Breakout Session 2: Psychiatry Patient Cases, Clinician Perspectives, and Discussion

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Disclosure

• I declare no conflicts of interest, real or apparent, and no financial interests in any company, product, or service mentioned in this program, including grants, employment, gifts, stock holdings, and honoraria.

• The University of Florida College of Pharmacy is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education.
Objectives

• Apply scientific and clinical principles to solve representative patient cases for genotype-guided drug therapy in psychiatry
• Recommend drug therapy changes that integrate individual genetic data with other relevant patient-specific clinical factors in psychiatry.
Patient A

- Patient A is a 9-year-old female with Fragile X syndrome (FXS), intellectual disability (mild to moderate), autism spectrum disorder (ASD), anxiety, and intermittent explosive disorder
- Presented for treatment of significant irritable tantrums, physical aggression, and self-harming behaviors
- Maintained on sertraline 150mg daily and trazodone 100 mg throughout the course of her treatment
- Initial CGI-S score was rated by the clinician as “5-markedly ill”
- Failed an aripiprazole titration to 7.5 mg - use associated with significant AEs including sedation and lethargy
Atypical antipsychotics for irritability

- Currently there are two atypical antipsychotics, risperidone and aripiprazole, that have been approved by the US Food and Drug Administration (FDA) for the treatment of irritability in youth with ASD
- Aripiprazole and risperidone are both metabolized by CYP2D6
Patient A

• CYP2D6 poor metabolizer (*4/*5, activity score: 0)
• She began a trial of paliperidone 1.5 mg PO daily
• After several dose adjustments over the course of two months to address ongoing irritability, she maintained a 6 mg paliperidone daily dose
• Following titration of paliperidone, Patient A had significant improvements in irritability, self-injury, and physical aggression
• CGI-I score was scored as “2-much improved” at 2 month follow up visit
• From unpublished retrospective case series by Drs. Pedapati, Wink and Erickson at CCHMC that includes two other similar cases
Patient B

- 24 year old male with severe panic disorder
- Medication failures:
  - Paroxetine: sedation at low dose, 10 mg
  - Fluoxetine 20 mg daily, significant GI distress
  - Venlafaxine associated with GI distress, dysasthesias, and worsening anxiety
- The only effective treatment--prior to his seeing Dr. Strawn--was low dose lorazepam (0.5 mg TID)
Paroxetine, fluoxetine, and venlafaxine all CYP2D6 substrates

SUPPLEMENTAL FIGURE S1. METABOLISM OF SSRIs, WHERE BOLDED ENZYMES REPRESENT A MAJOR METABOLIC PATHWAY.

Dr. Strawn suspected, based on the history, a CYP2D6 issue
Confirmed by testing to be CYP2D6*4/*5, activity score 0, poor metabolizer
Ultimately, Dr. Strawn chose to use tranylcypromine (MAOI) and he's done very well for >1.5 years
Patient C

• 9 year old male with generalized anxiety disorder after surviving leukemia & bone marrow transplant
• Psychiatric history: prior diagnoses of unspecified anxiety and GAD with therapy alone and no psychiatric hospitalizations
• Previous medication trials:
  – Fluoxetine 5 mg (half of normal starting dose) that was discontinued due to bed wetting and becoming disinhibited
  – Sertraline also produced similar side effects
Patient C

- PGx testing done twice – first time failed due to DNA from patient and donor
- Genotyping revealed: CYP2D6 (*2A/*4), CYP2C19 (*1/*1) and SLC6A4 L/S
- Report stated decreased likelihood of response to SSRIs due to presence of the short form of the SLC6A4 gene
- SNRI venlafaxine was in “use as directed” category
- Venlafaxine was started and titrated up to 75 mg/day, greatly resolved anxiety symptoms
Venlafaxine efficacy in GAD patients may be influenced by SLC6A4

Effect may be opposite in MDD/bipolar patients treated with venlafaxine

Proft et al. Pharmacopsychiatry 2014; 47(07): 245-250
Patient D

- 52 year old female with type II bipolar disorder
- Medication failures:
  - Non-response to: valproic acid, carbamazepine, clomipramine, citalopram, buproprion
  - Response but intolerable side effects: olanzapine-fluoxetine (weight gain, hyperglycemia)
- Responded to aripiprazole 10 mg/day for four months but depressive symptoms re-emerged

“Psychiatric Pharmacogenetics: from concepts to cases.” Durham & Thirumaran. 2017
Aripiprazole label

Dosage adjustment due to drug interactions (7.2):

<table>
<thead>
<tr>
<th>Factors</th>
<th>Dosage Adjustment of ABILIFY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Known CYP2D6 Poor Metabolizers</td>
<td>Administer half of usual dose</td>
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<tr>
<td>Known CYP2D6 Poor Metabolizers and strong CYP3A4 inhibitors</td>
<td>Administer a quarter of usual dose</td>
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<tr>
<td>Strong CYP2D6 or CYP3A4 inhibitors</td>
<td>Administer half of usual dose</td>
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<tr>
<td>Strong CYP3A4 inducers</td>
<td>Double usual dose over 1 to 2 weeks</td>
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<table>
<thead>
<tr>
<th>DOSAGE AND ADMINISTRATION</th>
<th>Initial Dose</th>
<th>Recommended Dose</th>
<th>Maximum Dose</th>
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<tbody>
<tr>
<td>Schizophrenia – adults (2.1)</td>
<td>10-15 mg /day</td>
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<td>30 mg /day</td>
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<tr>
<td>Schizophrenia – adolescents (2.1)</td>
<td>2 mg /day</td>
<td>10 mg /day</td>
<td>30 mg /day</td>
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<td>Bipolar mania – adults: monotherapy (2.2)</td>
<td>15 mg /day</td>
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<tr>
<td>Bipolar mania – adults: adjunct to lithium or valproate (2.2)</td>
<td>10-15 mg /day</td>
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<td>30 mg /day</td>
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<tr>
<td>Bipolar mania – pediatric patients: monotherapy or as an adjunct to lithium or valproate (2.2)</td>
<td>2 mg /day</td>
<td>10 mg /day</td>
<td>30 mg /day</td>
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Patient D

