Pharmacokinetics of Psychotrophics

Journal club meet date 15th sept

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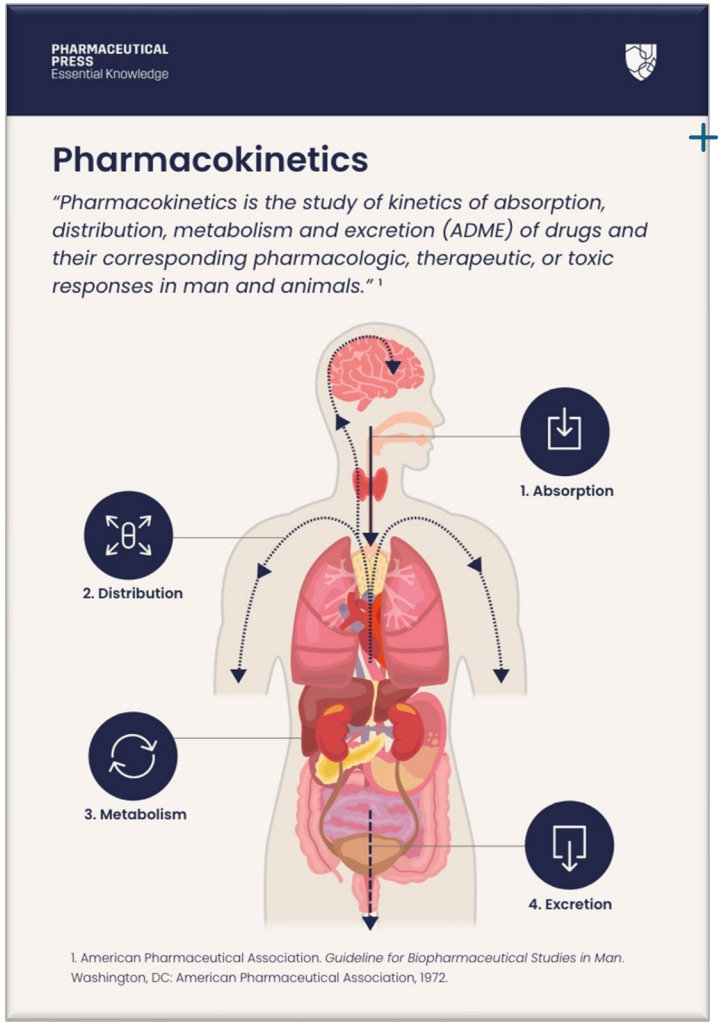
DEFINITION

- Pharmacokinetics is the study of the course of the absorption, distribution, metabolism and excretion (ADME) of a drug after its administration to the body.



ABSORPTION

ABSORPTION : Process by which the administered drug enters the systemic circulation

MODES OF ADMINISTRATION:

I.V.

I.M.

S.L.

P.O.

Modifying absorption

- Absorption can be modified by
  - Different routes of administration
  - Chemical property of the drug
  - Composition of the pill/ injectable
  - State of the body, eg :prokinetic states may give less times for absorption, Presence of food
- Food delays absorption for most drugs.
- Food improves absorption for certain drugs like: Ziprasidone, Lurasidone(almost 50 %change is absorption efficiency), Sertraline

Modifying Absorption

Controlled release formulations are designed and obtained to release active drugs with a specific release rate and at specific sites in order to increase therapeutic effects and benefits.

QUICK AND EFFICIENT ABSORPTION: Induction of sleep, relief from anxiety, control of agitation, seizures.

- ✓Sublingual routes
- ✓ODT
- ✓Intranasal routes
- ✓Modified release melatonin and zolpidem .
- ✓IM, IV routes.

- AVOIDANCE OF LOCAL EFFECTS IN THE STOMACH:

  Enteric coated tablet: Divalproex is designed to be enteric stable
- AVOIDANCE OF LOCAL EFFECTS ON THE GASTRIC TRACT:

  Delayed release / sustained Paroxetine
- REDUCED ADVERSE EFFECTS ASSOCIATED WITH PEAK BLOOD LEVELS:

  Bupropion extended release , Lithium ER
- ARTIFICIALLY EXTENDED HALF-LIFE, CONVENIENCE OF DOSING:

Clozapine , quetiapine, venlafaxine,
- IMPROVED COMPLIANCE:

  LAI
- LESS FLUCTUATION IN BLOOD LEVELS ACROSS THE COURSE OF THE DAY.

  Methyl phenidate

Disadvantages of Time Release formulations

- A disadvantage of time-release formulations is that they may be incompletely absorbed; this is a serious issue in patients with acute or chronic intestinal hurry disorders, such as gastroenteritis or irritable bowel syndrome.
- Time-release formulations may also be more expensive than immediate-release formulations, 25 percent more dosage for divalproex and paroxetine SR tablets.
- It may increase the size of the pill as one single dose is given: Valproate or oxcarbazepine tablets.

- Bioavailability is the fraction of the originally administered drug that arrives in systemic circulation and depends on the properties of the substance and the mode of administration, first pass metabolism.

Bioavailability is the fraction of the originally administered drug that arrives in systemic circulation.

