Pharmacogenetics in Psychiatric Disorders

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CE Information and Disclosure

- James J. Hunt is a Clinical Pharmacist at Terry Reilly Health Services
- He "declares no conflicts of interest, real or apparent, and no other financial interests in any company, product, or service mentioned in this program, including grants, employment, gifts, stock holdings, and honoraria"

Objectives

- Define pharmacogenetic terms and concepts
- Describe how genetic variations of liver enzymes can affect response to specific medications
- Understand the differences of kinetic and dynamic aspects of drug response
- Explain the role of the Clinical Pharmacogenetics Implementation Consortium (CPIC)
- Describe progress toward gathering and utilizing pharmacogenetic findings in routine clinical care

Genome Project

- 2003 - The Human Genome Project
  - Exciting in both scientific and lay communities
- Helped revolutionize our understanding of genetic variability and its contribution to health and disease

Collins et al. The Human Genome Project (2003)

Origins of Understanding

- Pharmacogenetics didn't start with the human genome project
- Its origins began in the early twentieth century
  - Archibald Garrod, a British physician, first suggested differences in drug action may be influenced by genetic variants
- Coined the term "Inborn Errors of Metabolism"
  - Published in 1923
    - Described how defective enzymes can lead to clinical effects from the buildup of internal or external substances

Garrod, Inborn Errors of Metabolism (1923)

First Understood Applications

- The first examples of genetic variability in drug response were profound
  - Succinylcholine-induced paralysis in patients with a deficiency of a cholinesterase enzyme
  - Isoniazid-induced hepatotoxicity in patients with N-acetylation deficiency
  - Primaquine-induced hemolytic anemia with glucose-6 phosphate dehydrogenase deficiency among blacks in the South Pacific during World War II
- These discoveries quickly illustrated that genetic variability can lead to important differences in how drugs affect the human body

Roden et al, Pharmacogenomics: the genetics of variable drug responses (2011)

What's in a Name?

- Pharmacogenetics:
  - the effect of a *single* gene on drug response
    - i.e. the effect of *CYP2C19* gene variability on the metabolism of Clopidogrel to its active metabolite
- Pharmacogenomics:
  - refers to the effects of *many* genes on a patient's response to treatment
- These terms are often used interchangeably
  - Most clinicians find either term acceptable

Personalized Medicine

- Pharmacogenetics and pharmacogenomics are both often used in conjunction with an approach to patient care referred to as **personalized medicine**
  - precision medicine
  - individualized therapy

"emerging practice of medicine that uses an individual's genetic profile to guide decisions made in regard to the prevention, diagnosis, and treatment of disease"

U.S. National Library of Medicine (2014).

Different, Yet the Same

- Pharmacogenetics, Pharmacogenomics, Personalized Medicine, Precision Medicine, Individualized Therapy…

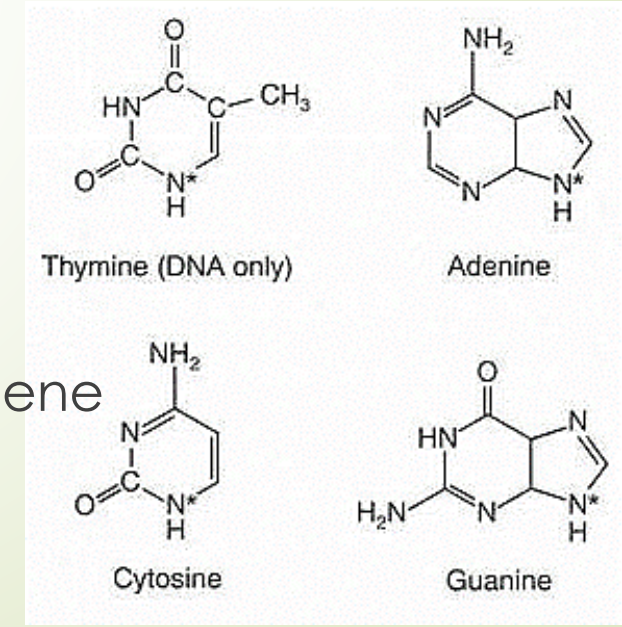
…all reflect an approach to drug therapy that accounts for unique genetic variability in a patient's response to medications

How would you describe pharmacogenetics?

