Polypharmacy and Pharmacogenomics: Implications in Transplantation

Jennifer N. Gray, Pharm.D.

9th Annual Nurse Practitioners Symposium

October 17 – 18th, 2013
Objectives

• Define Polypharmacy and Pharmacogenetics

• Describe the contribution of polypharmacy to adherence and medication errors

• Discuss the role of the transplant pharmacist/coordinator in combating polypharmacy

• Describe the contribution of pharmacogenetics/genomics and prescribing
What is Polypharmacy?
Polypharmacy Definitions

• Classifications vary in the literature and no consensus as to exact definition

1.) “Polypharmacy = inappropriate med use”
2.) “Use of at least one potentially inappropriate drug”
3.) “The presence of 6 or more concurrent medications”
4.) “Two or more meds to treat the same condition”
5.) “Medications prescribed greater than twice per day”
6.) “Complicated drug regimen affecting compliance”

1.) Polypharmacy = inappropriate med use

• Post transplant home meds fail to get restarted or are started back inappropriately
  – Herbals/NSAIDs/other pain meds/hormones
  – Sometimes unnecessary meds

• Outside physicians start extraneous meds
  – Medications may have an interaction with immunosuppressants or cause adverse events
2.) Polypharmacy = Use of at least one potentially inappropriate drug

• One drug can cause a disaster with tacrolimus/cyclosporine levels
  – If a patient uses a different pharmacy to fill the new prescription from the outside MD, you will not know/be notified about the drug interaction
  – **Example:** An outside MD prescribes Biaxin (clarithromycin) for community acquired pneumonia
3.) Polypharmacy = The presence of 6 or more concurrent medications

- 6 or more?? Welcome to transplant!

- At the very least, most organ transplant patients are taking ~6 new medications when they leave the hospital after transplant

- Most patients are also on additional meds to control symptoms
  - Anti-hypertensives, insulin, pain meds, stool softeners, psych meds, etc
4.) Polypharmacy = Two or more meds to treat the same condition

• Common mistake to not maximize one drug dosage, before starting another agent
  – A patient may be on a mid-range dose of one drug and then another agent is added to treat the same problem
  – Example:
    • Your patient is on Lisinopril 10mg daily and the doctor wants to add Amlodipine to better control BP
5.) **Polypharmacy** = Medications prescribed greater than twice per day

- Much easier for most patients to comply with a twice daily regimen

- Midday doses can be easily missed
  - Nystatin TID, Hydralazine TID, Clonidine TID

- Most med boxes have a “noon” slot, but requires patients to bring meds/vials with them everywhere they go
6.) Polypharmacy = Complicated drug regimen affecting compliance

- Complicated!? Welcome to transplant!!
- The harder we make it, the harder it will be for patients and caregivers to keep up
- Put yourself in their shoes, “Would I want to take all of these meds, each day, around the clock?”
Polypharmacy: Background

• PubMed search of the term “polypharmacy”
  – Resulted in 4037 generic hits
  – First article published in Archives of Internal Medicine in 1955, entitled:
    • “Vitamania, polypharmacy, and witchcraft”
  – Majority of information is in HIV/AIDS patients or in the elderly
Not Surprising…

• Outside of the HIV literature, there is very little information on this topic and most is done outside the United States

— Barriers to conduct research/clinical trial:
  • No gain for drug companies
  • A lot of work for individuals
Also Not Surprising...

• High likelihood of polypharmacy continuing to be a problem in the field of transplant

  – Generally speaking, complicated patients require complicated medication regimens

  – We are now transplanting older and more sick patients

    • In most cases means more maintenance meds
Other Issues Associated With Polypharmacy

- Medication Errors
- Noncompliance/Nonadherence
Could Pharmacogenomics help us with Polypharmacy?

....Potentially
Pharmacogenomics (PGx)/genetics (PGt)

- These terms are often used interchangeably
- No real consensus on exact definition
- In most sources, pharmacogenomics is a used as a broader term
- Taking this information from bench to bedside can be problematic
  - Philosophical issues
  - Societal issues
  - Cultural issues
Pharmacogenomics (PGx): Definitions

- “A science that examines the inherited variations in genes that dictate drug response and explores the ways these variations can be used to predict whether a patient will have a good response to a drug, a bad response to a drug, or no response at all”

- “The study of inter-individual variations in the whole genome”

- “The technology that analyzes how genetic makeup affects an individual's response to drugs”
Barriers to this Approach

• We don’t know all the genes involved in each specific drug response

• Patients DNA must be sequenced to find the genetic variations
  – Many variations within the human genome
  – This technology is slow and expensive

• Can this really work in “real life”?
Response to a Drug

- GENETICS
- Age
- Gender
- Body Size
- Concomitant Drugs
- Liver and Kidney Function

VANDERBILT UNIVERSITY MEDICAL CENTER
Buzz Word: Personalized Medicine

Does it make sense that a drug dose for a 100lb person is the same drug dose for a 300lb person?
Pharmaceutical companies are limited to creating drugs in a “one size fits all” model.

