

PSYCHOTROPIC DRUG INTERACTIONS

- NZMA GP Conference 2012
Psychopharmacology series
 - Qualified declarations
 - Guna Kanniah
 - Waikato Hospital

1 IN 4 PEOPLE HAVE A MENTAL HEALTH CONDITION

..... NZ HEALTH MINISTRY



Case study

- 68 yo female , no hx of psychiatric illness
- Feb 05: presented with major depressive disorder with significant sadness , inner tension,
- Difficulty In Concentration,
- Sleep impairment
- Appetite loss and pessimistic thoughts

MED HX :

- Atrial fib(AF) ttd with 250mcg digoxin
- 1mg warfarin od (2 years) (INR 1.7)
- no abnormal physiological findings
- day 3 paroxetine 20mg OD
- day 5 nausea, vomiting dizziness
- day 7 delirium, hallucinations, disorientation
- day 10 unable to eat , walk

CONTD.....

- Day 11 suspected digitalis intoxication
- serum digoxin 5.2ng/mL(NR 0.5-2.0 ng/mL)
- ECG ventricular premature contractions, complete av block
- no electrolyte disturbances
- day 12 all medications discontinued
- day 13-15 ECG bradycardiaAF
- digoxin level decreasing
- day 21 digoxin 250mcg OD and warfarin 1mg OD reinstated

CONT'D.....

- Delirium , disorientation decreased and recovered by day 28
- but moderate depressive symptoms
- bedridden during this period
- developed aspiration pneumonia
- primary tt with antibiotics
- May -moved to medical ward for intensive care
- Jun - died from pneumonia

What
happened???!!!!!



CLINICAL RELEVANCE OF DDI

- What percentage of the population at risk for a potential DDI?
- Pharmacoepid. surveys conducted in Denmark, England, Sweden, and the U S... multiple medxn is extensive
 - *Davies SJ J Psychopharmacol. 2007;21(2):153-160. Erratum in: J Psychopharmacol. 2008;22(6):698*
- What constitutes clinical relevance?
- Any clinically significant change in the patient's status due to a DDI makes that DDI clinically significant
 - *Ray et al N Engl J Med. 2004;351(11):1089-1096.*
 - *Preskorn J Psychiatr Pract. 2005;11(6):397-401.*

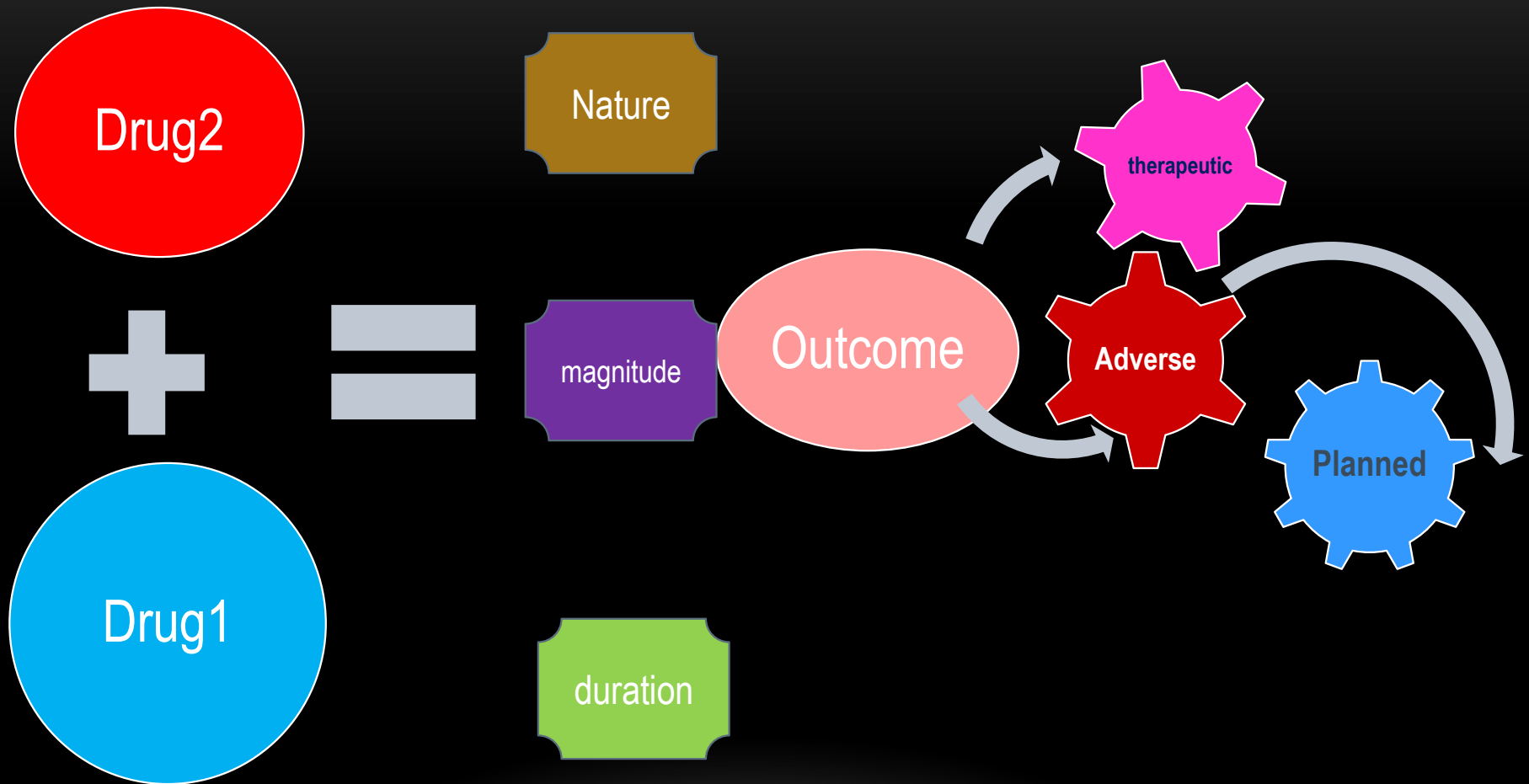
DDI

- 15-fold increase in percentage of patients on three or more psychiatric medications being seen at the Biological Psychiatry Branch of the National Institute of Mental Health from the early 1970s to the mid 1990s
- Patients on psychiatric medications are at risk for DDIs and these DDIs are likely to involve more than just two drugs. Thus, the problem may not just be the effect of drug A on drug B but this effect in the presence of drugs C and D as well.