- Absorption
- Different routes of administration
- Chemical property of the drug,
- Drug formulation.
- First Pass Metabolism
- Distribution
- Other factors like age, sex, physical condition, presence of food

DISTRIBUTION

- After a drug enters the systemic circulation, it is distributed to the body's tissues.
- Distribution is generally uneven because of differences in blood perfusion, tissue binding (eg, because of lipid content), regional pH, and permeability of cell membranes.
- For a drug that is highly tissue-bound, very little drug remains in the circulation; thus, plasma concentration is low and volume of distribution is high. Drugs that remain in the circulation tend to have a low volume of distribution.
- Plasma Having Free and bound drug Plasma protein Albumin and alpha 1 acid glycoprotein, Tissues especially Adipose tissue.
- Plasma levels May or may not co relate with it's levels in CNS .
- Drugs in fat compartment of the body will keep coming to plasma and may have sub therapeutic effects.
- Volume of distribution, systemic and extracellular compartments

Metabolism

- Definition: The process of change in the chemical composition so that it can be excreted easily.

LIVER IS THE MAJOR SITE, but can also occur in other tissues like skin, kidney, lungs, brain.

Consequence of Metabolism :

- Conversion to more polar(water soluble substance), pharmacological inert
- Pro Drug , into an active metabolite.

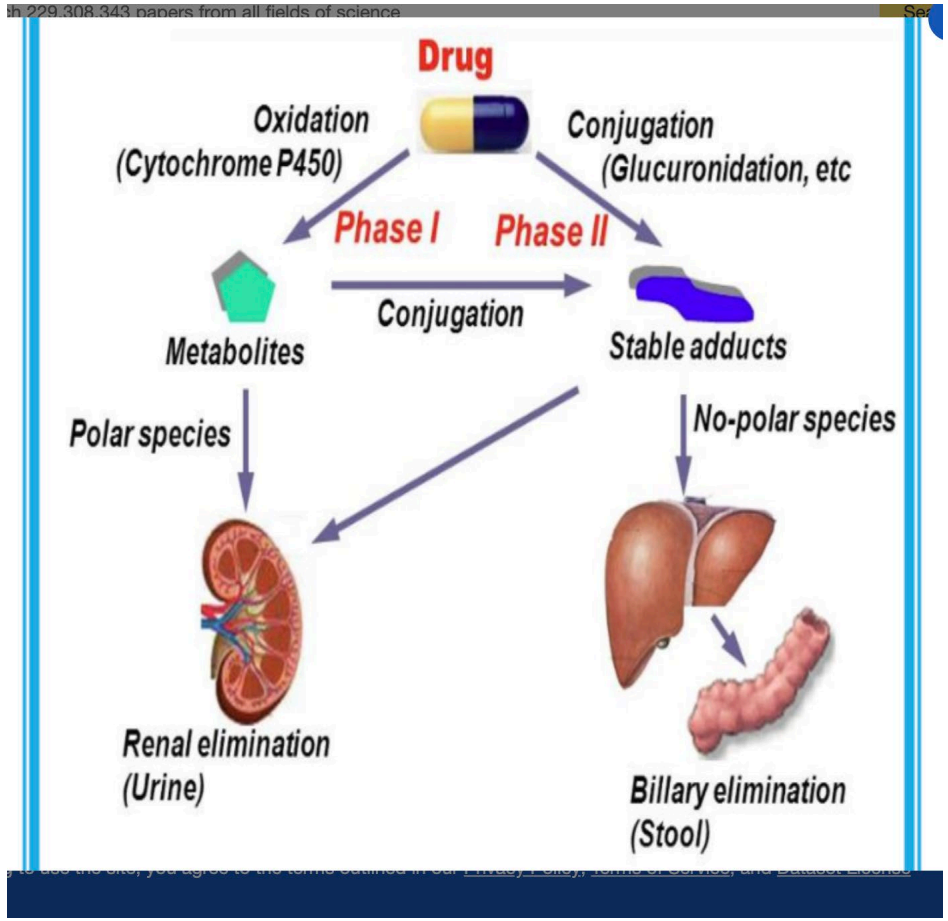
Metabolism

Phase 1 reactions

- OXIDATION(most common)
- REDUCTION
- HYDROLYSIS
- May cause formation of active moiety.
- CYP SYSTEM

