Antiepileptic Drug levels: use & abuse

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Advice on AED levels…

- Confused
- Oversimplified
- Overly negative

- AED levels can be useful
- *BUT…*
- Use with care

AED levels

- Basic principals of clinical pharmacology
- Historical perspective
- Clinical value of AED levels
- Indications for AED levels
- Misunderstandings about AED levels

Clinical Pharmacology

- Dose response curve
- Transient nature of drug-receptor interactions
- Pharmacodynamics
- Pharmacokinetics
- Individual biological variation

Dose Response Curve

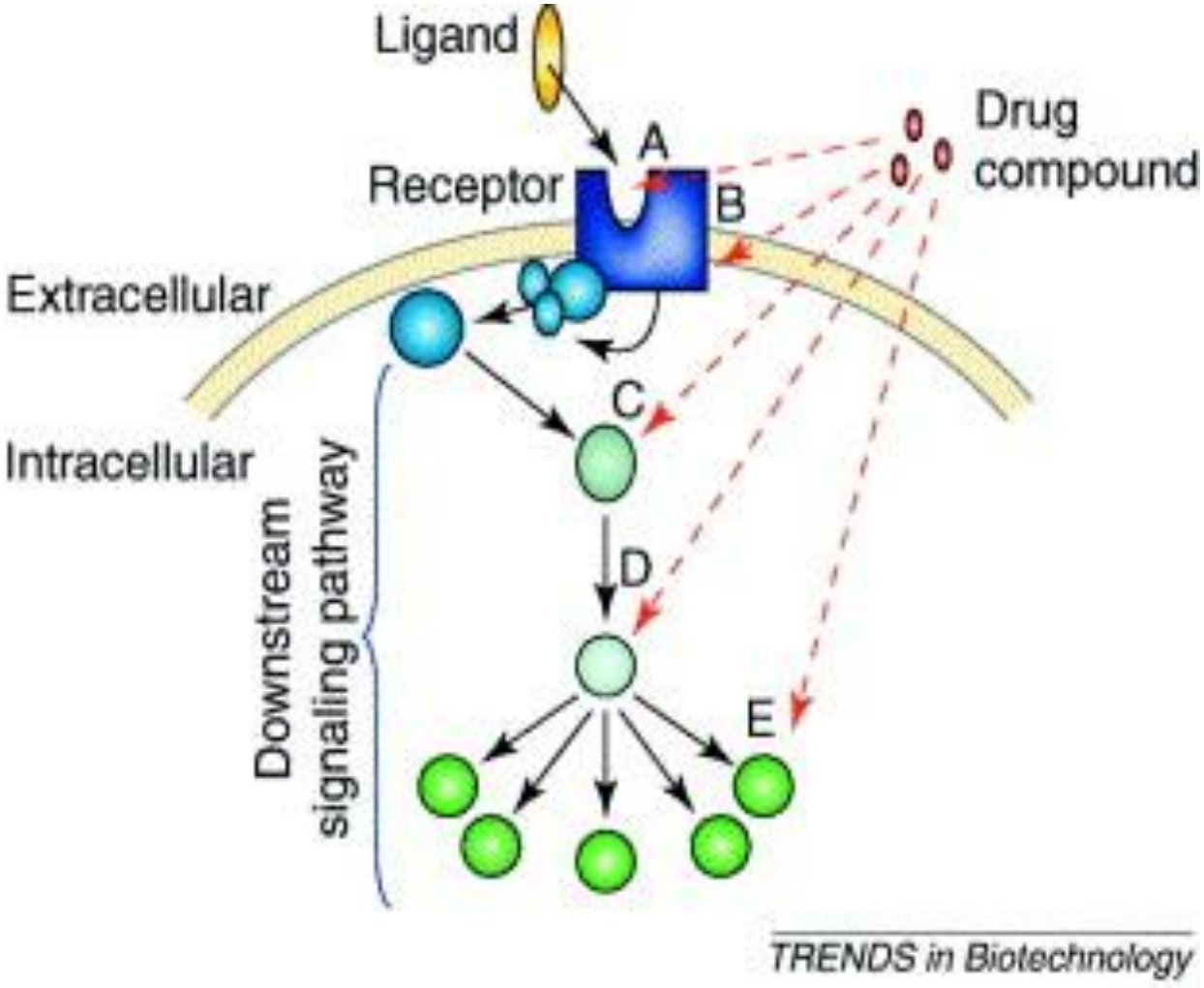
- Pick a response or effect to measure
- Pick doses from a range
  - Sub-therapeutic to Supra-maximal
- In an individual
  - Patch of cell membrane
  - Cell
  - Tissue sample
  - Organism / person
  - Sample of population

