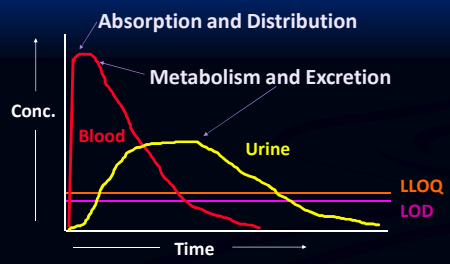
PHARMACOKINETICS

Laura M. Labay, Ph.D., F-ABFT, DABCC-TC

NAME 2019
TOX COMMITTEE

WHAT THE BODY DOES TO THE DRUG



ABSORPTION

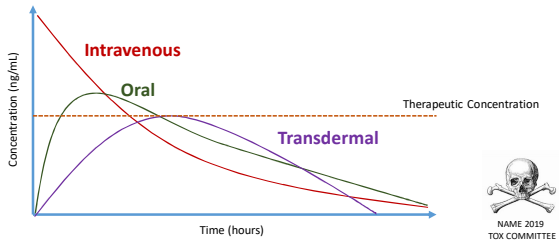
MOVEMENT OF DRUG FROM SITE OF ADMINISTRATION
TO THE BLOODSTREAM

https://www.rdmag.com/news/2017/01/researchers-use-light-launch-drugs-red-blood-cells

NAME 2019
TOX COMMITTEE

BIOAVAILABILITY - AUC

The proportion of a drug that enters the circulation when introduced into the body and so is able to have an active effect.



NAME 2019
TOX COMMITTEE

DETERMINANTS

- Physicochemical properties
- Formulation
- Route of administration

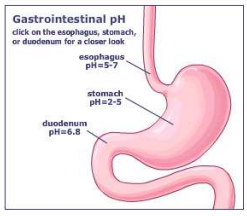
NAME 2019
TOX COMMITTEE

DEGREE OF IONIZATION

Degree of ionization → pK_a

pK_a → the pH at which the ionized and unionized forms exist in equal concentrations

The more the drug is in its unionized form, the more likely it is to be lipid-soluble and transferred by passive diffusion through the membrane.



NAME 2019
TOX COMMITTEE

pK_a RULES

pK_a RULES
pK_a is defined as the pH were a drug exists as 50% ionized and 50% unionized
If pK_a - pH = 0, then 50% of drug is ionized and 50% is unionized
Acidic groups become less ionized in an acidic environment Basic groups become less ionized in an alkaline environment

NAME 2019
TOX COMMITTEE

QUANTIFYING THE DEGREE OF IONIZATION

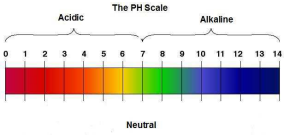
For every unit by which pH is changed, the ratio of unionized to ionized molecules changes 10-fold

EXAMPLE:

- When the pH is 2 units less than the pK_a, molecules of an acidic drug become 100x more un-ionized

pH = 3

pK_a = 5



NAME 2019
TOX COMMITTEE

PRACTICE QUESTIONS

1) The pK_a of sodium pentothal is 7.4 and the drug is acidic. If a patient is given sodium pentothal orally instead of by IV, will it put the patient to sleep? _____
2) Absorption from the GI tract is determined by:
   a) The pH of the medium and the pK_a of the drug
   b) The fraction of the drug that is non-ionized
   c) Lipid solubility of the non-ionized drug
   d) All of the above
   e) None of the above
3) Given a weak acid (pk_a 8.0), the ratio of ionized to non-ionized form of the drug at pH 4.0 most closely approximates:
   a) 2:1
   b) 1:1
   c) 1:1000
   d) 10,000:1
   e) None of the above
4) Compared to a weak acid (pK_a 8.0), another weak acid (pK_a 5.3), other factors being equal, would be:
   a) Absorbed from the GI tract at approximately the same rate
   b) Absorbed from the GI tract more slowly
   c) Absorbed from the GI tract more rapidly
   d) Unabsorbed from the GC tract
   e) More completely inactivated by gastric juice

NAME 2019
TOX COMMITTEE

PRACTICE QUESTIONS - ANSWERS

1) The pK_a of sodium pentothal is 7.4 and the drug is acidic. If a patient is given sodium pentothal orally instead of by IV, will it put the patient to sleep? YES
2) Absorption from the GI tract is determined by:
   a) The pH of the medium and the pK_a of the drug
   b) The fraction of the drug that is non-ionized
   c) Lipid solubility of the non-ionized drug
   d) All of the above
   e) None of the above
3) Given a weak acid (pk_a 8.0), the ratio of ionized to non-ionized form of the drug at pH 4.0 most closely approximates:
   a) 2:1
   b) 1:1
   c) 1:1000
   d) 10,000:1
   e) None of the above
4) Compared to a weak acid (pK_a 8.0), another weak acid (pK_a 5.3), with all other factors being equal, would be:
   a) Absorbed from the GI tract at approximately the same rate
   b) Absorbed from the GI tract more slowly
   c) Absorbed from the GI tract more rapidly
   d) Unabsorbed from the GC tract
   e) More completely inactivated by gastric juice

NAME 2019
TOX COMMITTEE

DISTRIBUTION

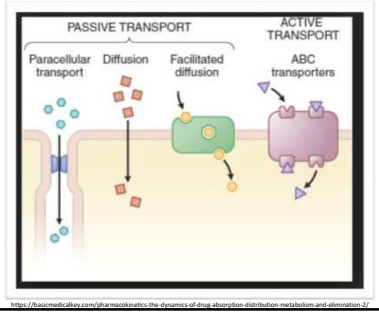
MOVEMENT OF A DRUG FROM ITS POINT OF ENTRY THROUGHOUT THE SYSTEMIC CIRCULATION AND INTO VARIOUS TISSUES

GOAL: FOR THE DRUG TO REACH ITS INTENDED SITE OF ACTION

NAME 2019
TOX COMMITTEE

TRANSMEMBRANE MOVEMENT

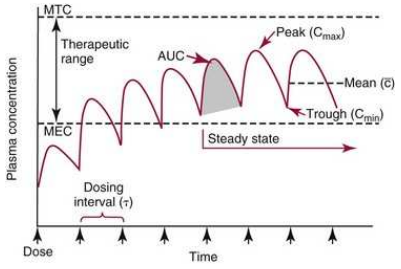
- Molecular Size
- Drug Polarity
- Lipid Solubility
- Membrane Structure



https://basicmedicalkey.com/pharmacokinetics-the-dynamics-of-drug-absorption-distribution-metabolism-and-elimination-2/

NAME 2019
TOX COMMITTEE

STEADY STATE CONCENTRATIONS



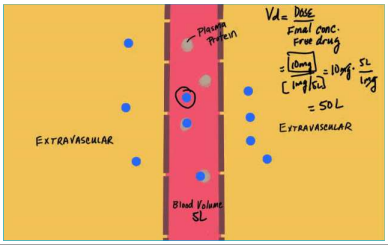
https://basicmedicalkey.com/therapeutic-drugs-and-their-management/

NAME 2019
TOX COMMITTEE

VOLUME OF DISTRIBUTION

A *HYPOTHETICAL* VOLUME INTO WHICH A DRUG IS DISTRIBUTED

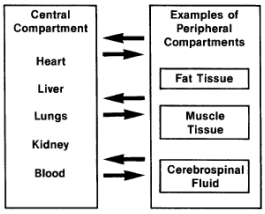
IT IS A MEASURE OF HOW READILY DRUG DIFFUSES OUT OF THE PLASMA INTO TISSUES



NAME 2019
TOX COMMITTEE

VOLUME OF DISTRIBUTION MEANING

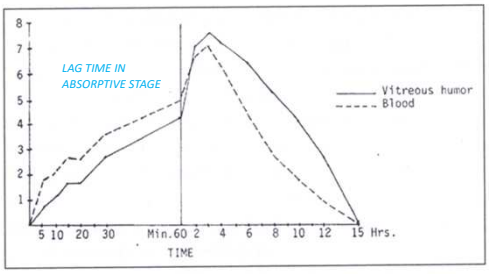
1. Reflects the extent of drug distribution
2. In general,
   - Low V_d → Drug confined to plasma
   - High V_d → Drug equilibrates with tissues & extravascular fluids



https://www.ashp.org/-/media/store%20files/pi2418-sample-chapter-1.pdf

NAME 2019
TOX COMMITTEE

DISTRIBUTION – VITREOUS FLUID



Hentsch R, Mueller Hp. [Animal Experimental Studies On The Concentration Of Ethanol In The Blood And Vitreous Body After Peroral Administration]. Albrecht Von Graefes Arch Ophthalmol. 1965 May 13;168:330-4. German.

NAME 2019
TOX COMMITTEE

CASE EXAMPLE

BRIEF CASE HISTORY (Attach Investigator Report If Possible)

2 year 4 month old female toddler found dead on floor of residence. Foul play suspected.

Positive Findings:

Compound	Result	Units	Matrix Source
Ethanol	133	mg/dL	001 - Heart Blood
Blood Alcohol Concentration (BAC)	0.133	g/100 mL	001 - Heart Blood
Ethanol	97	mg/dL	006 - Gastric Fluid
Isopropanol	5.1	mg/dL	006 - Gastric Fluid
Acetaldehyde	1.3	mg/dL	006 - Gastric Fluid
Acetone	1.7	mg/dL	006 - Gastric Fluid
Ethanol	216	mg/dL	004 - Vitreous Fluid
Acetone	5.4	mg/dL	004 - Vitreous Fluid
Sodium (Vitreous Fluid)	128	mmol/L	004 - Vitreous Fluid
Potassium (Vitreous Fluid)	>20	mmol/L	004 - Vitreous Fluid
Chloride (Vitreous Fluid)	115	mmol/L	004 - Vitreous Fluid
Urea Nitrogen (Vitreous Fluid)	59	mg/dL	004 - Vitreous Fluid
Creatinine (Vitreous Fluid)	1.3	mg/dL	004 - Vitreous Fluid
Ethanol	217	mg/dL	003 - Urine
Acetone	5.4	mg/dL	003 - Urine
Quinine	380	ng/mL	003 - Urine

AME 2019
TOX COMMITTEE

CALCULATION

$$Dose = Cp \times Vd \times Wt$$

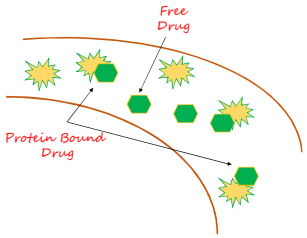
Cp → Plasma Drug Concentration (mg/L)
Vd → Volume of Distribution (L/Kg)
Wt → Weight (Kg)

NAME 2019
TOX COMMITTEE

PROTEIN BINDING

Protein bound drug is:

- Not metabolized or excreted
- Inactive
- Confined to a specific tissue or site
- High plasma protein binding decreases V_d



