14th Regional Teaching Course in Sub-Saharan Africa

Saturday, October 28 – Tuesday, October 31, 2023 Dar es Salaam, Tanzania

Overarching theme

Brain health across the life span

Pharmacological management of epilepsy:

choosing the ASM, rational polytherapy and pharmacoresistant epilepsy

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Disclosures

- No relevant disclosures

The Definition of Epilepsy

In 2005, the ILAE released a conceptual definition of seizures and epilepsy, followed by an operational (practical) definition in 2014.

Fisher et al. ILAE official report: a practical clinical definition of epilepsy. Epilepsia, 2014; 55:475-82.

Conceptual Definition of Epilepsy

Epilepsy is a disorder of the brain characterized by an enduring predisposition to generate epileptic seizures, and by the neurobiologic, cognitive, psychological, and social consequences of this condition. The definition of epilepsy requires the occurrence of at least one epileptic seizure.

ILAE OFFICIAL REPORT

Epilepsia
The Journal of the International League Against Epilepsy

A practical clinical definition of epilepsy

*Robert S. Fisher, †Carlos Acevedo, ‡Alexis Arzimanoglou, §Alicia Bogacz, ¶J. Helen Cross, #Christian E. Elger, **Jerome Engel Jr, ††Lars Forsgren, ‡‡Jacqueline A. French, §§Mike Glynn, ¶¶Dale C. Hesdorffer, ##B.I. Lee, ***Gary W. Mathern, †††Solomon L. Moshé, ‡‡‡Emilio Perucca, §§§Ingrid E. Scheffer, ¶¶¶Torbjörn Tomson, ###Masako Watanabe, and ****Samuel Wiebe

Epilepsia, 55(4):475–482, 2014

1. A least two unprovoked (or reflex) seizures occurring >24 h apart

2. One unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after two unprovoked seizures, occurring over the next 10 years

3. Diagnosis of an epilepsy syndrome

Epilepsy is considered to be resolved for individuals who had an age-dependent epilepsy syndrome but are now past the applicable age or those who have remained seizure-free for the last 10 years, with no seizure medicines for the last 5 years.

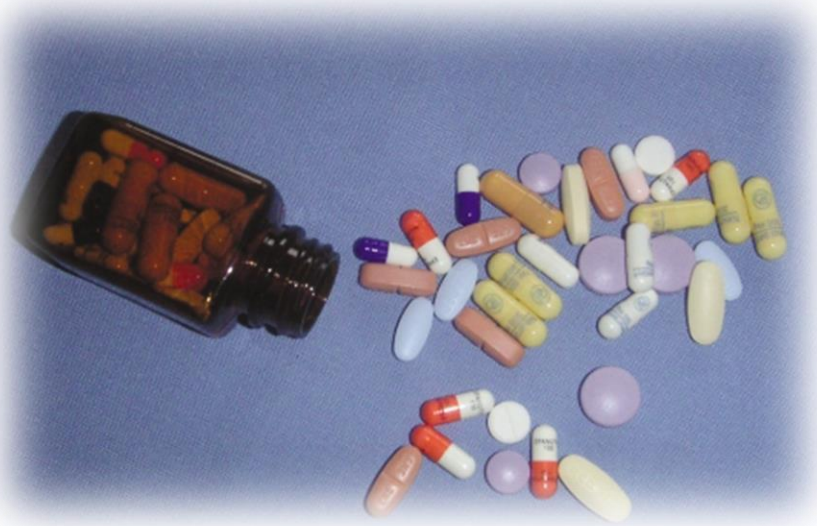
Treatment:

- *Up to 80% of pts can expect partial or complete control of seizures with appropriate treatment.*
- *antiseizure medications suppress but do not cure seizures*
- *An initial therapeutic aim is to use only one medication (monotherapy)*

GOALS OF MANAGEMENT

- !!! SEIZURE FREEDOM
- Monotherapy/ rational polytherapy
- No / minimum adverse effects

WHICH ASM TO CHOOSE?



Antiseizure medication

- An antiseizure medication (ASM) is a medication which decreases the frequency and/or severity of seizures in people with epilepsy

- Treats the symptom of seizures, not the underlying epileptic condition

- Does not prevent the development of epilepsy in individuals who have acquired a risk for seizures (e.g., after head trauma, stroke, tumor)

- Goal of therapy is to maximize quality of life by eliminating seizures (or diminish seizure frequency) while minimizing adverse medication effects

General Recommendations for first- line ASM treatment

first–line treatments for focal and focal-to-bilateral seizures

- Carbamazepine
- Valproate
- lamotrigine
- oxcarbazepine

Bilateral onset seizures; unknown seizure type and/or syndrome

- Valproate
- lamotrigine

Individual patient, individual treatment!