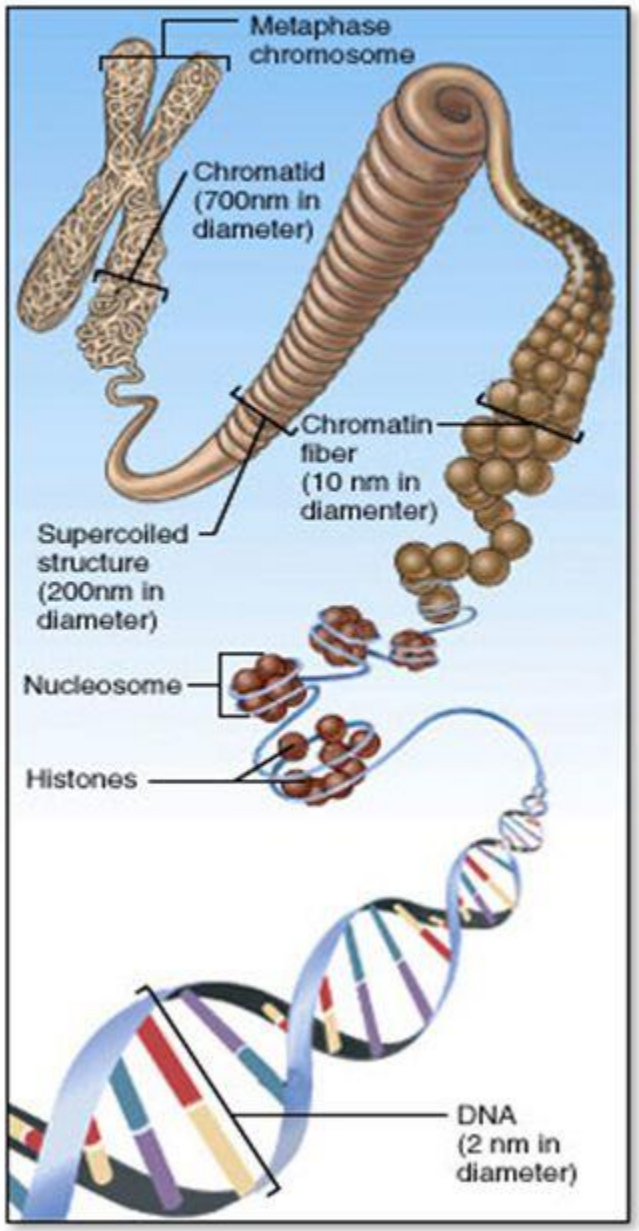
a) Pharmacogenetics started in 2003 with the completion of the Human Genome Project
b) Pharmacogenetics refers to the effect of a single gene on a response to a single drug
c) Pharmacogenetics refers to the effect of multiple genes on a response to a single drug
d) Pharmacogenetics is not making any progress in improving patient care

Science of Genetics

- Nucleated cells house genetic information
  - 46 chromosomes
    - 50% from Mom, 50% from Dad
  - Chromosomes made up of **D**eoxyribo**N**ucleic **A**cid
    - Thymine (T)
    - Cytosine (C)
    - Adenine (A)
    - Guanine (G)
  - Organized into units called gene



DNA



- **Deoxyribose nucleic acid** → type of nucleic acid
- **DNA function**
  - to hold genetic code
  - **Genetic code** = genetic instructions to make proteins
- DNA is found in **nucleus** of **eukaryotic** cells

Bases:

