Pharmacogenomics

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Pharmacogenetic Effects of CYP450 Genotypes

Genetics in Medicine: History

- The study of variation associated with illness and death
- History
  - Greek Civilization 500 BCE
    - Pythagorus (mathematical genius) discovered that some who ate fava beans became sick and others did not
  - Romans observed adverse effects of alcohol on the unborn fetus during pregnancy in some and not others
  - The Talmud (Jewish Law) contains notations pertaining to circumcision of newborn males
    - If the woman’s first and second male offspring were circumcised and died due to exsanguination, she should not circumcise the third
    - First account of genetic counseling

Pharmacogenetics Versus Pharmacogenomics

- Pharmacogenetics
  - Refers to a single gene variant and its association with drug response
  - CYP450-2C9 gene and the anticoagulant effects on warfarin
  - Effect of drug alone
- Pharmacogenomics
  - Refers to the interaction of multiple genes in determining drug response
  - CYP450-2C9 ultimate effects on the clotting factor genes and the warfarin response
  - Drug plus the effects on the target site

Pharmacogenetics History

- Pharmacogenetics – genetics and pharmacology
- 1959: The term was coined by a geneticist in Germany
- 1960: Fatal Malignant Hyperthermia due to a general anesthetic
- 1966: Genetic variation of alcohol dehydrogenase
- 1977: Abnormal metabolism of debrisoquine
  - A sympatholytic antihypertensive agent (CYP-2D6)
  - Poor and extensive metabolizers

Chromosomes

- Humans have 46 chromosomes in 23 pairs
- Each chromosome has gene carrying DNA
  - Blueprint determining looks, growth, and disease
  - A single continuous DNA double helix
  - Histones proteins
  - Non-histones proteins
- Chromatin
  - DNA complex + Histones + nonhistones
**Gene**

- Each gene occupies a particular place on a chromosome, a locus.
- A sequence of DNA encoding the information for production of a functional polypeptide chain or ribonucleic acid (RNA) molecule.
- Some regions of a chromosome are high in gene content, some are low.
- <10% of the DNA in the human genome encodes functional genes.
- DNA → RNA → Protein (transcription, translation).
- Gene Supremacy or an Inert Molecule that is the Architects Plan.

**Normal Human Chromosomes**

![Image of normal human chromosomes]

**Chromosome 21**

- The smallest chromosome in the human genome.
- Second human genome to be fully sequenced.
- 225 active genes.
- Down Syndrome: 3 copies of genes instead of 2.
- 1 of 700 births.
- Alzheimer’s disease.
- Lou Gehrig’s disease.

**Alleles – A Single copy of a gene**

- **Wild type Alleles**
  - Most commonly occurring gene.
  - The allele that was originally sequenced but not the most common.
- **Variant Alleles**
  - Genes that are considered polymorphic.
- **Homozygous Genotype**
  - Two identical alleles at a given locus.
- **Heterozygous Genotype**
  - Two different alleles at a given locus.
- **Phenotype**
  - The outward expression of an individual’s phenotype.
Pharmacogenomics Goal

- **Phenotype**
  - The outward expression of an individual’s phenotype
- **Polymorphisms**
  - Genetic variations that occur at a frequency of greater than 1% in the human population
- **Mutations**
  - Genetic alterations that occur at a frequency of less than 1% and cause inherited disease
- **Pharmacogenomics Goal**
  - Maximize pharmacotherapy outcomes to all patients based on their DNA or phenotype

Polymorphisms and Antiepileptic Drug Efficacy

- 10 - 20% of all patients with Epilepsy are completely resistant to therapy despite therapeutic levels
- Decreased CNS penetration of medications
  - Polymorphism related to the BBB transporter protein
  - MDR1, cloned MRP2 and MRP5 in the temporal regions of the brain was much higher in refractory epileptic patients

