Drug-Interactions and Their Clinical Relevance - II

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Assurex Health Inc. has funded a clinical trial using genetic screening to optimize effectiveness of antipsychotic medications in schizophrenia subjects.
Objectives

- Review pharmacological basis and types of drug interactions with an emphasis on gene–drug interactions;
- Discuss gene–drug interactions and differentiate with other types of drug interactions, especially drug–drug interactions;
- Discuss the consequences of the gene–drug and other drug interactions with clinical examples;
- Identify the important factors in determining the clinical significance of gene–drug and other drugs interactions.
Defining a Drug Interaction

“A measurable modification (in magnitude or duration) of the action of one drug by prior or concomitant administration of another substance.”

- Drug–drug (Prescription, OTC)
- Drug–herbal
- Drug–food
- Drug–disease
- Drug–alcohol

**Drug–gene interactions can be classified into:**
- Those that are due to polymorphism in PK genetic factors
- Those that are due to polymorphisms in PD genetic factors
Myths & Facts: Drug Interactions

- Always compromise clinical outcomes.
- Most adverse drug reactions are due to drug sensitivity.
- Not frequent enough to deserve our attention.
- Can only occur with pharmaceutical products.
- Most interactions are pharmacokinetic.
Pharmacogenetics (PG) vs. Pharmacogenomics (PGx)

- The study of the interaction between genetics and therapeutic drugs is variously called pharmacogenetics or pharmacogenomics.

PharmacoGENETics is used to
- Examine genetic differences (SINGLE GENE) in drug metabolism affecting individual responses to drugs.
- Explain unexpected drug response on a genetic basis.

PharmacoGENOMics is to
- Study genetic differences (MULTIPLE GENES) within a population to explain observed variability in drug response and tolerability.
- Predict drug response and occurrence of adverse reactions.

These terms are frequently used interchangeably.
Historical Perspectives

“By nature, men are nearly alike; by practice, they got to be wide apart.”
Confucius, Analects. Chinese Philosopher (551 BC – 479 BC)

“The dose makes the poison”
Paracelsus (1493–1541)
Paradoxical Approach of Modern Drug Development

• Clinical trials provide evidence of efficacy and safety at usual doses in *ideal* populations

• Physicians treat *individual* patients who can vary widely in their response to drug therapy
Drugs effective < 60% of the population
Genetic factors account for 20-95% of variability in elimination, efficacy and tolerability of drug
28% of hospitalized patients have adverse drug reactions (ADRs)
2.2 million serious ADRs
106,000 deaths in US/year
Cost of drug-related morbidity and mortality was $177 billion in 1998

Mitchell et al, 1979; Lazarou et al. 1998
Questions

- Why does someone need twice the standard dose to be effective?
- Why does this drug work for you but not me?
- Why do I have side-effects and you don’t?
- Why is anecdotal information irrelevant to your own health and treatment?
CASE 1: Breast CA Treated with Tamoxifen

- A patient with estrogen receptor–responsive breast CA treated with tamoxifen
- Develops MDD, treated with paroxetine 40 mg day
- Two years later patient experienced recurrence of breast CA

What could be the reason?

Stearns et al. 2003; Kelly et al. 2010
CASE 2: Case Examples
Death of a Breast-Fed Infant

- Breast feeding mother prescribed codeine at 60 mg BID PO for post–episiotomy pain
- After day 2, reduced to 30 mg BID PO after she developed somnolence and constipation
- On day 13 of breast feeding, her full term healthy male infant died

Why did the infant die?

Koren et al. Lancet 2006
CASE 3: Lack of Antidepressant Effects on High Dose Venlafaxine

- 40 year old patient does not experience any antidepressant effects with 300 mg/day of venlafaxine

What might be the reason?

Lobello et al 2010
CASE 4: Serious and Repeated Adverse Effects – Is DNA Involved?

- 23 year old borderline patient was admitted to the hospital
- Developed psychosis with SI and HI after father died with multiple ER visits
- Developed severe stiffness on when treated with perphenazine
- Past hx of NMS on Haldol; almost died
- Developed priapism on trazodone

WHY?