Adenine	Guanine
Thymine	Cytosine

Similarity in Diversity

- 3 billion base pairs in the human genome
- 99.6% are identical between any two people
  - ~ 24 million base pairs differentiate us from each other
    - variation/diversity occurs
  - Categories of genomic variation
    1. Polymorphism in one nucleotide (SNPs)
    2. Insertion/deletion of genetic info into a sequence of nucleotides
    3. Structural rearrangements (reshuffle) of DNA sequence

Kidd et al. Mapping and sequencing of structural variation from eight human genomes (2008)
Feero et al. Genomic medicine (2010)

Commonly Used Genetic Terms

Term	Definition
Gene	The basic physical unit of heredity
Chromosome	A structure inside a cell that contains genetic material in the nucleus of the cell
Single nucleotide polymorphism (SNP)	**A singe nucleotide change of a genetic sequence (e.g. G being replaced by C)**
Insertion mutation	An addition of a single or multiple base pairs to a genetic sequence
Deletion mutation	A loss of a single or multiple base pairs from a genetic sequence
Genotype	**The genetic makeup of an individual**
Phenotype	**Observable characteristics of the genotype (e.g. hair color)**
Allele	A version of a genetic sequence at a specific place in the genome
Star allele nomenclature	Signified as gene symbol, * allele number/*allele number (e.g. *CYP2C19**1/*2)
Basic allele nomenclature	Signified as gene symbol, position of polymorphism, allele/allele (e.g. *CYP2C19* 681 G/A)

What is a phenotype?

a) The genetic makeup of an individual
b) Observable characteristics of an individual
c) One version of a genetic sequence in a specific location of the genome
d) The basic physical unit of heredity

Pharmacokinetics vs. Pharmacodynamics

- Pharmacokinetics
  "*what the body does to the drug*"
  - absorption, distribution, metabolism, and excretion
- Pharmacodynamics
  "*what the drug does to the body*"
  - relationship between a drug's concentration, site of action, and its resultant clinical effects

U.S. Food and Drug Administration (2013)
Bier et al, Pharmacogenetics: Has the time come for pharmacists to embrace and implement the science? (2013)

Pharmacokinetics

- Pharmacokinetic variations are generally easier to characterize than pharmacodynamics
  - >80% of drugs are metabolized by the liver
    - Directly affected by pharmacokinetic variability
- Drug-metabolizing enzymes that are commonly influenced by genetic variations
  - CYP2C19, CYP2D6, and CYP2C9
- Patients are referred to as being:
  - Ultra-rapid metabolizers
  - Extensive or normal metabolizers
  - Intermediate metabolizers
  - Poor metabolizers

Bier et al, Pharmacogenetics: Has the time come for pharmacists to embrace and implement the science? (2013)

Pharmacodynamics

Effects of genetic variations on the pharmacodynamics of a drug ***involve more complex interactions*** at the level of receptors, enzymes, or signaling proteins, which make them ***more difficult to detect***

U.S. Food and Drug Administration (2013)
Bier et al, Pharmacogenetics: Has the time come for pharmacists to embrace and implement the science? (2013)

Pharmacokinetics/dynamics do not occur in a vacuum

- A well-documented example is Warfarin (Coumadin ®)
  - Pharmacodynamic characteristics
    - Driven by genetic variations in warfarin's target site
      - Vitamin K epoxide reductase complex (*VKORC1*)
  - Pharmacokinetic characteristics
    - Driven by genetic variation with metabolizing enzymes
      - CYP2C9

Kinetics or Dynamics?

