present meta-analysis found that perampanel is efficacious with acceptable response rate and seizure-free rate. However, there may be concerns with the higher proportion of adverse events noted with its use in both children/adolescents and adults. We found that the retention rates with use of perampanel as an add-on therapy among children and adolescents ranged between 65 to 77% within 24 months from start of treatment. For adults, the retention rate varied between 51 to 77% within 36 months of initiation of treatment. In both these age categories, the retention rate was higher in the first six months of starting the treatment. The findings indicate that the response rate in both children/adolescents and adults improved with time. The response rate was around 70% in children/adolescents and 52% in adults at 24 months of follow-up. On similar lines, the seizure-free rate also increased with the duration of treatment. Around 25% children and adolescents and 37% adults were seizure-free at 24 months follow-up period.

The proportion of children and adolescents re-
porting any treatment related adverse effects was 29% whereas this proportion was comparatively higher in adults (41%). Most of the reported adverse effects were seen in the first few months of starting the treatment. This is possibly the reason why we found lower retention rates after the first few months of treatment initiation. The common reported adverse effects were dizziness/drowsiness, somnolence, behavioral problems (irritability, aggression, anxiety, mood changes), postural instability/gait problems, fatigue and weight gain. Some of these adverse events also contributed to discontinuation of perampanel. It is clearly not understood the reasons for the observed adverse events. However, it is proposed that neuropsychiatric and behavioral side effects could be related to the AMPA-receptor-blockade-related subcortical network dysregulation involving GABA and the serotonin system. In lieu of these side effects, it is advisable that subjects undergoing treatment with perampanel should undergo a thorough psychiatric and behavioral assessment. Such an assessment should be conducted periodically throughout the treatment course and any dose modifications, if necessary, are done.

Even with a limited number of studies where perampanel was used as a monotherapy, the findings show that in adults, use as monotherapy offered better retention rates and fairly similar efficacy compared to use as combination therapy. There are benefits of using seizure medications as monotherapy, particularly with respect to increased compliance. As perampanel has a fairly long half-life of around 100 hours, it may be suited as a monotherapy. Furthermore, the use of perampanel as a monotherapy may be particularly useful in those who find it difficult to adhere to the multi-drug treatment schedule. However, there is an evident need to conduct studies aimed at investigating the efficacy and safety of perampanel monotherapy in patients with different types of seizures and in different age categories, such as children and adolescents as well as adults.

Limitations
There were some limitations in our analysis. First, we included studies with subjects having different forms of epilepsy. The efficacy and safety profile of perampanel might vary considerably between seizure types. We were unable to conduct a subgroup analysis based on the seizure type because included studies did not provide relevant data pertaining to each seizure type. Second, by limiting our inclusion criteria to studies published only in English, there is a potential risk of selection bias. We may have overlooked relevant studies published in other languages, which could have important findings and insights that are relevant to our research question. Third, in most of the studies, perampanel was used as an adjunct therapy and only a few studies used it as monotherapy. Consequently, we could not produce reliable synthesized evidence of use of perampanel as monotherapy. Fourth, we were unable to compare how the efficacy and safety profile of perampanel compares with that of other new-generation or conventionally used anti-epileptic drugs.

Conclusions
The findings suggest that perampanel could be an effective therapeutic drug for treatment of epilepsy in both child/adolescents and adults when used as an adjunct therapy. More data is required to comment on its use as monotherapy. A considerable proportion of subjects reported treatment related side effects, particularly those related to behavioral difficulties. The findings therefore underscore the need for a thorough psychiatric and behavioral assessment prior to being initiated on perampanel. There is a need for studies conducted with high quality and with long-term follow-up to confirm the findings of the current meta-analysis as well as generate newer insights regarding safety and efficacy.

Authors’ Contributions
PF conceived and designed the study, CZ and MH collected data and performed data analysis. PF wrote the draft of this manuscript. MH edited the manuscript.

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Conflict of Interests
The authors declare that there is no conflict of interests.

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Data availability statement
All the data used in the analysis is presented within the manuscript. For further information, specific studies (referenced in
the manuscript) could be referred.

Ethics Approval and Informed Consent
This systematic review and meta-analysis involved analyzing previously published data and did not involve any direct interaction with human subjects or animals. Therefore, no ethical clearance was required.

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