Epilepsy Treatment Principles

Last updated: September 18, 2024

Conservative management includes three areas:

1. **PHARMACOLOGIC**:
   1) treatment of underlying conditions
   2) suppression of recurrent seizures.

2. **PSYCHOSOCIAL**:
   1) employability, insurability
   2) avoidance of precipitating factors. see p. E1 >>

3. **LEGAL**:
   1) **reporting by physician** (required in some states)
   2) **lifestyle restrictions** (vary from state to state):

restrict life as little as possible!
recommendations must be documented very well in chart!

- ***driving motorized vehicles*** (patient should be advised to contact state agency that regulates driving privileges);
  - most states permit *automobile driving* if:
    a) seizures have not recurred (on or off medications) for 3 months ÷ 2 yr (even after first seizure); some states (Colorado, Nebraska) do not have regulations
    b) seizures occur only during sleep for last 3 years.
  - for *commercial driving* across state lines, patient must be 5-year seizure-free.
  - driving is not permitted during drug tapering (treatment termination; wait at least for 6 months after the last drug dose).

  - *aircraft pilots* are typically no longer permitted to fly.
  - some patients state they know when every seizure is coming and they can pull over.
    N.B. by EMU data, when patients would push button when they feel seizure is coming, only 44% of seizures could be identified by patients who thought they know each of their seizures.
- ***water precautions*** - do not swim alone, do not bath infants alone, wear life jacket in boat.
  N.B. patient can drown with as little as inch of water during flaccid postictal phase! – use showers instead of baths!
- ***heights*** - encourage use of helmets.
- ***fire*** (esp. burns related to cooking) – use microwave instead of cooking!
- ***power tools*** - supervision during use + safety devices (e.g. automatic shutoff switches).

DURING SEIZURE

N.B. **prolonged seizure** (**≥ 5 minutes**) must be treat as status epilepticus. see p. E7 >>

1. *Intravenous anticonvulsants are not required* for uncomplicated seizure!!!
2. **Protect from self-harm** (pillows, padded side rails, etc).
3. Loosen ***tight clothing and jewelry around neck***.
4. Gently hyperextend neck and thrust jaw to enhance breathing.
5. Roll patient into **left lateral decubitus position** to prevent aspiration.
   - this may cause more harm than good:
     1) greater risk for self-injury (such as dislocated shoulder).
     2) patients are not breathing during generalized tonic-clinic seizure - no high risk for aspiration until event ends.
   - roll patient onto side ***immediately after motor activity ceases*** (patients usually take deep breath immediately following seizure).
6. Mouth should not be opened forcibly (by object or finger)*, protecting tongue should not be attempted - teeth may be dislodged and aspirated + risk of significant injury to oropharynx; wait to suction oropharynx until end of seizure.
   *__bite block__ could protect tongue and allow suctioning access.
7. Rescue home treatment:
   a) one dose rectal DIAZEPAM gel (Diastat®) 10-20 mg (0.05-0.1 mg/kg) should be considered before transfer to ED.
   b) intranasal DIAZEPAM (Valtoco®) – FDA review.
   c) intranasal MIDAZOLAM (Nayzilam®) – FDA approved.
   d) buccal MIDAZOLAM into mouth (between gums and cheek) is twice as effective as rectal DIAZEPAM!
8. If seizures continue, EMS can give IV/IM* FOSPHENYTOIN
   *gets absorbed in 5 mins, therapeutic level in 10 minutes

PATIENT AND CAREGIVER COUNSELLING

Seizure and syncope precautions: The patient has been advised not to drive a motor vehicle or operate any potentially hazardous or dangerous equipment. The patient is directed to avoid ladders and high places, such as scaffolding, and to not even get up on a chair to change a light bulb. The patient is instructed to avoid swimming, bathing, or going near large bodies of water unless closely supervised. Lastly, if on seizure medication, the patient is instructed to avoid alcohol or drugs other than those prescribed by a physician.

First-Aid for Seizures. Specifically, the patient, friends, coworkers, employers, and family are advised of the following:

- do not restrain someone having a seizure;
- do not interfere with the seizure patient's movements;
- not to force anything between the teeth of someone having a seizure;
- not to try to force liquids or anything else into the person's mouth;
- to **place a blanket, pillow or coat beneath the head**, if possible, and to **turn the patient to one side** to help prevent aspiration of vomit;
- that it is not generally necessary to call EMS unless the seizure is followed almost immediately by another seizure, or if the seizure lasts more than 5-10 minutes, or if the patient has been injured during the seizure;
- that it is not usually necessary to call an ambulance and rush the patient to the hospital for a brief seizure that has stopped on its own;
- to keep a crowd from gathering around the person having a seizure;
- to **let the patient rest after the seizure** is over; and,
- if the seizure occurs at a place of work or at school, to notify the facility nurse or the patient's physician.

