ORIGINAL ARTICLE

Safety and Efficacy of the AMPA Receptor Antagonist Perampanel for Tremors: A Systematic Review

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ABSTRACT

Background. Perampanel is an antagonist of the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor. It is currently FDA-approved to treat focal and generalized tonic-clonic seizures in epilepsy, but recent evidence suggests its potential in treating severe and refractory tremors.

Objectives. To determine the safety and efficacy of perampanel in treating tremors via a systematic review of existing literature.

Methods. We performed a literature search on five large databases (PubMed, Cochrane, Google Scholar, HERDIN, and Scopus) for clinical studies within the last 10 years and screened a total of 1,539 unique articles for full assessment. We filtered out papers on epilepsy as well as hypokinetic diseases and assessed nine articles for quality assessment and review.

Results. A total of four case reports/series, four open-label trials, and one randomized controlled trial were assessed to be of fair to good quality. All trials showed that low-dose perampanel (2-4 mg/day) was safe and well-tolerated with minor adverse events reported by participants. A net benefit from baseline was observed in patients with essential and primary orthostatic tremors. However, current evidence is weak because the trials employed a non-randomized before-after study design with a small sample size and significant dropout rates.

Conclusion. Low-dose perampanel at 2-4 mg/day shows promising potential in treating refractory tremors and myoclonus in recent clinical studies, but current evidence is weak or anecdotal. Additional randomized controlled trials are needed to determine the conclusive benefit of perampanel for hyperkinesia.

Keywords: perampanel, AMPA receptors, dystonia, tremors, myoclonus, hyperkinesia

INTRODUCTION

Glutamate binds AMPA or NMDA receptors in the brain to activate the release of neurotransmitters and to trigger an action potential. In certain neurologic disorders, however, these glutamate receptors become overactivated, leading to hyperkinesia manifesting as myoclonus, dyskinesia, dystonia or tremors. Of the known receptors of glutamate, those that bind AMPA have been implicated in hyperkinetic movement disorders due to their capability of mediating glutamate excitotoxicity. Indeed, mouse models of generalized dystonia and tremors were shown to have improved motor function after exposure to experimental AMPA antagonists, highlighting the potential role of AMPA receptors in hyperkinesia.[1-3] Nonetheless, the clinical use and efficacy of AMPA antagonists for treating hyperkinesia have been scarce, and most studies are still in the early stages of clinical trials. To date, there are only a number of AMPA

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antagonists in the market that are FDA-approved for the treatment of epilepsy. In the Philippines, only perampanel is FDA-approved as adjunctive therapy for the treatment of focal and generalized tonic-clonic seizures in patients with epilepsy.[4] While it appears to provide substantial relief from seizures, its beneficial effects on hyperkinesia are not well-explored. This is particularly relevant to some forms of dystonia and tremors in the Philippines such as X-linked dystonia-parkinsonism, which primarily affects Filipino males with a mean age of 39 years and whose treatment currently remains elusive.[5] Likewise, in various forms of spastic paraparesis and paraplegia such as hereditary spastic paraparesis, tropical spastic paraparesis or konzo, aberrations in glutamate receptors have been implicated as cause for disease development, for which AMPA receptors may also play a role.[6,7] To this end, this systematic review aims to collate current knowledge and findings on the safety and efficacy of perampanel on tremors to determine the potential of this drug to treat hyperkinetic movement disorders that are currently not responsive to standard of care.

METHODS

Study Selection

In this study, a literature search was conducted at selected databases (NCBI Pubmed, Cochrane Library, Google Scholar, HERDIN, Scopus) using the PRISMA guidelines to gather current studies on the use of the recently FDA-approved drug perampanel for the treatment of non-epileptic tremors.[8] The search included the terms 'perampanel' matched with 'dystonia' or 'tremor' or 'hyperkinesia' to include all possible papers describing tremors, which yielded unique results including clinical studies written in both English and non-English language, and published as a journal article or as a conference proceeding or uploaded as an unpublished manuscript from January 2014 to August 2024 (Figure 1).

