Thank you
Learning Objectives

Recognize the potential for Drug response diversity among humans.
• Appreciate Gender differences exist that impact the effects of Drugs.
• Recognize and Appreciate Genetic Factors impact drug metabolism
• Recognize and Understand that Diabetes affect Patient response to Medications.
• Recognize and Appreciate that Pregnancy affect Drugs
Introduction

- Race, ethnicity, sex can contribute to inter-individual differences in drug exposure and or response, which may alter risk-benefit in certain populations.

- Inter-individual variability in drug disposition is a major cause of lack of efficacy and adverse effects of drug therapies.
The Heart of Drug Response
Varibility
Gender-based personalized Pharmacotherapy

- Male and female are prescribed the same amount of dosage even if most of the cases female require less dosage than male.
- Differences in body weight, cardiac output, plasma volume, and regional blood flow between men and women can also lead to sex differences in drug disposition.
Gender differences in Pharmacotherapy

• Sex-based differences have been found in four pharmacokinetic areas: absorption, distribution, metabolism, and elimination. Among these parameters, sex differences in metabolism are believed to be the major cause of differential pharmacokinetics between men and women.
Gender differences in Pharmacotherapy

- A well-known example is the faster alcohol absorption in women than in men.
- Since women have slower gastric motility and intestinal transit than men, they may need to wait longer between food consumption and medication if a drug is to be taken on an empty stomach.
Gender-based differences in Pharmacotherapy

- Compared to men, women have a higher percentage of body fat but lower body water content, which can affect the volume of distribution (Vd) of certain drugs. For lipophilic drugs such as opioids and benzodiazepines, the Vd is usually higher in women.

- Conversely, Vd for water-soluble drugs such as muscle relaxants is lower in women, leading to a higher initial plasma concentration.
Gender-based differences in Pharmacotherapy

• Both renal blood flow and glomerular filtration rate (GFR) are higher in men than in women. Therefore, women show a slower clearance of drugs that are actively eliminated via the kidney. Examples of these drugs include digoxin, methotrexate, gabapentin, and pregabalin.
Cytochrome P450 Enzymes
Drug-Variation Mechanisms

• It is important to remember that even if a drug is not metabolized by a specific CYP enzyme, it can affect the metabolism of other drugs through that pathway.

• Drug interaction potential is recognized as an important consideration in the evaluation of a new molecular entity.
Gender-based differences in Metabolism
Pharmacogenomics

- The terms pharmacogenomics and pharmacogenetics tend to be used interchangeably, and a precise, consensus definition of either remains elusive.
- Pharmacogenetics is generally regarded as the study or clinical testing of genetic variation that gives rise to differing response to drugs.
- Pharmacogenomics is the broader application of genomic technologies to new drug discovery and further characterization of older drugs.
Personalized Medicine

- There is an emerging goal among ‘translational scientists’ to make medical practice more personalized.

- Pharmacogenetics is an important step towards that goal.

- The effects of this movement are seen in many aspects of society.
Your DNA Affects Your Response to Drugs

DNA Test

Safe, effective

Safe, not effective

Unsafe, not effective

Unsafe, effective
Warfarin: A dosage story

- Most widely used anticoagulant in the world
  - A “blood thinner”
- Prescribed doses vary widely (1-40mg / daily)
- Therapeutic index is very low
  - High risk of bleeding early in treatment
- Two genes involved in metabolism: CYP2C9 and VKORC1
Drug-Drug Interactions (Warfarin)

- Sulfamethoxazole/trimethoprim and fluconazole inhibit the metabolism of warfarin (CYP2C9) and clearance causing hypoprothrombinemia.
- Azithromycin inhibits warfarin metabolism and elevates INRs (mechanism unknown)
- Ciprofloxacin, Clarithromycin, Erythromycin, Metronidazole all increase effect of warfarin.
- Research on the role of infection and other sources of inflammation to inhibit warfarin metabolism and increase INR values.
Opioid Analgesics and Pharmacogenetics

Narcotic analgesics are widely used for the treatment of severe pain, especially cancer pain. Morphine and other mu-opioid agonists are among the most commonly prescribed narcotic analgesics for moderate to severe pain.