DECISION TO HOSPITALIZE AND START TREATMENT

Factors **against** treatment:

1) risk of *adverse effects*, incl. all ASMs increase *risk of suicidality* 2-fold
2) unknown effects of long-term ASM treatment on *brain development*, *learning*, *behavior* - may be insidious and not apparent for many years!
3) anticonvulsant therapy *does not affect long-term prognosis* (ASM significantly reduces risk of recurrence, but does not guarantee remission).

Factors **for** treatment:

1) risk factors for *seizure recurrence* (patients with ≥ 1 of these risk factors probably should be treated):
   a) **focal onset**
   b) **abnormal EEG** (even interictal spikes* are not benign - affect neuropsychological function!!!!, e.g. impair learning).
      *interictal spike burden does not predict likelihood of seizures;
      there are no medications developed to treat spikes!
   c) **abnormal MRI**
   d) **abnormal neurologic examination** (incl. postictal Todd's paralysis)
   e) predisposing **neurologic injury** sufficient to cause seizures.
   f) **family history** of epilepsy
   g) **age** < 16 years
   h) seizures **presenting as status epilepticus**
   i) **seizure while sleeping** (twice risk of recurrence compared with seizures while awake).
   j) history of **neurologic deficit from birth**

risk of recurrence after first seizure:
normal EEG + normal MRI + no evidence of focal onset → risk 15% → do not treat.
abnormal EEG + abnormal MRI + focal onset → risk 80% → start treatment.

chance of second seizure:
normal MRI and EEG = 1 in 3
either test abnormal =1 in 2
both tests abnormal = 2 in 3

2) *consequence to patient* of recurrent seizures.
   - *short consciousness impairments* in **debilitated** patients - no need to treat as treatment is more harmful (but ask - is patient impaired due to such seizures?) vs. **high functioning** patient maybe impaired with *subclinical* seizures.

First seizure – transport to ED and admit for several hours of **observation** (most patients recover rapidly after isolated seizure).

- **screen for acute medical / neurologic illness** (i.e. determine if seizure was PROVOKED / UNPROVOKED): complete history, vital signs, general and neurologic examinations, basic chemistry studies, toxicology screen.
- **EEG** & **neuroimaging** need not be done emergently (can be done on outpatient basis – see p. E1 >>) unless high *likelihood of acute cerebral lesion* or patient *remains obtunded* for > 30 min.

> PROLONGED POSTICTAL CONFUSION suggests either ***ongoing seizure activity*** (status epilepticus) or ***underlying encephalopathic condition*** (toxic, metabolic, infectious, or structural).

- **hospitalization** is not necessary if all criteria can be fulfilled:
  1) no suspicion of ***underlying illness***
  2) ***responsible adult*** can observe patient closely at home
  3) ***follow-up is available*** (make appointments for MRI, EEG, and follow-up care with neurologist while patient is still in ED!)
- if criteria are not fulfilled, perform **neuroimaging** (at least CT) in ED; if with fever → add **lumbar puncture**.

UNPROVOKED / IDIOPATHIC seizure

> many persons who experience ***first unprovoked seizure*** never have second, so do not need treatment!; after ***second unprovoked seizure*** (reliable marker of epilepsy) risk for further recurrence is > 80% → start ASM therapy.

- hospitalization and treatment are unnecessary* for ***first unprovoked (afebrile) seizure*** with uneventful recovery and possible good follow-up;
  *but always consider ***risk factors*** **for seizure recurrence** (*see above*) and ***consequence to patient*** **of seizure recurrence** – if necessary, start ASM even after first seizure!
  e.g. patient with single, idiopathic seizure whose job depends on driving may prefer taking ASM rather than risking seizure recurrence and potential loss of driving privileges.
- if patient is going to have recurrence, most occur **within 3 months**.

PROVOKED / SYMPTOMATIC seizure

> If ***provoking factor cannot be promptly corrected*** → start ASM therapy.

N.B. diagnosis of epilepsy refers to recurrent seizures and cannot be made on basis of single episode, even if anticonvulsant treatment is administered!

INITIATING DRUG THERAPY

- always start with **MONOTHERAPY**.
- initial target dose should produce serum concentration in low-to-mid therapeutic range.
  N.B. PHENYTOIN requires large loading doses!

  - if therapeutic blood levels need to be achieved rapidly – use drugs for which loading doses are practical (PHENYTOIN, VALPROATE, PHENOBARBITAL, LEVETIRACETAM).
- patients should expect that minor side effects (mild sedation, slight changes in cognition, imbalance, etc) will typically resolve within few days.
- ***slowly increase (titrate) dosage*** until seizures are controlled* or toxic signs occur (do not rely solely on therapeutic levels, which is only range in which most patients have seizure control without side effects)

*ASM efficacy can only be evaluated in STEADY STATE (not earlier!) *see below*

"start low, go slow"

- consider Medic-Alert bracelet or necklace.

DRUG SELECTION

- drug selection is based on specific **SEIZURE TYPE** (or specific **EPILEPSY SYNDROME**).
- several drugs may be equally effective, and *agent toxicity* is often major consideration in drug selection.