The search strategy was done as such because many tremors result from a hyperkinetic disorder, and tremors resulting from hypokinetic disorders (i.e., resting tremors) may have a different mechanism and was explicitly separated from the search strategy. Meanwhile, some forms of tremors are dystonic, although tremors do not represent the whole clinical picture of dystonia. We additionally removed papers that did not have full-text access provided to the University of the Philippines Manila as well as those written on patients with both hyperkinesia and epilepsy, as well as hypokinetic diseases like Parkinson disease for which the effects of perampanel were also investigated. Meanwhile, non-English articles originally included in the screening were translated to English prior to appraisal, where applicable. The final articles included were then appraised for quality assessment before proceeding to data extraction and analysis for review. The database search was originally performed between April to August of 2024 for screening, quality assessment, and data extraction; However, due to the amount of time that lapsed since submission, the search was again performed in February of 2025 during the manuscript revision stage.

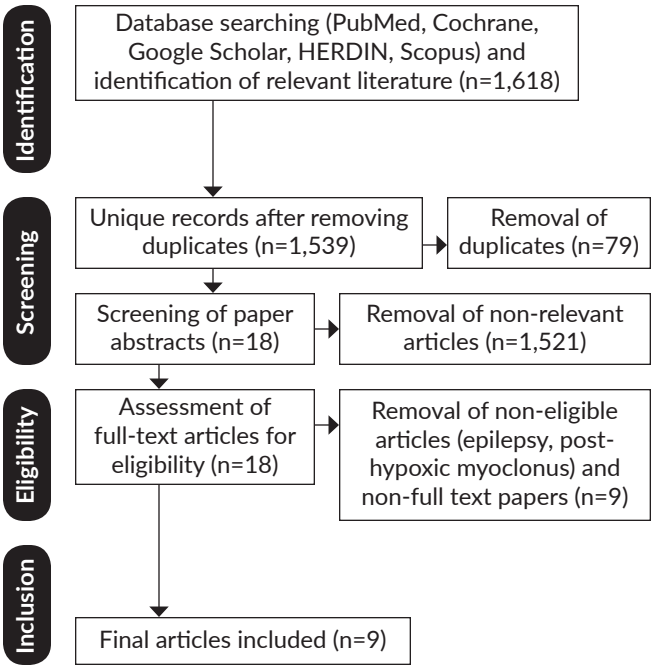

Figure 1. Workflow diagram for literature search and eligibility based on the PRISMA guidelines.

Inclusion and Exclusion Criteria

Studies were selected based on their relevance to the therapeutic effect of low-dose perampanel, either alone or in combination, on tremors. Only clinical studies studying the efficacy and/or safety of low-dose perampanel (1-4 mg/day) in adults greater than 18 yrs of age were screened, which included case reports, case series, cohort studies, open-label trials, or randomized controlled trials (RCTs) that compared outcomes versus baseline, standard of care, or placebo. Further, only articles published within the last 10 yrs were included. Both English and non-English publications were included in the database search, and journal articles, conference proceedings, or unpublished online manuscripts regardless of country of origin were assessed for eligibility. The primary outcome of eligible articles was an objective improvement in motor performance via a clinical rating scale, with secondary outcomes including perceived improvement of quality of life (QoL) factors. Exclusion criteria included preclinical studies, any AMPA receptor antagonist besides perampanel and multi-site antagonists that affect other sites aside from AMPA receptors such as topiramate. Since perampanel is currently approved for the treatment of seizures in epilepsy, only non-epileptic hyperkinetic movement disorders were included in the review, specifically cases of tremor that are either on polytherapy or are refractory prior to treatment. Lastly, only papers with full-text access or for whom UP Manila has subscription access to were included in this

study, as well as papers that had sufficient data for quality assessment. For papers without university access, copies were obtained via request from the respective corresponding authors.