NAME 2019
TOX COMMITTEE

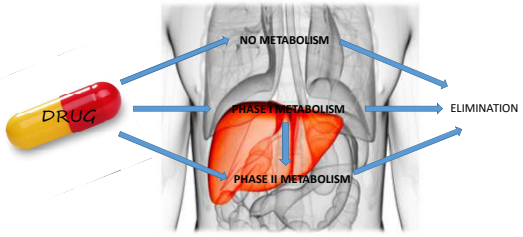
PROTEIN BINDING AND DISEASE

DRUG	UNBOUND %	UNBOUND % - DISEASE
Diazepam	2%	6% in liver disease
Furosemide	2%	6% in nephrotic syndrome
Phenytoin	9%	19% in renal disease
Triamterene	19%	40% in renal disease
Theophylline	35%	71% in liver disease
Digoxin	75%	82% in renal disease

NAME 2019
TOX COMMITTEE

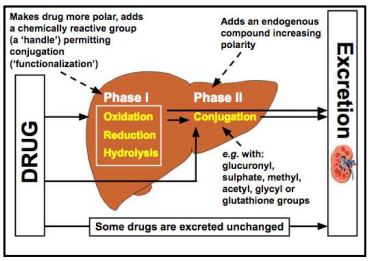
METABOLISM

BIOTRANSFORMATION OF PHARMACEUTICAL SUBSTANCES IN THE BODY



NAME 2019
TOX COMMITTEE

PHASE I AND II - OVERVIEW



https://www.studyblue.com/notes/note/n/pharmacology-elementary-drug-metabolism-and-renal-excretion-of-drug/deck/15711438

NAME 2019
TOX COMMITTEE

PHASE I METABOLISM

Chemical reactions – oxidation, reduction, hydrolysis

Oxidation reactions are catalyzed by cytochrome p450 enzymes

Isoenzyme	Comments
CYP1A	Important for methylxanthines and paracetamol; induced by smoking
CYP2A	Limited number of substrates; significant interindividual variability
CYP2B	Limited number of substrates
CYP2C	CYP2C9 is an important isoform; CYP2C19 shows genetic polymorphism
CYP2D	Metabolises numerous drugs; CYP2D6 shows genetic polymorphism
CYP2E	Metabolises alcohol
CYP3A	Main isoform in liver and intestine; metabolises 50–60% of current drugs
CYP4	Metabolises fatty acids

Extreme caution should be taken if co-administration with a CYP3A4 inhibitor or inducer is unavoidable

NAME 2019
TOX COMMITTEE

CYTOCHROME p450 INTERACTIONS

1) COMPETITION
If the drugs are substrates for the same CYP isoform, the metabolism of each may be _____.

2) INHIBITION
In general, inhibition _____ plasma concentrations of substrate drugs, but _____ concentrations may be decreased.

3) INDUCTION
In general, induction _____ plasma concentrations of substrate drugs.

NAME 2019
TOX COMMITTEE

CYTOCHROME p450 INTERACTIONS

COMPETITION
If the drugs are substrates for the same CYP isoform, the metabolism of each may be inhibited.

INHIBITION
In general, inhibition increases plasma concentrations of substrate drugs, but prodrug concentrations may be decreased.

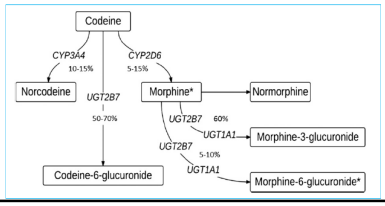
INDUCTION
In general, induction decreases plasma concentrations of substrate drugs.

NAME 2019
TOX COMMITTEE

PHASE II METABOLISM

"CONJUGATION REACTIONS"

1. Substrates are coupled covalently to an endogenous molecule
2. Transferases catalyze the reaction
3. The resulting molecule is polar and able to be excreted in urine



https://pediatrics.aappublications.org/content/pediatrics/138/1/e20153479.full.pdf

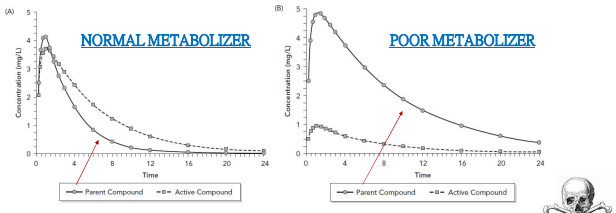
NAME 2019
TOX COMMITTEE

METABOLIZER FORMS

- Rapid metabolizer
- Normal metabolizer
- Intermediate metabolizer
- Poor metabolizer

NAME 2019
TOX COMMITTEE

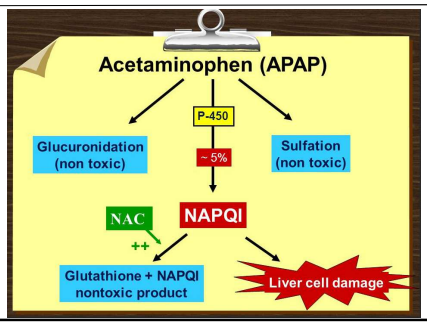
CONCENTRATION AND TIME PROFILE EXAMPLES



NAME 2019
TOX COMMITTEE

http://samples.jbpub.com/9781449652739/Chapter2.pdf

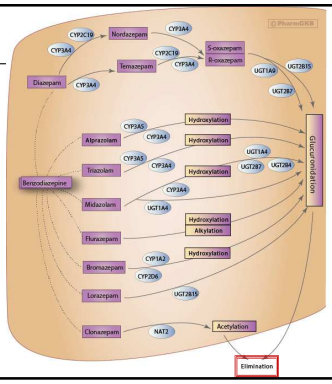
METABOLIC SYSTEMS AT CAPACITY



NAME 2019
TOX COMMITTEE

ELIMINATION

PROCESSES BY WHICH A DRUG IS REMOVED IN AN UNALTERED FORM AND/OR MODIFIED AS A METABOLITE

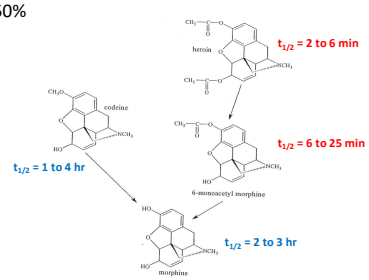


NAME 2019
TOX COMMITTEE

https://www.pharmgkb.org/pathway/PA165111375

HALF-LIFE ($t_{1/2}$)

THE TIME IT TAKES FOR THE CONCENTRATION OF A DRUG IN PLASMA TO DECREASE BY 50%



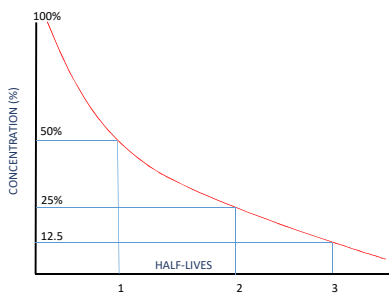
NAME 2019
TOX COMMITTEE

FIRST ORDER ELIMINATION

Most drugs undergo first order elimination

NAME 2019
TOX COMMITTEE

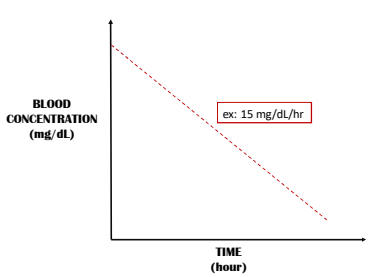
FIRST ORDER ELIMINATION



NAME 2019
TOX COMMITTEE

ZERO ORDER KINETICS

DEFINITION: A constant amount of drug is eliminated per unit time



Example:

100 mg/dL

85 mg/dL

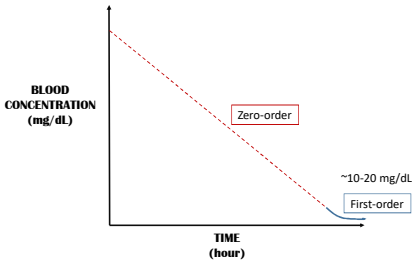
70 mg/dL

55 mg/dL

Etc.

NAME 2019 TOX COMMITTEE

ZERO ORDER TO FIRST ORDER – ETOH EXAMPLE



NAME 2019 TOX COMMITTEE

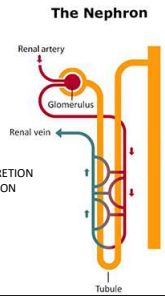
FACILITATION OF ELIMINATION BASED ON pH

MATRIX	pH
URINE	4.8 to 8.0
BLOOD	7.4

URINE pH AFFECTS DRUG EXCRETION

EXAMPLES:

METHAMPHETAMINE → ACIDIC URINE → INCREASES EXCRETION
BARBITURATE → ACIDIC URINE → INCREASES REABSORPTION



https://www.niddk.nih.gov/health-information/kidney-disease/kidneys-how-they-work

NAME 2019 TOX COMMITTEE

ELIMINATION - QUESTION

A patient has presented to the Emergency Department with a Barbiturate overdose. Would you recommend that the urine should be made acidic or alkaline to facilitate excretion?

NAME 2019
TOX COMMITTEE

ELIMINATION - QUESTION

A patient has presented to the Emergency Department with a Barbiturate overdose. Would you recommend that the urine should be made acidic or alkaline to facilitate excretion?

I would want to make the urine alkaline.

Why? This would cause the Barbiturate, a weakly acidic drug, to be ionized and not amenable to reabsorption.

NAME 2019
TOX COMMITTEE

POSTMORTEM PHARMACOKINETICS

NAME 2019
TOX COMMITTEE

From OXYCONTIN® Package Insert for Oxycodone HCl Controlled-Release Tablets

Regimen	Dosage Form	AUC (ng•hr/mL)†	C_{max} (ng/mL)	T_{max} (hrs)	Trough Conc. (ng/mL)
Single Dose	10 mg OxyContin	100.7 [26.6]	10.6 [20.1]	2.7 [44.1]	n.a.
	20 mg OxyContin	207.5 [35.9]	21.4 [36.6]	3.2 [57.9]	n.a.
	40 mg OxyContin	423.1 [33.3]	39.3 [34.0]	3.1 [77.4]	n.a.
	80 mg OxyContin*	1085.5 [32.3]	98.5 [32.1]	2.1 [52.3]	n.a.
Multiple Dose	10 mg OxyContin Tablets q12h	103.6 [38.6]	15.1 [31.0]	3.2 [69.5]	7.2 [48.1]
	5 mg immediate-release q6h	99.0 [36.2]	15.5 [28.8]	1.6 [49.7]	7.4 [50.9]

NAME 2019
TOX COMMITTEE

ASSUMPTIONS

- The drug was ingested and all of it was absorbed at the time of specimen collection.
- The drug was ingested only one time (e.g., a single dose).
- The drug concentration represents the peak (Cmax) blood-drug concentration.
- The drug concentration accurately reflects the circulating blood-drug concentration in the antemortem state in that it has been unaffected by such influences such as postmortem redistribution.
- The presence of metabolites and/or the drug's presence in other matrix types are not represented.
- The volume of distribution (Vd) and the blood to plasma drug ratio (b/p) of the drug is known.

