

MINI-REVIEW

Once-daily antiseizure therapy: Historical development and practical optimization

Kheng-Seang Lim^{1*}, Hui-Yin Yow², and Si-Lei Fong¹¹Division of Neurology, Department of Medicine, Faculty of Medicine, Universiti Malaya, Kuala Lumpur, Malaysia²Department of Pharmaceutical Life Sciences, Faculty of Pharmacy, Universiti Malaya, Kuala Lumpur, Malaysia

Abstract

Once-daily antiseizure medication (ASM) regimens improve adherence and reduce treatment burden. This review summarizes the historical development of once-daily ASM therapy, outlined key pharmacokinetic determinants for once-daily dosing, and proposed practical recommendations for once-daily regimens in routine epilepsy care. Based on pharmacokinetic studies, randomized and observational clinical trials, and expert consensus, the once-daily formulations of commonly used ASMs included older ASMs such as phenobarbital and phenytoin, and the newer generations including zonisamide, perampanel, and cenobamate. In recent years, extended-release (ER) or controlled-release (CR) formulations were produced, e.g., valproate ER, levetiracetam ER, carbamazepine CR, and topiramate ER. Older ASMs such as phenobarbital and phenytoin permit once-daily dosing by virtue of long elimination half-lives but are limited by narrow therapeutic range, extensive drug–drug interactions, and toxicity. Newer long-acting agents (zonisamide, perampanel, cenobamate) and ER or CR formulations of established ASMs achieve more stable 24-hour exposure and smoother peak–trough pharmacokinetics. The once-daily regimen is associated with better adherence, which may in turn support improved seizure control. Bedtime administration with peak concentrations during sleep suited patients with predominantly nocturnal or early-morning seizures. However, cost and limited availability of newer agents and ER formulations in many lower- and middle-income countries restricted their use despite clear clinical advantages. Once-daily dosing of ASMs is important to enhance adherence, which may help improve seizure control in selected patients. Clinicians should prioritize once-daily monotherapy where feasible, titrate these ASMs slowly, incorporate therapeutic drug monitoring for narrow-index drugs, and provide clear counselling on missed doses and behavioral adverse effects.

***Corresponding author:**Kheng-Seang Lim
(kslimum@gmail.com)

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1. Introduction

Once-daily antiseizure medication (ASM) regimens offer a pragmatic way to improve adherence, reduce treatment burden, and align drug exposure with nocturnal seizure patterns in selected patients with epilepsy. Newer once-daily ASMs and

extended-release (ER) formulations provide more favorable pharmacokinetics and tolerability than older agents, but careful titration, timing, and patient selection remain crucial to maximize benefits and minimize harm.^{1,2}

Epilepsy requires long-term, often lifelong, pharmacotherapy, and suboptimal adherence to ASMs is a major cause of breakthrough seizures, emergency visits, and reduced quality of life. Increasing dosing frequency is consistently associated with lower adherence, which has driven interest in simplified once-daily regimens where pharmacologically appropriate. Once-daily dosing can be particularly attractive when scheduled at night, potentially minimizing daytime somnolence and leveraging sedative properties to improve sleep in patients with insomnia or sleep deprivation.²⁻⁵

In addition to convenience, once-daily dosing at night may optimize seizure control in patients with predominantly nocturnal and early-morning seizures by aligning peak ASM concentrations with the period of greatest seizure risk. However, not all ASMs are suitable for once-daily use, and pharmacokinetic, pharmacodynamic, and safety considerations must guide the selection of drugs and formulations for once-daily therapy.^{3,6,7}

Therefore, this review consolidates the historical narrative of once-daily ASM therapy, tracing its evolution from early long half-life agents (phenobarbital, phenytoin) through extended- or controlled-release reformulations of established ASMs to purpose-designed, inherently long-acting newer-generation agents (zonisamide, perampanel, cenobamate), within a single, integrated timeline. It proposes an explicit pharmacokinetics-adherence-outcome framework, linking dosing-frequency pharmacokinetics to medication adherence, seizure control and healthcare utilization, and highlights chronotherapeutic bedtime dosing for nocturnal or early-morning seizures. It also discusses cost and availability barriers in low- and middle-income countries, and translates the evidence into practical recommendations for clinical practice. The conceptual framework and the relationship among its components are depicted in [Figure 1](#).