Dose Response Curve

- The desired effect(s)
- The unwanted effect(s)

- The dose
  - Administered
  - Circulating
  - At the receptor

Drug – Receptor interactions



Midazolam

- Anaesthetic
- Antiepileptic
- Hypnotic
- Anxiolytic
- Sedative

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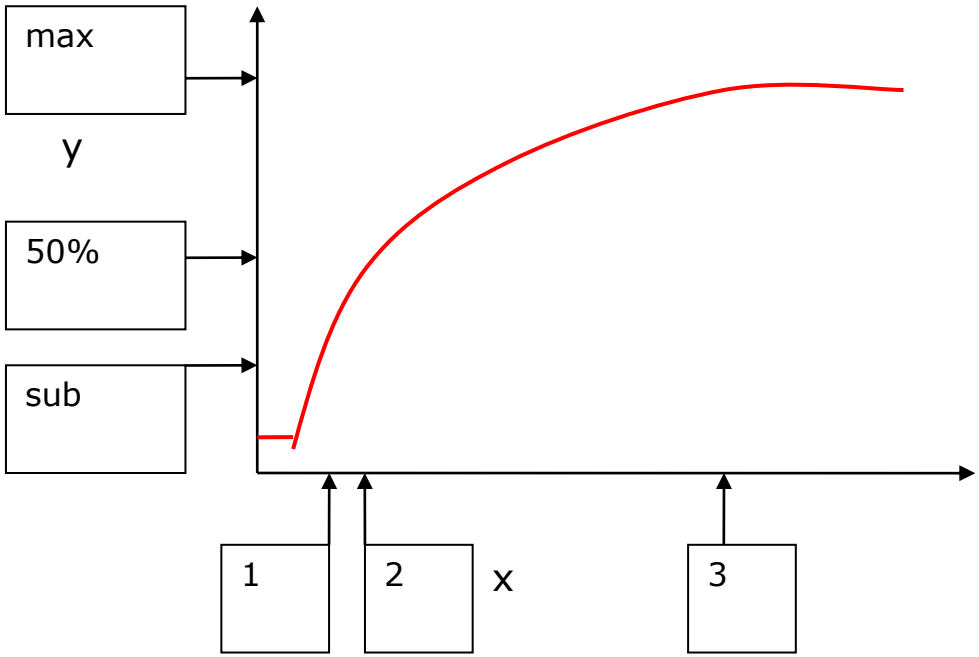
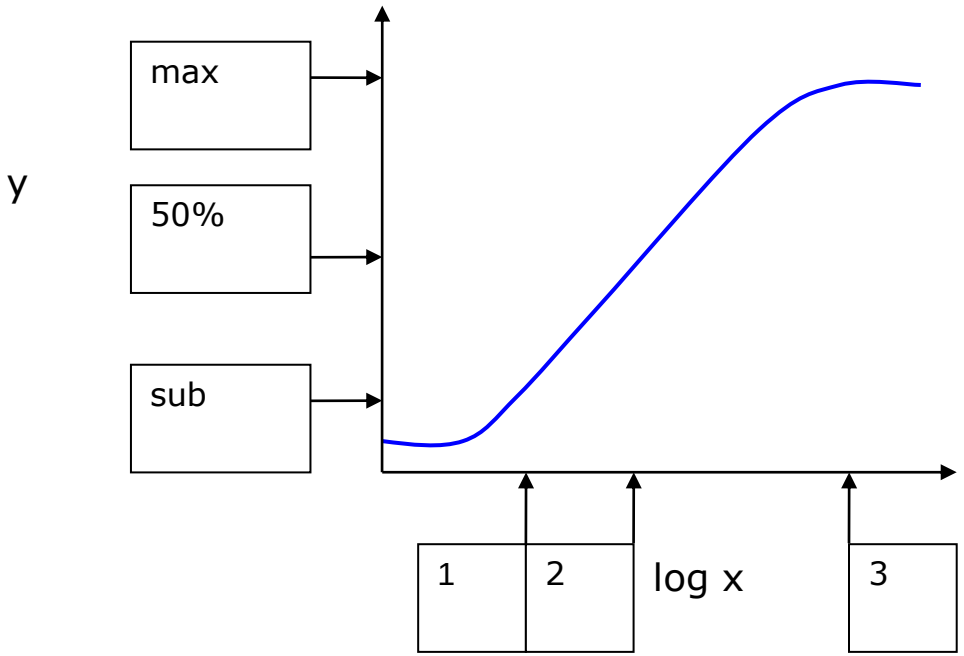
a) Dose response curve

