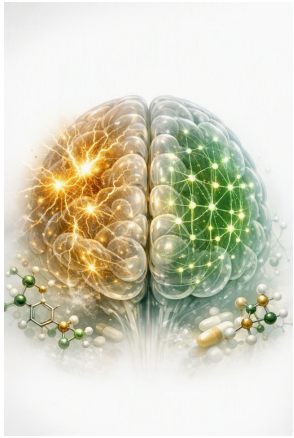
EST 30th ANNIVERSARY ANNUAL MEETING

The Changing Landscape of Anti-Seizure Medications

YOTIN CHINVARUN. MD. Ph.D. FAES.



1

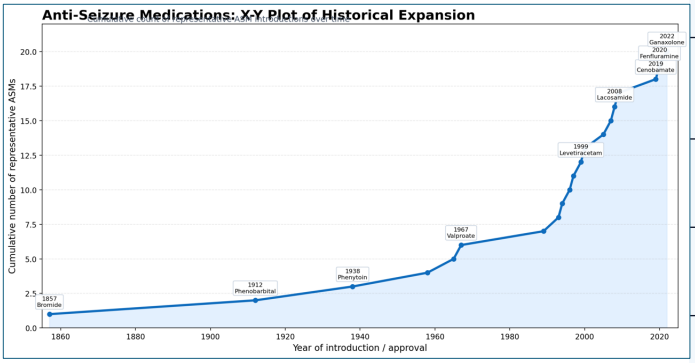
EST 30th ANNIVERSARY ANNUAL MEETING

INTRODUCTION

- The International League Against Epilepsy argued that currently approved medications should be collectively called **antiseizure medications** rather than **antiepileptic drugs**
- This change reflects the fact that almost all approved agents demonstrated symptomatic seizure suppression rather than proven prevention or reversal of epileptogenesis
- When clinicians say “antiepileptic,” patients may infer that underlying disease has been corrected.
  - The term “ASM” is more precise and more honest about what most current therapies actually do
  - It also leaves conceptual space for future agents that may truly modify disease biology

2

Antiseizure medication: History



Era	Representative shift
1857-1938	Bromides, then phenobarbital and phenytoin established the first durable pharmacologic era.
1958-1967	Ethosuximide, carbamazepine, and valproate expanded syndrome coverage and long-term outpatient treatment options.
1989-2000	The modern acceleration phase introduced lamotrigine, topiramate, gabapentin, and levetiracetam.
2005-2009	Pregabalin, rufinamide, lacosamide, and eslicarbazepine strengthened mechanism diversity and cleaner PK profiles.
2019-2022	Cenobamate, fenfluramine, and ganaxolone signaled stronger DRE impact and syndrome-directed development.

3

EST 30th ANNIVERSARY ANNUAL MEETING

The long therapeutic arc

- **Bromides** introduced in 19th century and established principle that recurrent seizures were pharmacologically suppressible
- **Phenobarbital** and **phenytoin** then defined 1st durable era of efficacy, but also 1st era of chronic neurotoxicity and interaction burden

- **Carbamazepine** and **valproate** broadened syndrome coverage and became enduring global standards
- Later, **lamotrigine, topiramate, oxcarbazepine, levetiracetam**, and related drugs shifted the field toward better tolerability and cleaner pharmacokinetics

- The newest period is different because approvals increasingly reflect **narrower indications, targeted syndromes, and more explicit safety positioning**

4

EST 30th ANNIVERSARY ANNUAL MEETING

Legacy agents remain clinically relevant

Phenobarbital remains highly relevant where affordability-availability dominate care	**Phenytoin** still matters in acute and chronic care despite nonlinear kinetics and long-term toxicity	**Carbamazepine** remains a focal epilepsy benchmark but carries induction and hyponatremia liabilities	**Valproate** remains one of strongest broad-spectrum agents but now heavily constrained by reproductive safety concerns

Older drugs did not disappear when newer agents arrived. Instead, their relative position changed as tolerability, access, and life-stage concerns became more visible in routine practice

5

EST 30th ANNIVERSARY ANNUAL MEETING

The value proposition of newer ASMs

- **Newer ASMs** expanded because many offered comparable seizure efficacy with cleaner pharmacokinetics, fewer interactions, and more acceptable chronic tolerability, especially in ambulatory care, in older adults, and in patients with complex medication lists
- Improved convenience also changed prescribing behavior, because drugs that are easier to start and easier to continue accumulate a practical advantage over time
- **Levetiracetam** became emblematic of this trend because speed, simplicity, and formulation flexibility translated into broad real-world uptake
- **Lamotrigine** became another emblem because retention and mood profile often mattered as much as efficacy