- CYP2D6: normal metabolizer
- CYP2C19: rapid metabolizer
- Aripiprazole increased to 15 mg
- Insurance didn’t cover 15mg dose but symptoms improved
- Fluoxetine added to inhibit CYP2D6 (titrated up to aripiprazole dose reduced to 10 mg every other day)
- Patient in remission for 1 year

“Psychiatric Pharmacogenetics: from concepts to cases.” Durham & Thirumaran. 2017

Concomitant administration of paroxetine (PRX) and fluvoxamine (FLV) decrease the clearance of aripiprazole.

Patient E

• 5 year old boy with fetal alcohol syndrome, ADHD, Tourette’s, and extreme behavioral problems

• Medication history:
  – Clonidine for tics, added fluoxetine 5 mg/day at age 6
  – Fluoxetine increased to 30 mg/day, produced vomiting and diarrhea, hospitalization
  – Fluoxetine increased to 40 mg/day, nausea, vomiting, hospitalization, disorientation
  – Age 8: OCD diagnosed, started on methylphenidate for ADHD, titrated up to 60 mg/day, fluoxetine increased to 80 mg/day
  – Brief generalized seizure

Patient E cont.

- Current recommended maximum dose of fluoxetine 60 mg/day
- Age 9: Fluoxetine increased to 100 mg/day, increasing complaints of vomiting and dizziness, unsteady gait
- Tonic-clonic seizure of brief duration with fever
- Second seizure for 30 minutes followed by cardiopulmonary arrest, unresponsive to all interventions
- Autopsy revealed blood concentration of fluoxetine was 21 ug/mL, death listed as homicide because parents controlled medication
- Legal investigation of adoptive parents threatened removal of other children
- Parents requested review by child psychiatrist trained in clinical pharmacology
Patient E cont.

- Normal fluoxetine concentrations 0.1-0.5 ug/mL, lethal concentration in other kids: 5-6 ug/mL
- Ratio of fluoxetine to norfluoxetine was found to be ~1 in many tissues (21 ug/mL of each in blood)
- Not consistent with acute ingestion (parent drug would be much higher than metabolite)
- CYP2D6 poor metabolizer ("two mutant alleles")
- Charges against parents dropped

https://www.pharmgkb.org/pathway/PA161749012
Clinical Perspectives

- Pharmacogenetic tests are being marketed directly to patients as a way to find the medication that will work for them
- Some patients bring PGx testing results with them to their first appointment or ask for it at their first appointment
- Some parents are adamant that the patient be put on a medication based on a PGx report
- Many medications on PGx reports are not approved for use in pediatrics
- Nurses are struggling with how to explain to patients what the test does/doesn’t do
Research Perspectives

- Evidence is lacking or conflicting for some of the medications and variants tested on some of the reports, but people may equate more genes with a “better” test
- Just because an enzyme is involved in the metabolism of a medication doesn’t mean that variants in that gene influence response
- Most PGx studies in psychiatry have not been performed in pediatrics
- None of the clinical trials of PGx-guided dosing in psychiatry have included pediatric patients
Anecdote 1

- Mother asked about PGx testing she heard about her neighbor had completed to find the right drug
- Her daughter (13 years old) has been on several medications (>4) when 8 years old and stopped because mother felt she was being a “guinea pig”
- Obtained cheek swab after discussing the nature of what the test is for and that it still may take some time to find medicine that she might tolerate
- They did seem to get a better understanding upon leaving
- Education for clinicians could help patient & parent understanding of pharmacogenetic testing
Anecdote 2

• Mother of a young male patient with ADHD and anxiety requested PGx testing
• Previously failed one SSRI with previous doctor prior to moving, sertraline was not effective at that time
• Mother was insistent on getting results over the phone rather than at follow-up appointment
• When APRN started to discuss the CYP2C19 reduction in function, the mother started crying and asked if there was a supplement for this and then asked to be seen by an expert in this field
• Patient transferred to MD with considerable expertise
• Same APRN may be able to help one family understand but not another
Anecdote 3

- ADHD patient on max dose of methylphenidate (Concerta) and had tried most stimulants with side effects or no effect
- PGx testing performed – all ADHD medications were in “Use as directed” category on report
- Patient did not return for follow-up visits
Variability in response to these drugs can be attributed to many things
Summary

• Patients are interested in using pharmacogenomics to guide decision on which neuropsych medication to choose
• Clinicians are open to using neuropsych PGx but more cautious and many feel like they need more education on it
• The choice of a neuropsych medication is complex, influenced by many things, with pharmacogenomics being a tool to add to the discussion
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  • Susan Franer, APRN
  • Dianne Meyer, APRN
  • Cindy Prows, APRN
References

• Proft et al. Pharmacopsychiatry 2014; 47(07): 245-250
• Aripiprazole label: https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=c040bd1d-45b7-49f2-93ea-aed7220b30ac
• https://www.pharmgkb.org/pathway/PA161749012