Biomarkers to Enrich and Predict Response to Rapidly Acting Antidepressants

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• I have no conflicts to disclose.
• Any opinions expressed are my own and do not represent the opinions of the US Government
Agenda

• Obstacles and Opportunities in Suicide Research

• Potential Biomarkers of SI Response to Ketamine
  • Latent profile analysis of potential SI remitters, responders and non-responders.
  • Potential biomarkers of interest including plasma, neuroimaging, sleep markers
  • Future objective biomarkers of implicit suicide risk such as the Suicide Implicit Association Task (S-IAT)
Obstacles to Suicide Research

Ethical Concerns

Clinical Trials are More Restrictive
Antidepressant trials more likely to exclude suicidal individuals
Zimmerman 2015

Conflation of Long-Term and Acute Suicide Risk Factors

Suicide Risk Factor Research has Not Advanced in 50 Years
Meta-analysis of 365 studies
Franklin 2016

No Objective Measures of Suicide Risk

Reliance on Self-Report of Suicidal Thoughts, Plans and Behaviors
Separation from Depression

Few Biomarkers of SI Response

Few Treatments for Suicide Risk for the Short-Term
Past Work Across the Spectrum of Suicide Risk

**Long-Term Risk**
- Fear-Potentiated Startle  
  Ballard, 2014
- History of Sexual Abuse  
  Ballard, 2015
- Familial Transmission of Suicide Attempt  
  Ballard, 2019

**Short-Term Risk**
- Gamma Power in Anterior Insula  
  Gilbert, Under review
- Nocturnal Wakefulness  
  Ballard 2016
- Glucose metabolism in BA25  
  Ballard, 2014

**Response to Treatment**
- Anhedonia  
  Ballard, 2017
- Depression
- Suicide Ideation

**Additional Study References**
- Ballard, 2019
- Ballard, 2015
- Vande Voort 2017
- Gilbert, Under review
- Ballard, 2016
Suicide Risk: Real-Time perspective

What was different here?

As compared to here?

Bryan 2017, fluid vulnerability theory
Modeling before and after the suicide attempt: STEP BD data

Ballard, Farmer, et al., Under Review
Depressive Symptoms Before and After Suicide Attempt
Meta-Analysis of Ketamine and Suicidal Ideation (n = 167)

Effect of a Single Dose of Ketamine on Suicidal Ideation

Proportion of Study Subjects Without Suicidal Ideation at Each Time Point After Ketamine Administration

SI Response to Ketamine: Define Responders and Non-Responders

Latent class growth curve analysis used to model change in SI after ketamine administration (n = 128)
- Class 1 (Non-Responders)
- Class 2 (Responders)
- Class 3 (Remitters)

Ballard et al., 2018

Special thanks to Dr. Cristan Farmer
# Potential Predictors of SI Response

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Model Fit</th>
<th>Remitter: Non-Responder</th>
<th>Remitter: Responder</th>
<th>Responder: Remitter</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>$\chi^2 = 6.14, p = .05$</td>
<td>1.02 (0.98-1.07)</td>
<td>1.05 (1.01-1.10)</td>
<td>0.97 (0.94-1.01)</td>
</tr>
<tr>
<td>History of Self-Injury</td>
<td>$\chi^2 = 9.50, p = .01$</td>
<td>0.08 (0.01-0.70)</td>
<td>0.23 (0.03-2.03)</td>
<td>0.36 (0.12-1.04)</td>
</tr>
<tr>
<td>History of Sexual Abuse</td>
<td>$\chi^2 = 5.25, p = .07$</td>
<td>4.12 (1.17-14.49)</td>
<td>0.57 (0.19-1.64)</td>
<td>2.33 (0.74-7.35)</td>
</tr>
<tr>
<td>Length of Current Episode (months)</td>
<td>$\chi^2 = 6.66, p = .04$</td>
<td>1.00 (1.00-1.01)</td>
<td>1.01 (1.00-1.02)</td>
<td>0.99 (0.98-1.00)</td>
</tr>
<tr>
<td>Suicidal Ideation at Admission</td>
<td>$\chi^2 = 10.44, p = .01$</td>
<td>0.22 (0.06-0.90)</td>
<td>1.17 (0.25-5.38)</td>
<td>0.19 (0.06-0.60)</td>
</tr>
<tr>
<td>IL5</td>
<td>$\chi^2 = 5.51, p = .06$</td>
<td>1.40 (0.85-2.31)</td>
<td>1.79 (1.07-2.98)</td>
<td>0.78 (0.51-1.19)</td>
</tr>
</tbody>
</table>