This narrative review was conducted by identifying the relevant literature from PubMed and Scopus since database inception to January 2026, using combinations of the search terms “once-daily,” “extended-release,” “antiseizure medication,” “pharmacokinetics,” “epilepsy,” “adherence,” and “clinical implications,” together with individual antiseizure medications (e.g., phenobarbital, phenytoin, zonisamide, perampanel, cenobamate, valproate, levetiracetam, carbamazepine, topiramate). Searches were restricted to English-language publications involving adult populations. Reference lists of relevant articles were also

hand-searched to identify additional sources. Given the narrative nature of this review, no formal quality appraisal or risk-of-bias tool was applied to the included literature. Selection and synthesis were based on the authors’ clinical and pharmacological expertise and the relevance of each source to the review’s objectives.

2. Historical evolution of once-daily antiseizure medications

The evolution of once-daily ASMs reflects broader advances in pharmacology, drug formulation, and an increasing emphasis on patient-centered epilepsy care. Early ASM therapy, beginning in the 20th century, relied heavily on drugs with long half-lives, such as phenobarbital and phenytoin, which permitted once- or twice-daily dosing but were limited by significant adverse-effect burdens, including ataxia, cognitive impairment, gingival hypertrophy, acne, hirsutism, and osteoporosis.^{7,8}

Mid-20th-century ASM development prioritized seizure suppression over dosing convenience. First-generation ASMs, including carbamazepine and valproic acid, were effective, but typically required two or three daily doses due to relatively short half-lives, peak-related adverse effects, autoinduction, and interindividual pharmacokinetic variability.^{7,8} At this stage, once-daily administration was uncommon and generally limited to selected patients receiving drugs with longer half-lives or lower seizure risk profiles.

A significant shift occurred in the late-20th and early 21st centuries with the recognition that complex dosing regimens contributed to poor adherence and breakthrough seizures. Studies increasingly demonstrated that non-adherence was a major, yet modifiable, cause of treatment failure in epilepsy.⁹⁻¹¹ This insight coincided with advances in clinical pharmacokinetics, enabling better characterization of concentration–response relationships and supporting rational dose optimization.

The introduction of ER and controlled-release (CR) formulations in the 1990s and early 2000s represented a major milestone in the evolution of OD ASMs. Carbamazepine ER and valproate ER formulations were among the earliest examples, designed to smooth peak-trough fluctuations and allow once- or twice-daily dosing with fewer concentration-related adverse effects.^{12,13}

More recently, development of newer generation ASMs with inherently long half-lives and favorable safety profiles, including zonisamide, perampanel, and cenobamate, has further expanded the once-daily therapeutic landscape.^{3,14-16} ER or XR formulations of levetiracetam and topiramate can also be given once daily, although availability and cost

