Rapid Acting Treatments for Depression: Ketamine and Beyond
North Carolina Psychiatric Association
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Lawrence Park, M.D.

Experimental Therapeutics and Pathophysiology Branch
Division of Intramural Research Program
National Institute of Mental Health
Presenter Disclosure

Lawrence Park

The following personal financial relationships with commercial interests relevant to this presentation exist:

No relationships to disclose.
Outline

- NIMH: Experimental Therapeutics & Pathophysiology Branch
- Psychopharmacological Development
- Glutamate System and Mood Disorders
- Ketamine for Depression
- Other Glutamatergic Modulators for Depression
- Neurobiology of Suicide
National Institute of Mental Health
Intramural Research Program

• NIH Clinical Center
  • Dedicated research facility
  • CORE facilities
• Dedicated Inpatient Unit
  • Multidisciplinary team model
  • Allows for study of unmedicated subjects
• Treatment Resistant Depression Population
  • 24 year duration of illness
  • 50% disabled
  • 50% attempted suicide
  • 7+ antidepressants ineffective
  • 60% ECT ineffective

Mark O. Hatfield Clinical Research Center
Experimental Therapeutics and Pathophysiology Branch

Target → Proof of Concept (POC) Study → Improved Treatment
Drug Development in the past 60 years

Need to identify new molecular targets

Insel and Skolnick 2006
Neuroscience: Challenges in Medication Development

- Higher order brain function difficult to model preclinically
- Limited segregation of patients into biological strata
- Attrition in late stages increases costs
- Sheer complexity of our brain disorders

Up to 15 years/$4-11 billion

Miller Science 2010
Depression: The Need for Improved Treatments

Problems with Current Antidepressants:

- Low remission rates
- Lag of onset of antidepressant effects
- Questionable efficacy in bipolar depression

Next generation antidepressant

Rapid onset: Hours/day

Major Depressive Episode

Initiate Treatment

Standard antidepressant
(Monoaminergic)

Lag of onset: 10-14 weeks

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Rapid Antidepressant Effect of Ketamine in Unmedicated Treatment Resistant MDD (n=18) by Zarate et al. Arch Gen Psychiatry 2006

- **HAMD Following a Single Ketamine Infusion**
  - **Response**: 50% decrease in HAMD
  - **Time**: Weeks

- **Monoaminergic Antidepressant**
  - 62-65%

- **Statistical Significance**:
  - ***p<0.001, **p<0.01, *p<0.05

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Zarate et al. Arch Gen Psychiatry 2006
Rapid Antidepressant Effect of Ketamine in Treatment Resistant Bipolar (BP) Depression

First BP Study of Ketamine (n=18)
- Diazgranados et al. Arch Gen Psych 2010

Replication BP study (n=15)
- Zarate et al. Biol Psych 2012

MADRS

- Ketamine
- Placebo

***p<0.001, **p<0.01, *p<0.05
Development of Ketamine Research/Treatment

1. Ketamine in Clinical Practice Settings: research/off-label use
   - U.S. government patent (depression)
   - Licensed by J&J (Esketamine) FDA 'breakthrough therapy designation'
   - Off-label use of ketamine worldwide
     - >12 companies developing glutamatergic modulators for depression
     - >40 NIMH grants

2. Develop ketamine-like drugs (without dissociative side effects)
   - More NMDA subunit selective drugs

3. Understand ketamine’s mechanism of action from synapses through a range of systems

4. Is there more to the story with the “ketamine paradigm”: ketamine’s metabolites
   - Intramural & Extramural Collaboration
     - University of Maryland
     - NCATS
     - NIA
     - UNC
     - NIMH
Repeat Dose IV Ketamine

Candidate Glutamatergic Modulators for Depression

- Na Channel
  - Riluzole
  - mGluR2 PAM
    - JNJ-4041813
    - ADX41149
  - mGluR2/3 Antagonists
    - MGS0039
    - LY341495
  - mGluR2/3 NAMs
    - R04491533
    - R04499819

- mGluR5 NAMs
  - AZD2066
  - STX-107
  - R04917523
  - RG7090 (Basimglurant)

- NMDA Complex Modulators

- AMPA Potentiator
  - ORG-26576

- GlyT-1 Inhibitors
  - Sarcosine
  - Bitopertin

- Glycine Agonists
  - D-serine
  - Rapastinel (Glyx-13)
  - NRX-1074

- Glycine Partial Agonists
  - D-cycloserine

- Glycine Antagonists
  - 4-CI-KYN (AV-101)

- EAAT2 Enhancers
  - Ceftriaxone
  - Diazoxide
NMDA Complex Modulators

**Broad NMDA antagonists**
- *Ketamine*
- Memantine
- AZD6765
- DM/Q

**NR2B antagonists**
- Ro 25-6981
- Ifenprodil
- Traxoprodil
- Evotec-101
- MK-0657*

**Glycine site**
- D-Serine
- D-cycloserine
- GLYX-13
- 4-CI-KYN*

*Figures and diagrams credit to Nature Publishing Group and Evotec*
Is Glutamate Burst Critical to a Rapid Antidepressant Effect?

