Treatment Of Schizophrenia: Focus On Psychopharmacology & Adherence

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Objectives

• Explore the consequences of relapse for patients with schizophrenia who discontinue medications

• Discuss patient- and system-level indicators that may aid in early identification of patients with a high potential for discontinuing antipsychotic therapy

• Address how clinicians can use basic pharmacogenomic concepts to guide dosing of antipsychotics to maximize potential benefit and avoid adverse effects
WHAT ARE THE CONSEQUENCES FOR PATIENTS WITH SCHIZOPHRENIA WHO EXPERIENCE A PSYCHOTIC RELAPSE?
Schizophrenia: Neurodevelopmental, Neurodegenerative, or Both?

- Should schizophrenia be conceptualized as a neurodevelopmental or neurodegenerative (neuroprogressive) disorder, or a combination of both?\textsuperscript{1,2}
  - Data have been generated implicating both for the past century\textsuperscript{1–3}

- Several types of brain abnormalities have been reported at the time of first episode of illness\textsuperscript{1}

- The hypothesis that schizophrenia has a progressive neurodegenerative component has re-emerged\textsuperscript{2}
  - Based primarily on \textit{in vivo} longitudinal magnetic resonance imaging (MRI) studies and postmortem findings

Duration of Untreated Psychosis: Neurobiological and Clinical Correlations

- A meta-analysis of 26 studies involving 4490 first-episode patients assessed association between duration of untreated psychosis (DUP) and outcomes\(^1\)
  - Patients with long DUP were significantly less likely to achieve remission

- One study compared regional grey matter volume differences between patients with first-episode psychosis (FEP) with short vs long DUP\(^2\)
  - A significant whole brain grey matter volume reduction was noted in patients with longer DUP
  - Significant grey matter volume reductions in the inferior-orbital region and parietal area were noted in the long-DUP group

<table>
<thead>
<tr>
<th>Outcomes significantly associated with DUP(^1)†</th>
<th>Worse outcomes associated with longer (vs shorter) DUP(^1)†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total symptoms</td>
<td>Total symptoms</td>
</tr>
<tr>
<td>Positive symptoms</td>
<td>Positive symptoms</td>
</tr>
<tr>
<td>Negative symptoms</td>
<td>Overall functioning</td>
</tr>
<tr>
<td>Depression/anxiety</td>
<td>Social functioning</td>
</tr>
<tr>
<td>Overall functioning</td>
<td>Quality of life</td>
</tr>
</tbody>
</table>

\(^*\)At 6 and 12 months.
\(^†\)At 6 months.
\(^‡\)80 patients were separated into two groups using a median split of DUP: short-DUP group (18 weeks or less, n=40) and long-DUP group (greater than 18 weeks, n=40).

Progressive Brain Changes in Schizophrenia

- A 1-year follow-up study of patients with FEP (n=34) and matched health control participants (n=36) reported¹:
  - Significant reductions in total brain volume (-1.2%; equal to 10-12 ccs) and gray matter volume of the cerebrum (-2.9%), and significant increases (7.7%) in lateral ventricle volume
  - Decrease in global gray matter volume significantly correlated with worse outcome at 2 years and with higher cumulative dose of antipsychotic medication

- A meta-analysis of 18 studies involving 1155 patients with schizophrenia and 911 healthy control participants investigated longitudinal changes of cortical gray matter²*
  - Whole-brain gray matter volume reduction was inversely correlated with exposure to antipsychotic treatment only in patients treated with first-generation antipsychotics or mixed treatments†
  - In patients treated only with second-generation antipsychotics, cumulative exposure to antipsychotics did not correlate with gray matter volume changes and was not associated with cortical tissue loss†

*Study follow-up duration ranging from 7.30 ± 1.00 (SD) to 86.4 ± 45.40 (SD) months.
†Results from a subgroup meta-analyses.
FEP, first-episode psychosis; SD, standard deviation.
Progressive Brain Changes in Schizophrenia (continued)