They use a mixture of “average” patients in which to test the drug and determine drug dosing across a broad range of other variations. This assumption of one size can fit all is what can often lead to adverse drug reactions (ADRs).
Impacts on Drug Company Research

• The hope would be to streamline clinical trial phases of research using pharmacogenomics

• Groups of participants would be those most likely to benefit from the drug
  – Eliminate those people how would be known “non responders”

• Less rejections from the market if we eliminate those patients we suspect might have an adverse event
......Maybe for some people and some drugs....one size fits all does make sense?
ONE SIZE DOES NOT FIT ALL

ONE SIZE FITS ALL.
EXCEPT FOR YOU, OF COURSE.
A Growing Problem...

- More drugs, more side effects, sicker patients, less money to go around, less people to do more work....

All add up to adverse drug reactions (ADRs)

- How many times have you prescribed an medication to many patients with no issues?
  - Then one patient has an unexpected bad reaction
Exciting New Possibilities?

• https://www.youtube.com/watch?v=b3T1b3eb6Go&list=PLucLRYfUxMGgMFZZmWlqsV8g5_bBeRgF

• https://www.youtube.com/watch?v=CrlFzhZWOO8&list=PLucLRYfUxMGgMFZZmWlqsV8g5_bBeRgF

• https://www.youtube.com/watch?v=lzN9Ay6w248&list=PLucLRYfUxMGgMFZZmWlqsV8g5_bBeRgF
Recall one of the definitions of Polypharmacy....
3.) Polypharmacy = The presence of 6 or more concurrent medications

- 6 or more?? Welcome to transplant!
- At the very least, most organ transplant patients are taking ~6 new medications when they leave the hospital after transplant
- Most patients are also on additional meds to control symptoms
  - Anti-hypertensives, insulin, pain meds, stool softeners, psych meds, etc
• If we could individualize each patient’s medications and know what would work and what may not work
  – Polypharmacy could potentially be reduced
  – Possibly avoid prescribing inappropriate medications to which a patient may not respond
  – We could also avoid prescribing additional medications that are added to treat side effects
P R E D I C T
Pharmacogenomic Resource
For Enhanced Decisions
In Care & Treatment

PREDICT Team:
Marc Beller, Erica Bowton, Julie Field, & Jennifer Mitchell
The PREDICT program uses drug-gene testing to optimize patient’s drug therapy; it is part of Vanderbilt’s personalized medicine initiative.

**Project Goals:**
1. To prospectively identify patients who are likely to receive target medications in the next 3 years
2. To genetically test these patients
3. To tailor their drug therapy according to the results

**Objective:**
Personalized drug therapy based on genetic makeup to ensure …

- The right drug.
- The right dose.
- The first time.
The PREDICT panel tests 184 SNPs within 34 genes which are known to impact drug therapy.

Other drug-genome interactions (DGIs) will be added with no need to retest these patients.

Clopidogrel, simvastatin, warfarin, and thiopurine gene results are currently tested.

PREDICT, a one-time test, provides a lifetime of opportunities for therapeutic intervention:

1. Guide selection of drug and dosages
2. Improve patient outcomes
3. Avoid unnecessary drug-related complications
4. Decrease health care costs

Sample Drugs | Enzyme
---|---
**Clopidogrel** | CYP2C19
**Warfarin** | CYP2C9
**Tacrolimus** | CYP3A5
**Tamoxifen** | CYP2D6
**Codeine** | CYP2D6
Quinidine | CYP2D6
Carvedilol | CYP2D6
Metoprolol | CYP2D6
Prasugrel | CYP2C19
Propafenone | CYP2D6
Propranolol | CYP2D6
Ticagrelor | CYP2C19
Atomoxetine | CYP2D6
Fluoxetine | CYP2C6
Fluvoxamine | CYP2C9
Risperidone | CYP2D6
Tiotropium | CYP2D6

**Warfarin** | VKORC1
**Simvastatin** | SLC01B1
**Thiopurines** | TPMT

*Denotes drug-genome interactions that are live or within the development pipeline.
PREDICT Test Ordering Specifics

• PREDICT = Pharmacogenomic Panel = PDX

• Various modes of order entry
  – OPOC, Paper Requisition, VOOM, HEO/Wiz

• Standard blood draw
  – Lavender top tube, 3-5 mL

• Turnaround time of ~4-5 days
• No consent is required
• Currently available at no cost to the patient
Why focus on Tacrolimus?