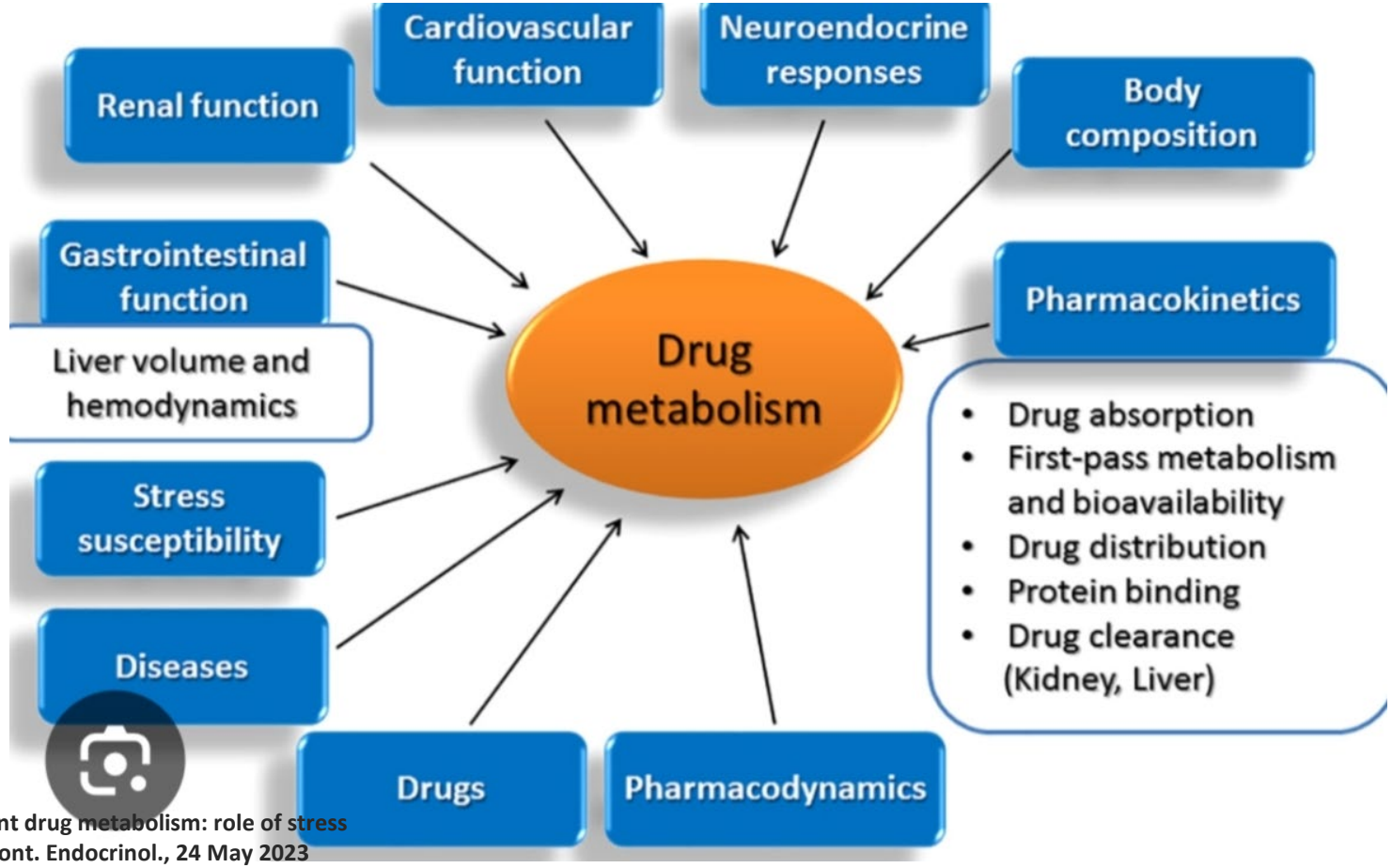
Phase 2 reactions

- Conjugation with an endogenous substance (eg, glucuronic acid(most common) ,sulfate, glycine, Glutathione.
- To make drug more polar, soluble in bile or urine.



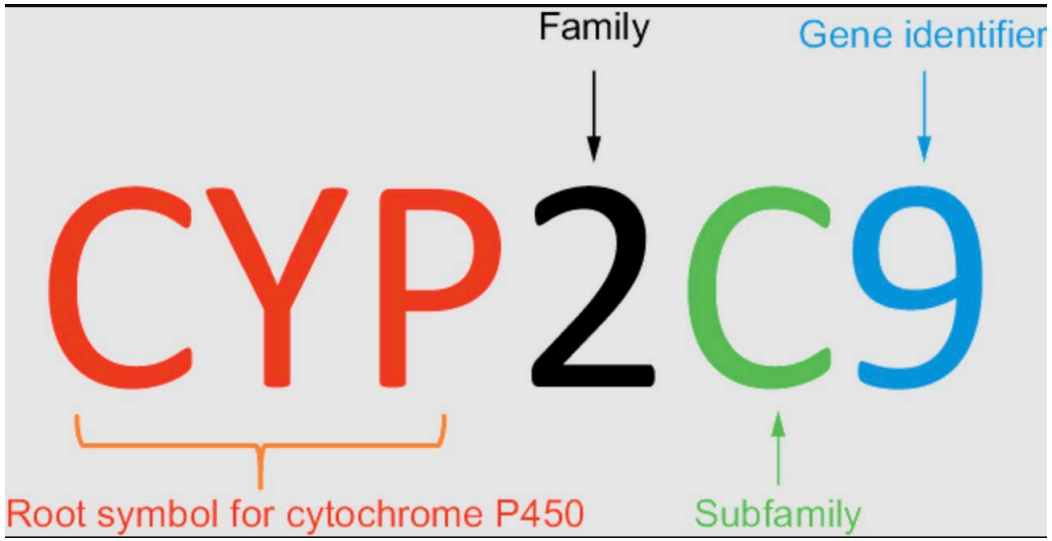
- For many drugs, metabolism occurs in 2 phases.
- Some drugs undergo only phase I or phase II reactions
- Phase 1 reactions are affected more in liver diseases.
- Lorazepam undergoes only phase 2, safer in liver diseases .

https://www.msdmanuals.com/en-in/professional/clinical-pharmacology/pharmacokinetics/drug-metabolism



Age-related modifications in CYP-dependent drug metabolism: role of stress
Maria Konstandi[1*] Elizabeth O. Johnson[2] Front. Endocrinol., 24 May 2023
Sec. Endocrinology of Aging
Volume 14 - 2023 | https://doi.org/10.3389/fendo.2023.1143835

Cytochrome p450 group of enymes



Haem proteins found in the ER(microsomes) of Liver, intestine cells, kidney cells.

Found mostly liver kidney and intestine.