For focal seizures, ASMs that work for adults also work for kids ≥ 4 yo (kids ≥ 2 yo are similar to adults in brain EEG, transmitters, electrophysiology)

Seizure Type	First-line Agents	Adjunctive Agents
Tonic-clonic	VALPROATE* CARBAMAZEPINE PHENYTOIN	PHENOBARBITAL PRIMIDONE LAMOTRIGINE TOPIRAMATE
Absence	ETHOSUXIMIDE VALPROATE*	LAMOTRIGINE TOPIRAMATE BENZODIAZEPINES ACETAZOLAMIDE PHENOBARBITAL CLONAZEPAM
Myoclonic	VALPROATE BENZODIAZEPINES	LAMOTRIGINE TOPIRAMATE FELBAMATE ZONISAMIDE ACETAZOLAMIDE KETOGENIC DIET
Tonic/atonic	VALPROATE BENZODIAZEPINES	LAMOTRIGINE TOPIRAMATE FELBAMATE VIGABATRIN
Focal (partial) onset	LAMOTRIGINE** CARBAMAZEPINE PHENYTOIN VALPROATE	GABAPENTIN OXCARBAZEPINE TOPIRAMATE PHENOBARBITAL / PRIMIDONE

		PREGABALIN ZONISAMIDE TIAGABINE LEVETIRACETAM

*VALPROATE is drug of choice for generalized seizures, esp. when ***several seizure types coexist*** or difficult to classify; except ***women of childbearing age*** – use LEVETIRACETAM instead!

**LAMOTRIGINE is drug of choice for focal epilepsy, esp. in elderly.

N.B. LEVETIRACETAM is inferior to CARBAMAZEPINE and LAMOTRIGINE in the treatment of focal epilepsy!

	PARTIAL seizures	GENERALIZED seizures		
		Tonic-Clonic	*Absence*	*Myoclonic*
Classic ASMs				
PHENYTOIN	1	1	*aggravates*	*aggravates*
CARBAMAZEPINE	1	1	*aggravates*	*aggravates*
VALPROATE	1-2	1	1	1
PHENOBARBITAL	3	2	–	±
PRIMIDONE	3	3	–	±
ETHOSUXIMIDE	–	–	1	±
CLONAZEPAM*	4	4	2	2
New ASMs (still not generally indicated as first choice for monotherapy)				
FELBAMATE	Effective	Effective	Effective	Effective
GABAPENTIN	Effective	±	*aggravates*	–
OXCARBAZEPINE	Effective	±	–	–
LAMOTRIGINE	Effective	Effective	Effective	Effective
TOPIRAMATE	Effective	Effective	±	Effective
TIAGABINE	Effective	±	*aggravates*	–
VIGABATRIN	Effective	±	–	–
ZONISAMIDE	Effective			Effective
LEVETIRACETAM	Effective			
PREGABALIN	Effective		?	

* tolerance development is problem

SANAD II – first choice in focal epilepsy

The SANAD II study of the effectiveness and cost-effectiveness of valproate versus levetiracetam for newly diagnosed generalised and unclassifiable epilepsy: an open-label, non-inferiority, multicentre, phase 4, randomised controlled trial. Marson A, Burnside G, Appleton R, et al. Lancet. 2021;397(10282):1375-1386 doi:10.1016/S0140-6736(2100246-4)

- randomised, open-label, controlled trial compared levetiracetam and zonisamide with lamotrigine as first-line treatment for patients with newly diagnosed focal epilepsy (990 patients, age ≥ 12 yo).
- trial findings do not support the use of levetiracetam or zonisamide as first-line treatments for focal epilepsy; LAMOTRIGINE should remain a first-line treatment for focal epilepsy and should be the standard treatment in future trials.

THERAPEUTIC DRUG MONITORING, ADJUSTING DOSAGE

- to minimize [drug] fluctuations, dosing interval should not exceed $T_{1/2}$ (advisable, < $T_{1/2}$ / 2; ideally, < $T_{1/2}$ / 3).
- **steady state** - equilibrium between drug intake and clearance;

  N.B. steady state is reached after time interval equal to **$5 \times T_{1/2}$**

Therapeutic blood level - range within which most patients experience ***improvement in seizure control*** and ***few or no adverse reactions***.

- blood levels are obtained during **steady-state** (i.e. no sooner than 5 × $T_{1/2}$ after dosage adjustment).
- therapeutic blood level should serve as general guide only;

patient's *individual clinical response* should prevail over *laboratory reading*

  - some become seizure-free with subtherapeutic concentrations;
  - some benefit from "toxic" levels without adverse effects.

  N.B. "subtherapeutic" drug level should be altered only if seizures remain uncontrolled!!!