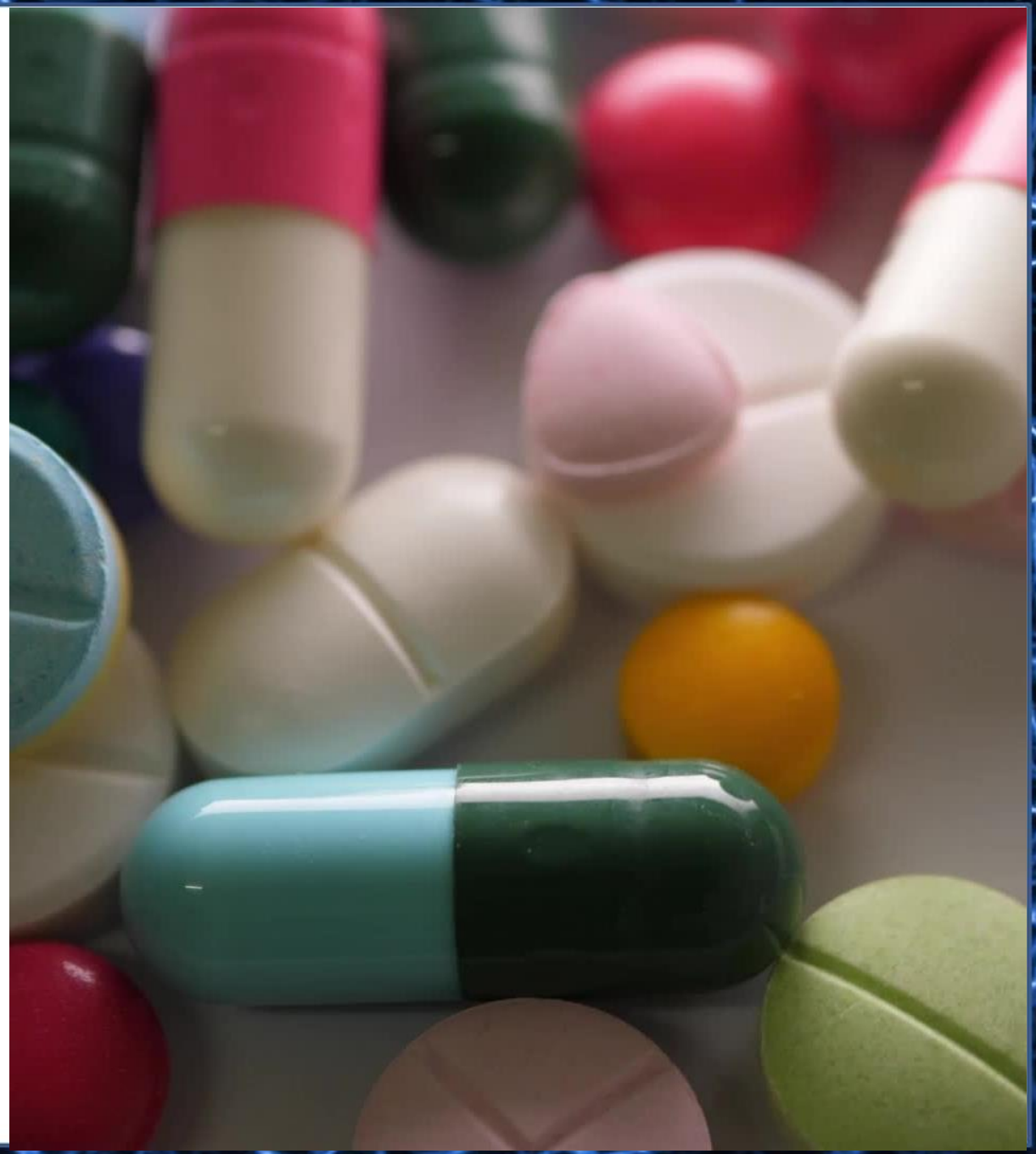
- **NEWER AGENTS DIFFER FROM OLDER medications BY**

Relatively lack of medication-medication interaction (simple pharmacokinetic profile)

Improved tolerability

HOWEVER THEY ARE

Costly with relatively limited clinical experience



Epilepsy syndrome and seizure type

- **valproate - juvenile myoclonic epilepsy;**
- **carbamazepine - frontal lobe epilepsy;**
- **ethosuximide - typical absence seizures.**

WHICH ASM TO CHOOSE?

Newer ASMs

- **Oxcarbazepine** — **focal / focal to bilateral seizures**
- **Tiagabine** — **Add-on therapy for focal onset seizures.**
- **Topiramate** — **Generalized tonic-clonic and focal onset seizures**
- **Vigabatrin** — **Restricted to infantile spasms or refractory epilepsy**

WHICH ASM TO CHOOSE?

Others

• Acetazolamide	Add-on therapy for focal, bilateral and absence seizures
• Clobazam	Add-on therapy
• Clonazepam	Myoclonic seizures
• Ethosuximide	Absence seizures

Pharmacokinetic Principles

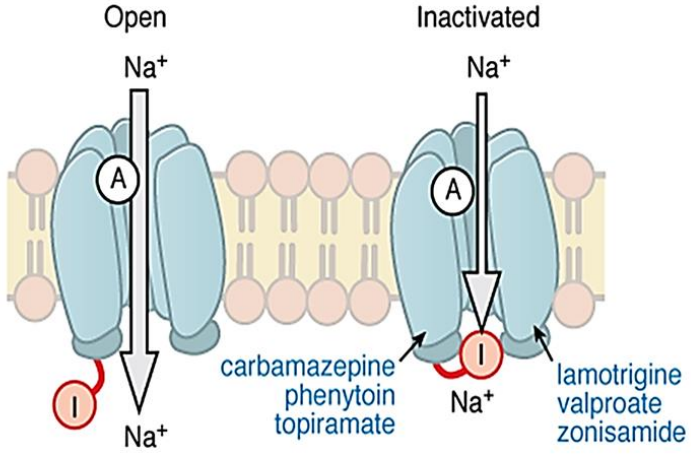
- Absorption: entry of medication into the blood
  - Essentially complete for all ASMs
    - Exception = gabapentin with saturable amino acid transport system.
  - Timing varies widely by medication, formulation and patient characteristics
  - Generally slowed by food in stomach (carbamazepine may be exception)
  - Usually takes several hours (important for interpreting blood levels)

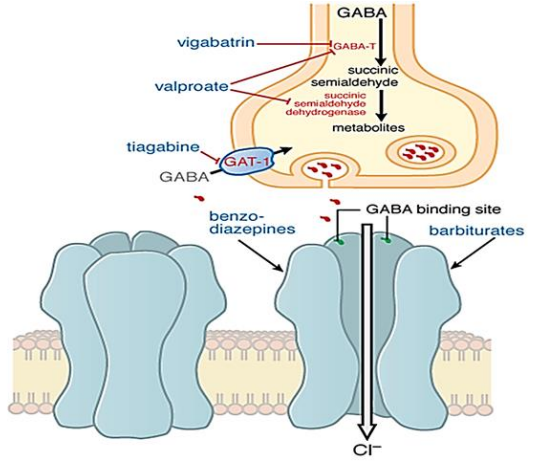
Pharmacokinetic Principles

- Elimination: removal of active medication from the blood by metabolism and excretion
  - Metabolism/biotransformation - generally hepatic; usually rate-limiting step
  - Excretion - mostly renal
  - Active and inactive metabolites
  - Changes in metabolism over time (auto-induction with carbamazepine) or with polytherapy (enzyme induction or inhibition)
  - Differences in metabolism by age, systemic disease

