INTRODUCTION
TO
CLINICAL PHARMACOLOGY

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04/20/16

Educational Objectives

At the conclusion of this presentation, the participant should be able to:

1. Remember the 3 key factors in drug response (Section 1):
    - 1.1. The drug
    - 1.2. The patient
    - 1.3. The prescriber
2. Appreciate that for understanding patient drug response, one must consider (Section 2):
    - 2.1. Personal, environmental and genetic factors
    - 2.2. Pharmacodynamics and pharmacokinetics
    - 2.3. Efficacy and safety
3. Summarize how the prescriber's role may also influence the prescription, including dosing (Section 3).

Abbreviations (used in this presentation)

- ADME: absorption, distribution, metabolism and excretion
- ADE: adverse drug event
- ADR: adverse drug reaction
- AP: antipsychotic
- CNV: copy number variation
- CYP: cytochrome P450
- DDI: drug-drug interaction
- FGAP: first-generation antipsychotic
- MDD: major depressive disorder
- P-gp: P-glycoprotein
- OCD: obsessive-compulsive disorder
- SGAP: second-generation antipsychotic
- SNP: Single nucleotide polymorphism
- UGT: Uridine 5'- diphosphate glucuronosyltransferase

Key Factors in Drug Response:

1. The Drug
2. The Patient
3. The Prescriber

Lecture Content

1. Drug Response: The Drug
2. Drug Response: The Patient

3. Drug Response: The Prescriber

Lecture Content

1. Drug Response: The Drug

2. Drug Response: The Patient

- 2.1. Personal, Environmental and Genetic Factors
- 2.2. Pharmacodynamics and Pharmacokinetics
- 2.3. Efficacy and Safety
- 2.4. Interactions between 2.1., 2.2., and 2.3.

3. Drug Response: The Prescriber

- 3.1. Prescriber's Role: Definition
- 3.2. Prescriber's Role: Limited Literature
- 3.3. Prescriber vs. Pharmacology
- 3.4. Prescriber's Role: Studies
- 3.5. Prescriber's Role: Haloperidol Dosing

1. Drug Response: The Drug

1. Drug Response: The Drug

Key elements are:

- Formulation: (e.g., extended release)
- Route: (e.g., injection)
- Dose:
  - To be interpreted within each patient's context (see personalized prescribing presentation)
  - Influenced by the prescriber

2. Drug Response: The Patient

2. Drug Response: The Patient

2.1. Personal, Environmental and Genetic Factors
2.2. Pharmacodynamics and Pharmacokinetics
2.3. Efficacy and Safety
2.4. Interactions between 2.1., 2.2 and 2.3.

2.1. Personal, Environmental and Genetic Factors

2.1. Personal, Environmental and Genetic Factors

- Classification according to three types of factors is somewhat arbitrary, but serves mnemonic purposes.
- This classification is not found in any pharmacology textbook.
- This terminology is used by Dr. de Leon in his articles.

First article using it: http://www.ncbi.nlm.nih.gov/pubmed/18687938
Article explaining it: http://www.ncbi.nlm.nih.gov/pubmed/18996200 with a pdf available http://uknowledge.uky.edu/psychiatry_facpub/43/

2.1. Personal, Genetic and Environmental Factors

- Personal (obtained from personal history):
  - Gender and age
  - Race (can reflect genetic variations)
  - Medical illnesses or pregnancy
- Environmental (potentially removable):
  - Smoking
  - Co-medication
  - Herbal supplements
  - Food and beverages
- Genetics: (assessed by genetic tests):
  - Genetic variations
  - Epigenetic variations: They are poorly understood but may explain how environmental factors influence genetics.

2.1. Personal, Genetic and Environmental Factors

- Epigenetics: http://www.ncbi.nlm.nih.gov/mesh/?term=epigenetic+processes
  - A genetic process by which the adult organism is realized via mechanisms that lead to the restriction in the possible fates of cells, eventually leading to their differentiated state.
  - Mechanisms involved cause heritable changes to cells without changes to DNA sequence:
    - DNA methylation,
    - histone modification,
    - DNA replication timing,
    - nucleosome positioning, and
    - heterochromatization

    which result in selective gene expression, or repression.

In the future epigenetic tests may be available.

2.1. Personal, Environmental and Genetic Factors

2.1.1. Personal Factors: Race as Example
2.1.2. Environmental Factors: Herbal Supplements as Example
2.1.3. Genetic Factors: Focus on Genetic Variations

