

Optimal Use of Perampanel in Elderly Asian Patients with Epilepsy: Expert Opinion

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Abstract: Managing epilepsy in the elderly remains complicated largely due to factors related to aging. In this population, management practices are increasingly shifting towards the use of newer-generation anti-seizure medications (ASMs) as they are generally associated with better tolerability and safety profiles than older ones. Perampanel is a new ASM with broad-spectrum efficacy and a favorable safety profile. However, because of the lack of information and experience in its use, the prescription of perampanel has not been optimized in the elderly in the real-world setting in Asia. A group of epilepsy experts across the region convened at a series of virtual meetings to share their experience and discuss recommendations on perampanel use in elderly patients, including dose optimization, considerations with treatment initiation, and strategies to manage adverse events and maximize tolerability. This article summarizes key clinical and real-world evidence for perampanel in the elderly and consolidates the experts' opinions on optimizing perampanel use in elderly Asian patients with epilepsy, providing practical guidance for clinicians to address challenges related to treatment initiation and tolerance.

Keywords: perampanel, elderly, epilepsy, real-world experience, Asia

Introduction

In Asia, approximately 23 million people are living with epilepsy,¹ with old age (>65 years) being one of the peaks for incidence.^{2–4} Managing epilepsy in the elderly remains complicated largely due to factors related to aging. Clinical manifestations of seizures in the elderly can be different from the general adult population, resulting in misdiagnoses.^{5,6} Comorbidities and concomitant medications are common among this population^{7–9}; some of these conditions underlie epilepsy, act as differential diagnoses, or affect anti-seizure medication (ASM) choice.^{6,9} Physiological changes at old age further affect the pharmacokinetics and pharmacodynamics of many ASMs.^{5,9,10} With the rapidly aging population in Asia,¹¹ the elderly with epilepsy represents a growing, unique patient group.

A recent comparative analysis of clinical trial data showed that among some new-generation ASMs, adjunctive cenobamate was associated with the most favorable efficacy outcomes in adults with focal seizures.¹² Nevertheless, similar investigations have not been carried out in the elderly, and efficacy has been shown to be generally comparable across commonly used ASMs in this population so far.^{9,13} As such, the determining factors for choosing an initial medication in elderly patients are safety and tolerability, including potential adverse events (AEs), drug–drug interactions (DDIs) and the ASM's impact on comorbidities. In this population, management practices are increasingly shifting away from the use of older-generation ASMs in favor of newer ones,¹⁴ as the latter are generally associated with fewer DDIs with other medications that elderly patients are usually taking.^{10,15}

Perampanel is a first-in-class α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor antagonist approved for the treatment of epilepsy.^{10,16} It is one of the newer ASMs with broad-spectrum efficacy and a favorable safety profile, making it a suitable alternative to older-generation ASMs in elderly patients.¹⁰ However, the use of perampanel has not been optimized in the elderly in the real-world setting across Asia because of the lack of information and experience in this population. To address this gap, epilepsy experts from seven Asian countries (China, India, Indonesia, Japan, Philippines, Taiwan, and Thailand) convened at a series of virtual meetings in October and November 2021 to review clinical evidence of, and discuss recommendations on, perampanel use in the elderly.

This paper summarizes key clinical and real-world evidence for perampanel in the elderly, describes practical guidance for clinicians across the region to optimize perampanel use, and address challenges related to treatment initiation and tolerance in elderly Asian patients with epilepsy.

Key Clinical and Real-World Evidence on Perampanel

Based on clinical trial data and real-world experience, perampanel is observed to have broad-spectrum efficacy in different seizure types, and good safety and tolerability profiles among elderly patients.^{17–24} Clinical trial and real-world data focusing on this patient population are summarized below.

Clinical Trial Data

A pooled subgroup analysis of elderly patients aged ≥ 65 years ($N=28$) in three Phase III, multinational, randomized, double-blind and placebo-controlled studies was carried out to assess the efficacy and safety of perampanel.¹⁷ Perampanel demonstrated consistent efficacy in elderly and adult patients. Seizure frequency per 28 days was reduced by a median of 16.9% and 12.5% from baseline for the 8- and 12-mg/day elderly groups, respectively (versus 26.5% and 26.7% in the adult subgroups). Elderly patients were generally responsive to perampanel, with 50% responder rates at 22.2% and 42.9% in the 8- and 12-mg/day groups, respectively (versus 34.9% and 33.9% in the adult subgroups). AE incidence was generally similar between the elderly and adult subgroups (85.0% vs 77.4%) but dizziness, fatigue and falls were reported more frequently in the former (45% vs 29%, 25% vs 9%, 25% vs 5%, respectively). The four patients who discontinued treatment because of AEs were on perampanel 12 mg/day.

