Pharmacokinetics/Pharmacodynamics/Pharmacogenomics PRN and Central Nervous System PRN Focus Session—An Update of Psychotropic Pharmacogenomics
Activity Number: 0217-0000-15-140-L01-P, 1.50 hours of CPE credit; Activity Type: A Knowledge-Based Activity

Tuesday, October 20, 2015
1:30 p.m. to 3:00 p.m.
Plaza Room B

Note: This session is being recorded for future playback. A complimentary copy of these recordings will be available to all 2015 ACCP Global Conference on Clinical Pharmacy registrants approximately two weeks after the conclusion of the conference.

Moderator: Keith A. Moore, Pharm.D., BCPS
Chief Scientific Officer, ICIOMICS Life Sciences, LLC, Fairfield, Ohio

Agenda

1:30 p.m. Evaluate the Latest Pharmacogenomic Research on Managing Metabolic Syndrome/Obesity with Psychotropic Medications
Vicki L. Ellingrod, Pharm.D., FCCP
John Gideon Searle Professor of Clinical and Translational Pharmacy, University of Michigan, Ann Arbor, Michigan

2:00 p.m. Pharmacogenetics of Serotonin and Dopamine System Genes in Psychiatry
Jeffrey R. Bishop, Pharm.D., MS, BCPP
Associate Professor, University of Minnesota, Department of Experimental and Clinical Pharmacology, College of Pharmacy, Minneapolis, Minnesota

2:30 p.m. Clinicians’ Ability to Implement Pharmacogenomic Testing into Psychopharmacotherapy Comprehensive Medication Management (CMM) Services
Megan Ehret, Pharm.D., MS, BCPP
Behavioral Health Clinical Pharmacy Specialist, Specialist Department of Defense Fort Belvoir Community Hospital, Fort Belvoir, Virginia

Conflict of Interest Disclosures
Jeffrey R. Bishop: Advisory board for Physicians’ Choice Laboratory Services, and Janssen.
Megan Ehret: no conflicts to disclose.
Vicki L. Ellingrod: no conflicts to disclose.
Keith A. Moore: Employee of ICIOMICS Life Sciences, LLC.
### Learning Objectives

1. Describe the pharmacologic mechanisms of managing metabolic syndrome with psychotropic medications.
2. Evaluate the impact of genetic variations on antipsychotics induced metabolic syndrome.
3. Review the latest pharmacogenomic research surrounding psychotropic induced obesity and/or metabolic syndrome.
4. Identify genetic variability in serotonin and dopamine system genes that may impact drug mechanisms.
5. Describe associations between these polymorphisms and treatment outcomes.
6. Discuss how or if these genetic variants may impact clinical care.
7. Describe the logistics of acquiring, assessing and utilizing patients’ genetic information to guide psychopharmacotherapeutic decisions.
8. Demonstrate the application of pharmacogenomic testing results in the management of treatment-resistant depression.
9. Identify the optimal means of capturing the clinical and economic impact of the integration of clinical pharmacogenomic testing into a pharmacist-delivered CMM service.

### Self-Assessment Questions

Self-assessment questions are available online at [www.accp.com/gc15](http://www.accp.com/gc15).
Learning Objectives

1. Describe the pharmacologic mechanisms of managing metabolic syndrome with psychotropic medications
2. Evaluate the impact of genetic variations on antipsychotics induced metabolic syndrome
3. Review the latest pharmacogenomic research surrounding psychotropic induced obesity and/or metabolic syndrome

Loss of Life Years in Schizophrenia

Colton CW et al 2006
- Compared the mortality of public mental health clients in eight states with state mortality – using age-adjusted death rates, standardized mortality ratios, and years of potential life lost
  - Virginia – 13.5 years
  - Arizona – 31.8 years
  - Texas – 29.3 years
  - Missouri 27.9 years
  - Utah - 26.9 years
  - Oklahoma – 36.3 years

Conflict of Interests

NO conflicts to disclose

- Dr. Ellingrod’s research is supported by:
  - NIMH (K08MH064158 and R01 MH082784-01)
  - NIH-NCCR, GCRC/CTSA Program (UL1RR024986)
  - Chemistry Core of the Michigan Diabetes Research and Training Center (NHP/00 DK 20572)
  - University of Michigan College of Pharmacy Vahlteich Award
  - Washtenaw Community Health Organization (WCHO), the Ann Arbor Veterans Affairs Medical Center, and the Detroit-Wayne County Community Mental Health Agency (OW/CMA)
  - National Alliance for Research In Schizophrenia and Depression (NARSAD)
  - Prechter Longitudinal Study and the Depression Center