Polymorphisms & SSRI’s Efficacy

- 30-40% of patients with Depression do not respond to SSRIs
- Genetic polymorphisms in the serotonin transporter
  - 5-HT Transporter gene SLC6A4 on chromosome 17 of patients with depression
  - Higher levels of the "I" allele of 5-HTTLPR leads to reduced 5-HT uptake as compared to the "s" allele
    - I/I homozygotes respond best
    - I/s heterozygotes
    - s/s homozygotes respond least

SSRIs Block the Serotonin Transporter System

Patients receiving paroxetine or nortriptyline
- I/I responded in 2 weeks
- s/s or s/s responded in 4 weeks

Patients with Depression and psychotic symptoms responded best to fluvoxamine alone if they carry at least one "I" allele

Most studies were done with Europeans and Koreans

We don’t know if other disorders are influenced by 5-HTT polymorphisms (GAD, OCD)

CYP variability of SSRIs may play a role
Antipsychotic-Induced Weight Gain

Mechanism
- Antihistaminic, antimuscarinic, 5-HT₂C receptor blockade
- The prevalence of weight gain and obesity is highest in patients with mental illness
- Schizophrenia patients have a high risk of CHD
- Higher risk of diabetes and hyperlipidemia
- Weight gain may persist despite nutritional consultation and exercise
- Weight gainers are most likely to discontinue therapy

Antipsychotic-Induced Weight Gain (After 10 Weeks)

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Trade Name</th>
<th>Weight gain (lbs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clozapine</td>
<td>Clozaril</td>
<td>9</td>
</tr>
<tr>
<td>Thioridazine</td>
<td></td>
<td>8</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>Zyprexa</td>
<td>8</td>
</tr>
<tr>
<td>Chlorpromazine</td>
<td>Thorazine</td>
<td>5</td>
</tr>
<tr>
<td>Risperidone</td>
<td>Risperdal</td>
<td>4.5</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>Seroquel</td>
<td>4</td>
</tr>
<tr>
<td>Aripiprazole</td>
<td>Abilify</td>
<td>1.5</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>Haldol</td>
<td>1</td>
</tr>
<tr>
<td>Ziprasidone</td>
<td>Geodon</td>
<td>0</td>
</tr>
</tbody>
</table>

Pharmacogenetics and Antipsychotic-Induced Weight Gain

- Polymorphism of 5-HT₆ receptor has been associated with weight gain, obesity and type 2 diabetes
- Polymorphism of the 5-HT₆ receptor gene consists of a C to T substitution, and alters the expression of the gene
- The distribution of C alleles was associated with more weight gain than the variants with the T allele
  - Highest weight gain: C/C >> C/T > T/T least weight gain
- Corroborated with trials describing weight gain with chlorpromazine and risperidone of 2 kg in 10 weeks
- Olanzapine trials: 10% weight gain in 6 weeks
- Olanzapine: CYP-2D6 *1/*3, and *4 genotype were at greater risk than *1/*1 group

Nicotine Metabolism

Cigarette Smoke → Nicotine → CYP2A6 (80%) → CYP2D6 → Cotinine → Tyrosine Hydrolase → L-Tyrosine → Dopamine → Dopamine Receptors

L-Tyrosine

CYP-2A6 Activates Nicotine Precarcinogens

- CYP2A6 activates to cytotoxic, genotoxic, and mutagenic metabolites
- NNK = 4-(methylnitrosoamine)-1-(3-pyridyl)-1-butanone
  - The most potent tobacco procarcinogen
- Dimethylnitrosamine
- Alfatoxin B1
- Benzopyrene
- 6-Aminochrysene
- Defective CYP2A6 decreases carcinogenicity

Carriers of CYP2A6 Defective Allele(s)

- Dependent smokers adjust their smoking behavior to maintain a target level
- Individuals with a defective CYP2A6 allele(s) metabolize nicotine more slowly
  - Higher and longer nicotine levels
- Will need to smoke fewer cigarettes to maintain nicotine level
- Protected from tobacco dependence
Methoxsalen (Oxsoralen-Ultra)
Indications: Psoriasis, Vitiligo, Lymphoma