In another long-term (up to 4 years) post-hoc analysis of patients aged ≥ 60 years with partial-onset seizure, with or without secondary generalization ($N=71$), adjunctive treatment with perampanel 2–12 mg/day reduced seizure frequency by $\geq 50\%$ in more than a third of patients, with a median of $>95\%$ in the first 2 years.¹⁸ The most common AE was dizziness during years 1 (47.9%) and 2 (12.5%), and fall during years 3 (15.8%) and 4 (14.3%). The safety profile in these patients was consistent with the overall population and no new safety signals emerged.

Real-World Data: Across Europe

The FYDATA (Follow-up of 1 Year Data of paTients on perAm-panel) study was a retrospective, observational study investigating the effectiveness and safety of adjunctive perampanel in patients with focal epilepsy across 18 Spanish hospitals.¹⁹ Patients aged ≥ 65 years ($n=25$) had a more favorable clinical response to perampanel than those aged ≤ 65 years ($n=439$). Binary logistic regression showed that age ≥ 65 years was a significant predictor of seizure freedom at 12 months (odds ratio 3.194; $P=0.040$).

Another study reported the effectiveness and tolerability of adjunctive perampanel in patients aged ≥ 65 years ($N=92$) across 12 Italian epilepsy centers.²⁰ Mean perampanel doses were 4, 5, and 6 mg/day at 3, 6, and 12 months, respectively. Adjunctive perampanel was associated with improved seizure control: at 12 months, 57.6% of the patients achieved $\geq 50\%$ reduction in baseline monthly seizure frequency, and 23.9% were seizure free. It was also associated with good tolerability with no reports of severe AEs. The elevated risks of dizziness, balance disorders, and falls, which were previously reported in the pooled analysis of Phase III clinical studies,¹⁷ were not found in this analysis.

In pooled, multicenter, observational data on the routine use of perampanel across Europe, perampanel was found to be effective and well tolerated in individuals aged ≥ 65 years ($N=134$).²¹ The mean perampanel dose used was 6 mg/day, which was lower than the 8 mg/day used in the overall population. No unexpected AEs were observed and the overall rates were similar to those in previous reports. At 12 months, seizure-free rate was 28.3% and treatment retention rate was 47.8%. Consistent with what was observed in the FYDATA study,¹⁹ the likelihood of seizure freedom increased with age.

Real-World Data: Asia-Specific

In a retrospective review of patients with a mean age of 60.4 years in a neurological intensive unit in Taiwan, perampanel was found to be an effective add-on treatment for refractory status epilepticus.²² Among the 22 patients on perampanel, it was given as a median fourth ASM; the median initial dose was 2 mg/day and the median maximum dose was 4 mg/day. 72.7% of the patients were free from clinical and electrographic seizures within 4 days.

Another retrospective, non-interventional study was conducted in a specialist epilepsy center in Taiwan to evaluate the clinical efficacy and safety of perampanel as adjunctive therapy in patients aged ≥ 60 years with focal epilepsy (N=27).²³ The mean perampanel dose was 4.5 mg/day. Twelve-month seizure freedom was observed in 45% of the patients; 65% of the patients had $\geq 75\%$ seizure frequency reduction, and the median reduction of seizure frequency in elderly patients was significantly higher than that in the non-elderly group (-64% vs -36% ; $P=0.049$).