DEFINITIONS - DRUG-DRUG INTERACTION (DDI)

- the presence of a second drug alters the nature, magnitude, or duration of the effect of a given dose of a first drug.
 - These interactions can be therapeutic or adverse, planned or unintended,
 - But are always determined by the pharmacodynamics and pharmacokinetics of the drugs involved rather than their therapeutic indication.
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DRUG -DRUG INTERACTION DEFINITION



DRUG –DRUG INTERACTION (DDI)

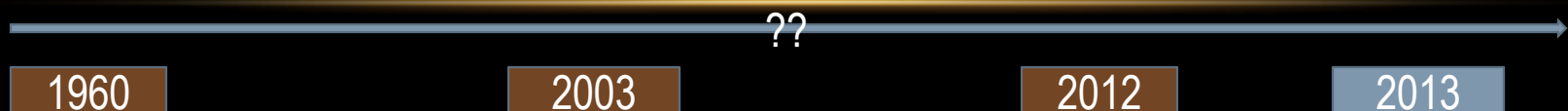
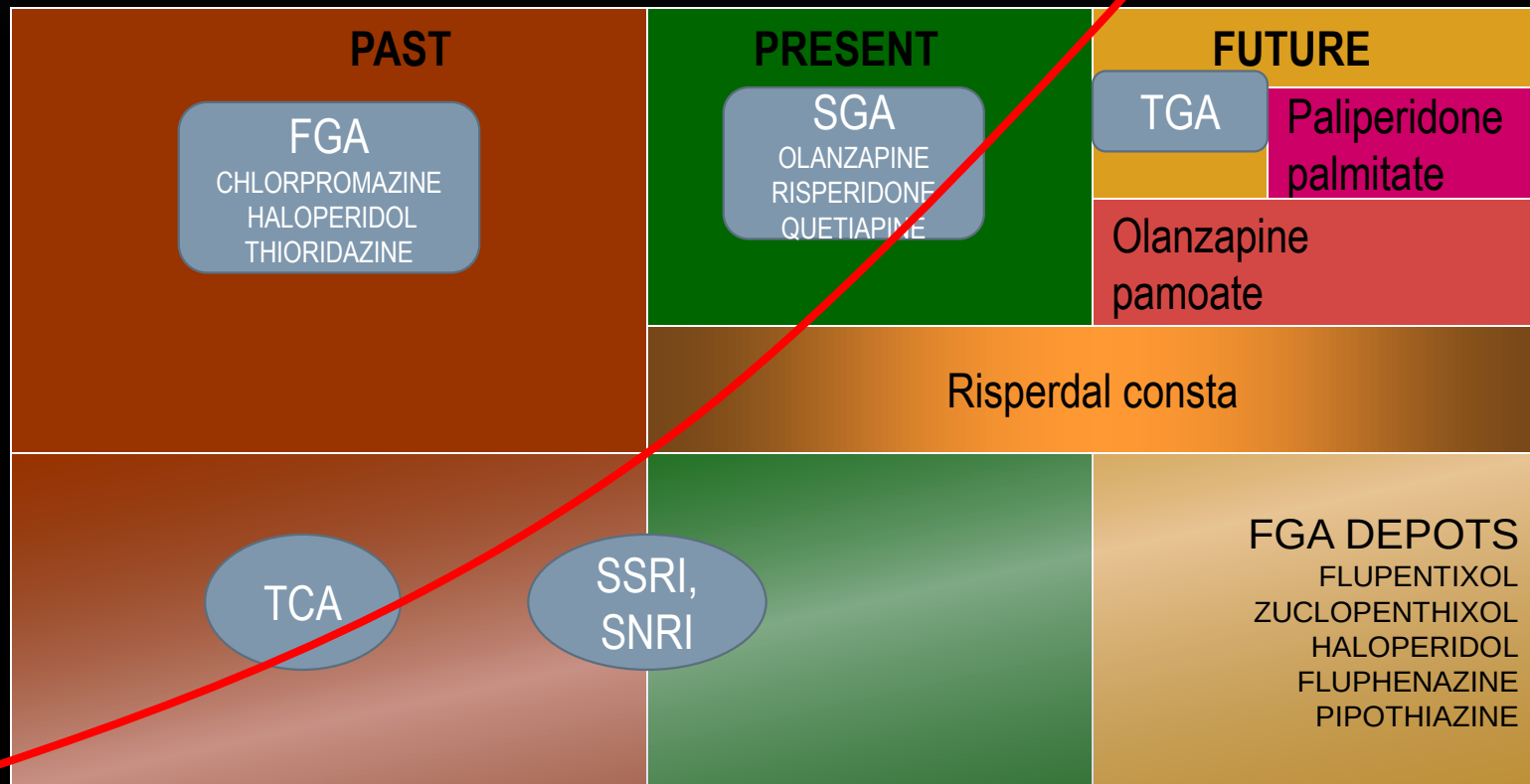
- “Altered nature” . Eg SSRI +MAOI
- “Altered magnitude,” smoking and clozapine.
- “Altered duration” Poor metabolisers, fast metabolisers

POLYPHARMACY:

THE REAL LANDSCAPE OF CLINICAL PRESCRIBING

- Over the last 20 years, a quantum leap in therapeutic options
- Challenges in keeping abreast of new developments.
- The prescriber has more treatment options, each with different pharmacodynamics and pharmacokinetics, to understand and weigh.

