

Semester I. Seminar 2.

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Exam topics 3-4

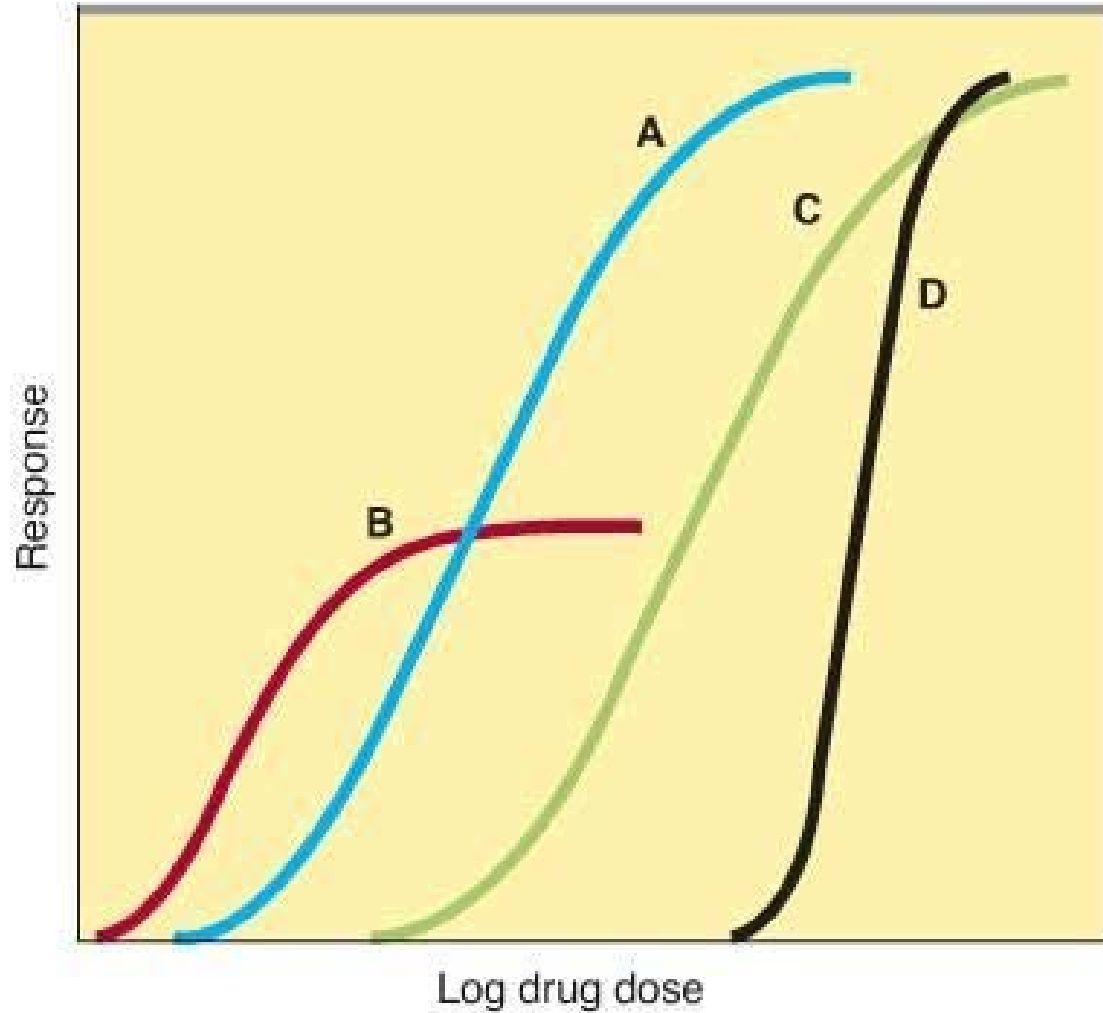
3.

- ▶ Graded and quantal dose-response relationships. Therapeutic index, therapeutic window
- ▶ Parasympatholytics
- ▶ Centrally acting sympathoplegic drugs

4.

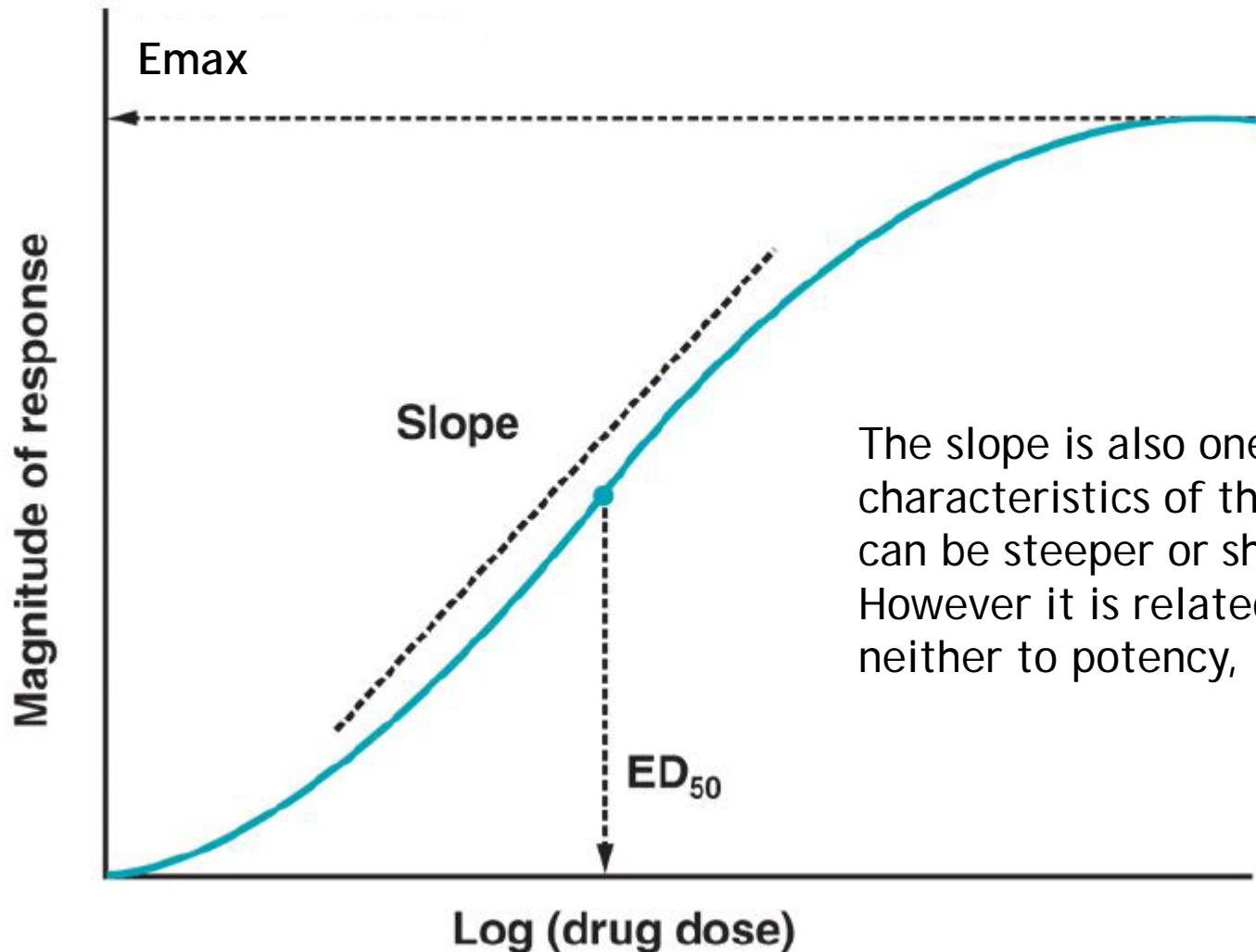
- ▶ Agonists and antagonists. Antagonism on the receptor level
- ▶ Sympathomimetics
- ▶ Pharmacology of renin/angiotensin system

Repetition



Which is more efficacious?
Which is more potent?