6

EST 30th ANNIVERSARY ANNUAL MEETING

ASM: Major mechanism

Family	Examples	Main value	Key concern
Sodium-channel modulators	CBZ, LTG, OXC, LCM, ESL, CNB	Focal epilepsy	Rash, conduction, dizziness, hyponatremia
SV2A ligands	LEV, BRV	Simple PK, rapid deployment	Behavioral adverse effects
GABAergic agents	PB, BZD, STP, ganaxolone	Potent suppression	Sedation and cognition
Mixed or niche targets	ETX, TPM, ZNS, PER, FBM	Broad-spectrum or syndrome fit	Psychiatric, metabolic, rare toxicities

Mechanism alone never replaces syndrome recognition, but it helps explain both synergy and toxicity stacking

7

EST 30th ANNIVERSARY ANNUAL MEETING

The sodium-channel story matured

- Sodium-channel drugs remained central because they continue to anchor focal epilepsy therapy
- Lamotrigine, lacosamide, eslicarbazepine, and cenobamate each occupy different clinical niches because their kinetics, tolerability, and mechanistic differ
- Lacosamide's selective slow inactivation helped reframe concept of sodium modulation
- Cenobamate added new layer by combining sodium-current effects with positive allosteric GABA-A activity
- This evolution shows how "same family" no longer means "same clinical role."

8

EST 30th ANNIVERSARY ANNUAL MEETING

Levetiracetam changed default prescribing

- **Levetiracetam** became a modern default because it could be started quickly, titrated simply, and used across inpatient and outpatient settings
  - Its **oral and intravenous formulations** improved continuity across care transitions
  - Its **low interaction burden** made it particularly attractive in older adults and medically complex patients
- These features gave levetiracetam unusual practical power even when it was not clearly superior on pure efficacy grounds.
- Its rise illustrates that convenience and systems-compatibility can be as influential as mechanism
- **The limitation, is neuropsychiatric tolerability**: Irritability, depression, aggression, and behavioral dyscontrol remain clinically important and often decisive
- Brivaracetam partly emerged from this context as an attempt to preserve SV2A logic while improving tolerability in selected patients

9

EST 30th ANNIVERSARY ANNUAL MEETING

Broad-spectrum versus syndrome-specific logic

- Broad-spectrum ASMs remain strategically valuable because many patients present before syndromic certainty is complete.
  - Valproate, lamotrigine, levetiracetam, topiramate, zonisamide, and perampanel are often attractive in mixed or uncertain phenotypes for that reason
- However, the modern field increasingly rewards sharper syndrome-specific choices when the phenotype is well characterized
- **Ethosuximide** remains strongly linked to absence epilepsy, while **fenfluramine** has reshaped Dravet treatment and **ganaxolone** marked targeted development in CDKL5 deficiency disorder.
  - This movement toward syndrome-aware approvals reflects a deeper change in therapeutic ambition
  - We are no longer satisfied with one-size-fits-all adjunctive logic for every epilepsy subtype

10

EST 30th ANNIVERSARY ANNUAL MEETING

The first drug still matters disproportionately

The first syndrome-fit drug still has an outsized effect on long-term trajectory	**Retention and tolerability** frequently separate acceptable first-line options more than efficacy does	**Changing early** is often wiser than passively escalating a poorly matched drug

- This principle is old, but its meaning has deepened in the current era
  - With more choices available, failure of initial monotherapy is increasingly informative.
- It should prompt re-examination of syndrome, tolerability, adherence, and comorbidity rather than automatic additive prescribing.

In this sense, the landscape changed not just because the number of agents increased, but because the diagnostic value of a treatment response has become more nuanced.