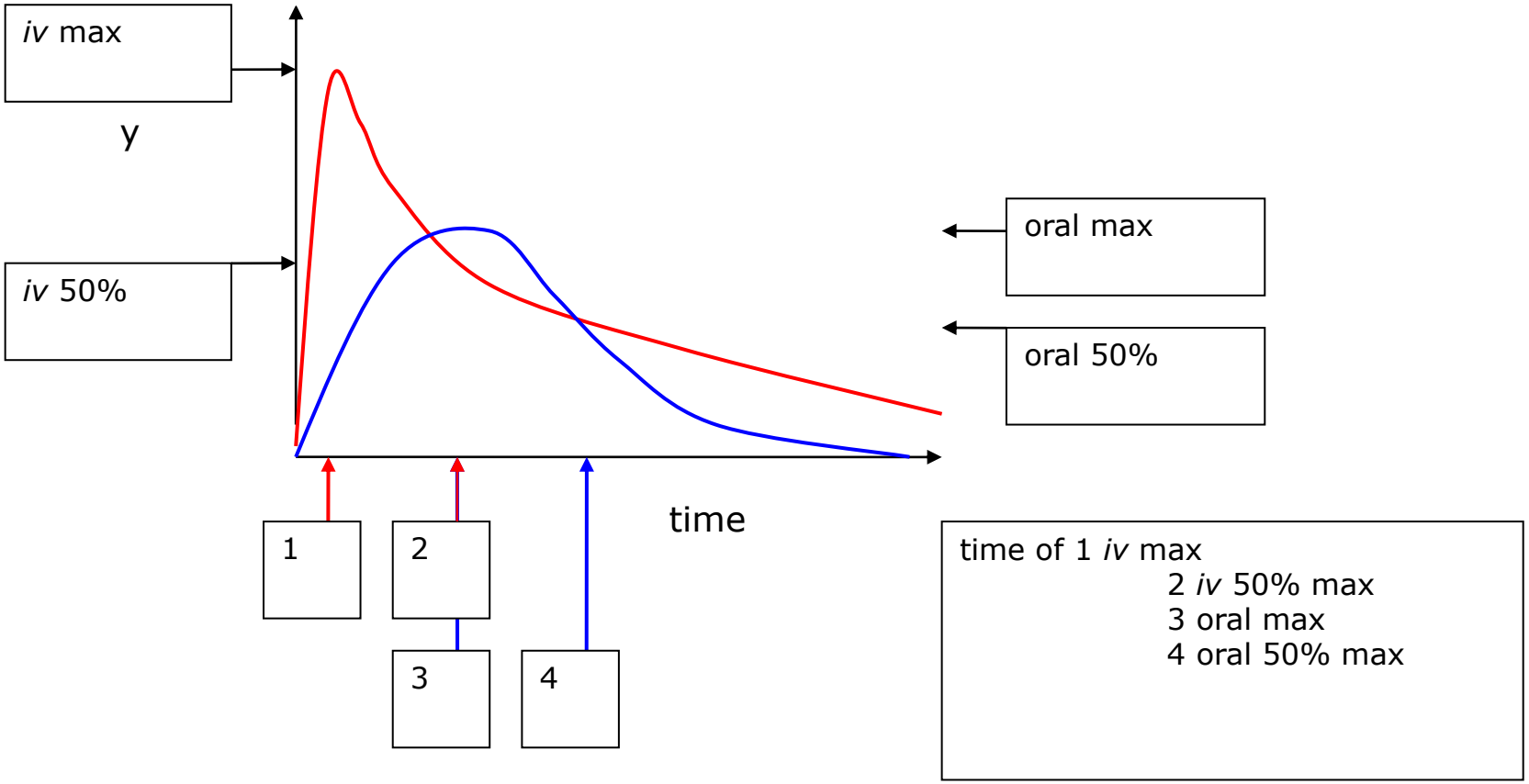


b) Log dose response curve



But what about time?

c) Time concentration graph



What is pharmacokinetics?

What is pharmacokinetics?