Which of the following is an example of genetic variation influencing the pharmacodynamic properties of a drug?

a) CYP3A4
b) CYP2D6
c) VKORC1
d) CYP2C19

Moving Toward Application

- Clinical Pharmacogenetics Implementation Consortium guidelines (CPIC)
  - Available through the Pharmacogenomics Knowledgebase (PharmGKB)
    - www.pharmgkb.org
- FDA-approved drug labeling
  - Available on drug package inserts
    - 100+ drugs include pharmacogenetic information
    - https://www.fda.gov/drugs/science-research-drugs/table-pharmacogenomic-biomarkers-drug-labeling

Clinical Pharmacogenetics Implementation Consortium (CPIC)

- Founded in 2009
- Guide clinical pharmacogenetics
  - Evidence-based guidelines
    - Peer-reviewed, updated, evidence based, freely accessible guidelines for gene/drug pairs
    - Clinical recommendations on *HOW to use* genetic information, rather than *WHETHER* genetic testing should be ordered
      - Constantly being updated and expanding as our understanding of pharmacogenetics grows

FDA-Approved Drug Labels

- Driven by evidence of the impact of pharmacogenetics on drug efficacy and toxicity
  - Most do NOT mandate genetic testing prior to prescribing or dispensing
    - Demonstrates recognition of pharmacogenetic impact
  - Categorized as:
    - Required
    - Recommended
    - Actionable
    - Informative

Drugs with FDA "Required" Pharmacogenetics Testing

- Cetuximab (Erbitux)
  - patients are unlikely to respond with a mutated form of the KRAS gene
- Trastuzumab (Herceptin)
  - treatment mainly benefits patients with HER2 protein expression
- Maraviroc (Selzentry)
  - indicated only for CCR5-tropic HIV-1 infection
- Dasatinib (Sprycel)
  - for adults with Philadelphia chromosome-positive chronic myeloid leukemia or acute lymphoblastic leukemia

Clopidogrel – *CYP2C19* example

- A prodrug that irreversibly inhibits platelet activity after a two-step bio-activation process mediated largely by CYP2C19
- Genetic variation in the gene that codes for this enzyme contributes to observed differences in antiplatelet activity
  - (*2/*2) poor
  - (*1/*2) intermediate
  - (*1/*1) extensive *"NORMAL or wild-type"*
  - (*1/*17 or *17/*17) ultra-rapid

Scott et al, Clinical Pharmacogenetics Implementation Consortium (2011),
Product info for Plavix (2013),
Mega et al. Reduced0function CYP2C19 genotype (2010)

CYP2C19 Testing *Not* Applied in General Consensus or Gold Standards

- American Heart Association/American College of Cardiology (AHA/ACC)
  - Recommends *against routine* genetic testing
- CPIC guidelines
  - Recommends genotyping in high-risk patients undergoing percutaneous coronary intervention (PCI)
- Some institutions are more broadly incorporating CYP2C19 genetic testing

Challenges with FDA Labeling

- Unfortunately, FDA pharmacogenetic labeling has not helped in the way intended
- A lot of information has been added that was not based on good science about outcomes research
  - Predicting blood levels or another surrogate marker is one thing
  - It is yet another thing to show that the information can be used to improve outcomes for patients

Boehringer et al, Pharmacogenetics (2015)

Thiopurines and TPMT Example

- Thiopurine methyltransferase (TPMT) enzyme inactivates these drugs
- Variant alleles decrease TPMT activity
  - 89% have normal activity
  - 10% have intermediate activity
    - 35% risk of toxicity
  - 0.33% (1/300) have low or deficient activity
    - Nearly all will experience toxicities
- Decreased TPMT activity leads to accumulation and increased risks of toxicities

Budhiraja et al. Azathioprine-related myelosuppression (2011)
Hosni-Ahmed et al, Thiopurine methyltransferase predicts the extend of cytotoxicity (2011)

TPMT Screening Recommend in Consensus and Guidelines

- CPIC guidelines
  - Evidence-based algorithm for genotype-guided dose reductions
- Pediatric Acute Lymphoblastic Leukemia (ALL)
  - Guidelines recommend genetic testing
- St. Jude Children's Research Hospital
- Children's Oncology Group (COG)