- no standard recommendations exist for timing of laboratory monitoring.
- INDICATIONS:
  1) **baseline**: after seizures are controlled, determine drug *levels needed to achieve seizure-free effectiveness*.
  2) **toxicity**: determine maximal ASM dose that patient can *tolerate without toxic effects*.
  3) **lack of efficacy vs. noncompliance**: before anticonvulsant is deemed failure, knowing whether patient has *achieved adequate drug level* is imperative; 30% patients miss at least 1 dose of medication every month (H: pill reminder boxes for all patients with epilepsy)

if problem is **TOXICITY**, *peak serum level* is desirable; if problem is **EFFICACY/COMPLIANCE** - use *trough serum level* (just before next dose)

N.B. supratherapeutic levels of some anticonvulsants (e.g. PHENYTOIN, CARBAMAZEPINE) can *cause* seizures! - be cautious about giving full loading anticonvulsant dose to patients on chronic therapy before checking serum level!

  4) **suspected pharmacokinetic change**:
     [1]*hepatic autoinduction*;
     [2]*concurrent medications* with **P-450 induction / inhibition** potential or **highly bound to serum proteins***;
     [3]*altered metabolism* (neonates ÷ young children, elderly, hepatic failure);
     [4]*altered protein binding** (uremia, hypoalbuminemia, pregnancy); esp. important for highly protein-bound drugs (PHENYTOIN, VALPROATE).

*measure of ***free drug fraction*** (vs. [total drug]) is advisable!

N.B. only free (protein-unbound) fraction penetrates BBB and produces desirable / undesirable effects

COMPLIANCE

Most common cause of *breakthrough seizures* is **noncompliance**!

- only 70% patients take anticonvulsant medications as prescribed.
- persistently low [drug] in face of increasing dosage generally implies poor compliance.
- caution with PHENYTOIN - 20% patients have poor absorption or rapid metabolism.
- risk factors for noncompliance:
    1) adolescents and elderly persons
    2) infrequent seizures
    3) dosage several times per day
    4) persisting toxic effects
    5) psychiatric symptoms (esp. depression)

BREAKTHROUGH SEIZURE

Known epileptic patient who has had single, typical seizure and whose mental status has returned to baseline need not be transported to ED (vs. **first seizure** → transport to ED).

A. Patient did not get ASM

N.B. **noncompliance** is most frequent cause!

- patients must be encouraged to ***take medications as prescribed*** and to ***arrange follow-up*** with their own physician as soon as possible.
- if patient stopped taking medication because he was drinking alcohol, advise to ***continue taking ASM even if drinking*** (while warning against respiratory depressive effects when combined with alcohol!).

If patient has run out of medication and has no refills on his prescription, he should be told to go to ED (or urgent care clinic) if someone can provide transportation;

- if not, patient is transported to ED by ambulance.
- in ED, only testing required is **serum anticonvulsant level**.

B. [ASM] is below upper limit of therapeutic range* → loading dose of ASM, increase maintenance dose and check level soon:

$$\mathbf{D} = \mathbf{Vd} \times \Delta\mathbf{C}$$

D – drug dose (mg/kg) required to achieve particular serum concentration (μg/mL)
Vd – volume of distribution (L/kg)
ΔC = desired concentration* - actual concentration

*if specific patient's optimal levels are unknown, reasonable target levels are at upper end of usual therapeutic ranges.

ASM	**Vd** (L/kg)
CBZ	0,8
PHT	0,8
PHB	0,6

VPA	0,2

- ***intravenous loading*** can be performed with PHB, PHT, VPA; ***oral loading*** is limited by toxic adverse effects (including nausea and vomiting), but required calculated dose can be spread out over day or more if necessary.

C. [ASM] is at the upper limit of therapeutic range → add second ASM

MONITORING OF ADVERSE EFFECTS

1. **CBC** – baseline + periodic assessment during CARBAMAZEPINE, ETHOSUXIMIDE, VALPROATE therapy.
2. **Liver transaminases** – baseline + periodic assessment during CARBAMAZEPINE, VALPROATE, PHENYTOIN, PRIMIDONE / PHENOBARBITAL therapy.
   — discontinue ASM if GGT exceeds twice normal.

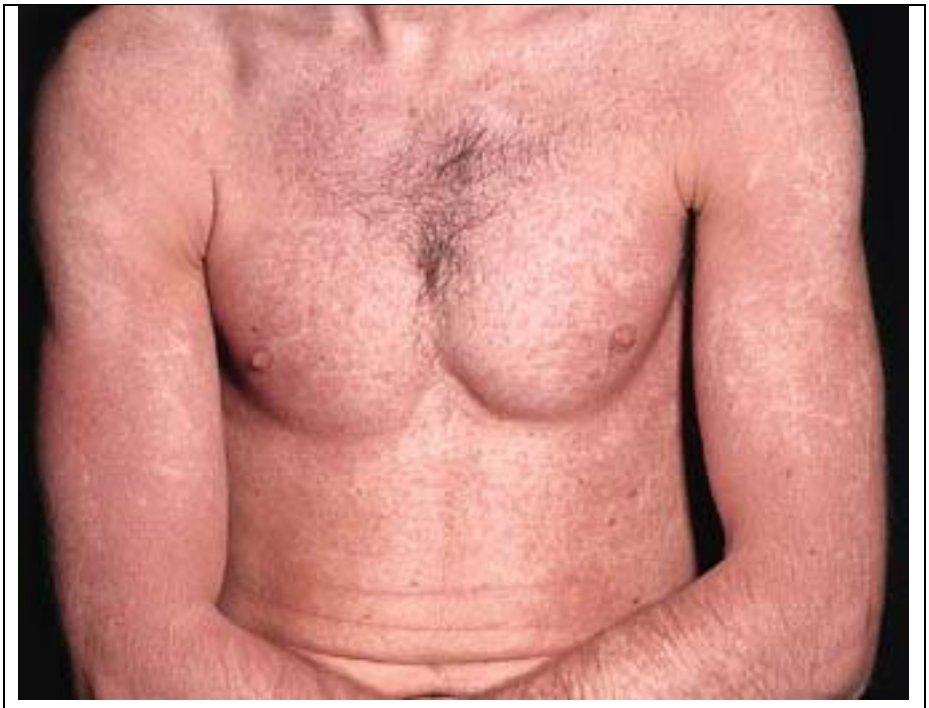
Most adverse drug effects are mild and **DOSE-RELATED**.