Graded dose-response relationship



The slope is also one of the characteristics of the curve, can be steeper or shallower. However it is related neither to potency, nor to efficacy.

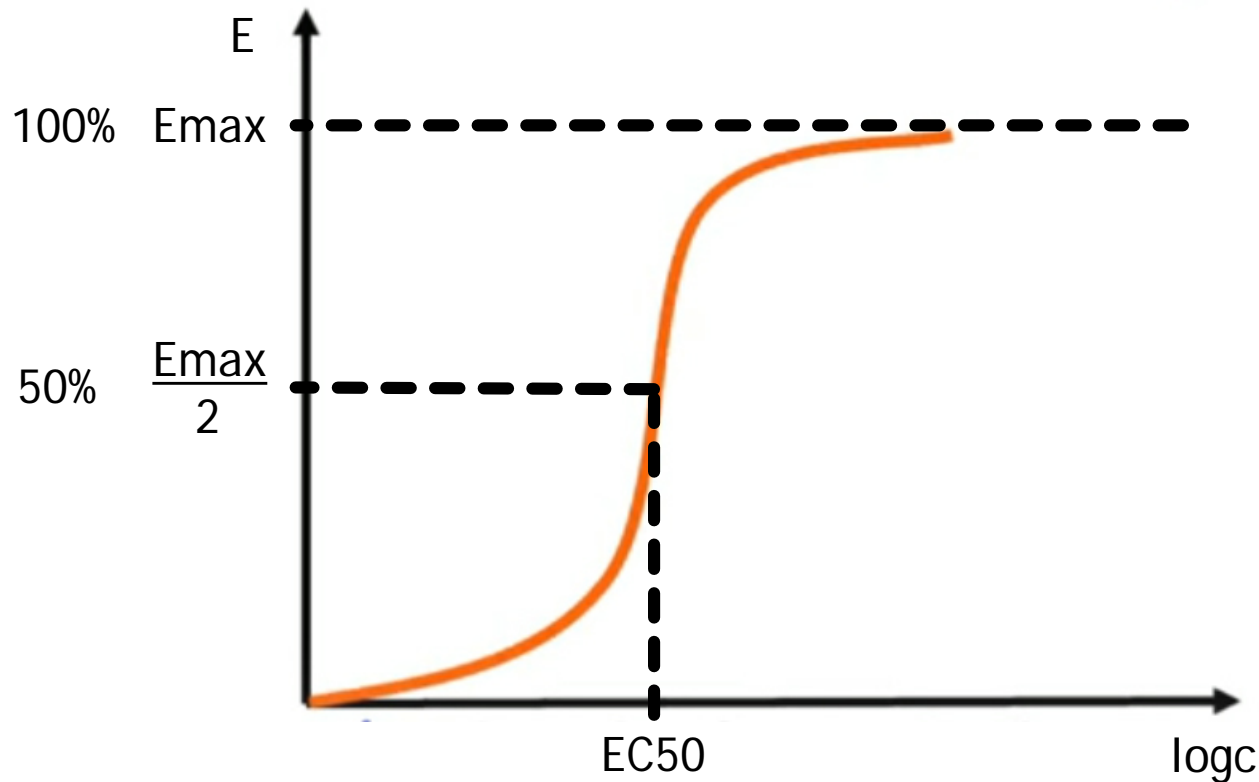
Graded and quantal
dose-response relationships.
Therapeutic index,
therapeutic window

Types of dose response curves

- ▶ Graded dose response curves
- ▶ Quantal dose response curves

Graded dose-response curve

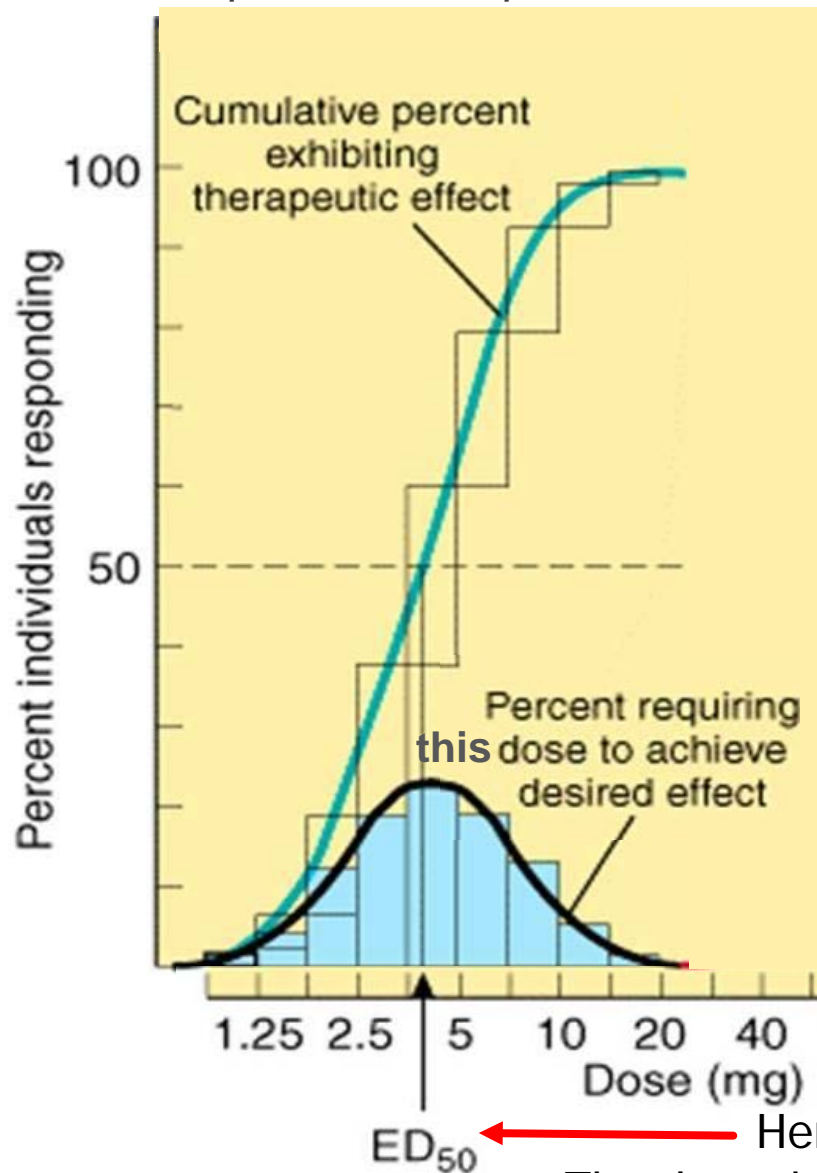
- ▶ Here the effect rises gradually (graded) until a maximum and it is characterized by a unit (= "parametric")



- ▶ A graded concentration-effect curve → applies to a single individual
- ▶ For a population → quantal concentration-effect curve is needed