The largest observational study to date investigated the efficacy and safety of long-term adjunctive perampanel treatment in Japanese patients who have epilepsy with focal seizures, with or without focal to bilateral tonic-clonic seizures or generalized tonic-clonic seizures (N=3716).²⁴ In a subgroup analysis of patients aged ≥ 65 years (n=690), the mean dose of perampanel used was 3.0 mg/day and the mean maximum dose was 3.5 mg/day – both of which were lower than those used in patients < 65 years old. The 50% responder rates were higher in the elderly patient group, regardless of seizure type. This may be attributed to a high proportion of patients in this group with a disease duration of < 10 years, suggesting that their condition developed at a later age. In all effectiveness parameters – improvement in seizure severity, seizure duration, daily activity, and overall condition – perampanel performed better in patients aged ≥ 65 years than those aged < 65 years. The retention rate at 52 weeks in the elderly patient group was 53.3%. The incidence of adverse drug reactions was significantly lower in patients aged ≥ 65 years than in those aged < 65 years (22.2% vs 36.2%). This may be due to the lower average dose of perampanel used in the former group. It was observed that co-administration of ASMs that promote perampanel metabolism also led to a significant decrease in adverse drug reactions in this study.

In a retrospective study of patients with Alzheimer's disease and elderly-onset epilepsy in Japan, cognitive function showed improvement in 58.3% of the patients after 6 months of daily 2-mg perampanel treatment.²⁵ While cognitive function in these patients deteriorated in the subsequent months, increasing the perampanel dose to 4 mg/day resulted in subsequent improvement. It was therefore suggested that increasing the perampanel dose to 4 mg/day at an early stage of treatment may improve cognitive function. A case report in Taiwan also supported the early administration of perampanel to improve cognitive performance in a patient with Alzheimer's disease complicated with non-convulsive seizures.²⁶

Best Practice Expert Recommendations

The expert group agreed that published data – though largely observational and small in number – together with their clinical experience, have demonstrated encouraging results with the use of perampanel in elderly patients so far, with good efficacy and no increased risk of AEs. In general, they find the efficacy and safety of perampanel in the elderly to be comparable with that in the general adult population. The following section describes the expert group's consolidated recommendations to implement into the clinical management of elderly Asian patients with epilepsy using perampanel (Box 1).

Dose Optimization in Elderly Asian Populations

In this population, perampanel at doses lower than the indicated starting and maintenance doses for the general population offers effective seizure reduction while minimizing AEs.^{22–24}

Starting Dose

The expert group recommends a starting dose of 2 mg/day, or 1 mg/day if the suspension formulation is available. The 1 mg/day starting dose should be particularly considered in elderly patients who have tolerability concerns.

Titration Strategy

Because of the increased likelihood for AEs in the elderly,²⁷ titration should be carried out slowly in this patient group. The expert group advise a “start low and go slow” approach by increasing the daily dose of perampanel by 1 mg every 3 or 4 weeks. Where

Box 1 Expert Recommendations on Perampanel Use in the Elderly

Dose optimization (the “start low and go slow” strategy)
• Starting dose: 1 or 2 mg/day • Titration: increase daily dose by 1 mg every 3 or 4 weeks • Maintenance dose: 4 mg/day
Key considerations prior to initiation <u>Comorbidities</u> • Psychiatric or behavioral disorders -Start with 1 mg/day and uptitrate no faster than 1 mg every 4 weeks -Monitor any sudden behavior change • Dementia -Consider increasing perampanel dose to 4 mg/day at an early stage if patient does not have comorbid psychiatric or behavioral disorders • Cardiac comorbidities -Perampanel can be safely used • Renal impairment -Mild: increase dose no more frequently than once every 3 or 4 weeks -Severe: consider excluding perampanel • Compromised hepatic clearance capability -Consider excluding perampanel • Undergoing hemodialysis -Consider excluding perampanel <u>Concomitant medications</u> • Enzyme-inducing ASMs: consider higher perampanel dose
Managing AEs and maximizing tolerability • If AEs occur during titration period: downtitrate to previous tolerated dose and uptitrate again at smaller increments than before • If AEs occur during maintenance period: reduce dose until AE resolves and slowly titrate to effective and tolerated maintenance dose again • Falls: real-world analyses have not found a significantly increased risk of falls in the elderly when the “start low and go slow” strategy is employed • Somnolence and sleep disorders: somnolence can be mitigated by taking perampanel shortly before bedtime, as indicated; perampanel’s favorable effect on sleep architecture is likely to benefit patients who suffer from sleep disorders • Psychiatric AEs and aggression: proactively monitor for psychiatric AEs, especially aggression, and adjust perampanel dose accordingly • Patient and caregiver education: inform on correct way and timing of taking perampanel; reassure them AEs can be effectively managed and treatment should not be stopped without consulting their physician

Abbreviations: AE, adverse event; ASM, anti-seizure medication.

the suspension formulation is not available, an alternative strategy to consider (in patients not taking any enzyme-inducing medication) is to administer perampanel tablets of 2-mg dose difference on alternate days to achieve an average increment of 1 mg. With the long half-life of perampanel (about 105 hours),²⁸ this approach is unlikely to result in significant fluctuation in plasma concentration.