57 ISOENZYMES

1A2

2C9,2C18,2C19

2D6

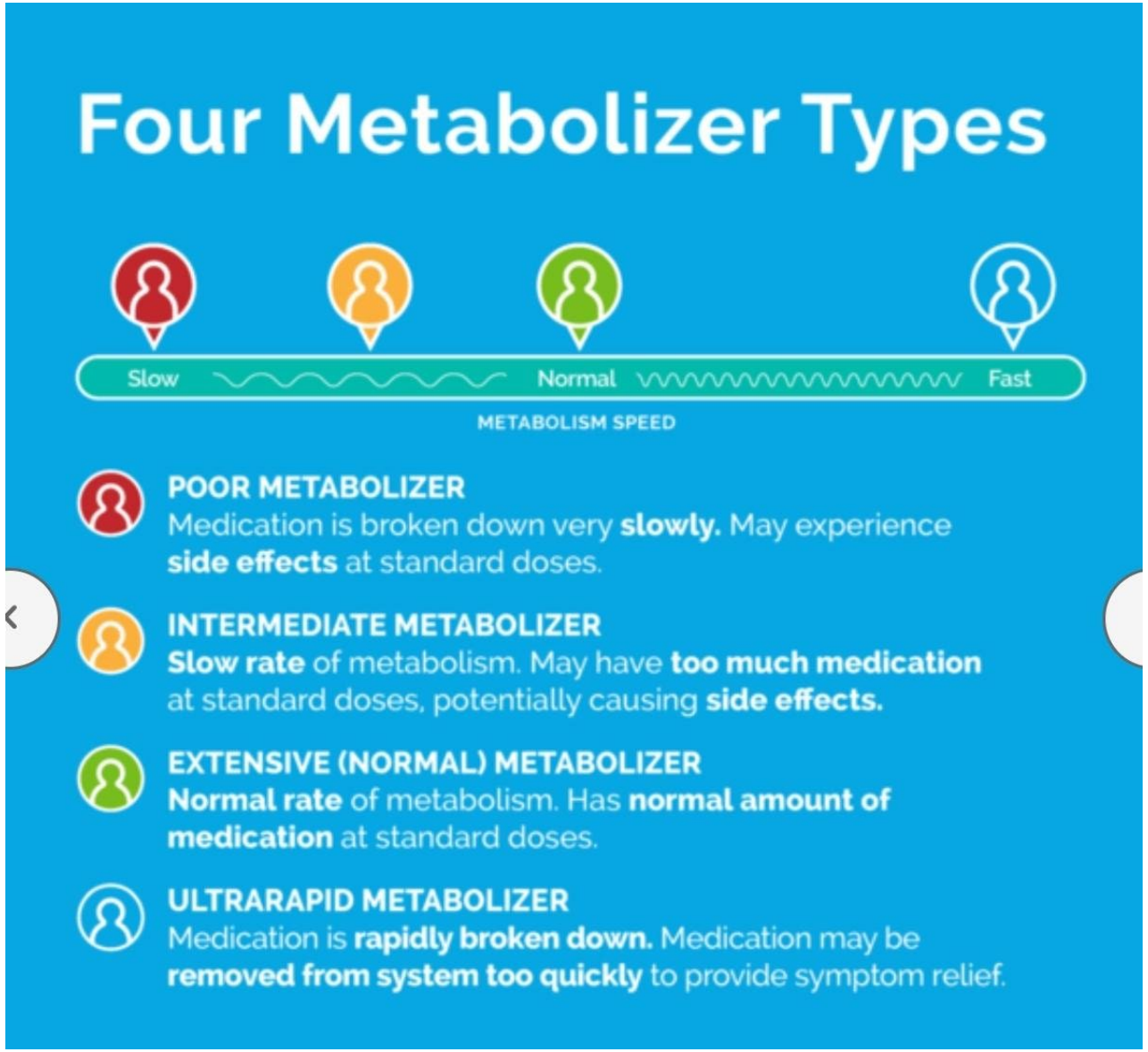
3A4

Cytochrome P-450

- They are Enzymes Found in microsomes ER membrane of Hepatocytes, kidney and intestinal cells,Brain, Skin, Lungs.
- Any drug: Substrate, Inducer, Inhibitor.
- Five enzymes (CYP3A4, CYP1A2, CYP2C9, CYP2C19, CYP2D6) account for the metabolism of the majority of commonly used drugs. CYP3A4 is the most frequent enzyme in the liver followed by CYP1A2, CYP2C9, CYP2C19 and CYP2D6.

- CYP2C19, CYP2C
- CYP2D6

POLYMORPHISM



Individual patients carrying CYP2D6*3, -*4, -*5, or -*6 variants should be given reduced doses of antidepressants to avoid or reduce drug side effects. In this scenario, metabolism of the drugs is the major factor affecting drug response and safety, and genetic variations are well established.

PHARMACOGENOMICS:
Still in infancy.
Can sometimes guide when there is lack of response
Treatment resistance
Personalised medicine(to avoid side effects).

Shetty P. Pharmacogenomics and its Future Implications in Treatment-resistant Depression. Ind J Priv Psychiatry

Clinical interactions for antidepressants

- Escitalopram does not have significant inhibitory activity.
- Fluoxetine and paroxetine inhibit their own metabolism, half life prolongs.
- Clomipramine also metabolised by and inhibits 3A4, commonly used , which could add up.
- Serotonin syndrome !
- Bupropion and dextromethorphan, CYP2D6 inhibition, t ½ tends from 4 to 22 hours for dextromethorphan
  Bupropion and Venlafaxine ,3 fold increase venlafaxine levels.(Hogrefe 20th edition)

Table 3. Inhibition of Human CYP 450 Isoenzymes by Selective Serotonin Reuptake Inhibitors

	CYP450 Isoenzymes				
SSRIs	1A2	2C9	2C19	2D6	3A3/4
Fluvoxamine	+++	++	+++	+	++
Fluoxetine	+	++	+/++	+++	+/++
Paroxetine	+	+	+	+++	+
Sertraline	+	+	+/++	+	+
Citalopram	0/+	0	0/+	0/+	0

Source: References 2, 4.

