



Review

Clinical practice guidelines for the administration of third-generation anti-seizure medications

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ABSTRACT

Purpose: This guideline evaluated previous clinical studies that examined the use of third-generation antiseizure medications (ASMs) to treat epilepsy in order to provide treatment recommendations from a clinical practice perspective, thus aiming to enhance clinicians' understanding of these drugs and improve the standardization of clinical treatment.

Methods: A systematic literature search was conducted to identify studies that examined third-generation ASMs. The included literature was rated using the 2011 Oxford Centre for Evidence-based Medicine (OCEBM) levels of

Abbreviations: AAN, American Academy of Neurology; AE, adverse event; AES, American Epilepsy Society; AGREE II, Appraisal of Guidelines for Research and Evaluation II; AMPA, α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; ASMs, anti-seizure medications; AUC, area under the curve; BRV, brivaracetam; BTRE, brain tumour-related epilepsy; CAAE, China Association Against Epilepsy; CBD, cannabidiol; CBZ, carbamazepine; CLcr, creatinine clearance; CNB, cenobamate; CNKI, China National Knowledge Infrastructure; Dress, drug reaction with eosinophilia and systemic symptoms; DS, Dravet syndrome; ECG, electrocardiogram; eGFR, estimated glomerular filtration rate; ENT1, equilibrative nucleoside transporter 1; ESL, eslicarbazepine; FDA, Food and Drug Administration; 5-HT₂, 5-hydroxytryptamine receptor 2A; FFA, fenfluramine; GABA, γ -aminobutyric acid; GPR55, G protein-coupled receptor 55; GTCS, generalized tonic-clonic seizures; IGE, idiopathic generalized epilepsy; IOM, Institute of Medicine; JME, juvenile myoclonic epilepsy; KCNQ, potassium voltage-gated channel subfamily Q; LCM, lacosamide; LGS, Lennox-Gastaut syndrome; mTOR, mammalian target of rapamycin; OCEBM, Oxford Centre for Evidence-Based Medicine; PER, perampanel; PGB, pregabalin; PREPARE, Practice guideline REgistration for transPAREncy; PTE, posttraumatic epilepsy; QD, once daily; RCT, randomized controlled trials; RIGHT, Reporting Items for Practice Guidelines in Healthcare; RFN, rufinamide; SeLECTS, self-limited epilepsy with centrotemporal spikes; STP, stiripentol; TRPV1, transient receptor potential vanilloid subfamily member 1; TSC, tuberous sclerosis complex.

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evidence, and recommendations were formulated. The strength of the recommendations was determined based on the evidence level and drug safety profiles.

Results: This guideline examines 10 third-generation ASMs: pregabalin (PGB), rufamide (RFN), lacosamide (LCM), perampanel (PER), eslicarbazepine (ESL), brivaracetam (BRV), stripentol (STP), cannabidiol (CBD), cenobamate (CNB) and fenfluramine (FFA). Recommendations were developed for 13 clinical questions.

Conclusion: This guideline provides a detailed evaluation of the current evidence and treatment recommendations regarding third-generation ASMs. This guideline will help clinicians to better understand these medications and offer guidance for clinical practice.

1. Introduction

Epilepsy is one of the most common chronic neurological diseases; it affects approximately 50 million people worldwide, with over 4 million new cases annually. In China, the prevalence of epilepsy ranges from approximately 4‰–7‰; the prevalence of active epilepsy is 4.6‰; and the annual incidence of epilepsy is approximately 30 cases per 100,000 individuals [1,2].

Anti-seizure medications (ASMs) are the most important and fundamental treatment for epilepsy. Dozens of ASMs are currently available. Compared with first- and second-generation ASMs, third-generation ASMs have certain advantages in terms of efficacy and safety [3,4], with some third-generation ASMs showing breakthrough benefits for specific seizure types or epilepsy syndromes. In addition to ASMs, other medications have been found to exhibit antiseizure effects. Everolimus, a mammalian target of rapamycin (mTOR) inhibitor, has been approved by the Food and Drug Administration (FDA) for the treatment of seizures associated with the tuberous sclerosis complex (TSC) [5,6]. Everolimus is currently considered a disease-modifying therapy and is not classified as an ASM [7].

To assist clinicians in comprehensively understanding third-generation ASMs and offer guidance for clinical practice, an expert panel systematically searched and evaluated the literature. We referenced the latest guidelines and consensus, including the 2018 *Practice guideline update summary: Efficacy and tolerability of the new antiepileptic drugs* by the American Academy of Neurology (AAN) and American Epilepsy Society (AES) [8,9], the 2023 *Clinical Practice Guidelines: Epilepsy* by the China Association Against Epilepsy (CAAE) [1], and the 2025 *Chinese Expert consensus on use of Sodium Channel Blockers for the treatment of focal epilepsy* by the CAAE [10]. This guideline organizes and evaluates previous studies examining third-generation ASMs in the form of clinical questions and provides recommendations. Furthermore, this guideline focuses solely on discussing and recommending third-generation ASMs. Considering that first-, second-, and third-generation ASMs each have distinct characteristics and different degrees of clinical utility, individualized drug selection should comprehensively consider therapeutic evidence across all three generations.

2. Overview of third-generation ASMs

This guideline adopts the definition of third-generation ASMs from the 2023 CAAE *Clinical Practice Guidelines: Epilepsy*, supplemented by recent literature [1,3]. The third-generation ASMs included in this guideline are pregabalin (PGB), rufinamide (Banzel), lacosamide (LCM), perampanel (PER), eslicarbazepine (ESL), brivaracetam (BRV), stripentol (STP), cannabidiol (CBD), cenobamate (CNB), and fenfluramine (FFA). Table 1 summarizes the mechanisms of action for these 10 ASMs.

3. Guideline development methods

The expert panel comprises senior epileptologists and neurologists from leading tertiary hospitals across diverse regions of China, all of

whom are members of Neurophysician Branch of the Chinese Medical Doctor Association. This guideline was developed in accordance with the clinical practice guideline concepts of the American Institute of Medicine (IOM) and the development process and methodological standards outlined in the *WHO Handbook for Guideline Development*. Furthermore, this guideline references the Appraisal of Guidelines for Research and Evaluation II (AGREE II) instrument and follows the reporting standards of the Reporting Items for Practice Guidelines in Healthcare (RIGHT) statement for both its protocol and the final document. This guideline is registered on the Practice guideline REGistration for transPAREncy (PREPARE) platform (No. PREPARE-2025CN334). Furthermore, this guideline references the Appraisal of Guidelines for Research and Evaluation II (AGREE II) instrument and follows the reporting standards of the Reporting Items for Practice Guidelines in Healthcare (RIGHT) statement for both its protocol and the final document. This guideline is registered on the Practice guideline REGistration for transPAREncy (PREPARE) platform (No. PREPARE-2025CN334).