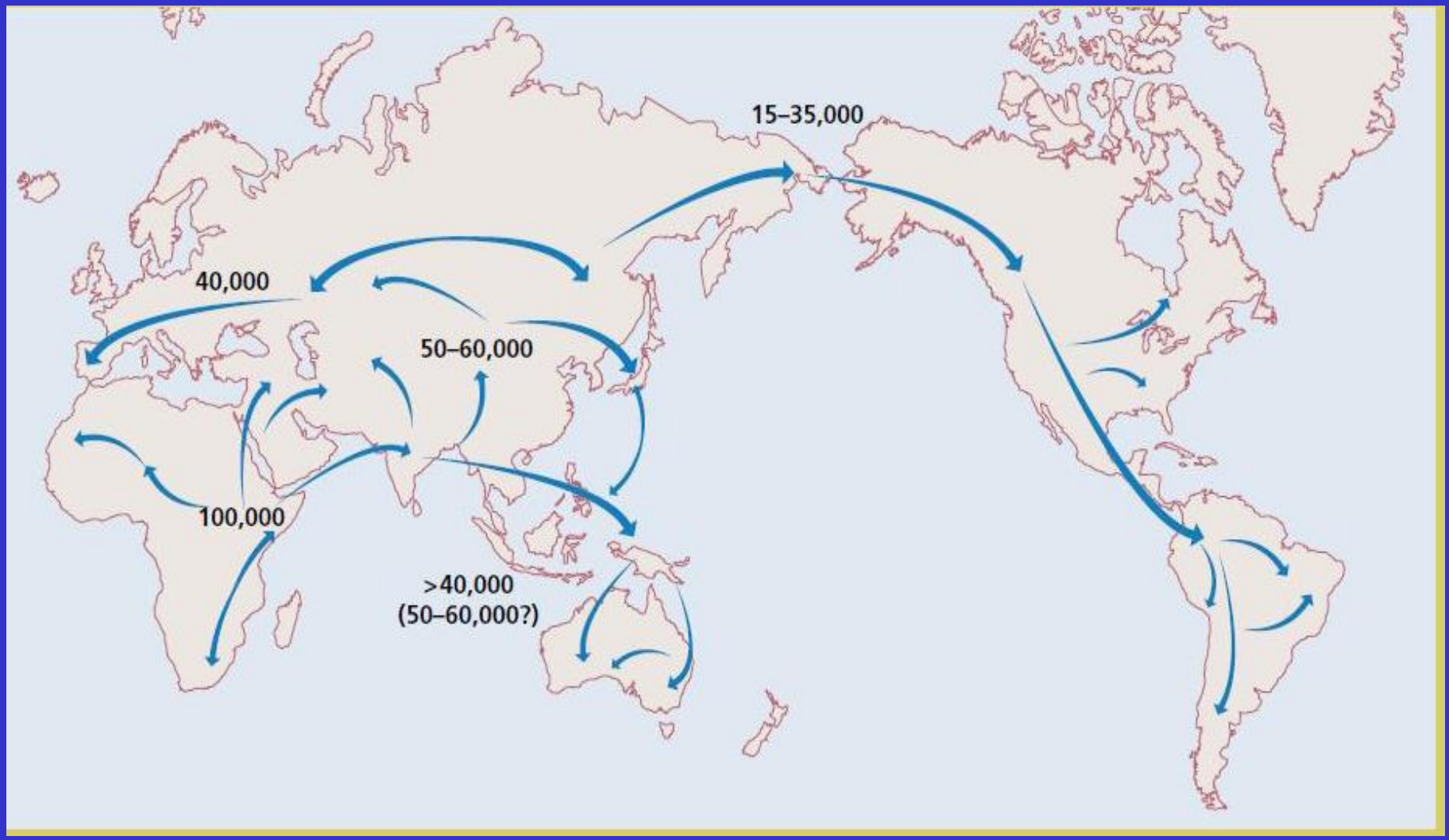
2.1.1. Race as an Example of Personal Factors

2.1.1. Personal Factors: Race

- Race is a complex concept.
- It is not easy to make distinctions between racial groups based on biology.
  http://www.bentham.org/cppm/Sample/cppm7-4/003AF.pdf
- DNA differences in various people groups in different areas of the world indicate that humans originally came from Africa.

2.1.1. Personal Factors: Race and Human Migrations

http://www.ncbi.nlm.nih.gov/pubmed/12610536

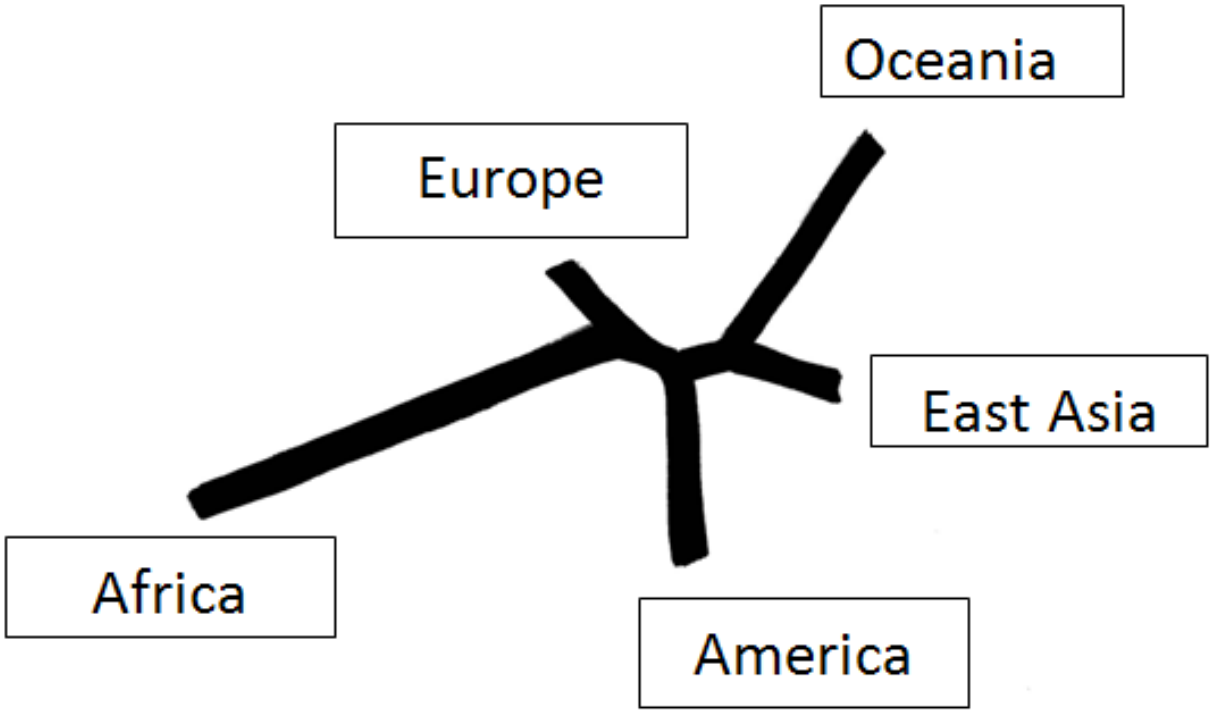


2.1.1. Personal Factors: Race

- Race can be a helpful concept in clinical practice and pharmacology if we understand its limitations.
- Genetic advances have provided some understanding of racial differences, based on the calculation of genetic distances.
- Genetic distances can be represented with trees or numbers (the usual range is 0-1).

