Role of Pharmacogenetic Testing in Psychiatry
This program is paid for by Otsuka Pharmaceutical Development & Commercialization, Inc. and Lundbeck, LLC.

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Objectives of Today’s Discussion

- Discuss the possible role of pharmacogenetics and relevant genetic factors in psychiatry
- Discuss benefits of pharmacogenetics in psychiatry testing and the rationale against its routine use in clinical practice
- Evaluate data assessing the utility of pharmacogenetic testing in major depressive disorder
- Review patient and clinician considerations for implementing pharmacogenetic testing in practice
Potential Role of Pharmacogenetics in Psychiatry
Pharmacogenetics Aims to Improve Treatment by Customizing Medication According to an Individual’s Genetic Profile

A “one size fits all” approach is commonly used to prescribe medication

Pharmacogenetics aims to provide information tailored to an individual’s genetic profile, which may affect the dose, safety, and efficacy of a drug

Pharmacogenetic Testing Can Identify Genetic Factors That May Influence Medication Effects

Candidate genes are genes that are suspected to be related to a disease on the basis of their location on a chromosome

Alleles are alternate variations of a gene

SNPs are the most common type of genetic variation in people and represent a difference in a single nucleotide in a stretch of DNA

Genotype refers to an individual’s genes whereas phenotype refers to the expression of these genes as observable traits

Pharmacogenetic testing can help HCPs understand how patients may respond to certain medications

Drug metabolism is the process of drugs being chemically altered by the body, primarily in the liver via CYP450 enzymes

Side effects (or adverse events) are unexpected or undesired reactions to a drug

HCP, healthcare provider.

Pharmacogenetic Testing Can Identify Genetic Factors That May Affect Drug Safety and Efficacy

Pharmacokinetic factors
Genes affecting drug absorption, distribution, and clearance

Examples of pharmacokinetic factors

Ultrarapid metabolizers
Genetic mutations in CYP450 leading to greater than normal rate of metabolism

Extensive metabolizers
Wild-type CYP450 expression "Normal" rate of metabolism

Poor metabolizers
Genetic mutations in CYP450 leading to little or no enzyme activity

Pharmacodynamic factors
Genes affecting receptors, transporters, or neurotransmission

Examples of pharmacodynamic factors

Genotype affecting neurotransmission
Long vs short allele of the serotonin transporter gene can impact antidepressant efficacy

Genotype affecting drug availability
Variations of the MTHFR gene can impact conversion of dietary folate to bioactive folate and its efficacy for alleviating depression


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Use of Pharmacogenetics in the Clinical Setting: Perspectives and Clinical Experience

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USC School of Pharmacy
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Results of Pre-Webinar Survey Question 1

Have You Ever Ordered and/or Recommended Pharmacogenetic Testing?

- Yes: 51%
- No: 49%

Data based on responses from 352 webinar registrants who responded to the pre-webinar survey question as of June 22, 2020.
Results of Pre-Webinar Survey 2

How Often Do You Use or Recommend Pharmacogenetic Testing Results for Practice?

Data based on responses from 183 webinar registrants who responded to the pre-webinar survey question as of June 22, 2020.
Results of Pre-Webinar Survey 3

When Would You Order Pharmacogenetic Testing?

- **As a part of first-line treatment**: 2%
- **For patients with treatment-resistant conditions**: 30%
- **For patients with adverse events**: 11%
- **For adjusting dosage of medication**: 24%
- **Other**: 33%

Data based on responses from 46 webinar registrants who responded to the pre-webinar survey question as of June 22, 2020.

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Potential Benefits and Limitations of Pharmacogenetic Testing in Psychiatry
Pharmacogenetic Testing Has Been Shown to Improve Clinical Outcomes for Patients With Depression

Randomized clinical trial found higher rates of remission* and response† for patients with severe depression‡ receiving treatment with addition of pharmacogenetic testing (n=352) compared with those receiving treatment as usual (n=333)¹

A meta-analysis of >1700 patients with depression further confirmed the benefits of pharmacogenetic testing on treatment efficacy as individuals receiving pharmacogenetic testing were almost twice as likely to achieve remission relative to those receiving treatment as usual²

HAM-D17, 17-item Hamilton depression rating scale.

*Remission was defined as HAMD-17 score <7. †Response was defined as 50% reduction in HAMD-17 score. ‡Severe depression was defined as HAM-D17 score >24.