11

EST 30th ANNIVERSARY ANNUAL MEETING

Combination therapy is more rational now

- Polytherapy used to be dominated by empiric accumulation
- In contrast, modern combination therapy increasingly aims for **mechanistic complementarity and cleaner pharmacology**
  - The goal is to combine efficacy while minimizing pharmacokinetic conflict and pharmacodynamic stacking of dizziness, somnolence, mood toxicity, or cognitive slowing
- It represents a real change in everyday practice
- The availability of cleaner drugs and more refined mechanism groupings makes rational polytherapy more achievable than before
- Good combination therapy now often means fewer total liabilities rather than more total molecules

12

EST 30th ANNIVERSARY ANNUAL MEETING

The new drivers of selection

- What changed most in the last decade is not simply the menu of drugs, but the weighting of decision variables
- **Safety architecture** now routinely rivals or exceeds pure seizure efficacy in determining first-line preference
- **Pregnancy, age, psychiatry, interactions, and access all influence hierarchy**
  - This shift is especially visible in tertiary epilepsy care where life-stage and comorbidity complexity are the rule rather than the exception
- The modern ASM conversation therefore more multidimensional than earlier eras

13

EST 30th ANNIVERSARY ANNUAL MEETING

Reproductive safety reordered the field

- Valproate remains one of the most effective broad-spectrum ASMs, especially in idiopathic generalized epilepsies
- However, the field's therapeutic hierarchy changed profoundly once reproductive safety moved to the center of decision-making
  - The result is that many clinicians now treat valproate as a powerful but constrained drug rather than a routine default.

This is one of the clearest examples of a landscape change driven by safety rather than new efficacy alone

- WHO's recent essential-medicines review specifically endorsed lamotrigine and levetiracetam as first-line monotherapy choices for women and girls of childbearing potential with generalized-onset seizures.
- That recommendation is strategically important because
  - It also reflects the degree to which reproductive risk now changes first-line thinking globally, not only in high-resource settings

14

EST 30th ANNIVERSARY ANNUAL MEETING

Older adults changed first-line habits

- The aging epilepsy population forced clinicians to rethink what “best tolerated” really means
- In older adults, dizziness, hyponatremia, gait instability, sedation, and interaction burden can be more consequential than modest efficacy differences.
- Polypharmacy also means enzyme-inducing drugs create wider collateral damage than in the past
- These pressures helped elevate lamotrigine, levetiracetam, gabapentin, and lacosamide in many real-world pathways

15

EST 30th ANNIVERSARY ANNUAL MEETING

Psychiatric comorbidity now strongly shapes choice

- Psychiatric comorbidity is no longer a secondary consideration in advanced epilepsy prescribing
- Depression, anxiety, irritability, aggression, insomnia, and cognitive complaints often determine whether a technically effective drug is actually usable
- Lamotrigine can be attractive in depression-prone patients, while selected GABAergic strategies may help when anxiety or sleep fragmentation coexists.

This makes the “best drug” partly a neuropsychiatric decision rather than only a seizure decision.

- Conversely, levetiracetam, perampanel, topiramate, and zonisamide can complicate mood, behavior, or cognition in susceptible patients
- These risks do not eliminate their value, but they do change patient selection and follow-up intensity
- In practical terms, psychiatric tolerability has become one of the major currencies of modern ASM prescribing

16

EST 30th ANNIVERSARY ANNUAL MEETING

Drug interactions moved to center stage

- Drug interactions have always existed in epilepsy care, but they now influence treatment hierarchy more visibly because patient medicine lists are more complex
- Contraception, anticoagulation, transplant medicine, chemotherapy, cardiology agents, and psychotropics all sharpen the penalty for enzyme induction or inhibition.
  - As a result, “clean PK” has become a major therapeutic selling point rather than a minor convenience.
- Internal ASM interactions also matter more when using modern rational polytherapy.
- **Lamotrigine with valproate**, or **cenobamate with clobazam**, phenytoin, or phenobarbital, requires active dose planning rather than reactive troubleshooting

