An Update on the Treatment and Research of Treatment-Resistant Depression and Bipolar Disorder

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Experimental Therapeutics & Pathophysiology Branch (ETPB)
Division of Intramural Research Program
National Institute of Mental Health
1990s Fellowship Clinical Psychopharmacology

McLean Hospital

- Bipolar & psychotic disorders clinic
  - 300 + patients with severe illness
  - See how bad illness was and suffering

- Experimental Therapeutics Clinic
  - Clozapine
  - LY 170053 (+ weight, + mood)
  - R 64 766 (+mood)
  - ICI 204,636 (+mood)
  - **Research unit?**
Mood disorders: a major cause of disability

- >10% of individuals suffer from a mood disorder each year
- Depression is one of THE leading causes of disability worldwide
- An increase in the death rate at any age, independent of suicide, smoking, or other risk factors
- ~1 million deaths from suicide/yr Individuals with major depression sometimes describe an emotional pain much worse than any physical pain that they have experienced
- Mood disorders are: disturbances of mood, behavior, circadian and activity levels
- Mood disorders are disturbances of synapses and circuits
Treatment-Resistant Depression (TRD) increased morbidity and mortality

- Higher rates of medical and psychiatric co-morbidity
- Greater healthcare utilization and costs
  - Hospitalized TRD had 7× the annual health care costs of the outpatient TRD group and 19× the costs of the comparison group
  - Higher costs for imaging tests, physician visits, psychiatric hospitalizations, and number of working days lost
- High risk of suicide (~15%)
  - Report more hopelessness and prominent suicidal ideation
  - 1/3 of patients reported significant suicidal ideas or gestures

TRD and psychosocial functioning

- The Longitudinal Interval Follow-up Evaluation (LIFE) scale was used to measure psychosocial functioning in 92 patients with TRD
- Specific impairments noted
  - Mild-to-moderate impairment in work-related activities
  - Good-to-fair interpersonal relations
  - Poor level of involvement in recreational activities
  - Mild impairment of ability to enjoy sexual activity
- However, patients and clinicians rated global social adjustment as poor

## Main clinical and biological risk factors for TRD

<table>
<thead>
<tr>
<th>Factor</th>
<th>Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Comorbid anxiety disorder</td>
<td>OR=2.6</td>
</tr>
<tr>
<td>Current suicidal risk</td>
<td>OR=2.2</td>
</tr>
<tr>
<td>Nonresponse to the 1(^{st}) antidepressant</td>
<td>OR=1.6</td>
</tr>
<tr>
<td>Melancholic</td>
<td>OR=1.5</td>
</tr>
<tr>
<td>Bipolarity</td>
<td>OR=1.6</td>
</tr>
<tr>
<td>Early onset of first depressive episode</td>
<td>OR=2.3</td>
</tr>
<tr>
<td>High rate of depressive recurrences</td>
<td>OR=1.5</td>
</tr>
<tr>
<td>Lack of full remission after a previous episode</td>
<td>OR=10.4</td>
</tr>
<tr>
<td>5-HT(1A) C1019G polym GG genotype + A allele of BDNF G196A</td>
<td>3.17</td>
</tr>
<tr>
<td>NTRK2 gene polymorphism (T-thaplotype)</td>
<td>1.43</td>
</tr>
<tr>
<td>Functional polymorphism of GRIN2B</td>
<td>1.55</td>
</tr>
</tbody>
</table>

Bennabi et al. J Affec Disord 2015
## TRD overview: levels of resistance

<table>
<thead>
<tr>
<th>Stage</th>
<th>Treatment Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No single adequate trial of medication</td>
</tr>
<tr>
<td>1</td>
<td>Failure to respond to an adequate trial of 1 medication</td>
</tr>
<tr>
<td>2</td>
<td>Failure to respond to 2 different monotherapy trials of medications with different pharmacologic profiles</td>
</tr>
<tr>
<td>3</td>
<td>Stage 2 plus failure to respond to augmentation of 1 of the monotherapies</td>
</tr>
<tr>
<td>4</td>
<td>Stage 3 plus failure of a second augmentation strategy</td>
</tr>
<tr>
<td>5</td>
<td>Stage 4 plus failure to respond to ECT</td>
</tr>
</tbody>
</table>