- A prospective longitudinal study evaluated structural magnetic resonance (sMR) data* collected from 202 patients in the Iowa Longitudinal Study of first-episode schizophrenia vs 125 healthy control participants
  - Changes were most severe during early years after onset and occurred at severe levels only in a subset of patients
  - Progressive changes were correlated with cognitive impairment

<table>
<thead>
<tr>
<th>Decreased gray matter regions</th>
<th>Decreased white matter regions</th>
<th>Corresponding increase in cerebrospinal fluid</th>
</tr>
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<tbody>
<tr>
<td>Total cerebral</td>
<td>Total cerebral</td>
<td>Lateral ventricles</td>
</tr>
<tr>
<td>Frontal</td>
<td>Frontal</td>
<td>Frontal</td>
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<tr>
<td>Thalamus</td>
<td>Temporal</td>
<td>Temporal</td>
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<tr>
<td></td>
<td>Parietal</td>
<td>Parietal sulci</td>
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</tbody>
</table>

*sMR and cognitive testing were performed at intake and at 2, 5, 9, 12, 15, and 18 years. Mean interval between first and last available scan was 7.2 years (SD 3.79; maximum 15 years).

SD, standard deviation.

WHAT INDICATORS COULD HELP CLINICIANS IDENTIFY PATIENTS WITH HIGH POTENTIAL FOR DISCONTINUING ANTIPSYCHOTICS?
Medication Adherence

- Medication adherence is the extent to which a person's behavior coincides with the medical advice given. It may include¹:
  - Refusing to attend medical appointments or start a treatment program
  - Early discontinuation
  - Incomplete implementation of doctor's instructions

- Adherence differs from compliance by including patient participation in the decision-making process²

- Nonadherence to medication is the most robust predictor of relapse after FEP²

FEP, first-episode psychosis.
A recent systematic review analyzed 38 studies of 51,796 patients*
- Adherence ranged from 60% to 81% in studies measuring subjectively and objectively, and from 34% to 80% in studies measuring subjectively

*Patients were diagnosed with bipolar disorder, schizophrenia, schizoaffective disorder, or schizophreniform disorder who were being treated with antipsychotics; 10,385 included patients had schizophrenia, 544 had schizoaffective disorder, 516 had schizophreniform disorders, and 53 had psychosis not otherwise specified.

## Factors Involved in Adherence to Treatment in First-episode Psychosis*: an Analysis of 33 Studies

<table>
<thead>
<tr>
<th>Factors Associated With Nonadherence to Treatment in First-episode Psychosis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patient-related Factors</strong></td>
</tr>
<tr>
<td>• Younger age</td>
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<tr>
<td>• Lower level of education</td>
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<tr>
<td>• Persistent substance use</td>
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<tr>
<td>• Any lifetime substance use disorder</td>
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<tr>
<td>• No previous contact with psychiatric care</td>
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<tr>
<td>• Lack of insight</td>
</tr>
<tr>
<td>• Lower cognitive abilities</td>
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<tr>
<td>• Poor quality of life</td>
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<tr>
<td>• Forensic history</td>
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<tr>
<td>• Unemployment</td>
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<tr>
<td>• History of physical abuse</td>
</tr>
<tr>
<td>• Lower functioning level</td>
</tr>
<tr>
<td>• Negative attitude toward treatment</td>
</tr>
<tr>
<td><strong>Environment-related Factors</strong></td>
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<tr>
<td>• No family involved in treatment</td>
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<tr>
<td>• Having grown up without one or both parents</td>
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<tr>
<td>• Lack of social activities</td>
</tr>
<tr>
<td><strong>Medication- or Treatment-related Factors</strong></td>
</tr>
<tr>
<td>• Rapid remission of negative symptoms</td>
</tr>
<tr>
<td>• Therapeutic alliance</td>
</tr>
<tr>
<td>• Voluntary first admission (when hospitalized)</td>
</tr>
<tr>
<td><strong>Disorder-related Factors</strong></td>
</tr>
<tr>
<td>• More positive symptoms</td>
</tr>
<tr>
<td>• Longer duration of untreated psychosis</td>
</tr>
<tr>
<td>• More relapses</td>
</tr>
</tbody>
</table>

*FEP, first-episode psychosis.