- typically appear when drug is first given or when dosage is increased.
- usually, but not always, correlate with blood concentrations.
- reversible on lowering dosage or discontinuing drug.
- many are common to virtually all antiepileptic drugs - sedation, mental dulling, impaired memory and concentration, mood changes, dizziness, GI upset.
  N.B. all ASMs depress CNS even in therapeutic concentrations!

IDIOSYNCRATIC adverse effects are ***rare***, but ***most serious*** (life-threatening) reactions to ASMs; similar for all ASMs:

1. Rash – most frequent idiosyncratic reaction
2. Exfoliative dermatitis, erythema multiforme, Stevens-Johnson syndrome
3. Agranulocytosis, aplastic anemia, thrombocytopenia
4. Pseudolymphoma syndrome
5. Hepatic failure
6. Pancreatitis
7. Connective tissue disorders

N.B. no laboratory test can identify individuals specifically at risk!



Hypersensitivity to phenytoin - symmetrical, bright-red, exanthematous eruption, confluent in some sites; associated lymphadenopathy.

Antiepileptic drugs ≈ 2-fold increase risk of suicidal behavior / ideation (0.43%) compared to placebo (0.22%).

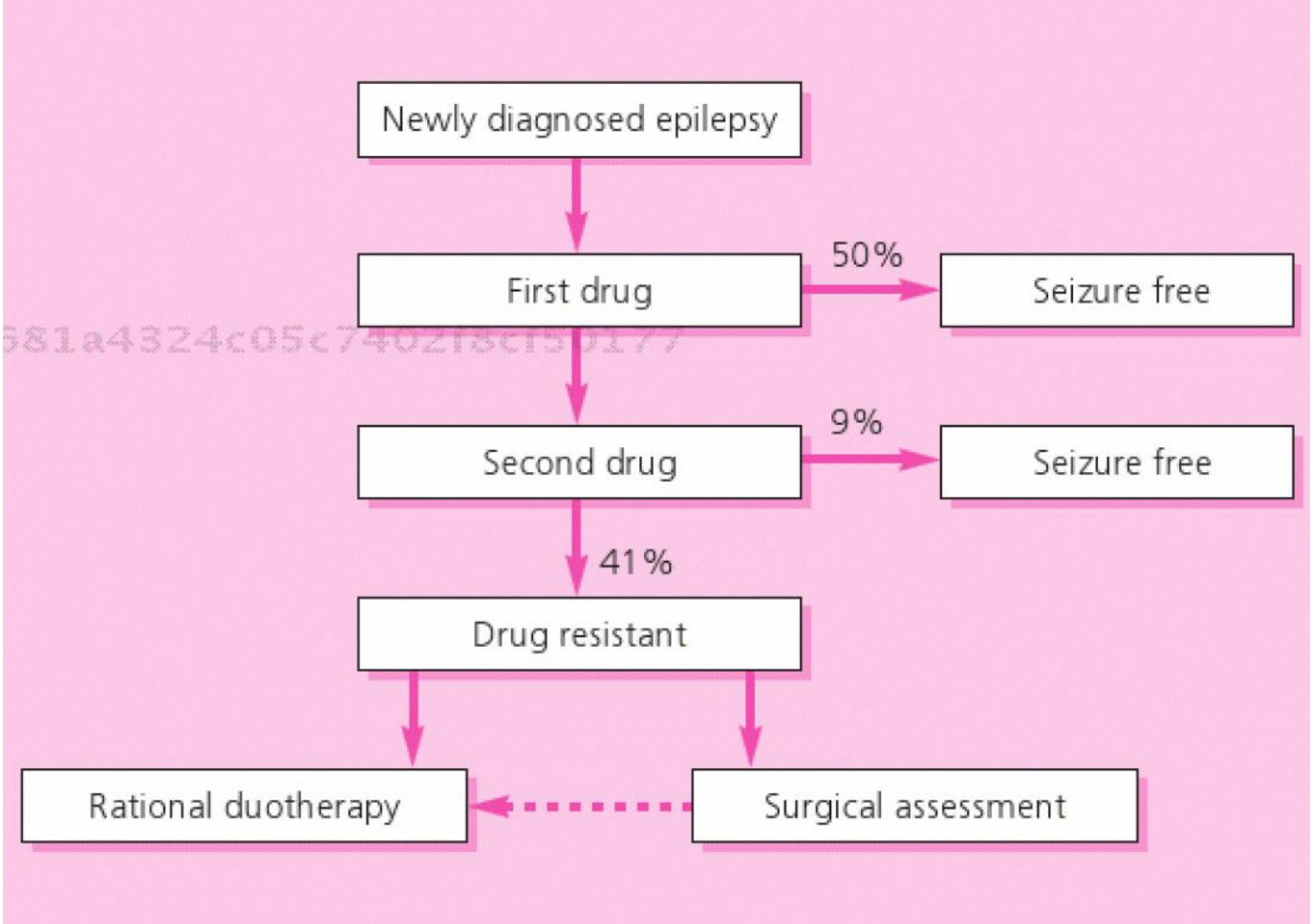
EXACERBATIONS

a) **noncompliance** (draw blood level).
b) **alcohol** drinking.
c) intercurrent **infection** (H: temporary increase dosage if seizures occur during intercurrent infection).
d) **change in lifestyle** (emotional stress, menses, sleep deprivation).

CHANGING DRUG

If seizures continue despite *adequate trial of monotherapy* + *documented compliance*, then **switch to another ASM**:

- maintain patient on first drug (dose may be reduced to that was well tolerated) while second drug is added;
- dose of second drug is adjusted to decrease seizure frequency without causing toxicity;
- only once this is achieved, first drug can be gradually withdrawn (usually over weeks unless there is significant toxicity);
- dose of second drug is further optimized.



POLYTHERAPY

If monotherapy does not work – there is no class I evidence what to do next:

a) try **MONOTHERAPY WITH DIFFERENT DRUG**.
   - 80% of epileptics can be controlled on monotherapy.