17

EST 30th ANNIVERSARY ANNUAL MEETING

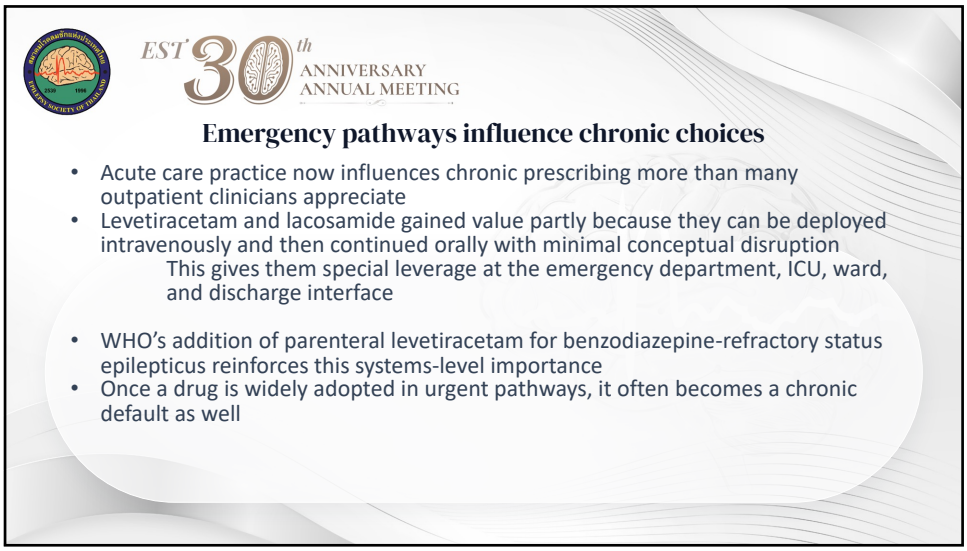
Therapeutic drug monitoring has a different role now

- Therapeutic drug monitoring remains crucial for classic drugs with nonlinear kinetics, narrow windows, adherence uncertainty, pregnancy-related changes, or toxicity concerns
  - It is still indispensable in selected scenarios involving phenytoin, valproate, carbamazepine, phenobarbital, and lamotrigine
- However, the monitoring culture around newer agents is more selective and question-driven

This marks a change from earlier eras when levels were sometimes pursued more routinely and reflexively.

- For many newer agents, clinical effect and tolerability more informative than indiscriminate trough chasing
- Targeted monitoring may still be valuable in renal dysfunction, pregnancy, suspected nonadherence, or unexplained toxicity
- The broader lesson is that TDM remains important, but its role has become more purposeful
  - The landscape changed from “monitor everyone” to “monitor when the answer will alter care.”

18


EST' 30th
ANNIVERSARY
ANNUAL MEETING
Emergency pathways influence chronic choices
• Acute care practice now influences chronic prescribing more than many outpatient clinicians appreciate
• Levetiracetam and lacosamide gained value partly because they can be deployed intravenously and then continued orally with minimal conceptual disruption
This gives them special leverage at the emergency department, ICU, ward, and discharge interface
• WHO's addition of parenteral levetiracetam for benzodiazepine-refractory status epilepticus reinforces this systems-level importance
• Once a drug is widely adopted in urgent pathways, it often becomes a chronic default as well

19


EST' 30th
ANNIVERSARY
ANNUAL MEETING
Drug-resistant epilepsy is no longer a single bucket
• Modern DRE care is more differentiated than older "try another add-on" approaches
• Newer adjunctive options improved flexibility, but bigger change that drug-resistant epilepsy now triggers broader strategic thinking
• Next step may be surgery, neuromodulation, dietary therapy, immunotherapy, or syndrome-specific escalation rather than automatic pharmacologic layering
• WHO evidence summaries highlighted roles for newer adjunctive agents such as lamotrigine, levetiracetam, and topiramate in drug-resistant tonic-clonic epilepsy
• Yet the modern lesson is not that every difficult patient simply needs another drug
• Rather, DRE has become a pivot point for reclassification, referral, and multimodal planning

20

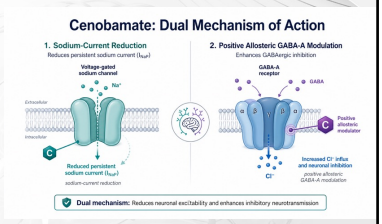
EST 30th ANNIVERSARY ANNUAL MEETING

Cenobamate raised expectations in focal DRE

- **Cenobamate** has altered expectations because clinical efficacy in focal drug-resistant epilepsy appears unusually strong in many real-world and trial settings
- Its combination of sodium-current effects and positive allosteric GABA-A modulation contributes to its distinct profile

- The excitement around cenobamate reflects a sense that the field had not seen such persuasive focal DRE efficacy signals for some time
- However, the drug also illustrates the cost of potency

- Slow titration, DRESS precautions, somnolence, QT shortening, and multiple interaction adjustments mean that its success depends on expert handling



21

EST 30th ANNIVERSARY ANNUAL MEETING

Fenfluramine signals syndrome-directed development

- **Fenfluramine** represents more than a new adjunctive option

- It symbolizes an era in which drug development is increasingly organized around specific developmental epileptic encephalopathies rather than broad seizure-label expansion

- **Its relevance in Dravet syndrome** helped illustrate that some severe epilepsies deserve and can support highly tailored therapeutic programs