De Leon et al. 2006. Psychosomatics
CASE 5: Misinterpretation of Genetic Report

A patient with treatment refractory schizophrenia titrated gradually to usual doses of clozapine
- Developed AEs.
- Clozapine dose increased further with increase in adverse effects.
- Clozapine & norclozapine levels came back high.
- Dose reduced with significant improvement.
- Dose increased again resulting in recurrence of AEs.
- Psychopharm consult recommended dose reduction.
- Patient responded well without AEs.

WHY?
Case 1 & 2: Both codeine and tamoxifen are prodrugs requiring CYP2D6 to become active.
Case 1 is Ultra-rapid and Case 2 is poor metabolizer.
Case 3: Ultra-rapid metabolizer for CYP2D6.
Case 4: Both poor metabolizers for CYP2D6.
Case 5: Poor metabolizer for CYP1A2.
Think about the range of different outcomes ranging from:
- the GOOD (dose adjustments)
- the BAD (efficacy & tolerability) and
- the UGLY (safety).
### Phase I: CYP450 Enzyme Polymorphism

<table>
<thead>
<tr>
<th>Enzyme</th>
<th>Percentage</th>
<th>Polymorphisms</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP3A4</td>
<td>40%-45%</td>
<td>Rare</td>
</tr>
<tr>
<td>CYP2D6</td>
<td>20%-30%</td>
<td>*2xN, *4, *10, *17, *41</td>
</tr>
<tr>
<td>CYP2C9</td>
<td>10%</td>
<td>*2, *3</td>
</tr>
<tr>
<td>CYP2C19</td>
<td>5%</td>
<td>*2, *3</td>
</tr>
<tr>
<td>CYP1A2</td>
<td>5%</td>
<td>*1K</td>
</tr>
<tr>
<td>CYP2B6</td>
<td>2%-4%</td>
<td>-</td>
</tr>
<tr>
<td>CYP2E1</td>
<td>2%-4%</td>
<td>-</td>
</tr>
<tr>
<td>CYP2A6</td>
<td>2%</td>
<td>*4, *9</td>
</tr>
<tr>
<td>CYP2C8</td>
<td>1%</td>
<td>*3</td>
</tr>
<tr>
<td>CYP3A5</td>
<td>&lt;1%</td>
<td>*3</td>
</tr>
</tbody>
</table>

- Responsible for metabolism of 40% of all Rx drugs
- 57 Different active genes responsible for drug metabolism, primarily in the liver.
- 17 Different families

*Ingelman-Sandburg, 2004.*
Inheriting Genes from Parents

Alleles for CYP450 Enzyme 2B6
- *1 normal activity
- *6 reduced activity
- *4 increased activity

- *1/*4 Increased
- *4/*6 Normal
- *1/*6 Intermediate
- *6/*6 Decreased

6 have decreased activity
*1, *2, *4 and others have copy number polymorphisms
CYP450 2D6 Metabolizer Phenotypes

**Ultrarapid (UM):** Rapid rate of metabolism

**Extensive (EM):** Normal metabolism

**Intermediate (IM):** Reduced rate of metabolism

**Poor (PM):** Slow rate of metabolism

All of these variations in phenotype can make dosing and management of medications increasingly difficult.
CYP2D6 AND TCAs

TCA dose adjustments are recommended for 2D6 PM and UM.

Paroxetine Plasma Levels by Dose

CYP2D6 & OTHER ANTIDEPRESSANTS

**Recommendation:**

2C19 PM: 60% of standard doses

2C19 EM: 110% of standard doses

Antidepressant Efficacy Compromised by Decreasing Tolerability

**Treatment Alternatives to Relieve Depression (STAR*D) Trial**

<table>
<thead>
<tr>
<th>Step</th>
<th>QIDS-SR16 Response</th>
<th>Adverse Effects (intolerance)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>47%</td>
<td>16%</td>
</tr>
<tr>
<td>2</td>
<td>27%</td>
<td>20%</td>
</tr>
<tr>
<td>3</td>
<td>15%</td>
<td>26%</td>
</tr>
<tr>
<td>4</td>
<td>18%</td>
<td>34%</td>
</tr>
</tbody>
</table>

Antipsychotic dose adjustments are recommended for 2D6 PM and UM.