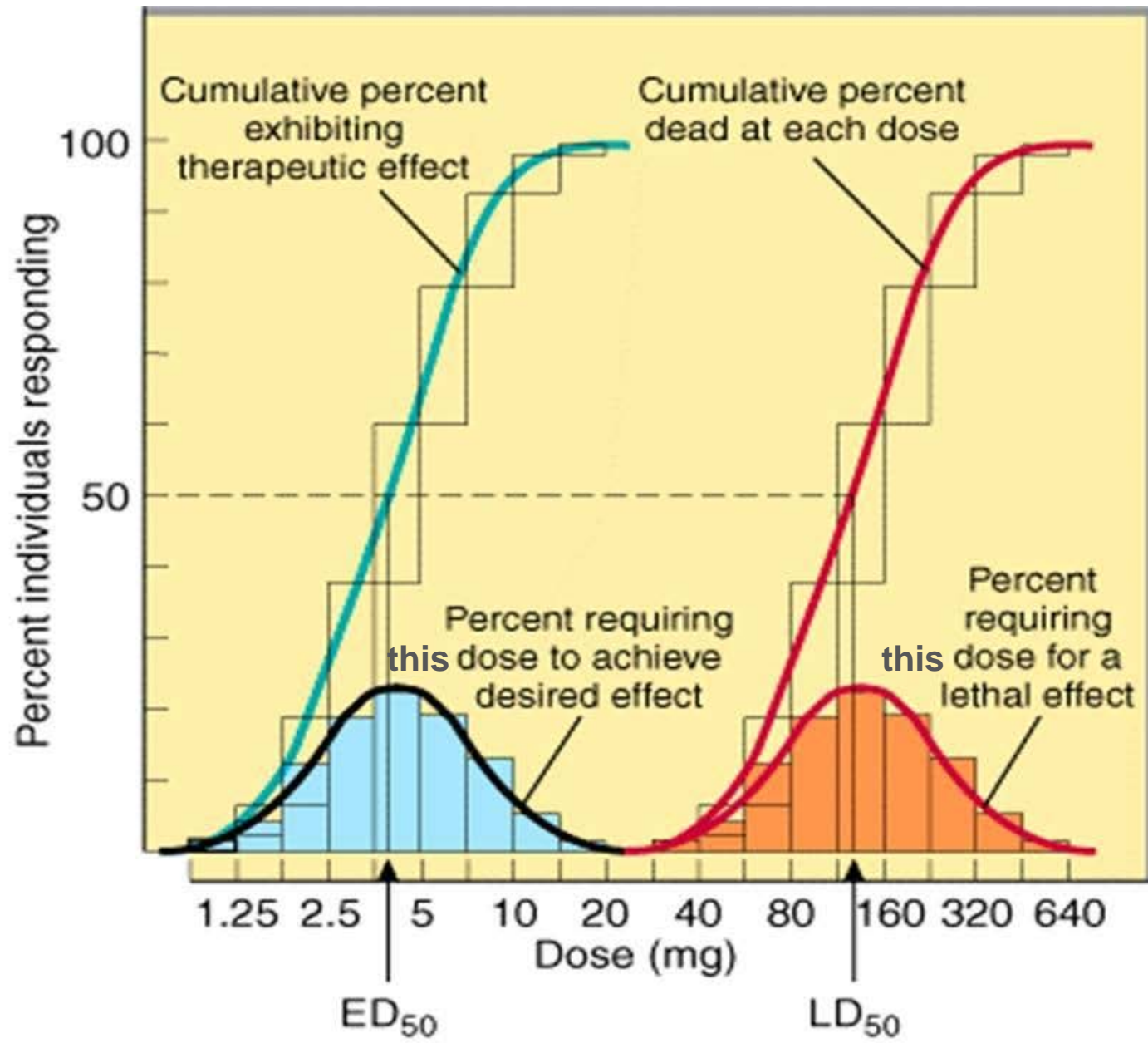
Quantal dose-response relationship

- Here the response is "all or nothing", whether a given criteria is met or not (=quantal; non-parametric, doesn't have a dimension)

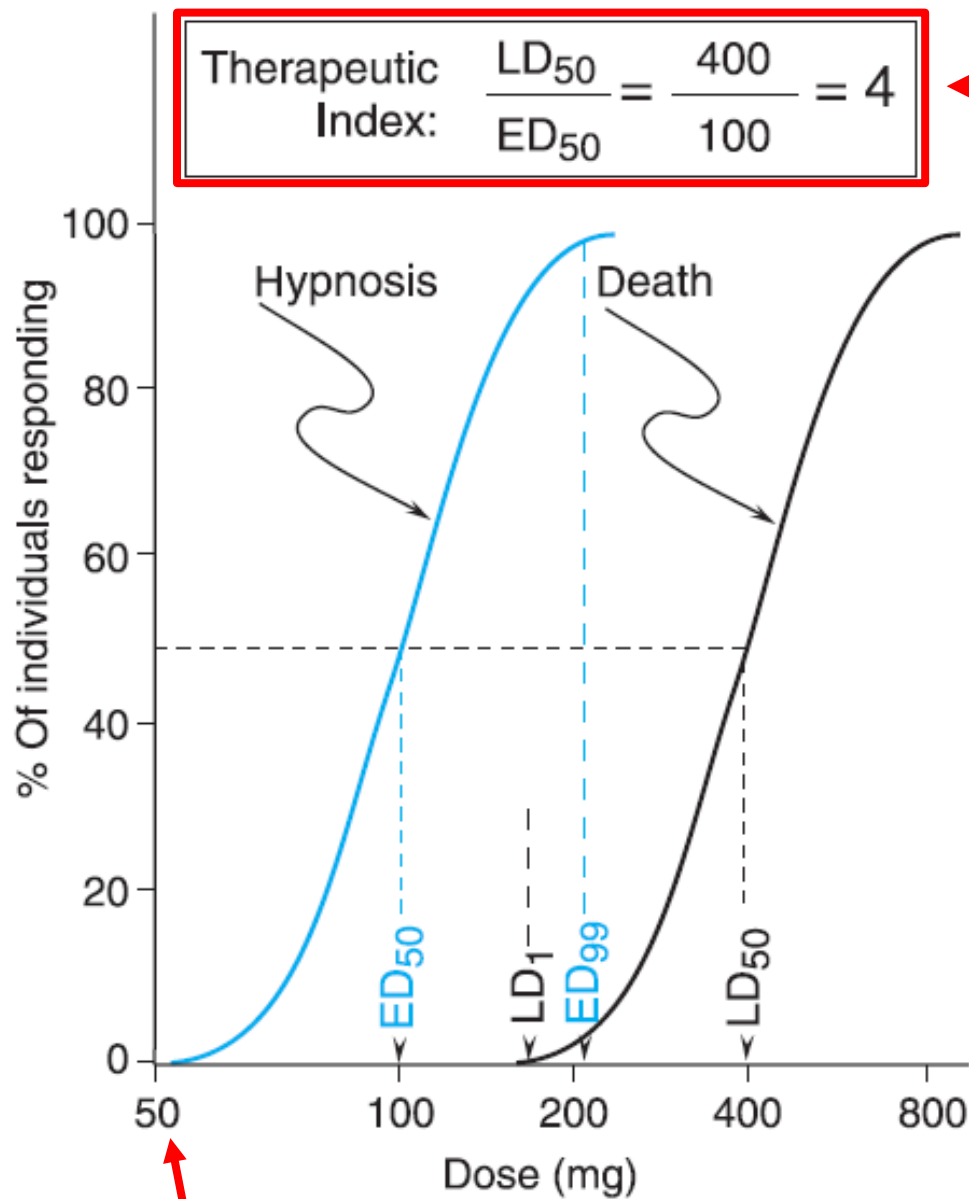


Here: "median effective dose 50"
The dose that elicits the effect in 50% of responders.

