Addiction Is in the Genes: How Pharmacogenetics Plays a Role in Opioid Addiction

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Disclosure

All planners, presenters, and reviewers of this session report no financial relationships relevant to this activity.
Objectives

• Describe pharmacogenetic testing results as they correlate to opioid therapy.
• Apply acquired knowledge of pharmacogenetic testing and results to simulated patient cases in order to recommend appropriate opioid therapy options.
Objectives

• Evaluate the practical use of various pharmacogenetic reports for pain management treatment options.
• Identify ways in which pharmacogenetics could be used to optimize pain management treatment regimens and aid in minimizing addiction, abuse, and adverse drug effects.
Introducing JA......
JA is a 45 year old Caucasian male.

**PMH:** Diabetes
Hypertension
Chronic back pain
Depression

**Current Meds:**
Metformin 1000 mg PO BID
Lisinopril 40 mg PO QDay
Sertraline 200 mg PO QDay
Hydrocodone/APAP 5/325 mg 1-2 tablets Q 4-6 hours
Oxycodone 5 mg PO Q12H PRN breakthrough pain

**Social History:**
Does not smoke or use illicit drugs
Drinks alcohol socially
Married with 2 children (ages 13 and 15)
Has worked as a car salesman for 12 years

**Family History:**
Father battled alcoholism
2 brothers, neither of which have addictive tendencies
Opioid Overview

- Opioids are a class of drugs that are used as a prescription pain reliever (PPR) for acute and chronic pain.
  - Feeling of well-being
  - Slow down functions of the central nervous system, including respiration
Opioid Epidemic in the US

- 20.5 million Americans had a substance use disorder in 2015
  - 2 million had a substance use disorder involving prescription pain relievers
  - 591,000 had a substance use disorder involving heroin\(^1\).
- In 2015, 33,091 people died from overdosing on opioids\(^2\).
  - 20,101 with PPRs and 12,990 related to heroin
- In 2012, 259 million prescriptions were written for opioids
  - More than enough to give every American adult their own bottle\(^3\)
- Opioid prescribing rates nearly doubled from 1994 to 2007 among adolescents and young adults\(^3\)

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1 2015 National Survey on Drug Use and Health (SAMHSA), 2 MMWR, 2016; 65(50-51);1445–1452 (CDC) 3 Fortuna, etal. Pediatrics 2010;126(6):1108-1116
Opioid Epidemic in the US

• Prescription opioids have steadily increased in annual costs related to misuse (crime, lost work productivity, and health care)
  ➢ Analysis of 2007 data – $55.7 billion\(^1\)
  ➢ Analysis of 2013 data - $78.5 billion\(^2\)

“In the past, addiction was viewed as stemming from an individual’s moral failing and weakness of will. With the advances in scientific research, biological theories of addiction as a “brain disease” are now widely accepted; however, this point of view is still controversial.”
Causes of Addiction

Nature vs. Nurture
Causes of Addiction

**Nature (Genetics)**
Drug exposure may lead to enhanced positive or negative effects

**Nurture (Environmental)**
Family beliefs, pressure from peers, and overall attitudes may influence perceptions

**CNS Changes (Somatic)**
Potentially altered communication via neurotransmitters
Addiction and Genetics

- Drug exposure
- Drug access
- Genetic Predisposition
Addiction and Genetics

• Kendler/Prescott studies from 1992-1999
  – Heritability in the range of 50-60%

• Kendler 1997
  – Swedish Twin Registry from 1902-1949 and temperance board registration
  – The prevalence of AD was similar between monozygotic and dizygotic/fraternal twins
  – Concordance rate was higher with monozygotic twin
  – Heritability was stable over time and environmental changes
Addiction and Genetics

• Tsuang et al.
  – Data from the Vietnam Era Twin Registry
  – Drug use disorder was defined as receiving a diagnosis of drug abuse or dependence according to DSM-III-R
  – A significant difference between concordance rates for monozygotic vs. dizygotic twins indicated a genetic influence on drug use disorder
  – Results support the application of molecular genetic approaches to elucidate the genetic influence on drug use disorder
Addiction and Genetics