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Patient Genetic Profile May Affect Folate Metabolism and Thus Utility of Folate Supplementation for Alleviating Depression

**MTHFR 677** encodes enzyme crucial for reducing precursor molecules to bioavailable form of folate.  

1. **MTHFR 677, CC variant**
   - Normal enzyme activity

2. **MTHFR 677, CT variant**
   - \(~67\%\) of normal enzyme activity

3. **MTHFR 677, TT variant**
   - \(~25\%\) of normal enzyme activity

Randomized controlled trial found that patients receiving bioactive form of folate (L-methylfolate) had higher response rates depending on **MTHFR genotype** (N=61). [3]

HAM-D28, 28-item Hamilton depression rating scale; NS, nonsignificant.

* MTHFR regulates conversion of 5,10-methylentetrahydrofolate to 5-methyltetrahydrofolate.  
† Treatment minus placebo with response rate based on >50% reduction in HAM-D28 score.

Pharmacogenetics Has Led to Suggested Modifications to Some Dosing Regimens Used in Psychiatry

<table>
<thead>
<tr>
<th>Drug class</th>
<th>Example management strategies in poor metabolizers*</th>
</tr>
</thead>
<tbody>
<tr>
<td>5HT-1A agonists</td>
<td>Max dose 10 mg/d</td>
</tr>
<tr>
<td>Atypical antipsychotics</td>
<td>Dose to be reduced</td>
</tr>
<tr>
<td>Barbiturates</td>
<td>Consider dosage adjustment</td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>Consider dosage adjustment</td>
</tr>
<tr>
<td>D2-partial agonists</td>
<td>Halve the usual dose</td>
</tr>
<tr>
<td>NDRIs</td>
<td>Consider dosage adjustment</td>
</tr>
<tr>
<td>Reversible MAOIs</td>
<td>Consider dosage adjustment</td>
</tr>
<tr>
<td>SNRIs</td>
<td>Halve the usual dose</td>
</tr>
<tr>
<td>SSNRIIs</td>
<td>Consider dosage adjustment</td>
</tr>
<tr>
<td>SSRIs</td>
<td>Dose to be reduced†</td>
</tr>
<tr>
<td>Tricyclics</td>
<td>Halve the usual dose; monitor levels</td>
</tr>
</tbody>
</table>

D2, dopamine receptor 2; 5HT-1A, serotonin receptor 1A; MAOI, monoamine oxidase inhibitor; NDR, norepinephrine and dopamine reuptake inhibitor; SNRI, serotonin and norepinephrine reuptake inhibitor; SSNRI, selective serotonin and norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor.

*Sample of potential management strategies is included but does not comprehensively reflect management strategy for every drug within drug class. †Extent of recommended dose reduction depends on type of medication within drug class.

Although Pharmacogenetic Testing Appears Promising, Its Clinical Use Is Generally Not Currently Recommended

Many agencies and organizations do not recommend routine clinical use of genetic testing in psychiatry

**CDC** formed the EGAPP Project, which found insufficient evidence for use of genetic testing in clinical decision-making regarding antidepressant therapy.¹

**FDA** warns against use of pharmacogenetic testing for major depressive disorder because of insufficient evidence proving causal relationship between genetic profile and drug efficacy.²

**ACNP** states that they do not currently support use of genetic testing in psychiatry for general clinical use or direct-to-consumer use because of insufficient evidence.³

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What are some limitations of evidence assessing pharmacogenetic testing that may explain the rationale against its widespread clinical use?

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ACNP, American College of Neuropsychopharmacology; CDC, Centers for Disease Control and Prevention; EGAPP, Evaluation of Genomic Applications in Practice and Prevention; FDA, US Food and Drug Administration.

Many Alternate Explanations Factor Into Interpretation and Utility of Pharmacogenetic Testing Results

**Expectation bias**¹

Expectation bias and attitude about testing may influence clinical outcomes such as mood.

For example, patients may feel more positive after receiving treatment customized for their use.

**Limitations of genetic explanations**²

Clinical outcomes are complex and influenced by multiple genes exerting small effects.

Several nongenetic factors may also impact pharmacology:

- Duration of illness
- Age at onset
- Baseline anxiety
- Subtype of illness
- History of trauma
- Psychosis

**Clinical considerations**³

For poor metabolizers, low doses may reduce adverse events; however, clinicians typically begin treatment with low doses as a general rule.

Prediction of adverse events with pharmacogenetic testing may result in cost savings, but cost-effectiveness data are lacking.