The PubMed, Web of Science, Embase, Cochrane Library, China National Knowledge Infrastructure (CNKI), and Wanfang Data Knowledge Service Platform databases were searched from inception to April 15, 2025, to identify studies that examined the included ASMs. The included studies were rated using the 2011 Oxford Centre for Evidence-Based Medicine (OCEBM) Levels of Evidence system (Table 2). All panel members reviewed titles and abstracts, and two experts independently assessed the full-text articles. Our systematic literature search identified 556 publications, from which 332 were excluded due to lack of relevance to the guideline scope. Consequently, 234 articles were ultimately included in the analysis.

Through literature review and interview with clinicians, the 13 clinical questions to be included in this guideline were confirmed at the online kick-off meeting held on May 22nd. During this meeting, the guideline development working group also delineated the scope of third-generation ASMs, which served as the foundation for subsequent evidence screening and recommendation drafting. The expert panel drafted preliminary recommendations based on evidence quality, benefit–risk balance of interventions, and values/preferences of the target population. The recommendation strength was determined by integrating evidence levels and drug safety profiles (Table 3). A favorable safety profile was defined through a comprehensive evaluation of multiple criteria, including a low incidence and severity of common adverse events, which was maintained in comparative meta-analyses showing no significant excess in adverse event rates relative to other ASMs, no identification of unique safety concerns in clinical trials, the absence of boxed warnings, a wide therapeutic index that minimizes toxicity risks.

During this phase, experts assessed the appropriateness of the statements, provided anonymous comments, and could propose additional recommendations based on clinical experience. The manuscript was subsequently revised according to this collective feedback. Following this, a face-to-face panel discussion was convened on June 13th where the working group reviewed the included articles, draft statements and the scope of third-generation ASMs, and experts clarified points, debated divergent viewpoints, and justified their positions. A first-round voting process was performed through an anonymous web-

Table 1

Third-generation ASMs and their mechanisms of action (ordered by FDA approval time) [11–14].

ASMs	Mechanism of Action
Pregabalin, PGB	An inhibitor of $\alpha 2\delta$ subunit-containing voltage-dependent calcium channels
Rufinamide, RFN	Increases the fast inactivation of voltage-gated Na^+ channels; stimulates Ca^{2+} -activated K^+ currents while inhibiting voltage-gated Na^+ currents
Lacosamide, LCM	Increases slow inactivation of voltage-gated Na^+ channels
Perampanel, PER	A selective noncompetitive antagonist of AMPA receptors
Eslicarbazepine, ESL	Increases fast inactivation voltage-gated Na^+ channels, and increases the slow inactivation of voltage-gated Na^+ channels
Brivaracetam, BRV	Binds to the SV2A protein, multiple ionic mechanism in electrically excitable cells including M-type K^+ current, large-conductance Ca^{2+} -activated K^+ channel and voltage-gated Na^+ current
Stiripentol, STP	Acts as a positive allosteric modulator of GABA A receptor and interferes with GABA reuptake and metabolism
Cannabidiol, CBD	Acts on G-protein coupled receptor GPR55, transient receptor potential cation channel TRPV1, voltage-gated sodium channels, and equilibrative nucleoside transporter 1 (ENT1)
Cenobamate, CNB	Inhibits persistent sodium currents (inap) and acts as a positive allosteric modulator of GABA A receptor
Fenfluramine, FFA	A serotonergic 5-HT2 receptor agonist and an $\sigma 1$ receptor antagonist

Abbreviations: AMPA, α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; ENT1, equilibrative nucleoside transporter 1; FDA, Food and Drug Administration; GABA, γ -aminobutyric acid; GPR55, G protein-coupled receptor 55; KCNQ, potassium voltage-gated channel subfamily Q; TRPV1, transient receptor potential vanilloid subfamily member 1; 5-HT2, 5-hydroxytryptamine receptor 2A.

Table 2

Levels of evidence.

Evidence Level*	Description
Class I	Systematic review of randomized controlled trials (RCTs)
Class II	RCTs or observational study with significant efficacy
Class III	Nonrandomized controlled cohort/follow-up study
Class IV	Case series, case–control study, or historically controlled study
Class V	Mechanism-based reasoning

* Evidence level may be downgraded owing to poor study quality, lack of rigor, indirectness (study design mismatch), inconsistency between studies, or very small absolute benefit. The evidence level may be increased because of the very large absolute benefit.

Table 3

Strength of recommendations.

Strength of recommendations	Definition	Evaluation criteria
Level A	Strong recommendation	Class I evidence with favourable safety profile
Level B	Moderate recommendation	Class II evidence with favourable safety profile or Class I evidence with safety considerations
Level C	Cautious recommendation	Class III evidence with favourable safety profile or Class II evidence with safety considerations
Level D	Restricted recommendation	Class IV evidence with favourable safety profile

*Recommendation strength may be downgraded if evidence suggests that efficacy is uncertain.

based questionnaire using a 5-point Likert scale. The agreement rate was defined as the proportion of panel members who scored the recommendation as a 4 ("agree") or 5 ("strongly agree"). After modification, the final expert recommendation statement on each clinical question was determined through a second-round formal anonymous web-based questionnaire. The technical roadmap for guideline development is

presented in Fig. 1.

4. Evidence analysis

Clinical Question 1: For adult patients with focal seizures, are these ASMs effective as add-on therapy in reducing seizure frequency?

PGB was examined in 5 Class I studies [15–19] and 7 Class II studies [20–26]. The findings indicated that PGB was effective as add-on therapy for adult patients with focal seizures. One Class II study showed that administering PGB at a dosage of 300 mg/d or 600 mg/d to adult patients with focal seizures as add-on therapy led to significantly higher treatment response rates than lamotrigine at dosages of 300 mg/d or 400 mg/d [25].

RFN was examined in 5 Class I studies [16,18,19,27,28] and 2 Class II studies [29,30]. The findings indicated that RFN was effective as add-on therapy for adult patients with focal seizures.

LCM was examined in 12 Class I studies [15,16,18,19,28,31–37] and 4 Class II studies [38–41]. The findings indicated that LCM was effective as add-on therapy for adult patients with focal seizures.

PER was examined in 14 Class I studies [15,18,19,28,34–37,42–47] and 4 Class II studies [48–51]. The findings indicated that PER was effective as add-on therapy for adult patients with focal seizures.

ESL was examined in 11 Class I studies [15,18,19,28,34–37,45,52,53] and 5 Class II studies [54–58]. The findings of the Class I studies indicated that ESL was effective as add-on therapy for adult patients with focal seizures. However, a Class II study revealed that the efficacy of ESL at a dosage of 800 mg/d was not significantly better than that of the placebo [55]. Once daily (QD) dosing was significantly more effective [58].