2.1.1. Personal Factors: Race and the Genetic Tree

http://www.ncbi.nlm.nih.gov/pubmed/9223254 **Free article in PubMed**



Based on Figure 1 from that article

2.1.1. Personal Factors: Race and Genetic Distances

http://www.ncbi.nlm.nih.gov/pubmed/12493913

	Genetic distance (index range of 0-1)					
	Af	MidE	CS Asia	Eur	EastAsia	Oceania
MidE	.033					
CS Asia	.037	.008				
Eur	.040	.005	.008			
East Asia	.054	.038	.026	.038		
Oceania	.068	.059	.049	.061	.047	
America	.101	.081	.068	.079	.060	.102

Af: Africa; Eur: Europe; MidE: Middle East; CS Asia: Central and South Asia.

Based on supplementary Table 1 from that article

2.1.1. Personal Factors: Race and Individual Genes

- Trees and distances are constructed using multiple genes.
- Each gene has a different distribution within different ancestries.
- With some pharmacological genes, race can be used as a “proxy” for genes.

2.1.1. Personal Factors: Race vs. Ethnicity

- In the US, “race” classification is a very complex subject influenced by politics.
- The so-called “Caucasians” have mainly European ancestry. Genetic distances suggest these people are not very different genetically from Middle Easterners or Central Asians.
- The so-called “African Americans” usually have different percentages of African and European genes.
- The so-called “Hispanics” are NOT a racial group. This is a complex ethnic classification.

2.1.1. Personal Factors: Race vs. Hispanic Ethnicity

- To have some clue about genetics in Hispanics you need to ask about their ancestry.
- Dr. de Leon's experience with Mexican-Americans:
  - Those from Mexican rural areas are likely to have mainly American ancestry (Amerindians). As described by the map, the original American populations came from East Asian migrations to America.
  - Those from Mexican urban areas may have also various quantities of European ancestry.
- Caribbean Islanders (Cubans and Puerto Ricans) have different percentages of European, African and American ancestry. http://www.ncbi.nlm.nih.gov/pubmed/25431893

2.1.2. Herbal Supplements as an Example of Environmental Factors

2.1.2. Environmental Factors: Herbal Supplements

- The influence of herbal supplements has been neglected by physicians, but is included in the following:
  - Book:

    http://www.amazon.com/Essential-Herb-Drug-Vitamin-_Interaction-Guide-Medications/dp/0767922778/ref=sr_1_1?s=books&ie=UTF8&qid=1279572316&sr=1-1

  - Two-part review article focused on pharmacokinetic drug interactions (freely available at PubMed):

    http://www.ncbi.nlm.nih.gov/pubmed/22322396
    http://www.ncbi.nlm.nih.gov/pubmed/22565299

2.1.3. Genetic Variations

2.1.3. Genetic Factors: Genetic Variations

- The vast majority of genetic variations are thought to be neutral (they do not contribute to phenotypic variations).

http://www.ncbi.nlm.nih.gov/pubmed/19293820

- Classification according to frequency:
  - Rare.
  - Common. Polymorphisms are usually defined as those genetic variations present in at least 1% of the population.

2.1.3. Genetic Factors: Genetic Variations

Classification according to composition:

- Single nucleotide polymorphism (SNP): A single nucleotide variation in a genetic sequence that occurs at appreciable frequency in the population http://www.ncbi.nlm.nih.gov/mesh. SNPs are the most frequent and best studied genetic variations.
- Structural variants (no standard classification): http://www.ncbi.nlm.nih.gov/pubmed/19293820
  - Copy number variations (CNV): Stretches of genomic DNA that exist in different multiples between individuals. http://www.ncbi.nlm.nih.gov/mesh
  - Less common genetic variations (insertions-deletions, block substitutions and DNA sequence inversions).

2.2. Pharmacokinetics and Pharmacodynamics

2.2. Pharmacokinetics and Pharmacodynamics

- Pharmacokinetics:
  - Drug concentration (usually in blood)
  - Body to drug

- Pharmacodynamics:
  - Site of action

  (mainly brain receptors in psychiatry)
  - Drug to body

2.2. Pharmacokinetics and Pharmacodynamics

2.2.1. Pharmacokinetics

2.2.2. Pharmacodynamics

2.2.1. Pharmacokinetics

2.2.1. Pharmacokinetics

- Metabolic enzymes are the better understood components of the pharmacokinetic phases: ADME (absorption, distribution, metabolism, and excretion).
- Since the mid-1990s, drugs have been withdrawn from the market due to drug-drug interactions (DDIs) explained by the cytochrome P450 (CYP). The FDA requires metabolism studies for any new drug to be marketed.

2.2.1. Pharmacokinetics

- Metabolic enzymes:
  - Functionalizing enzymes: oxidation, reduction or hydrolysis (Phase I). cytochrome P450: CYP
  - Conjugation enzymes (Phase II). Uridine 5'- diphosphate glucuronosyltransferases (UGTs)

- Transporters:
  P-glycoprotein (P-gp)

2.2.2. Pharmacodynamics

2.2.2. Pharmacodynamics

Psychiatric drugs have actions at:

- The brain:
  - Receptors
  - Transporters

- The periphery:
  - Brain effects
  - Receptors in the periphery
  - Transporters in the periphery
  - Other (lipid metabolism?)

2.3. Efficacy and Safety

2.3. Efficacy and Safety

2.3.0. Efficacy and Safety
2.3.1. Efficacy
2.3.2. Safety

2.3.0. Efficacy and Safety

2.3.0. Efficacy and Safety

2.3.0.1. Definition

2.3.0.2. Literature

2.3.0.1. Efficacy and Safety: Definition

2.3.0.1. Efficacy and Safety: Definition

- Efficacy is how well the desired effect is obtained in the patient.
  http://www.ncbi.nlm.nih.gov/pubmed/15554250
- Safety's goal is to avoid adverse drug reactions (ADRs). Psychiatric textbooks use the old terminology "side effects" instead of ADRs.

