Mood Disorders: glutamate dysfunction, treatments, and need for glutamate biomarkers

IOM Workshop on Glutamate-related Biomarkers in Drug Development for Disorders of the Nervous System
Washington, D.C

Carlos A. Zarate, Jr., M.D
Experimental Therapeutics
Mood and Anxiety Disorders Program,
Intramural Program, NIMH
Disclosure

- Funding
  - Intramural research program/NIMH
  - NARSAD Independent investigator award
  - No funding from industry
- Listed on a patent application submitted for the use of ketamine in depression. I have assigned my right on the patent to the US government
- Off label use of ketamine
Developing novel therapeutics for the treatment of severe mood disorders: urgency of the problem

- Depression is one of THE leading causes of disability worldwide, for Americans between 15 and 44 years of age
- The National Comorbidity Survey Replication study reported a prevalence of 6.6%, with half of the cases classified as “severe” or “very severe”
- Depression is associated with high rates of morbidity and mortality
  - Over 32,000 suicides in the United States
  - An increase in the death rate at any age, independent of suicide, smoking, or other risk factors
- There is no evidence that shows a meaningful decrease in the rates of suicide or disability from depression with current treatments

WHO 2002; Kessler et al. JAMA 2003; Wang Arch Gen Psych 2005; Insel and Wang Psych Services 2009
Remission rates in outpatients with major depression STAR*D (n=2,876)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Mood stabilizer + AD (N=179)</th>
<th>Mood stabilizer + Placebo (N=187)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Durable recovery</td>
<td>24%</td>
<td>27%</td>
</tr>
</tbody>
</table>

Available Treatments for Mood Disorders are less than Optimal

- Low remission rates
- Delay of onset (weeks to months)
- Personal and social problems (job, marriage, kids)
- Increase risk of suicidal behavior (mostly 1st 30 days of an AD)

Sachs et al. NEJM 2007

Trivedi et al. NEJM 2006
Drug Development in the past 50 years

- Lithium
- Anticonvulsants
  - Divalproex
  - Carbamazepine
  - Lamotrigine
  - Topiramate
  - Oxcarbazepine
  - Levetiracetam
- Antipsychotics
  - Clozapine
  - Risperidone
  - Olanzapine
  - Quetiapine
  - Ziprasidone
  - Aripiprazole

Antidepressants **ONLY** serotonin and norepinephrine based (‘me too drugs’)

Except for Li all available FDA approved treatments for BPD are anticonvulsants or Antipsychotic drugs

Insel and Skolnick Mol Psychiatry 2006;11:11-17
Modulation of the glutamatergic system may have antidepressant effects

- Repeated administration of AD down-regulate NMDA receptor function
- Animal Models of depression
  - NMDA antagonists (MK-801 and AP-7) have antidepressant effects
  - AMPA receptor potentiator (LY392098) has antidepressant effects
- Antidepressant studies in humans
  - Post-mortem studies
  - Imaging studies

SSRI: 33% remission in 10-14 wks

NMDA/AMPA: 33% remission in 1 day?
1 study?
2 studies?
2 studies in 2 different disorders

2 studies in 2 different disorders + same pre-treatment biomarker predicting response? > convincing
Ketamine is widely used non-barbiturate, disassociate anesthetic mainly for ambulatory surgery and chronic pain.

- Ketamine is 10-50 times less potent than PCP in blocking.
- Non-competitive NMDA receptor antagonist.
- Psychotomimetic properties (5-20%).
- Abused as “club drug”.
- Studied in: schizophrenia, cognition, alcoholism, chronic pain, neuroprotection.

**Can the Onset of Action of Antidepressants be Accelerated?**

**Modification in synaptic AMPA & NMDA receptors**

**SSRIs**

**NRIs**

**SNRIs**
Robust, rapid & relatively sustained antidepressant effects of low dose ketamine, and response rates to ketamine in a double-blind placebo crossover trial in patients with treatment-resistant major depression

Zarate et al. Arch Gen Psychiatry, 2006

**33% remission day 1**
A double-blind placebo-controlled study of an NMDA Antagonist (Ketamine) in bipolar depression

Drug Free Period
2 weeks

Placebo

Ketamine

Placebo

Ketamine

2 weeks
Ketamine i.v.
(0.5 mg/kg over 40 min)