PSYCHOTROPIC TIMELINES

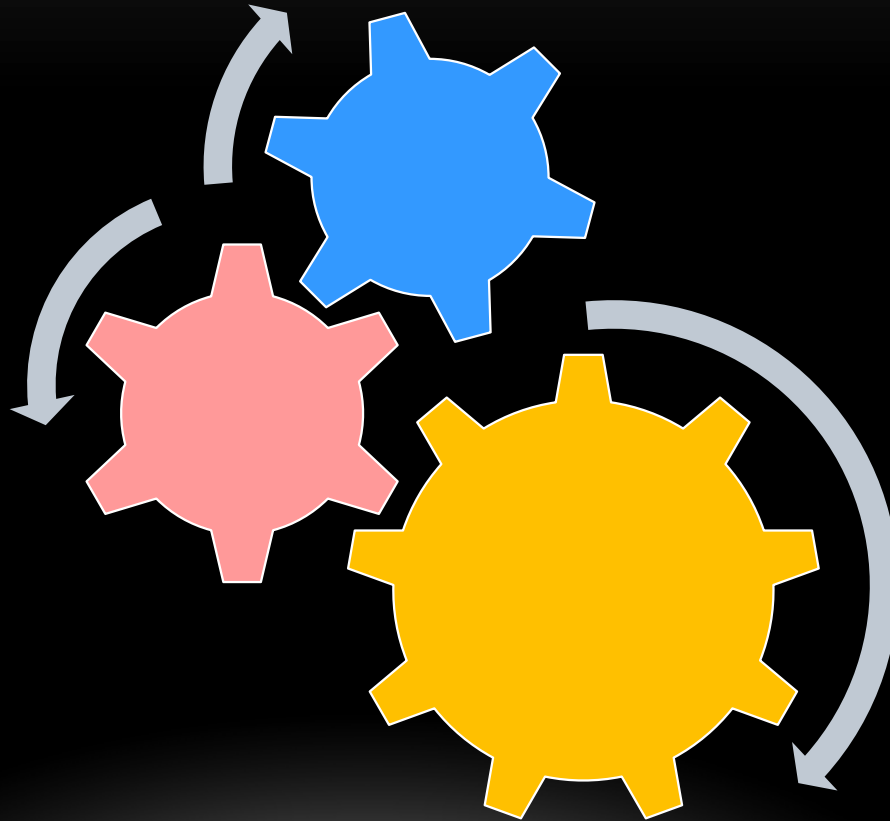


- From 7,000 to as many as 98,000 deaths are caused by adverse drug events each year, more than those caused by smoke inhalation or airplane accidents, causes of death for which the US has generated elaborate, nationwide safety control systems.
- *Phillips DP, Bredder CC. Morbidity and mortality from medical errors: an increasingly serious public health problem. Annu Rev Public Health. 2002;23:135-150*

US HAS GENERATED ELABORATE, NATIONWIDE SAFETY CONTROL SYSTEMS TO PREVENT DEATHS DUE TO AIRPLANE ACCIDENTS, NOTHING APPROACHING SUCH AN EFFORT HAS BEEN DONE TO PREVENT DEATHS DUE TO DDI



STRATEGIES TO MINIMIZE ADVERSE OUTCOMES FROM UNINTENDED DDIS



STRATEGIES

- The risk DDIs is increasing in concert with both the increasing number of pharmaceuticals available and the number of patients on multiple medications.



- To avoid adverse DDIs, the prescriber must keep in mind fundamental principles of pharmacology and good clinical management.

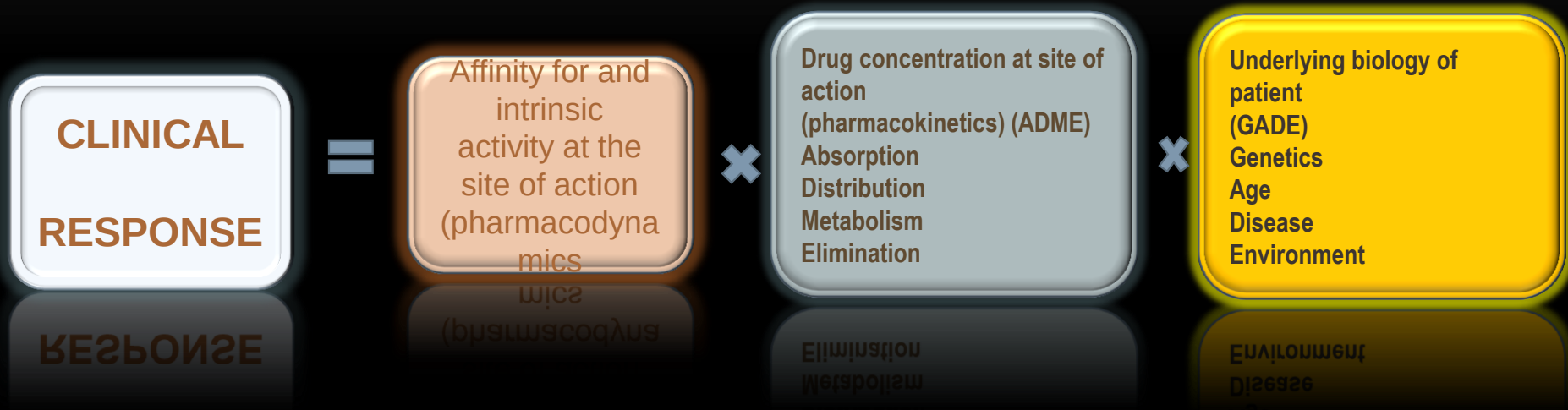
STRATEGIES

- Be an expert on these medications commonly used.
 - **That** includes their generic and brand names, pharmacokinetics, pharmacodynamics, adverse effects, and potential DDIs.
 - This insulates against advertising claims and one's patients from prescribing errors.
 - Develop your own personal formulary.
-

PHARMACOKINETICS

- Be aware of the routinely used doses and the serum half-life of the drugs.
- Be aware of its mechanism(s) of action and binding profile for relevant specific receptors
- Be aware of potential pharmacodynamically mediated DDIs and their likely clinical outcomes for the patient.
- *S.H. Preskorn, D. Flockhart Primary Psychiatry 54 December 2009 2, 7–9).40,41,72-78*

PHARMACODYNAMIC AND PHARMACOKINETIC EQUATIONS



$$\text{Concentration} = \frac{\text{dosing rate}}{\text{clearance}}$$

PHARMACODYNAMIC VARIABLE

- Equation 1 presents the 3 variables that determine the effect a drug will produce in a patient.
- First, the drug must work on a site of action (the first variable in Equation 1) which is capable of producing the effect observed. For all drugs, except anti-infectives, the site of action is a human regulatory protein such as a receptor, enzyme, or uptake pump.
- By binding to its target(s), the drug is capable of altering the functional status of the targets and thus altering human physiology.
- The ability of the drug to alter the functional status of a given regulatory protein is the mechanism underlying its potential action(s) (ie, its pharmacodynamics).

PHARMACOKINETIC ASPECTS

- For the drug to express its potential action(s), a sufficient amount must reach the target to affect it to a physiologically relevant extent.
- That is the domain of the second variable in Equation 1. Drug concentration in relation to the drug's binding- affinity profile determines what sites of action the drug will bind to and to what degree. At low concentrations, the drug will bind to its highest affinity target. As the concentration increases, the drug will bind more substantially to that target until it is saturated. It will also begin binding to lower affinity targets.⁸

PHARMACOKINETIC ASPECTS

- Thus, the second variable in Equation 1 is the drug's pharmacokinetics (or drug movement), which has four phases summarized by the acronym **ADME**:
 - **Absorption** of the drug from the site of administration into the body,
 - **Distribution** of the drug to the various compartments of the body (eg, plasma, termed the “central compartment,” and tissues, or “deeper compartments” such as the brain),
 - **Metabolism** or biotransformation into more polar substances, and finally,
 - **Elimination** from the body.
-

EQUATION 2

- Illustrates that drug concentration is a function of the dosing rate the patient is taking relative to their ability to clear the drug.
- This equation explains why clearance is as important as dose in determining the nature, magnitude, and duration of a drug's effect on the patient.