Topic Reviews


PGx of Antipsychotic Associated Metabolic Syndrome

- Genetic factors thought to play a role in Antipsychotic Induced Weight Gain (AIWG) and metabolic syndrome
  - Serotonergic System (HTR2C)
  - Melanocortin receptor family (MC4R)
  - Leptin system (LEP and LEPR)
  - Neuropeptide Y (NPY)
  - Cannabinoid Receptor 1 (CNR1)
  - Methylene tetrahydrofolate reductase (MTHFR)
  - Catechol-o-methyl transferase (COMT)
Melanocortin 4 Receptor (MC4R)

- Melanocortin 4 protein
  - G protein coupled receptor that binds to α-melanocyte stimulating hormone
  - Physiology
    - Responsible for pigmentation of hair and skin
    - Also plays a role in feeding and emergency homeostasis
    - Knock out mouse model = obesity

- Candidate for Weight Related Phenotype
  - Genome Wide Association Studies (GWAS)
    - \( N = 77,226 \) adults with BMI measures
    - rs17782313 strongly associated with BMI
    - Each C allele associated with BMI differences of 0.049 (0.22 kg/m\(^2\)) \((p=2.9x10^{-15})\)
    - “Our findings establish that common variants near \(MC4R\) influence fat mass, weight and obesity risk at the population level”

- Association with AIWG
    - Rs489688 AA genotype associated with greater AIWG, continued significance after controlling for baseline wt
  - Chowdhury et al (2013) – 224 schizophrenia patients
    - No significant relationship but rs8087522 A allele, rs17782313 C allele and rs11872799 G allele associated with discopine weight gain
  - Čzenwensky et al (2013) – 345/341 schizophrenia patients x 4 weeks tx
    - Rs17782313 C allele associated with AIWG
    - Rs489688 A allele had higher risk of weight gain and BMI increase in tx naïve

- MC4R rs489688 and AIWG

Subjects and Methods

- Two hundred thirty-seven subjects were included in this cross-sectional analysis
  - Inclusion Criteria
    - DSM-IV diagnosis of schizophrenia, schizophreniform disorder, or schizoaffective disorder, or bipolar disorder
    - Between the ages of 18-90 years of age
    - Their primary physician determines that they should be treated with an antipsychotic and they have been receiving this medication for at least 6 months.
  - Subjects were seen in the MCRU and fasted for 8 hours before their study visit
  - After informed consent was obtained, subjects underwent the following procedures
    - Laboratory Measures/ Metabolic Syndrome screening
    - Blood drawn for DNA
    - Medication history interview
    - Smoking and Physical Activity assessment
    - 24 hour food recount x 3
    - Schizophrenia cohort
      - Endothelial function testing \((n=62)\)

Ellingrod VL et al, J Clin Psychopharmacol. 2012 Apr;32(2):261-5. PMC3622480
Subject Demographics

- **Subjects**
  - Mean age = 47.6 ± 11.7 years (median=46)
  - N = 127 Schizophrenia, N = 110 Bipolar disorder
  - 72% Caucasian followed by African Americans (20%)
  - 51% were male
  - more common in the schizophrenia group (66% versus 35%, p<0.0001).
  - 41% met metabolic syndrome criterion
  - The schizophrenia group had a higher percentage of current cigarette smokers (60% versus 34%, p < 0.001)

MTHFR/COMT and Metabolic Syndrome

- **Metabolic Syndrome risk**
  - Metabolic syndrome prevalence was highly associated with age and smoking status, as well as an interaction between the MTHFR 677TT and COMT 158Val alleles ($\chi^2$=33.8, p<0.001).
  - After controlling for age and smoking status, the MTHFR/COMT interaction remained significant ($\chi^2$=7.19, p=0.0073) and WG-AAP use showed a trend for significance ($\chi^2$=3.21, p=0.07).
  - The MTHFR/COMT interaction produced an odds ratio of 1.58 (95% CI=1.15-8.3) for metabolic syndrome risk.

MTHFR/COMT and Metabolic Syndrome Risk

- **Endothelial Functioning**
  - The MTHFR/COMT risk alleles interacted with folate exposure and was significantly associated endothelial functioning ($F = 5.43, df = 3,62, p = 0.0023$).