NAME 2019
TOX COMMITTEE

TRUE or FALSE

1. The conjugation of morphine with glucuronide acid decreases the narcotic activity of the drug hastens excretion.
2. The metabolism of diazepam to nordiazepam is an example of an oxidative (Phase I) reaction.
3. The ionized form of a drug is the form which readily crosses the membrane.
4. If a weakly basic drug is given by IV, it will not be found in the stomach.
5. A weak acid would demonstrate an increased renal clearance if the urine was alkanized.
6. A weakly acidic drug is equally absorbed from the stomach and small intestine.
7. Normally, the blood has a pH of 7.4

NAME 2019
TOX COMMITTEE

TRUE or FALSE

1. The conjugation of morphine with glucuronide acid decreases the narcotic activity of the drug hastens excretion. TRUE
2. The metabolism of diazepam to nordiazepam is an example of an oxidative (Phase I) reaction. TRUE
3. The ionized form of a drug is the form which readily crosses the membrane. FALSE
4. If a weakly basic drug is given by IV, it will not be found in the stomach. TRUE
5. A weak acid would demonstrate an increased renal clearance if the urine was alkanized. TRUE
6. A weakly acidic drug is equally absorbed from the stomach and small intestine. FALSE
7. Normally, the blood has a pH of 7.4 TRUE

NAME 2019
TOX COMMITTEE

Pharmacokinetics is concerned with the rate at which drugs enter the body, distribute within it, and then leave. Includes metabolism.

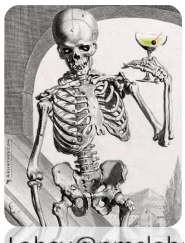
Metabolic reactions tend to make a drug progressively more water soluble so it can be eliminated in the urine.

The V_d of a drug is the volume in which it would need to distribute so that the concentration in the body is equal to that of the blood.

Most drugs are eliminated following first-order processes.

NAME 2019
TOX COMMITTEE

QUESTIONS?



Laura.Labay@nmslabs.com

NAME 2019
TOX COMMITTEE

Genetic Polymorphisms

Jirair Gevorkyan, Ph.D., F-ABFT

NAME 2019
TOX COMMITTEE

Objectives

1. Understand the basis and application of genetic information in relation to drug response and toxicity.
2. To distinguish genetics and enzymes behind strong and weak metabolic responders.
3. Understand how genetic polymorphisms can be applied to postmortem toxicology and death investigations.

NAME 2019
TOX COMMITTEE

Outline

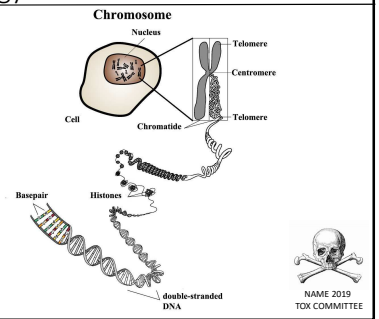
- Introductory Concepts
  - Central Dogma
  - Mutations
  - Structure and Function
- Polymorphisms
  - Consequences in Pharmacology
  - Cytochrome P450s
- Application to Toxicology
  - Relevant Polymorphisms and Drugs
  - Case Examples

NAME 2019
TOX COMMITTEE

Central Dogma of Biology

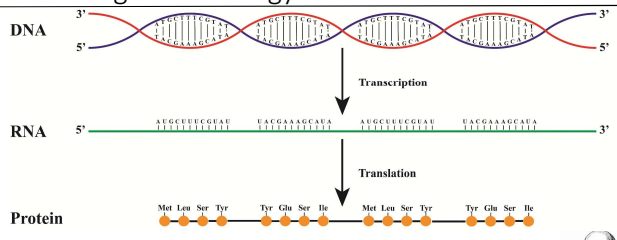
Hereditary information
- Humans Chromosome: 46
- Dogs: 78
- Cats: 38
- Fruit Flies: 8

Consistent Differences
- Between species
- Between subpopulations
- Between individuals



NAME 2019 TOX COMMITTEE

Central Dogma of Biology

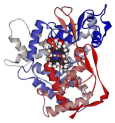


But also…
Effects of ribozymes, proteins, metabolites produce bidirectionality
Post transcriptional/translational modifications, somatic epitypes, epigenetics

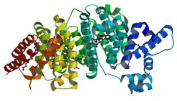
NAME 2019 TOX COMMITTEE

Central Dogma of Biology

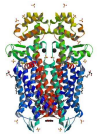
- Structure -> Function
- Genotype -> Phenotype



CYP2C9



Human Serum Albumin



μ-opioid receptor

https://www.raminrahni.com/animation

NAME 2019 TOX COMMITTEE

Mutations

Single Nucleotide Polymorphisms

3'-ACGCCTTGACGACGCTTAC-5'
5'-TGCGGAACTGCTGCGAATG-3'

3'-ACGCCTTGACGAAGCTTAC-5'
5'-TGCGGAACTGCTTCGAATG-3'

Insertion/Deletion

3'-ACGCCTTGACGACGCTTAC-5'
5'-TGCGGAACTGCTGCGAATG-3'

3'-ACGCCTTGACGAACGCTTAC-5'
5'-TGCGGAACTGCTTGCGAATG-3'

3'-ACGCCTTGACGAGCTTAC-5'
5'-TGCGGAACTGCTCGAATG-3'

Short Tandem Repeat

3'-ACGCCTTGACGACAGCAGCAGCTTAC-5'
5'-TGCGGAACTGCTGACGACGACGAATG-3'

3'-ACGCCTTGACGACAGCAGCAGCAGCAGCTTAC-5'
5'-TGCGGAACTGCTGACGACGACGACGACGAATG-3'

Seond letter

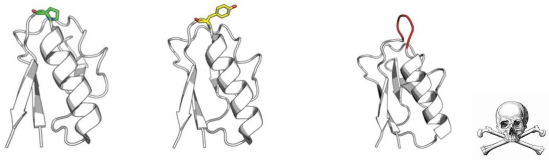
First letter	U	C	A	G	Third letter
U	UUU Phe, UUC Phe, UUA Leu, UUG Leu	UCU Ser, UCC Ser, UCA Ser, UCG Ser	UAU Tyr, UAC Tyr, UAA Stop, UAG Stop	UGU Cys, UGC Cys, UGA Stop, UGG Trp	U C A G
C	CUU Leu, CUC Leu, CUA Leu, CUG Leu	CCU Pro, CCC Pro, CCA Pro, CCG Pro	CAU His, CAC His, CAA Gln, CAG Gln	CGU Arg, CGC Arg, CGA Arg, CGG Arg	U C A G
A	AUU Ile, AUC Ile, AUA Ile, AUG Met	ACU Thr, ACC Thr, ACA Thr, ACG Thr	AAU Asn, AAC Asn, AAA Lys, AAG Lys	AGU Ser, AGC Ser, AGA Arg, AGG Arg	U C A G
G	GUU Val, GUC Val, GUA Val, GUG Val	GCU Ala, GCC Ala, GCA Ala, GCG Ala	GAU Asp, GAC Asp, GAA Glu, GAG Glu	GGU Gly, GGC Gly, GGA Gly, GGG Gly	U C A G

NAME 2019
TOX COMMITTEE

Mutations, Structure and Function

DNA TCATATGCA**CCC**CGT
Peptide S Y A **P** R

Mutation	Silent Substitution	Dissimilar Substitution	Insertion
DNA	TCATATGCACCACGT	TCATATGCATATCGT	TCATATGCAGGAGGCCCCCGT
Peptide	S Y A P R	S Y A Y R	S Y A G G P R



DOI: 10.1042/BJ20121221

NAME 2019
TOX COMMITTEE

Genetic Polymorphisms

Inter-individual genetic variability

Person 1 Chromosome 5

Copy 1 3'-TGACGATGCTTAC-5'
5'-ACTGCTACGAATG-3'

Copy 2 3'-TGACGAAGCTTAC-5'
5'-ACTGCTTCGAATG-3'

Person 2 Chromosome 5

Copy 1 3'-TGACGATGCTTAC-5'
5'-ACTGCTACGAATG-3'

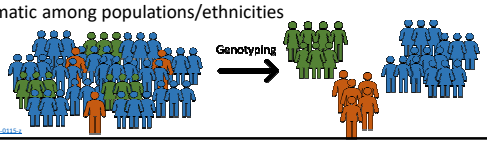
Copy 2 3'-TGACGACGCTTAC-5'
5'-ACTGCTGCGAATG-3'

Person 3 Chromosome 5

Copy 1 3'-TGACGACGCTTAC-5'
5'-ACTGCTGCGAATG-3'

Copy 2 3'-TGACGACGCTTAC-5'
5'-ACTGCTGCGAATG-3'

Systematic among populations/ethnicities



DOI: 10.1186/s12920-015-0115-z

NAME 2019
TOX COMMITTEE

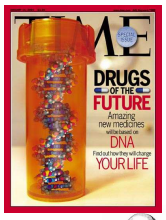
Genetic Polymorphisms

Pharmacogenetics
- Individual gene-drug interactions, usually one or two genes that have dominant effect on a drug response

Pharmacogenomics
- Genomic influence on drug response, often using high-throughput data, sequencing, SNP chip, expression, proteomics

Pharmacodynamic
- Receptors, ion channels, immune molecules

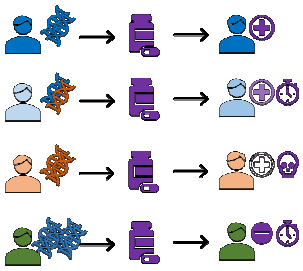
Pharmacokinetic
- Transporters, metabolic enzymes, plasma protein binding



NAME 2019
TOX COMMITTEE

Metabolizer Forms

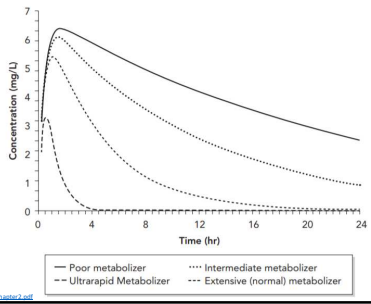
- Normal metabolizer
- Intermediate metabolizer
- Poor metabolizer
- Ultrarapid metabolizer



Parent drug and metabolite activity are important

NAME 2019
TOX COMMITTEE

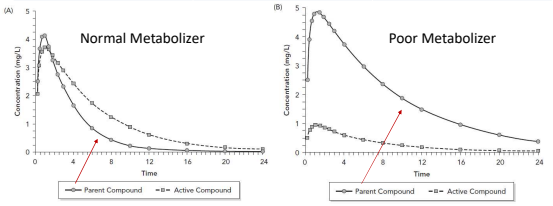
Metabolizer Forms



NAME 2019
TOX COMMITTEE

Metabolizer Forms

Analyte	Poor Metabolizer	Ultrarapid Metabolizer
Prodrug, Active Metabolite	poor efficacy, accumulation of prodrug	good efficacy, rapid effect
Active Drug, Inactive Metabolite	good efficacy, but accumulation may have adverse effects	poor efficacy, need a greater dose or slow release formula



http://samples.jbpub.com/9781449627739/27739ch02.pdf

NAME 2019
TOX COMMITTEE

Practice Question

1) A mutation is defined as any change in a DNA sequence away from normal. A polymorphism is a DNA sequence variation that is common in the population. TRUE or FALSE
2) A poor metabolizer may have one of the following genetic predispositions:
   a) Two functioning alleles related to drug metabolism
   b) One functioning and one non-functioning alleles related to drug metabolism
   c) Two non-functioning alleles related to drug metabolism
   d) More than two functioning alleles related to drug metabolism
3) An ultra rapid metabolizer may have one of the following genetic predispositions:
   a) Two functioning alleles related to drug metabolism
   b) One functioning and one non-functioning alleles related to drug metabolism
   c) Two non-functioning alleles related to drug metabolism
   d) More than two functioning alleles related to drug metabolism
4) Pharmacogenetics is the study of
   a) study of how people respond differently to drug therapy based upon their genetic makeup or genes
   b) how genes affect a person's response to drugs
   c) the science of drugs
   d) the study of genes and their functions

