Ketamine: Why now? How? Where do we go from here?

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Disclosures

Sources of Research Support

1. Department of Veterans Affairs, VA National Center for PTSD
2. Department of Veterans Affairs/Department of Defense, Consortium for the Alleviation of PTSD
3. National Center for Advancing Translational Science, NIH
4. National Institute on Alcohol Abuse and Alcoholism
5. National Institute of Mental Health

Consulting Relationship (>$5,000)
Janssen, Novartis, Sunovion, Takeda,

Stock Equity (>$10,000)
BioHaven Medical Sciences, ArRETT, Blackthorn, Spring

Patents:
1. Glutamatergic treatments (licensed to Biohaven Medical Sciences)
2. Intranasal ketamine for depression (licensed to Janssen Pharmaceuticals)
3. AMPA-R antagonist for alcoholism
4. Naloxone to reduce ketamine abuse liability
5. Decision support for antidepressant treatment

Speaker’s Bureau: None

Paid Editorial Relationship
Biological Psychiatry - Editor
It Is Time to Address the Crisis in the Pharmacotherapy of Posttraumatic Stress Disorder: A Consensus Statement of the PTSD Psychopharmacology Working Group

To the Editor:

There is an urgent need to address a critical lack of advancement in the psychopharmacologic treatment of posttraumatic stress disorder (PTSD).
FDA-approved treatments: SSRI s

• Modest efficacy
  • About 10% difference in response vs placebo
  • Smaller effect size than psychotherapy
  • Unclear synergy with psychotherapy

• Slow:
  • Sertraline separates from placebo at 10 weeks

• Poorer outcomes in military/veteran populations?

PTSD Multicenter Trials Supported by the VA CSP
Biomarkers, Psychotherapy, Medication

- CSP 334: Psychophysiology biomarker (Heart rate)
- CSP 420: Group PE vs. Present-Centered Therapy
- CSP 494: Individual PE vs PCT
- **CSP 504: Risperidone**
- CSP 519: Smoking Cessation
- **CSP 563: Prazosin**
- CSP 575: Genomics of PTSD (Ongoing)
- CSP 591: PE vs. Cognitive Processing Therapy (Ongoing)

Outline

• Glutamate synaptic dysfunction and loss in PTSD
• Toward ketamine treatment for PTSD
• Where do we go from here?
Glutamate: The problem with cortisol

Adrenal Glands

Cortisol is harmful:
Chronic stress: persistent cortisol elevations

Glial dysfunction
(Glutamate Synaptic Dysregulation)

Cortisol is helpful:
PTSD: inadequate cortisol elevations relative to optimal stress response

Aberrant GR signaling alters synaptic regulation
- Glucocorticoid receptor
- FKB5 (GR chaperone)
- SGK1

Synaptic Pruning
mGluR5: key modulator of neuroplasticity

mGluR=Metabotropic glutamate receptor

Stoppel et al. Cell Rep 2017
Glucocorticoid contribution to stress vulnerability via mGluR5?

• **Acute** stress (hypercortisolemia): downregulation of mGluR5 and docking protein, Homer 1b/c
  • Pattern similar to major depression

• **Chronic** mild stress upregulates mGluR5 protein
  • blocked by GR antagonist

• *Does PTSD look like acute stress (MDD) or CMS?*

mGluR5 upregulation in PTSD

mGluR5 $V_T$ (receptor number) is increased in several brain regions in PTSD patients assessed with PET.

S. Holmes et al. *Proc Natl Acad Sci* 2017

mGluR5 $V_T$ in PFC correlates with severity of avoidance.

![Graph showing mGluR5 $V_T$ in PFC](image)
Measuring gene expression (mRNA level) to study cellular regulation

Central Dogma of Gene Expression.

Through the production of mRNA (transcription) and the synthesis of proteins (translation), the information contained in DNA is expressed.

PTSD: cortisol modulation of mGluR5 trafficking to synapse?