BRV was examined in 12 Class I studies [16,18,19,28,34–37,45,59–61] and 6 Class II studies [62–67]. The findings of the Class I studies indicated that BRV was effective as add-on therapy for adult patients with focal seizures. However, a Class II study revealed that the efficacy of BRV at a dosage of 50 mg/d was not significantly better than that of the placebo [66].

STP was examined in 1 Class III study [68]. The results indicated that STP might be effective as add-on therapy for adult patients with focal seizures.

CBD was examined in 1 Class II study [69]. The findings did not prove that CBD was effective as add-on therapy for adult patients with focal seizures [69].

CNB was examined in 10 Class I [19,28,34–37,61,70–72] and 3 Class II studies [73–75]. The findings indicated that CNB was effective as add-on therapy for adult patients with focal seizures.

Detailed descriptions of the abovementioned studies are shown in Appendix Table 1.

FFA has no relevant studies.

Recommendation: For add-on therapy in adults with focal seizures, PGB, RFN, LCM, PER, BRV, and CNB are recommended as preferred options (Level A). ESL may be selected as an alternative (Level B). STP may also be considered (Level C). (Agreement Rate: 100 %)

Clinical Question 2: For adult patients with focal seizures, are these ASMs effective as monotherapy in reducing seizure frequency?

PGB was examined in 2 Class II studies [76,77] and 1 Class III study [78]. The findings of the Class II studies indicated that PGB was inferior to lamotrigine as monotherapy for adult patients with focal seizures. One Class III study showed that PGB might be effective as monotherapy for adult patients with focal seizures [78].

LCM was examined in 1 Class I study [79] and 1 Class II study [80]. The Class I study revealed that the seizure-free rate in newly diagnosed epilepsy patients who received LCM as monotherapy was not significantly different from that of the carbamazepine (CBZ), levetiracetam, zonisamide or ESL monotherapy groups. The discontinuation rate of LCM is significantly lower than that of CBZ [79]. A class II study

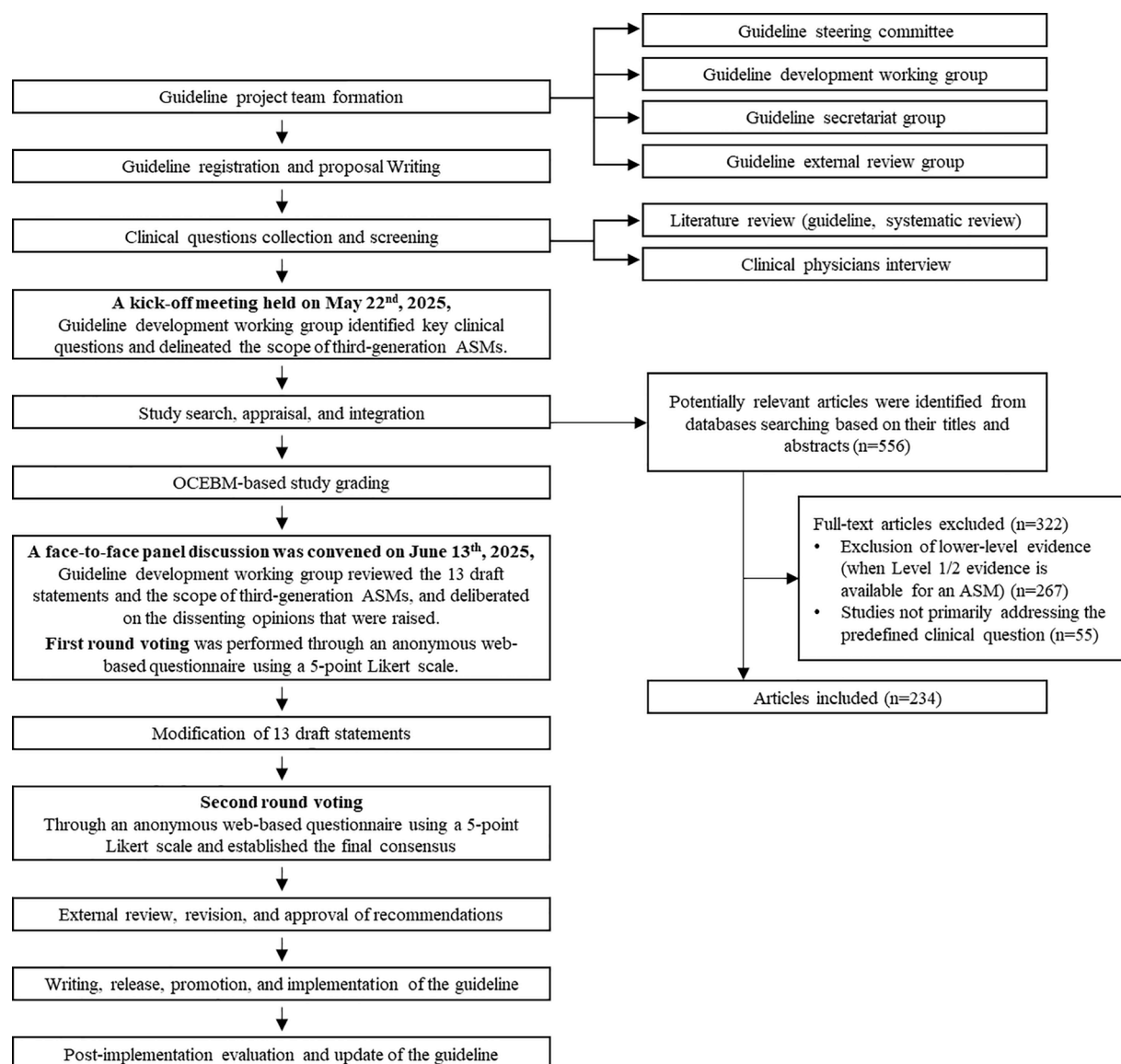


Fig. 1. Technical roadmap for guideline development.

revealed that the seizure-free rate of LCM at a dosage of 200–600 mg/d was noninferior to that of CBZ at a dosage of 400–1200 mg/d [80].

PER was examined in 3 Class III studies [81–83]. The findings indicated that PER might be effective as monotherapy for adult patients with focal seizures.

ESL was examined in 1 Class I study [79] and 1 Class II study [84]. The findings indicated that ESL was effective as monotherapy for adult patients with focal seizures. The Class II study revealed that the seizure-free rate of ESL at a dosage of 800–1600 mg/d was noninferior to that of CBZ at a dosage of 200–600 mg/d.