Clinical handbook of psychotropic drugs,20thedition, Hogrefe publication

Clinical Interactions for Antipsychotics

- Clozapine metabolised by 3 major Enzymes.
- Smoking strong inducer and hence will decrease the levels of antipsychotics esp. Clozapine
- Inhibitor of CYP2D6 fluoxetine, paroxetine and high dose sertraline,
- HIV fungal infections, macrolides (except azithromycin), inhibitors so levels may increase.
- TB , carbamazepine… inducer, hence can cause loss of effect.

Table 2. Inhibitors and Inducers of Antipsychotic-Metabolizing Cytochrome P450 Enzymes

Cytochrome P450 (CYP) Enzyme Subtype	Inhibitor	Inducer
CYP1A2 Involved in metabolism of clozapine, olanzapine	Fluvoxamine Grapefruit juice in large quantities	Cigarette smoking
CYP2D6 Involved in metabolism of clozapine, olanzapine, risperidone	SSRIs (especially fluoxetine, paroxetine, high-dose sertraline)	
CYP3A4 Involved in metabolism of clozapine, quetiapine, ziprasidone	Erythromycin and other macrolide antibiotics Ketoconazole and other antifungal drugs Protease inhibitors	Barbiturates Carbamazepine Phenytoin Rifampin Glucocorticoids

Abbreviation: SSRI = selective serotonin reuptake inhibitor.

(Primary Care Companion J Clin Psychiatry 2003;5[suppl 6]:22–25

Clinically significant reactions

- Lamotrigine and valproate .
- Valproate inhibits LTG metabolism by 50 % on dosages above 250 mg of Valproate.

(this is in contrast to carbamazepine , phenytoin who are enzyme inducers)

Kanner AM. When thinking of lamotrigine and valproic acid, think "pharmacokinetically"! Epilepsy Curr. 2004 Sep-Oct;4(5):206-7. doi: 10.1111/j.1535-7597.2004.04515.x. PMID: 16059503; PMCID: PMC1176375.

- Bupropion and dextromethorphan

  (t1/2 of 4 hours), CYP2D6 inhibition by bupropion, t1/2 increasing to 22 hours.
- CYP3A4 inducer Carbamazepine, oxcarbazepine, rifampin can increase metabolism of OC pills.

TB drugs

- Rifampicin inducer 1A2, 2D6, 2C19, 3A4.. Antidepressant consideration
- Isoniazid , CYP interactions are not so strong, but it itself inhibits MAO in plasma.

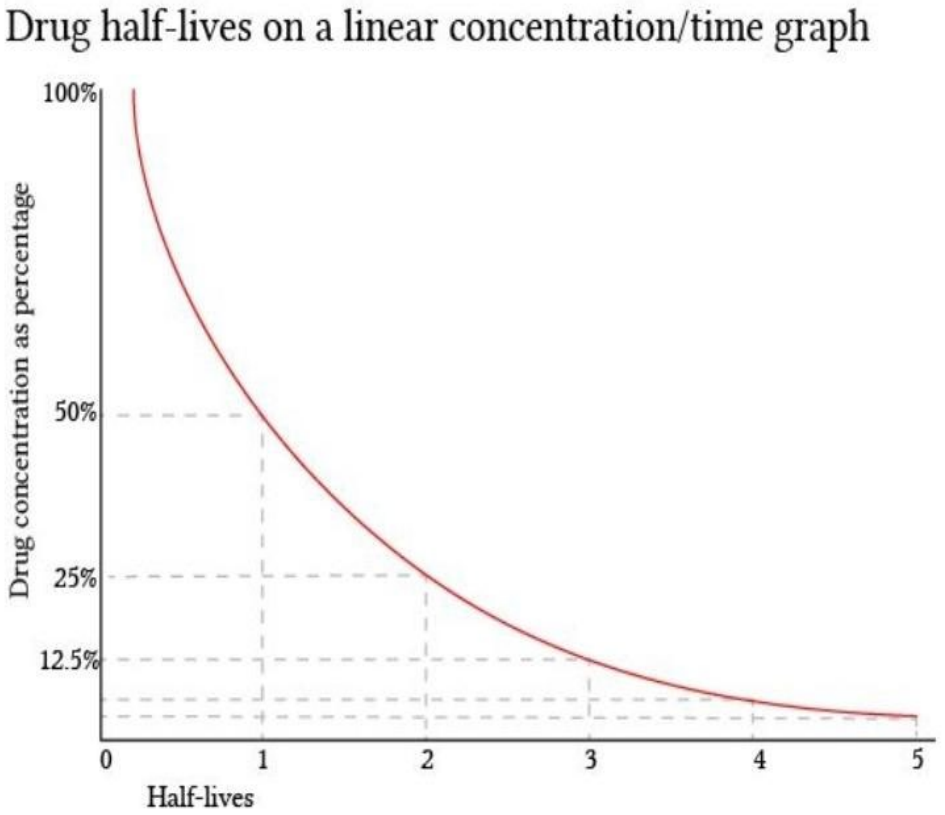
HIV

- Protease inhibitors are inhibitors at 3A4.
- Start low, go slow, as lower doses maybe more effective.