2.3.0.2. Efficacy and Safety: Literature

2.3.0.2. Efficacy and Safety: Literature

- These terms are not used or indexed in pharmacology books but are frequently used in clinical articles.
- Some articles use the term “drug tolerability” instead of “drug safety”.
- Some articles use the term “adverse drug event” (ADE) instead of ADR.

2.3.1. Efficacy

2.3.1. Efficacy

2.3.1.1. Clinical Issues

2.3.1.2. Pharmacological Issues

2.3.1.1. Efficacy: Clinical Issues

The most important issue is the distinction between efficacy (clinical trial) and effectiveness (clinical practice).

2.3.1.1. Efficacy: Clinical Issues

- Efficacy is defined in different ways in different clinical trials.

- Acute vs. maintenance treatment
  - Acute treatment usually focuses on a decrease in symptoms on a scale.
  - Maintenance usually focuses on avoiding relapses.

2.3.1.1. Efficacy: Clinical Issues

- If you are interested in the complexity of defining response in schizophrenia trials:

  http://www.ncbi.nlm.nih.gov/pubmed/17287825

- More recently, researchers are starting to define remission and recovery criteria but clinical trials of severe mental illness, such as schizophrenia and bipolar disorder, do not usually describe them.

2.3.1.1. Efficacy vs. Effectiveness

- The literature frequently differentiates between drug efficacy and effectiveness.
- Definitions http://www.ncbi.nlm.nih.gov/pubmed/11107885:
  - Efficacy: results of a systematic intervention
  - Effectiveness: generalizability of an intervention with established efficacy: applicability and feasibility.
- They are part of a continuum:
  - Randomized placebo-controlled clinical trials study drug efficacy.
  - Pragmatic (or practical) clinical trials are better for studying drug effectiveness. http://www.ncbi.nlm.nih.gov/pubmed/15863782

2.3.1.1. Efficacy: Pharmacological Issues

The most important issue is the limited understanding of the pharmacodynamic mechanism of psychiatric drugs.

APs are used as an example.

2.3.1.2. Efficacy: Pharmacology

- Psychiatric drugs are effective for different psychiatric diagnoses.
- Pharmacological mechanisms across various diagnoses are not well-studied or understood.

2.3.1.2. Efficacy: AP Pharmacology

- All APs are approved for
  - Schizophrenia psychosis.
- Approved indications for some specific APs:
  - Bipolar disorder(mania, relapse, depression)
  - Resistant major depression
  - Irritability in children with autism.
- Off-label:
  - Dementia (psychosis & agitation): ↑ deaths
  - Drug-induced psychosis
  - Delirium
  - Tourette syndrome
  - Treatment-resistant OCD
  - Personality disorders.

2.3.1.2. Efficacy: AP Pharmacology

- Main pharmacodynamic mechanism:
  - "Antipsychotic" rather than anti-schizophrenia drugs
  - Dopamine hypothesis: blocking D_2 receptors

- It is unclear which pharmacodynamic mechanisms explain efficacy in other diagnoses.
  - The dopamine hypothesis is usually assumed for efficacy in most diagnoses.
  - For depression, are there other important receptors for efficacy? They are **hypothetical** mechanisms.

2.3.1.2. AP Efficacy in Depression

http://www.ncbi.nlm.nih.gov/pubmed/22332980

- **Hypotheses** in bipolar depression include:
  - High 5-HT_{2A}/D_2 receptor ratio
  - Role for 5-HT_{2A} or α_2 blockade

- **Hypotheses** in adjunctive treatment in major depression include:
  - 5-HT_{2A} blockade (shared by approved SGAPs).
  - 5-HT_{1A} partial agonism for aripiprazole and norquetiapine.
  - 5-$HT2_C$ antagonist and inhibition of noradrenaline transporter by norquetiapine, the main active quetiapine metabolite.

2.3.1.2. AP Efficacy in Depression

http://www.ncbi.nlm.nih.gov/pubmed/22332980

- Extreme complexity of pharmacodynamic predictions:
  - at clinical dose, ziprasidone blocks reuptake of:
    - serotonin,
    - noradrenaline, and
    - dopamine,

    which may suggest the potential for antidepressant properties.
  - The only ziprasidone trial in bipolar depression indicated that this compound had no more efficacy than placebo.

2.3.1.2. Efficacy: Class Effect

- The FDA requires each classified drug to prove its efficacy.
- Physicians tend to consider all drugs within the class as alternatives. For example, all antipsychotics block D_2 receptors and are likely to use the same pharmacodynamic mechanism. All antipsychotics have NOT been approved for mania, but it is likely that all are anti-manic agents.

2.3.2. Safety

2.3.2. Safety

2.3.2.1. Clinical Issues

2.3.2.2. Pharmacological Issues

2.3.2.1. Safety: Clinical Issues

(ADRs can be classified by frequency)

2.3.2.1. Safety: Frequency Classification

http://www.amazon.com/Practitioners-Prescribing-Antiepileptics-Intellectual-Disabilities/dp/1461420113/ref=sr_1_2?s=books&ie=UTF8&qid=1333385489&sr=1-2

Dr. de Leon likes this classification:

- Common: ≥10%, usually delineated in the package insert (unless old).
- Relatively uncommon: <10%.
- Potentially lethal: very rare but important to remember.