   - failure of monotherapy indicates 80% chance that seizures will not be controllable pharmacologically.

b) try **POLYTHERAPY**.
   - currently (12/12/2018) there are 28 ASMs available = 378 possible duotherapies.
   - only 10% benefit significantly from addition of second drug.
   - when > 2 ASMs are required, consider ruling out nonepileptic seizures and refer for surgical evaluation.

- combination therapy with relatively nonsedating drugs (e.g. CBZ and VPA) is preferable to high-dose monotherapy with sedating drug (e.g. PHB, PRM).
- factors predicting that polytherapy will be necessary:
  1) partial epilepsy related to underlying structural lesion (vs. idiopathic epilepsy)
  2) multiple seizure types
  3) developmental delay.
- use drugs with different ***mechanisms of action*** and different ***side effect profiles***.
- in most cases *start with two of three first-line drugs* (i.e. CARBAMAZEPINE, PHENYTOIN, VALPROATE);
  - if unsuccessful, then add third *newer drug* (e.g. LAMOTRIGINE, GABAPENTIN);
  - if effective, least effective of first two drugs should be gradually withdrawn.
- if seizures continue despite adequate trials of several (> 2) ASMs → refer to **epilepsy center** – to consider ACTH / prednisone, ketogenic diet, epilepsy surgery.

ANTIEPILEPTIC DRUG INTERACTIONS

(effect on serum concentration of ASM along top row by addition of ASMs in first column):

Drug	PHB	PRM	PHT	CBZ	VPA	ETX	KLO	LTG	FLB	TPM	OXC	ZNS	VGB
PHB			variable	↓	↓	↓	↓	↓	0		↓	↓	
PRM			variable	↓	↓	↓	↓	↓	0		↓	↓	
PHT	0	↓		↓	↓	↓	↓	↓		↓	↓	↓	
CBZ	0	↓	variable		↓	↓	↓	↓	↓	↓	↓	↓	
VPA	↑	↑	variable	0*		variable	↑	↑	↑	↓		↓	
ETX	0	0	variable	0	0		0	0	0				
KLO	0	0	0	0	0	0		0	0				
LTG	0	0	0	0	0	0	0		0				
FLB	0	↑	↑	↓*	↑	0	0	0					
TPM	0	0	variable	0	↓								
OXC			↑										
ZNS													
VGB			↓										

*increases [CBZ-10,11-epoxide]

GBP, **LEV**, **PREGABALIN** have no drug interactions!!! – useful as add-on therapy.
GBP clearance is exclusively renal (not metabolized); **LEV** metabolism is minimal.
PHB, PRM, PHT, CBZ are **P-450 inducers**.
VPA, FLB are **P-450 inhibitors**.

TERMINATING DRUG THERAPY, PROGNOSIS

IDIOPATHIC epilepsy – patients may be treated chronically (often for life).