There is great variation in human response to opioid analgesia. This variation could be explained by genetic variation in metabolizing enzymes and transporters mediating opioid pharmacokinetics as well as by genetic variation in receptors and signal transduction elements mediating pharmacodynamics.
Opioid Analgesics and Pharmacogenetics

Many genes have been studied to identify pharmacogenomic markers in opioid therapy, including genes implicated in the pharmacodynamics (OPRM1, COMT) and pharmacokinetics (CYP2D6, CYP3A4/5, ABCB1) of opioids.

Opioids are heavily used in the treatment of patients with cancer-related pain, and individual genetic variation affects the pharmacokinetics and pharmacodynamics of opioids. The evidence linking commonly used opioids has been reviewed for patients with cancer and the genetic variants reported to modulate response and results.
Undoubtedly, the application of personalized medicine is anticipated to improve treatment efficacy and safety. Pharmacogenomics may be a critical pathway to personalized medicine. Current evidence suggests that pharmacogenomics contribute to variation in efficacy and safety of opioids. However, most data come from case control studies and case reports. In addition, a recognized drawback in the field of pharmacogenomics is the common occurrence of false positive association between polymorphisms and the investigated outcome. Prospective studies are needed to further elucidate the clinical implications of available data as well as to define the guidelines for the clinical application of pharmacogenomic data.
Smoking and Drug Interactions

Clinical Base Literature

Cigarettes are Drugs
Tobacco and Drug Interactions (Cigarette Smoking)

- Hydrocodone/APAP - Decrease effect
- Oxycodone/APAP - Decrease effect
- Codeine/APAP - Decrease analgesic effect
- Propoxyphene/APAP - Increase doses needed because decrease analgesic effect.
- Lantus Insulin - Decrease Absorption
- Warfarin - Increased Clearance
Alcohol and Drug Interactions

- Alcohol is pharmacologically classified as a central nervous depressant.
- A drug interaction may occur when an individual combines depressant-type medications, such as tranquilizers or narcotic pain killers.
- Opioids and alcohol enhances the sedative effects of both substances, increasing the risk of death from overdose.
Alcohol and Drug Interactions

• Metronidazole inhibits alcohol dehydrogenase; causes severe alcohol intoxication reaction.

• Flushing, syncope, nausea, vomiting, chest pain, headache, tachycardia, anxiety, confusion.

• Avoid alcohol
**Figure 2**—Usually, one of the defenses stops the drug interaction before it can produce an adverse consequence. In this case, the patient's pharmacogenetic makeup protects against an adverse event. ADR = adverse drug reaction.

**Figure 3**—Sometimes "the holes line up," and the hazard arrow can penetrate each of the defenses unimpeded. Each defense also has other holes, which are called latent failures. These are gaps in the defenses that are not involved in the interaction between Drug A and Drug B, but rather would come into play with other drug interactions. As such, they are accidents waiting to happen. ADR = adverse drug reaction.
Diabetes Mellitus and affects on Medications

• Gastric emptying is frequently abnormal in patients with long-standing type 1 and type 2 diabetes mellitus.

• The degree of binding to plasma proteins is an important determinant of drug disposition and response. Non-enzymatic glycation of albumin produces conformational changes in the structure of albumin, which can increase the free fraction of acidic drugs like aspirin, penicillin and phenytoin in patients with type 1 and type 2 diabetes.
Diabetes Mellitus and affects on Medications

- Building on the assertion centered on the direct relationship between diabetes mellitus and obesity, the effect of obesity on cytochrome P450 appears to be isozyme-specific with the activity of cytochrome P450 3A4 decreasing. The clearance of cytochrome P450 (CYP) 3A4 substrates is lower in obese patients in comparison with non-obese patients. Conversely, researchers saw trends indicating higher clearance values via the following cytochrome P450 isoenzymes: CYP1A2, CYP2C9, CYP2C19 and CYP2D6.