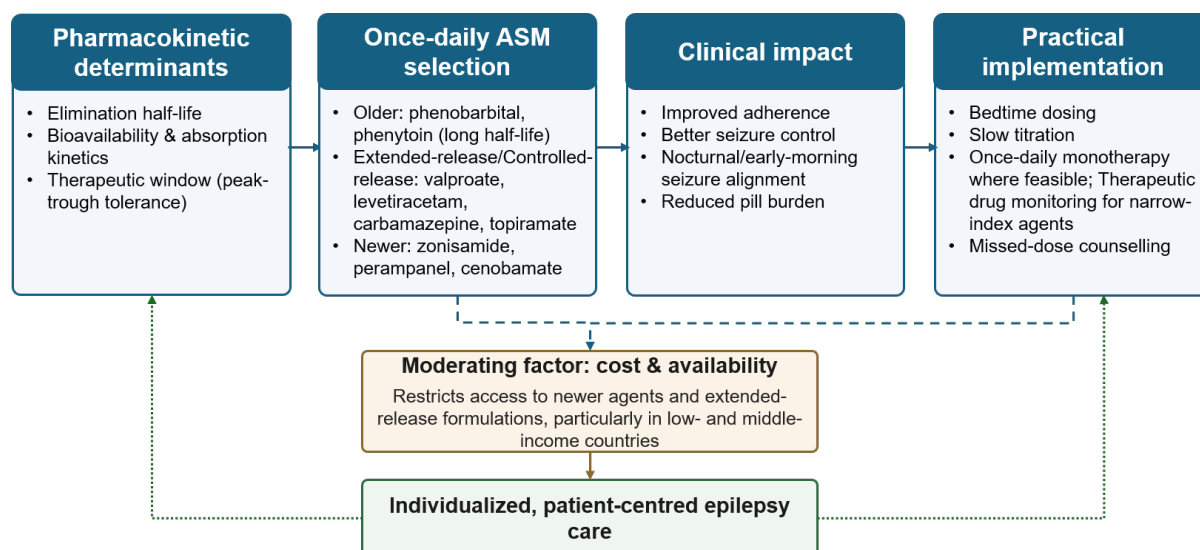


Figure 1. Conceptual framework for once-daily antiseizure medication therapy, showing the relationships between pharmacokinetic determinants, agent selection, clinical impact, practical implementation, and the moderating influence of cost and availability on individualized, patient-centered epilepsy care. Dashed arrows: cost and availability moderate agent access. Dotted arrows: individualized outcomes feedback into ongoing agent choice and titration.

vary by region.^{4,17,18} These formulation-driven innovations marked a transition from purely pharmacodynamic drug development to an integrated pharmacokinetic-patient-centered approach.

3. Pharmacokinetic rationale for once-daily dosing

The feasibility of once-daily dosing for ASMs is fundamentally determined by their pharmacokinetic properties, which govern systemic drug exposure over a 24-hour dosing interval. Key parameters influencing suitability for once-daily administration include elimination half-life, absorption kinetics, formulation characteristics, protein binding, metabolic pathways, and interindividual variability. An optimal once-daily ASM maintains plasma concentrations within the therapeutic window throughout the dosing interval while minimizing peak-related toxicity and trough-related loss of seizure protection.¹⁹

Key pharmacokinetic determinants influencing once-daily suitability include:

- Elimination half-life at least approaching or exceeding 24 h (or effectively prolonged by ER technology), ensuring sustained plasma levels across the dosing interval.^{3,14-16}
- Predictable absorption and high oral bioavailability, minimizing variability in exposure with once-daily administration.^{14,15,20}
- A therapeutic window that tolerates modest peak-

trough fluctuations without compromising efficacy or safety.³

Beyond mechanistic considerations, pharmacokinetics intersects directly with medication adherence. Simplified dosing regimens reduce treatment complexity and cognitive burden, which have been consistently associated with improved adherence across chronic diseases, including epilepsy.²¹ Thus, pharmacokinetic suitability for once-daily dosing enables technical feasibility and, by supporting adherence, may plausibly contribute to sustained treatment persistence and indirectly, long-term seizure control.

4. Once-daily ASMs: Examples of older versus newer ASMs

Once-daily ASMs have emerged through two distinct but overlapping developmental pathways. Older ASMs achieved once-daily dosing primarily due to intrinsically long elimination half-lives, whereas newer ASMs increasingly incorporate pharmacokinetic optimization and formulation strategies during drug development to support simplified dosing. Understanding these differences provides important insight into the evolution of epilepsy pharmacotherapy and informs rational ASM selection (Table 1).

4.1. Phenobarbital

Phenobarbital has a terminal half-life typically exceeding 90 h in adults and augments inhibitory neurotransmission by prolonging GABA_A receptor-mediated chloride

Table 1. Key pharmacokinetic parameters of older and newer once-daily antiseizure medications

ASM	$t_{1/2}$ (h)	Bioavailability (%)	Peak concentration (hours)	Comment	Ref.
Older generation					
Phenobarbital	90	>90	0.5–4.0	Very long half-life; extensive tissue distribution; autoinduction; limited by sedation and drug interactions	7,8
Phenytoin	24	85–90	5–7	Long half-life; nonlinear kinetics; autoinduction; limited dose-related and long-term toxicity and drug interactions	7,8
Newer generation					
Zonisamide	50–68	>90	2–6	Long half-life; limited by risk of acute kidney injury	7,8,22
Perampanel	70–110	100	0.5–3	Very long half-life; limited by dose-related psychiatric adverse effects	7,8
Cenobamate	50–60	88	1–4	Long half-life; limited by serious adverse effects and drug interactions	7,8

Abbreviations: ASM: Antiseizure medication; $t_{1/2}$: Elimination half-life.