Methoxsalen: CYP-2A6 Inhibitor

Effects of Methoxsalen on Nicotine Concentration in Blood
And on the Desire to Smoke

<table>
<thead>
<tr>
<th>Blood Nicotine Concentration (µg/ml)</th>
<th>Desire to Smoke</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>6.8</td>
</tr>
<tr>
<td>10 mg Methoxsalen</td>
<td>11.8</td>
</tr>
<tr>
<td>30 mg Methoxsalen</td>
<td>12.1</td>
</tr>
</tbody>
</table>

Ethanol Metabolism

- **Ethanol**
  - ADH + Alcohol Dehydrogenase
  - Aldehyde Dehydrogenase
  - Acetate enters the Krebs Cycle

- **Aldehyde Dehydrogenase Metabolism**
  - Accumulation may cause severe flushing
    - ALDH2*1 wild allele normal metabolism
    - ALDH2*2 variant allele inhibits metabolism
      - 80% of Native Americans
      - 50% of Asians
      - 3 - 30% of Caucasians

- **Ethanol Metabolism**
  - Gastric, hepatic and renal Alcohol Dehydrogenase (ADH) oxidizes a portion of ethanol
    - Wild type ADH2*1 normal metabolism
    - Variant alleles ADH2*2, rapidly metabolize ethanol
      - 85% Asians Men
      - 20% Caucasian Men
      - 10% African American Men
  - Chronic drinkers recruit the CYP450-2E1
    - Metabolize 30 - 40 mg/dL/hour

- **Alcohol-Drug Interactions**
  - Disulfiram inhibits aldehyde dehydrogenase, increasing acetaldehyde concentrations
  - Manifests as (within 10 - 20 minutes):
    - Vasodilation and catecholamine release
    - Flushing
    - Headache
    - Nausea and vomiting
    - Tachycardia
    - Hypotension
**Drug Which Can Cause a Disulfiram-Like Reaction**
- Metronidazole
- Cefoperazone
- Cefotetan
- Oral Hypoglycemics
  - Chlorpropamide
  - Tolbutamide
  - Tolazamide
- Nitrofurantoin
- Griseofulvin
- Chloramphenicol
- Furazolidone
- Quinacrine
- Procarbazine

**Alcohol Containing Products**
- Various Elixirs
- Acetaminophen Elixir
- Nyquil
- IV Phenytoin
- IV Bactrim
- IV Diazepam
- IV Lorazepam
- Salad Dressings
- Shampoos
- Shaving Creams
- Colognes
- Mouthwash
- Foods cooked with wine

**Patient Counseling For Disulfiram Reaction**
- Discontinue alcohol for 24 hours prior to aldehyde dehydrogenase inhibitor
- Discontinue aldehyde dehydrogenase inhibitor 24 - 72 hours prior to alcohol
- De-novo synthesis of this enzyme is ~ 6 days

**Drugs Which Increase Alcohol Levels**
- Inhibit hepatic metabolism of alcohol via gut alcohol dehydrogenase (ADH)
- Cimetidine - 300% increases in ethanol
- Ranitidine - 200% increases in ethanol
- Nizatidine - 200% increases in ethanol
- Verapamil - 30% increases in alcohol

**Cytochrome P (CYP)-450 Isoenzymes**
- Heme-containing enzymes
- Embedded primarily in the lipid bilayer of the endoplasmic reticulum of hepatocytes
  - Enterocytes of small intestine
  - Kidneys, lungs, brain
- Involved in Phase I reactions
  - Oxidation, reduction, hydrolysis

**1 g of Aspirin Increases Blood Ethanol Levels in Healthy Humans (26% increase in AUC)**

Nomenclature of the P450 Genes

- Nomenclature based on gene sequence
- Prefix CYP designates human cytochrome P450 (pronounced “cyp”)
- CYP3 designates the gene family
- CYP3A designates the subfamily
- CYP3A4 designates the individual gene
  - 97% identical in their amino acid sequence