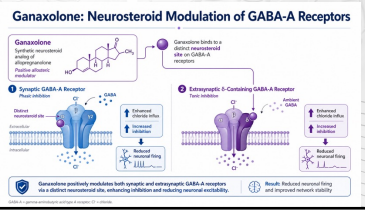
- The treatment also highlights that modern therapy may include infrastructure requirements such as cardiac monitoring and specialized access pathways.
  - Thus, the landscape is changing not just in pharmacology but in how treatment programs are built around drugs.
  - This is a major conceptual change from classic outpatient epilepsy prescribing

22

EST' 30th ANNIVERSARY ANNUAL MEETING

Ganaxolone points toward neurosteroid therapeutics

- Ganaxolone's approval is important not because it suddenly solves refractory epilepsy broadly, but because **it validates a neurosteroid therapeutic pathway in severe rare epilepsy context**
- It expands the modern field beyond older GABAergic intuitions into more explicitly targeted neurosteroid development
- The 2025 ASM update highlighted ganaxolone as one of the notable newly approved medications
- Approvals like ganaxolone also demonstrate that rarity is no longer a barrier to high-priority development
  - The field has become more comfortable with narrower labels when biological plausibility and clinical need are strong
- This is part of the same shift that produced more syndrome-directed programs in epileptology



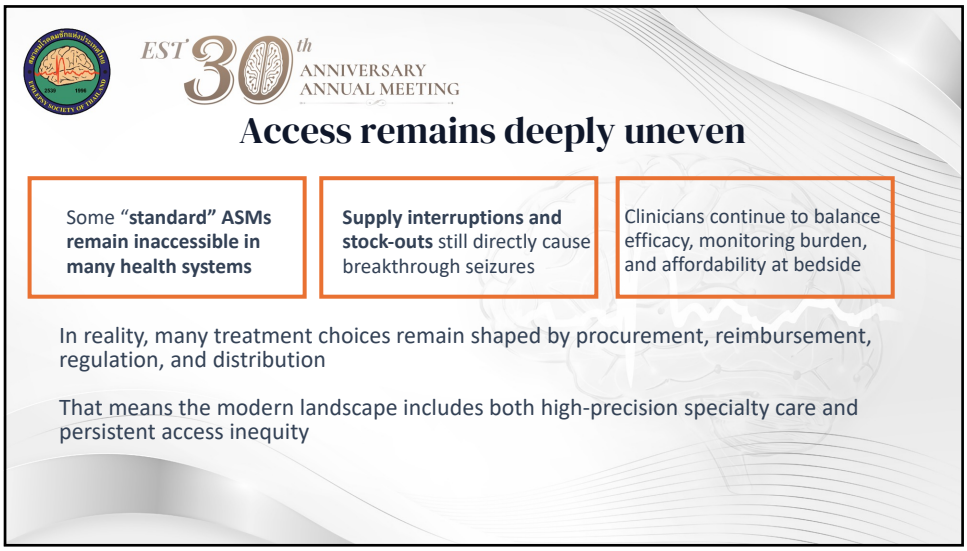
23

EST' 30th ANNIVERSARY ANNUAL MEETING

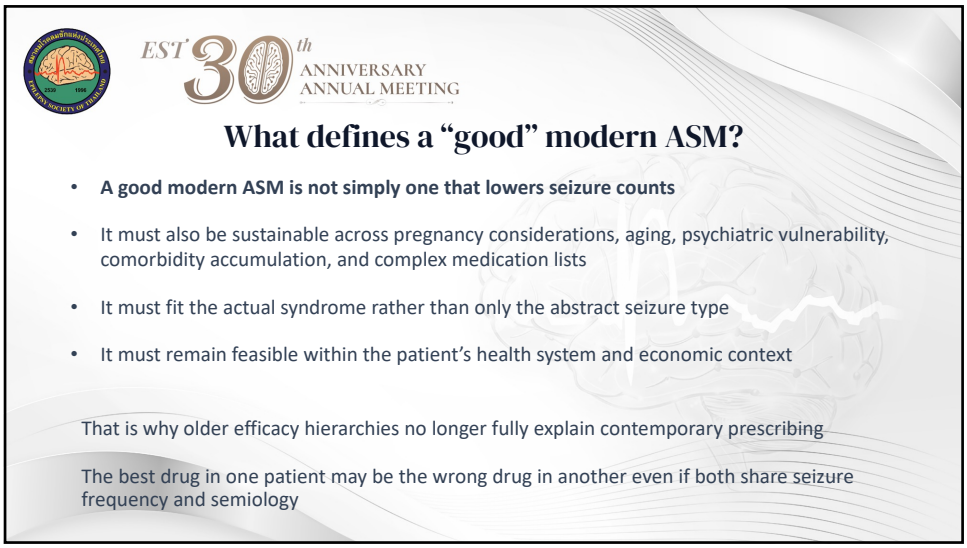
Essential medicines policy is part of the ASM landscape