Warfarin: *CYP2C9, VKORC1* Example

- CYP2C9 inactivates warfarin's S-enantiomer
  - 30^{+} variants with different frequencies by ethnicity
    - Variants associated in increased risk of bleeding
- VKORC1 converts vitamin K epoxide in the clotting cascade
  - Warfarin inhibits this process
    - Variants increase or decrease warfarin sensitivity/effect

Bleed risk vs Clot risk

Johnson et al. CPIC Guidelines for CYP2C9 and VKORC1 genotypes and warfarin dosing (2011)

Significant Genetic Information Limited Practice Application

- 2007 genetic info added to package insert
  - 2010 quick reference dosing guide added
- American College of Chest Physicians
  - Recommend *against routine* genetic testing
    - Limited randomized/controlled trials
- CPIC provides interpretation and dosing guide
- Some health systems provide warfarin pharmacogenetics service

Johnson et al. CPIC Guidelines for CYP2C9 and VKORC1 genotypes and warfarin dosing (2011)

What is the role of CPIC guidelines in clinical implementation of pharmacogenetics?

a) To help determine which medications require pharmacogenetic testing
b) To help identify which pharmacogenetic tests are needed for specific patients
c) To provide guidance on the appropriate timing for pharmacogenetic tests
d) To support the translation of pharmacogenetic knowledge into clinical practice

Potential Benefits of Genetic Testing

- 100+ drugs with FDA-labeled genetic info
- 70% of Americans take at least one drug
  - 50% take two or more
- Increased adherence
  - Patient buy-in, need/efficacy, side effects

U.S. Food and Drug Administration (2014)
Patterson et al. Prospective-retrospective biomarker analysis for regulatory consideration (2011)
Brandwaite et al, The role of medication adherence in the U.S. health care system (2013)
Hagg et al, The potential impact of pharmacogenetic testing on medication adherence (2013)
Charland et al, Providing patients with pharmacogenetic test results affects adherence to statin therapy (2013)

Positive Effects of Genotyping

- Enhance therapeutic drug monitoring (TDM)
  - Less "trial and error"
  - Buccal/saliva sample
  - Applied to multiple drugs
  - Lifetime consistency
  - Results not affected by interacting drugs/diseases
  - Specific knowledge of conditions not needed to interpret results

Crews et al, Development and implementation of a pharmacist-managed clinical pharmacogenetics service (2011)
Ensom et al, Pharmacogenetics: the therapeutic drug monitoring of the future? (2001)

Five Rights of Medication Use

1. Right Patient
2. Right Drug
3. Right Time
4. Right Dose
5. Right Route

Pharmacogenetics may provide another piece of information to maximize these rights

Grissinger, The five rights, NCBI

Challenges of Implementing Pharmacogenetics In Practice

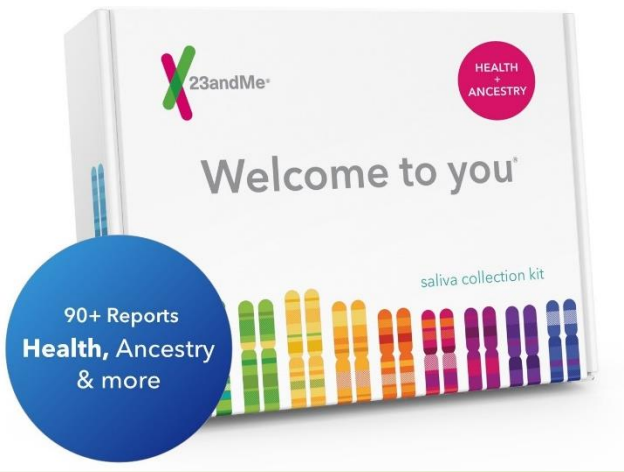
- Gaps in Knowledge
  - Relatively new knowledge
    - Clinical benefits not universally clear
    - Health professions education systems
      - Expanding, but not universally addressed
- Gaps in Resources
  - Genome project ~$3 billion
    - Recent systems ~ $1,000
    - Not universally covered
    - Organizational costs