Similarly to ED50, TD50 and LD50 also exist (= median toxic/lethal dose 50)



Therapeutic index



$$\text{Therapeutic Index: } \frac{LD_{50}}{ED_{50}} = \frac{400}{100} = 4$$

In preclinical studies of drugs, the *median lethal dose* (LD₅₀) is determined in experimental animals

In clinical studies

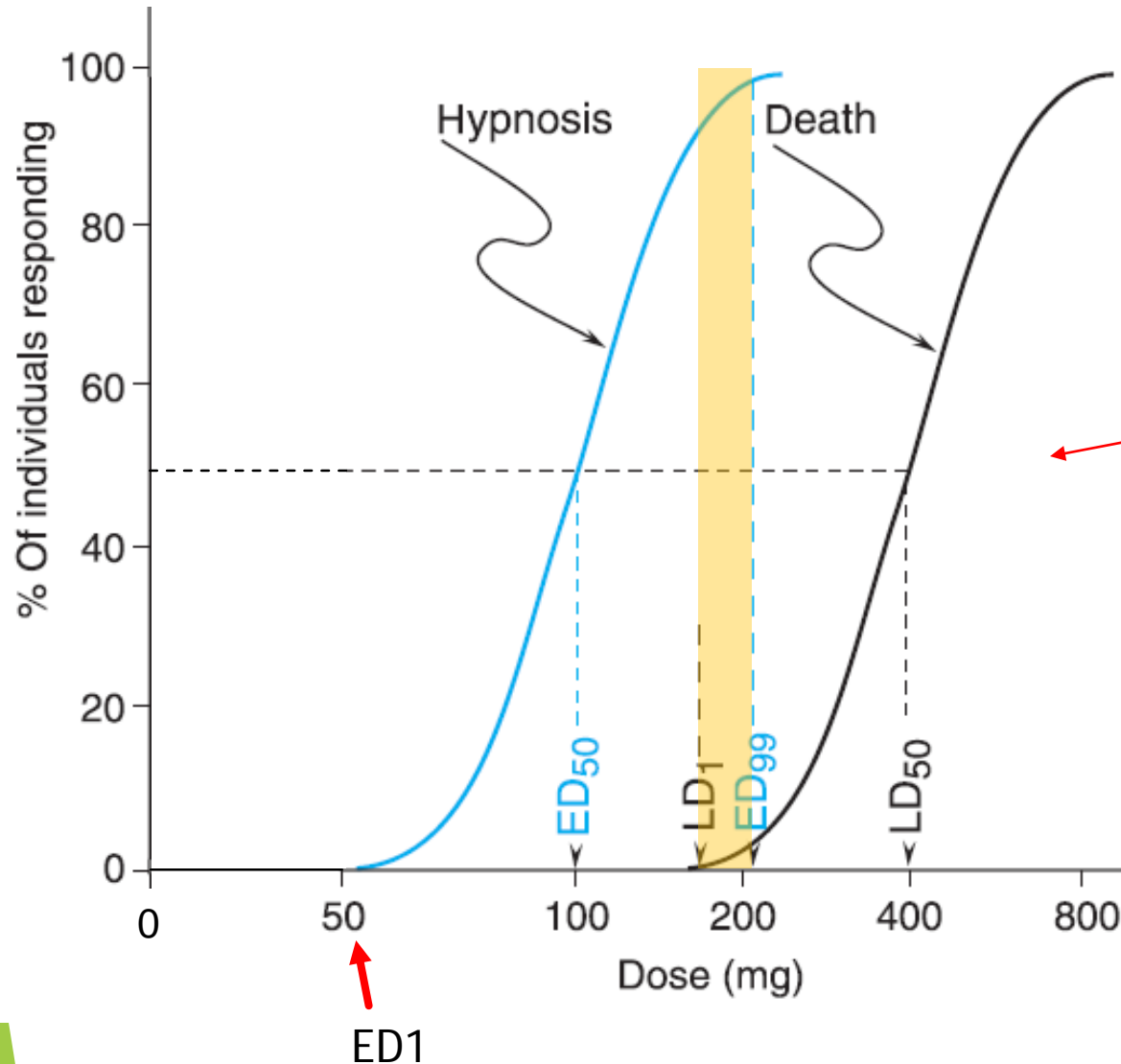
$$\text{Clinical therapeutic index: } \frac{TD_{50}}{ED_{50}}$$

ED₉₉ = this dose is effective in most of the population

ED₁ = only effective to some individual (below this dose no effect is seen in the population = minimal dose)

Similarly exists with TD/LD

Other indices



Safety zone: $\frac{LD_1}{(\text{Safety ratio}) ED_{99}}$

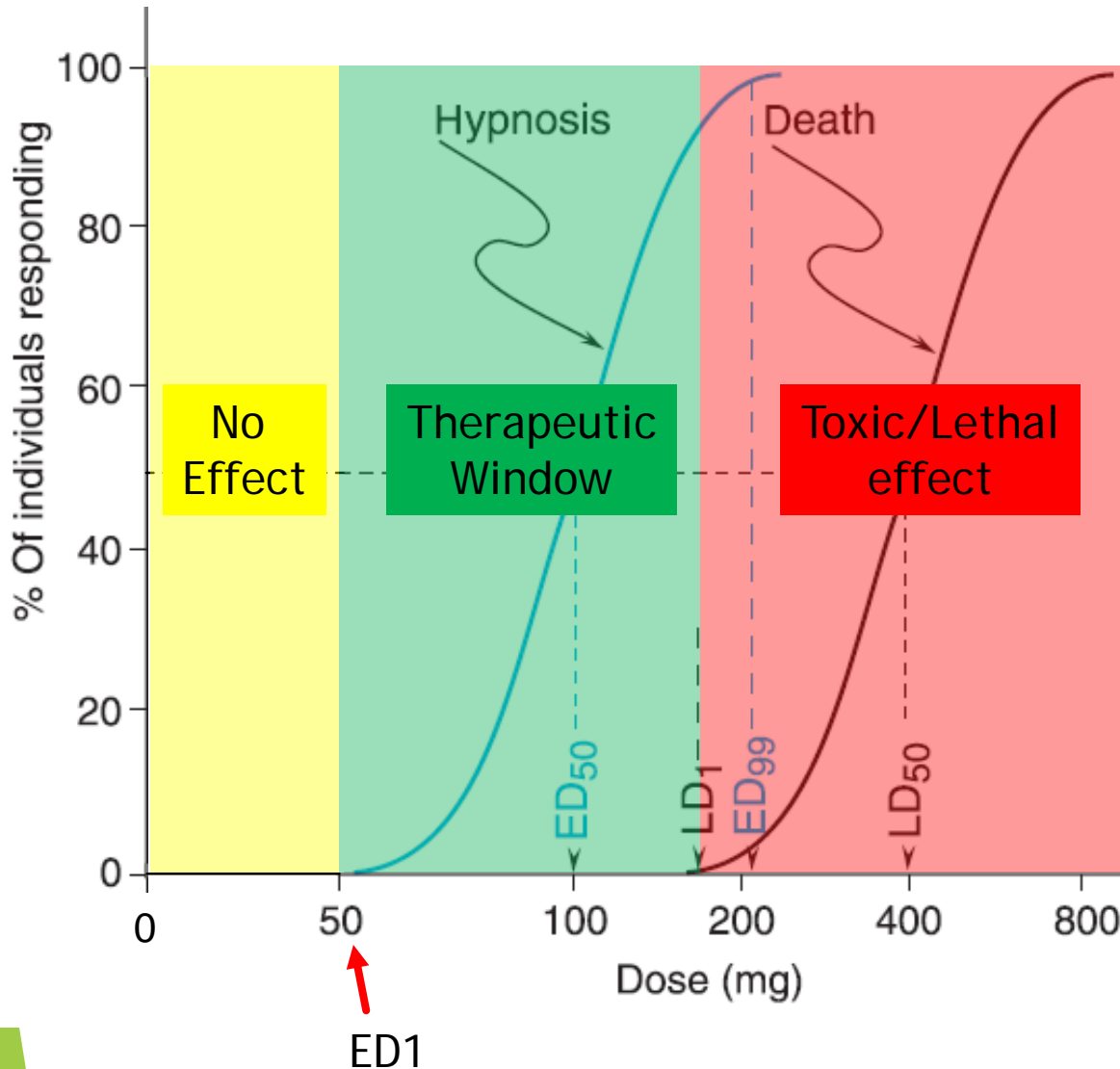
If lower than 1,
no safety zone exists
like here