Green text = modifiable factors
Red text = non-modifiable factors.

*A broad definition of FEP was used, including studies that considered FEP the first onset of psychotic symptoms or the first time of being treated for psychosis, up to 5 years retrospectively; publications referring to both affective and non-affective psychosis were included.

HOW CAN CLINICIANS USE BASIC PHARMACOGENOMIC CONCEPTS TO GUIDE DOSING OF ANTIPSYCHOTICS?
Pharmacogenomics and the Effects of Cytochrome P450 Metabolism on Drug Response

• Cytochrome P450 (CYP450) enzymes are essential for the metabolism of many medications\(^1\)

• CYP450 enzymes exhibit genetic variability, resulting in different phenotypes\(^1\)
  – CYP2D6, 2C9 and 2C19 are common targets for genetic testing\(^2\)

• Inhibitors and inducers alter the activity of CYP450 enzymes and metabolism of drugs\(^1\)
  – Information regarding CYP450 metabolism and its potential for inhibition or induction can often be found in the drug label

• Genotype testing may inform the choice of drug and dosing\(^1\)

CYP, cytochrome P.

Pharmacogenetic Testing: Where Are We Now?

- The U.S. FDA lists >160 drugs with “Pharmacogenomic Biomarkers in Drug Labeling”
  - Many include recommendations for therapy adjustment based on genetics
- As of mid-2016, the CPIC had published pharmacogenetic guidelines for 33 drugs
- Despite the increase in knowledge, only 10% of physicians reported feeling adequately informed about pharmacogenetic testing according to a nationwide survey
  - Only 13% had ordered a pharmacogenetic test within the past 6 months
- Barriers to implementation include:
  - Logistics of performing accurate and rapid turnaround genotyping
  - Lack of infrastructure or standardized format for pharmacogenetic test results in EHRs
  - Lack of infrastructure or standardized format for pharmacogenetic clinical decision support in EHRs
  - Lack of prospective genotype-directed randomized trial validation
  - Clinician inexperience with interpreting/acting on pharmacogenetic information
  - Scarcity of clear and consistent recommendations for testing
  - Cost and reimbursement considerations

CPIC, Clinical Pharmacogenetics Implementation Consortium; EHRs, electronic health records; FDA, Food and Drug Administration; U.S., United States.
Pharmacogenetic Decision-support Tools in Psychiatry

- Pharmacogenetic studies have shown links between genetic variants and pharmacotherapy outcomes
  - Led to development of pharmacogenetic-based decision support tools
    - Tools report patient’s genotype, predicted phenotype, and provide information to guide drug selection and/or dosing decisions and flag potential drug–drug interactions
- The U.S. has 13 available pharmacogenetic decision-support tools
  - Of the 46 genes included in ≥1 pharmacogenetic tools, 53% have only preliminary or low supporting evidence, and only 20% met criteria for the highest level of evidence
    - Only 3 were relevant to psychotropic drugs commonly used in psychiatry practice (CYP2D6, CYP2C19, and HLA-B)
- Studies examining usefulness have focused on antidepressants exclusively
  - Clinical usefulness for antipsychotic therapy is unproven
- The existence of such tools is not proof of evidence of clinical usefulness
  - An evaluation of 22 available tools relevant to psychiatry practice suggested that research on validity, reliability, clinical usefulness, and cost effectiveness was needed before universal adoption into clinical practice

CYP, cytochrome P; HLA, human leukocyte antigen; U.S., United States.

CDC Office of Public Health Genomics: Classification Criteria

**Tier 1**
- FDA label requires use of test to inform choice or dose of a drug
- CMS covers testing
- Clinical practice guidelines based on systematic review supports testing

**Tier 2**
- FDA label mentions biomarkers
- CMS coverage with evidence development
  - Clinical practice guideline, not based on systematic review, supports use of test
  - Clinical practice guideline finds insufficient evidence but does not discourage use of test
  - Systematic review, without clinical practice guideline, supports use of test
  - Systematic review finds insufficient evidence but does not discourage use of test
  - Clinical practice guideline recommends dosage adjustment, but does not address testing

**Tier 3**
- FDA label cautions against use
- CMS decision against coverage
  - Clinical practice guideline recommends against use of test
  - Clinical practice guideline finds insufficient evidence and discourages use of test
  - Systematic review recommends against use
  - Systematic review finds insufficient evidence and discourages use
  - Evidence available only from published studies without systematic reviews, clinical practice guidelines, FDA label or CMS labels coverage decision

CDC, Centers for Disease Control and Prevention; CMS, Center for Medicare and Medicaid Services; FDA, Food and Drug Administration.