Evaluation approach to antidepressant TRD

- Adequate trial
  - Duration of treatment
  - Dosage of medication

- Behavioral/Environmental factors
  - Poor family support
  - Marital partner perceived as uncaring
  - Multiple losses, bereavement
  - Job-related stress
  - Financial problems
  - Unemployment

- Adherence
  - Patient education
  - Medication intolerance

- Diagnosis
  - Medical
  - Other psychiatric
STAR*D
Pharmacotherapy of TRD: next step

- Optimize dose
- Titrate to high dose
- Switch
- Augment
- ECT
- Psychotherapy
Switch vs. Augment

Level 3

Randomize

Switch Options:
- MRT
- NTP

Augmentation Options:
- L-2 Tx + Li
- L-2 Tx + THY

20-25% remission

Level 4

Randomize

Switch Options:
- TCP
- VEN-XR + MRT

<15% remission

MIRT = mirtazapine; NTP = nortriptyline; TCP = tranylcypromine; Tx = treatment; Rush AJ et al. Control Clin Trials 2004
Mean Scores on the Hamilton Depression Rating Scale, by Visit in a Randomized Trial of Antidepressant Monotherapy or Combination Treatment

<table>
<thead>
<tr>
<th>Available modalities for TRD</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Atypical antidepressants</strong></td>
</tr>
<tr>
<td><strong>Combination antidepressants</strong></td>
</tr>
<tr>
<td><strong>Psychostimulants</strong></td>
</tr>
<tr>
<td><strong>Lithium</strong></td>
</tr>
<tr>
<td><strong>Thyroid hormone</strong></td>
</tr>
<tr>
<td><strong>Buspirone</strong></td>
</tr>
<tr>
<td><strong>Glutamatergic</strong></td>
</tr>
<tr>
<td><strong>Complementary alternative/nutraceuticals</strong></td>
</tr>
<tr>
<td><strong>Inflammatory-immune based</strong></td>
</tr>
<tr>
<td><strong>Psychotherapy</strong></td>
</tr>
<tr>
<td><strong>Neuromodulatory</strong></td>
</tr>
<tr>
<td><strong>Aerobic exercise</strong></td>
</tr>
</tbody>
</table>

McIntyre J Affect Disord 2014
Specific depressive subtypes may suggest specific treatment modifications

- Depression with anxiety
- Depression with psychotic features
- Atypical depression (MAO inhibitors)
- Depression with substance abuse
- Bipolar depression (start with mood stabilizer)
- Depression with personality disorder
Anxious Depression

- Prevalence of comorbid anxiety symptoms in MDD range from 45-60%

- Comorbid anxiety symptoms with MDD
  - Greater severity of depressive severity and functional impairment
  - Poorer treatment outcome and greater risk of depressive relapse (STAR*D)
  - Increased risk of suicidality
  - Higher social distress and higher incidence of alcohol and drug abuse
  - Less likely to respond to medications (e.g., citalopram)
Remission Rates in Level 2 of STAR*D Anxious vs. Non-Anxious MDD

Percent (%)

- Anxious MDD
- Non-Anxious MDD

* p < .05

Fava et al. AJP 2008
Depression with Psychotic Features

• Misdiagnosis of psychotic depression is common even in academic centers
• Delusions or hallucinations
• Typically mood-congruent
• Associated with:
  ▪ Increased severity
  ▪ More frequent hospitalization
  ▪ More frequent suicide
  ▪ Less frequent spontaneous remission
• Combination pharmacotherapy needed

A Double-blind Randomized Controlled Trial of Olanzapine Plus Sertraline vs Olanzapine Plus Placebo for Psychotic Depression: Study of Pharmacotherapy of Psychotic Depression (STOP-PD) (N=259)

Remission rates

[Graph showing remission rates for different treatment groups over time.]