Data Extraction

Each article was analyzed for eligibility by two independent reviewers, with consensus decided by a third reviewer in case of conflicting results. Only full-text papers on the safety and efficacy of perampanel on tremors and those with sufficient data for quality assessment were chosen and included in the systematic review. In each paper, the following data were collected: first author, year of publication, patient demographics (age, sex, ethnicity if available, current medications), sample size, intervention and control doses, outcome assessment tools, clinical outcomes, and adverse events. Data were pooled and presented in tables to determine the magnitude of effect of perampanel as well as the frequencies of desired outcomes in the population.

Quality Assessment Tools for Selected Studies

Each paper was then qualitatively assessed depending on the study design. Briefly, case reports and case series were assessed using the NIH Quality Assessment Tool for Case Reports/Series,[9] while non-randomized cohort studies and open-label trials using a before-and-after interventional study design were assessed using the NIH Quality Assessment Tool for Before-After (Pre-Post) Studies with no Control Group[9]. Lastly, the only randomized clinical trial included in this study was assessed using the Revised Cochrane Risk-of-Bias Tool 2.[10,11] The risk of bias of the included studies were then individually assessed and summarized based on the risk-of-bias tools used. For the only RCT included in this study, a summary of its potential biases was included in Figure 2.

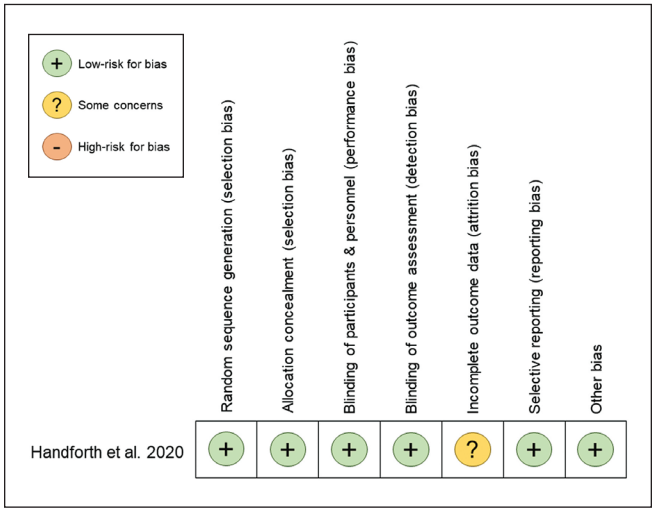

Figure 2. Quality assessment of included RCTs using the Cochrane Risk-of-bias tool (RoB 2).

Synthesis of Results

Data extracted were then collated and presented as follows: sample size, mean age in years, disease, perampanel dosage and frequency, adverse events, outcome measuring tools, and frequencies of the primary and secondary outcomes. For all open-label trials and RCTs included in the systematic review, the frequencies of adverse events that occurred as a consequence of perampanel administration were pooled to determine the relative safety and tolerability concerns of the drug. However, due to differences in population, the inclusion/exclusion criteria, the study design, and measured outcome parameters on quantifying the effect of low-dose perampanel on tremors, a synthesis of results via a meta-analysis was not possible. Instead, results from each study was discussed systematically, both individually and in relation to the results of other studies.

Ethics Statement

This study was registered at the Research Grants Administration Office of the National Institutes of Health (RGAO-2023-1871) and the Research Implementation and Development Office of the College of Medicine (RIDO 2023-1871) at the University of the Philippines Manila. Meanwhile, the study was classified as 'Exempted' by the Research Ethics Board of the University of the Philippines Manila (UPMREB 2024-0350-EX). The review protocol was approved via Technical Review of RIDO and may provide access to the protocol as necessary. Meanwhile, the study was not registered at the PROSPERO database for systematic reviews nor at the Open Science Framework (OSF) Registry.