• Van den Bree et al.
  – Monozygotic and Dizygotic twins of both genders.
  – Illicit drug use (5 times in lifetime) and DSM-III diagnoses of drug abuse or dependence
  – Higher levels of addiction with male than females
  – Association of genetics and drug addiction
Causes of Addiction: Evidence of Heritability

Causes for Addiction

Genetic Variability

Wild Type Allele: Widely accepted sequence for the gene for the majority of the populations

Variant Allele: Alternative sequences for the same gene or different variations at the same genetic locus

Opioids

Natural & Semisynthetic

Codeine → Morphine → Oxycodone → Hydromorphone → Hydrocodone → Diacetylmorphine (Heroin)
Opioids

**Synthetic**

Methadone

Meperidine

Fentanyl
Pharmacokinetics

• Enzyme Metabolism
  - CYP2D6
  - CYP3A4
  - Lesser extent
    - CYP2B6
    - Methadone
    - Tramadol
    - Meperidine
    - CYP2C19
    - Methadone
    - Meperidine
    - CYP1A2
    - Methadone
    - UGT2B7
    - Lesser extent
      - UGT1A1
      - UGT1A3

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https://www.pharmgkb.org/literature/6772815
Pharmacokinetics

- Transporters
  - ABCB1
  - SLC22A1
CYP2D6 Metabolizing Enzyme

- Four Phenotypes – Poor, Intermediate, Extensive and Ultra-rapid.
- Poor metabolizers had lower risk of becoming dependent on opioids.
- Encodes for a monoxygenase which is localized to the endoplasmic reticulum.
- Identified as being the most polymorphic with over 60 different alleles.

**Pharmacokinetics**

- **Activating**
  - Codeine
  - Hydrocodone
  - Oxycodone
  - Tramadol

- **Deactivating**
  - Codeine
  - Hydrocodone
  - Oxycodone
  - Tramadol
<table>
<thead>
<tr>
<th>Phenotype</th>
<th>Frequency</th>
<th>Genetic Basis</th>
<th>Implications of 2D6 for Agents Activated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poor Metabolizer (PM)</td>
<td>~5 to 10%</td>
<td>No functional alleles present</td>
<td>Lack of therapeutic effects may be observed</td>
</tr>
<tr>
<td>Intermediate Metabolizer (IM)</td>
<td>~20 to 40%</td>
<td>Either one functional and one mutant/deficient allele or two partially active/deficient alleles present</td>
<td>May show reduced effects</td>
</tr>
<tr>
<td>Extensive Metabolizer (EM)</td>
<td>~60 to 80%</td>
<td>Either two active alleles or a combination of one active and one partially active allele present</td>
<td>Should be able to achieve therapeutic effects with normal dosing</td>
</tr>
<tr>
<td>Ultra-rapid Metabolizer (UM)</td>
<td>~1 to 5 %</td>
<td>Three or more active alleles present</td>
<td>Increase risk of toxicity; lower dose may be required</td>
</tr>
</tbody>
</table>

Adapted from: Zdanowicz, Martin M. Concepts in pharmacogenomics. ASHP, 2010
Pharmacokinetics:
Other Polymorphic Drug Metabolizing Enzymes

• CYP3A4 (*1G)- Decrease with inactivating the drug
  – Fentanyl, Hydromorphone, Oxycodone, Oxymorphone, Methadone
  – (Lesser Extent) Morphine, Codeine, Hydrocodone, Meperidine

• UGT2B7 (*2)- Decrease levels of glucuronidation
  – Hydromorphone, Oxycodone, Oxymorphone, Methadone, Morphine, Codeine
Pharmacokinetics: Polymorphic Drug Transporter

- **ABCB1 (P-Glycoprotein)**
  - Efflux pump in the digestive tract, kidneys, liver, and brain
  - 3 common polymorphisms (1236C>T, 2677G>T, 3435C>T)
  - Haplotype (1236T, 2677G, 3435T)
    - Increased efflux activity with levels of methadone
    - Conflicting results
    - Drug interactions impact pump functionality
Pop Quiz!