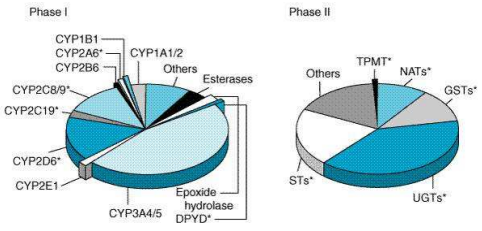
NAME 2019
TOX COMMITTEE

Practice Question

1) A mutation is defined as any change in a DNA sequence away from normal. A polymorphism is a DNA sequence variation that is common in the population. TRUE or FALSE
2) A poor metabolizer may have one of the following genetic predispositions:
   a) Two functioning alleles related to drug metabolism
   b) One functioning and one non-functioning alleles related to drug metabolism
   c) Two non-functioning alleles related to drug metabolism
   d) More than two functioning alleles related to drug metabolism
3) An ultra rapid metabolizer may have one of the following genetic predispositions:
   a) Two functioning alleles related to drug metabolism
   b) One functioning and one non-functioning alleles related to drug metabolism
   c) Two non-functioning alleles related to drug metabolism
   d) More than two functioning alleles related to drug metabolism
4) Pharmacogenetics is the study of
   a) study of how people respond differently to drug therapy based upon their genetic makeup or genes
   b) how genes affect a person's response to drugs
   c) the science of drugs
   d) the study of genes and their functions

NAME 2019
TOX COMMITTEE

Metabolic Enzymes



Other important genetic polymorphisms outside of metabolic enzymes (VKORC1, ABCE)

NAME 2019 TOX COMMITTEE

ISBN 0-07-142280-3

Genetic Polymorphisms

Table 1. Pharmacogenetics of Phase I Drug Metabolism.*

Drug-Metabolizing Enzyme	Frequency of Variant Poor-Metabolism Phenotype	Representative Drugs Metabolized	Effect of Polymorphism
Cytochrome P-450 2D6 (CYP2D6)	6.8% in Sweden 1% in China[17]	Debrisoquin[15] Sparteine[15] Nortriptyline[23] Codeine[27,28]	Enhanced drug effect Enhanced drug effect Enhanced drug effect Decreased drug effect
Cytochrome P-450 2C9 (CYP2C9)	Approximately 3% in England[29] (those homozygous for the *2 and *3 alleles)	Warfarin[29,30] Phenytoin[31,32]	Enhanced drug effect[29-32]
Cytochrome P-450 2C19 (CYP2C19)	2.7% among white Americans[33] 3.3% in Sweden 14.6% in China[17] 18% in Japan[33]	Omeprazole[34,35]	Enhanced drug effect[35,37]
Dihydropyrimidine dehydrogenase	Approximately 1% of population is heterozygous[38]	Fluorouracil[39,40]	Enhanced drug effect[39,40]
Butyrylcholinesterase (pseudocholinesterase)	Approximately 1 in 3500 Europeans[41]	Succinylcholine[9,41]	Enhanced drug effect[9,41]

* Examples of genetically polymorphic phase I enzymes are listed that catalyze drug metabolism, including selected examples of drugs that have clinically relevant variations in their effects.

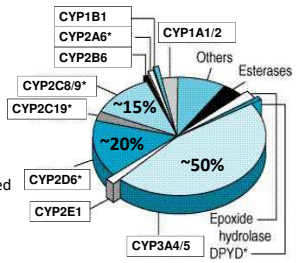
DOI: 10.1056/NEJMra030021

NAME 2019 TOX COMMITTEE

Cytochrome P450 (CYP450)

Critical for metabolism of drugs
- Oxidize drugs
- Making drugs more water-soluble

Clinically relevant if inactivated
- Inhibition (grapefruit)
- Downregulation
- Drug-Drug Interaction
- CYP3A4 covers ~50 %
  - Most consequential if inactivated

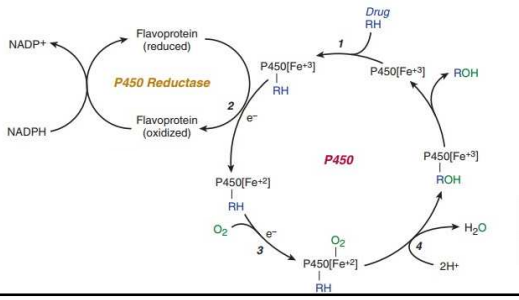


CYP2C9*2A
- Superfamily
- Family
- Subfamily
- Isozyme
- Allele
- Suballele

NAME 2019 TOX COMMITTEE

ISBN 0-07-142280-3

CYP450 Mechanism

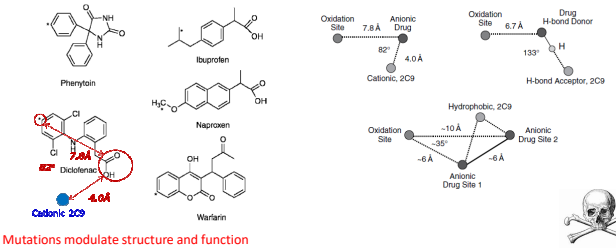


ISBN: 0071825053

NAME 2019
TOX COMMITTEE

CYP450 Structure and Function

CYP2C9 Substrates



Mutations modulate structure and function
CYP450 Polymorphs vary in activity and affect pharmacokinetics

ISBN: 978-0-1236-9520-8

NAME 2019
TOX COMMITTEE

CYP450 Polymorphisms

TABLE 1
Importance of Polymorphic CYP for the Metabolism of Drugs and Carcinogens

Enzyme	Substrates	Polymorphism frequency	Functional effects	Most important polymorphic variants
CYP1A1	Carcinogens	Relatively high	Unproven	No important functional variant alleles
CYP1A2	Drugs, carcinogens	High	Rare	CYP1A2*1F, CYP1A2*1K
CYP1B1	Carcinogens, estrogens	Rare null alleles, frequent missense mutations	At least seven haplotypes with similar activity	CYP1B1*3
CYP2A6	Nicotine, drugs, carcinogens	High in Orientals, less frequent in Caucasians	Important for nicotine metabolism	CYP2A6*1B, CYP2A6*4, CYP2A6*9, CYP2A6*12
CYP2B6	Drugs	High	Reduced drug metabolism	CYP2B6*5, CYP2B6*6, CYP2B6*16
CYP2C8	Some drugs	High	Reduced drug metabolism	CYP2C8*3
CYP2C9	Drugs	Relatively rare in Caucasians	Very significant	CYP2C9*2, CYP2C9*3
CYP2C19	Drugs	High	Very significant	CYP2C19*2, CYP2C19*3, CYP2C19*17
CYP2D6	Drugs	Very high	Very significant	CYP2D6*2-to CYP2D6*4, CYP2D6*5, CYP2D6*10, CYP2D6*17
CYP2E1	Carcinogens, solvents, few drugs	Low	No significant cases have been reported	No important functional variant alleles
CYP3A4	Drugs, carcinogens	Low	No or small	CYP3A4*1B
CYP3A5	Drugs, carcinogens	High	Significant	CYP3A5*3, CYP3A5*6, CYP3A5*7
CYP3A7	Drugs, carcinogens	Low	Some	CYP3A7*2

DOI: 10.1093/toxsci/kfs374

NAME 2019
TOX COMMITTEE

CYP450 Polymorphisms

Table 3 Mean frequencies of *CYP2C9*, *CYP2C19*, and *CYP2D6* genetic variants in different geographic regions[a]

Variant	Southern Africa	Middle Africa	Western Africa	Eastern Africa	Northern Africa	Mixed Africa[b]	Southern Europe	Western Europe	Northern Europe	Eastern Europe	Mixed Europe[c]
*CYP2C9*2*	0 (30)	0 (98)	0.3 (508)	4.3 (324)	13.4 (932)	1.6 (1650)	14.4 (5518)	12.0 (4388)	11.5 (7978)	11.1 (1052)	13.1 (3156)
*CYP2C9*3*	0 (30)	0 (98)	0.3 (508)	1.2 (324)	10.2 (932)	1.5 (1172)	9.6 (5518)	7.3 (2152)	7.4 (7978)	6.9 (1052)	6.7 (3156)
*CYP2C9*5*	0 (30)	0 (98)	2.0 (318)	0.3 (690)	0 (60)	0.5 (726)	ND	0 (242)	0 (684)	0 (580)	0 (526)
*CYP2C9*11*	0 (30)	2.4 (98)	1.6 (318)	0 (24)	1.7 (60)	2.0 (604)	ND	0.4 (242)	0.6 (284)	ND	0.5 (274)
*CYP2C19*2*	21.7 (152)	ND	13.0 (222)	14.9 (1696)	11.0 (494)	15.0 (938)	13.3 (2634)	14.0 (4140)	16.3 (5262)	11.4 (580)	12.8 (2040)
*CYP2C19*3*	0 (152)	ND	0 (222)	0.7 (1696)	0.2 (494)	1.7 (738)	0 (1992)	0.2 (3392)	0.2 (2478)	0.3 (580)	0.1 (1938)
*CYP2D6*2*	31.5 (182)	55.0 (102)	11.8 (484)	27.2 (1110)	28.3 (60)	23.0 (810)	30.2 (996)	29.3 (1666)	32.4 (878)	31.7 (84)	28.8 (2640)
*CYP2D6*3*	0 (182)	0 (102)	0 (484)	0.1 (1502)	0 (60)	0.4 (1302)	1.5 (3262)	1.1 (3682)	1.9 (3788)	0.8 (954)	1.2 (3568)
*CYP2D6*4*	1.1 (182)	0.7 (102)	6.5 (484)	3.0 (1502)	11.7 (60)	6.8 (1302)	16.8 (3262)	18.9 (3682)	17.6 (3788)	17.5 (954)	19.4 (3568)
*CYP2D6*5*	12.5 (182)	5.7 (102)	5.4 (484)	3.9 (1110)	3.3 (60)	6.6 (1302)	2.1 (2696)	5.1 (1666)	2.6 (1726)	1.5 (954)	2.8 (3568)
*CYP2D6*6*	0 (30)	0 (102)	0 (484)	0 (370)	0 (60)	0.4 (502)	1.1 (2402)	0.5 (3196)	1.4 (1496)	0.4 (664)	0.8 (2260)
*CYP2D6*9*	0 (30)	0 (102)	0 (484)	0 (24)	0 (60)	0.2 (502)	1.5 (702)	3.5 (1666)	2.0 (934)	0 (84)	2.1 (2260)
*CYP2D6*10*	0 (30)	4.2 (102)	4.5 (484)	5.2 (670)	0 (60)	5.6 (810)	2.4 (702)	2.9 (1666)	1.4 (920)	2.4 (664)	4.8 (2640)
*CYP2D6*17*	18.7 (182)	7.9 (102)	17.5 (484)	18.4 (1110)	8.3 (60)	20.6 (1302)	0.1 (492)	0 (488)	0 (316)	0 (84)	0.5 (2640)
*CYP2D6*29*	3.1 (30)	3.1 (102)	9.1 (98)	18.2 (236)	0 (60)	7.2 (502)	0 (100)	0 (98)	0 (316)	0 (84)	0.1 (1344)
*CYP2D6*41*	0 (30)	0.7 (102)	6.2 (98)	0 (24)	8.3 (60)	ND	4.5 (100)	7.1 (98)	4.9 (316)	11.4 (84)	14.0 (500)
*CYP2D6*1xN*	7.1 (30)	6.7 (102)	0 (98)	1.7 (236)	0 (60)	1.2 (502)	0.4 (702)	0.6 (1666)	2.6 (316)	0.6 (664)	1.2 (916)
*CYP2D6*2xN*	0 (30)	0 (102)	1.9 (484)	8.8 (458)	28.3 (60)	2.0 (1302)	2.0 (2682)	1.2 (1666)	1.5 (920)	1.5 (664)	3.3 (2224)
*CYP2D6*4xN*	0 (30)	0.7 (102)	7.0 (98)	2.5 (236)	0 (60)	0.3 (502)	0.8 (702)	0.5 (1666)	0 (316)	0 (664)	0.1 (916)
*CYP2D6*10xN*	0 (30)	0 (102)	0 (98)	0 (24)	0 (60)	ND	0.4 (492)	0 (488)	0 (316)	0 (84)	0 (500)
*CYP2D6*41xN*	0 (30)	0 (102)	0 (98)	0 (24)	0 (60)	ND	0 (100)	0 (98)	0 (316)	0 (84)	0.8 (500)