2.3.2.1. Safety: Clinical Definition

- Hospital pharmacies usually have a system for recording ADRs.
- They frequently use modifications of the Naranjo scale: http://www.ncbi.nlm.nih.gov/pubmed/7249508
  This scale has criteria for:
  - Definite
  - Probable
  - Possible
  - Doubtful
- New scale: Liverpool scale (better):
  http://www.ncbi.nlm.nih.gov/pubmed//22194808

2.3.2.2. Safety: Pharmacological Issues

(ADR mechanism classification is a complex area in development)

2.3.2.2. Safety: Pharmacology

- ADR mechanism classification is a complex area in development. http://www.ncbi.nlm.nih.gov/pubmed/16180936
- The first influential ADR classification:
  - Type A: predictable, common, and related to the pharmacological action of the drug
  - Type B: unpredictable, uncommon, and usually not related to the pharmacological action of the drug (idiosyncratic reactions)

2.3.2.2. Safety: Pharmacology

- Renamed later as:
  - Type A: Dose-related
  - Type B: Non-dose-related
- Some authors realized other ADRs need to be included: http://www.ncbi.nlm.nih.gov/pubmed/11081549
  - Long-term ADRs (dependence)
  - Teratogenic and carcinogenic

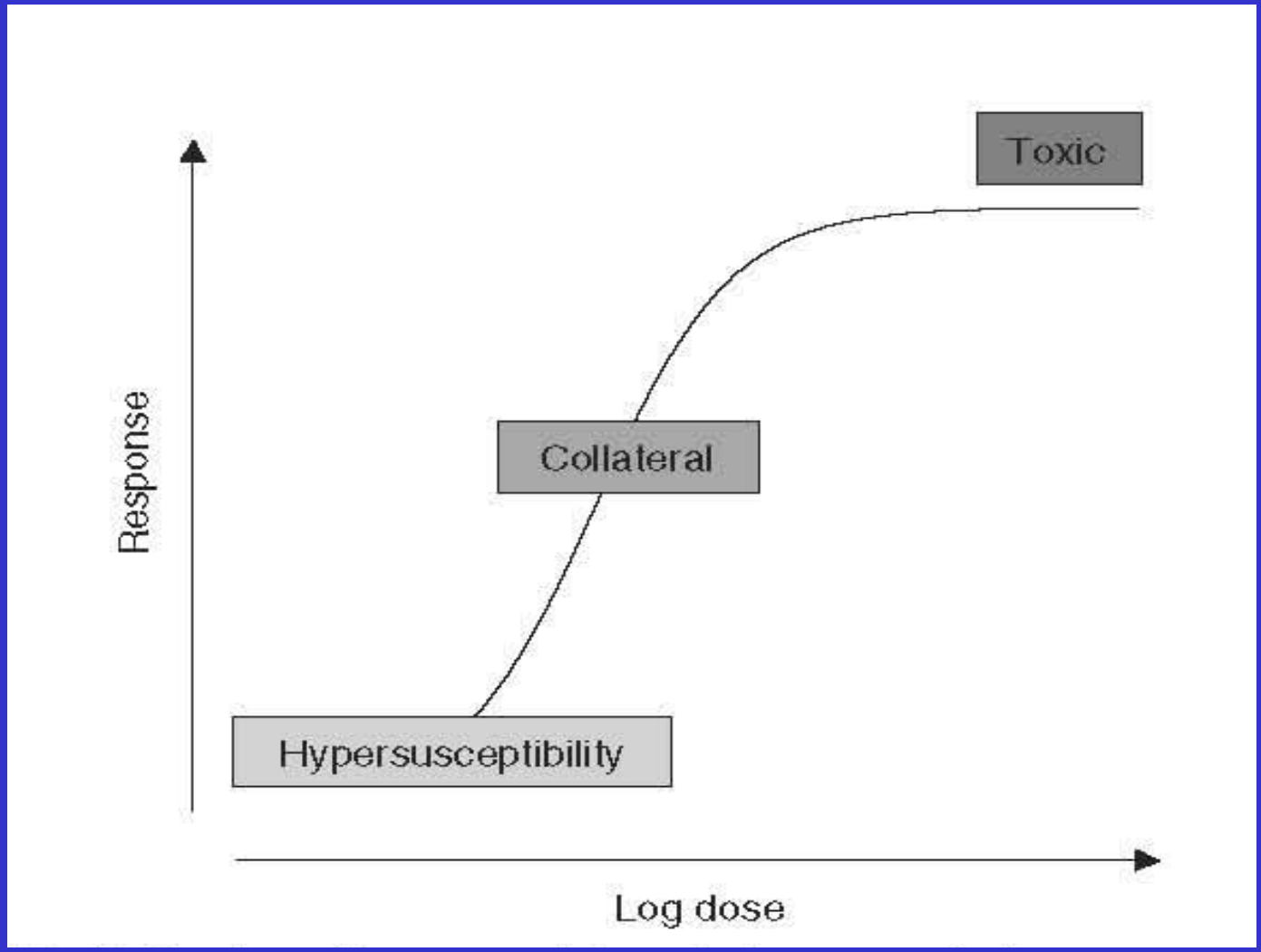
2.3.2.2. Safety: Most Recent Classification

http://www.ncbi.nlm.nih.gov/pubmed/16180936

- According to plasma concentration:
  - Toxic effects (supratherapeutic)
  - Collateral effects (therapeutic)
  - Hypersusceptibility reactions (subtherapeutic)
    (e.g., idiosyncratic and hypersensitivity)
- According to time:
  - Time-independent
  - Time-dependent (first dose-delayed)

2.3.2.2. Safety: ADRs and Concentration

http://www.ncbi.nlm.nih.gov/pubmed/16180936



2.4. Interactions

2.4. Interactions

- Dr. de Leon refers to interactions among:
  - Personal, Environmental & Genetic Factors
  - Pharmacokinetics and Pharmacodynamics
  - Efficacy and Safety
- These interactions are not discussed in textbooks.