RESULTS

Search Results

In this study, we screened all abstracts and filtered out 1,521 non-relevant articles and assessed 18 articles for full-text review after the removal of duplicates. These papers were initially screened on the basis of their titles and abstracts, if the study included perampanel on its own or as part of combination therapy in the experimental group, and if the studies investigated the effect of perampanel on tremors. Additionally, preclinical studies were filtered out, including those investigating the effects of perampanel *in vitro* and *in vivo* in animals. After initial screening, the full texts of the remaining papers (n=18) were appraised to determine their eligibility for quality assessment and data analysis on the basis of their objectives, methodologies, study populations, and results. From here, articles were removed if they involved tremors in epilepsy patients, whose outcomes may not be relevant to non-epileptic tremors, as well as if they involved tremors that resulted from hypokinetic diseases such as Parkinson disease (i.e., resting tremors), which may have a different mechanism from the tremors that are being investigated. We further filtered articles whose full-text copies were not available in the repositories of the university,

Table 1. Summary of Extracted Data from Included Non-randomized Studies and Randomized Controlled Trials

Study	Sample Size (N)	Mean Age (Yrs)	Sex (M/F)	Disease	Intervention	Dosing and Duration	Adverse Events	Outcome Measuring Tools	Outcomes (%)
Gironell et al., 2019	12	69.5 ± 9.7	M = 10 F = 2	Essential tremor	Perampanel only or as adjunct	2-4 mg/ day at night, 8 weeks	Dizziness (n=4) Nausea (n=4) Instability (n=4)	TCRS Glass Scale	Tremor reduction (47%) Reduced severity (61-70%)
Handforth et al., 2020	26	70.4 ± 14.1	M = 15 F = 11	Essential tremor	Perampanel only or as adjunct	2-8 mg/day, 14 weeks	Imbalance/falls (n=11) Dizziness (n=8) Fatigue (n=6) Irritability (n=6) Impaired cognition (n=4) Somnolence (n=4)	TETRAS-P TETRAS-ADL QUEST SGIC	>50% tremor reduction (27%) Improved QoL (36.4%) >50% reduction in ADL burden or marked improvement in symptoms (54.5%)
Van der Woude et al., 2022	27	66.7 ± 8.0	M = 9 F = 18	Orthostatic tremor	Perampanel only	4 mg/day, 10-40 weeks	Dizziness (n=5) Sleepiness (n=4) Increased tremor (n=3) Nightmares (n=2) Tiredness (n=2) Skin rash (n=2) Blurry vision (n=2)	HADS iADL SF-36	Tremor reduction (56%) Increased standing time (56%) Decrease in anxiety and depression (33%)
Gironell et al., 2022	50	67.4 ± 6.0	M = 20 F = 30	Essential tremor	Perampanel only	2-4 mg/day, 4-56 weeks	Dizziness (n=16) Instability/falls (n=16) Weight gain (n=2) Depression (n=2)	TCRS Glass Scale	Tremor reduction (90%) Non-persistence of therapeutic effect at 56 weeks (70%)
Diaz-Feliz et al., 2023	18	75.1 ± 12.03	M = 7 F = 11	Essential tremor	Perampanel only or as adjunct	4 mg/day, 4 weeks	Dizziness (n=1) Gait instability (n=5) Irritability (n=1)	Fahn-Tolosa-Marin Tremor Clinical Rating Scale	Tremor reduction (44%) Non-persistence of therapeutic effect at 4 weeks (28%)

as well as papers with lacking information on the dosing of perampanel.

Study Quality and Clinical Study Characteristics

Each article included for quality assessment and review had an average of 27 recruited patients (not including case reports/series), ranging from a sample size of 12 to 50 involving both male and female patients with a mean age >65 yrs (Table 1). The primary outcomes for the appraised studies included tremor reduction, symptom relief, and tolerability after intake of perampanel versus baseline or control, using The Essential Tremor Rating Assessment Scale (TETRAS-P), Tremor Clinical Rating Scale (TCRS), Glass Scale, and the Fahn-Tolosa-Marin Tremor Rating Scale. Meanwhile, secondary outcomes included changes or impacts on activities of daily living (ADL), depression, quality of life (QoL), using the QoL and Subject Global Impression of Change scales, among others (Table 1). Most studies employed a pretest-posttest study design except for the open label trial of Gironell and colleagues, which had 11 patients with tremor treated with low-dose perampanel and 15 patient controls on placebo. Meanwhile, case reports/series determined efficacy via serial neurologic exams, electromyogram (EMG) monitoring, and subjective improvement as reported by the patients (Table 2).