Clinical Relevance

- > 300 million scripts for drugs metabolized via polymorphic enzymes each year
- Of the top 27 drugs cited in ADR reports
  - 59% metabolized by at least one enzyme with poor metabolizer (PM) genotype
  - 38% metabolized by CYP2D6
    - A highly variable gene with 17 common, clinically relevant polymorphisms.
    - Located at a site on chromosome 22.
    - Duplications can occur in ultra-rapid activity.

*Phillips et al, JAMA, 286 (18), 2001, 2270-2279*
Current Medication Decision Factors

- Patient Experience
- Adverse Effects
- Family History
- Illness
- Adherence
- Cost

Medication Selection
Personalized Medication Selection Factors

- Pharmacogenomics
- Patient Experience
- Adverse Effects
- Adherence
- Illness
- Family History
- Cost
Benefits of Genetic Analysis

- Identification of early predictors of drug efficacy and/or tolerability
- Other advantages:
  - Ease of obtaining appropriate DNA information
  - Illuminating molecular substrates of psychotropic action
  - Immutability of genetic information
  - Increasingly low cost of genotyping assays
- Drugs with improved efficacy and tolerability will have improved medication adherence.
Dr. Mrazek received an e-mail from a patient who chose not to take any medication after he failed three trials with different ADs.

As a last resort, he asked for a genetic profile, which indicated that only 2 ADs were suitable.

Patient started taking 1 of those ADs and experienced remarkable improvement in his symptoms.

He wrote in his email:

“Do you remember the opening scenes from The Wizard of Oz?” “The film begins in black-and-white and suddenly is transformed into brilliant color. That change is less dramatic than the change in my life.”
120 drugs have PG information in the PDR
> 30 CNS drugs have PG information in PDR
1 in 4 patients receive CNS drugs with this information
However, the information could not be easily translated to clinical practice.
The FDA and Pharmacogenomics

- The Food and Drug Administration (FDA) includes pharmacogenomic language in the package inserts of many of the medications in the GeneSight Psychotropic test:

<table>
<thead>
<tr>
<th>Medication</th>
<th>Text</th>
<th>CYP2D6 Metabolism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aripiprazole</td>
<td>“The aripiprazole dose in PM patients should initially be reduced to one-half (50%) of the usual dose.”</td>
<td>CYP2D6 PM</td>
</tr>
<tr>
<td>Citalopram</td>
<td>“The maximum dose should be limited to 20 mg/day in patients who are CYP2C19 poor metabolizers.”</td>
<td>CYP2C19 PM</td>
</tr>
<tr>
<td>Thioridazine</td>
<td>“The use of thioridazine in patients known to have reduced activity of P450 2D6 are contraindicated.”</td>
<td>CYP2D6 IM or PM</td>
</tr>
<tr>
<td>Vortioxetine</td>
<td>“The maximum recommended dose of BRINTELLIX is 10 mg/day in known CYP2D6 poor metabolizers.”</td>
<td>CYP2D6 PM</td>
</tr>
</tbody>
</table>
### Practice Patterns of 352 Psychiatrist Survey

<table>
<thead>
<tr>
<th>Statement</th>
<th>% Agree</th>
</tr>
</thead>
<tbody>
<tr>
<td>I feel competent to discuss genetic information regarding psychiatric illness with patients and their families</td>
<td>23</td>
</tr>
<tr>
<td>I feel it is my role to discuss genetic information regarding psychiatric illness with patients and their families</td>
<td>83</td>
</tr>
<tr>
<td>My medical training has prepared me to discuss genetic information regarding psychiatric illness with patients and their families</td>
<td>15%</td>
</tr>
</tbody>
</table>

*Finn et al. 2005*
FDA-Approved Roche Chip for Cytochrome P450 Genes: CYPC19 and CYP2D6
### Some Clinically Relevant Drugs for 2D6 and 2C19 testing