THE LAST VARIABLE IN EQUATION 1

- is the interindividual differences among patients, which can shift the dose-response curve making patients either more or less sensitive to the effect of the drug.
- These differences (ie, biologic variance among patients) are summarized by the acronym **GADE**:
 - **G**enetics,
 - **A**ge,
 - **D**isease, and
 - **E**nvironment.
- The environment variable refers to the internal environment of the body, which includes other drugs or dietary substances the patient may be taking

THERAPEUTIC DRUG MONITORING

- Thus, the goal of therapeutic drug monitoring (TDM) is not to simply know whether the concentration is therapeutic, but to know whether the patient's ability to clear the drug is usual or not.
- If not, the results of TDM can provide a rational basis for determining what sort of an adjustment in the dosing rate must be made to compensate for the patient's unusual clearance.

CLINICAL RELEVANCE

- In understanding and avoiding untoward effects mediated by the co-prescription of a drug capable of either inducing or inhibiting the enzymes responsible for the clearance of the victim drug.
- Induction can increase the clearance of the victim drug such that its concentrations fall below what is usually therapeutic, resulting in either loss of efficacy or withdrawal symptoms.⁸⁹
- Inhibition can decrease the clearance of the victim drug such that its concentrations rise, causing consequences, which may range from an increase in the frequency and severity of dose-dependent adverse effects, such as EPS in the case of conventional antipsychotics to life-threatening toxicity in the case of tricyclic antidepressants.

HOW TO SIMPLIFY PHARMACOKINETIC INTERACTIONS ^{26,90}

- Drug A Affects  CYP Enzyme X
- CYP Enzyme X Metabolizes  B, C, D, E
- Therefore, Drug A Affects*  B, C, D, E
- * Could be inhibition or induction.
- CYP=cytochrome P450.

PHARMACOKINETICS

Mutations in genes
encoding receptors, ion
channels & other
molecular drug targets