Lithium (0.6-1.2 mEq/L) or Valproate (50 – 125 ug/mL)

Open treatment Phase
6 weeks

Double Blind Phase
4 weeks

- MEG
- PET
- EEG
- BDNF
# Demographic/Clinical Characteristics Bipolar Disorder (N=18)

<table>
<thead>
<tr>
<th>Demographic/Clinical Characteristics</th>
<th>Age, Years</th>
<th>Length of illness, Years</th>
<th>Length of current MDE, Months</th>
<th>Length of hospitalization prior to randomization, Days</th>
<th>Number of psychotropic medications on admission</th>
<th>Lifetime failed antidepressant trials*</th>
<th>N (%)</th>
<th>Sex, Female</th>
<th>12 (67)</th>
<th>Disability</th>
<th>12 (67)</th>
<th>Unemployed</th>
<th>17 (94)</th>
<th>Life history suicide attempt</th>
<th>9 (50)</th>
<th>Alcohol abuse or dependence</th>
<th>8 (44)</th>
<th>Anxiety disorder</th>
<th>6 (33)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Treatment</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Current MDE</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Lithium</strong></td>
<td>7 (39)</td>
<td>16 (89)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Antidepressants</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Duloxetine</strong></td>
<td>7 (39)</td>
<td>13 (72)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>SSRIs</strong></td>
<td>6 (33)</td>
<td>18 (100)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Bupropion</strong></td>
<td>5 (28)</td>
<td>16 (89)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Venlafaxine</strong></td>
<td>2 (11)</td>
<td>11 (61)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Trazodone</strong></td>
<td>2 (11)</td>
<td>7 (39)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>MAOIs</strong></td>
<td>1 (6)</td>
<td>7 (39)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>TCA</strong></td>
<td>0 (0)</td>
<td>7 (39)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Antipsychotics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Quetiapine</strong></td>
<td>9 (50)</td>
<td>16 (89)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Aripiprazole</strong></td>
<td>2 (11)</td>
<td>10 (56)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Risperidone</strong></td>
<td>2 (11)</td>
<td>8 (44)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Ziprasidone</strong></td>
<td>2 (11)</td>
<td>7 (39)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Olanzapine</strong></td>
<td>1 (6)</td>
<td>7 (39)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Anticonvulsants</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Valproate</strong></td>
<td>6 (33)</td>
<td>14 (78)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Lamotrigine</strong></td>
<td>3 (17)</td>
<td>13 (72)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Carbamazepine</strong></td>
<td>1 (6)</td>
<td>9 (50)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>ECT</strong></td>
<td>2 (11)</td>
<td>10 (56)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Robust, rapid & relatively sustained antidepressant effects of low dose ketamine, and response rates to ketamine in a double-blind placebo crossover trial in patients with treatment-resistant Bipolar depression

DiazGranados et al. in press
Change in the Depression Scores Over One Week in Major Depressive Disorder

**HDRS**

-60 40 80 110 230 D1 D2 D3 D7

![Graph showing HDRS scores over time with arrows indicating Infusion at -60, 40, 80, 110, and 230 minutes.]

Zarate et al. Arch Gen Psych 2006

---

Change in the Depression Scores Over One Week in Bipolar Depressive Disorder

**HDRS**

-60 40 80 110 230 D1 D2 D3 D7 D10 D14

![Graph showing HDRS scores over time with arrows indicating Infusion at -60, 40, 80, 110, and 230 minutes.]

DiazGranados et al. in press
Rapid Decreases in high suicidal ideation with ketamine over 4 hours in TRD

Baseline SSI
- High SSI (≥4) (n=10)
- Low SSI (≤3) (n=23)

Scale for Suicidal Ideation (SSI)

- d= 2.36 (1.56-3.16)
- d= 1.27 (0.62-1.92)

DiazGranados et al. in press
Mechanism of Action of Ketamine and Development of surrogate (clinical & biological) endpoints

Ketamine 0.5 mg/kg over 40 min

Ketamine ½ life 2hs

50% response

50% non-response

Drug-free

14-day Drug-free

6 hs

14-day Drug-free

50% response

50% non-response

Drug-free

Ongoing response

Relapse

- MEG
- EEG
- PET
- fMRI
- 13C
- BDNF, VEGF
  - metabolomic, proteomic

-Large Tx Effect size
- "Control" of environment
- 100% adherence to tx (or other meds)
- Studied in drug-free period before and after
- No substance use
- Low Placebo effect
- Facility coordinating multiple procedures
- Relatively short trials to capture bio-signatures of response, remission, and relapse
Using EEG to study synaptic potentiation in the human brain
(local SWA increases with synaptic potentiation)

EEG/MEG recordings of SWA can provide electrophysiologic
evidence for local changes in cortical synaptic strength.