- Low Levels
- High Levels
- Rejection
- Side Effects
- Malignancies
Genotyping indicates patient may have **INCREASED** 3A5 activity based on a detection of **TWO** expression alleles for CYP3A5

**HYPO-RESPONDER**
Suggest dose **increase**

Genotyping indicates patient may have **INCREASED** 3A5 activity based on a detection of **ONE** expression alleles for CYP3A5

**HYPO-RESPONDER**
Suggest dose **increase**

Genotyping indicates the patient is a **NON-EXPRESSOR** for CYP3A5

**Standard RESPONDER**
Use Standard Dosing
### PREDICT Results

#### StarTracker Quality Dashboard

**Notation indicates test is due for repeat and value may be outdated.**

<table>
<thead>
<tr>
<th>Patient-specific guidelines</th>
<th>MedicationsLog</th>
<th>Update</th>
<th>Update (free text)</th>
<th>NoChange</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>General Information:</strong> (03/19/13 13:33, Mitchell, Jennifer K for Mitchell, Jennifer K.)</td>
<td><strong>Adverse and Allergic Drug Reactions:</strong> (03/19/13 13:33, Mitchell, Jennifer K for Mitchell, Jennifer K.)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test Patient</td>
<td>No known allergies</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Structured Problems:</strong> (03/19/13 13:33, Mitchell, Jennifer K for Mitchell, Jennifer K.)</td>
<td><strong>Drug Genome Interactions:</strong> (01/02/13 15:10, Byrd, Jeff)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No current problems as of 03/19/2013 13:33:03</td>
<td>clopidogrel sensitivity: POOR METABOLIZER, REDUCED ANTI-PLATELET EFFECT - gene: CYP2C19 - gene result: *2/*2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>warfarin sensitivity: Hyper Responder - gene results: VKORC1 A/A; CYP2C9 *2/*2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>simvastatin sensitivity: HIGH MYOPATHY RISK, MINOR ALLELE HOMOZYGOUS (C,C) - gene: SLC01B1 - gene result: *5/*5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>thiopurine sensitivity: HIGH MYELOTOXICITY RISK, MINOR ALLELE HOMOZYGOUS - gene: TPMT - gene result: *3a/*3a</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>tacrolimus sensitivity: HYPO RESPOIDER - gene: CYP3A5 - gene result: *1/*1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Note: Most genetic variants with therapeutic considerations demonstrate reproducibility of greater than 98%. Please visit <a href="http://www.mydruggenome.org">www.mydruggenome.org</a> for additional information.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Medications:</strong> prepare to print</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>print and give pt.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Show Hx of medications</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Drug/Herb Interactions (03/19/13 13:33, Mitchell, Jennifer K for Mitchell, Jennifer K.)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>No current medications as of 03/19/2013 13:32:20</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Randomized study to evaluate whether adaption of FK doing according the CYP3A5 genotype would allow earlier achievement of target blood concentrations of FK in renal tx recipients

- 280 kidney recipients
  - 140 in “Adapted-dose” group
  - 140 in Control group

**Frequencies of CYP3A5 Alleles**

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Total</th>
<th>Control Group</th>
<th>Adapted-dose group</th>
</tr>
</thead>
<tbody>
<tr>
<td>*1/*1</td>
<td>10 (4.2%)</td>
<td>6 (5%)</td>
<td>4 (3.4%)</td>
</tr>
<tr>
<td>*1/*3</td>
<td>40 (16.9%)</td>
<td>18 (15%)</td>
<td>22 (19%)</td>
</tr>
<tr>
<td>*3/*3</td>
<td>186 (78.8%)</td>
<td>96 (80%)</td>
<td>90 (77.6%)</td>
</tr>
</tbody>
</table>
Prospective Pretransplantation Adaption
Renal Transplant Patients

CONTROL
Fixed dose of 0.2mg/kg/day

ADAPTED

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Daily Dose (mg/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>*1 carrier</td>
<td>0.30</td>
</tr>
<tr>
<td>*3/*3</td>
<td>0.15</td>
</tr>
</tbody>
</table>

Thervet et al, 2010

Trough tacrolimus levels categorized by CYP3A5 genotype.
Optimization of Initial Tacrolimus Dose Using Pharmacogenetic Testing