channel opening.^{7,8} This long half-life readily supports once-daily dosing as it allows for sustained plasma concentrations over a prolonged interval, often as a nightly dose, and has made phenobarbital a mainstay treatment in resource-limited settings. However, chronic use of phenobarbital is associated with sedation, cognitive slowing, behavioral changes, and osteoporosis, along with potent cytochrome P450 induction that drives significant drug-drug interactions.^{23,24}

Given these limitations, once-daily phenobarbital is now rarely used as first-line therapy in high-income settings but remains important where cost and availability constrain options, with careful monitoring of cognition, mood, bone health, and interacting medications.²⁵ Therapeutic drug monitoring (TDM) is useful to ensure trough levels remain within the therapeutic range when employing once-daily regimens.²⁴

4.2. Phenytoin

Phenytoin blocks voltage-gated sodium channels and exhibits nonlinear (Michaelis–Menten) pharmacokinetics, with saturable hepatic metabolism leading to disproportionate increases in serum concentration with small dose increments.^{7,8} While its effective half-life allows once- or twice-daily dosing in some patients, the narrow therapeutic index and risk of dose-related neurotoxicity (ataxia, nystagmus, encephalopathy) of phenytoin make once-daily dosing challenging without close TDM.^{7,8,19,24}

Long-term phenytoin use is associated with gingival hypertrophy, hirsutism, peripheral neuropathy, and osteoporosis, which have driven a shift toward newer ASMs for chronic therapy.⁷ When used, consolidation to once-daily dosing is generally reserved for stable patients with well-characterized pharmacokinetics, using trough levels to balance seizure protection and toxicity risk.⁷

4.3. Zonisamide

Zonisamide is a sulfonamide derivative that blocks voltage-gated sodium channels and T-type calcium channels and has weak carbonic anhydrase inhibitory activity, providing broad-spectrum antiepileptic effects. It has high oral bioavailability (>90%), a time to peak concentration of 2–6 h, and a long elimination half-life of around 60 h in monotherapy, all of which support once-daily dosing.⁷ Steady state is reached in approximately 2 weeks, and the drug is primarily cleared via CYP3A4 metabolism and renal excretion.^{14,20}

Clinical studies demonstrate that zonisamide is effective as adjunctive therapy and as once-daily monotherapy for partial-onset seizures, with a tolerability profile characterized mainly by somnolence, dizziness, and weight loss.²⁶ Once-daily dosing of zonisamide may improve adherence, but careful titration and monitoring for metabolic acidosis and kidney stones are recommended, particularly in patients with pre-existing renal disease or concomitant carbonic anhydrase inhibitors.²²

4.4. Perampanel

Perampanel is a selective, non-competitive AMPA glutamatergic receptor antagonist with a long effective half-life of approximately 70–110 h, permitting once-nightly dosing.^{7,8} It is approved as adjunctive therapy for focal-onset seizures and primary generalized tonic-clonic seizures, with gradual weekly titration recommended to limit dizziness, somnolence, and gait disturbance.²⁷ Because of its prolonged half-life, missed doses may have less abrupt impact on seizure control than with short-acting ASMs, but adverse effects can also persist longer.^{15,28}

A key concern with perampanel is dose-related psychiatric and behavioral adverse events, including irritability, aggression, hostility, and mood changes, which require proactive screening and ongoing monitoring.^{29,30} Once-nightly dosing of perampanel may attenuate subjective dizziness and somnolence during daytime, but clinicians must counsel patients and caregivers about behavioral warning signs and consider lower target doses in individuals with psychiatric comorbidities.²⁷