Conclusions

- Risk of metabolic syndrome significantly higher in those with a serious mental illness
  - May impact years lost due to CVD
- Several different neurotransmitter and hormones have been identified as potential targets for pharmacogenomics predictors of AIWG and metabolic syndrome risk with antipsychotics

Summary

- MC4R rs489683 A allele associated with significant weight gain
  - May be more prominent in treatment naïve pts
  - PGx companies including MC4R on testing panels
  - Unknown impact of using this information preventatively
  - Not all data on MC4R in agreement
Folate Hypothesis in Schizophrenia
- Genetic variation related to folate metabolism may be associated risk for CVD as well as PFC function/negative symptoms
- Those with MTHFR T/COMT Val allelic combinations may be at greatest risk
- Also starting to be included on pgx testing panels

Impact of folate supplementation?
Pharmacogenetics of serotonin and dopamine system genes in psychiatry

Jeffrey R. Bishop, PharmD, MS, BCPP
October 20, 2015

Learning Objectives

- Identify genetic variability in serotonin and dopamine system genes that may impact drug mechanisms
- Describe associations between these polymorphisms and treatment outcomes
- Discuss how or if these genetic variants may impact clinical care

Introduction

- Clinical questions:
  - Is pharmacogenomic information helpful?
  - Should you test?
    - Status of inclusion of 5HT and DA variants in drug labeling and guidelines
    - What to do with test information when it already exists?
- Scientific questions:
  - What is the functional, mechanistic, and association basis for drug-gene pairs
  - Evidence grading?
- Practical questions:
  - Test availability, assay specific considerations
      - Financial

Background: Serotonin neurotransmission

Image from: http://www.ib.cnea.gov.ar

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Nature Reviews | Drug Discovery

Background: Dopamine neurotransmission

Image from: http://www.ib.cnea.gov.ar

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**Test availability**

<table>
<thead>
<tr>
<th>Pharmacogenomics Laboratory</th>
<th>Drug Metabolism Groups</th>
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</tr>
</tbody>
</table>

**SLC6A4** (Serotonin Transporter)

- Pharmacodynamic target of 5-HT reuptake drugs
- Promoter polymorphism (5HTTLPR)
  - 44bp insertion/deletion
  - rs25531 SNP affects 5HTT expression
    - L=long (insertion), S=short (deletion)
    - L/L>L/S>SS
    - LG subtype functions like S

**SLC6A4 – clinical associations**

- Widely studied across many neuropsychiatric disorders
  - Associations with anxiety-related personality traits, neurobiology of emotion etc (Canli 2007)
  - Irritable bowel (Zhang 2014), migraine (Liu 2011), others
- Pharmacogenetics studies
  - Antidepressant response/tolerability (depression)
  - Antidepressant response/tolerability (autism) - mixed
  - Antidepressant tolerability (bipolar disorder) - mixed
  - Others

**HTR2A** (Serotonin-2A Receptor)

- Regulates 5HT signaling at post synaptic terminals
- Pharmacodynamic influences on anxiety, psychosis, sleep, sexual function, cognition others
  - Antidepressants and antipsychotics
- Pharmacogenetic studies
  - Antidepressant and antipsychotic response/tolerability
  - Depression, psychosis, autism, others

**Summary**

- rs6311 C allele favors response
- rs6313 T allele favors response
- rs7997012 G allele favors response

Meta-analysis of N=11 studies (1775 patients) of HTR2A and antidepressant response in depression

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**COMT**

(Catechol-o-methyltransferase)

- COMT enzyme expressed throughout the brain - highest activity in the prefrontal cortex (PFC)
- Accounts for ~60% of dopamine (DA) metabolism in the prefrontal cortex
  - rs4680 (Val158Met) Met allele results in reduced enzyme activity
- Studies of cognition, ADHD, antidepressant response

**DRD2**

(Dopamine-D2 Receptor)

- One regulator of post synaptic DA signaling
  - DA pathways in brain: mesolimbic, mesocortical, tuberoinfundibular, nigrostriatal
- Disease associations:
  - Tourette syndrome (Yuan 2015), ADHD (Pan 2015), schizophrenia (Yao 2015), alcohol dependence (Wang 2013), others
- Primary pharmacodynamic target of all currently approved antipsychotic agents

**Evidence grading**

- Clinical Pharmacogenomics Implementation Consortium (CPIC)
- International Society of Psychiatric Genetics
- American College of Clinical Chemistry (ACCC)
- Royal Dutch Association for the Advancement of Pharmacy established the Pharmacogenetics Working Group
- Evaluation of Genomic Applications in Practice and Prevention (EGAPP)