ASMs: Molecular and Cellular Mechanisms Overview

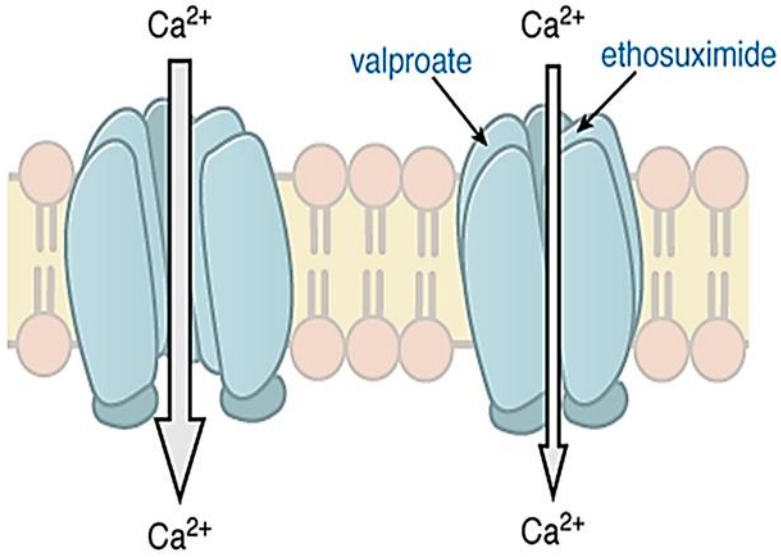
- **Blockers of repetitive activation of sodium channels**:
  - **phenytoin**, **carbamazepine**, oxcarbazepine, **valproate**, felbamate, **lamotrigine**, **topiramate**, zonisamide, rufinamide , **lacosamide**
- **GABA enhancers (direct or indirect):**
  - **barbiturates**, **benzodiazepines, carbamazepine, valproate**, felbamate, **topiramate**, tiagabine, vigabatrin
- **Glutamate modulators:**
  - **Phenytoin, gabapentin, lamotrigine, topiramate, levetiracetam**, felbamate
- **T-calcium channel blockers:**
  - ethosuximide, **valproate**, zonisamide



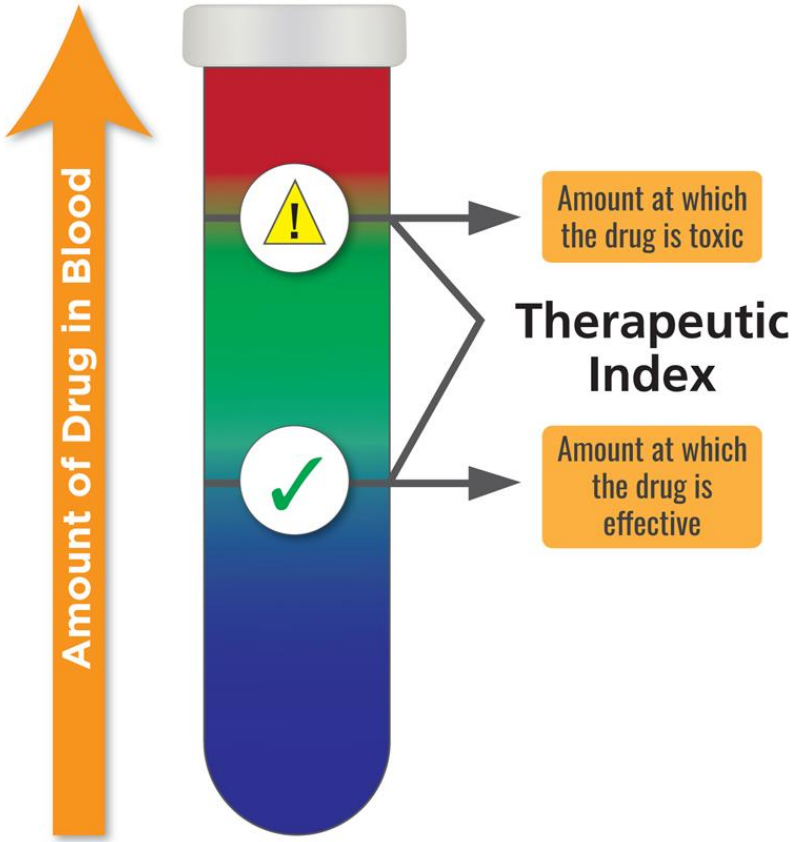


ASMs: Molecular and Cellular Mechanisms Overview

- N- and L-calcium channel blockers:
  - **lamotrigine, topiramate, valproate**, zonisamide
- H-current modulators:
  - **gabapentin, lamotrigine**
- Blockers of unique binding sites:
  - **gabapentin, levetiracetam, pregabalin, lacosamide**
- Carbonic anhydrase inhibitors:
  - **topiramate**, zonisamide