HAM-D change scores

[Graph showing HAM-D change scores for different treatment groups over time.]

Specific depressive subtypes may suggest specific treatment modifications

- Depression with anxiety
- Depression with psychotic features
- Atypical depression (MAO inhibitors)
- Depression with substance abuse
- Bipolar depression (start with mood stabilizer)
- Depression with personality disorder
Controlled trials for treatment-resistant, acute bipolar depression from six trials involving 263 bipolar I or II disorder patients

Examination of the utility of psychotherapy for patients with TRD: A systematic review

- Current evidence examining the effect of psychotherapy as augmentation or substitute therapy for TRD is sparse and mixed results.
- Psychotherapy in TRD may:
  - Modify maladaptive cognitions and behaviors with cognitive restructuring, behavioral activation, or skills training.
  - Mitigate side effects of antidepressants
  - Patients may prefer to not take medications: help with non-adherence.

Trivedi et al. J Gen Int Med 2010
Realistic expectations and a disease management model for depressed patients with persistent symptoms

• For some patients, there appears to be a ceiling effect in our ability to treat their despite augmentation, switching, and combined strategies

• Continued attempts to treat these patients to remission may be demoralizing to patients and ultimately counterproductive

• Management of persisting depressive sxss may be well served by adding a disease management component to the overall tx strategy

• Importance of learning to cope with depressive sxss, interpersonal functioning, autonomy, self-acceptance, quality of life and positive relations with others

Remission rates in outpatients with major depression STAR*D (n=2,876)

- Low remission rates
- 2 trials or 6 mo for 50% remission

Recovery rates with antidepressant tx bipolar depression (STEP-BD) (n=366)

<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>

Combining Medications to Enhance Depression Outcomes (CO-MED) trial (N=665)

- Escitalopram + PBO
- Bupropion + Escitalopram
- Venlafaxine + Mirtazapine

No difference on primary outcome

Lithium treatment-moderate dose use study (LiTMUS) (n=200)

- Bipolar Disorder I or II
  - Li + OPT
  - Placebo + OPT

Primary outcome: Overall illness severity on clinical improvement

Sachs et al. NEJM 2007; Trivedi et al. NEJM 2006; Rush et al. Am J Psych 2011; Calabrese APA 2010
Drug Development in the past 60 years

- Except for Li all available FDA approved treatments for Bipolar disorder are anticonvulsants or Antipsychotic drugs
  - Lithium
  - Anticonvulsants
    - Divalproex
    - Carbamazepine
    - Lamotrigine
    - Topiramate
    - Oxcarbazepine
    - Levetiracetam
  - Antipsychotics
    - Clozapine
    - Risperidone
    - Olanzapine
    - Quetiapine
    - Ziprasidone
    - Aripiprazole
    - Lurasidone

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

Need to identify new molecular targets – genomics, epigenomics, circuits

Insel and Skolnick Mol Psychiatry 2006;11:11-17
Declining interest in psychiatric drug development

Is Pharma Running Out of Brainy Ideas?
Recent cutbacks raise concerns about the future of drug development for nervous system disorders

G. Miller, Science, 329:481-596, July 30, 2010

Neuroscience: challenges in medication development

- Sheer complexity of diseases
- Higher order brain function difficult to model preclinically
- Limited segregation of patients into biological strata
- Attrition in late stages driving up average costs
- Generics to beat and payer pressures

Up to 12 years

Up to $1.8 billion including failures

Money

Time
Research domain criteria (RDoC): toward a new classification framework for research on mental disorders

- Focus for RDoC is on neural circuitry, with levels of analysis progressing in one of two directions: upwards from measures of circuitry function to clinical sx's, or downwards to the genetic and molecular/cellular
- BUT parallel, complimentary and necessary processes
Defining Depression Circuits
Response Pathways