E Thervet\textsuperscript{1,2}, MA Loriot\textsuperscript{3}, S Barbier\textsuperscript{4}, M Buchler\textsuperscript{5}, M Ficheux\textsuperscript{6}, G Choukroun\textsuperscript{7}, O Toupance\textsuperscript{8}, G Touchard\textsuperscript{9}, C Alberti\textsuperscript{10}, P Le Pogamp\textsuperscript{11}, B Moulin\textsuperscript{12}, Y Le Meur\textsuperscript{13}, AE Heng\textsuperscript{14}, JF Subra\textsuperscript{15}, P Beaune\textsuperscript{3} and C Legendre\textsuperscript{1,2}

\textbf{Figure 3} Time to achieve tacrolimus $C_0$ target range (10–15 ng/ml).
## Results

### Table 3  Study end points

<table>
<thead>
<tr>
<th>End point</th>
<th>Control group</th>
<th>Adapted-dose group</th>
<th>Pvalue</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n = 120)</td>
<td>(n = 116)</td>
<td></td>
</tr>
<tr>
<td><strong>Primary end point</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proportion of patients with TAC $C_0$ in target range after six oral doses, % (95% CI)</td>
<td>29.1% (22.8–35.5)</td>
<td>43.2% (36.0–51.2)</td>
<td>0.030</td>
</tr>
<tr>
<td><strong>Secondary end points</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TAC $C_0$ at day 10, ng/ml (median (1st–3rd quartiles))</td>
<td>15.4 (10.6–21.2)</td>
<td>12.1 (9.1–15.2)</td>
<td>0.001</td>
</tr>
<tr>
<td>$CYP3A5^*1/*1$</td>
<td>5.6 (4.4–9.7)</td>
<td>14.0 (11.5–18.3)</td>
<td>0.035</td>
</tr>
<tr>
<td>$CYP3A5^*1/*3$</td>
<td>10.1 (6.8–14.6)</td>
<td>12.3 (8.6–17.9)</td>
<td>0.26</td>
</tr>
<tr>
<td>$CYP3A5^*3/*3$</td>
<td>16.6 (12.5–21.7)</td>
<td>12.0 (9.1–14.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Time to achieve target TAC $C_0$, days (median (1st–3rd quartiles))</td>
<td>7 (3–25)</td>
<td>6 (3–8)</td>
<td>0.001</td>
</tr>
<tr>
<td>$CYP3A5^*1/*1$</td>
<td>23 (6–24)</td>
<td>3 (3–27)</td>
<td></td>
</tr>
<tr>
<td>$CYP3A5^*1/*3$</td>
<td>7 (6–23)</td>
<td>6 (3–7)</td>
<td></td>
</tr>
<tr>
<td>$CYP3A5^*3/*3$</td>
<td>7 (3–25)</td>
<td>7 (3–8)</td>
<td></td>
</tr>
</tbody>
</table>
Results, cont.

• Delayed graft function incidence was similar between groups

• At 3 months, biopsy proven rejection:
  – 7.1% in the adapted dose group
  – 8.9% in the control group (p = NS)

• Adverse events:
  – 361 in the adapted dose group
  – 389 in the control group (p = NS)
Tacrolimus Therapy Hypo-responder

Genetic testing has been performed and indicates that this patient may have a DECREASED response to tacrolimus. (See StarPanel for patient-specific CYP3A5 gene result).

This patient has been tested for CYP3A5 variants. This test has identified the presence of an allele which is associated with a decreased response to tacrolimus. Hypo-responders have increased CYP3A5 activity and may require an increased dose of tacrolimus to achieve therapeutic effect.

Tacrolimus dose increase recommended.

Click here for more information

Order  Cancel

NOTE: NOTE: The Vanderbilt P&T Committee has approved this recommendation based on the detailed review of the literature and consensus guideline.
Future Directions

• As technology is further developed, patients will go to the doctor office and have their specific genomic panel

  – Drugs will be chosen based on this panel
  – Likelihood of ADRs will be reduced
  – Less chance of trying multiple drugs before finding one that works
Why does this matter to me?

• Healthcare is changing
  – Institutions are pushing for more productivity with less resources
  – Providers are spread thin, patients most times have limited incomes
  – Choosing the correct medication the first time will ultimately save money and hopefully decrease adverse events

• Tacrolimus isn’t going away
  – Correct dosing is always an issue
  – Pgx can directly impact our daily practice
Take Home Points

• Polypharmacy is a huge problem in organ transplantation and most post transplant regimens are:
  – Complicated
  – Include costly/high risk meds

• Polypharmacy adds to patient confusion, medication errors, and non-adherence

• Pharmacogenomics may be a helpful tool to use in the future to prescribe medications known to benefit the patient
Questions?

Thank you!!!
Polypharmacy and Pharmacogenomics: Implications in Transplantation

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You are about to exceed the limits of my medication.