4.5. Cenobamate

Cenobamate is a newer ASM indicated for focal-onset seizures in adults, associated with a dual mechanism involving preferential inhibition of persistent sodium currents and positive allosteric modulation of GABA_A receptors at a non-benzodiazepine site.¹⁶ It exhibits high oral bioavailability, an elimination half-life around 50–60 h, and is typically administered as a once-daily evening dose, titrated very slowly from 12.5 mg once daily to a usual maintenance dose of 200 mg once daily, with a maximum of 400 mg once daily in selected patients.^{7,8,16} A recent systematic review reported the promising efficacy of cenobamate, with over half of patients achieving $\geq 50\%$ seizure reduction and meaningful seizure-free rates even in drug-resistant epilepsy.³¹ However, serious adverse events, including drug reaction with eosinophilia and systemic symptoms (DRESS) and central nervous system adverse effects, necessitate slow titration and careful monitoring, particularly when combined with other ASMs that share metabolic pathways or sedative properties.³² Cenobamate is a CYP2C19 inhibitor and an inducer of CYP3A4 and CYP2B6, thereby increasing the potential for clinically significant drug–drug interactions.³² Expert consensus recommends pre-emptive dose reduction of concomitant clobazam, phenytoin, carbamazepine, and other ASMs during cenobamate titration to reduce risks of excessive sedation and ataxia in once-daily regimens.³³

4.6. Other once-daily and extended-released options

Extended-release (ER) formulations extend the once-daily paradigm to widely used ASMs that otherwise require multiple daily doses:

- Valproate ER/divalproex ER: ER valproate reduces peak–trough variability and can often be given once daily while maintaining comparable seizure control in generalized epilepsies, though careful dose adjustment and TDM remain important.^{13,34}
- Levetiracetam XR/ER: Once-daily extended-release levetiracetam shows similar efficacy to immediate-release divided dosing, with improved patient satisfaction and self-reported adherence in adolescents and adults switched from multiple daily doses.^{17,35,36}
- Carbamazepine CR: CR formulations permit once- or twice-daily dosing with smoother concentration profiles and reduced peak-related adverse effects, although twice-daily regimens are still common in practice.^{13,37}
- Topiramate ER: ER topiramate allows once-daily dosing with reduced paresthesia and cognitive adverse effects compared with immediate-release twice-daily regimens, offering another option for simplified therapy where available.^{4,38}

The evolution from older to newer once-daily ASMs reflects a fundamental shift in epilepsy drug development. Earlier agents achieved once-daily dosing primarily through extended half-lives but were constrained by narrow therapeutic indices and tolerability concerns. By contrast, newer ASMs are designed with favorable pharmacokinetic properties, linear dose-exposure relationships, reduced drug–drug interaction potential, and adherence-supportive dosing strategies from the outset of development. Importantly, newer once-daily ASMs align more closely with patient-centered epilepsy care, where regimen simplicity is recognized as a key driver of adherence and improved clinical outcomes.^{2,3}

5. Clinical implications and recommendations

5.1. Adherence and drug-dosing regimen

A systematic review published in 2001 demonstrated a clear inverse relationship between dosing frequency and medication adherence, with mean dose-taking compliance of 79% for once-daily regimens, declining to 69% for twice-daily and 51% for four-times-daily regimens.³⁹ More than a

decade later, this challenge persists. A recent meta-analysis reported that the pooled prevalence of adherence to ASM in India was only 49.9%.⁴⁰ Forgetfulness remains the most commonly reported barrier, affecting 48.2%–72.5% of people with epilepsy.^{41,42} Complex treatment regimens and multiple daily dosing schedules are consistently identified as major contributors to poor adherence.⁴⁰

Switching to ER formulations has been significantly associated with improved adherence.¹ Similar benefits have been observed when patients were switched from conventional-release to extended-release valproate, with acceptable medication compliance supporting long-term maintenance therapy in this chronic condition.⁴³ ER levetiracetam further exemplifies this principle: adolescents transitioned from twice-daily immediate-release to once-daily ER formulations reported higher satisfaction and perceived better adherence, while seizure control remained comparable.³⁶

5.2. Adherence and seizure control/outcome

Non-adherence is associated with poorer seizure control and higher healthcare costs, due to the increased rates of breakthrough seizures and hospitalization.^{44,45} This relationship is supported by clinical trial data showing that once-daily extended-release levetiracetam (LEV-XR), used as adjunctive therapy, significantly reduced partial-onset seizure frequency compared with placebo, achieving a 43% responder rate ($\geq 50\%$ seizure reduction).³⁵ This trial demonstrates the efficacy of the once-daily ER formulation compared with placebo, rather than a head-to-head comparison with an equivalent divided-dose regimen; direct evidence that once-daily dosing itself confers a seizure-control advantage over comparable multiple-daily-dose regimens remains limited. Any such benefit more plausibly reflects the improved adherence associated with simplified dosing rather than a direct pharmacodynamic effect of dosing frequency. Once-daily regimens may therefore improve seizure control by supporting adherence, rather than through a direct comparative advantage over equivalent divided-dose regimens.