BRV was examined in 2 Class III studies [85,86]. The findings indicated that BRV might be effective as monotherapy for adult patients with focal seizures.

CNB was examined in 2 Class III studies [87,88]. The findings indicated that CNB might be effective as monotherapy for adult patients with focal seizures.

Detailed descriptions of the abovementioned studies are shown in Appendix Table 2.

RFN, STP, CBD and FFA have no relevant studies.

Recommendation: For monotherapy in adults with focal seizures, LCM and ESL are recommended as preferred options (Level A). PGB, PER, BRV

and CNB may be considered (Level C). (Agreement Rate: 85 %)

Clinical Question 3: For paediatric patients with focal seizures, are these ASMs effective as add-on therapy in reducing seizure frequency?

PGB was examined in 2 Class II studies [89,90]. The findings indicated that PGB was effective as add-on therapy for paediatric patients aged 1 month–4 years (14 mg/kg/d) and 4–16 years (10 mg/kg/d) with focal seizures.

RFN was examined in 2 Class III studies [91,92]. The findings indicated that RFN might be effective as add-on therapy for paediatric patients aged ≥3 years with focal seizures.

LCM was examined in 1 Class I study [93] and 2 Class II studies [94,95]. The Class I study showed that LCM was effective as add-on therapy for paediatric patients with focal seizures [93]. The Class II studies indicated that LCM was effective as add-on therapy for paediatric patients aged ≥4 to <17 years with focal seizures and possibly effective for paediatric patients aged <4 years [94,95].

PER was examined in 1 Class I study [93] and 4 Class II studies [48–51]. The Class I study showed that PER was effective as add-on therapy for paediatric patients with focal seizures [93]. The Class II studies indicated that PER was effective as add-on therapy for juvenile

Table 4
Summary of adverse reactions associated with third-generation ASMs [214–223].

ASMs	Most common ($\geq 1/10$)	Common ($\geq 1/100$ to $< 1/10$)	Uncommon ($\geq 1/1000$ to $< 1/100$)	Rare ($< 1/1000$)	Unknown (incidence rate not available)	Warnings and precautions
PGB[214]	Dizziness, somnolence	Anxiety, confusion, irritability, abdominal pain, depression, fatigue, increased appetite, arthralgia, nasopharyngitis	Dysarthria, hallucination, cognitive impairment, heart failure, asthenia, anaemia, anorexia, joint swelling, dyspnoea	Dysautonomia, dyskinesia, parkinsonism, sleep disorder, shock, sinus arrhythmia, oesophageal ulcer, thrombocythemia, leukopenia	Not reported	Angioedema, hypersensitivity, suicidal behaviour and ideation, respiratory depression, dizziness, somnolence, discontinuation, peripheral oedema
RFN[215]	Headache, dizziness, somnolence, vomiting, nausea	Fatigue, rash, bronchitis, decreased appetite, increased appetite, pollakiuria, anxiety, anaemia, constipation	Leukopenia, decreased neutrophil count, thrombocytopenia, first-degree atrioventricular block, dysuria, haematuria, nephrolithiasis	Not reported	Not reported	Suicidal behaviour and ideation, central nervous system reactions, QT shortening, multiorgan hypersensitivity, discontinuation
LCM[216]	Headache, dizziness, diplopia, nausea	Cognitive disorder, somnolence, tremor, depression, insomnia, vomiting, constipation, tinnitus, rash, irritability	Syncope, atrioventricular block, bradycardia, atrial fibrillation, drug hypersensitivity, aggression, hallucination, suicidal ideation	Not reported	Incidence rate not available: convulsion, agranulocytosis, eosinophilia, Stevens-Johnson syndrome, toxic epidermal necrolysis	Suicidal behaviour and ideation, nervous system effects, discontinuation, cardiac rhythm and conduction abnormalities, DRESS/multiorgan hypersensitivity
PER[217]	Dizziness, somnolence	Ataxia, dysarthria, confusional state, diplopia, decreased appetite, increased appetite, anxiety, gait disturbance	Suicidal behaviour and ideation	Not reported	Incidence rate not available: Drug reaction with eosinophilia and systemic symptoms, Stevens-Johnson syndrome	Suicidal behaviour and ideation, nervous system effects, falls, DRESS/multi-organ hypersensitivity, discontinuation
ESL[218]	Headache, dizziness, somnolence, nausea	Ataxia, balance disorder, memory impairment, fatigue, diarrhoea, constipation, nystagmus	Not reported	Not reported	Not reported	Suicidal behaviour and ideation, serious dermatologic reactions, DRESS, angioedema, hyponatremia, neurological adverse reactions, discontinuation, drug induced liver injury, haematologic adverse reactions
BRV[219]	Somnolence, sedation, dizziness	Nausea, vomiting, constipation, fatigue, balance disorder, irritability	Not reported	Not reported	Not reported	Suicidal behaviour and ideation, neurological adverse reactions, psychiatric adverse reactions, hypersensitivity: bronchospasm and angioedema, discontinuation
STP[220]	Somnolence, ataxia, hypotonia, dystonia, insomnia, anorexia, decreased appetite, decreased weight	Hyperkinesia, aggression, irritability, behavioural disorder, oppositional behaviour, agitation, sleep disorder, vomiting, nausea	Diplopia, photosensitivity, rash, cutaneous allergy, urticaria, fatigue	Thrombocytopenia, liver function test abnormalities	Not reported	Somnolence, decreased appetite and decreased weight, decreased neutrophil count and thrombocytopenia, discontinuation, phenylketonuria, suicidal behaviour and ideation
CBD[221]	Somnolence, decreased appetite, diarrhoea, fatigue, rash, insomnia, infections, sleep disorder	Weight decreased, abdominal pain, sedation, irritability, gait disturbance, pneumonia, respiratory failure, drooling, aggression	Not reported	Not reported	Not reported	Hepatocellular injury, somnolence and sedation, suicidal behaviour and ideation, hypersensitivity reactions, discontinuation
CNB[222]	Somnolence, dizziness, fatigue, diplopia, headache	Blurred vision, nausea, constipation, diarrhoea, vomiting, dry mouth, abdominal pain, urinary tract infection, nasopharyngitis	Not reported	Not reported	Not reported	DRESS/multiorgan hypersensitivity, QT shortening, suicidal behaviour and ideation, neurological adverse reactions, discontinuation
FFA[223]	Decreased appetite, fatigue, somnolence, vomiting, diarrhoea	Rash, abnormal behaviour, increased blood prolactin, chills, upper respiratory tract infection, increased heart rate, urinary incontinence, nasopharyngitis	Not reported	Not reported	Not reported	Decreased appetite and decreased weight, somnolence, sedation, fatigue and asthenia, suicidal behaviour and ideation, discontinuation, serotonin syndrome, increase in blood pressure, glaucoma

aged ≥ 12 years and adult patients with focal seizures.