Variant	Western Asia	Southern Asia	Eastern Asia	South-Eastern Asia	Mixed Asia[d]	Melanesia	Australia	Northern America	Central America	South America	Chromosomes Total
*CYP2C9*2*	8.6 (1366)	5.6 (2396)	0.1 (7798)	0.6 (756)	2.4 (156)	0 (78)	ND	1.5 (404)	7.0 (386)	5.7 (2380)	41354
*CYP2C9*3*	9.0 (1366)	7.6 (2396)	3.8 (9186)	3.0 (756)	4.8 (156)	6.3 (78)	ND	3.0 (404)	4.0 (386)	4.4 (2380)	40028
*CYP2C9*5*	ND	0 (714)	0 (2646)	0 (442)	0 (156)	0 (78)	ND	ND	0 (196)	ND	8186
*CYP2C9*11*	ND	ND	0 (1282)	0 (22)	0 (68)	0 (78)	ND	ND	ND	ND	3384
*CYP2C19*2*	13.2 (1614)	33.5 (1646)	31.2 (7654)	29.0 (2954)	27.8 (550)	60.2 (11878)	35.5 (454)	15.7 (410)	9.7 (692)	8.3 (1934)	47944
*CYP2C19*3*	0.4 (1454)	0.6 (1646)	8.7 (7654)	4.6 (2954)	6.8 (550)	15.7 (11878)	14.3 (454)	0 (410)	0.1 (692)	0.1 (1934)	43308
*CYP2D6*2*	30.1 (1378)	30.8 (1614)	15.8 (2842)	9.0 (22)	ND	0 (78)	3.8 (478)	ND	22.2 (1284)	27.8 (706)	17414
*CYP2D6*3*	0 (1378)	<0.1 (1826)	0 (2050)	0 (232)	ND	0 (78)	0 (478)	0 (410)	0.4 (1884)	0.1 (978)	28200
*CYP2D6*4*	7.0 (1580)	8.2 (3788)	3.5 (3292)	1.4 (232)	ND	0 (78)	1.5 (478)	5.3 (410)	9.6 (1884)	11.2 (978)	31606
*CYP2D6*5*	2.6 (1580)	2.9 (1826)	6.4 (3288)	4.8 (232)	ND	1.5 (78)	7.5 (478)	ND	1.0 (1494)	2.1 (798)	23624
*CYP2D6*6*	1.1 (1206)	0 (720)	0 (1726)	0 (22)	ND	0 (78)	0 (478)	0 (180)	0.1 (700)	3.0 (810)	17486
*CYP2D6*9*	0.1 (1206)	0 (720)	0 (1280)	1.7 (232)	ND	0 (78)	0 (478)	ND	0 (310)	0 (556)	11708
*CYP2D6*10*	4.1 (1580)	6.9 (1826)	38.3 (3288)	52.0 (232)	ND	2.3 (78)	0.8 (478)	2.6 (410)	5.6 (1884)	5.0 (736)	19260
*CYP2D6*17*	1.5 (1580)	0 (1614)	0 (1604)	0.3 (232)	ND	0 (78)	0.2 (478)	ND	1.1 (1284)	0.4 (358)	14488
*CYP2D6*29*	0 (296)	0.2 (720)	0 (1280)	0 (22)	ND	0 (78)	ND	ND	0 (100)	0 (116)	5582
*CYP2D6*41*	16.9 (296)	10.5 (720)	3.8 (1280)	0 (22)	ND	0 (78)	ND	ND	0 (100)	0 (116)	4024
*CYP2D6*1 × N*	3.8 (1206)	0.5 (720)	0.2 (2138)	0.5 (232)	ND	11.6 (78)	ND	ND	3.2 (1284)	0.2 (358)	11308
*CYP2D6*2 × N*	3.9 (1580)	0.6 (720)	0.5 (1692)	0 (22)	ND	0 (78)	0 (478)	ND	2.4 (586)	2.8 (116)	15864
*CYP2D6*4 × N*	0.1 (1206)	<0.1 (720)	0 (1922)	0 (22)	ND	0 (78)	ND	ND	0 (100)	0.1 (358)	9698
*CYP2D6*10 × N*	0 (398)	0 (720)	0.8 (1726)	0 (22)	ND	0 (78)	ND	ND	0.5 (586)	0 (116)	5840
*CYP2D6*41 × N*	0 (296)	0 (720)	0.1 (480)	0 (22)	ND	0 (78)	ND	ND	0 (100)	0 (116)	3224

ND, not detected.
[a]Number of studied chromosomes is given in parentheses, for data on individual populations, see Supplementary Tables 1–3.
[b]Includes populations defined as African Pygmies, African American, Black American.
[c]Includes populations defined as European, Caucasian, Caucasian American, European American, White, Ashkenazi Jews, Sephardic Jews.
[d]Includes populations defined as Asian, East Asian, Southeast Asian.

DOI: 10.1097/FPC.0b013e32831ebb30

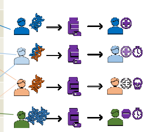
NAME 2019
TOX COMMITTEE

CYP2D6 Polymorphisms Examples

Table 1 | **Cytochrome P450 2D6 (*CYP2D6*) alleles and their effects on CYP2D6 enzyme activity**

CYP2D6 alleles	Allele designation	Enzyme activity	Allele abbreviation
*1, *2, *33, *35	Normal or wild type	Normal	EM
*3, *4, *5–*8, *11–*16, *18–*21, *36, *38, *40, *42, *44, *56, *62	Null	No protein, inactive or negligible	PM
*9, *10, *17, *29, *41, *59	Reduced activity	Decreased	IM
*22–*28, *30–*32, *34, *37, *39, *43, *45–*55	Unknown activity	Unknown	Not applicable
Duplicated alleles			
*1×*N*, *2×*N*, *35×*N*	Multiplication of normal alleles	Increased	UM
*10×*N*, *17×*N*, *29×*N*, *41×*N*	Multiplication of reduced activity alleles	Decreased	IM
*4×*N*, *6×*N*, *36×*N*	Multiplication of null alleles	Inactive or negligible	PM
*43×*N*, *45×*N*	Multiplication of alleles of unknown activity	Unknown	Not applicable

EM, extensive metabolizer allele; IM, intermediate metabolizer allele; PM, poor metabolizer allele; UM, ultra-rapid metabolizer allele.



Drug efficacy is different for each metabolizer form depending on substrate (prodrug vs active drug)

DOI: 10.1038/nrc2683

NAME 2019
TOX COMMITTEE

Practice Question

1) Cytochrome P450s catalyze
   a) Hydrolysis
   b) Redox reactions
   c) Dealkylation
   d) Deamination
   e) All of the above
2) Most clinically relevant inhibitory interactions are the consequence of inactivation of which enzyme?
   a) CYP1A2
   b) CYP2D6
   c) CYP2C9
   d) CYP2C19
   e) CYP3A4
3) What type of metabolizer form would be expected for an individual with multiple copies of non-functioning a cytochrome P450? _______________
4) Which of the two following CYP450 isozymes exhibit significant genetic polymorphism?
   a) CYP1A1
   b) CYP2B6
   c) CYP2D6
   d) CYP2C19
   e) CYP2E1

NAME 2019
TOX COMMITTEE

Practice Question

1) Cytochrome P450s catalyze
   a) Hydrolysis
   b) Redox reactions
   c) Dealkylation
   d) Deamination
   e) All of the above
2) Most clinically relevant inhibitory interactions are the consequence of inactivation of which enzyme?
   a) CYP1A2
   b) CYP2D6
   c) CYP2C9
   d) CYP2C19
   e) CYP3A4
3) What type of metabolizer form would be expected for an individual with multiple copies of non-functioning a cytochrome P450? Poor metabolizer
4) Which of the two following CYP450 isozymes exhibit significant genetic polymorphism?
   a) CYP1A1
   b) CYP2B6
   c) CYP2D6
   d) CYP2C19
   e) CYP2E1

NAME 2019
TOX COMMITTEE

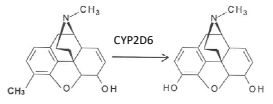
Application to Toxicology

- Pharmacogenetics based dose and clinical outcome
- Phenotype consideration in death investigations

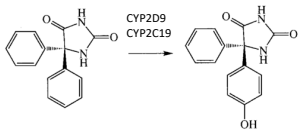
Enzyme	Drug Metabolized
CYP2C19	Amitriptyline, Imipramine, Diazepam, Citalopram, Carisoprodol, Clopidogrel, Desipramine, Omeprazole, Phenytoin
CYP2D6	**Amphetamines**, Codeine, Oxycodone, Hydrocodone, Methadone, Tramadol, Dextromethorphan, Metoclopramide, Desipramine, Metoprolol, Amitriptyline, Duloxetine, Fluoxetine, Haloperidol, Risperidone, Thioridazine
CYP2C9	**NSAIDs,** Valproic acid, Warfarin, Phenytoin, Glipizide, Ibuprofen, Celecoxib, Fluvastatin
CYP3A4	**Benzodiazepines**, Fentanyl, Methadone, Buprenorphine, Cocaine, Zolpidem, **Antibiotics, Calcium Channel Blockers, Statins, Steroids**
CYP2E1	Ethanol, Acetaminophen