- Researchers have observed experimentally that there is a decrease in protein levels and enzymatic activity of CYP450 3A4 in the presence of diabetes mellitus. CYP3A4 is the most abundantly expressed drug metabolizing enzyme in humans and is responsible for the breakdown of sedatives such as midazolam (Versed, Roche), triazolam (Halcion, Pfizer) and diazepam (Valium, Roche); the antidepressives amitriptyline (Elavil, Merck) and imipramine; the antiarrhythmics amiodarone (Cordarone, Sanofi Aventis), quinidine (Watson Pharmaceuticals), propafenone (Rythmol, GlaxoSmithKline) and disopyramide (Norpace, Pfizer); the antihistamines terfenadine, astemizole and loratadine (Claritin, Schering Plough); calcium channel antagonists such as diltiazem and nifedipine; and various antimicrobials and protease inhibitors.
Diabetes Mellitus and affects on Medications

Initially, diabetes mellitus causes microvascular and macrovascular changes that lead to hyperfiltration and an increased glomerular filtration rate.

As kidney dysfunction progresses, the renal excretion of the parent drug and/or its metabolites will be impaired, leading to their excessive accumulation in the body.
St John’s wort

- Many drug-drug interactions via induction of CYP 450 enzymes
- P-glycoprotein (PgP): involved in multidrug resistance, acts as a pump to remove drugs from cells
  - SJW induces; thus removes drugs from cells
  - Also regulates MDR-1 (multidrug resistance gene) and other drug transporters
Physiological Changes Occur during Gestation to affect Drug Plasma Concentrations

- Increases in plasma volume and increases in extracellular fluid space may alter a drug’s volume of distribution.
- Regional blood flow changes as noted with increased cardiac output and increased blood flow to uterine, renal, skin, and mammary tissue.
- Compensated respiratory alkalosis with a lowered partial pressure of carbon dioxide.
- Prolonged gastric evacuation occurs, and a decrease in plasma albumin.
- Noted liver cytochrome isoenzyme activity.
- Increase in renal blood flow and ↑ GFR.
**General Considerations**

- Almost all drugs cross the placenta to some extent.
- Majority of drugs have not been associated with adverse effects when taken during pregnancy.
- Weigh therapeutic benefits of drug to mother against its risk potential to developing fetus.
Transplacental Drug Passage to the Fetus

- Most drugs cross the placenta by mechanism of simple diffusion.
- Only a few drugs such as insulin, glucagon, and heparin have a high molecular weight which fails to cross the placenta to any significant degree ( > 1000 daltons).
- The drugs that cross the placenta usually reach fetal levels that are 50% to 100% of maternal serum levels.
- Disease states such as diabetes mellitus and toxemia of pregnancy can significantly alter the permeability of the placental membrane.
Adverse Effects of Drug Use in Pregnancy

- Spontaneous abortion
- Fetal growth retardation
- Teratogenicity
- Direct drug toxicity
- Neonatal drug withdrawal
- Long term effects on neurobehavioral development
- Carcinogenesis
Contraindicated Medications in Lactation

- Dicyclomine
- Dronedarone
- Fenofibrate
- Ketorolac
- Methimazole
- Methotrexate
- Statins
Clinical Coping

- Counteract “the idea that all drugs act the same in all patients” assist the Podiatric Physician with the following:
  - Open and nonjudgmental discussions with patients
  - Follow up pharmacogenetic use found in case histories
  - Explain importance of potential interactions
- **Avoid St John’s Wort and Warfarin Interactions**
- Be watchful for patients on complicated medical regimens. Be watchful and facilitate conversations about differences of drugs within individual patients within the scope of the Podiatric Assistant.
References

References