ESL was examined in 3 Class I studies [53,93,96] and 2 Class II studies [97,98]. The Class I studies did not consistently demonstrate efficacy. The Class II studies indicated that ESL at a dosage of 30 mg/kg/d was effective as add-on therapy for paediatric patients aged 6–16 years with focal seizures. There was an insufficient number of studies examining children aged < 6 years [97].

BRV was examined in 3 Class III studies [99–101]. The findings indicated that BRV might be effective as add-on therapy for paediatric patients with focal seizures.

STP was examined in 1 Class II study [102], which did not prove that STP was effective as add-on therapy for paediatric patients with focal seizures.

CNB was examined in 3 Class III studies [103–105]. The findings indicated that CNB might be effective as add-on therapy for paediatric patients with focal seizures.

Detailed descriptions of the abovementioned studies are shown in **Appendix Table 3**.

CBD and FFA have no relevant studies.

Recommendation: For add-on therapy in paediatric patients with focal seizures, LCM (≥ 4 years) and PER (≥ 12 years) are recommended as preferred options (Level A). PGB (1 month–4 years of age, dosage of 14 mg/kg/d; 4–16 years of age, dosage of 10 mg/kg/d) and ESL (6–16 years of age, dosage of 30 mg/kg/d) may be selected as alternatives (Level B). RFN (≥ 3 years of age), BRV, and CNB may be considered (Level C). (Agreement Rate: 95 %)

Clinical Question 4: For paediatric patients with focal seizures, are these ASMs effective as monotherapy in reducing seizure frequency?

LCM was examined in 3 Class III studies [106–108]. The findings indicated that LCM might be effective as monotherapy for paediatric patients with focal seizures.

PER was examined in 1 Class III study [107], which showed that PER might be effective as monotherapy for paediatric patients with focal seizures.

ESL was examined in 1 Class III study [109], which showed that ESL might be effective as monotherapy for paediatric patients with focal seizures. However, this study did not directly assess reductions in seizure frequency.

Detailed descriptions of the abovementioned studies are shown in **Appendix Table 4**.

PGB, RFN, BRV, STP, CBD, CNB and FFA have no relevant studies.

Recommendation: For monotherapy in paediatric patients with focal seizures, LCM and PER may be considered (Level C). ESL may be used with caution if other agents are unsuitable (Level D). (Agreement Rate: 100 %)

Clinical Question 5: For adult patients with generalized seizures, are these ASMs effective as add-on therapy in reducing seizure frequency?

PGB was examined in 1 Class II study [110], which did not prove that PGB was effective as add-on therapy for adult patients with generalized tonic-clonic seizures (GTCs).

LCM was examined in 1 Class III study [111], which showed that LCM might be effective as add-on therapy for adult patients with GTCs.

PER was examined in 2 Class III studies [112,113]. The findings indicated that PER might be effective as add-on therapy for adult patients with GTCs.

ESL was examined in 1 Class III study [114], which showed that ESL might be effective as add-on therapy for adult patients with GTCs.

BRV was examined in 1 Class III study [115], which showed that BRV might be effective as add-on therapy for adult patients with GTCs.

CNB was examined in 1 Class IV study [116], which showed that CNB might be effective as add-on therapy for adult patients with GTCs. However, no high-quality studies have assessed the use of CNB in this context.

Detailed descriptions of the abovementioned studies are shown in **Appendix Table 5**.

RFN, STP, CBD and FFA have no relevant studies.

Recommendation: For add-on therapy in adults with GTCs, LCM, PER, ESL and BRV may be considered (Level C). CNB may be used with caution if other agents are unsuitable (Level D). (Agreement Rate: 95 %)

Clinical Question 6: For adult patients with generalized seizures, are these ASMs effective as monotherapy in reducing seizure frequency?

LCM was examined in 1 Class III study [80], which showed that LCM might be effective as monotherapy for adult patients with GTCs.

PER was examined in 1 Class IV study [82], which showed that PER might be effective as monotherapy for adult patients with GTCs. However, no high-quality studies have assessed the use of PER in this context.

Detailed descriptions of the abovementioned studies are shown in **Appendix Table 6**.

PGB, RFN, ESL, BRV, STP, CBD, CNB and FFA have no relevant studies.

Recommendation: For monotherapy in adults with GTCs, LCM may be considered (Level C). PER may be used with caution if LCM is unsuitable (Level D). (Agreement Rate: 90 %)

Clinical Question 7: For paediatric patients with generalized seizures, are these ASMs effective as add-on therapy in reducing seizure frequency?

PGB was examined in 1 Class II study [110], which did not prove that PGB was effective as add-on therapy for paediatric patients with GTCs.

LCM was examined in 3 Class III studies [108,117,118]. The findings indicated that LCM might be effective as add-on therapy for paediatric patients with generalized seizures. However, no studies have assessed the use of LCM for treating specific seizure types in this context.

PER was examined in 1 Class III study [112], which showed that PER might be effective as add-on therapy for paediatric patients aged ≥ 12 years with GTCs. However, this study did not directly assess reductions in seizure frequency.

BRV was examined in 1 Class IV study [119], which showed that BRV might be effective as add-on therapy for paediatric patients with generalized seizures. However, no studies have assessed the use of BRV for treating specific seizure types in this context.

Detailed descriptions of the abovementioned studies are shown in **Appendix Table 7**.

RFN, ESL, STP, CBD, CNB and FFA have no relevant studies.

Recommendation: For add-on therapy in paediatric patients with GTCs, PER may be considered (Level C). There is limited evidence for the efficacy of other third-generation ASMs in treating certain types of generalized seizures. (Agreement Rate: 95 %)

Clinical Question 8: For paediatric patients with generalized seizures, are these ASMs effective as monotherapy in reducing seizure frequency?

LCM was examined in 1 Class III study [108], which showed that LCM might be effective as monotherapy for paediatric patients with generalized seizures. However, no studies have assessed the use of LCM for treating specific seizure types in this context [108]. Detailed descriptions of this study are shown in **Appendix Table 8**.

PGB, RFN, PER, ESL, BRV, STP, CBD, CNB and FFA have no relevant studies.

Recommendation: Currently, no third-generation ASMs have robust evidence supporting their efficacy as monotherapy for certain types of generalized seizures. (Agreement Rate: 95 %)

Clinical Question 9: For elderly patients, are these ASMs effective in reducing seizure frequency?

