Rapid Acting Antidepressants: Opportunities and Mechanisms

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Collaboration and Support

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BRAIN & BEHAVIOR RESEARCH FOUNDATION

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Janssen, Novartis, Sunovion, Takeda,

Stock Equity (>$10,000)
BioHaven Medical Sciences, Terran, Cadent, 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
Antidepressants: Early Triumphs

- **Lithium**: John Cade (1949)
  - "Antipsychotic" D2/-5HT2 Antagonism
- **MAO Inhibition**: Nathan Kline (1957)
- **Serotonin-Norepinephrine Reuptake Inhibitors**: Roland Kuhn (1957)
- **"Antipsychotic" D2/-5HT2 Antagonism**: Pierre Deniker (1953)
In biggest advance for depression in years, FDA approves novel treatment for hardest cases

The nasal spray works in a new way and is based on an old anesthetic, ketamine, that has been used as a party drug.

By Carolyn Y. Johnson and Laurie McGinley
March 5

The Food and Drug Administration approved a novel antidepressant late Tuesday for people with depression that does not respond to other treatments — the first in decades to work in a completely new way in the brain.
Outline

• The problem with antidepressants
• Why ketamine?
• From mechanisms to new treatments
Depression is worse than we thought

• **More common:** ~7% (narrow definition) but up to 20% (broad definition)

• **More disabling:** leading cause of disability in adults in U.S.

• **More lethal:**
  • Contributor to rising suicide rate
  • Shortens life by 10 years on average

Anxiety and Depression Association of America, Global Burden of Disease Study, Lancet; U.S. Substance Abuse and Mental Health Administration data; Lawrence et al. BMJ 2013
Antidepressants are less effective than we hoped

• **Too few:** 30% remission initially
• **Too incremental:** 30% non-reponse at 1 year
• **Too slow:** 2 months to remission
• **Too unstable:** ¾ of treatment resistant patients (step 3 and 4) relapse within 1 year

**NIMH STAR*D Trial:** Gaynes et al. Gen Hosp Psychiatry 2008; Rush et al. CNS Drugs 2009
Trajectories of Depression Severity in Clinical Trials of Duloxetine

Insights Into Antidepressant and Placebo Responses

Ralitza Gueorguieva, PhD; Craig Mallinckrodt, PhD; John H. Krystal, MD

PLACEBO
RESPONDER
76.3%
Outline

• The problem with antidepressants
• Why ketamine?
## Serotonin and norepinephrine focus based on drugs

<table>
<thead>
<tr>
<th>Technique</th>
<th>Amine</th>
<th>Which one?</th>
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<td>TRYP Depletion</td>
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<td>5HT/NE/DA</td>
<td>Both</td>
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Heninger et al. Pharmacopsychiatry 1996
Serotonin and norepinephrine cannot explain depression

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Moreno et al. Biol Psychiatry 1997; Salomon et al. Biol Psychiatry 1997;
A shift from serotonin/midbrain to glutamate and cortico-limbic circuits
Ketamine Produces BPRS Positive and Negative Symptoms in Healthy Subjects

Krystal et al. Arch Gen Psychiatry 1994  (n=18)
Antidepressant effects of ketamine

Hamilton Depression Scale: $p=.0001$

VAS, “High”
$P=.0001$

BPRS, Positive Symptoms of Schizophrenia
$P=.007$

R. Berman et al.  Biol Psychiatry 2000
Dose-Related Ketamine Efficacy
More dissociation≠More efficacy

Fava et al. Mol Psychiatry 2018

In patients (n=99)
Ketamine reduces suicidal ideation

Grunebaum M et al. AJP 2017
Esketamine protects against relapse (OR=0.3) in TRD Responders
Janssen Esketamine Study #3003 (JAMA Psychiatry 2019)

E. Daly et al.
Presented: ASCP May 29, 2018
Effective treatment with ketamine has its ups and downs over 2 yr (n=14)

Wilkinson et al. J Clin Psychiatry 2018

*The sample size decreases over time, reflecting that patients are at different stages of continuation/maintenance therapy and not reflecting patient dropout. Data for 1 of the patients were previously published in a case report. 27  
Abbreviation: QIDS-SR=Quick Inventory of Depressive Symptomatology-Self Report.
PTSD (n=41)

Feder et al. JAMA Psychiatry 2014

PTSD Symptoms

Depression
Ketamine accelerates fear extinction: Combine with PE or CPT?
Girgenti et al. Neurobiology of Disease 2017
New hope?

• Rapid relief – acute settings/severe symptoms
• Treatment-resistant symptoms
• Protection against relapse
Outline

• The problem with antidepressants
• Why ketamine?
• From mechanisms to new treatments
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
The human brain is a structure of unimaginable complexity.
Antidepressant effect is distinct from the symptoms of acute intoxication

In animals:
Acute (1hr): neural activation
Delayed (6 hr): new synapses

R. Berman et al. Biol Psychiatry 2000

Li et al. Science 2010
Ketamine stimulates rapid regrowth of synaptic connectivity in these regions
Duman and Aghajanian Science 2012
Reductions in PET synaptic marker (SV2A) correlate with reduced fMRI cortical functional connectivity

Reduced 11C-UCB-J associated with severe depression

Holmes et al. Nature Communications 2019
Ketamine stimulates rapid restoration of functional connectivity in depressed patients.
Hypotheses Regarding Ketamine Efficacy

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

Li et al. Science 2010
Autry et al. Nature 2011
Ketamine and glutamate release – inverted-U: Low doses increase, high doses decrease (Moghaddam et al. J Neurosci 1997)

Dose-related increases up to 10-30 mg/kg

50 mg/kg-no change
200 mg/kg-decrease
Ketamine increases glutamate release (13C-glutamine enrichment) in frontal cortex

Rate of conversion of glutamate to glutamate estimates glutamate release

Increase in glutamate release (Glu-Gln) without metabolism increase (Glu)

Abdallah et al. NPP 2019
Ketamine efficacy related to mGluR5 normalization?

Ketamine causes rapid and sustained reduction in mGluR5 availability: displacement/internalization

DeLorenzo et al. Biol Psychiatry 2015

Degree of displacement/internalization predicts Clinical response in depression

Greater mGluR5 displacement/internalization

Greater improvement

N=10

Greater mGluR5 displacement/internalization

Esterlis et al. Mol Psychiatry 2018
Other implicated mechanisms

• **Other network effects:**
  • Blockade of habenula burst firing
  • Indirect endogenous opiate effect?

• **Anti-inflammatory effects:**
  • Kynurenine pathway vs anti-cytokine
  • Inflammatory “subtypes of depression?”

• **Epigenetic effects:**
  • Resilience promoting

• **Neuroplasticity promoting**
  • Enhancing cognitive/behavioral therapies

New medications?

- Ketamine derivatives
  - R-ketamine
  - HNK
- Other NMDA-R antagonists
- AMPAkines
- mGluR2 antagonists
- BDNF facilitators
- mTORC1 facilitators
Summary

• New clinical opportunities: rapid effectiveness for treatment-resistant symptoms
• New mechanisms of action sheds light on brain mechanisms of depression and its treatment
• New classes of medications?