Post mortem PFC RNAseq: Shank1 but not mGluR5 is increased

*and* FKBP5 is decreased

(FKBP5 increased by cortisol)

S. Holmes et al. *Proc Natl Acad Sci* 2017
mGluR5 Summary

• mGluR5 upregulation in PTSD
• May arise from HPA alterations
• Treatments to normalize mGluR5?
  • *Glucocorticoid (prednisone)* or GR antagonist (*mefipristone*)?
  • *mGluR5 Negative Allosteric Modulators (NAMs)*
  • *Ketamine*?
High Cortisol
Low BDNF

Promote synaptic loss and dendritic atrophy

Reversed by antidepressant treatment

Berton et al. Nat Rev Neurosci 2006;7
A “connectionist” hypothesis

- Stress-induced loss of synaptic connectivity in PTSD impairs:
  - Adaptive executive deficits (memory, planning)
  - Executive control of emotion
  - Neuroplasticity

- Some treatments for PTSD may work by restoring connectivity:
  - Restore executive control of thought and emotion
  - Enhance plasticity (capacity to respond to treatment)
Supporting a connectionist hypothesis

Abdallah et al. Transl Psychiatry 2017 (dGBC seed-based tractography)
Paroxetiné (6 mo) increases hippocampal volume

Vermetten et al. Biol Psychiatry 2003
Summary: A Connectionist hypothesis

• Stress reduces synaptic connectivity
• PTSD symptoms are associated with MRI changes
• Long-term antidepressant treatment improves connectivity
• *What if this could happen better and quicker?*
Outline

• Glutamate synaptic dysfunction and loss in PTSD
• Toward ketamine treatment for PTSD
Ketamine

THE ANTI ANTIDEPRESSANT
Depression afflicts 300 million people. One-third don’t respond to treatment.

A surprising new drug may change that

BY MANDY OAKLANDER
Is depression a product of monoamine depletion?

<table>
<thead>
<tr>
<th>Technique</th>
<th>Amine</th>
<th>Depression?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tryp Depl</td>
<td>5HT</td>
<td>No</td>
</tr>
<tr>
<td>AMPT</td>
<td>NE/DA</td>
<td>No</td>
</tr>
<tr>
<td>TD + AMPT</td>
<td>5HT/NE/DA</td>
<td>No</td>
</tr>
</tbody>
</table>

Moreno et al. Biol Psychiatry 1997; Salomon et al. Biol Psychiatry 1997;
A shift from serotonin/midbrain to glutamate and cortico-limbic circuits
Rapid antidepressant effects of ketamine

Hamilton Depression Scale: \( p = .0001 \)

VAS, “High”
\( P = .0001 \)

BPRS, Positive Symptoms of Schizophrenia
\( P = .007 \)

R. Berman Biol Psychiatry 2000
Specificity of ketamine effects: greater and more persistent than midazolam

**Depression Severity: MADRAS**

**Response Rate: 50% Reduction**

J.W Murrough AJP 2013
Ketamine reduces suicidal ideation

Grunebaum M et al. AJP 2017
Other NMDA-R Modulators

• S-ketamine (Johnson & Johnson, Phase III)
• Repastinel (Glyx-13, Allergan)
• AZD6765 (unselective; AstraZeneca)
• D-cycloserine (glycine partial agonist)
• Nitrous oxide
• Dextromethorphan + quinidine (Nuedexta)
S-Ketamine shows dose-related efficacy

Initial Randomization

Placebo Non-Responders

Daly EJ et al. JAMA Psychiatry 2017
S-Ketamine robustly protects against relapse (OR=0.3) in TRD Responders to AD + Esketamine

Janssen Esketamine Study #3003

Cumulative Proportion of Subjects Who Remained Relapse Free; Maintenance Phase (Kaplan-Meier Estimates): Stable Responders
Long-term open label sustained efficacy (n=603)
Janssen Esketamine Sustain-2 Study

Figure 3: Mean (±SE) Montgomery-Asberg Depression Rating Scale total score over time (full analysis sets [IND and OP/MAINT]; observed case analysis)

Weekly: 24%
Some Every Other Week: 76%
Every Other Week: 38.1%
Variable (W/EOW): 37.8%

Full analysis sets for IND and OP/MAINT: patients who received ≥1 dose of nasal spray study medication or oral antidepressant in the open-label IND and OP/MAINT phases, respectively. AD; oral antidepressant; ESK, esketamine; IND, induction phase; MADRS, Montgomery-Asberg Depression Rating Scale; OP/MAINT, optimization/maintenance phase; SE, standard error

E. Wajs et al. Presented: ASCP May 29, 2018
Long-term open label sustained safety (n=603)
Janssen Esketamine Sustain-2 Study

Table 3: Treatment-emergent adverse events (full analysis sets [IND and OP/MAINT] and all enrolled analysis set)