LCM was examined in 1 Class I study [120] and 1 Class II study [80]. The Class I study revealed that LCM was effective as monotherapy for elderly patients. The seizure-free rate of LCM was noninferior to that of levetiracetam and lamotrigine [120]. The Class II study revealed that LCM at a dosage of 200–600 mg/d was effective as monotherapy for elderly patients. The seizure-free rate of LCM was higher than that of CBZ. The incidence rates of adverse events (AEs) and drug-related AEs

associated with LCM were both lower than those associated with CBZ [80].

PER was examined in 4 Class III studies [121–124]. The findings indicated that PER was effective as add-on therapy or monotherapy for elderly patients with focal or generalized seizures. The efficacy was similar to or even better than that in younger patients. The incidence of AEs in elderly patients was similar to that in younger patients. Common AEs in elderly patients included irritability, somnolence, dizziness, etc. [121–124].

ESL was examined in 2 Class III studies [125,126]. The findings indicated that ESL was effective as add-on therapy or monotherapy for elderly patients with focal seizures. The efficacy of ESL was significantly better among elderly patients than among younger patients. The most common AEs in elderly patients were dizziness, somnolence, and hyponatremia. No new safety issues have been identified. The incidence rates of AEs and serious AEs were higher in elderly patients than in younger patients, and the maximum tolerated dose was lower [125–128].

BRV was examined in 3 Class III studies [129–131]. The findings indicated that BRV was effective as add-on therapy for elderly patients with focal seizures. The efficacy of BRV among elderly adults was similar to or even better than that in younger patients. The safety profile of BRV in elderly patients was favourable. The most common AEs were headache, paraesthesia and somnolence, with no drug-related serious AEs or deaths reported.

CNB was examined in 1 Class III study [132], which showed that CNB was effective as add-on therapy for elderly patients with focal seizures [132]. The safety profile of BRV in elderly patients was favourable. The most common AEs were somnolence, dizziness and falls. A small number of AEs were more common in elderly patients than in younger patients.

Detailed descriptions of the abovementioned studies are shown in **Appendix Table 9**.

PGB, RFN, STP, CBD and FFA have no relevant studies.

Recommendation: For elderly patients with focal seizures, following electrocardiogram (ECG) screening to rule out cardiac conduction abnormalities, LCM is recommended as preferred therapy (Level A). PER, ESL, BRV and CNB may be considered (Level C). (Agreement Rate: 95 %)

Clinical Question 10: For women of childbearing age, do these ASMs have an impact on pregnancy outcomes?

PGB was examined in 2 Class III studies [133,134], and PER [135, 136], ESL [137,138], and BRV [137,139] were each examined in 2 Class IV studies. However, owing to the limited sample sizes, definitive conclusions could not be drawn regarding the safety of PGB, PER, ESL or BRV in terms of pregnancy outcomes.

LCM was examined in 3 Class III studies. The findings indicated that LCM did not increase the risks of adverse pregnancy outcomes, such as congenital malformations or preterm birth [140–142].

Detailed descriptions of the abovementioned studies are shown in **Appendix Table 10**.

RFN, CNB, STP, CBD and FFA have no relevant studies.

Recommendation: Limited evidence suggests that the use of LCM in pregnant women with epilepsy is not associated with increased risks of adverse pregnancy outcomes (Level C). For other third-generation ASMs, data on safety in pregnant women with epilepsy remain insufficient. The selection of medication for pregnant women with epilepsy requires particularly careful consideration in clinical practice. (Agreement Rate: 100 %)

Clinical Question 11: For patients with epilepsy of different aetiologies, are these ASMs effective in reducing seizure frequency?

One Class III study showed that PGB might be effective for brain tumour-related epilepsy (BTRE) [143].

Seven Class III studies indicated that LCM might be effective for BTRE [144–150]. Three Class III studies indicated that LCM might be effective for cerebrovascular disease-related epilepsy [151–153]. One Class III study showed that LCM might be effective for TSC-associated seizures [154]. For genetic epilepsy, a Class III study showed that LCM

might be effective for *CDKL5* deficiency disorder-related epilepsy, and 3 Class IV studies indicated that LCM might be effective for *KCNQ2*- or *MAP2K1*-related epilepsy [155–158].

Four Class III studies indicated that PER might be effective for BTRE [149,159–161], with no significant differences in efficacy or safety compared with lacosamide [149]. One Class II study revealed that PER was effective for cerebrovascular disease-related epilepsy, with non-inferior efficacy compared with oxcarbazepine [162]. One Class III study showed that PER might be effective for posttraumatic epilepsy (PTE) [159]. A Class III study [163] and a Class IV study [164] indicated that PER might be effective for TSC-associated seizures. For genetic epilepsy, a Class III study on the mutation type (*SCN1A*, *GNAO1*, *PIGA*, *PCDH19*, *SYNGAP1*, *CDKL5*, *NEU1*, *POLG*) revealed that PER might be effective [165].

One Class III study showed that ESL might be effective for BTRE [166]. One Class III study showed that ESL might be effective for cerebrovascular disease-related epilepsy [153].

Two Class III studies indicated that BRV might be effective for BTRE [167,168]. Two Class III studies showed that BRV might be effective for cerebrovascular disease-related epilepsy [168,169]. One Class III study showed that BRV might be effective for PTE [168].

One Class III study revealed that STP might be effective for TSC-associated seizures [170].

One Class II study showed that CBD was effective for TSC-associated seizures [171].

One Class III study revealed that CNB might be effective for epilepsy because of its structural aetiology [172]. A Class III study showed that CNB might be effective for TSC-associated seizures [173]. For genetic epilepsy, based on the mutation type (*SCN8A*), a Class III study revealed that CNB might be effective [174].

One Class IV study revealed that FFA might be effective for TSC-associated seizures [175], but high-quality studies are lacking.

RFN has no relevant studies.

Recommendation:

For epilepsy due to structural etiology, CNB may be considered (Level C).

For BTRE, PGB, LCM, PER, ESL and BRV may be considered (Level C).

For PTE, PER and BRV may be considered (Level C).

For TSC-associated seizures, CBD may be selected (Level B). LCM, PER, STP and CNB may be considered (Level C). FFA may be used with caution if other agents are unsuitable (Level D).

For cerebrovascular disease-related epilepsy, PER may be selected (Level B). LCM, ESL and BRV may be considered (Level C).

For genetic epilepsy, on the basis of mutation type, LCM (*CDKL5*), PER (*SCN1A*, *GNAO1*, *PIGA*, *PCDH19*, *SYNGAP1*, *CDKL5*, *NEU1*, *POLG*) and CNB (*SCN8A*) may be considered (Level C). LCM (*KCNQ2*, *MAP2K1*) may be used with caution (Level D). (Agreement Rate: 95 %)

Clinical Question 12: For different epileptic syndromes, are these ASMs effective in reducing seizure frequency?