The prospective cohort study and open-label trials included in this systematic review employed a non-randomized before-after study design with no control group, which were assessed as good to fair quality via the NIH Quality Assessment Tool for Before-After (Pre-Post) Studies with no Control Group. Meanwhile, the prospective cohort study by van der Woude et al. was assessed as having *'poor'* quality due to concerns with population sampling, blinding, and a lack of statistical analysis.[9,12] Meanwhile, the randomized placebo-controlled cross-over trial by Handforth and colleagues was assessed as having low-risk for bias using the Cochrane risk-of-bias tool, with only minimal concerns on attrition due to a high proportion of dropouts in a small sample size (16 out of 26), which was otherwise addressed by implementing an intent-to-treat analysis of the data and comparing it with data obtained from the completer population (Figure 2).[13]

The summary of extracted data from the included cohort study, open label trials, and an RCT is shown in Table 1. All five studies included investigated on the efficacy of perampanel for specific forms of tremor (four on essential tremor, one on orthostatic tremor). Most populations were above 60 years of age with variable proportions of males and females, and a substantial dropout rate was noted in most studies citing adverse events or non-therapeutic effects, which will be discussed.[12-16]

Due to the lack of high-quality and statistically powered controlled studies to assess the safety and efficacy of perampanel for hyperkinesia, this review also included all eligible case reports and case series exploring the use of perampanel for all forms of tremor. A total of three case reports and one case series were included and assessed as being of

Table 2. Summary of Case Reports/Series Using Perampanel for Hyperkinetic Abnormalities

Study	Age/Sex	Disease	Current Medications	Intervention	Outcome measuring tools	Outcomes
Mean age, yrs	66.9 ± 8.4					
Ruiz-Julian et al., 2018	75/M	Refractory POT	Clonazepam 1.5 mg/day Gabapentin 1.2 g/day Pregabalin 300 mg/day Primidone 750 mg/day Levodopa 300 mg/day Levetiracetam 1 g/day Topiramate 200 mg/day Zonisamide 200 mg/day	Perampanel 2-4 mg/day	Self-report Neurologic exam EMG monitoring	Full symptomatic relief after 2 months Persistence of 14 Hz rhythmic bursts in lumbar muscles (EMG)
Gironell et al., 2019 Mean age (N=20)	68.9 ± 6.3	POT	Clonazepam (N=11), dose NR Gabapentin (N=3), dose NR Pregabalin (N=4), dose NR Lorazepam (N=1), dose NR	Perampanel 2-4 mg/day	Fahn-Tolosa-Marin Tremor Clinical Rating Scale, part C	Tremor reduction, in 92% of participants Non-persistence of symptomatic relief at 3 months
Wadhwa et al., 2019	62/F	Refractory POT	Clonazepam 20 mg/day tapered to 0.25 mg/day	Perampanel 1-2 mg/day	Self-report Neurologic exam EMG monitoring	Significant symptomatic relief Persistence of 17-18 Hz tremor when standing
Grobe-Einsler et al., 2020	53/F	Refractory POT	Clonazepam 4 mg/day Gabapentin 2.4 g/day Primidone 500 mg/day Propanolol, dose NR	Perampanel 2-4 mg/day	Self-report Neurologic exam EMG monitoring	Significant symptomatic relief Persistence of 14-16 Hz tremor when standing

Table 3. List of Adverse Events due to Perampanel Use in Current Open-label Trials and RCTs