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GUIDED Trial: Assessing Pharmacogenetic Testing in Major Depressive Disorder
The GUIDED Trial Aimed to Assess Utility of Pharmacogenetic Testing for Patients With MDD

Patients with MDD were enrolled between April 2014 and February 2017 in the randomized controlled GUIDED trial\(^1,2\)

Guided care with pharmacogenetic testing\(^1\)
- n=560

Guided care with pharmacogenetic testing\(^2\)
- n=357

Treatment as usual\(^1\)
- n=607

Treatment as usual\(^2\)
- n=430

Primary analysis aimed to compare clinical outcomes related to MDD at 8 weeks

Post hoc analysis in subgroup of patients taking medications with predicted gene-drug interactions

GUIDED, Genomics Used to Improve DEpression Decisions; MDD, major depressive disorder.
Primary Outcome Was Only Statistically Significant in the Subgroup Analysis for Patients With MDD and Expected Gene-Drug Interactions

Patients receiving guided care with pharmacogenetic testing were found to have greater symptom improvement relative to those receiving treatment as usual in the primary\(^1\) and subgroup\(^2\) analyses at 8 weeks.

GUIDED, Genomics Used to Improve DEpression Decisions; HAM-D17, 17-item Hamilton depression rating scale; MDD, major depressive disorder.

Secondary Outcomes in the GUIDED Trial Demonstrated Clinical Improvements But Clinical Implications Were Limited

Patients receiving guided care with pharmacogenetic testing were found to have higher response and remission rates relative to those receiving treatment as usual in the primary\(^1\) and subgroup\(^2\) analyses at 8 weeks.

**Response rate**

<table>
<thead>
<tr>
<th></th>
<th>Pharmacogenetic testing</th>
<th>Treatment as usual</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary analysis</td>
<td>26</td>
<td>27</td>
<td>0.01</td>
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<tr>
<td>Subgroup analysis</td>
<td>20</td>
<td>19</td>
<td>0.008</td>
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</tbody>
</table>

**Remission rate**

<table>
<thead>
<tr>
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<th>Treatment as usual</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary analysis</td>
<td>15</td>
<td>10</td>
<td>0.007</td>
</tr>
<tr>
<td>Subgroup analysis</td>
<td>18</td>
<td>11</td>
<td>0.003</td>
</tr>
</tbody>
</table>

GUIDED, Genomics Used to Improve DEpression Decisions; HAM-D17, 17-item Hamilton depression rating scale; MDD, major depressive disorder.

Evidence From the GUIDED Trials Reflects Ongoing Debate in Pharmacogenetic Research

Benefits of pharmacogenetic testing for patients with MDD\(^1\)

- Reduced symptom severity
- Improved rate of remission
- Improved rate of response

Benefits may be relatively greater for patients with expected gene-drug interactions\(^2\)

Limitations of pharmacogenetic testing for patients with MDD\(^3\)

- Relatively low rates of remission limit clinical impact
- Need for proper statistical testing to inform clinical conclusions
- Expectancy bias
- Cost may be ~$2000/patient for remission

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Additional Considerations for Implementing Pharmacogenetic Testing in Practice
Pharmacogenetic Testing Clinical Considerations

When selecting a test, consider the following

- Genes and drugs the test covers
- Type of testing performed
- Type of results reported
- Insurance coverage and cost
- When should the test be offered

When interpreting results, consider the following

- Some genes (e.g., CYP2C19, CYP2D6, and HLA-B 1502) are adequately supported by the literature to inform pharmacotherapy decisions
- However, there are many other genotypes that are not well supported, and results should be interpreted with caution
- It is important to remember that results are only 1 piece of data and other data could inform clinical decisions
- Communication plan for discussing testing and results with patients

Clinician Discussion of Pharmacogenetic Concerns

Points to discuss with patients before pharmacogenetic testing

- How testing could inform drug efficacy, drug interactions, and side effects
- Role of genes in drug efficacy and safety
- Risks and benefits of testing
- Additional potential findings about disease risk and implications for relatives


Points to discuss with patients after pharmacogenetic testing

- Inform patients about any medication changes
- Explain any incongruencies between genotype and clinical outcomes
- Make any necessary referrals
- Discuss implications of additional disease and family risk
Collaborative Approach for Discussing Pharmacogenetic Testing With Patients

HCPs can work together to improve use and interpretation of pharmacogenetic testing

HCP, healthcare provider; PA, physician assistant.
Conclusions

While pharmacogenetic testing could offer a personalized medicine approach to psychiatry, there is no conclusive evidence that any pharmacogenetic test can predict psychotropic drug efficacy.

There is relatively strong evidence supporting use of pharmacogenetic testing to guide drug safety decisions (eg, dosing modifications for suspected poor metabolizers).

It is important to have specific questions when pursuing pharmacogenetic testing to gain clinically meaningful insight as well as to recognize any limitations to testing, as nongenetic factors also contribute to clinical outcomes.

There is no role yet for routine pharmacogenetic testing; therefore, its use and results should be interpreted with caution and communicated carefully to patients.
Discussion
Closing
Role of Pharmacogenetic Testing in Psychiatry