<table>
<thead>
<tr>
<th>2D6</th>
<th>2C19</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Antidepressants</strong></td>
<td><strong>Beta Blockers</strong></td>
</tr>
<tr>
<td>amitriptyline</td>
<td>carvedilol</td>
</tr>
<tr>
<td>clomipramine</td>
<td>metoprolol</td>
</tr>
<tr>
<td>desipramine</td>
<td>propafenone</td>
</tr>
<tr>
<td>imipramine</td>
<td>timolol</td>
</tr>
<tr>
<td>paroxetine</td>
<td>Others</td>
</tr>
<tr>
<td>venlafaxine</td>
<td>atomoxetine</td>
</tr>
<tr>
<td><strong>Antipsychotics</strong></td>
<td><strong>Others</strong></td>
</tr>
<tr>
<td>haloperidol</td>
<td>codeine</td>
</tr>
<tr>
<td>risperidone</td>
<td>dextromethorphan</td>
</tr>
<tr>
<td>thioridazine</td>
<td>flecainide</td>
</tr>
<tr>
<td></td>
<td>mexiletine</td>
</tr>
<tr>
<td></td>
<td>ondansetron</td>
</tr>
<tr>
<td></td>
<td>tamoxifen</td>
</tr>
<tr>
<td></td>
<td>tramadol</td>
</tr>
</tbody>
</table>

Polymorphisms in PD genes can affect drug action at its target (e.g. receptors, ion channels, GPCRs, immune molecules).

Polymorphisms in PK genes can affect drug concentration at its target (e.g. enzymes, plasma protein binding).

PK and PD are not mutually exclusive.
PD & PK (polygenic) Determinants of Drug Effects

Pharmacokinetics  Pharmacodynamics  Variation in Response

 Genetic Polymorphism of Drug Exposure  +  Genetic Polymorphism of Drug Sensitivity

 Drug Metabolism Genotypes  Drug Receptor Genotypes

| Genetically Regulated Heterogeneity in Drug Effects |
| Therapeutic Effect (%) | Toxicity (%) |

A

<table>
<thead>
<tr>
<th>Drug Conc.</th>
<th>wt/wt</th>
<th>wt/m</th>
<th>m/m</th>
</tr>
</thead>
<tbody>
<tr>
<td>Effect (%)</td>
<td>30</td>
<td>65</td>
<td>99</td>
</tr>
<tr>
<td>Time (hr)</td>
<td>24</td>
<td>24</td>
<td>24</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Effect (%)</th>
<th>Effect (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>wt/wt</td>
<td>75</td>
</tr>
<tr>
<td>wt/m</td>
<td>35</td>
</tr>
<tr>
<td>m/m</td>
<td>10</td>
</tr>
</tbody>
</table>

B

<table>
<thead>
<tr>
<th>Drug Conc.</th>
<th>wt/wt</th>
<th>wt/m</th>
<th>m/m</th>
</tr>
</thead>
<tbody>
<tr>
<td>Effect (%)</td>
<td>85</td>
<td>45</td>
<td>10</td>
</tr>
<tr>
<td>Time (hr)</td>
<td>24</td>
<td>24</td>
<td>24</td>
</tr>
</tbody>
</table>

<table>
<thead>
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<tbody>
<tr>
<td>wt/wt</td>
<td>85</td>
</tr>
<tr>
<td>wt/m</td>
<td>45</td>
</tr>
<tr>
<td>m/m</td>
<td>10</td>
</tr>
</tbody>
</table>

C

<table>
<thead>
<tr>
<th>Drug Conc.</th>
<th>wt/wt</th>
<th>wt/m</th>
<th>m/m</th>
</tr>
</thead>
<tbody>
<tr>
<td>Effect (%)</td>
<td>95</td>
<td>50</td>
<td>10</td>
</tr>
<tr>
<td>Time (hr)</td>
<td>24</td>
<td>24</td>
<td>24</td>
</tr>
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<td>50</td>
</tr>
<tr>
<td>m/m</td>
<td>10</td>
</tr>
</tbody>
</table>

Genetic variation affecting drug response are also known as gene–drug interaction. However, interactions between two (or more) drugs (drug–drug interactions) can also result in similar outcomes as gene–drug interactions. In other words, drugs can change the phenotype from extensive to poor metabolizer.
Gene-Drug Vs. Drug-Drug Interactions: Atomoxetine

**CYP2D6 Poor Metabolizers**

A 10-fold higher AUC and a 5-fold higher Cmax to a given dose

Average HL increases from 5.2 to 21.6 hrs.