Adverse event	Percent of total sample size (%)
Gait instability	36/133 (27.07%)
Dizziness	34/133 (25.56%)
Increased tendency to fall	27/133 (20.30%)
Fatigue/Tiredness	8/133 (6.02%)
Somnolence	8/133 (6.02%)
Irritability	7/133 (5.26%)
Impaired cognition	4/133 (3.01%)
Increased tremors	3/133 (2.26%)
Weight gain	2/133 (1.50%)
Confusion	2/133 (1.50%)
Depression	2/133 (1.50%)
Skin rash	2/133 (1.50%)
Blurry vision	2/133 (1.50%)
Headache	2/133 (1.50%)

good quality via the NIH Quality Assessment Tool for Case Reports/Series.[9] All four case papers included explored the use of perampanel for primary orthostatic tremors. The dose of perampanel was given at 2 to 4 mg once daily at night up to thrice daily, similar to the dosing regimen implemented by the RCT and open label trials included in this study. Patients had a mean age of 69.1 years and were often diagnosed with a refractory form of primary orthostatic tremor.[17-20] A summary of extracted data from these case reports/series is shown in Table 2.

Safety, Tolerability, and Efficacy of Perampanel

All of the studies included in this review consistently dispensed perampanel at a maintenance dose 2 to 4 mg once daily at night citing greater adverse events at higher doses, with some patients able to tolerate up to 6 to 12 mg/day. Regardless of dose, however, the most common adverse event reported in the open label trials and RCT was gait instability – occurring in about 27.07% of all patients taking the drug – followed by dizziness and an increased tendency to fall. A summary of adverse events based on these studies is summarized in Table 3. Although perampanel use has been associated with an increased risk for psychiatric events such as depression, anxiety and aggression, these adverse events were rarely reported in the trials.[21]

Due to the limitations in study design and the irreconcilable differences in measured outcome parameters on perampanel and tremors, a meta-analysis of drug benefit was not possible in this review. However, all studies reported a net benefit for perampanel on tremors, with a significant reduction in tremor scores and an improvement in activities of daily living (ADLs) or quality of life (QoL) from baseline scores (Table 1). Briefly, a net tremor reduction ranging from 20% to 90% was seen in patients given a low-dose of daily perampanel after a minimum of four weeks, either on its own or in combination with current polytherapy. Patients recruited in an RCT by Handforth and colleagues reported an average of 20% reduction in tremor amplitude, with three patients (N=11) having TETRAS-p score reductions greater than 50% compared with zero in the placebo group (N=15).[13] Similar results were obtained by Gironell and colleagues with four out of eight patients achieving subjective tremor

improvement of 70%, with a 47% relative reduction in the overall TCRS scores of all patients.[14] This pilot study was later followed-up using a larger sample size (N=50), where Gironell and colleagues found that 27 out of 30 patients had a 68% improvement in their TCRS and Glass scale scores, albeit noting non-persistence of the tremorolytic effect by 12 months.[15] On the other hand, patients recruited in the study of van der Woude and colleagues reported improvements in the Short-Form Health Survey (SF-36) scores, which was reflective of improvements in their QoL, anxiety and depression scores after one to four months of low-dose perampanel (4 mg/day).[12] For patients with essential tremor refractory to polytherapy, a significant overall improvement in the Fahn-Tolosa-Marin Tremor Rating Scale parameters (severity of tremor, motor tasks, and functional discapacity) was seen at four weeks of low-dose perampanel (4 mg/day); however, more than half (55%) of the patients withdrew prematurely due to adverse effects noting primarily the development of gait instability.[16]

Although none of the studies included specifically investigated the safety and tolerability of perampanel for patients with tremors as the primary outcome, most reported that low-dose perampanel at 2 to 4 mg was well-tolerated by the patients included in their study. The only publication found during the search that investigated the safety and tolerability of perampanel was an open-label phase 2a study for the use of perampanel in cervical dystonia, which investigated the tolerability and safety of this drug as its primary and secondary outcomes, respectively. In this study, the tolerable dose of perampanel which can be maintained for at least four weeks by patients taking the drug was 2 to 6 mg/day, with more than half of the participants (n=13) tolerating 2 to 4 mg/day of perampanel.[22] In terms of safety, no serious adverse events were reported and only dizziness, gait instability, irritability, and increased tendency to fall were the most common, similar to other studies included in this review (Table 1).