Ethical, Legal, Social Dilemmas

- Rationing of health care resources
- Widening health disparities
  - Large poverty-stricken populations
- Stigmatization
- Discrimination
- Privacy
  - HIPAA, GINA

Dressler, Integrating personalized genomic medicine into routine clinical care (2013)
GINA (2008)

Home Genetic Tests



- i.e. (23andMe)
  - Paving the way for home genetic tests
    - Gene markers linked to celiac disease, Parkinson's, Alzheimer's, breast cancer
      - NOT pharmacogenetic testing – not designed for tailoring drug/doses based on patient's genes
  - No proof of improved outcomes
  - High false-positive rate
  - May not cover all genetic markers
  - Cost of test, cost of unneeded care
  - Use/storage of data
  - Doesn't give "yes" or "no" about related health risks
  - Lifestyle, family history, environment play a role

Set Patient Expectations for Home Genetic Tests, Pharmacist Letter, 2018

More Complex than A Stoplight

- Red – Significant gene-drug interaction
- Yellow – Moderate gene-drug interaction
- Green – Use as directed

Reporting system can be misleading…

- Laboratory results, imaging studies, professional consultations…
  …information provided must be considered in context, by a professional

DelBello, et al. Pharmacogenetics in Psychiatry: Misconceptions, Challenges, and Successes (2017)

GeneSight® Psychotropic
COMBINATORIAL PHARMACOGENOMIC TEST

genesight

Patient, Sample
DOB: 7/22/1984
Order Number: 9904
Report Date: 4/1/2019
Clinician: Sample Clinician
Reference: 1456CIP

Questions? Call 855.891.9415 or email medinfo@genesight.com

ANTIPSYCHOTICS

USE AS DIRECTED
asenapine (Saphris®)
cariprazine (Vraylar®)
lurasidone (Latuda®)
paliperidone (Invega®)
thiothixene (Navane®)
ziprasidone (Geodon®)

MODERATE GENE-DRUG INTERACTION	
fluphenazine (Prolixin®)	1
olanzapine (Zyprexa®)	1
quetiapine (Seroquel®)	1
clozapine (Clozaril®)	1,8
haloperidol (Haldol®)	1,8

SIGNIFICANT GENE-DRUG INTERACTION	
chlorpromazine (Thorazine®)	1,6
aripiprazole (Abilify®)	1,6,8
brexpiprazole (Rexulti®)	1,6,8
iloperidone (Fanapt®)	1,6,8
perphenazine (Trilafon®)	1,6,8
risperidone (Risperdal®)	1,6,8
thioridazine (Mellaril®)	1,6,9

Does Pharmacogenetic Testing Make Sense?

- Promoted for a laundry list of meds
  - Not ready for prime time in most cases
- "Drug-Gene" interactions, similar to "Drug-Drug" interactions are one piece of the puzzle
- For most patients…
  - Limited proof testing improves outcomes, reduces adverse effects, or is cost effective
- Some situations warrant testing BEFORE starting therapy to avoid serious adverse reactions
  - HLA-B*1502 in Asian patients before Carbamazepine
  - HLA-B*5701 in HIV patients before Abacavir

Be aware of situations where pharmacogenetic testing makes sense, Pharmacist Letter, 2015

Mental Health Background

- > 10% of all outpatient office visits include a depression-related diagnosis
  - Centers for Disease Control and prevention (2016)
- Patients who require more medication trials to experience remission of depressive symptoms are more likely to relapse in the follow-up period than those who do not
  - National Institute of Metal Health (2001)

Kierce et al, Use of PHQ-9 and pharmacogenetic testing in clinical practice (2019)