Cognition
(attention-appraisal-action)

PF9/46 PM6 Par40 hc
MCC PCC

mF9/10 pACC24
oF11

na-vst thal
amg mb-vta

sACC25
a-ins hth bstem

Self-awareness insight

Interoception
(drive-autonomic-circadian)

CBT

Mood state

MEDS

Arch Gen Psych 61:34-41, 2004
New Experimental Medicine Studies

- Success rates for Phase II projects are the lowest for any phase in the discovery pipeline
- **Take advantage of new breakthroughs and tools**
- New paradigm for drug development based on “fast-fail,” i.e., focusing on proof of concept prior to proceeding to expensive Phase III trials
- Small, deep trials, focused on “experimental medicine” paradigms, to demonstrate target engagement, safety, and early signs of efficacy
- Potential biomarkers demonstrating target engagement could provide critical to the decision whether to proceed further (PET, fMRI, EEG/ERP, etc.)
Glutamatergic System: Anatomy, Physiology and Downstream Changes

- Presynaptic terminal
- Postsynaptic spine
- Increase in spine density
- Learning
- Memory
- Plasticity
SNMD Goals

Develop novel and rapid-acting pharmacological therapeutics for patients with severe and treatment resistant mood disorders.
Conceptual Framework for novel txs/biomarkers

- **POC studies**: Double-blind placebo-controlled cross-over trials in unmedicated subjects
- **Rapid acting antidepressants permit efficient studies**
- **Compare and Contrast Drugs**

**Neuroimaging**
- Periph. measures
- CSF

**Multimodal measures**

- **Response**
  - Biologically enriched subgroups
- **Non-response**
  - Identify neurobiology of response

- **Identify pre-treatment biomarkers of response**
- **Identify therapeutic relevance of agents**
Depression: The Need for Improved Treatments

Problems with Current Antidepressants:

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

Next generation antidepressant

Rapid onset: Hours/day

Lag of onset: 10-14 weeks

Standard antidepressant (Monoaminergic)

Major Depressive Episode

Initiate Treatment
Candidate Glutamatergic Modulators for Depression

Inh. glutamate release (Riluzole)
mGluR2 PAM
- JNJ-40411813/
  ADX71149
mGluR2/3 antagonists
- MGS0039
  (BCI-632)
- LY341495
mGluR2/3 NAMs
- R04491533
- R04499819

mGluR5 NAM
- AZD2066
- STX-107
- R04917523

NMDA Complex Modulators

GlyT-1 inhibitors
- Sarcosine
- Bitopertin

EAAT2 enhancers
- Ceftriaxone
Clinical insights may still trump molecular genomics for identifying new treatment targets.
Memantine (Namenda®)

- 1-amino-3,5-dimethyladamantane is a low to moderate affinity uncompetitive (open-channel) NMDA receptor antagonist
- Low to negligible affinity for GABA, benzodiazepine, dopamine, adrenergic, histamine and glycine receptors
- Approved by the FDA for the treatment of Alzheimer's disease
- Neuroprotective in animal models of ischemia, AD, and traumatic CNS injury
- Stimulates BDNF
- Synergistic effect in animal model of depression

Zarate et al. Am J Psychiatry 2006
NMDA Complex Modulators

NR2B antagonists
- Ro 25-6981
- Ifenprodil
- Traxoprodil
- Evotec-101
- CERC-301 (MK-0657)

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

Broad NMDA antagonists
- PCP
- Ketamine
- Memantine
- AZD6765

Clinical insights may still trump molecular genomics for identifying new treatment targets
Rapid Antidepressant Effect of Ketamine in Unmedicated Treatment Resistant MDD (n=18)

Zarate et al. Arch Gen Psychiatry 2006

HAMD Following a Single Ketamine Infusion

Response: 50% decrease in HAMD

**p<0.01, *p<0.05

**p<0.001

***p<0.001

Monoaminergic Antidepressant 62-65%

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)