- seizures can be ***controlled completely*** (at least 12 months seizure-free) in ≈ 50% epileptics, and ***meaningful improvement*** is achieved in 50% remaining patients.
- 10 years after diagnosis, probability of being in remission is:
  75% - if epilepsy was diagnosed at age < 10 years
  68% - if epilepsy was diagnosed at age 10-19 years
  63% - if epilepsy was diagnosed at age 20-59 years.

N.B. no available medical treatment can permanently eliminate ("cure") epilepsy!

New recommendation in terminology: use **antiseizure medication (ASM)** instead of **antiepileptic drug (ASM)**!

SECONDARY seizures – antiepileptic drugs are given until primary cause is corrected.

- despite removal of ***structural CNS lesion***, there is risk that seizure focus will **remain** in surrounding tissue or develop **de novo** (as result of gliosis and other processes induced by surgery, radiation, or other therapies) - most patients are therefore maintained on ASM for at least 1 year.

N.B. decision to terminate treatment is made on CLINICAL GROUNDS!

- there is no agreement on how long patient should be seizure-free before withdrawal
- there is no agreement on the best time period over which to withdraw ASMs.

Discontinuing ASM therapy is reasonable if been **seizure free for at least 2 years**.

ROLE OF EEG

- there is no agreement on prognostic value of EEGs

EEG class and seizure relapse rate in idiopathic epilepsy:

Class	-- EEG description --		Re-lapse rate	No. of relapses/ patients at risk
	Before treatment	Before with-drawal		
1	normal	normal	34%	11/31
2	abnormal	normal	11%	4/35
3	abnormal	improved	50%	2/4
4	abnormal	unchanged	74%	14/19

Callaghan N, Garrett A, Goggin T: Withdrawal of anticonvulsant drugs in patients free of seizures for two years. N Engl J Med 318; 942-6, 1988

SPEED OF WITHDRAWAL

Therapy should never be terminated abruptly - seizures may result.

- when evaluating patients on multiple drugs, withdraw most sedating ones first (usually barbiturates and clonazepam).

- **withdraw over 3-6 months** (BENZODIAZEPINES and BARBITURATES need to be discontinued even more slowly), although some allow to withdraw PHT, VPA, CBZ over 4 weeks.

Examples of dose decrements every 4 weeks: **CBZ** – 100 mg (3 mg/kg), **PHT** – 50 mg (1.5 mg/kg), **VPA** – 200 mg (6 mg/kg), **ETX** – 250 mg (4 mg/kg), **PRM** – 125 mg (4 mg/kg).

RECURRENCE

- most recurrences occur in **first 6 months** (50% in first 3 months) after discontinuing therapy - patients should be advised to avoid potentially dangerous situations (driving, unsupervised swimming) during this period.
  - risk for recurrence is 5.9%/month for 3 months, then 2.7%/month for 3 months, then 0.5%/month for 3 months
- return to previous ASM dose if seizure occurs.
- relapse is rare **after 2 years**!

Conditions for low risk of relapse (permanent drug-free remission):

1) onset before age 12 yrs. (i.e. **younger patients** have better prognosis!), excluding neonatal seizures.
2) complex or simple **partial seizures** (vs. generalized tonic-clonic seizures).
3) no difficulty establishing **seizure control** (29% relapse if 1st drug worked; 40% if change to 2nd drug was needed; 80% if change to 3rd drug was required)
1) **monotherapy**
2) **long** seizure-free **interval** (4 years rather than 2)
3) **few seizures** before remission (those with > 100 seizures before control had statistically significant higher relapse rate)
4) **normal sleep-deprived EEG** (esp. no epileptiform discharges or focal abnormalities) *see above*
   N.B. normal / abnormal EEG is only guide (not criterion) for treatment termination!
5) **normal neurologic examination** (incl. intelligence)
6) SPECIFIC EPILEPSY SYNDROME:
   all ***benign epilepsy syndromes of childhood*** - excellent prognosis.
   juvenile myoclonic epilepsy - high rate (80-90%) of relapse – patients must not be withdrawn from ASM therapy!

PREGNANCY CONCERNS

Epilepsy is most common neurological disorder encountered by obstetricians!

De novo seizures – consider ECLAMPSIA! see p. 2646 >>

P450 inducing ASMs (CBZ, PHT, PHB, PRM, FLB) increase failure rate of OCPs up to 4-fold!

Do not discourage woman from becoming pregnant! (> 90% women taking ASM have healthy babies).

ASMs are **teratogenic** + may precipitate* *failure of oral contraceptives*!
vs.
Frequent convulsions** can lead to **miscarriage** or **malformations**!

*P-450 inducing drugs (e.g. carbamazepine, phenytoin)
**hypoxia, reduced placental blood flow

It is currently recommended that pregnant women be maintained on effective drug therapy!

No "best" antiepileptic drug - drug of choice is one that is most appropriate to seizure type and that produces optimal control with fewest side effects; preferable **MONOTHERAPY** at lowest effective dose (esp. during 1st trimester).