Pharmacodynamic
variability

**LOCUS OF ACTION
“RECEPTORS”**

Bound $\rightleftharpoons$ Free

TISSUE RESERVOIRS

Free $\rightleftharpoons$ Bound

Pharmacokinetic
variability

Mutations in genes
encoding metabolic
enzymes

**SYSTEMIC
CIRCULATION**

ABSORPTION

METABOLISM

FREE DRUG

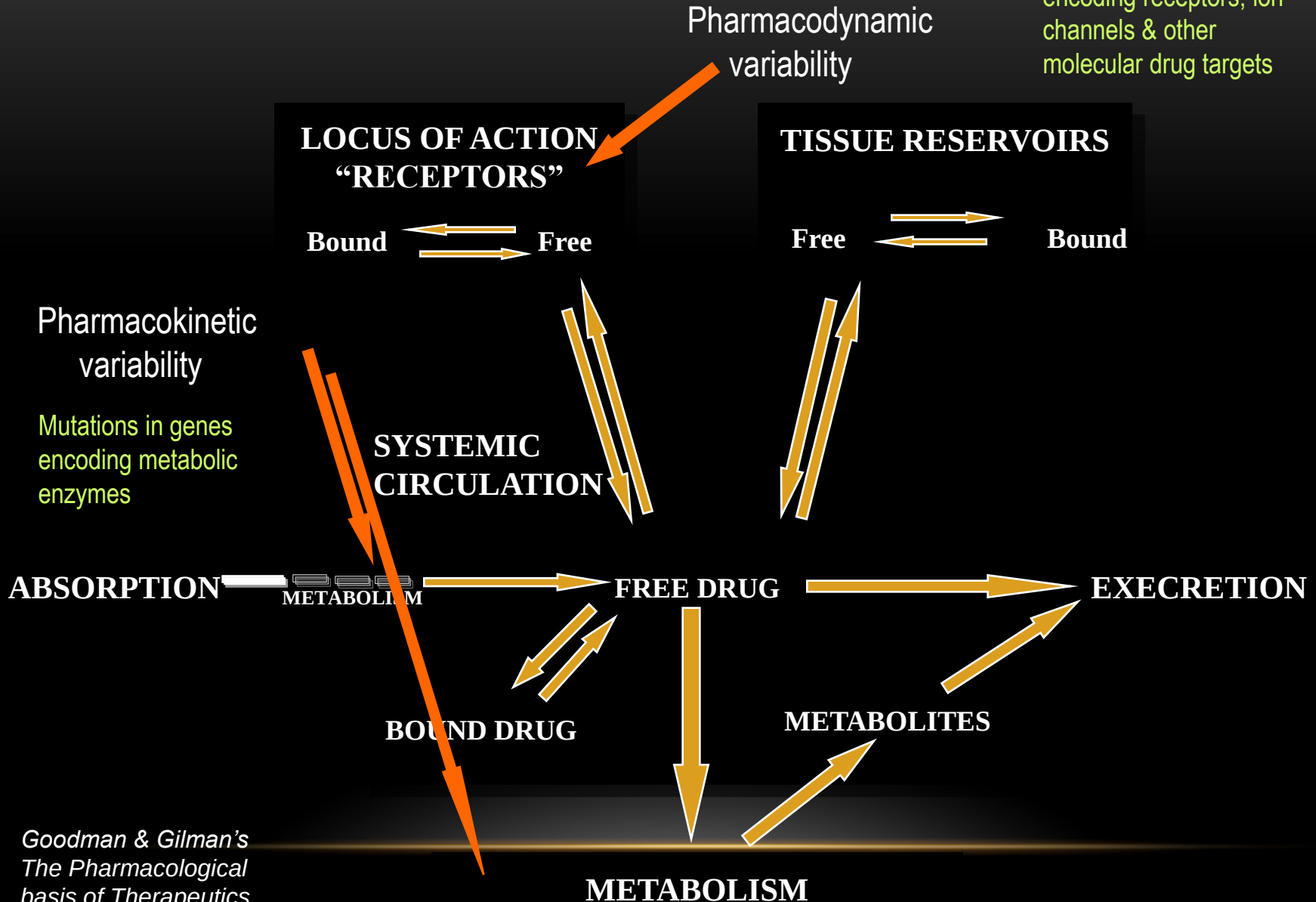
EXCRETION

BOUND DRUG

METABOLITES

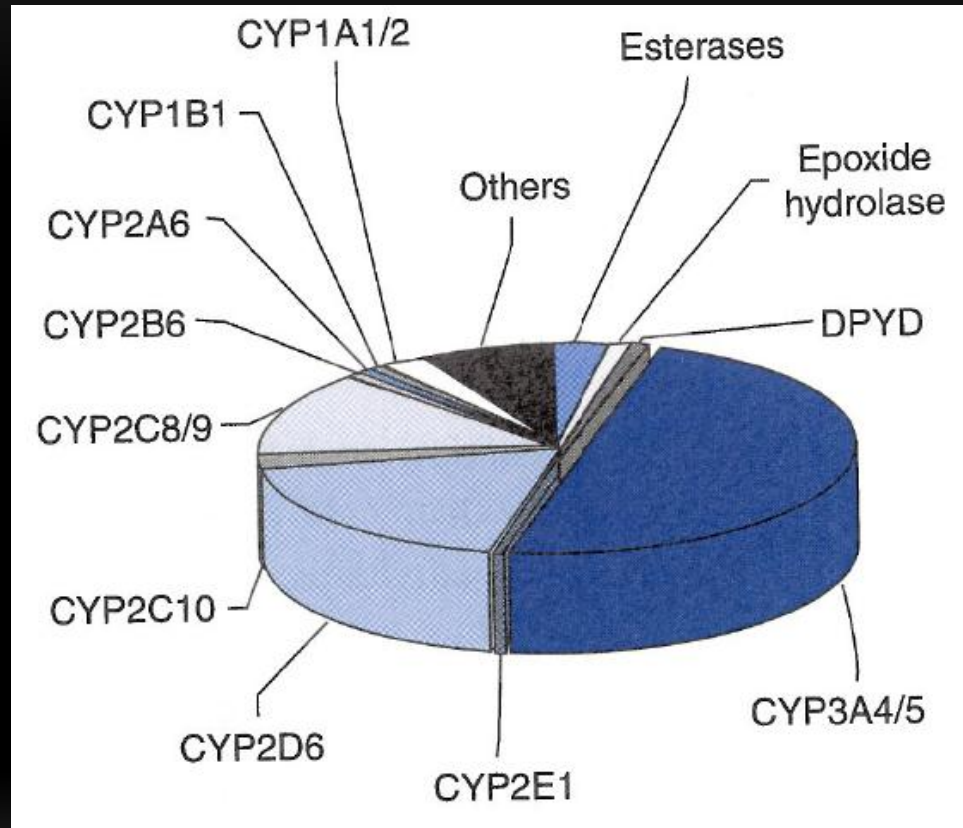
METABOLISM

*Goodman & Gilman's
The Pharmacological
basis of Therapeutics,
11th edn, pg 2.*



PHARMACOKINETICS: METABOLISM

- CYP450 enzyme families may be induced or inhibited by drugs
- Genetic variation accounts for inter-individual enzymatic variability (poor vs extensive metabolisers)
- Liver disease may also significantly affect drug metabolism



Goodman & Gilman's The Pharmacological basis of Therapeutics, 11th edn, p 71-91.

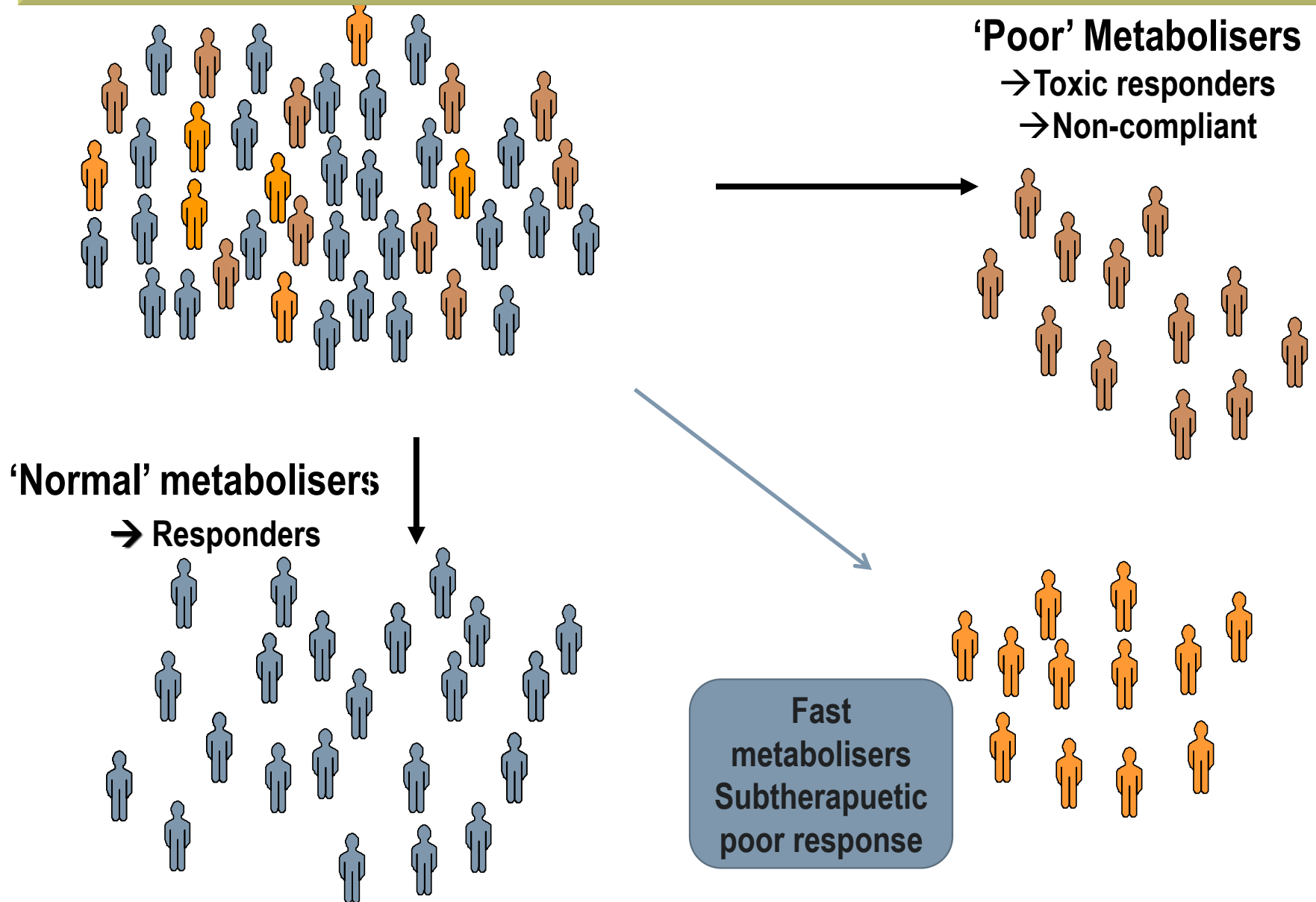
PHARMACOGENOMICS

- The study of how genetic variations in individuals or sub-populations affect response to drugs
 - Variability in drug metabolism due to genetic factors
 - Genetic variations in drug effects
 - Individual genotype may impact clinical response, adverse effects and efficacy
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CYTOCHROME P450S : EFFECT OF GENETIC POLYMORPHISM