Replication BP study (n=15)

Diazgranados et al. Arch Gen Psych 2010

Zarate et al. Biol Psych 2012

***p<0.001, **p<0.01, *p<0.05
Change in Depression Severity over time in Patients with TRD given a Single Infusion of Ketamine or Midazolam

Murrough et al. Am J Psych 2013
MADRS Total Score: Mean (SE) Change from Baseline (Observed Cases)

**X 2 / Week**

- **Placebo 2X/WK**
- **Ketamine 2X/WK**

**MADRS Total Score: Mean Change (SE) From Baseline**

-25
-20
-15
-10
-5
0
5

**Number of Subjects:**

Placebo: 16 16 15 13 13 13
Ketamine: 18 17 15 16 16 16

**Curtesy Jaskaran Singh Jansen Pharmaceuticals**

**X 3 / Week**

- **Placebo 3X/WK**
- **Ketamine 3X/WK**

**MADRS Total Score: Mean Change (SE) From Baseline**

-25
-20
-15
-10
-5
0
5

**Number of Subjects:**

Placebo: 16 16 15 16 16 14 16
Ketamine: 17 17 13 16 16 11 13
Next Steps in Ketamine Research/Treatment

1. Ketamine in Clinical Practice Settings: research/off-label use
   - Repeat infusions (pulse treatment—ECT)
   - Slower infusion over 100 min
   - Combination with lithium
   - Combination with standard treatments
   - Combination with ECT

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

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

4. Is there more to the story with the “ketamine paradigm”: ketamine’s metabolites
NMDA Complex Modulators

**NR2B Antagonists**
- Ro 25-6981
- Ifenprodil
- Traxoprodil
- Evotec-101
- CERC-301 (MK-0657)

**Glycine Site**
- D-Serine
- D-Cycloserine
- GLYX-13
- 4-CI-KYN

**NMDA Antagonists**
- PCP
- Ketamine
- Memantine
- AZD6765
Selective NR2B Antagonists Exert Antidepressant Effects

Change from Baseline in MADRS Total Score by Time Point, CP-101,606 vs. Placebo

<table>
<thead>
<tr>
<th>Day</th>
<th>CP-101,606</th>
<th>Placebo</th>
<th>Difference</th>
<th>Lower</th>
<th>Upper</th>
</tr>
</thead>
<tbody>
<tr>
<td>Period II, Week 0 (Day 5)</td>
<td>-14.1</td>
<td>-5.5</td>
<td>-8.6</td>
<td>-12.3</td>
<td>-4.5</td>
</tr>
<tr>
<td>Period II, Week 1 (Day 8)</td>
<td>-14.2</td>
<td>-7.1</td>
<td>-7.1</td>
<td>-10.5</td>
<td>-1.8</td>
</tr>
</tbody>
</table>

NR2B in Antagonist (MK-0657) in Major Depressive Disorder: Efficacy, Neurotrophic Factors (BDNF), and ACC Activity

- Oral doses (4-8 mg/day)
- No psychotomimetic effects

Drug Free Period

Placebo

NR2B antagonist

Placebo

NR2B antagonist

12 d

2 wks

12 d

NR2B Plasma Levels (nM)

Time (Hours)

NR2B in Antagonist (MK-0657) in Major Depressive Disorder: Efficacy, Neurotrophic Factors (BDNF), and ACC Activity

MEG: NR2B vs placebo N back

*BDNF p<.05

NMDA Complex Modulators

NR2B antagonists
- Ro 25-6981
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- Evotec-101
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Glycine site
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NMDA antagonists
- PCP
- Ketamine
- Memantine
- AZD6765
AZD6765: A Low-Affinity NMDA Channel Blocker

- AZD6765 was developed in Europe as an intravenous txt for stroke but was not further pursued because of a lack of efficacy
- AZD6765 is a low-trapping NMDA channel blocker
- AZD6765 well tolerated with dizziness, nausea, and vomiting, being the most common AEs. No psychotomimetic effects up to 160 mg
- Antidepressant effects in learned helplessness, FST
- Anxiolytic activity in the rat punished responding model