**CYP2D6 Inhibitors**

Atomoxetine concentration increases by 3-4 fold when given with paroxetine.

CYP2A6 metabolizes nicotine.

Genetic polymorphism of CYP2A6 determines which treatment is more effective.

Varenicline was more efficacious than nicotine patch with less adverse effects (AEs). in extensive metabolizers (EMs).

Thus, varenicline in EMs and nicotine patch in PMs could optimize quit rates while minimizing AEs.
• P-gp is an ATP-Binding Cassette B1 (ABCB1) protein transporter or efflux pump.
• Extrudes toxins and xenobiotics.
• Limits cellular uptake of drugs into brain & GIT.
• Genetic polymorphism in P-gp may cause gene-drug interactions.
P-glycoprotein Polymorphisms: Multidrug-Resistant (MDR) Epilepsy

**Genetic Findings:**
Homozygous for TT genotype have lower P-gp activity
Homozygous for CC genotype have greater P-gp activity
Heterozygous for CT genotype have intermediate P-gp activity

**Clinical Consequences:**
Patient with drug resistant epilepsy were 1.5 more likely than those with drug-responsive epilepsy to have CC genotype rather than the TT genotype ($p = .006$).

Transport Systems: P-gp: Variation in Drug Response

- Linked to development of multidrug resistance (MDR) in cancer cells.
- Plays a role in transport of β-amyloid out of the CNS.

Drug Concentrations in P-glycoprotein Knock-Out Mice vs Wild Type Animals

<table>
<thead>
<tr>
<th>Molecule</th>
<th>Plasma</th>
<th>Brain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyclosporine</td>
<td>1.9-fold</td>
<td>55-fold</td>
</tr>
<tr>
<td>Digoxin</td>
<td>1.9-fold</td>
<td>35-fold</td>
</tr>
<tr>
<td>Methadone</td>
<td>1.5-fold</td>
<td>15- to 23-fold</td>
</tr>
<tr>
<td>Risperidone</td>
<td>1.4-fold</td>
<td>13-fold</td>
</tr>
</tbody>
</table>

Interactions may be underestimated with plasma levels.
Limitations – Clinical Issues

- Polygenic drug response, making targeting different drugs complex.
- The environmental factors add further complexity in interpreting genetic results.
- Majority of studies have used a candidate gene approach based upon the pharmacology of a psychotropic (such as DRD2 and HTTLPR).
- Although effect sizes are statistically robust, they don’t guide on options for non-responsive genetic carriers.
- A task made more difficult by the fact that most widely used psychotropics have similar primary targets.
- Lack of prospective studies.
Ethnic Challenges

- Expensive and may compromise equity and access to drugs.
- Development of drugs may be targeted to those that work well with certain population groups.
- Any such targeting will need to be carefully implemented to avoid ethnically-based stigma.
- Similarly, ethnically-based genetic profiling is problematic as not all people within an ethnic group will have the same genetic polymorphisms.
Danish Pharmacogenomic Study in Schizophrenia Genotyping for CYP2D6 and CYP2C19

- Classified as poor metabolizers (PM; Danish = 8%) and ultra-rapid metabolizers (UM; Danish = 3%) (intermediate metabolizers excluded)
- 209 patients (mean age = 41 yrs.)
- Cost of genotyping = $179/patient
- Total Rx cost $23,361 for genetically guided group versus $27,350 for controls (a difference of 24% on costs after controlling for factors)
- However, Rx costs 177% higher in UM than normal metabolizers.
- Treatment changes after knowing UM status, reduced costs of psychiatric care from $67,000 to $20,000.
"Here's my sequence..."