Which of the following genes encode for a protein that would play a role in the metabolism of opioid drugs?

a. URGR8
b. R2D1
c. GKMB1
d. 2D6
Pharmacodynamics

- Four Main Opioid Receptors –
  - Mu Receptor
  - Delta Receptor
  - Kappa Receptor
  - ORL-1 Receptor
OPRM1 gene encodes for the mu opioid receptor

- rs1799971 (Asn40Asp) – variant decrease with opioid drugs (morphine) because there is a decrease in expression.
- 10-19% of the Caucasian population.

Pharmacodynamics

1 Beate et al PloS one 2013 24086514
Warrior vs Worrier

Catechol-O-methyltransferase (COMT)
- Catalyzes catecholamines, including neurotransmitters dopamine, epinephrine, and norepinephrine
- Results in one of the major degradative pathways of the catecholamine transmitters

<table>
<thead>
<tr>
<th>rs4680 (G): Warrier</th>
<th>rs4680 (A): Worrier</th>
</tr>
</thead>
<tbody>
<tr>
<td>Val</td>
<td>Met</td>
</tr>
<tr>
<td>Higher enzymatic activity</td>
<td>Lower enzymatic activity</td>
</tr>
<tr>
<td>Lower dopamine levels</td>
<td>Higher dopamine levels</td>
</tr>
<tr>
<td>Higher pain threshold</td>
<td>Lower pain threshold</td>
</tr>
<tr>
<td>Better stress resiliency</td>
<td>Enhanced vulnerability to stress</td>
</tr>
<tr>
<td>Lower risk for addiction</td>
<td>Increased risk for addiction</td>
</tr>
</tbody>
</table>
Other Genetic Markers

• Enzyme
  – MAOA (monoamine oxidase A)

• Receptors
  – ADRA2 (Alpha-2-adrenergic receptor)
  – DRD2 (dopamine receptor D2)
  – HTR1A (Serotonin Receptor)
  – HTR2A (Serotonin Receptor)

• Ion Channels
  – KCNS19 (POTassium Voltage-gated Channel Modifier)
  – CACNG2 (calcium voltage-gated Channel)
  – CACNA2D3 (calcium voltage-gated channel)

• Transporters
  – SLC6A3 (Dopamine Transporter)
Pop Quiz!

Which of the following variants means a patient is at a lower risk for addiction, has lower dopamine levels, and higher pain tolerance?

a. OPRM1
b. COMT (rs4680 (G))
c. ABCB1 (1236C>T)
d. 3A4*2
<table>
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<tbody>
<tr>
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</tr>
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<td>*1/*2</td>
<td>(I) Intermediate</td>
</tr>
<tr>
<td>CYPC19</td>
<td>*1/*1</td>
<td>N</td>
</tr>
<tr>
<td>CYP3A4</td>
<td>*1/*1</td>
<td>N</td>
</tr>
<tr>
<td>CYP3A5</td>
<td>*1/*3</td>
<td>I</td>
</tr>
<tr>
<td>CYP1A2</td>
<td>*1A/*1F</td>
<td>Induced Ultrarapid</td>
</tr>
<tr>
<td>COMT</td>
<td>A/A</td>
<td>Variant</td>
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Application of Pharmacogenetics with Addiction
Possible Pharmacogenetic Tests for Opioid Therapy

### Pain Panel

<table>
<thead>
<tr>
<th>Gene</th>
<th>Marker</th>
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<tbody>
<tr>
<td>CYP2D6</td>
<td>DRD2</td>
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<tr>
<td>BDNF</td>
<td>OPRM1</td>
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<td>COMT</td>
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Possible Pharmacogenetic Tests for Opioid Therapy

- CYP2D6
- CYP2C9
- CYP2B6
- CYP3A4
- DRD2
- CYP1A2
Possible Pharmacogenetic Tests for Opioid Therapy

Pharmacogenetics in Pain – Precision Pain Management

Prescribing can often be particularly challenging for pain management specialists since chronic pain sufferers are often being treated for other conditions such as depression, addiction or cancer. Our partners with the YouScript Precision Prescribing System can help improve pain management by determining each patient’s unique drug metabolizing capacity and which drugs and doses are likely to be most effective in treating their pain.