<table>
<thead>
<tr>
<th>Event</th>
<th>4-week IND phase (N=779)</th>
<th>48-week OP/MAINT phase (N=603)</th>
<th>IND and OP/MAINT phases (N=802)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with ≥1 TEAEs</td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>Patients with ≥1 SAEs</td>
<td>653 (83.8)</td>
<td>516 (85.6)</td>
<td>723 (90.1)</td>
</tr>
<tr>
<td>TEAEs leading to discontinuation of intranasal spray medication</td>
<td>17 (2.2)</td>
<td>38 (6.3)</td>
<td>55 (6.9)</td>
</tr>
<tr>
<td>TEAEs leading to discontinuation of oral AD</td>
<td>53 (6.8)</td>
<td>23 (3.8)</td>
<td>76 (9.5)</td>
</tr>
<tr>
<td>TEAEs leading to death</td>
<td>20 (2.6)</td>
<td>14 (2.3)</td>
<td>33 (4.1)</td>
</tr>
<tr>
<td>TEAEs leading to death</td>
<td>0</td>
<td>2 (0.3)</td>
<td>2 (0.2)</td>
</tr>
</tbody>
</table>

E. Wajs et al. Presented: ASCP May 29, 2018
Features

- **Safe:**
  - AE rate in 205 infusions = 1.95%
  - Psychosis/dissociation is transient manageable with support
  - Nausea managed with ondansetron pretreatment
  - Abuse liability with restricting to clinic administration

- **Effective in TRD and Suicidal ideation**
  - 75% response in clinics
  - Synergy with CBT (extending benefit)
  - ECT non-responders
  - Bipolar, Psychotic depression, Anxious, Comorbid pain

- **Sustained benefit:**
  - Biweekly-monthly administration
  - Clinical experience: >4 yr

Treating depression in context of pain

- Rapid improvement in depression and pain
- Ketamine is well-tolerated and safe
- Sustained by repeated dosing
PTSD (n=41)

PTSD Symptoms

Depression

(Feder et al. JAMA Psychiatry 2014)
Ketamine PTSD
Open Label
Efficacy (n=15)

Abbott et al.
J Clin Psychiatry
2018
CAP Ketamine Study

• Team: (West Haven) C. Abdallah, L. Averill, J. Krystal, (San Antonio): A. López-Roca, J. Roache, S. Young, et al.

• PTSD (n=198) from VA and DoD

• Dose related safety and efficacy (0, 0.2, 0.5 mg/kg)

• Treatment: 4 weeks

• Durability of benefit: 4 weeks

• Banking of biosamples
New roles for ketamine in the treatment of PTSD

• **Rapid Remission:**
  • Crisis intervention/suicide prevention?
  • Mitigating/shortening hospitalization?
  • Prevent missed work days?

• **Treatment-resistant PTSD**
Outline

- Glutamate synaptic dysfunction and loss in PTSD
- Toward ketamine treatment for PTSD
- Where do we go from here?
Key directions

• Optimize use of ketamine for PTSD
• Optimize ketamine (alternatives)
Ketamine accelerates fear extinction: combine with PE or CPT?
Girgenti et al. Neurobiology of Disease 2017

Effect is Dependent on AMPA-R

Effect is Dependent on mTOR
Key directions

• Optimize use of ketamine for PTSD
• Optimize ketamine (alternatives)
  • Need to understand how it works
Ketamine stimulates rapid regrowth of synaptic connectivity in these regions.
Ketamine stimulates rapid restoration of functional connectivity in depressed patients.

Chadi Abdallah C et al. NPP 2016
Hypotheses Regarding Ketamine Efficacy

Go Pathway: Trigger Glutamate Release
Stop Pathway: Block NMDA-R

NMDA
Akt/mTOR
Spine Growth

AMPA
BDNF

Li et al. Science 2010
Autry et al. Nature 2011
Ketamine efficacy related to mGluR5 normalization? mGluR5 NAMs?

In Hippocampus:
Ketamine reductions in mGluR5 correlated with MADRS total ($r=0.52$, $p=0.035$, 1-tailed)

Esterlis et al. Mol Psychiatry 2017; epub
Novel Non-NMDA Candidate Antidepressant Targets

1. mGluR2
2. GABA-A
3. AMPA
4. BDNF
5. TrkB
6. Akt/mTOR

Postsynaptic Dendritic Spine

References:
Li et al. Science 2010
Autry et al. Nature 2011
Summary: A new opportunity

• The promise:
  • Rapid action
  • Anti-suicidal
  • Treatment-resistant
  • Promote fear extinction

• Tip of the iceberg: novel mechanisms
  • PTSD
  • Treatment