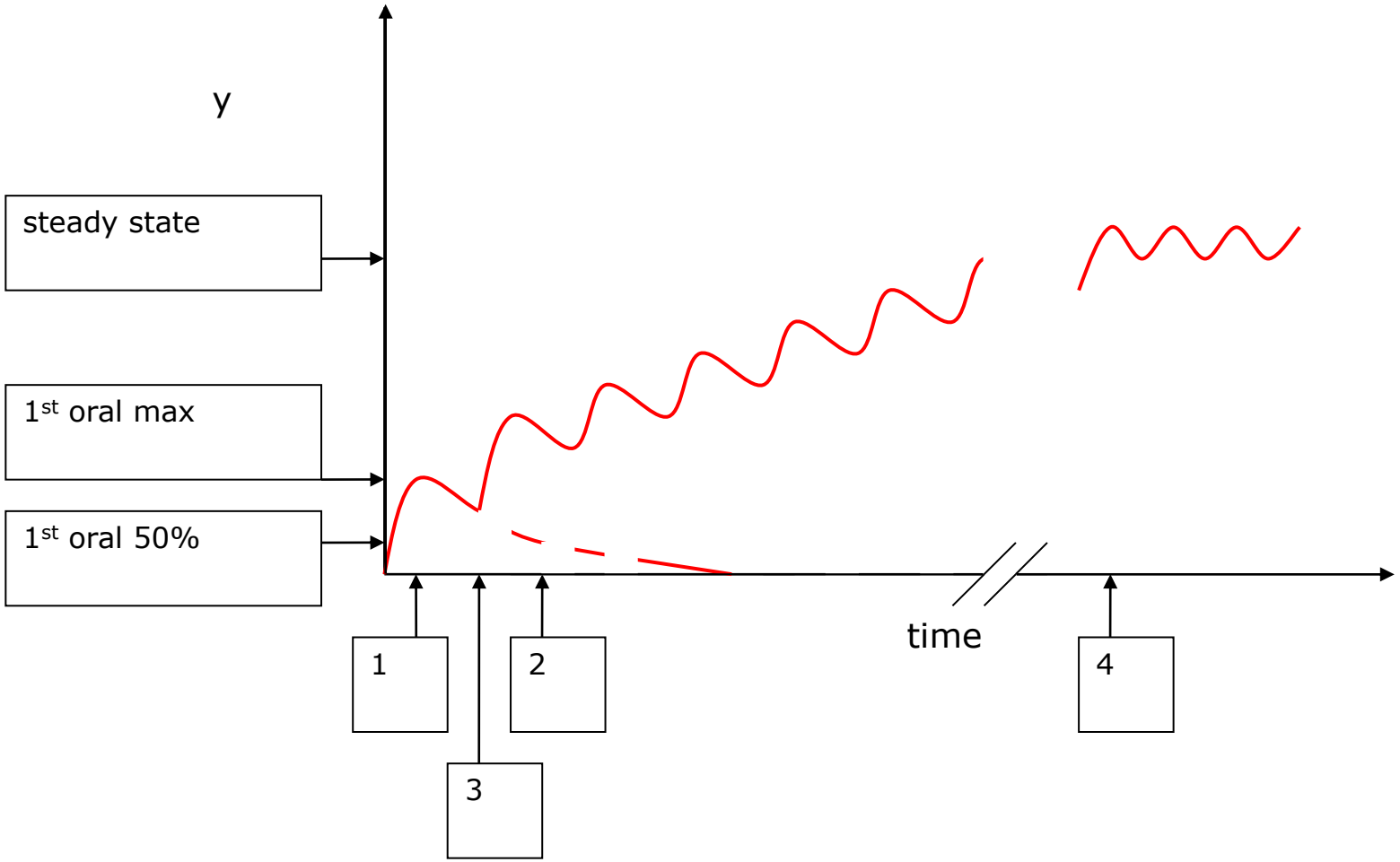
- Route of administration
- Absorption
- Bioavailability
- Distribution
- Metabolism
- Excretion
- Elimination

Dose intervals

- PK properties
- T1/2 linear or 1st order kinetics
- mg/hr zero order kinetics
- Intermediate Michaelis-Menten kinetics

- Individual biological variation
- Disease states
- Drug interactions

d) Time concentration graph



Puffer fish

The phenytoin story

Tyer JH et al. *British Medical Journal* 1970; **4**: 271-273.