For a given total daily dose and appropriate pharmacokinetic profile, simplifying dosing to once- or twice-daily schedules generally improves adherence, which may in turn reduce the risk of breakthrough seizures. Direct comparative evidence that reduced dosing frequency itself lowers seizure risk, independent of its effect on adherence, remains limited, and this potential benefit must be balanced against individual drug half-life and plasma concentration fluctuations. Beyond measurable adherence, once-daily regimens could also reduce pill burden and the

psychological impact of frequent medication reminders, which is particularly relevant for patients who are otherwise well and striving to maintain normal daily functioning.

5.3. Nocturnal and early-morning seizures, insomnia, and dose timing

Patients whose seizures cluster during sleep or early morning may benefit disproportionately from once-daily bedtime dosing. Night-time administration of long-acting ASMs or ER formulations can align peak plasma concentrations with the highest seizure risk interval while reducing daytime sedation, an approach consistent with chronotherapeutic strategies. Studies of once-nightly levetiracetam, for example, suggest that such regimens can maintain seizure control and improve convenience, though careful patient selection and follow-up are required.^{6,46}

For patients with co-existent insomnia or sleep deprivation, the sedative properties of certain ASMs, including phenobarbital, some benzodiazepines, and potentially perampanel or cenobamate in early titration, may confer additional benefit when administered at night.^{47,48} Clinicians must, however, balance these potential hypnotic advantages against the risk of morning “hangover,” impaired alertness, and falls, especially in older adults or those with comorbid sleep-disordered breathing.

5.4. Economic and availability constraints of once-daily ASM regimens

Although once-daily dosing of ASMs offers advantages in terms of adherence, which may in turn support improved seizure control, these benefits are often offset by cost and accessibility barriers. ER and once-daily formulations are typically more expensive than their immediate-release counterparts, limiting their affordability for many patients. In most lower- or middle-income countries, these formulations may be unavailable or unaffordable, restricting their use despite clear clinical advantages.⁴⁹ Among newer ASMs, zonisamide is relatively more affordable in these countries. Perampanel is available but remains unaffordable, while cenobamate, despite its promising efficacy, is not available in these countries.

As a result, the potential population-level benefits of simplified dosing regimens are not fully realized, underscoring the need to balance therapeutic optimization with cost-effectiveness and equitable access to care.

6. Practical titration and TDM recommendations

The key practical points from the outline can be synthesized into several recommendations. As no single dosing strategy suits every patient, these recommendations

should be individualized according to seizure pattern, pharmacokinetic characteristics, patient age, comorbidities, pregnancy potential, and concomitant medications:

- Consider bedtime dosing for once-daily ASMs where clinically appropriate: For patients whose seizures cluster nocturnally or in the early morning, or who experience troublesome daytime sedation, bedtime administration of once-daily ASMs may help align peak drug exposure with periods of greatest seizure vulnerability and reduce waking-hours adverse effects. Bedtime dosing is not, however, universally preferable: ASMs with pronounced next-morning sedation, patients with predominantly diurnal seizures, and those with shift-work schedules or early-morning cognitive demands may be better served by morning or split-timing administration. The optimal timing of once-daily dosing should therefore be individualized.
- Titrate slowly and start low: For long-acting or interaction-prone agents such as perampanel and cenobamate, initiate at low doses and titrate slowly, lengthening titration intervals if patients experience early-morning sleepiness or other central nervous system (CNS) adverse effects.
- Use once-daily monotherapy when feasible: Monotherapy with an once-daily ASM simplifies treatment, improves adherence and reduces drug-drug interactions. This approach is particularly suitable for focal epilepsy responsive to drugs like zonisamide or cenobamate, or in generalized epilepsies treated with valproate ER.
- Implement TDM for narrow-index drugs: For phenobarbital, phenytoin, valproate, and carbamazepine, TDM is valuable when consolidating to once-daily dosing or when adding interacting agents, to ensure trough concentrations remain therapeutic without excessive peaks.
- Adjust dosing when switching between immediate- and extended-release formulations: Immediate-release (IR) and ER formulations of the same ASM are not always bioequivalent on a milligram-for-milligram basis, and switching between them can alter peak concentration, trough concentration, and total daily exposure.⁵⁰ Conversion should follow product-specific labelling where available. Clinicians should anticipate a period of re-titration after any IR-ER switch and monitor for both loss of efficacy and new adverse effects, with therapeutic drug monitoring where feasible.
- Provide clear missed-dose counselling: Patients on OD regimens should receive explicit, drug-specific guidance on missed-dose management, as the clinical consequence of a missed dose is not uniform across