Special thanks to Dr. Cristan Farmer
## Potential Predictors of SI Response ……Another way

### Clinical and Demographic Predictors
- Age
- Age of Onset
- BMI
- College Graduate
- Current Anxiety Diagnosis
- Diagnosis
- Family History of ETOH Abuse
- Family History of Mood Disorders
- Family History of Suicide
- Gender
- History of Alcohol Abuse
- History of Alcohol Dependence
- History of Psychiatric Hospitalization
- History of Physical Abuse
- History of Self-Injury
- History of Sexual Abuse

### Clinical and Demographic Predictors Continued
- History of Substance Abuse
- History of Suicide Attempt
- History of Suicidal Ideation
- Hospital Admissions (#)
- Length of Current Episode (months)
- Length of Illness (months)
- Suicidal Ideation at Admission
- Smoking (Current)
- History of Substance Abuse

### Plasma Biomarkers*
- BDNF
- VEGF
- Cortisol
- IFN-γ
- TNF-α
- sTNFR1
- IL-2
- IL-5
- IL-6
- IL-8
- IL-10
- KYN
- KynA
- QA
- IDO
- S100B

* Both baseline and change at Day 1
Regional placement of the infralimbic cortex (red) and subgenual cingulate cortex (blue)

Significant correlation between baseline suicidal ideation and rMRGlu in the infralimbic cortex ($r = .59$, $p = .007$), but not depression ($p = .79$).

Significant association between reduction in suicidal ideation and decreased rMRGlu in the infralimbic cortex after ketamine ($r = .54$, $p = .02$), but not depression ($p = .69$)

Ballard, 2014

Special thanks to Dr. Allison Nugent
Potential Biomarker: Nocturnal Wakefulness

- Self-reported sleep difficulties is associated with future suicide attempt
- Sleep represents an important, potential modifiable acute risk factor for suicide
- Time period of **12-4:59 am** may be a particularly high-risk time for suicide

Bernert 2014; Perlis, 2014

Wakefulness in Depressed Patients
(n = 65)

Wakefulness in Healthy Controls
(n = 22)

Sleep Quality of Depressed Ideators

Sleep Quality of Depressed Non-Ideators

Significant time by ideation interaction for sleep between 12 and 4 am, $p = .007$

Time spent awake at 4 am predicted suicidal ideation the next day when controlling for depression severity, $p = .008$

Patients with an antisuicidal ketamine response showed less wakefulness the night after ketamine infusion, $p = .01$.


Potential Biomarker: Nocturnal Wakefulness

Patients with **continued suicidal thoughts** after ketamine

Patients **without suicidal thoughts** after ketamine

Special thanks to Dr. Jennifer Vande Voort
New Directions? Suicide Implicit Association Task (S-IAT)

Measures the implicit association of **self with death** as compared to the **self with life**.
Nock demonstrated that the S-IAT can predict suicide attempt at 6 month follow up
Nock et al., 2011

**Evaluated with 3T fMRI**

- On fMRI, greater activation in self/death compared to self/life in the bilateral anterior insula and right ventrolateral prefrontal cortex/lateral orbital cortex.
- On MEG, self/death exhibited higher gamma power in the left anterior insula and bilateral anterior temporal cortices

**Evaluated with MEG**

Ballard et al., 2018; In prep

Special thanks to Dr. Jessica Gilbert
Potential Impact for Neurobiology of Suicide Research

Biomarkers

Identify potential biomarkers of acute suicide risk and response to treatment
Sleep, imaging, actigraphy, response to suicide-specific tasks, blood biomarkers, precipitants to acute crisis

Assessment

Evaluate whether biomarkers can be incorporated into psychiatric assessment of suicide risk
Supplement self-report with objective measures. Predict who will respond to treatment

Treatment

Identify promising new treatments for suicide risk
Evaluate other potential interventions with rapid effects on SI
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Patients
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