NAME 2019
TOX COMMITTEE

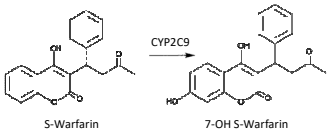
Application to Toxicology



Codeine Morphine



Phenytoin 4'-HPPH



S-Warfarin 7-OH S-Warfarin

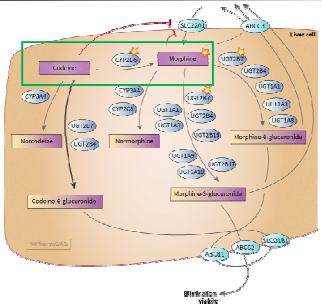
NAME 2019
TOX COMMITTEE

Application to Toxicology

Codeine Metabolism
- CYP2D6
- Prodrug, Active Metabolite

- poor efficacy, accumulation of prodrug

- good efficacy, rapid effect



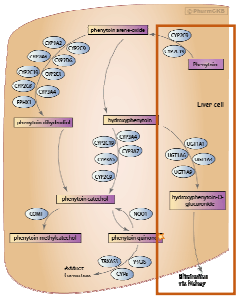
NAME 2019
TOX COMMITTEE

Application to Toxicology

Phenytoin Metabolism
- CYP2D9, CYP2C19
- Active drug, Inactive metabolite

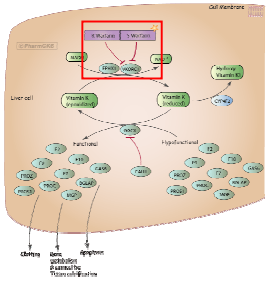
- good efficacy, but accumulation may have adverse effects

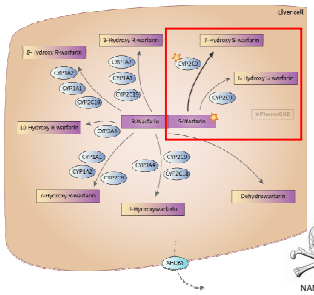
- poor efficacy, need a greater dose or slow release formula



NAME 2019
TOX COMMITTEE

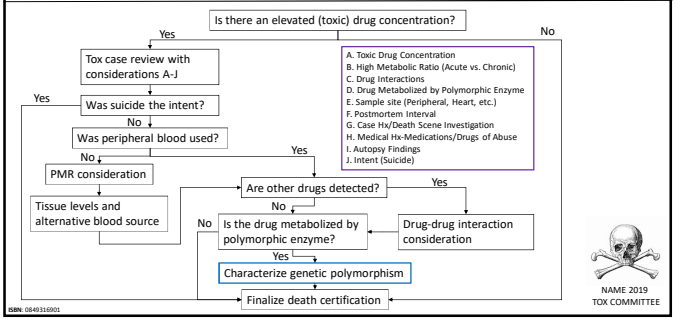
Application to Toxicology





NAME 2019
TOX COMMITTEE

Application to Death Investigation

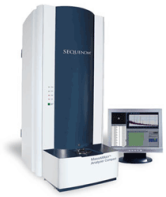


ISBN: 0849316901

NAME 2019
TOX COMMITTEE

Methodology

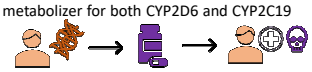
- Collection and preparation of samples
- Extraction by ionic resins or commercial kits (QIAGEN)
- Separation of DNA by gel electrophoresis
- Genotyping
  - Real-Time PCR System
  - Capillary Electrophoresis
  - MALFI-TOF



NAME 2019
TOX COMMITTEE

Case 1 (2D6 and 2C19 Poor Metabolizer)

- 46 year old Caucasian male diagnosed with depression
- Desipramine 50-250 mg daily over 1 month treatment as part of a safety and efficacy study
- Chest tightness occurring about 2 hours after desipramine dose, always while he was at rest
- Hospitalized when chest pain lasted 1 hour, ECG consistent with acute anterior wall myocardial ischemia
- Plasma desipramine concentration at 764 ng/mL
- Patient was studied with the drug-metabolizing probes, debrisoquin, mephenytoin, and dapsone
- Found to be poor metabolizer for both CYP2D6 and CYP2C19



DOI: 10.1038/clpt.1993.13

NAME 2019
TOX COMMITTEE

Case 2 (2D6 Poor Metabolizer)

- Adopted Caucasian 9 year old with be
- Behavioral issues
- 60 mg methylphenidate, 0.9 mg clonidine, and 80-100 mg fluoxetine daily
- Metabolic toxicity over 10 months
- Status epilepticus, cardiac arrest and death
- High fluoxetine and norfluoxetine
- Led to a legal investigation of the adoptive parents of the child
- Child had a completely defective CYP2D6 gene

TABLE 1. POST-MORTEM TOXICOLOGY RESULTS

Drug or metabolite	*Source*	*Concentration*
Promethazine	Blood	0.044 mcg/mL
Fluoxetine	Blood	21 mcg/mL
	Gastric contents	53 mcg/mL
	Liver	2,800 mcg/g
	Brain	24 mcg/g
	Kidney	38 mcg/g
Norfluoxetine	Blood	21 mcg/mL
	Gastric contents	38 mcg/mL
	Liver	2,200 mcg/g
	Brain	22 mcg/g
	Kidney	34 mcg/g

NAME 2019
TOX COMMITTEE

DOI: 10.1089/cap.2000.10.27

Case 3 (2D6 Ultrarapid Metabolizer)

- Full-term healthy male infant
- Grey skin and fallen milk intake by day 12, found dead on day 13
- Infant blood morphine 70 ng/mL (vs 0 ng/mL – 2·2 ng/mL)
- Mother prescribed codeine 30 mg and acetaminophen 500 mg (~1 tablet every 12 hrs over 2 weeks)
- Morphine concentration of 87 ng/mL in breastmilk
- Mother found to carry CYP2D6 gene duplication
- Resulted in FDA requiring manufacturers to include information to doctors about codeine and the risk of morphine overdose in breastfed infants

NAME 2019
TOX COMMITTEE

DOI: 10.1016/S0140-6736(06)69255-6 https://www.fda.gov/media/104268/download

Case 4 (2C9 Poor Metabolizer)

- 64 year old African – American female
- Hx of diabetes, asthma, stroke, depression, hypertension, alcohol abuse
- Placed on 100 mg phenytoin, 3x daily after 5-day hospital visit for status epilepticus
- Slurred speech, mental confusion, memory loss, ataxia 13 days later
- Pharmacogenetic characterization found the patient was homozygous for the null allele CYP2C9*6

Table 1 Actual and expected plasma phenytoin concentrations over the course of 41 days with day 1 as the day of presentation with phenytoin toxicity

Days after presentation with phenytoin toxicity	Actual plasma phenytoin concentration (μg/ml)	Expected plasma phenytoin concentration (μg/ml)
Day 1	49.5	49.5
Day 1 (2nd level)	40.3	47.3
Day 2	38.2	38.8
Day 3	38.8	30.5
Day 4	41.2	22.4
Day 5	38.9	14.7
Day 6	32.8	7.9
Day 7	32.1	2.8
Day 9	32.8	*BLQ
Day 11	30.0	BLQ
Day 12	25.1	BLQ
Day 14	24.9	BLQ
Day 15	22.0	BLQ
Day 16	21.2	BLQ
Day 41	5.3	BLQ

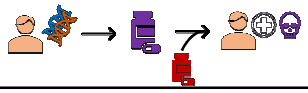
* BLQ (Below the lower limit of quantitation)

NAME 2019
TOX COMMITTEE

DOI: 10.1097/00008571-200012000-00008

Case 5 (2C9 Poor metabolizer)

- Elderly woman receiving 2.5 mg warfarin daily after a pacemaker one year previously
- Given celecoxib for joint pain 4 weeks prior
- Rx also included digoxin, ranitidine, and atorvastatin
- Developed ecchymoses with a decline in hemoglobin concentration from 160 to 85 g/L over one week
- Was found to be heterozygous for CYP2C9*2 and *3
- Metabolism of warfarin was perturbed and led to bleeding in the presence of variant CYP2C9 genes by coadministration of celecoxib



DOI: 10.1136/jmg.2003.006478

NAME 2019
TOX COMMITTEE

Limitations

- Genetic variation is only part of the puzzle, context is important
- Does not account for post translational modification
- Does not account for expressional modification
- Studies are primarily clinical, limited in postmortem
- Flat application of ethnic/race to phenotype is strongly discouraged
- Insightful information requires genetic testing
- Must consider postmortem interval, redistribution, age, environmental factors, drug interactions, etc

NAME 2019
TOX COMMITTEE

Summary

- Genetic polymorphisms are inter-individual variations in genetic code that are also systematic among populations/ethnicities
- Genetic Polymorphisms in metabolic enzymes like CYP2D6 and CYP2C19 contributes to inter-individual differences in drug response
- Examples of drug toxicities that can be predicted by P450 polymorphism include those exerted by codeine, tramadol, warfarin, etc
- Genetic polymorphisms can assist in the interpretation of drug concentrations in postmortem toxicology and drug death certification

NAME 2019
TOX COMMITTEE

Questions?

"Here's my sequence..."

New Yorker, 2000

Jirair Gevorkyan
Jgevorkyan@outlook.com

NAME 2019
TOX COMMITTEE

Drug Interactions

Luigino Apollonio, Ph.D.

NAME 2019 Annual Meeting – 20 October 2019

NAME 2019
TOX COMMITTEE

Outline

- Background
- Types and mechanisms of drug interactions
- Consequences
- Factors influencing interactions
- Avoiding interactions
- Reference information
- Case studies
- Final thoughts

NAME 2019
TOX COMMITTEE

Objectives

1. To identify the types and mechanisms of drug interactions for consideration in postmortem toxicology and death investigation
2. To identify factors influencing drug interactions, and potential consequences of interactions
3. To become more familiar with key resources on drug interactions, and to explore polypharmacy in case studies

NAME 2019
TOX COMMITTEE

Background

- Interaction between two or more drugs (or something else!) that prevents them from acting as expected
  - Drug-drug, food/beverage-drug, condition-drug
- A drug interaction may:
  - Affect the total population
  - Affect a particular subset of the population

NAME 2019
TOX COMMITTEE

Background

- Contraindicated
  - High risk of severe interaction – do not use
- Serious
  - Potential for a serious interaction – may require regular monitoring or alternative medication(s)
- Significant
  - Potential for an interaction – may require monitoring
- Minor
  - Interaction may not be significant or may be unlikely

?