ED₉₉ = this dose is effective in most of the population

ED₁ = only effective to some individual (below this dose no effect is seen in the population = minimal dose)

Similarly exists with TD/LD

Other indices



Therapeutic window =
The dose from ED1
until TD1 (or LD1)

This is indeed the
Population therapeutic window
(y axis is: % of responders)

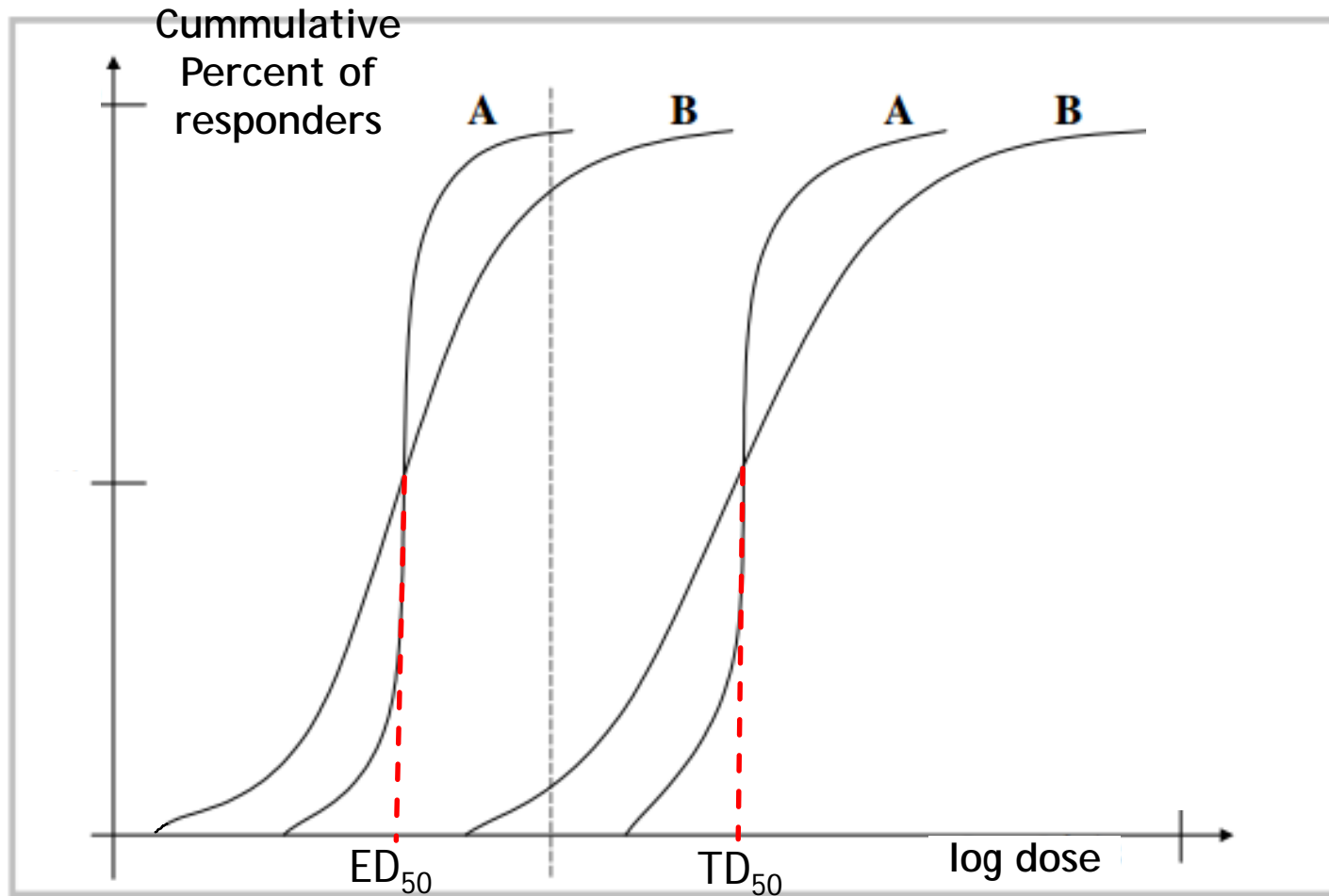
expresses a range of
concentrations at which the
likelihood of effectiveness is
high and the probability of
adverse effects is low

ED99 = this dose is effective in most of
the population

ED1 = only effective to some individual
(below this dose no effect is seen in the
population = minimal dose)

Similarly exists with TD/LD

Importance of the slope of the curve



Therapeutic Index $A=B$

Therapeutic Window $A \sim B$

Safety zone $A \gg B$

Drugs with narrow therapeutic index

- ▶ Administration of these drugs is critical
- ▶ Narrow Therapeutic Index → $TI < 2,0$
- ▶ Licensing procedure for these drugs is stricter

Examples:

- ▶ Safe drugs with **large therapeutic index**: penicillins, beta-agonists, thiazide diuretics.
- ▶ Drugs with **narrow therapeutic index**: digoxin, phenytoin, theophyllin, lithium

The background of the slide features abstract, overlapping green geometric shapes, primarily triangles and polygons, in various shades of green, creating a modern and dynamic visual effect.

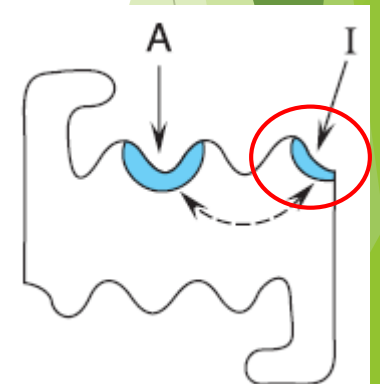
Agonists and antagonists. Antagonism on the receptor level

Agonists

Agonist: = activating ligand of a receptor,

- ▶ upon binding, it changes the conformation of the receptor by which activates a signal transduction cascade characteristic to that receptor
- ▶ Origin: endogenous OR exogenous
 - ▶ Endogenous ligands are agonists almost always
- ▶ Binding: reversible OR irreversible
- ▶ Place of binding: (relative to endogenous ligand) orthosteric OR allosteric
 - ▶ Orthosteric = binds to the same site as the endogenous agonist
 - ▶ Allosteric = binds to a different site

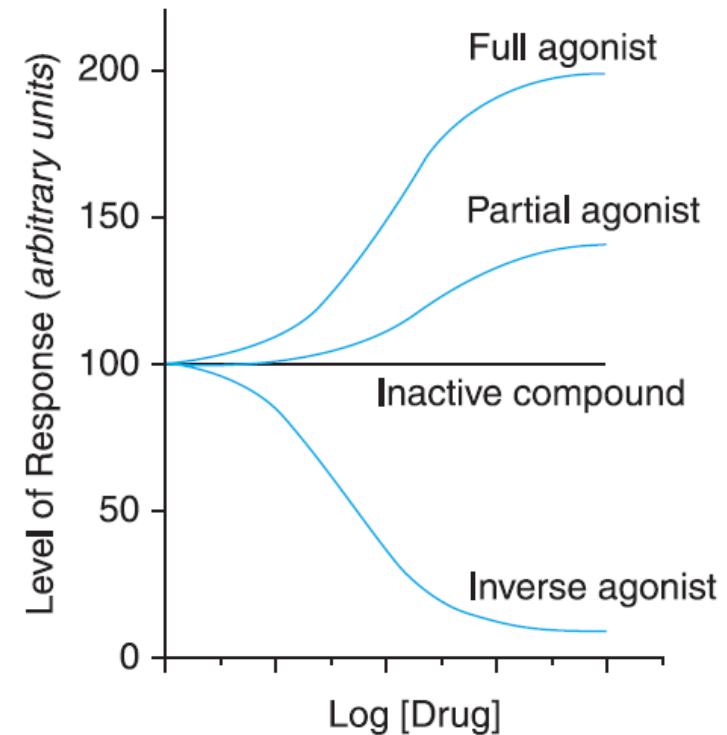
An allosteric enhancer/modulator is a ligand, that alone does not exert effect, but enhances the effect of an agonist bound to another site



Allosteric binding site

Agonists (cont.)