Genetic Polymorphism

- 3A4 – no genetic polymorphism
- 1A2 – no genetic polymorphism
- Genetic Polymorphism
  - 2A6
  - 2B6
  - 2C9
  - 2C19
  - 2D6

CYP450-2C9

- CYP-2C9*1 is the active wild type allele
- CYP-2C9*2 or CYP-2C9*3 are inactive variant alleles
  - 35% Caucasians & Europeans have variant alleles
    - Poor metabolizers (PMs)
  - 1 – 3% African Americans and Asians
  - Absent in 1% of Caucasians and African-Americans
  - *3/*3 genotype (homozygotes)
  - *4, *5, *6 detected and inactive

CYP450-2C9 Probes and Substrates

- In-vivo Probes
  - Tolbutamide (Orinase®)
  - Flurbiprofen
  - Losartan
  - Warfarin (7-hydroxywarfarin)
- Substrates
  - NSAIDs (most)
  - Ibuprofen
  - Diclofenac
  - Naproxen
  - Piroxicam
  - Metycloxicam
  - Coxsibs
- Substrates
  - Tolsemide (Demadex®)
  - Rifampin (Norvir®)
  - Glipizide
  - Glyburide
  - Glimepiride (Amaryl®)
  - Diazepam
  - Fluastatin
  - Rosuvastatin (Crestor®)
    - 10 mg daily
    - Asians reduced to 5 mg daily
    - 2 fold increase in AUC, Cmax
  - Phenyltoin

Metabolism of Celecoxib (Celebrex®)

- Hydroxylation
- CYP2C9
- Inactive alcohol metabolite
- Fluconazole
- Oxidation
- Conjugation
- Glucuronide of the acid metabolite
- Inactive acid metabolite (major)
Effect of CYP-2C9 Genotype on Phenytoin

- Primarily metabolized by CYP 2C9, and to a lesser extent 2C19
- Small changes in metabolism yield significant changes in serum levels
  - Michaelis Menten Pharmacokinetics
  - *1/*1 genotype = 314 mg/day
  - *2/*2 genotype = 217 mg/day
  - *3/*3 genotype = 150 mg/day

Metabolism of Warfarin

- S-warfarin (active) → 7-hydroxy warfarin (inactive)
- R-warfarin (active) → 3-hydroxy warfarin (inactive)

Effect of CYP-2C9 Genotype on Free S-Warfarin Clearance

Effect of CYP-2C9 Genotype on Free S-Warfarin Clearance

- Warfarin Dose by CYP2C9 Genotype

<table>
<thead>
<tr>
<th>CYP-2C9 Genotype</th>
<th>Dose (% of normal)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP <em>1</em>1 (wild type)</td>
<td>100</td>
</tr>
<tr>
<td>CYP <em>1</em>2</td>
<td>80</td>
</tr>
<tr>
<td>CYP <em>1</em>3</td>
<td>70</td>
</tr>
<tr>
<td>CYP <em>2</em>2</td>
<td>62</td>
</tr>
<tr>
<td>CYP <em>2</em>3</td>
<td>51</td>
</tr>
<tr>
<td>CYP <em>3</em>3</td>
<td>40</td>
</tr>
</tbody>
</table>

**Warfarin Mechanism of Action**

![Diagram showing Warfarin Mechanism of Action](image)

**VKORC1 Haplotypes and Warfarin Dose**

![Graph showing Effect of VKORC1 Haplotype Combination on Clinical Warfarin Dose](image)

**CYP-2C9 Inducers**

- Carbamazepine
- Phenobarbital
- Phenytoin
- Primidone
- Rifabutin
- Rifampin

**CYP-2C9 Inhibitors**

- Sulfamethoxazole
- Chloramphenicol
- Fluconazole
- Itraconazole
- Ketoconazole
- Metronidazole
- Omeprazole
- Isoniazid
- Ticlopidine
- Amiodarone
- Lovastatin
- Fluvastatin
- Gemfibrozil
- Zafirlukast
- Cimelidine/Ranitidine
- Fluoxetine
- Paroxetine
- Fluvoxamine
- Sertraline
CYP450-2C19