**COMT** – clinical associations

- ADHD – 6 studies
- Major depressive disorder – 6 studies
  - N=5 no effect (Nitsu 2013, Chiesa 2014), N=1 Val/Val improved response (Hopkins 2013)

**DRD2**

- Variants with clinically relevant associations
  - -141C Ins/Del (rs1799732) – deletion in 5' promoter region
    - Deletion variant – lower D2 expression (Arinami 1997)
    - Meta-analysis of 6 studies (n=698) – Deletion carrier status associated with poor clinical response (Zhang 2010)
  - Taq1A (rs1800497) – C>T polymorphism
    - Originally thought to be in DRD2 but now mapped to ANKK1 just downstream
    - “A1” allele associated with lower D2 binding (Jonsson 1999)
    - Meta-analysis of 4 studies (n=764) – A2 allele associated with increased tardive dyskinesia (Bakker 2008)

**Evidence grading**

- Level 5A: Annotation for a variant-drug combination in a CPIC or international society-endorsed PGx guideline, or implemented at a PGRN site or in another major health system.
- Level 5B: Annotation for a variant-drug combination that qualifies for level 5A where the variant is within a VIP (Very Important Pharmacogene) as defined by PharmGKB.
- Level 4: Annotation for a variant-drug combination where the preponderance of evidence shows an association. The association must be replicated in multiple studies but lacking clear evidence of an association.
- Level 3: Annotation based on a case report, non-significant study or in vitro, molecular or functional assay evidence only.
Clinical considerations

- Practical issues of how to translate association findings to clinical practice
- Statistical significance vs clinical significance
  - Pooled ORs ~1.2-2 for meta-analyses (vs ORs in 100s for HLA associations with deadly rash, for example)
- Limited data examining utility of PK/PD pharmacogenomic ‘panels’
- Relationships of these variants with other phenotypes (drug and non-drug)
  - Genetic counseling vs. pharmacogenetic counseling?

Conclusions

- Growing evidence supporting associations between 5HT and DA system gene variants and psychopharmacology treatment outcomes
- Not in drug labeling and not evaluated via consensus guidelines
- Laboratory tests exist
  - Should we test for 5HT and DA variants?
  - Considerations for therapy if test results already exist?
- Considerations related to associations with other phenotypes

THANK YOU....

Q&A?
Enhance the Clinicians’ Ability to Implement Pharmacogenomic Testing into Psychopharmacotherapy Comprehensive Medication Management Services

Megan J. Ehret, PharmD, MS, BCPP
Behavioral Health Clinical Pharmacy Specialist
Department of Defense
Fort Belvoir Community Hospital
10/20/15

Conflict of Interests

- None to disclose

Learning Objectives

- Describe the logistics of acquiring, assessing, and utilizing patients’ genetic information to guide psychopharmacotherapeutic decisions
- Demonstrate the application of pharmacogenomic testing results in the management of treatment-resistant depression
- Identify the optimal means of capturing the clinical and economic impact of the integration of clinical pharmacogenomic testing into a pharmacist-delivered CMM service

Logistics to Pharmacogenomics

- Genomic Tests
  - 1. Provider initiated
  - 2. Patient/Care Giver initiated
  - 3. When do I order?
- Labs
  - 1. Research
  - 2. Clinical
  - 3. Company
- Consent
  - 1. Standard form
  - 2. Samples online
  - 3. Where to file the form
- Logistics of Ordering and Sending
  - 1. Buccal
  - 2. Blood
  - 3. Other samples
- Return of Results
  - 1. Interpretation
  - 2. Notification of patient
  - 3. Where to file the results
- Utility of Results
  - 1. Dose changes
  - 2. Medication changes
  - 3. No results
- Retention of Results
  - 1. Patient ownership
  - 2. Labs section of chart
  - 3. Notification of other providers

Quest Diagnostics

Direct to Consumer Testing

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- When Cytochrome p450 is covered
  - CYP450 genotyping for the purpose of aiding in the choice of clopidogrel versus alternative antiplatelet agents, or in decisions on the optimal dosing for clopidogrel, may be considered medically necessary.