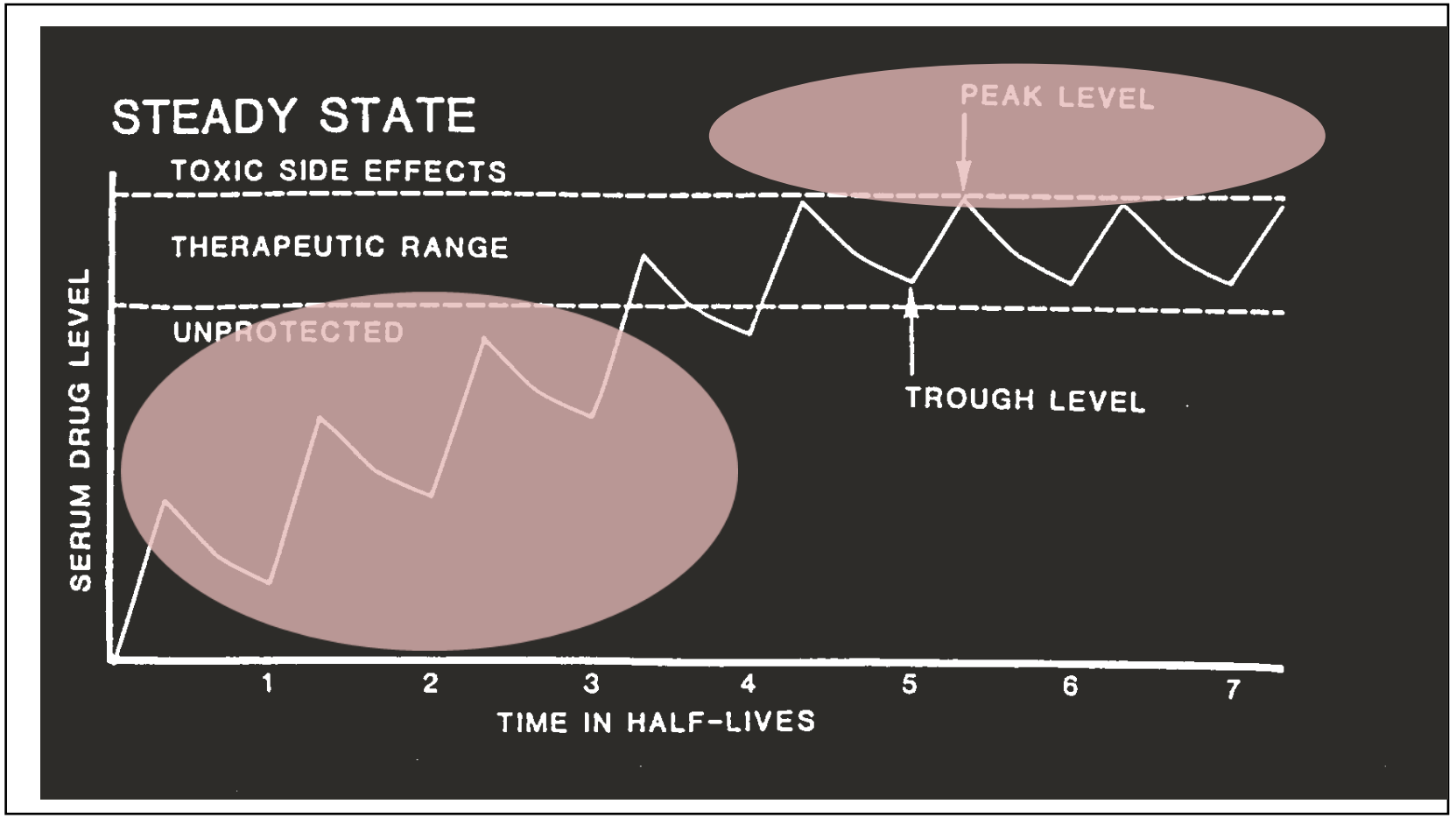


Therapeutic Index



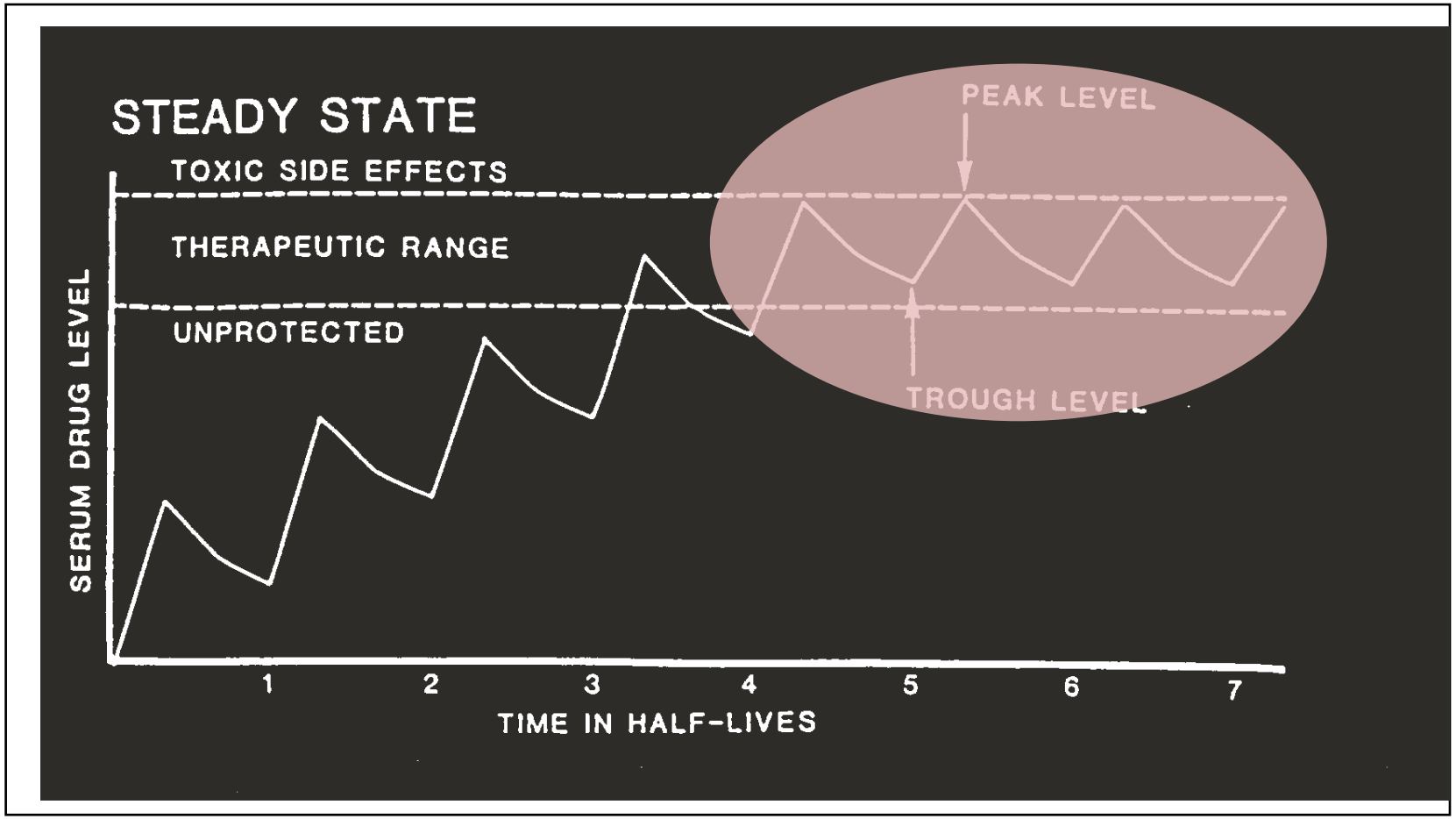
- T.I. = ED 5O% /TD 50%
- "Therapeutic range" of ASM serum concentrations
  - Limited data
  - Broad generalization
  - Individual differences