May-July 1968:

51 patients on phenytoin presented with 2-4 weeks:

Ataxia, diplopia, vomiting:

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All capsules contained 100 mg +/- 2 mg.

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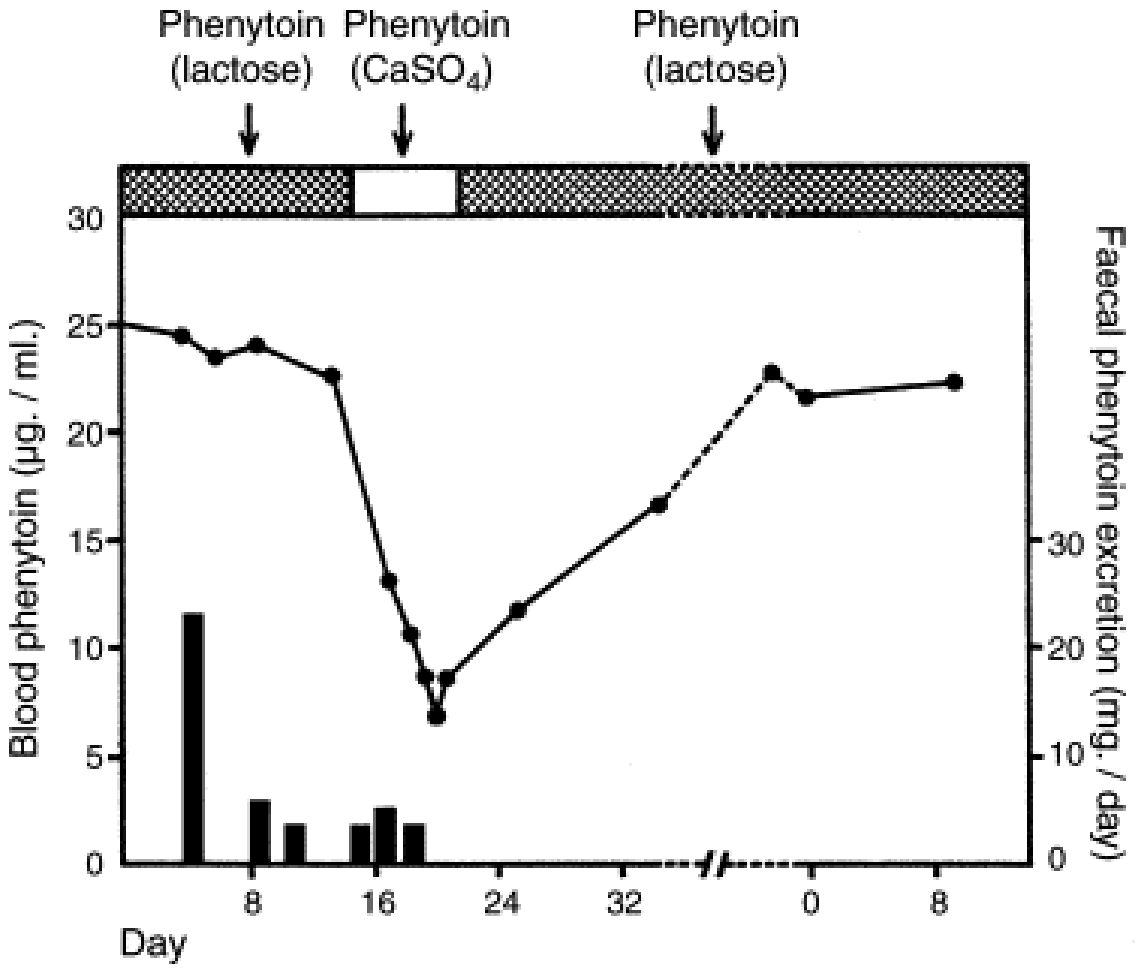
November 1967 change in excipient:

increased bioavailability

The phenytoin story



Blood phenytoin concentrations in a patient taking phenytoin (400 mg./day), with excipients respectively as shown (lactose, calcium sulphate, lactose). Vertical columns represent daily faecal excretion of phenytoin when measured.