For Lennox–Gastaut syndrome (LGS), RFN was examined in 3 Class I studies [176–178] and 2 Class II studies [179,180]. The findings indicated that RFN was effective as add-on therapy for LGS. For Dravet syndrome (DS), RFN was examined in 1 Class III study [181], which did not prove that RFN was effective as add-on therapy for DS.

For idiopathic generalized epilepsy (IGE), LCM was examined in 1 Class II study [182], which showed that LCM was effective as add-on therapy for GTCS in patients with IGE. For juvenile myoclonic epilepsy (JME), LCM was examined in 1 Class IV study [183], which showed that LCM might be effective as add-on therapy for JME. For LGS, LCM was examined in 1 Class III study and 4 Class IV studies [184–188]. The Class III study revealed that nearly 30 % of patients experienced deterioration. The Class IV studies indicated that LCM might be effective as add-on therapy for LGS. For self-limited epilepsy with centrotemporal spikes (SeLECTS), LCM was examined in 1 Class IV study [189], which showed that LCM might be effective as monotherapy for SeLECTS.

For LGS, PER was examined in 1 Class II study [190], which showed that the efficacy of PER as add-on therapy was not significantly better

Table 5
Recommendations for dosage adjustment of third-generation ASMs in patients with hepatic or renal impairment [214–223].

ASMs	Hepatic impairment	Renal impairment
PGB[214]	Dose adjustments are not required for patients with hepatic impairment.	In view of dose-dependent adverse reactions and since LYRICA is eliminated primarily by renal excretion, adjust the dose in adult patients with reduced renal function. Base the dose adjustment in patients with renal impairment on creatinine clearance (CLcr). For patients undergoing haemodialysis, adjust the pregabalin daily dose based on renal function. In addition to the daily dose adjustment, administer a supplemental dose immediately following every 4-hour haemodialysis treatment.
RFN[215]	Use of rufinamide in patients with severe hepatic impairment is not recommended. Caution should be exercised in treating patients with mild to moderate hepatic impairment.	Rufinamide pharmacokinetics in patients with severe renal impairment was similar to that of healthy subjects. Dose adjustment in patients undergoing dialysis should be considered.
LCM[216]	For patients with mild or moderate hepatic impairment, a reduction of 25% of the maximum dosage is recommended. The dose titration should be performed with caution in patients with hepatic impairment. The pharmacokinetics of lacosamide has not been evaluated in severe hepatic impairment. VIMPAT use is not recommended in patients with severe hepatic impairment.	For patients with mild to moderate renal impairment, no dosage adjustment is necessary. For patients with severe renal impairment or end-stage renal disease, a reduction of 25% of the maximum dosage is recommended. In all patients with renal impairment, the dose titration should be performed with caution. VIMPAT is effectively removed from plasma by haemodialysis. Following a 4-hour haemodialysis treatment, dosage supplementation of up to 50% should be considered.
PER[217]	In patients with mild and moderate hepatic impairment, the starting dose of FYCOMPA is 2 mg once daily. Increase dosage by increments of 2 mg once daily no more frequently than every 2 weeks. The maximum recommended daily dose is 6 mg for patients with mild hepatic impairment and 4 mg for patients with moderate hepatic impairment. FYCOMPA is not recommended for use in patients with severe hepatic impairment.	FYCOMPA can be used in patients with moderate renal impairment with close monitoring. A slower titration may be considered, based on clinical response and tolerability. FYCOMPA is not recommended in patients with severe renal impairment or patients undergoing haemodialysis.
ESL[218]	Dose adjustments are not required in patients with mild to moderate hepatic impairment. Use of APTIOM in patients with severe hepatic impairment has not been studied, and use in these patients is not recommended.	In patients with moderate and severe renal impairment, the initial, titration, and maintenance dosages should generally be reduced by 50%. Titration and maintenance dosages may be adjusted according to clinical response.
BRV[219]	Because of increases in BRIVIACT exposure, dosage adjustment is recommended for all stages of hepatic impairment. The recommended starting dosage for adults (16 years and older) or paediatric patients weighing 50 kg or more is 25 mg BID, with a maximum maintenance dosage of 75 mg BID. For paediatric patients weighing 20 kg to less than 50 kg, the recommended starting dosage is 0.5 mg/kg BID, with a maximum maintenance dosage of 1.5 mg/kg BID. For paediatric patients weighing 11 kg to less than 20 kg, the recommended starting dosage is 0.5 mg/kg BID, with a maximum maintenance dosage of 2 mg/kg BID. For paediatric patients weighing less than 11 kg, the recommended starting dosage is 0.75 mg/kg BID, with a maximum maintenance dosage of 2.25 mg/kg BID.	Dose adjustments are not required for patients with impaired renal function. There are no data in patients with end-stage renal disease undergoing dialysis, and use of BRIVIACT is not recommended in this patient population.
STP[220]	There has been no formal study of the pharmacokinetics of DIACOMIT in patients with liver impairment. However, since the drug is mainly metabolized by the liver, administration to patients with moderate or severe liver impairment is not recommended.	There is no formal study of the pharmacokinetics and metabolism of DIACOMIT in patients with renal impairment. However, since DIACOMIT metabolites are eliminated mainly through the kidney, administration to patients with moderate or severe renal impairment is not recommended.
CBD[221]	Dose adjustment is recommended in patients with moderate hepatic impairment or severe hepatic impairment. It may be necessary to have slower dose titration in patients with moderate or severe hepatic impairment than in patients without hepatic impairment. The starting dosage for mild hepatic impairment is 2.5 mg/kg BID, with a maintenance dosage range of 5 to 10 mg/kg BID. For moderate hepatic impairment, the starting dosage is 1.25 mg/kg BID, with a maintenance dosage range of 2.5 to 5 mg/kg BID. For severe hepatic impairment, the starting dosage is 0.5 mg/kg BID, with a maintenance dosage range of 1 to 2 mg/kg BID.	Cannabidiol undergoes minimal renal clearance, and no dose adjustment-related content is reported in the prescribing information.
CNB[222]	XCOPRI should be used with caution in patients with mild to moderate hepatic impairment. In these patients, the maximum recommended dosage is 200 mg once daily and additional dosage reduction may be considered. Use of XCOPRI in patients with severe hepatic impairment is not recommended.	XCOPRI should be used with caution and dosage reduction may be considered in patients with mild to moderate and severe renal impairment. Use in patients with end-stage renal disease undergoing dialysis is not recommended.
FFA[223]	Administration of FINTEPLA to patients with hepatic impairment is not recommended.	In patients with estimated glomerular filtration rate (eGFR) 15 to 29 mL/min/1.73m ² , do not exceed the maximum daily dosage of FINTEPLA of 20 mg. In patients with eGFR 15 to 29 mL/min/1.73m ² and concomitant stiripentol use, do not exceed the maximum daily dosage of FINTEPLA of 17 mg. FINTEPLA has not been studied in patients with eGFR < 15 mL/min/1.73m ² .