- ▶ Magnitude of effect: full OR partial
- ▶ "Direction" of effect: "normal" OR inverse
 - ▶ Inverse: in case of receptors with constitutive activity (without any ligand) → inhibiting spontaneous activation
 - ▶ It changes receptor-conformation (=agonist) but in a different way, thus activates a signal-transduction, but differently as well



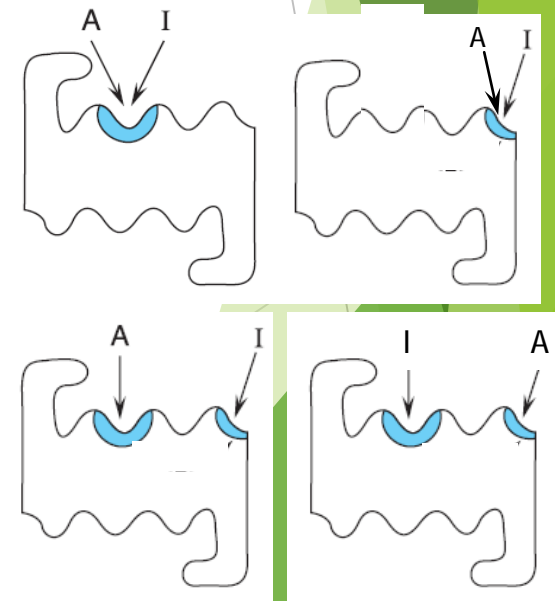
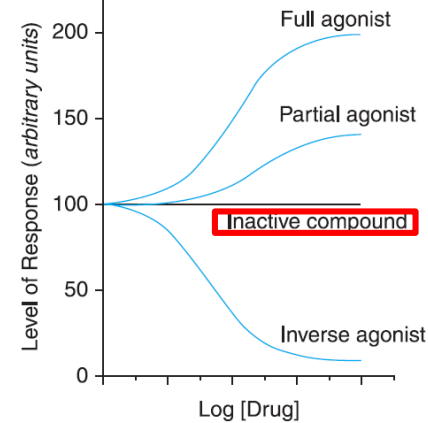
Antagonists

Antagonist: = non-activating ligand

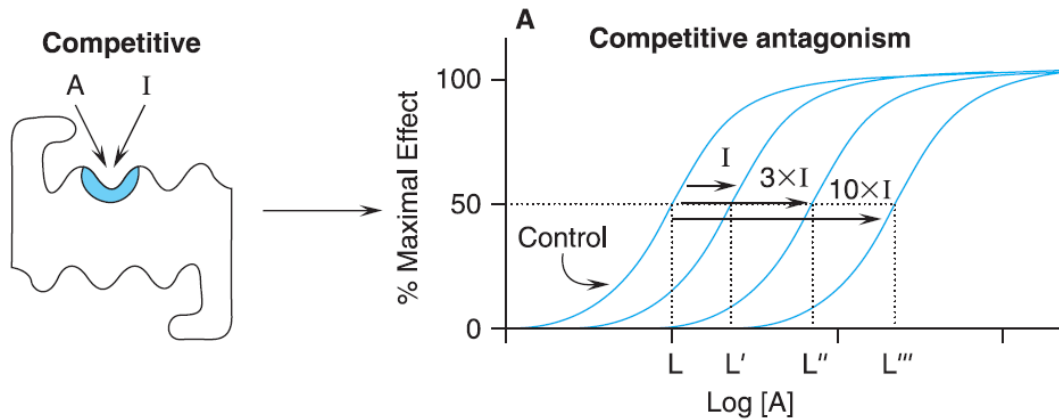
- ▶ upon binding, it does not activate the conformation change and signal transduction cascade characteristic to that receptor

(may activate a different conformation change, which in turn does not activate signal transduction cascade e.g.: allosteric antagonist. Here the conformational change only deforms the orthosteric binding site.)

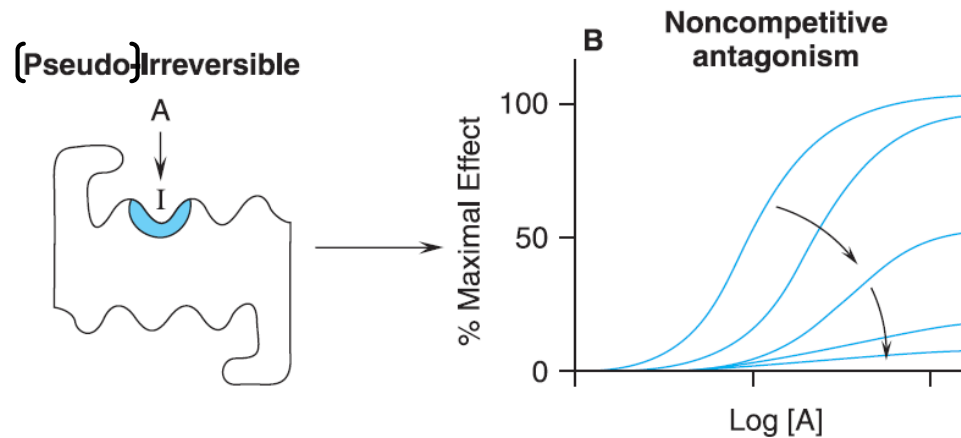
- ▶ Binding: reversible OR irreversible
- ▶ Place of binding: (relative to endogenous ligand) orthosteric OR allosteric
- ▶ Place of binding: (relative to any agonist) syntopic OR allotopic
- ▶ Relationship between agonist and antagonist: competitive OR non-competitive (next 2 slides)



Antagonism on the receptor-level



With higher antagonist conc. E/c curve of agonist shifts to the right → EC_{50} increases.

