Personalized Biomarkers for Treatment Selection

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"We can envision a future in which clinical decision-making is complemented by tools and measures that help to diagnose individual clinical biotype profiles and tailor treatments to these profiles."

**PSYCHIATRIC NEWS**

**Special Report**

**Precision Psychiatry: Are We Getting Closer?**

We are witnessing the emergence of precision medicine for psychiatry. This article discusses precision psychiatry as an integrative approach, one that pulls together the scientific foundation of the discipline and recent neuroscientific, technological, and computational advances and directs them at closing the gap between discovery and clinical translation. **LEANNE M. WILLIAMS, PH.D.**
Heterogenous Disorders

Integrate Sources of Data

- Symptoms
- Circuits
- Physiology
- Cognition
- Labs, Genetics
- Life Experience

New Stratifications: Clinical Biotypes
- Biotype 1
- Biotype 2
- Biotype 3
- Biotype 4
- Biotype 5
- Biotype 6
- Biotype 7
- Biotype 8

Personalized Treatment Options

Cognitive type
Diagnostic Criteria for Depressive Disorder

- Low mood
- Loss of interest, pleasure
- Weight change
- Sleep problems
- Agitation or slowing
- Fatigue
- Problems concentrating, making decisions
- Feeling worthless, guilty
- Suicidal thoughts
Why are these cognitive problems important for improving depression?

- They are a big contributor to poor social and occupational function
- They are not alleviated by current antidepressants
- They contribute to the recurrence of episodes of depression
- They increase risk of suicide
- They occur in younger people with depression, not just in later life

Targeting improvement of cognitive impairments is an important goal for treatment for people to return to full function
International Study to Predict Optimized Treatment for Depression (iSPOT-D), a randomized clinical trial: rationale and protocol

Leanne M Williams1,2,*, A John Rush5, Stephen H Kosiow1,4, Stephen R Wisniewski5, Nicholas J Cooper6, Charles B Nemcroft7, Alan F Schatzberg9, Eyal Gordon1,5
n = 1008

What are the treatment outcomes for the cognitive subtype?

- Escitalopram
- Sertraline
- Venlafaxine-XR

Among major depressive disorder, **22% are cognitively challenged**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Intrinsic</th>
<th>Intrinsic</th>
<th>Intrinsic</th>
<th>Evoked by</th>
<th>Evoked by</th>
<th>Evoked by</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Default Mode</td>
<td>Salience</td>
<td>Attention</td>
<td>Sad Stimuli</td>
<td>Threat Stimuli</td>
<td>Happy Stimuli</td>
<td>NoGo Stimuli</td>
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**Identified Key Regions & Connections**

<table>
<thead>
<tr>
<th>Circuit</th>
<th>Default Mode</th>
<th>Salience</th>
<th>Attention</th>
<th>Negative Affect - Sad</th>
<th>Negative Affect - Threat</th>
<th>Positive Affect</th>
<th>Cognitive Control</th>
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**Quantifying Hypothesized Dysfunction**

<table>
<thead>
<tr>
<th>Circuit Dysfunction Score</th>
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<tbody>
<tr>
<td>(C_{D1,D2} + C_{D1,D3} + C_{D1,D4} + C_{D1,D5})/5 + (C_{C1,C2} + C_{C1,C3} + C_{C1,C4} + C_{C1,C5})/5</td>
</tr>
</tbody>
</table>

Goldstein-Piekarski, Ball … Williams. Biological Psychiatry 2021
Cognitive control activation

- dLPFC left
- dLPFC right
- dACC

- Cognitively challenged
- Cognitively intact

P = .003, p = .04
Does this cognitively challenged subtype respond to conventional antidepressants? No
χ² = 4.4, p = 0.036

Rate of remission (HDRS-17)

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<th></th>
<th>Cognitively challenged</th>
<th>Cognitively intact</th>
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<tbody>
<tr>
<td>Percentage</td>
<td>38%</td>
<td>46%</td>
</tr>
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</table>

χ² = 4.4, p = 0.036
Function and Quality of Life

- **Social, occupational function**
- **Quality of life, physical**

- **Cognitively challenged**
- **Cognitively intact**

P<.001, p=.003
Cognitive problems are not improved by conventionally antidepressants. In fact, they **causally mediate** poorer symptom and quality of life outcomes.

The causal mediation effect is large: **0.70**

Hack, Tozzi, Zenteno in prep
Could we treat this subtype in a more personalized way? Yes
ENGAGE trial funded by NIH under the Science of Behavior Change initiative
Ma et al. JAMA, 2019; Williams et al., Behav. Res, Therapy, 2018.
ENGAGE trial funded by NIH under the Science of Behavior Change initiative
Ma et al. JAMA, 2019; Williams et al., Behav. Res, Therapy, 2018.
Cognitive control circuit activation increased over 6, 12 and 24 months

Zhang X et al. Biological Psychiatry 2021

NIMH R01.

https://www.mirecc.va.gov/visn21/

50 participants by end this year
Selective therapies to target the cognitive control circuit

Assessments

Circuit biomarker guided treatment

Guanfacine -IR

Stanford Innovative Medicine Accelerator (IMA)
Biomarker imaging guided trial, ‘BIG’
**Guanfacine** targets cognitive control

- Guanfacine-immediate release
- Selective for $\alpha_2$ receptors in prefrontal brain regions
- Increases activation in the cognitive control circuit
- Improves cognition
- Meets safety/availability criteria

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Illustrative case: Ms. A

- 52 yo female

- “I haven't been able to concentrate on work for a month now. I haven't put out anything productive…I find myself be easily distracted.”

- Guanfacine 1 mg daily for one week, then 2 mg daily
After 8 weeks of Guanfacine

- Had the motivation to return to work during pandemic.
- Able to focus on projects; started planning ahead
The vision is for a bay area-wide precision mental health trial that evaluates **biotype matching with multiple treatment options in parallel**
We invite your research participation
We welcome your partnership

Grateful thanks to our supporters, collaborators and participants
To participate in our personalized mental health research

Project information: https://med.stanford.edu/pmhw/clinic-project

Contact: pmhw_admin@stanford.edu