Steady State and Half Life



From Engel, 1989

Steady State and Half Life



From Engel, 1989

WHICH medication FIRST?

‘one size fits all’

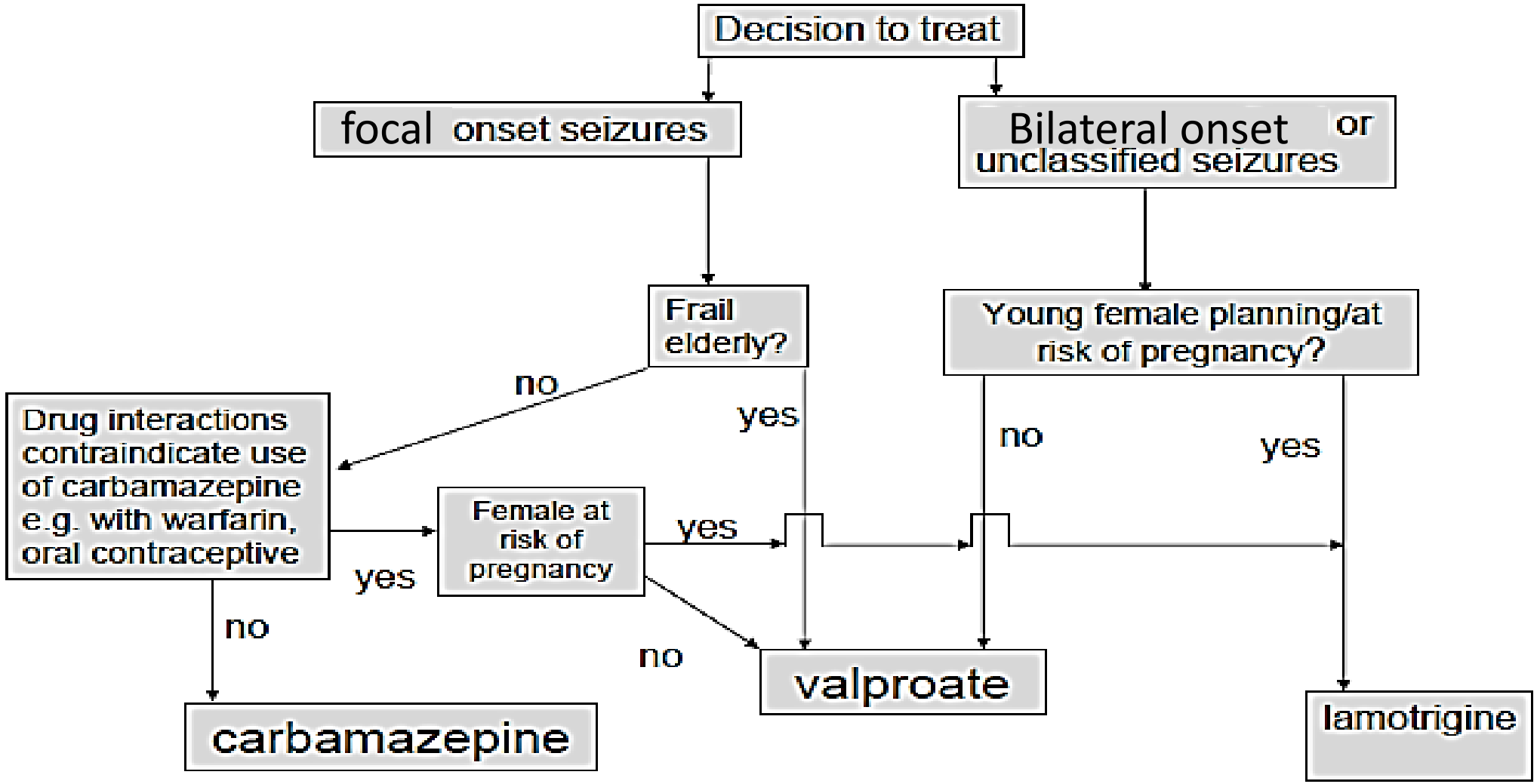
WHICH medication FIRST?

WHICH medication FIRST?

~~'one size fits all'???~~

- Epilepsy syndrome/seizure type
- Age
- Sex
- Comorbidities

ALGORITHM FOR CHOICE OF FIRST ASM



ASM Serum Concentrations

- Serum concentrations are useful when optimizing ASM therapy, assessing adherence, or teasing out medication-medication interactions.
- They should be used to monitor pharmacodynamic and pharmacokinetic interactions.
- Should be done when documenting a serum concentration when a patient is well controlled.

ASM Serum Concentrations

- Serum concentrations are also useful when documenting positive or negative outcomes associated with ASM therapy.
- Most often individual patients define their own “therapeutic range” for ASMs.
- For the new ASMs there is no clearly defined “therapeutic range”.