NAME 2019
TOX COMMITTEE

Background

- Polypharmacy
  - Use of multiple medications
    - Benefit-Risk Assessment
  - Associated risks across general and specialist care
- DIs estimated to cause over 2% of annual hospitalizations in the USA (Carpenter et al 2019)
  - Bethi et al (2018): From a total of 433 prescriptions (46%) had one or more potential DDIs (range of 1-13 DIs per prescription)
    - Older patients and those prescribed >6 drugs were at 'major risk'
  - Gujjarlamudi (2016): Prevalence of 'inappropriate' medication use in the elderly ranges from 11.5-62.5% (citing Guaraldo et al 2011)
    - Risk of DI estimates at 13% for two drugs, 58% for five drugs, and 82% for seven or more drugs (citing Fulton and Allen, 2005)

NAME 2019
TOX COMMITTEE

Background

- Pharmacokinetic interactions
  - Increase or decrease in:
    - Absorption
    - Distribution
    - Metabolism
    - Elimination
- Additive
- Synergistic
- Antagonistic

- Pharmacodynamic interactions
  - Homodynamic
    (same receptor)
    (pure/partial agonists; competitive/ noncompetitive/uncompetitive antagonists)
  - Heterodynamic
    (different receptors)

NAME 2019
TOX COMMITTEE

Mechanisms

- Absorption mechanisms
  - Change in intestinal blood flow
  - Change in metabolism in the intestine
  - Change in gastric emptying/intestinal motility
  - Change in gastric acidity
  - Change in intestinal flora
  - Change in solubility
- Distribution mechanisms
  - Effects of body changes – lean muscle, increased fat
  - Changes in protein binding

NAME 2019
TOX COMMITTEE

Mechanisms

- Metabolism mechanisms
  - Cytochrome p450 effects
    - Leads to changes in the concentration and effect of a drug or its metabolites
    - Enzyme induction
    - Enzyme inhibition
- Elimination mechanisms
  - Renal effects – decrease in renal blood flow, GFR, tubular secretion
  - Urine pH – weak acids or bases in the urine
  - Biliary excretion – reabsorption in the intestine (enterohepatic recirculation)

NAME 2019
TOX COMMITTEE

Consequences

- Increase or decrease in the beneficial or adverse effects of drugs
  - Reduction in desired effects
    - failure of therapy
    - may need increased dosage
  - Increase in adverse effects
    - Increase in frequency or severity of adverse effects
- May be unpredictable
- May lead to medication non-compliance

NAME 2019
TOX COMMITTEE

Practice Questions

1) Drug interactions may be categorized (not least) to pharmacokinetic interactions and pharmacodynamic interactions? TRUE or FALSE
2) The risk of an adverse drug event has been estimated at what percent (%) for a person taking five drugs?
   a) 13%
   b) 28%
   c) 58%
   d) 82%
   e) 85%
3) Consequences of drug interactions include which of the following?
   a) Reduction in desired effects
   b) Failure of therapy
   c) Increase in adverse effects
   d) Increase in frequency or severity of side effects
   e) All the above

NAME 2019
TOX COMMITTEE

Practice Questions

1) Drug interactions may be categorized (not least) to pharmacokinetic interactions and pharmacodynamic interactions? TRUE or FALSE
2) The risk of an adverse drug event has been estimated at what percent (%) for a person taking five drugs?
   a) 13%
   b) 28%
   c) 58%
   d) 82%
   e) 85%
3) Consequences of drug interactions include which of the following?
   a) Reduction in desired effects
   b) Failure of therapy
   c) Increase in adverse effects
   d) Increase in frequency or severity of side effects
   e) All the above

NAME 2019
TOX COMMITTEE

Factors

- Genetics
- Physiology/pathophysiology/disease (hepatic, renal)
- Age
- Lifestyle
- Dosing regimen
- Duration of therapy
- Time(s) of administration
- Degree of, and agents in, polypharmacy
- Therapeutic index

NAME 2019
TOX COMMITTEE

How are patients to avoid DIs?

- Ask HCPs about interactions
- Keep a list of current medications
- Inform HCPs of medications, and include OTCs, foods, vitamins, supplements, herbals/traditional medications
- Inform HCPs when medications are stopped/started
- Inform HCPs about lifestyle changes
- Understand why one is taking each medication
- Be aware of side effects
- Try to eliminate unnecessary meds – ask to simplify meds or discontinue if possible
- Take only as prescribed

NAME 2019
TOX COMMITTEE

Tools: Prescribing Information

- Warnings and Precautions (includes Black Box Warnings)
- Dosage and Administration
- Contraindications
- Adverse Reactions
- Drug interactions
- Use in specific populations

- Examples: Warfarin, Sertraline, Mycophenolic acid, Metoprolol

NAME 2019
TOX COMMITTEE

Warfarin PI

- Black Box Warning
  - Drugs, dietary changes, and other factors affect INR levels achieved with coumadin therapy.
- Drug Interactions
  - Concomitant use of drugs that increase bleeding risk, antibiotics, antifungals, botanical (herbal) products, and inhibitors and inducers of CYP2C9, 1A2, or 3A4.
  - Consult labeling of all concurrently used drugs for complete information about interactions with [warfarin] or increased risks for bleeding.

NAME 2019
TOX COMMITTEE

Warfarin PI

- Drug Interactions
  - Drugs may interact with [warfarin] through pharmacodynamic or pharmacokinetic mechanisms.
  - Pharmacodynamic mechanisms for drug interactions with [warfarin] are synergism (impaired hemostasis, reduced clotting factor synthesis), competitive antagonism (vitamin K), and alteration of the physiologic control loop for vitamin K metabolism (hereditary resistance).
  - Pharmacokinetic mechanisms for drug interactions with [warfarin] are mainly enzyme induction, enzyme inhibition, and reduced plasma protein binding.
  - It is important to note that some drugs may interact by more than one mechanism.

NAME 2019
TOX COMMITTEE

Warfarin PI

- Drug Interactions

Table 3: Drugs that Can Increase the Risk of Bleeding

Drug Class	Specific Drugs
Anticoagulants	argatroban, dabigatran, bivalirudin, desirudin, heparin, lepirudin
Antiplatelet Agents	aspirin, cilostazol, clopidogrel, dipyridamole, prasugrel, ticlopidine
Nonsteroidal Anti-Inflammatory Agents	celecoxib, diclofenac, diflunisal, fenoprofen, ibuprofen, indomethacin, ketoprofen, ketorolac, meflenamic acid, naproxen, oxaprozin, piroxicam, sulindac
Serotonin Reuptake Inhibitors	citalopram, desvenlafaxine, duloxetine, escitalopram, fluoxetine, fluvoxamine, milnacipran, paroxetine, sertraline, venlafaxine, vilazodone

Table 2: Examples of CYP450 Interactions with Warfarin

Enzyme	Inhibitors	Inducers
CYP2C9	amiodarone, capecitabine, cotrimoxazole, etravirine, fluconazole, fluvastatin, fluvoxamine, metronidazole, miconazole, oxandrolone, sulfinpyrazone, tigecycline, voriconazole, zafirlukast	aprepitant, bosentan, carbamazepine, phenobarbital, rifampin
CYP1A2	acyclovir, allopurinol, caffeine, cimetidine, ciprofloxacin, disulfiram, enoxacin, famotidine, fluvoxamine, methoxsalen, mexiletine, norfloxacin, oral contraceptives, phenylpropanolamine, propafenone, propranolol, terbinafine, ticlopidine, tolcapone, verapamil, zileuton	nafcillin, omeprazole, phenobarbital, phenytoin, cigarette smoking
CYP3A4	alprazolam, amiodarone, amlodipine, aprepitant, atorvastatin, atazanavir, busulfan, cilostazol, cimetidine, ciprofloxacin, clarithromycin, conivaptan, cyclosporine, danazol/stanozol, diltiazem, erythromycin, fluconazole, fluoxetine, fluvoxamine, fosaprepitant, imatinib, indinavir, isoniazid, itraconazole, ketoconazole, lapatinib/nilotinib, nefazodone, nelfinavir, nilotinib, oral contraceptives, posaconazole, ranitidine, ranolazine, ritonavir, saquinavir, telithromycin, tipranavir, voriconazole, zileuton	armodafinil, aminoglutethimide, aprepitant, bosentan, carbamazepine, efavirenz, etravirine, modafinil, nafcillin, phenytoin, pioglitazone, prednisone, rifampin, rufinamide

Some botanicals may cause bleeding events when taken alone (e.g., garlic and Ginkgo biloba) and may have anticoagulant, antiplatelet, and/or fibrinolytic properties. These effects would be expected to be additive to the anticoagulant effects of COUMADIN. Conversely, some botanicals may decrease the effects of COUMADIN (e.g., co-enzyme Q_{10}, St. John's wort, ginseng). Some botanicals and foods can interact with COUMADIN through CYP450 interactions (e.g., echinacea, grapefruit juice, ginkgo, goldenseal, St. John's wort).

NAME 2019
TOX COMMITTEE

Sertraline PI

- Contraindications
  - Concomitant use of MAOIs, or use within 14 days of stopping MAOIs
  - Concomitant use of pimozide [QT prolongation and ventricular arrhythmias]
  - Concomitant use of disulfiram (oral solution only) [reaction with alcohol]
- Warnings and Precautions
  - Serotonin Syndrome: Increased risk when co-administered with other serotonergic agents (e.g., SSRI, SNRI, triptans), but also when taken alone. If it occurs, discontinue [sertraline] and initiate supportive treatment.
    - (also includes amphetamines, TCAs, fentanyl, lithium, tramadol, buspirone, and others)
  - Increased Risk of Bleeding: Concomitant use of aspirin, nonsteroidal anti-inflammatory drugs (NSAIDs), other antiplatelet drugs, warfarin, and other anticoagulants may increase this risk.

NAME 2019
TOX COMMITTEE

Sertraline PI

- Drug Interactions
  - Protein-bound drugs: Monitor for adverse reactions and reduce dosage of [sertraline] or other protein-bound drugs (e.g., warfarin) as warranted.
  - CYP2D6 substrates: Reduce dosage of drugs metabolized by CYP2D6

Monoamine Oxidase Inhibitors (MAOIs)	
Clinical Impact:	The concomitant use of SSRIs including ZOLOFT and MAOIs increases the risk of serotonin syndrome.
Intervention:	ZOLOFT is contraindicated in patients taking MAOIs, including MAOIs such as linezolid or intravenous methylene blue *[See Dosage and Administration (2.5), Contraindications (4), Warnings and Precautions (5.2)]*.
Examples:	selegiline, tranylcypromine, isocarboxazid, phenelzine, linezolid, methylene blue
Pimozide	
Clinical Impact:	Increased plasma concentrations of pimozide, a drug with a narrow therapeutic index, may increase the risk of QT prolongation and ventricular arrhythmias.
Intervention:	Concomitant use of pimozide and ZOLOFT is contraindicated *[See Contraindications (4)]*.
Other Serotonergic Drugs	
Clinical Impact:	The concomitant use of serotonergic drugs with ZOLOFT increases the risk of serotonin syndrome.
Intervention:	Monitor patients for signs and symptoms of serotonin syndrome, particularly during treatment initiation and dosage increases. If serotonin syndrome occurs, consider discontinuation of ZOLOFT and/or concomitant serotonergic drugs *[See Warnings and Precautions (5.2)]*.
Examples:	other SSRIs, SNRIs, triptans, tricyclic antidepressants, fentanyl, lithium, tramadol, tryptophan, buspirone, St. John's Wort