- ◆ Different Metabolic Phenotype Groups
 - ◆ Ultra-rapid metabolisers (UM)
 - ◆ Normal or extensive metabolisers (EM)
 - ◆ Intermediate or slow metabolisers (IM)
 - ◆ Poor metabolisers (PM)

Patients' outcome treated with usual dose



CLINICAL EFFECT OF METABOLIC PHENOTYPES

↑ Side effects
↓ Adherence
D-D interactions

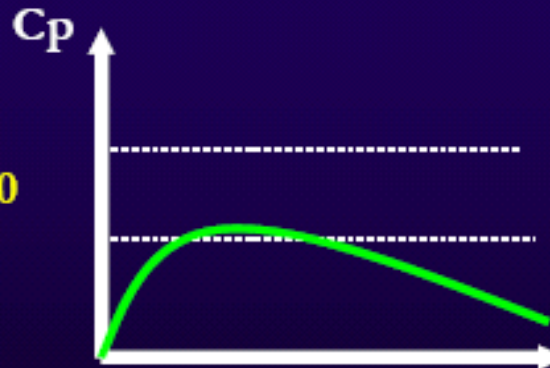
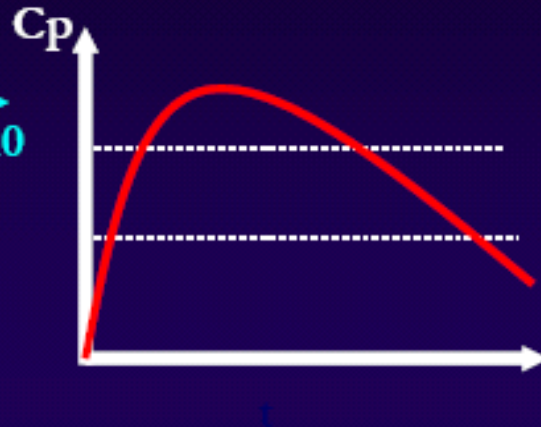
➤ **Poor metabolisers :**

$Cl = 10$

Same dose

➤ **Ultra metabolisers**

$Cl = 100$



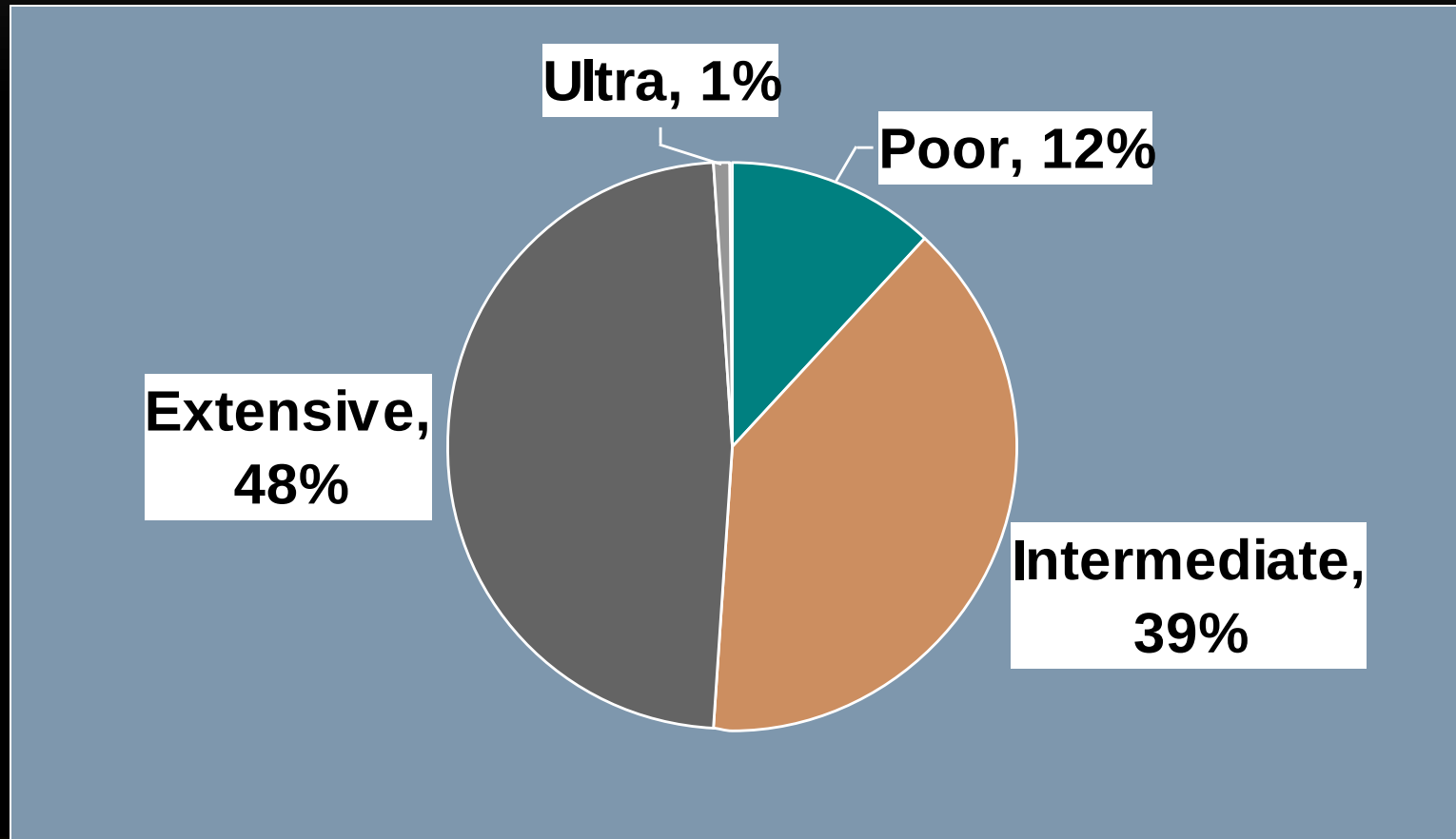
Dose

Kinetics

Systemic exposure

Clinical response

AUSTRALIAN POPULATION (2D6)