Visuomotor Task: Local SWA Increase

Synaptic Plasticity: Enhanced AMPA throughput

Response

NO Synaptic Plasticity: NO Enhanced AMPA throughput

No Response

EEG/MEG recordings of SWA can provide electrophysiologic
evidence for local changes in cortical synaptic strength.
Ketamine affects SWA

SWA Overnight Timecourse

- p<.01 (Bonferroni corrected) Baseline 3 vs 1&2
- p<.01 (Bonferroni corrected) Ketamine 3 vs 1&2
- p<.01 (Bonferroni corrected) N3 3 vs 1&2
Ketamine effects are specific for SWA

Power for each frequency bin was normalized by the Power for same bin for the whole Baseline night NREM

Increase SWA and antidepressant response: $r = -0.73, p = 0.024$

Zoom in on SWA range

* = $p < 0.05$
Activation Studies Implicate Anterior Cingulate in Cognitive & Affective Processing

Increasing activation of the rostral ACC while seeing repeated fearful faces predicts fast antidepressant response to ketamine

Rostral ACC

Right Amygdala

Positive response

Salvadore et al., Biol Psychiatry 2009
Anterior cingulate desynchronization and functional connectivity with the amygdala during a working memory task predict rapid antidepressant response to ketamine

Salvatore et al. Neuropsychopharmacology 2010

$r = 0.82, \ p = 0.0002$

$r = -0.73, \ p = 0.0021$
ACC desynchronization during a working memory task predicts rapid antidepressant response to ketamine in two different disorders

Unipolar depression

Bipolar depression
Mediators of Depression Response to Ketamine

- Decreased Left Amygdala (FDG PET)
- Decreased Left AMPC (FDG PET)
- Decreased Left SPC (FDG PET)
- Decreased Left FPC (FDG PET)
- Decreased Left VLPC (FDG PET)
- Increased Right VLPC (FDG PET)
- Decreased Right Hippocampus (FDG PET)
- Increased BDNF
- Increased Left Ventral Striatum (FDG PET)
- Decreased Left Anterior Insula (FDG PET)
- Increased Norketamine Level
- Increased Right STG (FDG PET)
- Increased Right FPC (FDG PET)
- Increased Ketamine Level
- Increased VEGF
Conclusions

- The glutamate system is relevant to the mechanism of antidepressant action
- The results support the hypothesis that directly targeting the NMDA receptor complex may bring about rapid antidepressant effects in both unipolar and bipolar depression
- The fact that 2 different studies in 2 different disorders produce same remission rates at an early time point (day 1) with the same pre-treatment biomarker predicting response strongly argues that NMDA/AMPA in ACC region is a relevant therapeutic target for rapid antidepressant response
- Anterior cingulate cortex activity modulation may be key to antidepressant response
- Neurobiological parameters may be valuable predictors of treatment response, possibly explaining more variation than common subdiagnostic classifications
Mark O. Hatfield Clinical Research Center
Intramural Research Program/NIMH

Nancy DiazGranados
Lobna Ibrahim
Giacomo Salvadore
R. Machado-Vieira
Alan Mallinger
Nancy Brutsche
Wally Duncan
Nadia Hejazi
Libby Jolkovsky
Yamila Carmona
Madeline Gupta
E Smith-Jackson
Rezvan Ameli
Sergio Bauza
David Latov
Jackie Baumann
C. Wheeler-Castillo

Brenda Phillips
David Luckenbaugh
Eva Kakoza
7SE staff, OT, VT, RT
OP4
7SW sleep lab
LMP (Du, Chen, Manji)
Section on Neuroimaging
Affective Pathophysiology Lab
NCF staff
Intramural research pgm
Office of the Clinical Director/NIMH
MEG CORE facility
Anesthesia (Quezado, Kammerer)
Tononi University Wisconsin
NARSAD
Patient and their families