Maintenance Dose

The expert group recommends that the optimal maintenance dose is 4 mg/day. As perampanel has demonstrated low-dose efficacy in elderly patients with minimal AEs,^{22–24} the maintenance dose for this patient group can be lower than the recommended 8 mg/day for the general adult population.

Key Considerations When Initiating Perampanel

As with all ASMs, the decision to initiate perampanel should take into consideration any comorbidities and concomitant medications the patients have. While there are no data available on the pharmacokinetics of perampanel in elderly Asians, its pharmacokinetics²⁹ and tolerability³⁰ have not been shown to be different between Asians and non-Asian

adults. The expert group advise special considerations, such as alternative dosing and titration strategies, in certain patients to minimize undesirable side effects.

Comorbidities

The expert group advises carefully evaluating patients' medical histories – especially for history of psychiatric or behavioral disorders in the patient or in their first-degree family members. In these patients, the lower perampanel starting dose of 1 mg/day should be considered. It is pertinent to employ a slow titration approach (no faster than 1 mg every 4 weeks) to prevent amplification of existing conditions or emergence of new psychiatric AEs. Physicians should educate caregivers on the importance of monitoring any sudden behavior change in these patients and when to consult a physician, and to bear in mind that patients should not discontinue treatment without their physician's advice.

From the expert group's clinical experience, focal seizures and myoclonic seizures often occur in patients with neurodegenerative conditions such as Alzheimer's disease. In patients with Alzheimer's disease, seizures can hasten cognitive decline.^{31–33} It is therefore essential to control seizures in these patients without compromising their cognitive function. As suggested by initial findings, perampanel may effectively control seizures and contribute to improvement of cognitive function.^{25,26} Consistent with published data,²⁵ the expert group suggests increasing the perampanel dose to 4 mg/day at an early stage, as long as it is tolerable in the patient and if the patient does not have comorbid psychiatric or behavioral disorders. It is also important to monitor for any behavior changes during the course of treatment.

Stroke is a leading cause of seizures and epilepsy in the elderly.³⁴ Perampanel is generally well tolerated when used to treat patients with epilepsy with vascular etiology in clinical practice.³⁵ In animal models, perampanel has been shown to improve cognitive impairment after cerebral ischemia and neurological outcomes following intracerebral hemorrhage, and exert neuroprotective effects against experimental ischemic stroke.^{36,37} To date, there are no published data suggesting that similar effects of perampanel in human populations have been studied.

The expert group agreed that perampanel is an appropriate ASM in patients with cardiac comorbidities. As perampanel does not modulate sodium channels, it does not affect the cardiac conduction system.¹⁰ Additionally, perampanel is not an enzyme inducer and therefore does not decrease the plasma concentration of commonly used cardiovascular drugs.^{9,10}

In elderly patients with mild renal impairment, titration should be carried out slowly – increasing the dose no more than once every 3 or 4 weeks – and patient response should be closely monitored. In patients with severe renal dysfunction, as well as those undergoing hemodialysis or with compromised hepatic clearance capability, consider excluding perampanel as a treatment option.

Concomitant Medications

It is common for elderly patients to use several drugs to manage multiple comorbidities, which increases the risk of DDIs.³⁸ Perampanel is extensively metabolized in the liver and is therefore susceptible to interactions with cytochrome P450 substrates, although it does not affect the metabolism of co-administered drugs through enzyme induction or inhibition to a relevant extent.¹⁰ The expert group agreed that perampanel has a low potential for DDIs of clinical significance; such DDIs, if any, do not affect the tolerability of the drug. However, enzyme-inducing ASMs may reduce the plasma level of perampanel as they promote the metabolism of concomitant ASMs.³⁹ In patients on concomitant enzyme inducers, higher starting and maintenance doses of perampanel may be considered. The expert group advises close monitoring of these patients for clinical response and tolerability.