THE POTENTIAL FOR DIFFERENT, NEWER ANTIDEPRESSANTS TO BE THE PERPETRATOR OF A DDI MEDIATED BY EFFECTS ON CYP ENZYMES³⁸

<u>Drug</u>	<u>No or Minimal Effect (<20%)*</u>	<u>Mild (20%–50%)*</u>	<u>Moderate (50%–150%)</u>	<u>Substantial (>150%)</u>
Citalopram	1A2, 2C9/10, 2C19, 3A3/4	2D6	–	–
Desvenlafaxine	1A2, 2C9/10, 2C19, 2D6, 3A3/4	–	–	–
Duloxetine	1A2, 2C9/10, 2C19, 3A3/4	–	2D6	–
Escitalopram	1A2, 2C9/10, 2C19, 3A3/4	2D6	–	–
Fluoxetine	1A2	3A3/4	2C19	2D6, 2C9/10
Fluvoxamine	2D6	–	3A3/4	1A2, 2C19
Nefazodone	1A2, 2C9/10, 2C19, 2D6	–	–	3A3/4
Paroxetine	1A2, 2C9/10, 2C19, 3A3/4	–	–	2D6
Sertraline	1A2, 2C9/10, 2C19, 3A3/4	2D6	–	–
Venlafaxine	1A2, 2C9/10, 2C19, 3A3/4	2D6	–	–

Milnacipran, mirtazapine and selegiline, based on in vitro modeling, are unlikely to produce clinically detectable inhibition of these five CYP enzymes.

* Percent increase in plasma levels of a coadministered drug dependent on this CYP enzyme for its clearance.

DDI=drug-drug interaction; CYP=cytochrome P450.