- CYP-2C19*1 is the active wild type allele
  - Extensive metabolizers
- CYP-2C19*2 and CYP-2C19*3 are inactive variant alleles
  - 30% Asians are poor metabolizers (PMs)
  - 10% African Americans PMs
  - 5% Caucasians are PMs
- *2 is found in 13% of Caucasians
- *3 is found in almost all Asians
- *3 rare in Caucasians

CYP450-2C19 Probes and Substrates

- In-vivo probes
  - Mephenytoin
  - 5-enantiomer is hydrolyzed by 2C19
- Omeprazole
  - 5-Hydroxylated to 5-hydroxyomeprazole
- Substrates
  - Voriconazole
  - Cyclophosphamide
  - Progesterone
  - R-Warfarin

Substrates
- Citalopram (Celexa®)
- Diazepam (Valium®)
- Olomipraine
- Imipramine
- Desipramine
- Amitriptyline
- Nortriptyline
- Primidone
- Topiramate

CYP-2C19 Genetic Polymorphism and PPIs

- 80% CYP-2C19
  - Omeprazole (Prilosec®)
  - Esomeprazole (Nexium®)
- CYP-2C19 and 3A4
  - Unknown percentages
  - Lansoprazole (Prevacid®)
  - Rabeprazole (Aciphex®)
  - Sulfoxtransferases [-2C19]
  - Nonsaturable
  - Pantoprazole (Protonix®)

- Poor Metabolizers
  - 15% Chinese
  - 14% Koreans
  - 22% Japanese
- Beneficial Effects in PMs
  - PUD – H. Pylori
  - PMs: 100% heal
  - Heterozygotes: 60-90% heal
  - Homozygotes (EMs): 30-70% heal
  - GI Bleeding, GERD

Omeprazole Metabolic Pathway

- Omeprazole (Inactive prodrug)
- Sulfenamid (Active Moiety)

CYP3A4

- 5-hydroxy-- (Inactive)
- Omeprazole--sulfone (Inactive)

CYP2C19

Plasma Omeprazole Level Among CYP2C19 Genotypes After Omeprazole 20 mg Single Dose

- Cmax (ng/mL)
  - EM 200
  - IM 450
  - PM 1200

T = 10 hours

Therapeutic level

Eradication Rates as a Function of CYP 2C19 Genotypic Patterns

Psychotropic Dosing for 2C19

<table>
<thead>
<tr>
<th>Drug</th>
<th>PM (%)</th>
<th>IM (%)</th>
<th>UM (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amitriptyline (Elavil)</td>
<td>53</td>
<td>81</td>
<td>109</td>
</tr>
<tr>
<td>Clomipramine (Anafranil)</td>
<td>62</td>
<td>79</td>
<td>110</td>
</tr>
<tr>
<td>Doxepin (Sinequan)</td>
<td>45</td>
<td>91</td>
<td>105</td>
</tr>
<tr>
<td>Imipramine (Tofranil)</td>
<td>58</td>
<td>83</td>
<td>108</td>
</tr>
<tr>
<td>Trimipramine (Surmontil)</td>
<td>45</td>
<td>52</td>
<td>111</td>
</tr>
<tr>
<td>Fluoxetine (Prozac)</td>
<td>70</td>
<td>86</td>
<td>107</td>
</tr>
<tr>
<td>Sertraline (Zoloft)</td>
<td>75</td>
<td>90</td>
<td>105</td>
</tr>
<tr>
<td>Citalopram (Celexa)</td>
<td>61</td>
<td>84</td>
<td>108</td>
</tr>
<tr>
<td>Fluvoxamine/Maprotiline</td>
<td>93/100</td>
<td>97/100</td>
<td>1001/100</td>
</tr>
<tr>
<td>Clozapine (Clozaril), 1A2</td>
<td>78</td>
<td>91</td>
<td>104</td>
</tr>
</tbody>
</table>