Similarly, all case reports/series reported a marked improvement in or near-complete recovery of tremors after 2 to 6 mg/day of perampanel, with persistence of benefit after two to six months of follow-up (Table 2). This suggests that AMPA receptors have a central role in the pathogenesis and progression of primary orthostatic and essential tremors, and that antagonism of these receptors may have an outstanding clinical benefit especially for refractory cases of disease.

DISCUSSION

The main objective of the study was to determine the safety and efficacy of low-dose perampanel in treating tremors via a systematic review. Based on existing literature, the regulation of AMPA receptors is a promising approach to treat refractory cases of tremor. However, a major limitation is the apparent infancy of the concept and the scarcity of clinical studies investigating this mechanism in tremors, which precluded any conclusive evidence for this study. Nonetheless, we showed that low-dose perampanel given at 2-4 mg/day consistently afforded a net reduction in tremors and an increase in ADL and QoL scores from baseline of patients enrolled in the RCT and open-label trials included in this study. Likewise, a collation of case reports and case series suggested a promising benefit to patients with refractory tremors who are also on polytherapy. Peramapanel continues to be an effective medication for focal and generalized seizures in epilepsy and is FDA-approved in the United States for this indication in patients aged 12 years and above. In the Philippines, perampanel has been used to treat focal seizures and those with secondary generalization in the pediatric age group and has been shown to be safe and relatively effective.[4] Its mechanism of action is the non-competitive inhibition of AMPA glutamate receptors in the brain, which is thought to modulate glutamate excitotoxicity in epilepsy.[23,24]

Currently, first-line agents for tremors include propranolol 10 mg TID or primidone 25 mg ODHS, while for dystonia the use of botulinum neurotoxin-A (BoNT-A) has been recommended for many various types such as cervical and idiopathic dystonia.[25,26] However, in most of the papers included in this systematic review, many of these drugs have been ineffective as monotherapy in several cases of tremors, reasons for which may be multifactorial. As a result, these drugs are often prescribed together as part and parcel of polytherapy, resulting in adverse events and eventually leading to the discontinuation of these drugs. Hence, there is a need to find new drugs either as monotherapy or as adjuncts in these patients to improve their functionality and quality of life.

This systematic review presents a promising benefit of using perampanel for tremors in hyperkinetic movement disorders with a relatively safe drug profile. Many cases of tremor that are refractory to polytherapy are currently being treated using deep brain stimulation, which is a costly and invasive procedure that makes use of an implantable device to deliver electrical pulses to the brain.[27] Its efficacy in refractory forms of tremor has been significant in certain patients, however, not all patients are eligible for this procedure and its accessibility remains an issue due to procedural cost and the number of in-hospital equipment available. To this end, the use of the relatively new drug perampanel may contribute significantly to the extent of medical management possible for cases of refractory tremor, especially those who are financially constrained to avail of deep brain stimulation. However, the results shown in this systematic review do not in any way provide conclusive evidence on the efficacy of perampanel for tremors, and more randomized controlled studies with sufficient sample size and statistical power to detect a net benefit are needed to determine the true efficacy of perampanel for these patients.

CONCLUSION

Perampanel at a low dose of 2 to 4 mg/day has some efficacy in reducing tremors in recent clinical studies. However, the level of evidence is weak due to a scarcity of randomized controlled studies on the topic. The most common adverse effects of taking the drug include dizziness, gait instability, and an increased risk to fall, all of which are experienced regardless of dose and frequency. Recent studies suggest that the therapeutic effect of perampanel on tremors persist variably over time, with some showing retained benefit at two to six months but with loss of benefit at six to 12 months follow-up. More studies are needed to obtain conclusive evidence on the therapeutic effect of perampanel for hyperkinetic movement disorders.

Acknowledgments

The authors would like to thank the PGH Department of Neurosciences for the guidance and technical review of the manuscript.

Data Availability Statement

Supplementary data is available from the corresponding author upon reasonable request.

Statement of Authorship

All authors certified fulfillment of ICMJE authorship criteria.

Author Disclosure

All authors declared no conflicts of interest.

Funding Source

None.

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