The phenytoin story

- Bioavailability
- Anticipating toxicity & dose adjustment
- Target Range vs Therapeutic Range
- Width of Therapeutic Index

Drug manufacturing

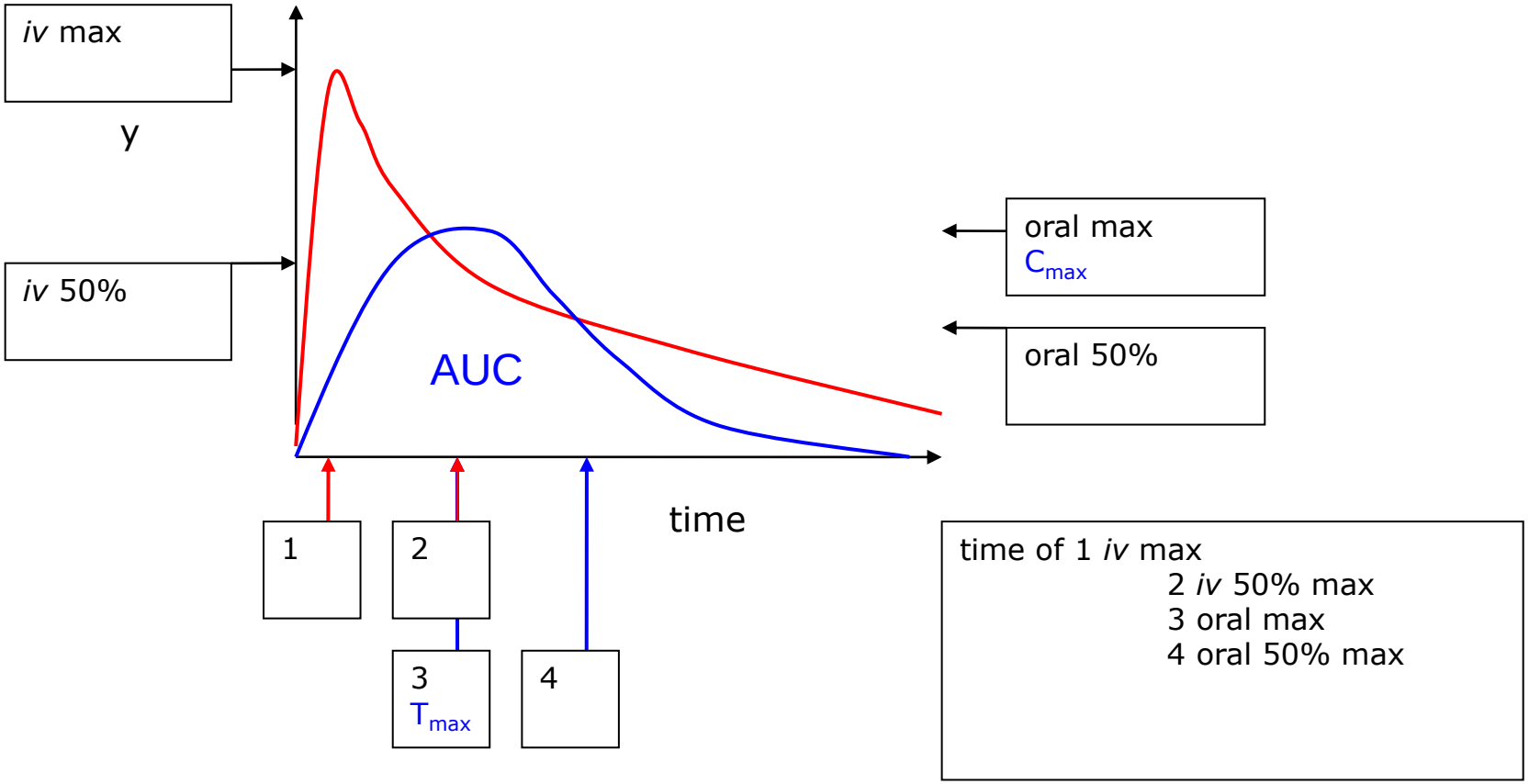
Regulations are tight:

- Amount must be consistent mg/tablet
- Bioavailability must be consistent:
  - Between batches
  - Between manufacturers

1. AUC
2. C_{max}
3. T_{max}

Single or multidose studies in 12 or more healthy adult volunteers: 90%CI: 80-125%

c) Time concentration graph



tetrodotoxin

AED dose adjustment

- Treatment goal
- Risks of toxicity
- Seizure frequency
- Constructing a narrative