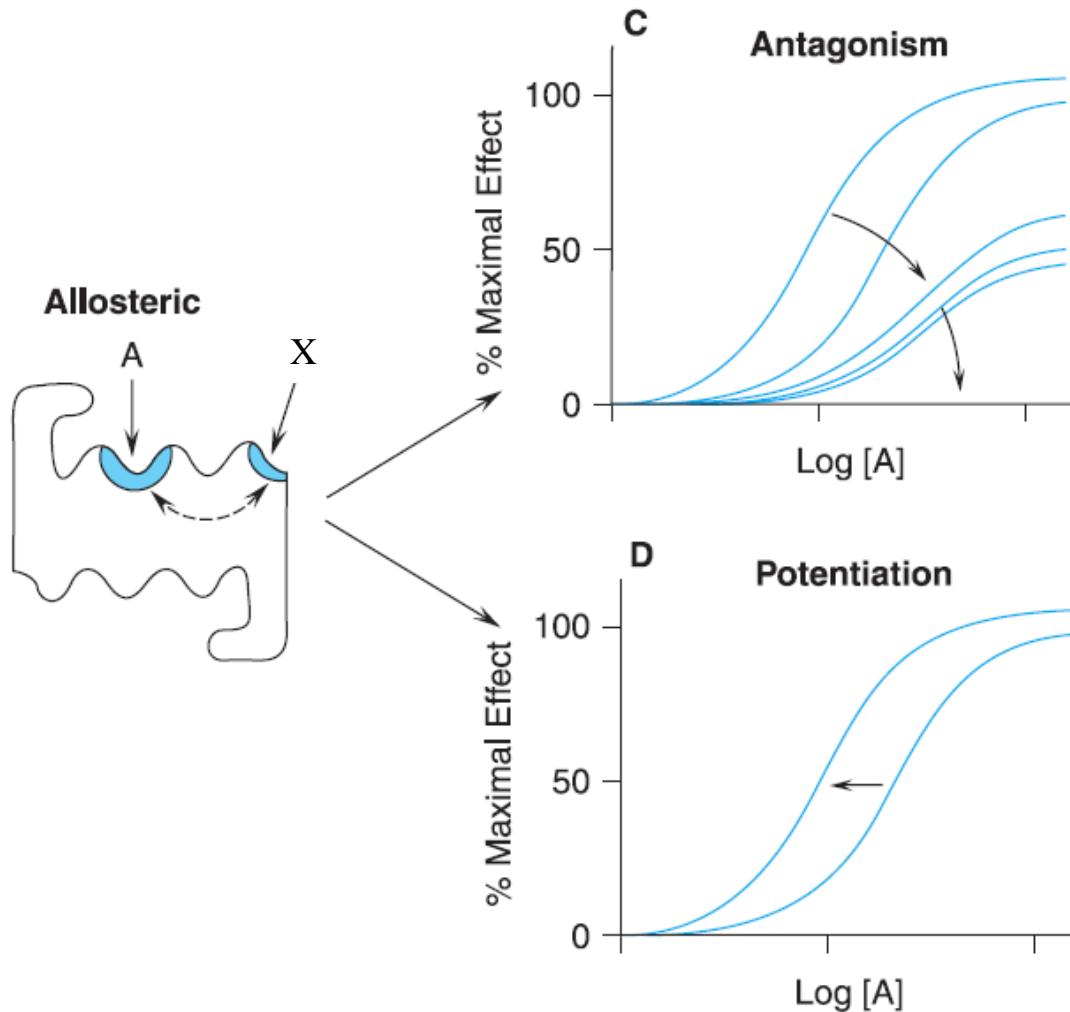


Irrev. = covalent bond
(persists until
receptor-turnover)

Pseudo = slow dissociation
but no covalent bond

With higher antagonist conc. E/c curve of agonist lies down to X axis. → E_{max} decreases.

Other receptorial interactions

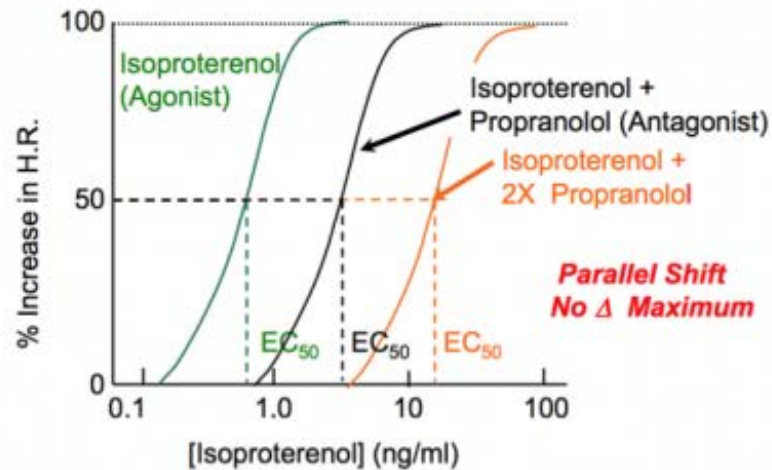


No competition →
behaves as
non-competitive antagonism

Concrete example

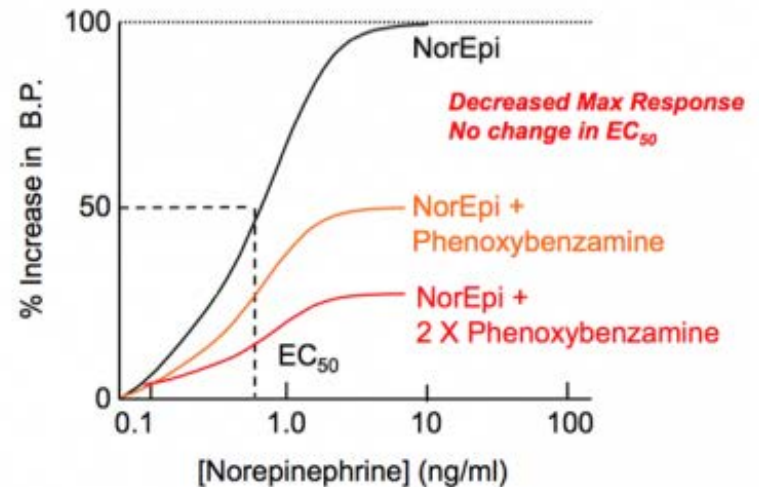
A

Competitive Inhibition



B

Noncompetitive Inhibition



Drug supply in Hungary

The background of the slide features abstract, overlapping geometric shapes in various shades of green, ranging from light lime to dark forest green. These shapes are primarily located on the right side and bottom of the frame, creating a modern, layered effect against the white background.

Pharmacy

- ▶ A **pharmacy** (US term) or a **chemist's** (UK term) is a health care provider establishment in which pharmacy (the health profession) is practiced. It is primarily a healthcare institute and just secondarily a private company.
- ▶ Health care services of pharmacy:
 - ▶ Compounding of medicines
 - ▶ Drug retail trade
 - ▶ Dispensing of medications
 - ▶ Clinical services, Pharmaceutical care
 - ▶ Reviewing medicines for safety and efficacy
 - ▶ Providing drug informations
- ▶ Residential medicine supply is provided by different types of pharmacies, during which medications and related professional information is provided for the patients directly.

Types of pharmacies in Hungary

- ▶ Community pharmacy
 - ▶ Provides direct and comprehensive medicine supply for the population
- ▶ Branch pharmacy
 - ▶ a subsidiary of a community pharmacy
the associated community pharmacy is the "parent company"
 - ▶ In small villages (population lower than 3000-4000)
 - ▶ Reduced services
- ▶ Handheld pharmacy
 - ▶ In the smallest villages (population lower than 1000)
the general practitioners supply their patients with medications
 - ▶ The GP submits a request to a handheld pharmacy,
which will be legally bound to the person of the GP
 - ▶ Only essential medicines are kept in storage
 - ▶ It is also legally associated to a single community pharmacy
- ▶ Hospital pharmacy
 - ▶ Supplies hospitals and clinics with medications
(internal drug supply only)
- ▶ Prescription-traffic pharmacy
 - ▶ Type of hospital pharmacy which has community drug supply as well
(external drug supply as well)
- ▶ Veterinary pharmacy
 - ▶ Specialised to animal medicines
 - ▶ In (human) pharmacies a special permission is needed to be allowed to
distribute animal medicines, but that's also a possibility

Ceases to operate,
if community
pharmacy is established

From where can an outpatient get medicines?

- ▶ Community pharmacies
- ▶ Other shops, petrol stations
 - ▶ Special permission is needed
 - ▶ Only some OTC medicines
- ▶ Medicine wholesaler
 - ▶ Medical oxygen (oxygen cylinder)
 - ▶ Continuous ambulatory peritoneal dialysis (CAPD) solution
- ▶ From internet
 - ▶ Only OTC medicines
 - ▶ Through package sending
 - ▶ ONLY pharmacies are allowed to

From where can a pharmacy buy medicines?

- ▶ From licensed medicine wholesaler only
- ▶ From no other place (even not from another pharmacy)
- ▶ In case of demand every medicine should be obtained by the pharmacy. If out of stock, patient should be informed about the time of acquisition.



Everything is under strict legal control.