ASMs. For ASMs with long elimination half-lives (e.g., phenobarbital, perampanel), a single missed dose is often buffered by residual drug levels, whereas for ASMs with shorter half-lives, a missed dose can produce a more pronounced trough and a higher risk of breakthrough seizures.⁵¹ As a general rule, the missed dose should be taken as soon as remembered unless it is close to the next scheduled dose, in which case it should be skipped rather than doubled; patients who miss multiple consecutive doses should contact their treating clinician.

- Address adherence barriers holistically: While once-daily dosing improves convenience, adherence is multifactorial. Education should include counselling on seizure triggers, medication timing, lifestyle factors, and the importance of uninterrupted therapy. In settings where TDM is unavailable, symptom-based monitoring and seizure diaries remain essential tools.
- Anticipate drug-specific adverse effects: While most ASMs have the potential to cause sedation and fatigue, individual once-daily ASMs carry distinct adverse-effect profiles that should inform agent selection and monitoring.⁷ For example, perampanel is associated with irritability, aggression and mood alterations; phenytoin has a narrow therapeutic index with non-linear elimination kinetics that predisposes to toxicity at higher doses, including nystagmus, diplopia and ataxia. Monitoring should be tailored to the specific agent rather than assuming a uniform safety profile across once-daily ASMs.

The recommendations above require further modification in several vulnerable groups, in whom pharmacokinetic handling, tolerability, and risk-benefit balance differ from the general adult population:

- Older adults: Age-related declines in renal and hepatic clearance, reduced serum albumin, and polypharmacy increase the risk of drug accumulation and interactions.⁵² Lower starting doses, slower titration, and closer monitoring for sedation, cognitive impairment, and falls are advisable; bedtime dosing should be reconsidered where next-morning sedation or nocturnal falls risk is a concern.
- Renal and hepatic impairment: ASMs that are predominantly hepatically metabolized (e.g., valproate, carbamazepine, phenytoin) or eliminated by both hepatic and renal excretion (e.g., perampanel, phenobarbital, topiramate and zonisamide) may require dose reduction or altered dosing intervals in organ impairment.⁵³ Once-daily regimens should not be assumed to be equally suitable across all agents in this context, and product-specific dose-adjustment guidance should be followed.

- Pregnancy and pregnancy potential: Pregnancy-related pharmacokinetic changes, including increased clearance and volume of distribution, can reduce trough concentrations and increase breakthrough-seizure risk with once-daily dosing.⁵⁴ Dose adjustments with close monitoring are required during pregnancy to maintain stable plasma levels. Teratogenicity considerations, particularly for valproate, should also guide agent selection in individuals of childbearing potential, independent of dosing frequency.⁵⁵
- Children: Weight-based dosing, pharmacokinetic variability, and formulation availability limit the applicability of adult once-daily strategies.⁵⁶ Adherence support should also account for caregiver- and school-administration logistics rather than patient self-administration alone.

7. Conclusion

Once-daily dosing of ASMs, particularly with night-time administration, represents an important strategy to improve adherence, convenience, and alignment of drug exposure with seizure risk in appropriately selected patients with epilepsy. Long-acting ASMs such as zonisamide, perampanel, and cenobamate, alongside ER formulations of established agents including valproate and levetiracetam, provide multiple options for once-daily monotherapy or simplified regimens, provided that titration is slow, TDM is used where appropriate, and interactions and adverse effects are carefully managed. For patients with predominant nocturnal or early-morning seizures or difficulties adhering to complex regimens, Once-daily ASM therapy can offer substantial clinical and quality-of-life benefits, underscoring the need to systematically consider dosing frequency as part of individualized epilepsy care.

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Writing—original draft: Kheng-Seang Lim

Writing—review & editing: Hui-Yin Yow, Si-Lei Fong

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