ELIMINATION KINETICS

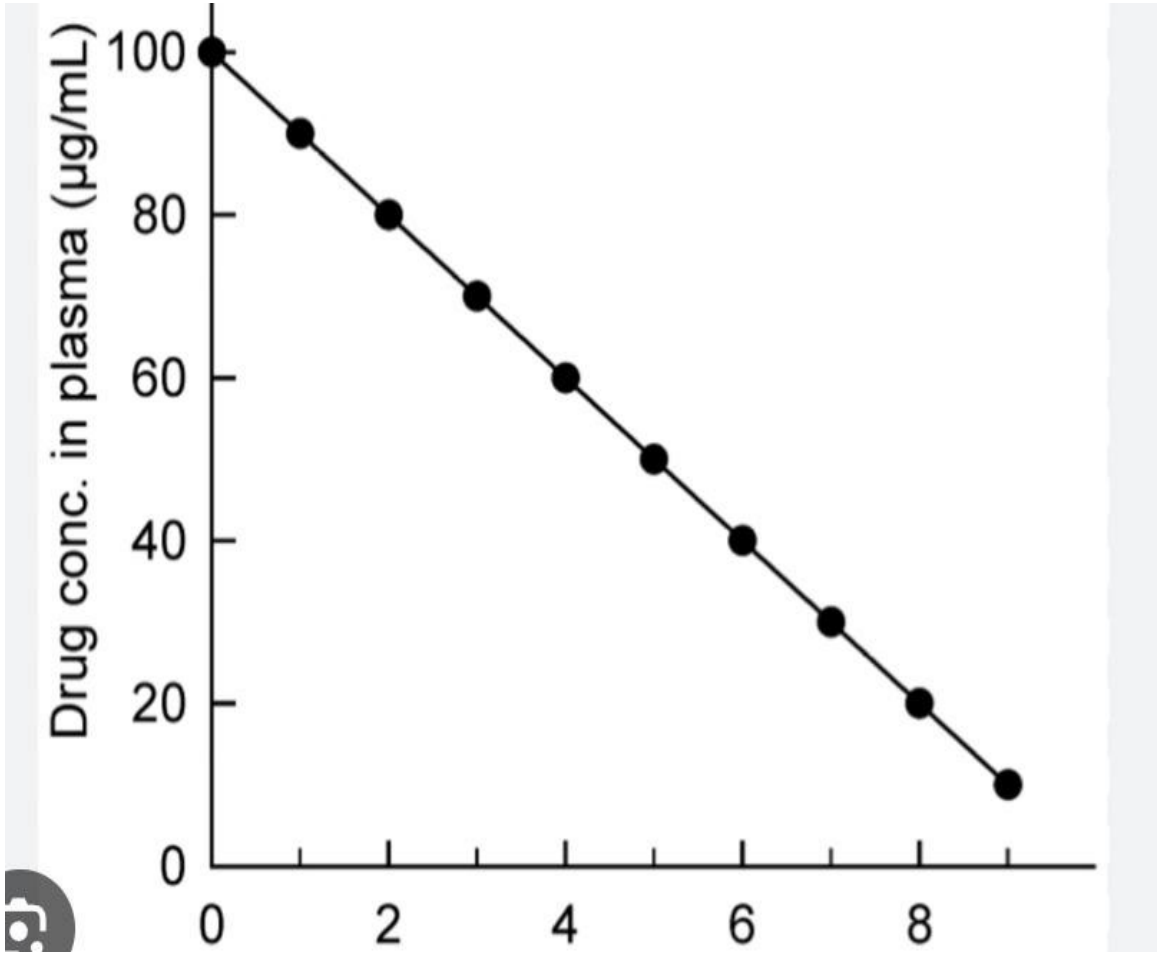
First order kinetics/ Linear Kinetics

- Rate of elimination of the drug is not constant, proportion of eliminated drug is constant.
- Rate May increase or decrease with the drug concentration.