Adapted from Duman, 2014
Ketamine Mechanism of Action: Pre-clinical Evidence

Ketamine produces a rapid surge in extracellular glutamate

AMPAs antagonism blocks the antidepressant effects of ketamine in animals in the forced swim test

Maeng et al. Biol Psych 2008

Ketamine (10 mg/kg) Ketamine (20 mg/kg) Ketamine (30 mg/kg)

Saline Ketamine (10 mg/kg) Ketamine (20 mg/kg) Ketamine (30 mg/kg)

Rapid reversal of complex behavioral phenotype

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RDoC
Temporal Development of Main Effects and Side Effects of Ketamine

Dissociative side effects
Ketamine metabolites?

Zarate et al. Arch Gen Psych 2006; Zarate et al. Biol Psych 2012;

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Ketamine Metabolites

Blocking Ketamine Metabolism Abolishes Antidepressant Effect

- Side effects, addiction
- Rapid Antidepressant (hrs)

NMDAR Inhibition-Independent Antidepressant Actions of Ketamine

- (R,S)-ketamine (single dose) exerts rapid and sustained antidepressant effects but associated with undesirable side effects
- Antidepressant action is blocked by blocking ketamine metabolism
- (2S,6S;2R,6R)-hydroxynorketamine (HNK) exerts behavioral, electroencephalographic, electrophysiological and cellular antidepressant actions in mice
- R enantiomer of HNK may have greater antidepressant effect
- R enantiomer of HNK does not appear to be related to side effects
- Antidepressant effects are blocked with AMPA antagonist

Zanos et al. Nature in press
## Deaths per 100,000 population, age-adjusted

<table>
<thead>
<tr>
<th>Cause</th>
<th>2000</th>
<th>2013</th>
<th>2014</th>
</tr>
</thead>
<tbody>
<tr>
<td>All causes</td>
<td>869.0</td>
<td>731.9</td>
<td>724.6</td>
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<tr>
<td>Heart disease</td>
<td>257.6</td>
<td>169.8</td>
<td>167.0</td>
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<tr>
<td>Cancer</td>
<td>199.6</td>
<td>163.2</td>
<td>161.2</td>
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<tr>
<td>Chronic lower resp.</td>
<td>44.2</td>
<td>42.1</td>
<td>40.5</td>
</tr>
<tr>
<td>Unintentional injuries</td>
<td>34.9</td>
<td>39.4</td>
<td>40.5</td>
</tr>
<tr>
<td>Stroke</td>
<td>60.9</td>
<td>36.2</td>
<td>36.5</td>
</tr>
<tr>
<td>Alzheimer’s disease</td>
<td>18.1</td>
<td>23.5</td>
<td>25.4</td>
</tr>
<tr>
<td>Diabetes</td>
<td>25.0</td>
<td>21.2</td>
<td>20.9</td>
</tr>
<tr>
<td>Influenza/pneumonia</td>
<td>23.7</td>
<td>15.9</td>
<td>15.1</td>
</tr>
<tr>
<td>Kidney diseases</td>
<td>13.5</td>
<td>13.2</td>
<td>13.2</td>
</tr>
<tr>
<td>Suicide</td>
<td>10.4</td>
<td>12.6</td>
<td>13.0</td>
</tr>
</tbody>
</table>

Health, United States, 2015, CDC
Mortality from Medical Causes

Peak 1965–1995

Current 2009–2012

Suicide

Stroke (~20,000)

AIDS (~30,000)

Heart Disease (~1.1 Million)

ALL (Leukemia) (~6,000)

Percent of Peak

25

50

75

100
Suicide Remains a Significant Public Health Issue

Figure 1. Age-adjusted suicide rates, by sex: United States, 1999–2014

NOTES: Suicide deaths are identified with codes U03, X60–X84, and Y87.9 from the International Statistical Classification of Diseases and Related Health Problems, Tenth Revision. Access data for Figure 1 at: http://www.cdc.gov/nchs/data/databriefs/db241_table.pdf#1.

Rapid Decreases in Suicidal Ideation (SI) with Ketamine in MDD and BD

Diazgranados et al., Biol Psychiatr 2010

***p<0.001, **p<0.01, *p<0.05
Wakefulness is Associated with Next-day Suicidal Ideation in Depressed Patients

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, \( p = .008 \)

Ballard et al J Clin Psych, in press
Wakefulness in Depressed Patients and Healthy Controls

Data collected using polysomnography
Relationship Between Wakefulness from 12:00 AM – 4:59 AM and Antisuicidal Response to Ketamine

Vandevoort, Ballard, Niciu in review
Neurobiology of Suicide Protocol: 15-M-0188

- Identify patients in current suicidal crisis
  - Suicide attempt or acute suicidal thoughts in last 2 weeks
  - Admission to inpatient unit– 7SE, CC, NIH
- Multimodal assessment to identify biomarkers of suicidal ideation
  - Dimensional perspective for suicidal thoughts/behaviors
- Replicate “rapid model paradigm” used for antidepressants treatments to develop rapid-acting anti-suicidal treatments
  - Evaluate ketamine and sleep deprivation in suicidal individuals
  - Identify neural correlates of antisuicidal response

- Polysomnography
- MRS
- PET
- MEG
- fMRI
- Structural MRI

Environment, psychosocial stress, personality, trauma, support systems, ...............
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Contact:

lawrence.park@nih.gov

http://patientinfo.nimh.nih.gov/
1-877-MIND-NIH (1-877-646-3644)
moodresearch@mail.nih.gov