# CDC Office of Public Health Genomics Database Search: Mental Illness

## Pharmacogenomic tests by disorder*

<table>
<thead>
<tr>
<th>Disease/Disorder</th>
<th>Test to be Assessed</th>
<th>Tier Classified</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-psychotic depression</td>
<td>CYP450 testing</td>
<td>Tier 3</td>
</tr>
<tr>
<td>Schizophrenia, bipolar I disorder, autistic disorder</td>
<td>CYP2D6</td>
<td>Tier 2</td>
</tr>
<tr>
<td>Schizophrenia</td>
<td>CYP2D6</td>
<td>Tier 2</td>
</tr>
<tr>
<td>Schizophrenia, schizoaffective disorder</td>
<td>CYP2D6</td>
<td>Tier 2</td>
</tr>
<tr>
<td>Schizophrenia, bipolar I disorder, major depressive disorder, autistic disorder</td>
<td>CYP2D6</td>
<td>Tier 2</td>
</tr>
<tr>
<td>Depression</td>
<td>CYP2D6</td>
<td>Tier 2</td>
</tr>
<tr>
<td>Major depressive disorder, social anxiety disorder</td>
<td>CYP2D6</td>
<td>Tier 2</td>
</tr>
<tr>
<td>Depression</td>
<td>CYP2D6</td>
<td>Tier 2</td>
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<td>Depression</td>
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</tr>
<tr>
<td>Depression</td>
<td>CYP2D6</td>
<td>Tier 2</td>
</tr>
<tr>
<td>Depression, obsessive compulsive disorder, bulimia nervosa, panic disorder</td>
<td>CYP2D6</td>
<td>Tier 2</td>
</tr>
<tr>
<td>Depression</td>
<td>CYP2D6</td>
<td>Tier 2</td>
</tr>
<tr>
<td>Depression</td>
<td>CYP2D6</td>
<td>Tier 2</td>
</tr>
</tbody>
</table>

*Based on a database search for “Mental illness” with filters activated to show the following diseases: “Depressive disorder, Major Depressive Disorder, Schizophrenia”. CDC, Centers for Disease Control and Prevention; CYP, cytochrome P.*

Pharmacogenetic Decision-support Tools in Psychiatry: Selected Resources

- **FDA Table of Pharmacogenomic Biomarkers in Drug Labeling**¹
  - [http://www.fda.gov/Drugs/ScienceResearch/ResearchAreas/Pharmacogenetics/ucm083378.htm](http://www.fda.gov/Drugs/ScienceResearch/ResearchAreas/Pharmacogenetics/ucm083378.htm)
  - Includes several antipsychotics – dosing in 2D6 poor metabolizers

- **CPIC²**
  - [https://cpicpgx.org/guidelines/](https://cpicpgx.org/guidelines/)
  - No specific guidelines for antipsychotics, several for antidepressants – guidance for ultra-rapid metabolizers and poor metabolizers

- **Drug Interactions/CYP substrates, inhibitors and inducers³**
  - [http://medicine.iupui.edu/CLINPHARM/ddis/main-table](http://medicine.iupui.edu/CLINPHARM/ddis/main-table)
  - Includes many psychotropic agents

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³ Indiana University School of Medicine, Department of Medicine, Clinical Pharmacology. Flockhart Table. Available at: [http://medicine.iupui.edu/CLINPHARM/ddis/main-table](http://medicine.iupui.edu/CLINPHARM/ddis/main-table). Accessed February 2017.

CPIC, Clinical Pharmacogenetics Implementation Consortium; CYP, cytochrome P; FDA, Food and Drug Administration.
QUESTIONS