“RATIONAL POLYTHERAPY”

- Different mechanisms of action
- Potentiating pharmacokinetic interactions
- Avoid combinations with similar mechanism of actions and/or unhelpful pharmacokinetic interactions

The Cytochrome P-450 Isozyme System

- Enzymes most involved with medication metabolism
- Nomenclature based upon homology of amino acid sequences
- Enzymes have broad substrate specificity and individual medications may be substrates for several enzymes
- The principal enzymes involved with ASM metabolism include **CYP2C9, CYP2C19 & CYP3A4**

ASM Inducers: The Cytochrome P-450 Enzyme System

- **Broad Spectrum Inducers**:
  - phenobarbital - CYP1A2, 2A6, 2B6, 2C8/9, 3A4
  - primidone - CYP1A2, 2B6, 2C8/9, 3A4
  - phenytoin - CYP2B6, 2C8/9, 2C19, 3A4
  - carbamazepine - CYP1A2, 2B6, 2C8/9, 2C19, 3A4
- **Selective CYP3A Inducers**:
  - oxcarbazepine - CYP3A4 at higher doses
  - topiramate - CYP3A4 at higher doses
  - felbamate - CYP3A4
- Tobacco/cigarettes - CYP1A2

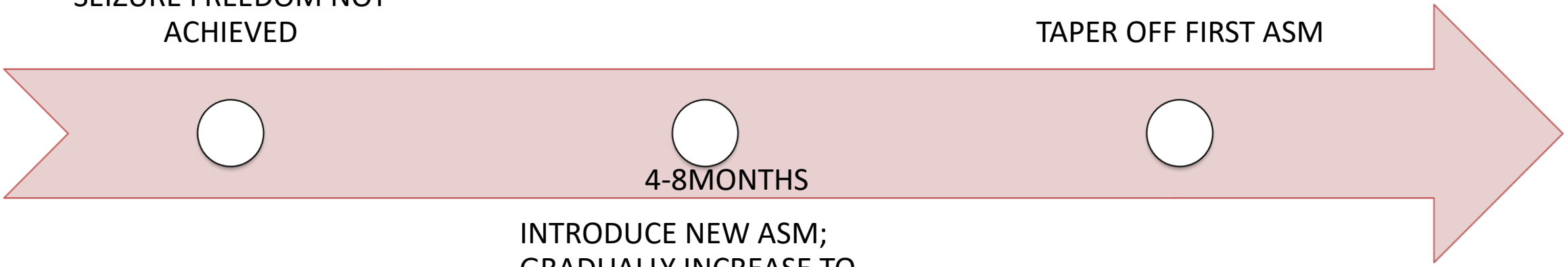
medication Metabolizing Enzymes: UDP- Glucuronyltransferase (UGT)

- Important pathway for medication metabolism/inactivation
- Currently less well described than CYP
- Several isozymes that are involved in ASM metabolism include:
  - UGT1A9 (VPA)
  - UGT2B7 (VPA, lorazepam)
  - UGT1A4 (LTG)

AEDs THAT INDUCE HEPATIC ENZYMES	NON-ENZYME INDUCING AEDs
Carbamazepine	Acetazolamide
Oxcarbazepine	Benzodiazepines
Phenobarbital	Ethosuximide
Phenytoin	Gabapentin
Primidone	Lamotrigine
Topiramate	Levetiracetam
	Tiagabine
	Valproate
	Vigabatrin