- The WHO Model List of Essential Medicines has long reflected historical backbone of global epilepsy treatment through carbamazepine, phenobarbital, phenytoin, and valproic acid
- That framework matters because national formularies and procurement systems often follow it
  - When **WHO added oral levetiracetam for focal-onset and generalized-onset seizures, and parenteral levetiracetam for benzodiazepine-refractory status epilepticus**, it signaled that global standard was shifting
- Essential-medicines recognition affects access, affordability, procurement behavior, and national therapeutic norms. In that sense, WHO policy is part of the practical pharmacology of epilepsy care

24


EST 30th
ANNIVERSARY
ANNUAL MEETING
Access remains deeply uneven
Some "standard" ASMs remain inaccessible in many health systems
Supply interruptions and stock-outs still directly cause breakthrough seizures
Clinicians continue to balance efficacy, monitoring burden, and affordability at bedside
In reality, many treatment choices remain shaped by procurement, reimbursement, regulation, and distribution
That means the modern landscape includes both high-precision specialty care and persistent access inequity

25


EST 30th
ANNIVERSARY
ANNUAL MEETING
What defines a "good" modern ASM?
A good modern ASM is not simply one that lowers seizure counts
It must also be sustainable across pregnancy considerations, aging, psychiatric vulnerability, comorbidity accumulation, and complex medication lists
It must fit the actual syndrome rather than only the abstract seizure type
It must remain feasible within the patient's health system and economic context
That is why older efficacy hierarchies no longer fully explain contemporary prescribing
The best drug in one patient may be the wrong drug in another even if both share seizure frequency and semiology

26

EST 30th ANNIVERSARY ANNUAL MEETING

How to choose now

- The practical question in 2026 is no longer only which drug can work, but which drug can work best in this person's full clinical context.
- **That includes syndrome fit, reproductive considerations, comedications, psychiatric profile, age, cognition, and access**
- Modern prescribing is therefore increasingly an exercise in therapeutic prioritization
- The abundance of options is helpful only when matched with disciplined decision logic
  - This is why expert epileptology remains highly valuable despite the growing drug menu
  - More choices increase the need for better judgment.

27

EST 30th ANNIVERSARY ANNUAL MEETING

A practical focal epilepsy treatment

Drug	Why choose	Best context	Main constraint
Lamotrigine	Retention and mood profile	Chronic ambulatory care	Slow titration, rash
Levetiracetam	Speed and simplicity	Urgent start, hospital transition	Behavioral adverse effects
Lacosamide	Clean PK and focal efficacy	Older adults, polypharmacy	PR interval, dizziness
Cenobamate	Strong DRE efficacy	Expert refractory practice	Slow titration, interactions

28

EST 30th ANNIVERSARY ANNUAL MEETING

A practical generalized epilepsy

- **Valproate remains the efficacy reference point for many generalized epilepsies,** especially generalized tonic-clonic and juvenile myoclonic patterns
- In selected patients without reproductive limitation, it remains difficult to replace on pure efficacy grounds

The field changed not because valproate became weak, but because its risk-benefit interpretation became more constrained and more patient-specific.

- Lamotrigine and levetiracetam often move forward when reproductive safety dominates the decision
- However, realistic counseling is still required because comparative efficacy may differ by syndrome and seizure type
  - This makes generalized epilepsy management more nuanced than simply substituting one drug for another.