CYP450

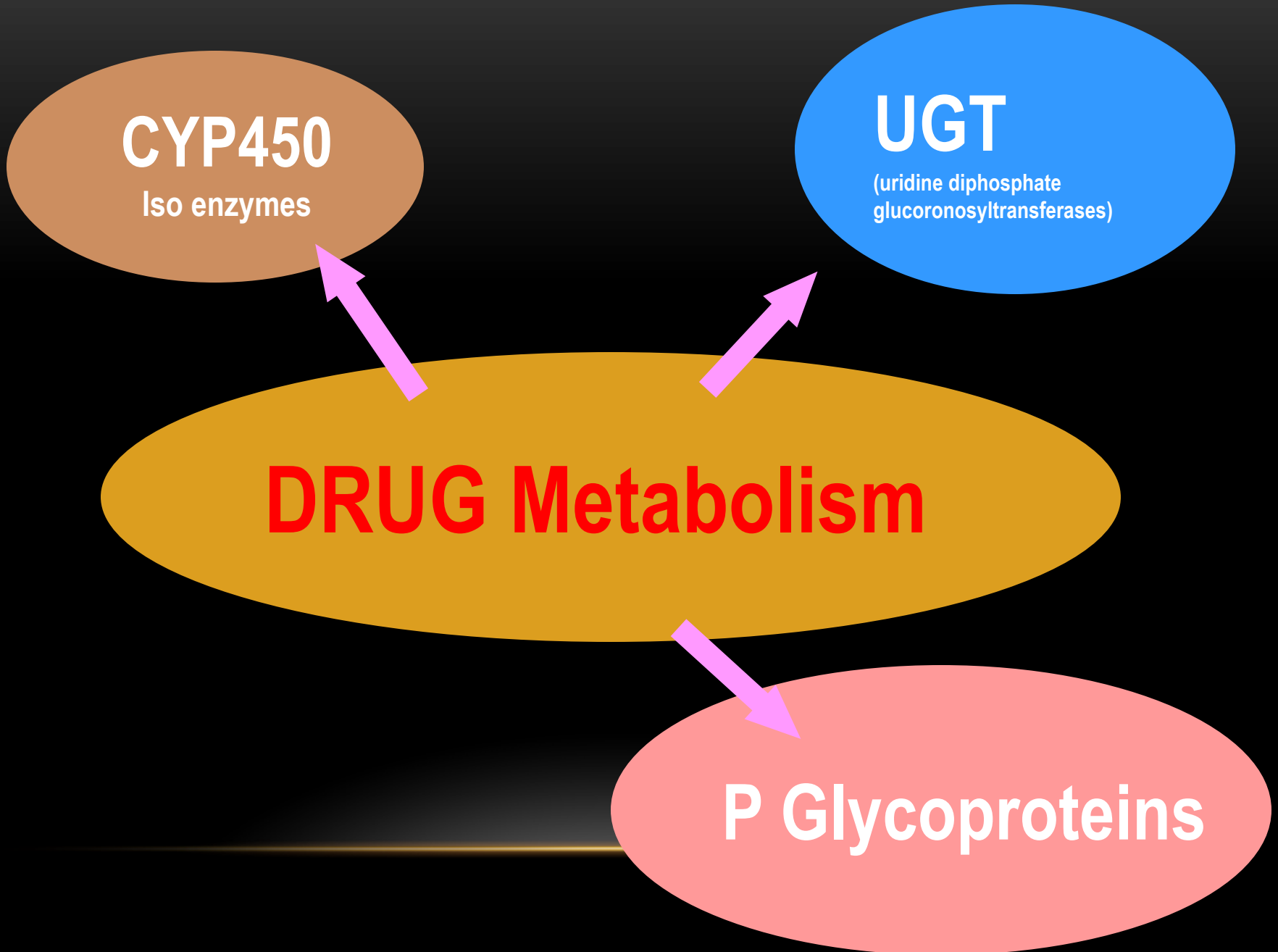
Iso enzymes

UGT

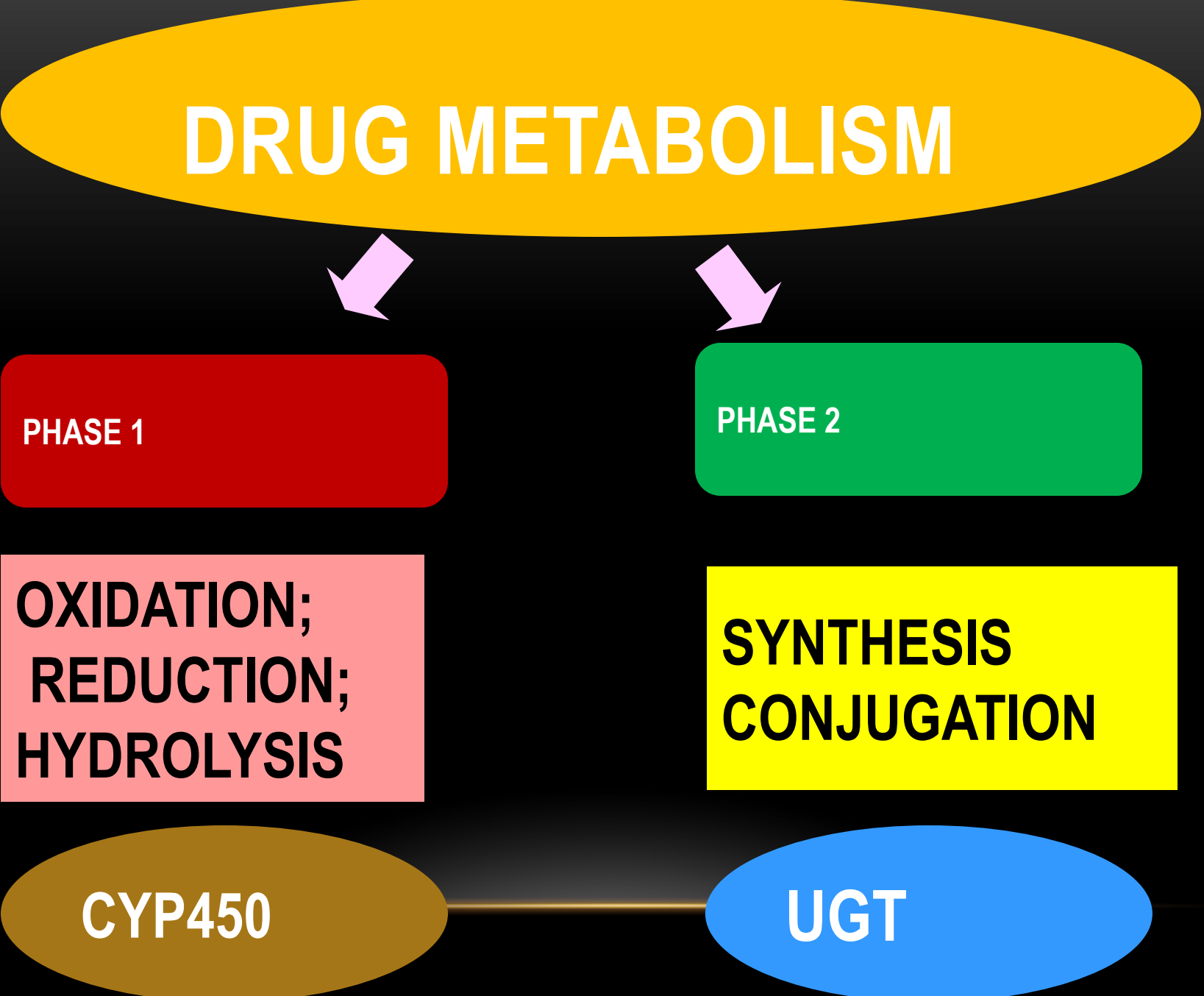
(uridine diphosphate
glucuronosyltransferases)

DRUG Metabolism

P Glycoproteins



DRUG METABOLISM



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graph TD; A([DRUG METABOLISM]) --> B[PHASE 1]; A --> C[PHASE 2]; B --> D[OXIDATION; REDUCTION; HYDROLYSIS]; C --> E[SYNTHESIS CONJUGATION]; D --> F([CYP450]); E --> G([UGT]); F --- G;
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The diagram illustrates the two phases of drug metabolism. At the top, a yellow oval labeled 'DRUG METABOLISM' has two arrows pointing down to 'PHASE 1' (red rounded rectangle) and 'PHASE 2' (green rounded rectangle). Below 'PHASE 1' is a pink rectangle listing 'OXIDATION; REDUCTION; HYDROLYSIS', which points to a brown oval labeled 'CYP450'. Below 'PHASE 2' is a yellow rectangle listing 'SYNTHESIS CONJUGATION', which points to a blue oval labeled 'UGT'. A horizontal line connects the 'CYP450' and 'UGT' ovals at the bottom.

PHASE 1

PHASE 2

**OXIDATION;
REDUCTION;
HYDROLYSIS**

**SYNTHESIS
CONJUGATION**

CYP450

UGT

P-GLYCOPROTEINS

- Efflux pump system - transporting compounds from intracellular space to extracellular matrix
- An ATP Dependant extruding transporter
- Present in tissues, gut lumen lining; lines the capillaries of the BBB, renal tubules
- Regulator of absorption and bioavailability
- Each transporter has its array of substrates, inhibitors and inducers!!

P-GLYCOPROTEINS

- **P-Gp inhibitors** antagonize the extrusion and lead to greater retention and absorption of substrate
- **P-Gp inducers** increase P-Gp levels , leading to greater extrusion and excretion
- Role of P-Gp in mediating psychotropic drug interactions recently being unravelled

- *Carson et al Psychopharmacology. Bull 2002*
- *Aust. ADR Bulletin 2001, Vol20, No.20*

P-GLYCOPROTEINS

- **Inducers**

- Dexamethasone
- Morphine
- Rifampicin
- St Johns Wort

- **Inhibitors**

- Amiodarone
- Amitriptyline
- Chlorpromazine
- Fluphenazine
- Haloperidol
- Paroxetine

CASE STUDY.... WHAT ACTUALLY HAPPENED

- Paroxetine is a **CYP 2D6 inhibitor**
- Paroxetine is also a **potent P-glycoprotein inhibitor**
- Digoxin is a substrate of P- glycoprotein
- **High digoxin conc. resulted from P glycoprotein inhibition in the kidney by paroxetine**
- **difficult to distinguish early sx of digoxin toxicity and SSRI side effects**

DROGBA'S ONCE IN A LIFETIME PENALTY SHOT...



DRUG INFORMATION CAN BE OVERWHELMING....



**OR WE SIMPLY CANT KEEP UP...
WITH THE ADVANCES ...**

Batkhela.com



**THAT'S WHERE PHARMACISTS
COULD GIVE A HELPING HAND.....**



PERSONAL FORMULARY - ESSENTIAL KNOWLEDGE FOR EACH DRUG

- Know the dosage forms available for the drugs prescribed.
- Pharmacokinetic data
 - Enzymes or transporters responsible for elimination
 - Half life and effect of renal or liver impairment
 - Pharmacokinetic variability among ethnic groups
- Pharmacodynamic data
 - Receptor affinity and specificity relative to other drugs
 - Clinical impt. Adverse effects
- Clinical Trial Data
 - Ongoing familiarity with all major clinical trials and studies