HOW TO INTRODUCE A NEW ASM

MAXIMUM TOLERABLE DOSE OF APPROPRIATE ASM – SEIZURE FREEDOM NOT ACHIEVED

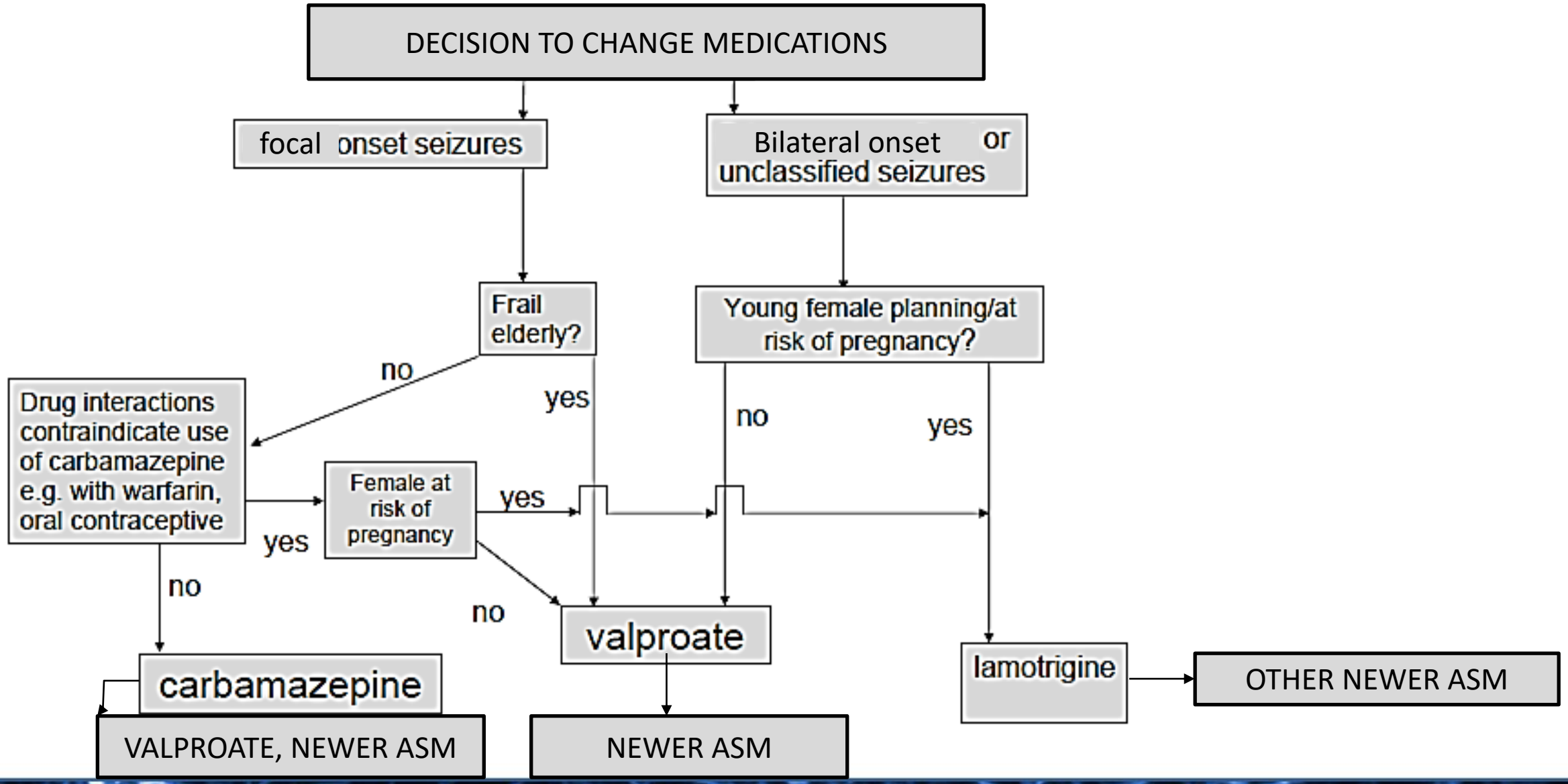


4-8MONTHS

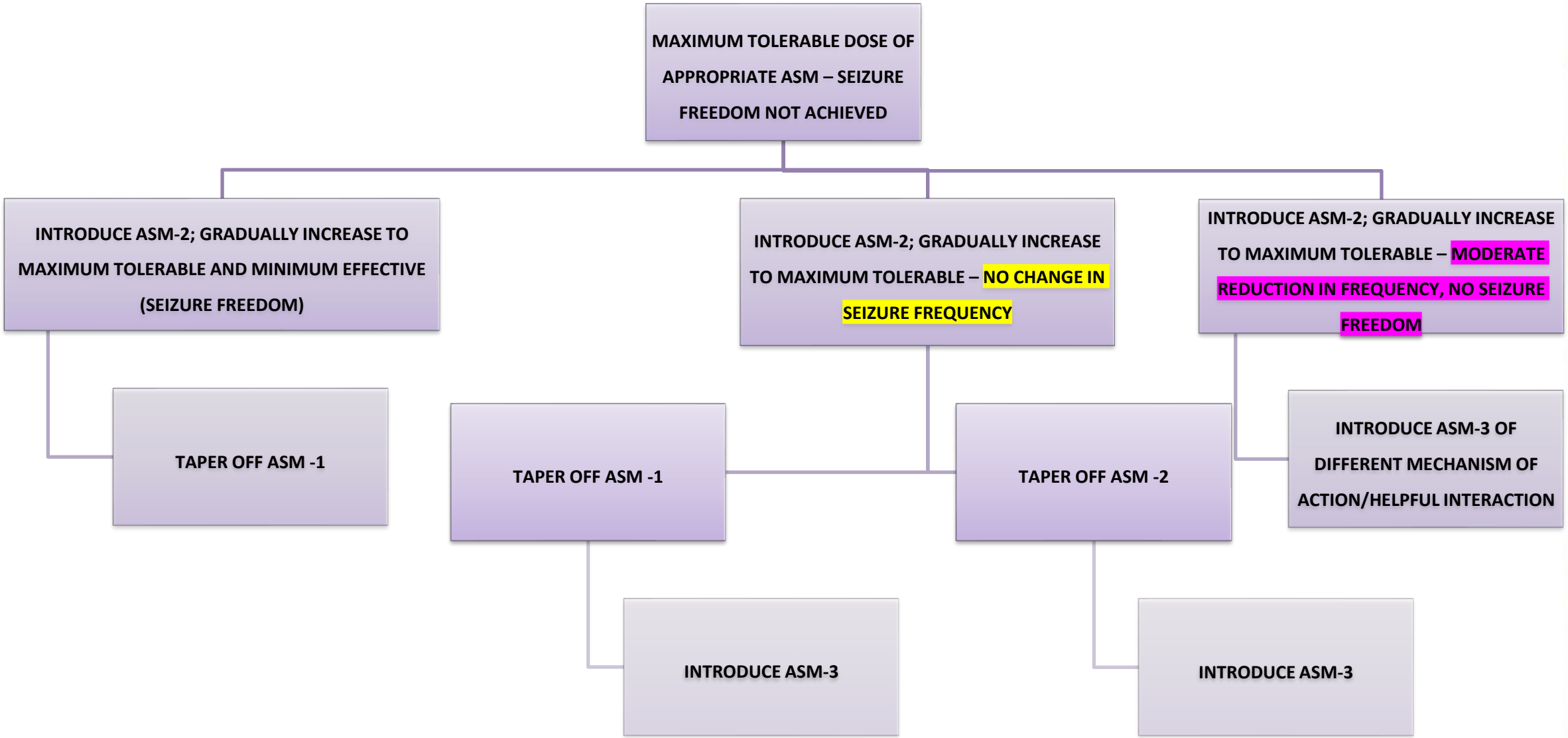
INTRODUCE NEW ASM; GRADUALLY INCREASE TO MAXIMUM TOLERABLE AND MINIIMUM EFFECTIVE (SEIZURE FREEDOM)