Background Continued…

- Psychiatric pharmacotherapy generally take time and patience from both patient and provider
  - 30-50% do not respond adequately to 1st trial
    - It can take months to years to find the right fit
    - Exposure to ineffective agents, adverse drug effects, complications of untreated illness
      - Only 37.5% achieve remission
- Of the drugs listed with pharmacogenomic biomarkers, approximately 16% are indicated for mental illness

Hefti, Pharmacogenomic testing for mental illness pharmacotherapy (2016)
Yasgur, Pharmacogenetics in psychiatry: Promising developments and potential pitfalls (2018)

PHQ-9

- 15 adults with major depressive disorder
  - Patient Health Questionnaire-9 (PHQ-9)
    - Base line vs 6-week post-pharmacogenetic testing
    - 14/15 lower PHQ-9 score
    - 6/15 medication use with significant drug-gene interactions
      - Medication use discontinued in 50% patients
      - 50% continued therapy as providers deemed it reasonable in spite of drug-gene interactions
- Pharmacogenetic testing is a useful tool, but does not replace provider judgement

Kierce et al, Use of PHQ-9 and pharmacogenetic testing in clinical practice (2019)

Pharmacogenetic Testing (PGx) vs. Treatment as Usual (TAU)

- Key to 'trial-and-error "prescribing in psychiatry
- Evidence of gene-drug interactions
  - Primary focus on antidepressants
    - CYP2C19 and CYP2D6
  - Symptom Improvement (P = 0.107)
  - Improvement in response (P = 0.013)
  - Improvement in remission (P = 0.007)

Yoshida et al, The coming-of-age of pharmacogenetic testing in clinical psychiatry (2019)

While promising…
Some issues still need addressing

1. Most studies evaluated patients who have not responded to previous treatment
2. Test panels across academic centers and industry differ substantially

What's needed?

- More prospective RCTs needed to evaluate level of treatment resistance and cost-benefits
- PGx tests are not interchangeable
  - Standardization and further research still needed

Yoshida et al, The coming-of-age of pharmacogenetic testing in clinical psychiatry (2019)

Limitations Remain

- Pharmacogenetic testing assesses pharmacokinetic aspects of patient response
  - Liver enzymes (CYP450 system)
    - *What the body does to the drug*
- Much are the variability in patient response is based on pharmacodynamics
    - *What the drug does to the body*

Limandri BJ, Pharmacogenetic testing: Why is it so disappointing? (2019)

Genetic testing primarily addresses pharmacokinetic aspects of drug response, why doesn't it address pharmacodynamics as well?

a) Pharmacodynamics involves more complex interactions at the level of receptors, enzymes, or signaling proteins, which make them more difficult to detect

b) Pharmacodynamics are not affected by genetics

c) Pharmacodynamics addresses what the body does to the drug and doesn't impact clinical outcomes

d) Pharmacokinetics addresses what the drug does to the body, which is most important

Pharmacogenetic Application in Mental Health

- May be reasonable to consider when:
  - Patients don't respond to usual doses or multiple mental health meds
  - Patients experience significant side effects with low doses
- Pharmacogenetics
  - One piece of the puzzle
    - Response and tolerability impacted by multiple factors
      - Kidney/liver function, diet, smoking, other meds

Put pharmacogenetic testing for mental health meds in perspective, Pharmacist Letter, 2018

Summary

- Pharmacogenetics is complex and understanding some basic terminology will improve your interaction with healthcare providers and patients
- Pharmacogenetics is a tool used to understand how genetic variations of enzymes (primarily CYP enzymes from the liver) impact pharmacologic response to specific medications
- A patient response to pharmacotherapy is impacted by both kinetic and dynamic aspects
  - What the body does to the drug, and what the drug does to the body – Both are impacted by genetics
- Clinical Pharmacogenetics Implementation Consortium (CPIC) provides guidelines for the application of genetic information
- Pharmacogenetics is a growing and promising field with meaningful application in patient care
  - However, there is still much to learn about the application of this technology

Questions?

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