Perampanel's unique mechanism of action, which is complementary to other ASMs,⁴⁰ makes it suitable for adjunct or combination therapy. Population pharmacokinetic analysis showed that perampanel has no clinically relevant impact on the clearance of most commonly used concomitant ASMs.⁴¹ While some physicians may be cautious about adding perampanel to levetiracetam, a study has found that concomitant use of the two drugs does not amplify or result in additional psychiatric AEs in elderly patients.²⁰

Strategies to Manage AEs and Maximize Tolerability in the Elderly

At the point of initiation, patients and caregivers should be informed of common side effects of perampanel and how to manage them. They should also be educated about the correct way of taking perampanel once daily before bedtime to maximize

tolerability and minimize the impact of AEs. The once-daily dosing of perampanel²⁸ has the advantage of maximizing adherence, which is crucial in seizure control.^{10,42} Its long half-life can also reduce the impact of a missed dose.^{28,43}

It is not uncommon for perampanel-related AEs to occur during the early phase of treatment.⁴⁴ Patients should be reassured that these AEs can be effectively managed following their physician's advice and that they should not discontinue treatment without consulting their physician. In general, the risk of AEs can be minimized by adopting the “start low and go slow” approach: initiate perampanel at a low dose and titrate slowly to the necessary maintenance dose. If AEs occur during the titration period, downtitrate to the previous tolerated dose and uptitrate again at smaller increments than before; if the AE develops during the maintenance period, reduce perampanel dose until the AE resolves, and titrate slowly to an effective and tolerated maintenance dose again.

Falls

While falls have been reported to occur more frequently in elderly than adult patients on perampanel in clinical trials,¹⁷ real-world analyses have not found this to be the case.^{20,24} Such discrepancies could be explained by the high dosing (8–12 mg/day) and fast titration (daily dose uptitrated at 2 mg each week)¹⁷ that are characteristic of the clinical trials.²⁰ This underpins the importance of the “start low and go slow” strategy for elderly patients.

Somnolence and Sleep Disorders

In the expert group's clinical practices, somnolence is the most common AE with perampanel in the elderly. The expert group suggests that somnolence can be mitigated by taking perampanel shortly before bedtime, as indicated.

Poor sleep quality negatively affects daily cognitive function and quality of life (QoL) in patients with epilepsy, which could worsen seizure control.⁴⁵ Perampanel's favorable effect on sleep architecture without worsening daytime sleepiness,⁴⁵ coupled with its indication to be taken before bedtime,²⁸ is likely to benefit patients who suffer from sleep disorders.^{16,45,46}

Cognitive AEs

Compromised cognitive function is a common effect associated with some ASMs^{9,10,13,27} and cognitive deficits may negatively affect patients' QoL,^{47,48} which may in turn lead to treatment discontinuation. Although published data in this regard are lacking in elderly patients, evidence in adults has shown that the drug is not associated with significant cognitive AEs.^{49,50} The expert group found this favorable cognitive profile in elderly patients to be consistent with the general adult population based on their clinical experience. Management of cognitive AEs is the same as other AEs, as aforementioned.

Psychiatric AEs and Aggression

It is of particular importance to proactively monitor for psychiatric AEs and altered behavior, especially aggression, in the early phases of perampanel initiation. In the expert group's clinical practices, development of aggression as a side effect is most likely to lead elderly patients to discontinue the drug. Management of psychiatric AEs and aggression is the same as other AEs, and withdrawal of perampanel may be considered based on the physician's judgment.

Conclusion

The elderly represents a unique patient population that calls for special management considerations. When it comes to ASM choice in the elderly, safety profile and ease of use are important to increase adherence and tolerability. This expert group agreed that perampanel is a viable therapeutic option in the elderly and recommend several practical strategies for clinicians across Asia to implement into their clinical practice when managing epilepsy in this patient population. It is agreed that perampanel is suitable in a variety of clinical settings and has broad-spectrum efficacy in different seizure types and epilepsy syndromes, as well as in patients with various comorbidities. Additionally, perampanel has low potential for clinically significant DDIs and a favorable safety and tolerability profile. Careful dosing titration and monitoring of AEs are essential to enhancing tolerability. Most importantly, a “start low and go slow” approach is recommended for treatment initiation and titration to ensure adherence and success of therapy.

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