- ***newer epilepsy meds*** less likely to cause birth defects.
- switching medications is not recommended (risk of losing seizure control).
- consider drug withdrawal in patients with prolonged seizure-free periods and seizures not impairing consciousness.

LAMOTRIGINE - one of preferred treatments during pregnancy (low incidence of congenital malformations!!!)
VALPROATE - highest risk for major congenital malformations of all antiepileptics

American Academy of Neurology (AAN), American Epilepsy Society (AES), Society for Maternal-Fetal Medicine (SMFM) guideline 2024:

- guideline recommends LAMOTRIGINE, LEVETIRACETAM, and OXCARBAZEPINE.
- guideline advises against ASMs associated with neurodevelopmental complications: VALPROIC ACID, PHENOBARBITAL, and TOPIRAMATE.
- guideline states that the daily FOLIC ACID before and during pregnancy may decrease the risk of neural tube defects and improve neurodevelopmental outcomes.

1. Epileptic women (regardless of treatment!) have ***1.5-3 times higher rates of PREGNANCY COMPLICATIONS*** (intrapartum bleeding, abruptio placentae, premature labor, stillborn births, pre-eclampsia, eclampsia).

2. 25-50% epileptic women experience ***increased seizures during pregnancy*** - mostly due to [ASM]↓ associated with physiologic changes:
   1) volume of distribution↑
   2) hepatic microsomal activity↑ + protein binding↓ → clearance↑

   N.B. ASM dosage requirements increase during pregnancy!

ASM levels (total & free) should be followed frequently during pregnancy, at least once per trimester (esp. after 1st trimester) – baseline, at 18-19 and at 34-36 weeks, postpartum monthly (for 3 months).

Changes in free ASM levels during pregnancy:
CBZ ↓ 11%, PHB ↓ 50%, PHT ↓ 31%, VPA ↑ 25%

3. ***Major fetal malformations*** increase from 2% (in general population) → 4-6% (single ASM during pregnancy) → 10% (≥ 2 concurrent ASMs during pregnancy).

   N.B. all ASMs can produce similar anomalies!

   - formerly particular profiles were attributed to specific drugs (e.g. FETAL HYDANTOIN SYNDROME, FETAL VALPROATE SYNDROME).
   - most common syndrome:
     1) microcephaly, facial dysmorphism, cleft lip, cleft palate
     2) cardiac defects
     3) digital hypoplasia, nail dysplasia
     4) growth retardation, developmental delay.
   - VALPROATE (!!!) and CARBAMAZEPINE increase **neural tube defects**;

H: preconceptive **folic acid, 1-4 mg/d** + **prenatal diagnosis** (serum ***α-fetoprotein*** at 15-18 week, ***ultrasonography*** and ***amniocentesis*** at 15-19 weeks).

- most critical period is first 5 weeks of gestation.

  Because considerable proportion of pregnancies are unplanned and are discovered after 4th week of gestation, all epileptic women who have child-bearing potential should be treated with FOLIC ACID 1-2 mg/d.

4. ***Minor anomalies*** are also increased independent of treatment status (although ASM therapy increases risk further to slight degree).

5. All ASMs (esp. enzyme-inducers) promote ***hemorrhagic diathesis in newborns***; routine **vitamin K 1 mg i/m** for babies is occasionally inadequate.
   H: additional **oral vitamin K, 10 mg/d** for mother *during last month* of pregnancy (or 20 mg/d during last 2 weeks or 10 mg IV 4 hours before birth).

6. Prenatal exposure to ASMs, particularly to multiple drugs, is associated with ***impaired fine motor skills*** in infants at 6 months of age.

7. ***Sedating ASMs*** (e.g. benzodiazepines, phenobarbital) given shortly before delivery can produce "floppy infant syndrome"

BREAST FEEDING

- ASMs are *excreted into breast milk*.
- ratio of **[DRUG] in breast milk / [DRUG] in serum**:
  - 80% - for ETHOSUXIMIDE
  - 40-60% - for PHENOBARBITAL
  - 40% - for CARBAMAZEPINE
  - 15% - for PHENYTOIN
  - 5% - for VALPROATE.
- given overall benefits of breast feeding + lack of evidence for long-term harm to infant by being exposed to ASM, epileptic mothers should be encouraged to breastfeed.
- ***monitor drug effects on infant*** (lethargy, poor feeding, etc).

NEONATES, INFANTS

- require *similar loading doses* per kilogram of body weight as adults.
- ***metabolize drugs faster*** than adults.
- rapid increase in total volume of distribution.

ELDERLY

- high incidence of epilepsy.
- physiologic changes (creatinine clearance↓, albumin level↓, hepatic drug metabolism↓), concomitant disease and concomitant medications → ***ASM adverse effects*** (esp. CNS).
  H: *lower doses & slower titration*.
- use ASM with fewer interactions (e.g. GABAPENTIN, LAMOTRIGINE).

BIBLIOGRAPHY for ch. "Epilepsy and Seizures" → follow this LINK