- When Cytochrome p450 is not covered
  - CYP450 genotyping for the purpose of aiding in the choice of drug or dose to increase efficacy and/or avoid toxicity for all other drugs is considered investigational, aside from determinations in the separate policies noted above. This includes, but is not limited to, CYP450 genotyping for the following applications:
    - Selection or dose of selective serotonin reuptake inhibitor (SSRI)
    - Selection or dose of selective norepinephrine reuptake inhibitors (SNRIs)
    - Selection or dose of tricyclic antidepressants
    - Selection or dose of antipsychotic drugs
    - Selection or dose of antiepileptic drugs
    - Selection or dose of immunosuppressant for organ transplantation
    - Selection or dose of beta blockers
    - Managing treatment with tamoxifen for women at high risk for or with breast cancer
    - Managing treatment with codeine dosing, or of efavirenz and other antiretroviral therapies for HIV (common component of highly active antiretroviral therapy for HIV)
    - Dosing and management of antiretroviral therapies for HIV

- The use of genetic testing panels that include multiple CYP450 mutations is considered investigational.

Corporate Medical Policy; 11/14

The 1200 Patients Project

- Preemptive comprehensive pharmacogenomic genotyping of all enrolled patient participants
- Interactive formatics portal serving as both a repository for patient-specific pharmacogenomic results and an instantaneous delivery-consultation system to interpret such results

Clin Pharmacol Ther 2012

The 1200 Patients Project

- 812 patients enrolled (90% of those approached)
- 608 successfully genotyped
- 268 clinic encounters where results were available
  - 86% of time physicians accessed database
  - 100% of red were clicked, 72% yellow, 20% of green
  - 85% clinical pharmacogenomic information was available for at least 1 drug the pt. was taking


TREATMENT RESISTANT DEPRESSION

Treatment Resistant Depression

- 48-yo Caucasian male; MDD; no somatic disorders
- Citalopram 20 mg/day increased to 40 mg/day
- Bilateral resting hand tremor: propranolol 20 mg/day
- Persistent lack of energy and anxiety persisted

Am J Psychiatry 2014;171:8

Treatment Resistant Depression

- Citalopram switched to venlafaxine XR 75 mg/day and progressed increased to 300 mg/day
- No improvement and lack of energy increased
- Admitted to psychiatry with the following symptoms:
  - Anxiety
  - Lack of energy/general weakness
  - Difficulties falling asleep

Am J Psychiatry 2014;171:8
**Treatment Resistant Depression**

- Denies
  - Sadness
  - Social withdrawal
  - Anhedonia
  - SI
- Physically
  - Hypertonia
  - Diaphoresis
  - Chronic sustained secretory diarrhea
  - Ankle clonus
  - Patellar hyperreflexia [Am J Psychiatry 2014;171:8]

**Labs:**
- All normal

**Imagining**
- Cerebral contrast MRI: normal

**Rating Scale**
- HAMD: 23
  - Six items indicate anxiety or somatic symptoms

**WHAT ARE THE NEXT STEPS?**

- Venlafaxine plasma concentration: 900 ng/ml
- O-desmethylvenlafaxine plasma concentration: <50 ng/ml

**CYP2D6**
- CYP2D6 *4/*4 (poor metabolizer phenotype)

**What could we have done differently if we had known the results of genomic testing prior to the initiation of citalopram?**
- Chosen a non-CYP450 2D6 substrate medication
- Chosen a lower starting and maintenance dose for citalopram and venlafaxine
### Treatment Resistant Depression

- Decrease the dosage of venlafaxine
- Improvement of symptoms
- HAMD: 6

**Am J Psychiatry 2014;171:8**

### Capturing It All

### Electronic Medical Record

- Laboratory Results
- Pharmacogenomic Consults - present statically in the EMR
- Automated alerts - fire only when an affected drug is ordered or dispensed to a pt. with an actionable pharmacogenetic test result


### How to Capture the Impact

- Novel research study designs that reflect heterogeneity and complexity of real-world pts.
  - Medical comorbidity
  - Polypharmacy
  - Diversity in genetic ancestry
  - Age
  - Gender
  - Environmental exposures

**Hamilton S. Biol Psychiatry 2015**

### Routine Clinical Practice

- Clear, curated, peer-reviewed pharmacogenetic guidelines
- Compare costs of utilization of genomic testing to standard of care
  - Costs of genomic testing
  - Medications costs
  - Cost of pharmacist time
  - Hospitalization costs
  - Quality of Life costs

### Guideline Based Practice - CPIC

- [https://www.pharmgkb.org/page/cpic](https://www.pharmgkb.org/page/cpic)

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Genetic Testing Registry

Genetic Testing Registry

Pharmacist’s Responsibilities

- Advocate- rational and routine use of testing
- Provide- test result interpretation and clinical guidance
- Optimize- medication therapy
- Educate
- Support- research, consortia, and network guides