CYP-2C19 Inhibitors and Inducers

- Inhibitors
  - Felbamate
  - Fluoxetine
  - Fluvoxamine
  - Sertraline
  - Omeprazole
  - Ticlopidine
  - Topiramate
  - Isoniazid

- Inducers
  - Carbamazepine
  - Phenobarbital
  - Phenytin
  - Primidone
  - Rifabutin
  - Rifampin
  - Dexamethasone

CYP450-2D6

- CYP-2D6*1 and CYP-2D6*2 are active alleles and wild type
- Extensive metabolizers (90% White, Asians, & Native Americans)
- CYP-2D6*9, *10 or *17 are partially active alleles
- Intermediate Metabolizers (IMs)
- CYP-2D6*3 and CYP-2D6*4 are inactive alleles and variants
- 20% of African-Americans are PMs
- 5 - 10% of Whites are PMs
- 1-3% Asians are PMs
- CYP-2D6*11*1 or *2
  - Ultrarapid metabolizer (UMs) (duplication of active allele)
- 1 - 10% of population; 5 – 25% of Arabian & North-East African

CYP 2D6 Polymorphism

Dose Adjustment for CYP2C19
Dose Adjustment for CYP-2D6 Substrates

Antidepressant Adjustment for 2D6

<table>
<thead>
<tr>
<th>Drug</th>
<th>PM (%)</th>
<th>IM (%)</th>
<th>EM (%)</th>
<th>UM (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amitriptyline</td>
<td>73</td>
<td>92</td>
<td>111</td>
<td>130</td>
</tr>
<tr>
<td>Desipramine</td>
<td>42</td>
<td>83</td>
<td>125</td>
<td>167</td>
</tr>
<tr>
<td>Doxepin</td>
<td>36</td>
<td>82</td>
<td>127</td>
<td>172</td>
</tr>
<tr>
<td>Imipramine</td>
<td>28</td>
<td>79</td>
<td>131</td>
<td>183</td>
</tr>
<tr>
<td>Nortriptyline</td>
<td>53</td>
<td>96</td>
<td>119</td>
<td>142</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>78</td>
<td>94</td>
<td>107</td>
<td>120</td>
</tr>
<tr>
<td>Fluvoxamine</td>
<td>69</td>
<td>93</td>
<td>112</td>
<td>131</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>66</td>
<td>90</td>
<td>114</td>
<td>138</td>
</tr>
<tr>
<td>Sertraline</td>
<td>99</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Citalopram</td>
<td>98</td>
<td>100</td>
<td>101</td>
<td>102</td>
</tr>
</tbody>
</table>

Anti-Psychotic Adjustment for 2D6

<table>
<thead>
<tr>
<th>Drug</th>
<th>PM (%)</th>
<th>IM (%)</th>
<th>EM (%)</th>
<th>UM (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perphenazine</td>
<td>31</td>
<td>80</td>
<td>129</td>
<td>178</td>
</tr>
<tr>
<td>Thoridazine</td>
<td>40</td>
<td>85</td>
<td>126</td>
<td>140</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>76</td>
<td>97</td>
<td>107</td>
<td>126</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>61</td>
<td>96</td>
<td>122</td>
<td>139</td>
</tr>
<tr>
<td>Risperidone</td>
<td>87</td>
<td>96</td>
<td>106</td>
<td>116</td>
</tr>
<tr>
<td>Aripiprazole</td>
<td>70</td>
<td>92</td>
<td>113</td>
<td>134</td>
</tr>
</tbody>
</table>

Clozapine 1A2, Quetiapine & Ziprasidone 3A4.