Regulations of pharmacies

- ▶ Establishment: regulated
- ▶ Ownership: specialist
- ▶ Operation: specialist (Personal pharmacy operating license)
- ▶ Regulation-development: shared between state and profession
- ▶ Licensing: state
- ▶ Supervision: state
- ▶ Sanctioning: state

Requirements for operation of a pharmacy in Hungary

Required:

- ▶ Establishment license
 - ▶ This depends on e.g. number of inhabitants, distance from next pharmacy
- ▶ Operating license
 - ▶ Material conditions
 - ▶ Premises (rooms) pl: patient traffic/economic entrance, officina (retail storefront), laboratory etc.
 - ▶ Equipments pl: patendula (mixing bowl), pistil (mixing „spoon”), manipulator (for aseptic drug compounding) etc.
 - ▶ Personnel requirements
 - ▶ Qualified assistants, Pharmacist
- ▶ In case of community pharmacy :
 - ▶ Pharmacist who bears personal pharmacy operating license (= leader of pharmacy)
 - ▶ liability insurance

Personal license

- ▶ **Personal pharmacy operating license:**
- ▶ Given to a pharmacist with sufficient experience, this license entitles the pharmacist for the leadership of a community pharmacy
- ▶ Given by the National Public Health Service (ÁNTSz) - by the Chief Pharmaceutical Officer
- ▶ Authorize for leadership of only one community pharmacy
- ▶ As a penalty it can be withdrawn for 5 years (e.g. upon committing of a crime)

Structure of the Prescription

In Hungary

Pharmaceutical prescriptions

- ▶ **What is a prescription?**

A prescription is the instruction given by a physician, dentist or veterinarian to a pharmacist

- ▶ **Form of a prescription:**

A prescription may be written in ink or printed.

- ▶ **The language of a prescription:**

May be the mother tongue of some country. In the case of Hungarian prescriptions the official language is partly Latin, partly Hungarian.

- ▶ ***Receptura* (latin)**

The knowledge of writing a prescription.

Prescription-writing in Hungary

- ▶ Eligibility criteria for prescription writing and the method of prescribing are regulated by law.
- ▶ Medicines ordered by the doctor can be **prescription only** or without prescription (OTC = Over The Counter) medications.
 - ▶ Harmless medicines may be ordered by the doctor simply by words. Strong agents are prescription only.
- ▶ Prescription must be written onto a designated prescription-paper published by the National Health Insurance Fund (OEP). This is personalized, contains a personal bar code, and only one doctor, the authorized doctor may use it.
- ▶ Authentication/certification: stamp and signature of the doctor
 - ▶ In case of error-correction stamp and signature once again
- ▶ On 1 prescription, only 1 drug should be prescribed (but this may have more components (see later *Formula magistralis*))

Structure of the prescription

► 1. Inscriptio

► Data of doctor



- Name of doctor
- Name of Workplace
- Address of Workplace
- Phone-number
- License No. (in case of private practice)
- Unique identifier of prescription (bar-code)

► Data of patient

- Name of patient
- Address of patient
- Date of birth of patient
- National Health Insurance No. of patient („TAJ” Number; 9 characters)



► Data of prescription

- International Classification of Diseases (ICD) No. („BNO” Number; 5 characters)
- Date of prescription
- Substitutability checkbox
- Support type of National Health Insurance Fund (OEP)
- Specialist doctors's seal number
- Date of recommendation
- Patient care journal No.

ORSZÁGOS EGÉSZSÉGBIZTOSÍTÁSI PÉNZTÁR ORVOSI VÉNYE			
Az orvos adatai: Dr. Orvos Pál infomix Kft teszt praxis 1027 Budapest II. Bem rkp 53. T:214-5083 Ág.kód.:010099999		 (21)0801234500119117	
Beteg neve, címe: Infomix Teszt 1027 Budapest II. Bem rkp. 53.		Születési dátum: 1 9 9 0	
EU:		ENY:	
Továbbképzésmenetési adatai (TDJ-cím): 0 1 2 0 1 3 0 1 4	RNO: 2 0 1 2 0 2 2 8	Költségtérítési dátum: 2 0 1 2 0 2 2 8	
Jogcímkék: <input checked="" type="checkbox"/> X	<input type="checkbox"/> Igény szám	<input type="checkbox"/> Hó	<input type="checkbox"/> Évi díj
Szakorvosi javaslatra vonatközo adatai:	Költségtérítési adatai:	Javasló kifizetés dátuma:	Biztosítási szám adatai (számlázás): 0 0 2 2 8 1 0 0 3
Rfx: ABILIFY 15 MG TABLETTA 56x Scat.orig. No unam (I) D.S.: naponta 2x1 tabletta			
Kiváltható : 2012.02.28-tól		Ellátva : 2012.03.27-ig	
P. H.			
beteg aláírása	termék átvételének aláírása	orvos aláírása	
Kiadás dátuma: A termék kiadásának kézzelgy: A recept végző kézzelgy:			
Extra vonalkód: 			

Structure of the prescription

- ▶ **2. Invocatio**
was used to invoke the muse
(ask for her help)
nowadays it is just one word:
Take! In latin (Recipe! = Rp.)
- ▶ **3. Ordinatio (praescriptio)**
Physician's directions to the pharmacist.
Have to be written in latin.
- ▶ **4. Signatura**
Physician's directions to the patient.
Have to be written in the language of the patient.
- ▶ **5. Subscriptio**
signature of the patient
signature of the recipient (obligatory)
stamp(!) and signature of the doctor (both are obligatory)
- ▶ **6. Adscriptio**
Notes of the pharmacist:
Date of handing-out; signature of dispensing person; signature of verifier person; identifier of the pharmacy; extra bar code for easy handling of the prescription (contains the data of „ordinatio“/„prescriptio“)

ORSZÁGOS EGÉSZSÉGBIZTOSÍTÁSI PÉNZTÁR ORVOSI VÉNYE									
Az orvos adatai: Dr. Orvos Pál infomix Kft teszt praxis 1027 Budapest II. Bem rkp 53. T:214-5063 Ág.kód.:010099999					 (21)0801234500119117				
Beteg neve, címe: Infomix Teszt 1027 Budapest II. Bem rkp. 53.					Számlázási dátum: 1990				
ENY:									
EL:									
Tenyészleletvizsgálati eredmény (TCA-címek): 012013014		BNC:		Kalkulus dátuma: 20120228			Nem számlázható		
Jogcímkód: <input checked="" type="checkbox"/> X		<input type="checkbox"/> I		<input type="checkbox"/> II		<input type="checkbox"/> III		<input type="checkbox"/> IV	
Szakorvosi javaslatra szükség adatai:		Kalkulus orvos adatai:		Javasló kalkulációs dátuma:			Bemutatókalkulusi dátuma (számlázás): 002281003		
Rg: ABILIFY 15 MG TABLETTA 56x Scat.orig. No unam (I) D.S.: naponta 2x1 tablettá									
Kiváltható : 2012.02.28-tól Ellátva : 2012.03.27-ig									
P.H.									
beteg aláírása			termék átvételének aláírása			orvos aláírása			
Kiadás dátuma: A termék kiadásának kelte:									
A recept vége! Kérjük:									
Extra vonalkód:									
									

Curiosity:

Pharmaceutical Latin Abbreviations

- ▶ The 'Subscriptio' section of US prescription (although written for the patient) often contains *Latin* abbreviations (these are parts of the public knowledge).
Otherwise the language of the US prescription is english. :P

Abbreviations	Full form	Meaning
Po	Per os	Through the mouth
Prn	Pro re nata	As necessary
Ac	Ante cibum	Before meal
Cc	Cum cibo	With food
Pc	Post cibum	After meal
Sid	Semel in die	Once a day
Bid	Bis in die	Twice a day
Tid	Ter in die	Three times a day
Qid	Quarter in die	Four times a day
Qqd	Quaque die	Daily
Qqh	Quaque hora	Hourly
Ss	Semis	Half