2.4. Interactions

2.4.1. Interaction of Personal, Environmental and Genetic Factors with Other Dimensions
2.4.2. Interaction of Pharmacokinetics and Pharmacodynamics with Other Dimensions
2.4.3. Interaction of Efficacy and Safety with Other Dimensions
2.4.4. Figures Representing These Interactions
2.4.5. Interactions: Conclussion

2.4.1. Interaction of Personal, Environmental and Genetic Factors with Other Dimensions

2.4.1. Interaction of Personal, Environmental and Genetic Factors with Other Dimensions

- Personal factors can influence:
  - Pharmacokinetics and pharmacodynamics
  - Efficacy and safety
- Environmental factors can influence:
  - Pharmacokinetics and pharmacodynamics
  - Efficacy and safety
- Genetic factors can influence:
  - Pharmacokinetics and pharmacodynamics
  - Efficacy and safety

2.4.2. Interaction of Pharmacokinetics and Pharmacodynamics with Other Dimensions

2.4.2. Interaction of Pharmacokinetics and Pharmacodynamics with Other Dimensions

- Pharmacokinetics can be influenced by:
  - Personal, environmental and genetic factors

  And influence both:
  - Efficacy and safety

- Pharmacodynamics can be influenced by:
  - Personal, environmental and genetic factors

  And influence both:
  - Efficacy and safety

2.4.3. Interaction of Efficacy and Safety with Other Dimensions

2.4.3. Interaction of Efficacy and Safety with Other Dimensions

- Efficacy can be influenced by:
  - Personal, environmental and genetic factors
  - Pharmacokinetics and pharmacodynamics

- Safety can be influenced by:
  - Personal, environmental and genetic factors
  - Pharmacokinetics and pharmacodynamics

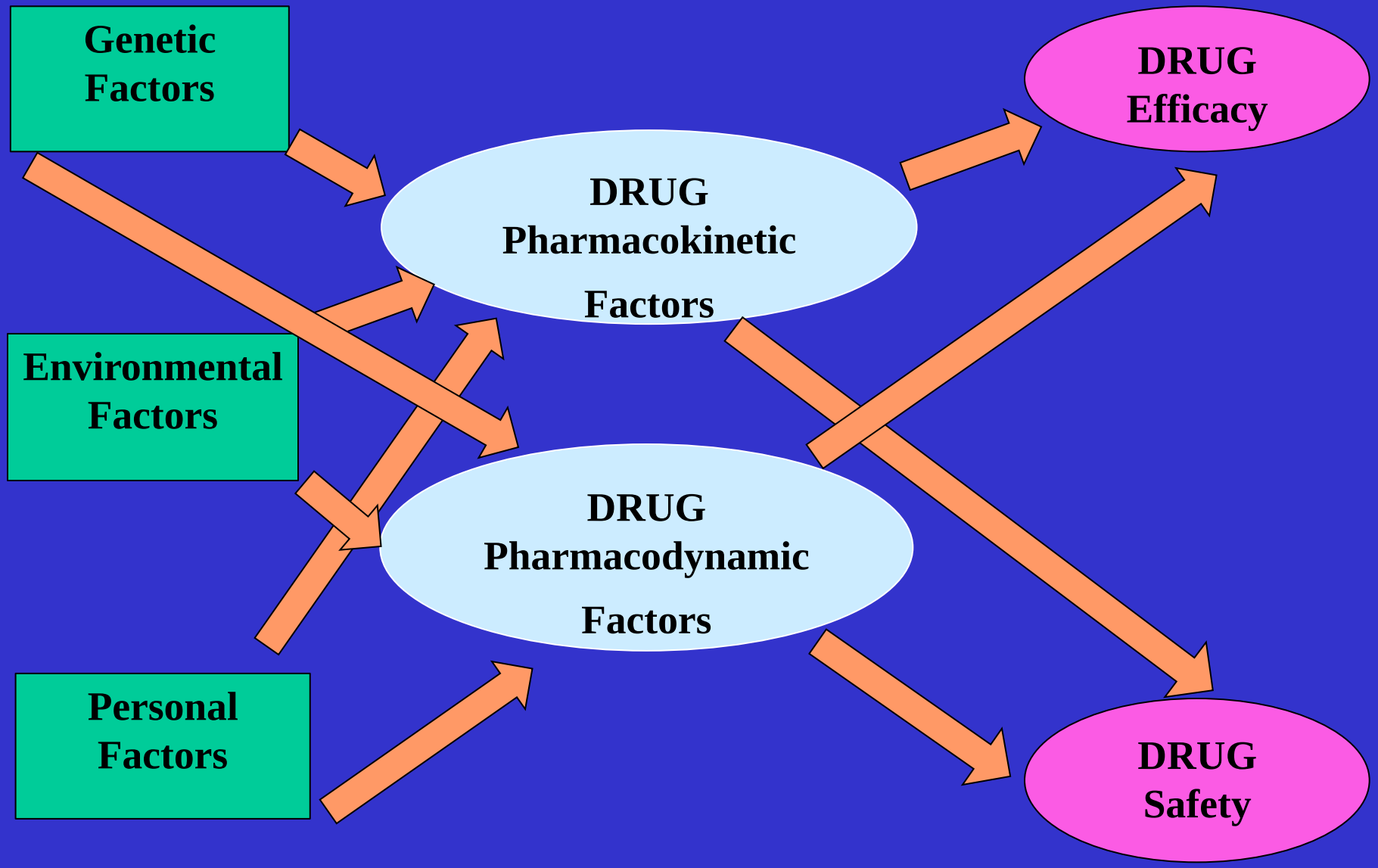
2.4.4. Figures Representing These Interactions