Abbreviations: eGFR, estimated glomerular filtration rate; BID, twice daily; AUC, area under the curve
Mild hepatic impairment: Child–Pugh Class A, total score 5–6 points; Moderate hepatic impairment: Child–Pugh Class B, total score 7–9 points; Severe hepatic impairment: Child–Pugh Class C, total score ≥10 points.
Mild renal impairment: creatinine clearance (CLcr) >50–80 mL/min; Moderate renal impairment: CLcr >30–50 mL/min; Severe renal impairment: CLcr ≤30 mL/min.

than that of placebo. For IGE, PER was examined in 1 Class I study [191] and 1 Class II study [192]. The Class I study revealed that the seizure freedom rate of PER as add-on therapy was not significantly better than that of placebo [191], but the safety profile was favourable. The Class II study revealed that PER for IGE with GTCS could significantly increase 50 % response rate [192]. For SeLECTS, PER was examined in 1 Class III study [193], which showed that PER might be effective for SeLECTS.

For DS, ESL was examined in 1 Class IV study [194], which showed that ESL might be effective for DS.

For epileptic syndromes, BRV was examined in 1 Class III study [195] and 1 Class IV study [196]. The findings indicated that BRV might be effective for various epileptic syndromes, including potential efficacy in JME based on limited evidence within these studies, though no systematic subgroup analysis has been conducted on its efficacy across specific syndrome types.

For DS, STP was examined in 5 Class I studies [197–201] and 1 Class II study [202]. These findings indicate that STP was effective as add-on therapy for DS.

For LGS, CBD was examined in 2 Class I studies [177,178] and 2 Class II studies [203,204]. All the results indicated that CBD was effective as add-on therapy for LGS. For DS, CBD was examined in 4 Class I studies [198–201] and 1 Class II study [205]. All of these findings indicated that CBD was effective as add-on therapy for DS.

For IGE, CNB was examined in 1 Class IV study [206], which showed that CNB might be effective for patients with juvenile myoclonic epilepsy (JME). For LGS, CNB was examined in 1 Class IV study [207], which showed that CNB might be effective for LGS. For DS, CNB was examined in 2 Class IV studies [208,209]. The findings indicated that CNB might be effective for DS.

For LGS, FFA was examined in 1 Class II study [210], which showed that FFA was effective as add-on therapy for LGS. For DS, FFA was examined in 4 Class I studies [198–201] and 3 Class II studies [211–213]. The findings indicated that FFA was effective as add-on therapy for DS.

Detailed descriptions of the abovementioned studies are shown in **Appendix Table 11**.

PGB has no relevant study.

Recommendation:

For IGE, LCM and PER may be selected in patients with GTCSs (Level B).

LCM, BRV and CNB may be used with caution in patients with JME (Level

D).

For LGS, RFN and CBD are recommended as preferred options (Level A). FFA may be selected as an alternative (Level B).

For DS, STP, CBD and FFA are recommended as preferred options (Level A).

For SeLECTS, PER may be considered (Level C). LCM may be used with caution if PER is unsuitable (Level D). (Agreement Rate: 100 %)

Clinical Question 13: For patients with hepatic or renal impairment, how should the dosage be adjusted when using third-generation ASMs?

Generally, third-generation ASMs have favourable safety profiles, and a summary of their adverse reactions is presented in **Table 4**. Hepatic or renal insufficiency may affect the metabolism of ASMs in vivo. If necessary, blood drug concentrations should be monitored to facilitate timely adjustment of medication dosages [1]. The methods for adjusting the dosage of third-generation ASMs in patients with hepatic or renal insufficiency are shown in **Table 5**.

Recommendation: *For patients with hepatic or renal impairment receiving ASMs, serum drug concentrations should be monitored when clinically indicated, and dosage adjustments should be made according to the severity of impairment of their hepatic or renal function. (Agreement rate: 95 %)*

5. Conclusion

This guideline involves a detailed review of the clinical studies for third-generation ASMs in the treatment of epilepsy. On the basis of the quality of evidence and results of studies, recommendations for clinical application are provided. **Table 6** summarizes the evidence levels and recommendation strengths for Clinical Questions 1–10. Overall, studies of third-generation ASMs are relatively robust for adjunctive therapy in adult patients with focal seizures and in specific syndromes. Future exploration is needed for their use in generalized seizures and in different age groups (such as paediatric and elderly patients), as well as safety in women of childbearing age. Besides, further inputs from patient advocates are encouraged. As more third-generation ASMs become available in China, this guideline will be updated to incorporate new studies and recommendations.

Table 6
Evidence levels and recommendation strengths for clinical questions 1–10.

ASMs	Adult patients with focal seizures		Paediatric patients with focal seizures		Adult patients with generalized seizures		Paediatric patients with generalized seizures		Special populations	
	Add-on therapy	Monotherapy	Add-on therapy	Monotherapy	Add-on therapy	Monotherapy	Add-on therapy	Monotherapy	Elderly patients	Women of childbearing age**
PGB	IA	IIIC*	IIB (1 month–4 years, 14 mg/kg/d; 4–16 years, 10 mg/kg/d)	NA	NA	NA	NA	NA	NA	NA
RFN	IA	NA	IIIC (≥3 years)*	NA	NA	NA	NA	NA	NA	NA
LCM	IA	IA	IA (≥4 years)	IIIC*	GTCS: IIIC*	GTCS: IIIC*	GTCS: IIIC*	NA	Focal: IA	IIIC*
PER	IA	IIIC*	IA (≥12 years)	IIIC*	GTCS: IIIC*	GTCS: IVD*	NA	NA	Focal: IIIC*	NA
ESL	IB	IA	IB (>6 years, 30 mg/kg/d)	IIID*	GTCS: IIIC*	NA	NA	NA	Focal: IIIC*	NA
BRV	IA	IIIC*	IIIC*	NA	GTCS: IIIC*	NA	NA	NA	Focal: IIIC*	NA
STP	IIIC*	NA	NA	NA	NA	NA	NA	NA	NA	NA
CBD	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
CNB	IA	IIIC*	IIIC*	NA	GTCS: IVD*	NA	NA	NA	Focal: IIIC*	NA
FFA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA

NA, not available.

* Class III and IV studies are self-cohort studies or case reports with a low level of evidence, so care should be taken in clinical application.

** Recommendations for women of childbearing age are limited to the safety of ASM use during pregnancy.

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Declaration of competing interest

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Supplementary materials

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