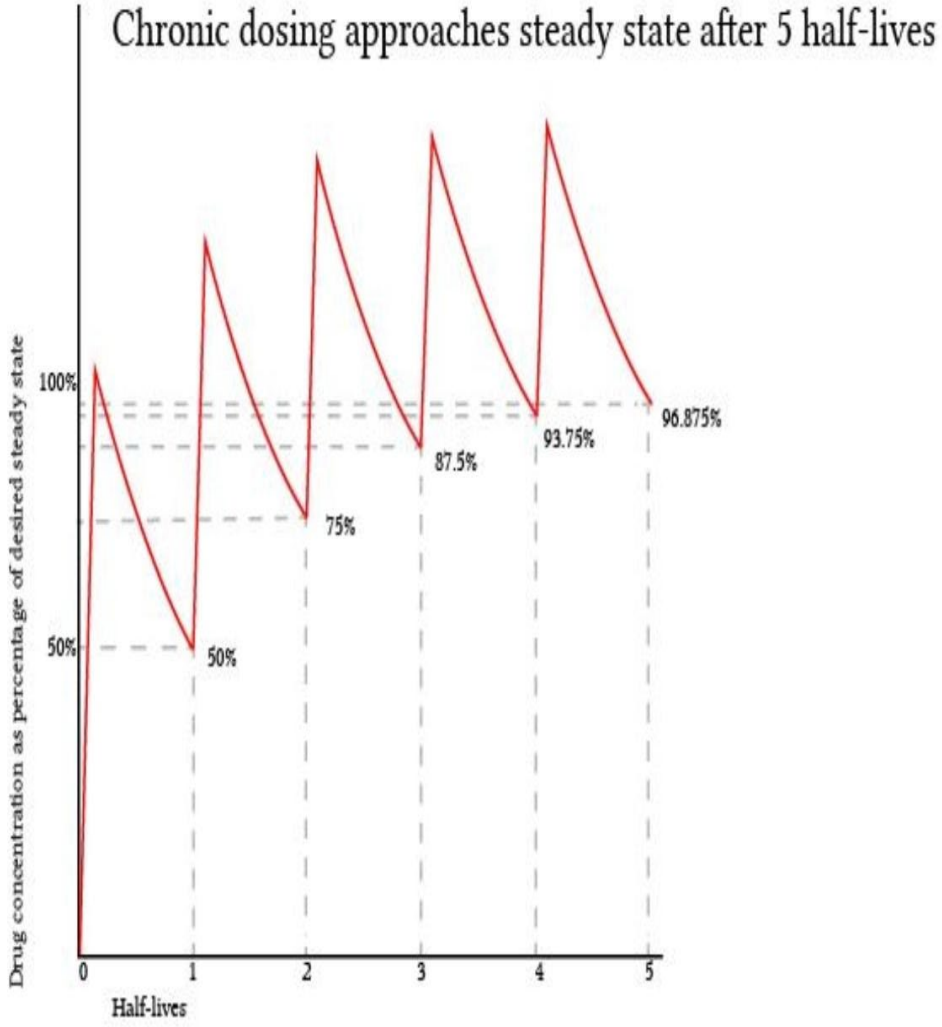
Zero order Kinetics

- Same amount of drug is eliminated per unit time.
- Not dependent on the amount of drug concentration.
- Alcohol, phenytoin, drugs at higher concentration, toxic levels when saturation of metabolism and or excretion mechanism.



Half life and Steady state

- The half-life represents the time required to reduce the plasma concentration of the drug reached in steady-state by 50%.
- Following repeated administration of a drug, a steady-state is reached when the quantity of drug eliminated in the unit of time equals the quantity of the drug that reaches the systemic circulation in the unit of time.
- 4 to 5 half lives needed for SS and elimination.



Dosing and tapering

Appropriate loading dose is necessary to reach therapeutic concentrations more quickly, similar to those obtainable in the steady-state. The steady-state concentration is also achievable with a series of close-up administrations to achieve the plasma concentration useful for the therapeutic effect in a very short time. Then it is possible to continue with maintenance dose.

Maintenance dose may be changed to accommodate the change in elimination rate.

Tapering or decreasing dose	• Longer t ½ drugs like Fluoxetine, Aripiprazole, Cariprazine • Stop and resume method
Loading dose	• Help reach desired concentration faster.(limitations)
Longer acting drugs	• Missed doses occasionally. • May not matter

Drugs with Shorter half

- Antipsychotics: clozapine(12 hrs), quetiapine(12 hrs)

Dosed as sustained release preparations for less frequent dosing, immediate release for sedation or agitation.

- Venlafaxine, Desvenlafaxine,(10 hrs), Fluvoxamine(9 to 20 hours).
- Propranolol
- Levetiracetam
- Gabapentin
- Pregabalin
- paroxetine
- Carbamazepine (12 to 17 hours on repeat dosage) , Oxcarbazepine (7 to 20 hours)
- Methyl phenidate I.M. 3 to 5 hrs, extended release 8 to 12 hours.
- Alprazolam 10 to 15 hours , lorazepam.

- Drugs with long half-lives take a long time to reach steady state. This is usually of little consequence in psychiatry because time to onset of clinical benefit is usually independent of the half-life of psychotropic drugs.
- A long half-life can be disadvantageous if rapid washout is desired for any reason, including the experience of adverse effects or toxicity.

- Drugs with a long half-life have a long duration of action, but drugs with a long duration of action do not necessarily have a long half-life. Thus, orally administered drugs in delayed-release formulations have a longer duration of action only because the rate of absorption is delayed; the half-life of the drug is no different from that in immediate-release formulations.
- Similarly, the prolonged action of long-acting injection (LAI) antipsychotic drugs is only because of slow release of the active drug into blood; again, the half-life of the drug is no different from that in other formulations.
- Hit and run MOA
- Maol
- Disulfiram
- Lithium

Elimination

- Liver cirrhosis. Shorter duration of action drugs, lower dosages.
- Kidney illness, GFR should be checked, GFR > 50 ml reduction needed but drugs can be given, 30 to 50 ml, used with cautioned.

Table 2. Some Neuropsychopharmacologic Agents That Are Not Metabolized or Are Minimally Metabolized by CYP Enzymes in the Liver

Anxiolytics
Pregabalin[8]
Lorazepam[9]
Antidepressants
Milnacipran[10]
Desvenlafaxine[11]
Low doses of amisulpride,[12,13] sulpiride,[14] and levosulpiride[15]
Antipsychotics
Paliperidone[13]
High doses of amisulpride,[12,13] sulpiride,[14] and levosulpiride[15]
Anticonvulsants and mood stabilizers
Gabapentin[8]
Levetiracetam[16]
Lithium[17]
Lamotrigine[18]
Dementia treatment
Memantine[19]

Drugs That Escape Hepatic Metabolism
Chittaranjan Andrade, MD
Published: July 15, 2012, JCP