TAPER OFF FIRST ASM

ALGORITHM FOR CHOICE OF SECOND ASM WHEN FIRST HAS FAILED



HOW TO INTRODUCE A NEW ASM



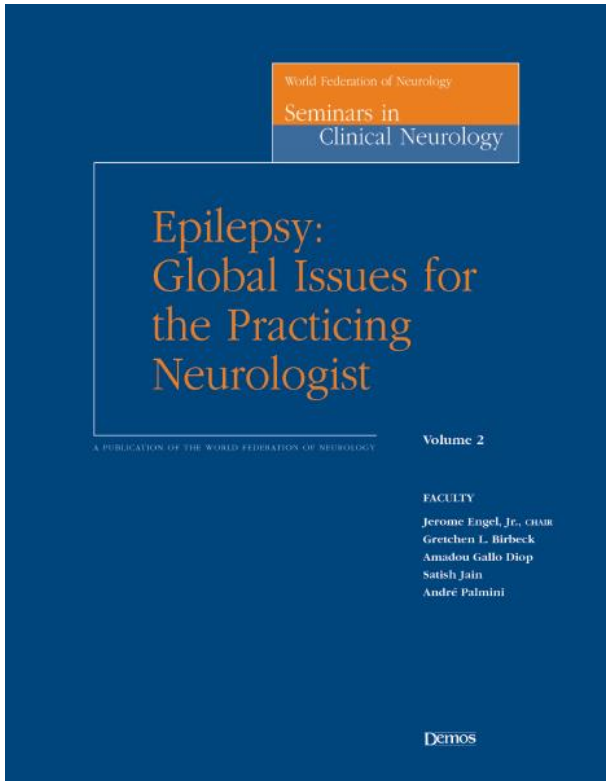
Intractable Epilepsy

Epilepsia, 51(6):1069–1077, 2010
doi: 10.1111/j.1528-1167.2009.02397.x

SPECIAL REPORT

Definition of drug resistant epilepsy: Consensus proposal by the ad hoc Task Force of the ILAE Commission on Therapeutic Strategies

*[1]Patrick Kwan, †Alexis Arzimanoglou, ‡Anne T. Berg, §Martin J. Brodie, ¶W. Allen Hauser, #[2]Gary Mathern, **Solomon L. Moshé, ††Emilio Perucca, ‡‡Samuel Wiebe, and §§[2]Jacqueline French



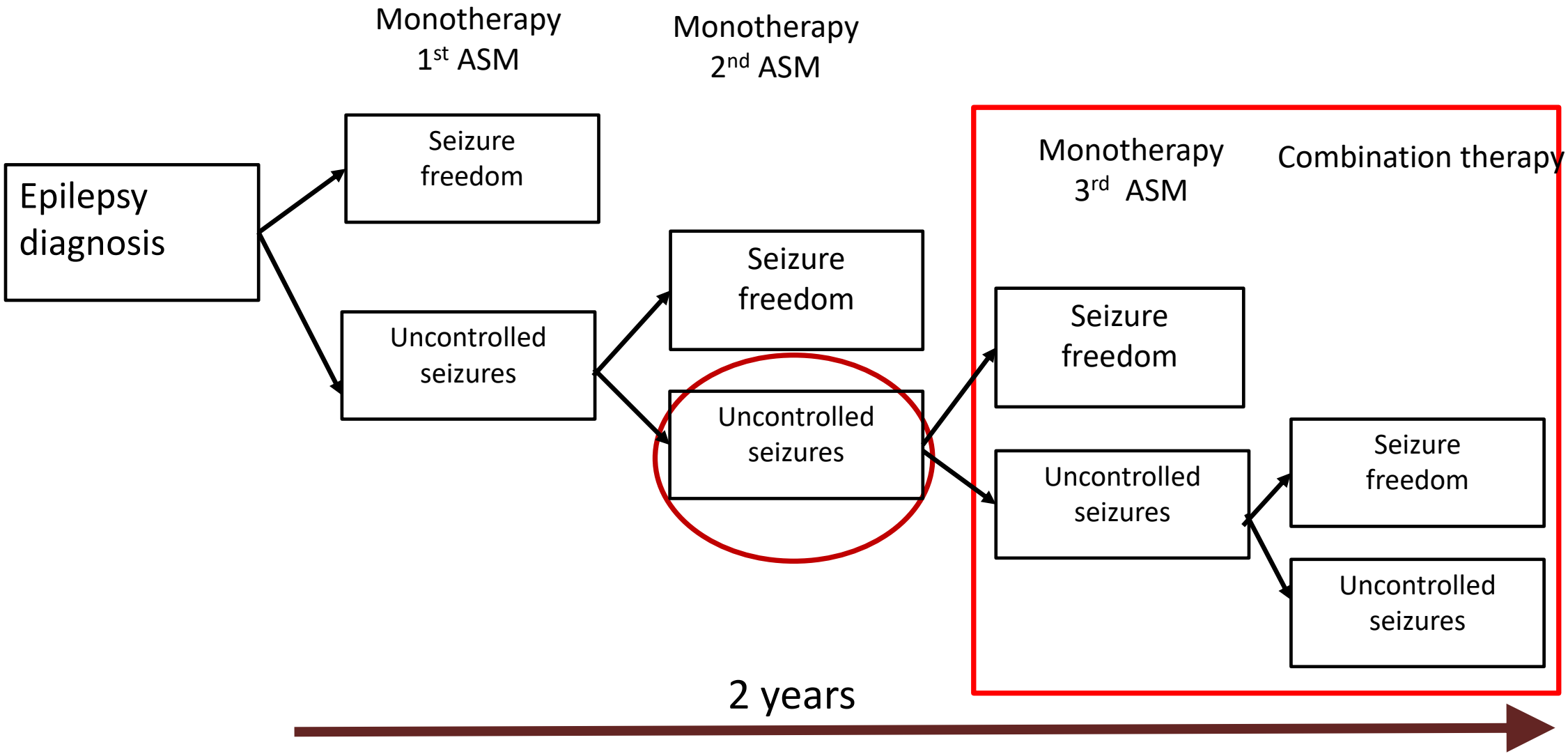
- ILAE definitions:

✓Drug resistant epilepsy

  – Epilepsy in which seizures persist and seizure freedom is very unlikely to be attained with further manipulation of ASM therapy: ‘‘failure of adequate trials of two tolerated and **appropriately chosen** and used ASM schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom’’

Kwan et al Epilepsia 2009

Determination of Pharmacoresistance



TAKE HOME POINTS

- Be sure that treatment failure is not due to inappropriate choice of ASM
- Confirm compliance (with serum concentration if needed)
- Strive towards monotherapy
- If polypharmacy mandated by treatment response, use ASM of varying mechanisms of action
- Know drug interactions, comorbidities
- If 3 or more ASMs have failed - alone and in combination–> pharmaco-resistance (further trials are unlikely to be successful (**if first 3 ASMs appropriately chosen)**

THE END

THANK YOU