NAME 2019
TOX COMMITTEE

Sertraline PI

Drugs that Interfere with Hemostasis (antiplatelet agents and anticoagulants)	
Clinical Impact:	The concurrent use of an antiplatelet agent or anticoagulant with ZOLOFT may potentiate the risk of bleeding.
Intervention:	Inform patients of the increased risk of bleeding associated with the concomitant use of ZOLOFT and antiplatelet agents and anticoagulants. For patients taking warfarin, carefully monitor the international normalized ratio *[See Warnings and Precautions (5.3)]*.
Examples:	aspirin, clopidogrel, heparin, warfarin
Drugs Highly Bound to Plasma Protein	
Clinical Impact:	ZOLOFT is highly bound to plasma protein. The concomitant use of ZOLOFT with another drug that is highly bound to plasma protein may increase free concentrations of ZOLOFT or other highly-bound drugs in plasma *[See Clinical Pharmacology (12.3)]*.
Intervention:	Monitor for adverse reactions and reduce dosage of ZOLOFT or other protein-bound drugs as warranted.
Examples:	warfarin
Drugs Metabolized by CYP2D6	
Clinical Impact:	ZOLOFT is a CYP2D6 inhibitor *[See Clinical Pharmacology (12.3)]*. The concomitant use of ZOLOFT with a CYP2D6 substrate may increase the exposure of the CYP2D6 substrate.
Intervention:	Decrease the dosage of a CYP2D6 substrate if needed with concomitant ZOLOFT use. Conversely, an increase in dosage of a CYP2D6 substrate may be needed if ZOLOFT is discontinued.
Examples:	propafenone, flecainide, atomoxetine, desipramine, dextromethorphan, metoprolol, nebivolol, perphenazine, thioridazine, tolterodine, venlafaxine
Phenytoin	
Clinical Impact:	Phenytoin is a narrow therapeutic index drug. ZOLOFT may increase phenytoin concentrations.
Intervention:	Monitor phenytoin levels when initiating or titrating ZOLOFT. Reduce phenytoin dosage if needed.
Examples:	phenytoin, fosphenytoin

NAME 2019
TOX COMMITTEE

Mycophenolic acid PI

- Warnings and Precautions
  - A variety of drugs have potential to alter systemic MPA exposure when co-administered with [MPA].
  - Therefore, determination of MPA concentrations in plasma before and after making any changes to immunosuppressive therapy, or when adding or discontinuing concomitant medications, may be appropriate to ensure MPA concentrations remain stable.
- Drug Interactions
  - See FPI for drugs that may interfere with systemic exposure and reduce [MPA] efficacy: antacids with magnesium or aluminum hydroxide, proton pump inhibitors, drugs that interfere with enterohepatic recirculation, telmisartan, calcium-free phosphate binders.

NAME 2019
TOX COMMITTEE

Mycophenolic acid PI

Antacids with Magnesium or Aluminum Hydroxide	
Clinical Impact	Concomitant use with an antacid containing magnesium or aluminum hydroxide decreases MPA systemic exposure *[see Clinical Pharmacology (12.3)]*, which may reduce CELLCEPT efficacy.
Prevention or Management	Administer magnesium or aluminum hydroxide containing antacids at least 2h after CELLCEPT administration.
Proton Pump Inhibitors (PPIs)	
Clinical Impact	Concomitant use with PPIs decreases MPA systemic exposure *[see Clinical Pharmacology (12.3)]*, which may reduce CELLCEPT efficacy.
Prevention or Management	Monitor patients for alterations in efficacy when PPIs are co-administered with CELLCEPT.
Examples	Lansoprazole, pantoprazole

NAME 2019
TOX COMMITTEE

Mycophenolic acid PI

Clinical Impact	Concomitant use with calcium free phosphate binders decrease MPA systemic exposure [see *Clinical Pharmacology (12.3)*], which may reduce CELLCEPT efficacy.
Prevention or Management	Administer calcium free phosphate binders at least 2 hours after CELLCEPT.
Examples	Sevelamer

Table 6. Drug Interactions with CELLCEPT that Affect Other Drugs

Drugs that Undergo Renal Tubular Secretion	
Clinical Impact	When concomitantly used with CELLCEPT, its metabolite MPAG, may compete with drugs eliminated by renal tubular secretion which may increase plasma concentrations and/or adverse reactions associated with these drugs.
Prevention or Management	Monitor for drug-related adverse reactions in patients with renal impairment.
Examples	Acyclovir, ganciclovir, probenecid, valacyclovir, valganciclovir
Combination Oral Contraceptives	
Clinical Impact	Concomitant use with CELLCEPT decreased the systemic exposure to levonorgestrel, but did not affect the systemic exposure to ethinylestradiol [see *Clinical Pharmacology (12.3)*], which may result in reduced combination oral contraceptive effectiveness.
Prevention or Management	Use additional barrier contraceptive methods.

Proton Pump Inhibitors (PPIs)	
Clinical Impact	Concomitant use with PPIs decreases MPA systemic exposure [see *Clinical Pharmacology (12.3)*], which may reduce CELLCEPT efficacy.
Prevention or Management	Monitor patients for alterations in efficacy when PPIs are co-administered with CELLCEPT.
Examples	Lansoprazole, pantoprazole
Drugs that Interfere with Enterohepatic Recirculation	
Clinical Impact	Concomitant use with drugs that directly interfere with enterohepatic recirculation, or indirectly interfere with enterohepatic recirculation by altering the gastrointestinal flora, can decrease MPA systemic exposure [see *Clinical Pharmacology (12.3)*], which may reduce CELLCEPT efficacy.
Prevention or Management	Monitor patients for alterations in efficacy or CELLCEPT related adverse reactions when these drugs are co-administered with CELLCEPT.
Examples	Trimethoprim/sulfamethoxazole, bile acid sequestrants (cholestyramine), rifampin as well as aminoglycoside, cephalosporin, fluoroquinolone and penicillin classes of antimicrobials.
Drugs Modulating Glucuronidation	
Clinical Impact	Concomitant use with drugs inducing glucuronidation decreases MPA systemic exposure, potentially reducing CELLCEPT efficacy, while use with drugs inhibiting glucuronidation increases MPA systemic exposure [see *Clinical Pharmacology (12.3)*], which may increase the risk of CELLCEPT related adverse reactions.
Prevention or Management	Monitor patients for alterations in efficacy or CELLCEPT related adverse reactions when these drugs are co-administered with CELLCEPT.
Examples	Telmisartan (induces glucuronidation); isavuconazole (inhibits glucuronidation)

NAME 2019
TOX COMMITTEE

Metoprolol PI

- Warnings and Precautions
  - Bronchospastic Disease: Avoid beta blockers [use lowest dose, or consider concomitant beta2-agonists)
  - Pheochromocytoma: First initiate therapy with an alpha blocker [due to observed paradoxical increase in BP]
- Drug Interactions
  - Catecholamine-depleting drugs may have an additive effect when given with beta-blocking agents.
  - Patients may be unresponsive to the usual doses of epinephrine used to treat allergic reaction.
  - CYP2D6 Inhibitors are likely to increase metoprolol concentration.
  - Concomitant use of glycosides, clonidine, and diltiazem and verapamil with beta-blockers can increase the risk of bradycardia.
  - Beta-blockers including metoprolol, may exacerbate the rebound hypertension that can follow the withdrawal of clonidine.
  - Alcohol interferes with the extended release properties of this product.

NAME 2019
TOX COMMITTEE

Case Studies

- F, 55, femoral blood
  - Benztropine - QUAL
  - Cyclobenzaprine – 58 ng/mL
  - Bupropion (w/ metabolite) – 75 ng/mL (670 ng/mL)
  - Tramadol (w/metabolite) – 830 ng/mL (ODM- 83 ng/mL)
  - Topiramate – 5400 ng/mL
  - Caffeine - QUAL
  - Cotinine - QUAL
  - Fentanyl (w/metabolite) – 1.1 ng/mL (NF 1.2 ng/mL)
  - Paroxetine – 63 ng/mL
  - Pregabalin – 7.7 mg/L
  - Ziprasidone – 13 ng/mL

NAME 2019
TOX COMMITTEE

Case Studies

- F, 55, femoral blood
  - Diphenhydramine – 0.328 mg/L
  - Dextromethorphan – 0.686 mg/L
  - Chlorpromazine – 0.076 mg/L
  - Trazodone – 0.399 mg/L
  - Olanzapine – QUAL
  - Donepezil – QUAL

NAME 2019
TOX COMMITTEE

Case Studies

- M, 56, femoral blood
  - Dextromethorphan – QUAL
  - Doxepin (w/metabolite) – 0.097 mg/L
  - Ketamine (w/metabolite) – 0.826 mg/L
  - Mirtazapine – QUAL
  - Cocaine (w/metabolites) – 38 ng/mL (heart blood, BE >800 ng/mL)
  - Nicotine and cotinine – QUAL
  - Caffeine – QUAL
  - Oxycodone – 23 ng/mL
  - THC (w/metabolites) – 1.9 ng/mL (heart blood)

NAME 2019
TOX COMMITTEE

Case Studies

- M, 32, femoral blood
  - Methadone (w/EDDP) – 0.672 mg/L
  - Mirtazapine – 0.101 mg/L
  - Nicotine and cotinine – QUAL
  - Caffeine – QUAL
  - Gabapentin – 3.8 mg/L
  - Hydroxyzine – 42 ng/mL

NAME 2019
TOX COMMITTEE

Case Studies

- F, 47, femoral blood
  - Gabapentin – 17 mg/L
  - Amitriptyline (w/ NT) – QUAL (0.342 mg/L)
  - Sertraline (w/ metabolite) – QUAL
  - Diphenhydramine – 0.520 mg/L
  - Lidocaine (w/ metabolite) – QUAL
  - Cotinine – QUAL
  - Cocaine (w/ metabolites) – 103 ng/mL (BE 128 ng/mL)
  - *Urine: Also promethazine, dextromethorphan, doxylamine*

NAME 2019
TOX COMMITTEE

Case Studies

- F, 79, femoral blood
  - Amitriptyline (w/ NT) – 0.402 mg/L (0.415 mg/L)
  - Bupropion (with metabolite) – QUAL
  - Citalopram (w/ metabolite) – 0.466 mg/L
  - Diphenhydramine – 0.162 mg/L
  - Cotinine – QUAL
  - Oxycodone – 112 ng/mL
  - 7-aminoclonazepam – QUAL
  - Memantine - QUAL

NAME 2019
TOX COMMITTEE

Case Studies

- M, 38, femoral blood
  - Clonazepam (w/ metabolite) – 2.7 ng/mL (44 ng/mL)
  - Clomipramine (w/metabolite) – 900 mg/L
  - Fluoxetine (w/metabolite) – 410 ng/mL (270 ng/mL)
  - Trazodone (w/metabolite) – 32 mcg/mL (0.059 mcg/mL)
  - Dextromethorphan (w/ metabolite) – 110 ng/mL (15 ng/mL)
  - Caffeine – QUAL
  - Cotinine – QUAL

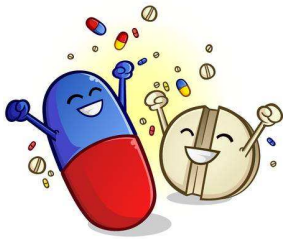
NAME 2019
TOX COMMITTEE

Final thoughts

- Polypharmacy may be necessary – but needs to be managed well
- Contraindicated, serious and significant risks of DIs may contribute to, but not be obvious in, fatal outcomes
- Patients and HCPs both share responsibility for appropriate polytherapy
- Regulatory references are living documents that reflect key DI information
- Prescribed, licit, and illicit drug combinations are the norm in death investigations – toxicologists can help wade through the information ☺

NAME 2019
TOX COMMITTEE

Questions



Luigino Apollonio
lapollonio@cuyahogacounty.us

Thank you!

NAME 2019
TOX COMMITTEE