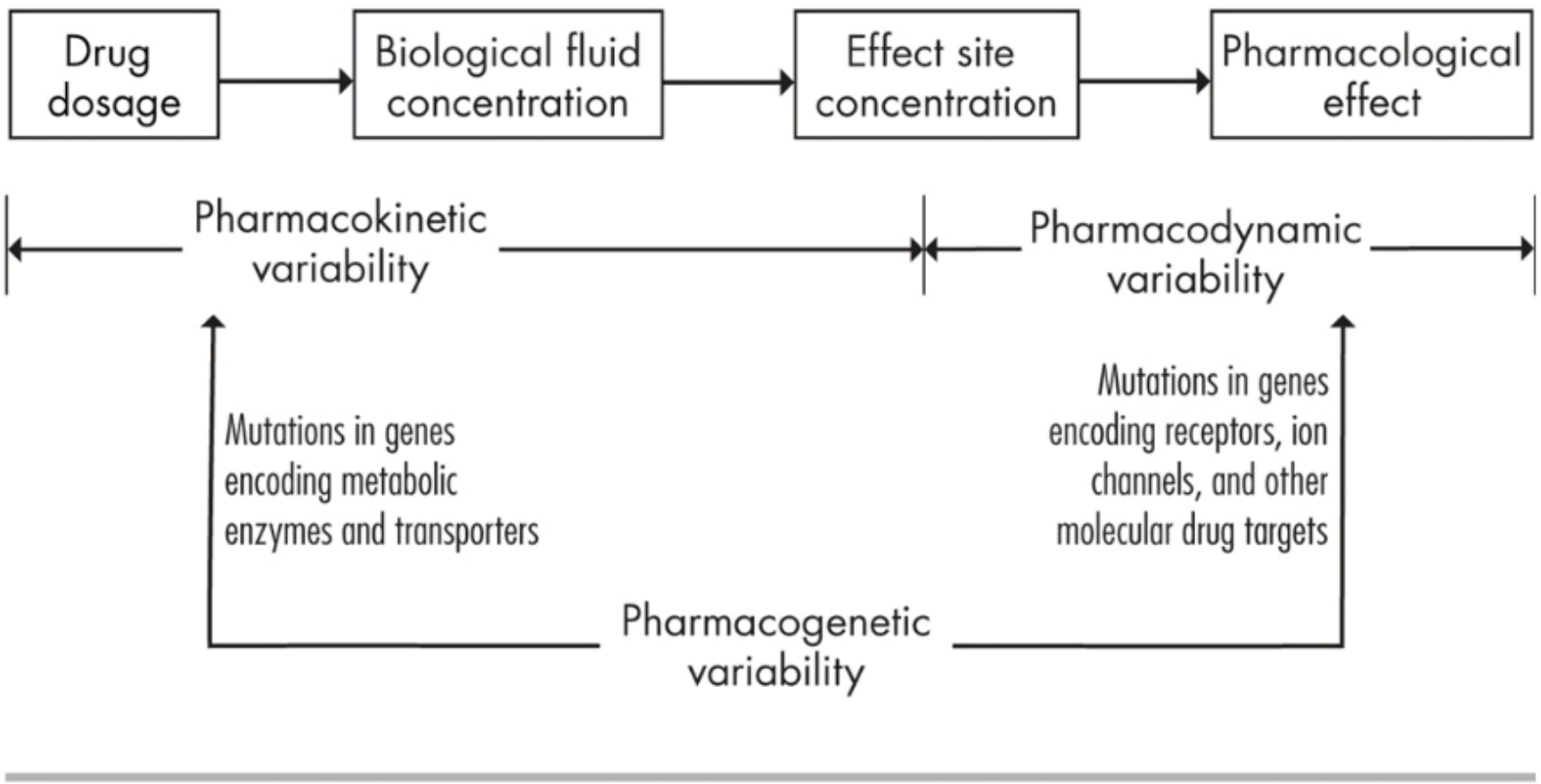
Elderly

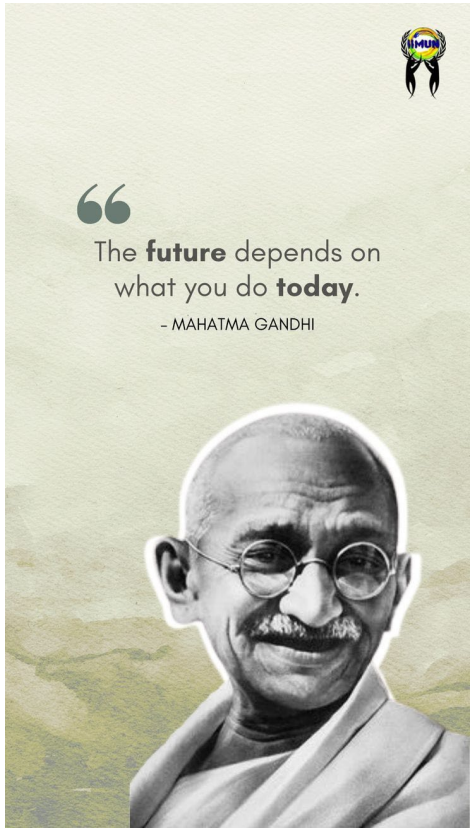
- Reactions with antidiabetic drug, antihypertensive, amiodarone,
- Poor metabolism and excretion, more fat than muscle, less plasma proteins.

What is a pharmacokinetically clean drug

- Good absorption…not affected by food
- Linear pharmacokinetics.
- Less protein binding.
- Is not an enzyme inducer or Inhibitor
- Can be administered as per convenience (immediate release, or extended release, long acting..etc).
- Easy to eliminate

Pharmacogenetics




The future depends on what you do today.
- MAHATMA GANDHI


HAPPY
Dussehra
Wishing you a very happy Dussehra

THANK YOU