For example, a patient presenting with chronic lower back pain may have a long history of uncontrolled pain, multiple trials of pain medications, and non-specific drug sensitivities or side effects. The patient could be a candidate for one of several FDA-approved medications, many of which carry pharmacogenetic information on their labeling (see table, below). If the patient is also being treated for one or more co-morbid conditions, or is taking herbal

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Other Factors to Consider

- Contributing factors of the patient
  - Concomitant mental health disorders
  - Personal/Family History
  - Legal History
  - History of sexual abuse

- Overlapping genetic vulnerabilities
Strength Of Opioids

- Potency of the Drug – is based on concentration of the drug as well as factors such as:
  - Affinity – ability to bind better to a specific receptor
  - Efficacy – ability to cause a response when bound to the receptor
- **Hydrocodone** is rated around 0.2 higher than morphine
- **Oxycodone** is 0.3 stronger than morphine
- A higher dose of **hydrocodone** is required to achieve the same effect as a lower dose of **oxycodone**.
- **Fentanyl** is the highest with a potency that is 80 times of morphine.

https://treatmentandrecoverysystems.com/blogs/thinking-about-addiction/understanding-opioid-potency/
Can Genetics be Used for Treatment?

• Antagonist
  – Naltrexone

• Genetics
  – OPRM1
    • Rs1799971 (Asn40Asp)
    • Patients respond better to the variant due to the lower expression
Clinical Assessment

• Screen
  – Patient + Spouse/Significant Other Interview
  – Home Environment
  – Medical Records
  – Screening Tools
    • Opioid Risk Tool
    • The Screener and Opioid Assessment for Patients with Pain- Revised
      – https://www.opioidrisk.com/node/1209

• Risk-Stratify
  – Low-Risk
  – High-Risk

PLUS Pharmacogenetic Test Results
Risk Stratification

• Low Risk
  – Can be deemed high risk if in a high-risk environment

• High Risk
  – Assessment
  – Structure
  – Monitoring

• Very High Risk
  – Structure
Structure

- Utilization of counselling or support groups
- One practitioner/One Pharmacist
- Shorter dispensing intervals
- Minimization of “breakthrough” pain medication
- No early refills or medication replacement
- Opioid prescribing agreements
Evidence

- High-risk patients in structured program were able to manage medication similarly to low-risk patients
- 50% reduction in misuse behaviors in a population with careful prescribing and monitoring

Clinicians walk a fine line.... there is an ethical obligation to relieve pain while, at the same time, minimizing harm and long-term consequences

Jovey R. Br J Pain 2012;6(1):36-42
What to Choose?

- Potency of the opioid
- Duration of action
- Formulation/Route of Administration

To date, no abuse deterrent or abuse resistant opioids have been proven.
Implementation of Genetic Testing with Clinical Assessment Outcomes

• Genetic testing presents more information to assist in conquering a national epidemic

• These results are a small piece of a big puzzle
Back to JA.....
JA is a 45 year old Caucasian male.

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Key Takeaways

- **Key Takeaway #1**
  - Genetics play a role in predisposition of opioid addiction, therefore it is an important piece of information that could aid in medication therapy decisions

- **Key Takeaway #2**
  - Pharmacogenetics could be utilized to optimize pain management treatment regimens and aid in minimizing/treating individuals who are addicted to the medication

- **Key Takeaway #3**
  - Always assess risk and implement structure into the management of chronic opioid users
QUESTIONS?
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