Opioids and 2D6 Interactions

<table>
<thead>
<tr>
<th>Metabolism Pathway</th>
<th>Metabolite</th>
</tr>
</thead>
<tbody>
<tr>
<td>Codeine (Tylenol 3°)</td>
<td>O-demethylation (2D6) → Morphine (active)</td>
</tr>
<tr>
<td>Glucuronidation</td>
<td>Codeine-6-glucuronide (active)</td>
</tr>
<tr>
<td>N-demethylation (CYP3A)</td>
<td>Norcodeine (active)</td>
</tr>
<tr>
<td>Tramadol (Ultram®)</td>
<td>O-demethylation (2D6)</td>
</tr>
<tr>
<td>Active</td>
<td>(2 – 4x as active)</td>
</tr>
<tr>
<td>Hydrocodone (Vicodin®)</td>
<td>O-demethylation (2D6)</td>
</tr>
<tr>
<td>Vicoprofen®</td>
<td>N-demethylation</td>
</tr>
<tr>
<td>Active</td>
<td>6-keto-reduction</td>
</tr>
<tr>
<td>Oxycodone (Perocet®)</td>
<td>CYP450-2D6</td>
</tr>
<tr>
<td>Active</td>
<td>Nor-oxycodone (active)</td>
</tr>
</tbody>
</table>

Metabolism of 5-HT₃ Blockers

CYP450-2D6 Substrates

- TCAs
- Fluoxetine
- Paroxetine
- Mirtazapine
- Trazodone
- Venlafaxine
- Desvenlafaxine
- Venlafaxine
- Donepezil
- Loratadine
- Tamoxifen
- Pilocarpine
- Mesorfinol
- Propafenone
- Metoprolol
- Timolol
- Bisoprolol
- Clobazamapine
- Dextromethorphan
- Codeine, Morphine
- Meperidine
- Norprenpro (seizuregenic)
- Methadone
- Tramadol
**Clinical Consequences of 2D6 Polymorphisms**

- Metoprolol
  - PMs have 5-fold greater risk of bradycardia than EM
- 2D6 Antidepressants and Antipsychotics
  - 45% EPS in PMs Vs 15% EPS in EMS

**AmpliChip CYP450 Test (Roche Diagnostics)**

- FDA Approved in US
- Analyzes 29 polymorphisms and mutations
  - CYP2D6
    - Poor
    - Intermediate
    - Extensive
  - Ultra-rapid
  - CYP2C19
    - Poor
    - Extensive
- Results within 8 hours

**Genelex: GeneMedRX DNA Drug Reaction Profile Testing**

- Licensed and accredited provider of DNA testing
- CYP2C9
  - PM, IM, EM, UM
- CYP2C19
  - PM, EM
- CYP2D6
  - PM, IM, EM, UM
- CYP1A2

- $250 per test
- $600 for panel
- $1,000 for 5 (1A2, NAT)
- Provide the blood collection kit or buccal swabs
- Test results in 14 days or 5 days for $100
- 800-523-3080

[http://www.healthanddna.com/professional/pharmacogenetics.html](http://www.healthanddna.com/professional/pharmacogenetics.html)

**Examples of Recently Approved First Generation Diagnostic Tests**

Tests are Based on Genotyping for Drug-Metabolizer Status and Facilitate Dosage Adjustments

<table>
<thead>
<tr>
<th>Description</th>
<th>GE</th>
<th>Junilab</th>
<th>Third Wave</th>
</tr>
</thead>
<tbody>
<tr>
<td>GE</td>
<td>CodeLinc™ Human CYP450 SNP Bioarray, 9 genes</td>
<td>DrugMET™ 8 genes</td>
<td>Invader® CYP450 2D6, used by LabCorp</td>
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<tr>
<td></td>
<td>Invader® UDG1A1 to use with irinotecan (colorectal Ca)</td>
<td>At least 7 other companies</td>
<td></td>
</tr>
</tbody>
</table>

**Conclusions**

- Determining genetic polymorphisms can allow for prediction of AED and SSRI efficacy and toxicity
- Determining CYP 2C9 polymorphisms can allow for precise dosing of phenytoin, warfarin, and -2C9 substrates
- Determining CYP 2C19 polymorphisms can allow for maximum H. Pylori eradication rates
- Determining CYP 2D6 polymorphisms can allow for improved pain management
- Determining CYP 2D6 polymorphisms can minimize toxicity for -2D6 substrates
- Genetic testing for the CYP450 system is FDA approved and available

[Thanks!](#)