When to measure AEDs

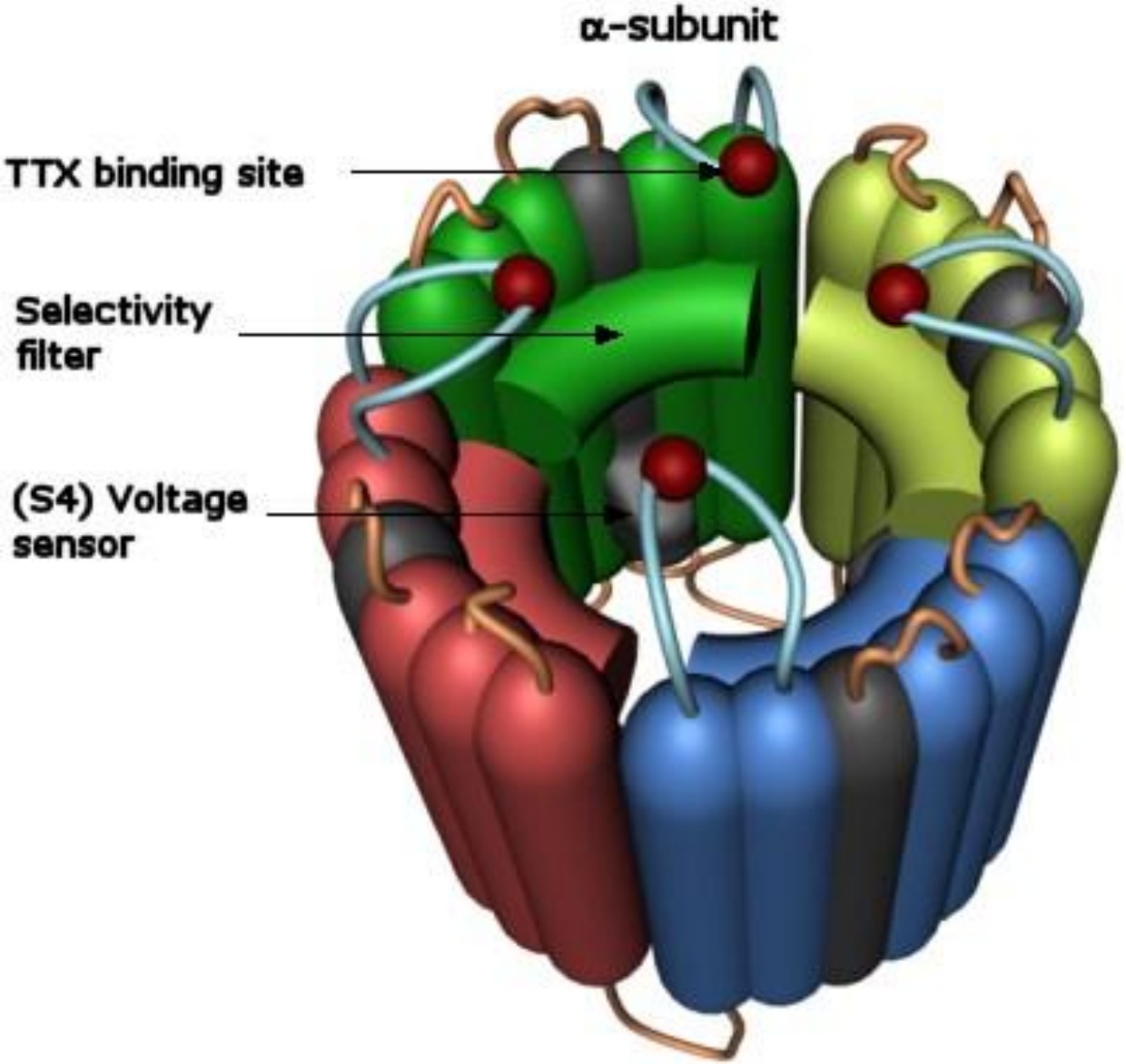
Approximate Target Ranges (plasma or serum)

	mg/l	µmol/l
Carbamazepine	4-12	16-50
Ethosuximide	40-100	300-750
Lacosamide	10-20	
Lamotrigine	1.5-20*	
Levetiracetam	6-40	
Phebobarbitone	10-50	45-225
Phenytoin	10-25	40-100
Topiramate	5-20	
Valproate	40-100	270-700

When to measure AEDs

- ICU; PICU; NICU
- ED
- OPD

Sodium channel α sub-unit



Conclusions

- AED levels can be very useful
- But not often needed as a routine (PHT)
- Not often needed at steady state *per se*
- Not often needed strictly timed

- Compliance / Adherence / Concordance /
- Communication / Partnership