2.4.4. Figures Representing These Interactions

2.4.4.1. Interaction Figure to Facilitate Remembering Concepts
2.4.4.2. Interaction Figure to Represent Reality

2.4.4.1. Interaction Figure to Facilitate Remembering Concepts

2.4.4.1. Interaction Figure to Facilitate Remembering Concepts



2.4.4.2. Interaction Figure to Represent Reality

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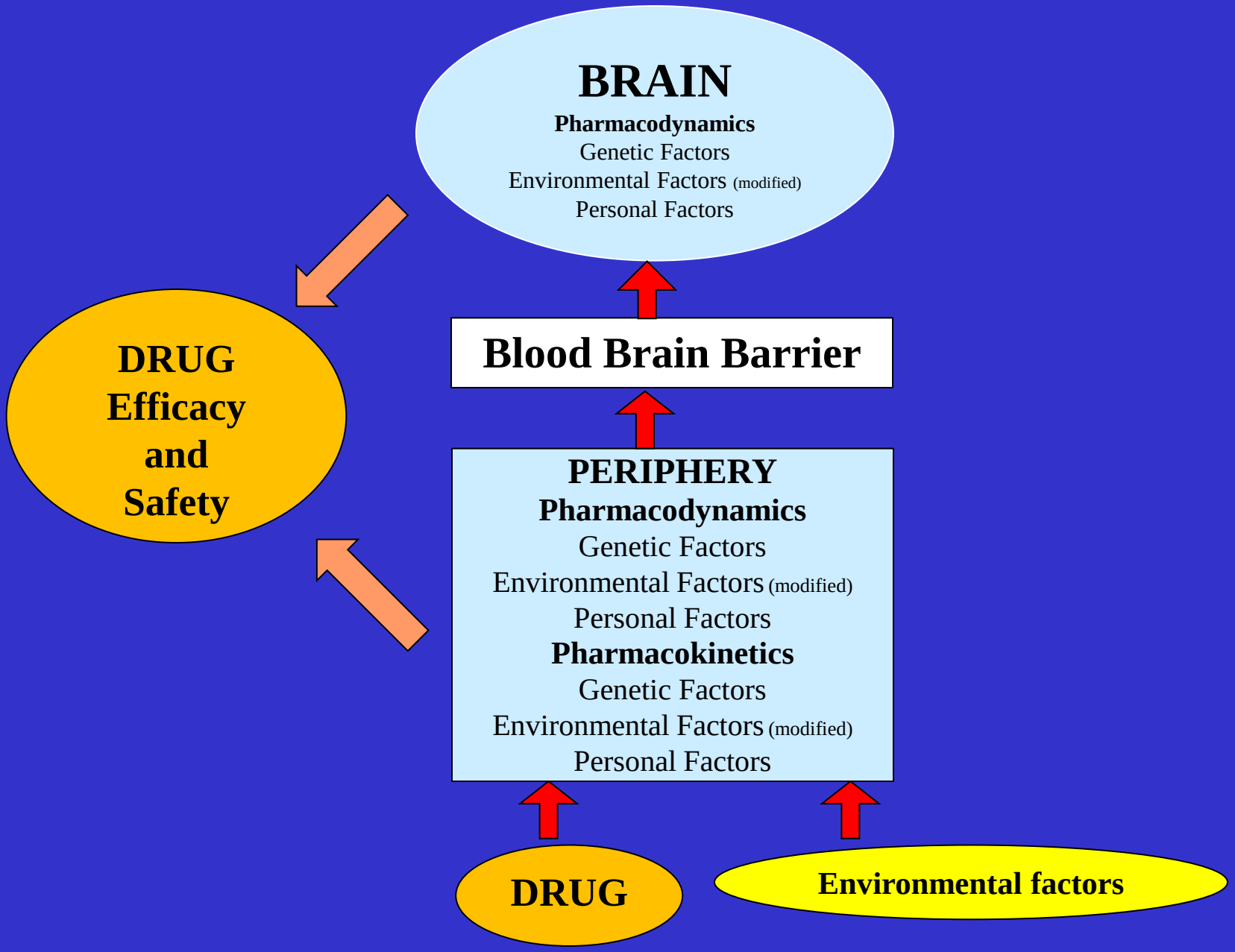

2.4.4.5. Interactions: Conclusion

2.4.4.5. Interactions: Conclusion

- Pharmacokinetics **facilitates** pharmacodynamics:
  - Sufficient drug concentration for efficacy.
  - Drug concentrations that are too high may contribute to poor safety in general.
- Pharmacodynamics determines:
  - Efficacy, when adequate drug concentration is present.
  - Safety, when concentration is sufficient for "toxicity". Specific ADRs in a patient are determined by pharmacodynamic factors.

3. Drug Response: The Prescriber

3. Drug Response: The Prescriber

This issue is usually ignored by pharmacological textbooks.

Dr. de Leon cannot ignore it because, when he supervises prescribers, some of the problems he must deal with are the results of “unusual prescribers” who are different from other prescribers.

3. Drug Response vs. The Prescriber's Role

3.1. Prescriber's Role: Definition
3.2. Prescriber's Role: Limited Literature
3.3. Prescriber vs. Pharmacology
3.4. Prescriber's Role: Studies
3.5. Prescriber's Role: Haloperidol Dosing

3.1. Prescriber's Role: Definition

3.1. Prescriber's Role: Definition

- Ideally, drugs and doses should be selected according to patient needs. This will be discussed in the presentation on personalized prescription.

- In clinical practice, the prescriber's attitudes and experiences appear to be important, too, in drug selection and dosing.

3.2. Prescriber's Role: Limited Literature

3.2. Prescriber's Role: Literature

- Clinicians frequently use doses and drug selections that differ from those recommended by guidelines or controlled studies completed by pharmaceutical companies.
- The prescriber's role has rarely been studied in psychiatry. Some old studies focused on patient racial differences. These prescribing differences are difficult to interpret unless one controls for confounding factors, including racial differences in pharmacokinetics and pharmacodynamics.

3.3. Prescriber's Role vs. Pharmacology

(Not described in textbooks,
but important in Dr. de Leon's view)

3.3. Prescriber vs. Pharmacology

- The role of the prescriber may be different for different drugs.
- The first generation of APs and antidepressants was relatively toxic (poor safety).
  APs and antidepressants more recently marketed are relatively free of toxicity (better safety) even in overdoses.
- The prescriber has
  - more "freedom" with less toxic drugs, and
  - less "freedom" with more toxic drugs.
- The effect of drug safety on dose prescribing is better described with the therapeutic window concept.