29

EST 30th ANNIVERSARY ANNUAL MEETING

When to change early rather than add blindly

Pseudo-failure from underdosing or poor adherence should be recognized before labeling resistance.	**Phenotype mismatch** such as worsened myoclonus or absence under sodium-channel blockade should trigger reassessment.	**Sometime the best next drug is subtraction of the wrong current one**

These principles sound simple, but they are often neglected in refractory clinics

The modern drug menu tempts clinicians to add rather than rethink

Yet many treatment failures reflect fit problems rather than lack of available molecules

30


EST 30th
ANNIVERSARY
ANNUAL MEETING
Red flags that still deserve respect
Despite therapeutic progress, several old lessons remain valid
Rash risk still matters with aromatic agents and lamotrigine, especially during rapid titration.
Hyponatremia remains clinically important with carbamazepine and oxcarbazepine.
Psycho-behavioral toxicity under levetiracetam or perampanel can still destabilize otherwise promising regimens
Long-term metabolic, bone, endocrine, cognitive, and vascular consequences also remain highly relevant in chronic care

31


EST 30th
ANNIVERSARY
ANNUAL MEETING
One field, many sub-landscapes
Neonates remain dominated by phenobarbital-centered pathways despite efforts to improve developmental exposure profiles.
Children increasingly benefit from syndrome-specific thinking and rare-disease programs.
Pregnancy creates a separate landscape driven by teratogenic hierarchy and changing serum concentrations.
Autoimmune epilepsy may require immunotherapy logic more than iterative conventional ASM expansion.

32

EST 30th ANNIVERSARY ANNUAL MEETING

Precision medicine is real, but unevenly real

- Precision medicine is now meaningful in selected developmental epileptic encephalopathies and rare genetically defined disorders
  - In these contexts, syndrome-informed or pathway-informed therapy can genuinely alter drug choice and expectations
  - This is one of the most exciting parts of the current field
- At the same time, most adult focal epilepsy prescribing still depends more on phenotype, tolerability, comorbidity, and systems pragmatism than on genotype-driven drug matching.
- Overstating precision medicine risks distorting current reality
  - The field is advancing, but not uniformly across all epilepsy populations.

Thus, precision medicine should be presented as a selective achievement and an aspirational direction, not yet a universal daily practice standard.

33

EST 30th ANNIVERSARY ANNUAL MEETING

Disease modification remains the unmet breakthrough

- The most important limitation of the current ASM era is that it remains largely symptomatic
- The ILAE terminology paper makes this explicit by separating antiseizure action from true antiepileptogenic or disease-modifying effects
  - Despite decades of research, convincing human evidence for robust disease modification remains limited
- This is why the field still experiences recurrent frustration despite more than thirty approved drugs
- A future therapy that reliably changes the biology of epilepsy would represent a deeper landscape change than any current incremental expansion of symptomatic options

34

EST 30th ANNIVERSARY ANNUAL MEETING

What the next decade may bring

More narrow approvals for rare, molecularly informed epilepsies are likely	Network-level therapies may increasingly combine drugs, biomarkers, and stimulation strategies	Real-world comparative effectiveness data may influence routine prescribing more strongly than before

The 2025 pipeline update described more than 200 therapeutics under development across the epilepsy space, with near-to-market candidates and multiple novel routes still being explored
This suggests that the next stage of progress may be broader than simply “new ASM number 31 or 32.”

It may involve different mechanisms, different delivery strategies, and different definitions of success

35

EST 30th ANNIVERSARY ANNUAL MEETING

A contemporary prescribing algorithm

- **First, define the seizure type, epilepsy syndrome, and whether the patient’s problem is truly epilepsy alone**
- **Second, filter options** through reproductive status, age, cognition, psychiatric profile, renal-hepatic context, and co-medications
- **Third, choose the most sustainable effective drug** rather than the most familiar reflex choice
- **Fourth, re-evaluate early** when the phenotype or adverse-effect story does not fit
- **Fifth, do not delay escalation to surgery, neuromodulation, diet, immunotherapy, or syndrome-specific pathways** when pharmacologic logic is exhausted

36

Take home message

The field has moved from broad anticonvulsant empiricism toward mechanism-aware and phenotype-aware prescribing.	Safety architecture, especially reproductive risk and interaction burden, now strongly reorders first-line preferences.	The next major shift will likely depend as much on disease modification and access reform as on new molecules.

That is the conceptual frame most worth carrying back into clinical practice

37

In conclusion

- The best ASM in 2026 is no longer simply the one that suppresses seizures, It is the one that controls seizures while fitting the patient's syndrome, life stage, reproductive context, psychiatric profile, and treatment environment
  - That is why the field feels so different from a decade ago
- More drugs matter, but better selection matters more
- The future may bring still more choice, but also more responsibility to individualize wisely
- For ASM treatment, this is the core challenge and the core opportunity of the changing landscape of anti-seizure medications

38