3.3. Therapeutic Window or Index

- Therapeutic window (or therapeutic index) is the dose range between ineffective and toxic:
  - Narrow: more likely to reach toxicity
  - Wide: difficult to reach toxicity

3.3. Therapeutic Window vs. Prescriber's Role

- Drugs with a narrow therapeutic window:
  - Harder to avoid toxicity
  - Prescribers are restricted by pharmacology, making it easier to use pharmacological knowledge to predict dosing.
- Drugs with a wide therapeutic window:
  - Heavily influenced by prescriber preference or biases, as pharmacological knowledge may not help in predicting dosing.

3.4. Prescriber's Role vs. Pharmacology: Studies

(Two of his studies shaped Dr. de Leon's view)

3.4. Prescriber's Role vs Pharmacology: Studies

- Two pharmacoepidemiological studies on the prescription of APs helped Dr. de Leon to develop his view on the prescriber's role vs. the therapeutic window regarding dosing in the clinical environment.
- They helped him to understand:
  - Drugs with a narrow therapeutic window do not allow for excessive dosing unless the clinician ignores ADRs.
  - The dosing of drugs with wide therapeutic windows is very much influenced by prescriber attitudes.

3.4. Prescriber's Role vs. Pharmacology: Studies

3.4.1. First Study
3.4.2. Second Study
3.4.3. Conlcusion

3.4.1. Prescriber's Role vs. Pharmacology: First Study

3.4.1. Prescriber's Role:First Study

- In a naturalistic study exploring high doses of FGAPs in 2 state hospitals:
  - Differences were found despite using a crude way of comparing doses (chlorpromazine equivalents).
  - Smoking (pharmacokinetics) and old age (pharmacokinetics & pharmacodynamics) influenced the prescription of high doses.
  - Prescribers' attitudes appeared to influence high prescription dose. Prescribers appeared to be influenced by diagnosis, drug class, chronicity, patient's race and also by "hospital culture".

http://www.ncbi.nlm.nih.gov/pubmed/12444813

3.4.2. Prescriber's Role vs. Pharmacology: Second Study

3.4.2. Prescriber's Role: Second Study

- In a naturalistic study exploring high doses of olanzapine in another state hospital:
  - Surprisingly, pharmacokinetic factors (gender and smoking), which influence plasma olanzapine levels in controlled studies, had no effect in predicting high doses.
  - Prescribers' attitudes had important effects; high doses were influenced by chronicity and personal practice. After controlling for other confounders, some prescribers appeared more prone to prescribe high doses. http://www.ncbi.nlm.nih.gov/pubmed/15323601

3.4.3. Prescriber's Role vs. Pharmacology: Conlusdion After Two Studies

3.4.3. Prescriber's Role: Conclusion

- First study:
  - Pharmacological factors were important.
  - Prescribers' attitudes were important.
  - Typical APs are relatively narrow therapeutic window drugs. In the 1980s, antipsychotic ADRs were considered "normal" and easily ignored by psychiatrists.
- Second study:
  - Pharmacological factors were NOT important.
  - Prescribers' attitudes were important.
  - Olanzapine is a wide therapeutic window drug. Metabolic ADRs are the most important ADRs for olanzapine but are more a long-term than an immediate concern.

3.5. Prescriber's Role vs. Haloperidol Dosing

3.5. Prescriber's Role: Haloperidol Dosing

- The changes in haloperidol dosing, with progressively decreased dosing from the 1980s to the 2000s, may be explained by the introduction of SGAPs.
- Haloperidol was considered a wide-therapeutic-window drug by psychiatrists in the 1980s, since they considered extrapyramidal symptoms "normal".
- Less "tolerance" of extrapyramidal symptoms by patients and prescribers after the introduction of SGAPs has converted haloperidol to a narrow-therapeutic-window drug.

3.5. Prescriber's Role: Haloperidol Dosing

- The haloperidol package insert mentions 20 mg tablets. Doses up to 15 mg/day are recommended; the statement, "To achieve prompt control, higher doses may be required in some cases" is included.

  http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?id=12785#nlm34068-7

- A tablet of 20 mg of haloperidol is equivalent to a 20 mg or 10 mg tablet of risperidone.

  http://www.amazon.com/Handbook-Psychiatric-Therapy-Hyman Arana/dp/0781774861/ref=sr_1_1?ie=UTF8&s=books&qid=1278707314&sr=1-1

Dr. de Leon doubts any current prescriber would use a 20 mg or 10 mg risperidone tablet.

3.5. Prescriber's Role: Haloperidol Dosing

- Megadoses of haloperidol were used in the 1970s and 1980s. Extrapyramidal symptoms typically started at 4-5 mg/day and increased up to 40-50 mg/day. They vanished at doses >60 mg/day.
  http://www.amazon.com/Creation-Psychopharmacology-David-Healy/dp/0674015991/ref=sr_1_1?ie=UTF8&s=books&qid=1279070126&sr=1-1
- An influential 1988 review article indicated that high doses >12 mg/day of haloperidol were not better. It noted, "Trends toward lesser overall clinical benefits of high doses may reflect untoward extrapyramidal or other central nervous system effects leading to behavioral and cognitive symptoms." http://www.ncbi.nlm.nih.gov/pubmed/2892478

3.5. Prescriber's Role: Haloperidol Dosing

- The SGAP trials frequently included haloperidol as a control. This led to a realization of the need to use lower haloperidol doses:
  - The first trials used 20-30 mg/day.
  - More recent trials used < 15 mg/day.

http://www.ncbi.nlm.nih.gov/pubmed/16848649

- A recent review article describing an international consensus recommended a target haloperidol dose of 5-10 mg/day.

http://www.ncbi.nlm.nih.gov/pubmed/20360319

Questions

-Please review the 10 questions in the pdf titled "Questions for presentation Introduction to Clinical Pharmacology".

-You will find the answers on the slide after the "Thank you" slide. No peeking until you have answered all the questions.

-If you do not answer all the questions correctly, please review the Power Point presentation one more time to reinforce the pharmacological concepts.

Thank you

Answers

1. A
2. A
3. B
4. A
5. B
6. D
7. A
8. B
9. A
10. A