<table>
<thead>
<tr>
<th></th>
<th>Ketamine</th>
<th>MK-801</th>
<th>Memantine</th>
<th>Active Remacemide</th>
<th>AZD6765</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trapping (%)</td>
<td>82%</td>
<td>76%</td>
<td>70%</td>
<td>64%</td>
<td>52-59 %</td>
</tr>
</tbody>
</table>
A Double-Blind Placebo-Controlled Study of NMDA Antagonist (AZD6765) in Treatment-Resistant Depression (N=22)

No dissociative, psychotomimetic or euphoric effects

Zarate et al. Biol Psych 2012
MADRS Score Change during the 3-week Treatment and 5-week Follow-up Period in Lanicemine 100 mg, 150 mg and Placebo Groups
NMDA Complex Modulators

NR2B antagonists
- Ro 25-6981
- Ifenprodil
- Traxoprodil
- Evotec-101
- CERC-301 (MK-0657)

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

NMDA antagonists
- PCP
- Ketamine
- Memantine
- AZD6765
D-cycloserine in TRD

• D-cycloserine (DCS) is a broad spectrum antibiotic used for over 30 years in tuberculosis and urinary tract infections
  • Produced euphoria, improvement in well being, appetite
  • Preclinical and clinical data suggest that at dosages ≥100 mg/day DCS acts as a functional NMDAR antagonist and may have antidepressant effects

<table>
<thead>
<tr>
<th>Scale</th>
<th>Drug</th>
<th>Wk 0</th>
<th>Wk 6</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>HAMD</td>
<td>DCS</td>
<td>20.8 ± 9</td>
<td>14.6 ± 7</td>
<td>0.51</td>
</tr>
<tr>
<td>Placebo</td>
<td>24.4 ± 7</td>
<td>17.4 ± 8</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


C-201: Glyx-13 Reduces Depression Scores and does not Cause Psychotomimetic Side Effects

- No clear demonstration of action at glycine site
- ½ life minutes
- Dose response: inverted U shape
- CADSS not obtained

Moskal et al. Expert Opin Investig Drugs 2014
Is Glutamate Burst Critical to a Rapid Antidepressant Effect?

Adapted from Duman, 2014
Medial prefrontal cortex layer V pyramidal cells in BDNF Val66Met knock-in mice have both apical and basilar dendritic atrophy.

Antidepressant response to Ket in the forced swim test is attenuated in BDNF Val66Met knock-in mice.

Liu et al. Biol Psychiatry 2012
62 patients (NIMH, Yale) with BDNF SNP data and HAMD score at 230 minutes post ketamine infusion

- 41 ValVal, 19 MetVal, 2 MetMet

Genetics: BDNF Val66Met polymorphism and antidepressant efficacy of ketamine in MD

Model explains 28% of the variance

$L = 0.025$

Laje, Lally et al. Biol Psych 2013
Using EEG to study synaptic potentiation in the human brain (local SWA increases with synaptic potentiation)

Synaptic Plasticity: Enhanced AMPA throughput

Response

NO Synaptic Plasticity: NO Enhanced AMPA throughput

No Response

Visuomotor Task: Local SWA Increase

EEG/MEG recordings of SWA can provide electrophysiological evidence for local changes in cortical synaptic strength
Ketamine and SWA

- Slow wave activity (SWA) as a marker of synaptic potentiation
- Ketamine injections in rat PFC are associated with increases in synaptic strength (Li et al., 2010)
- Injections of ketamine in rats increase SWA during NREM sleep
- SWA could be a marker for synaptic plasticity which is a potential mechanism for ketamine’s antidepressant effect

Slow wave oscillations

- cortically generated 0.5-4.5 Hz oscillation
- power represents synchronization across circuits
- reflect synaptic density, strength, efficacy

SWA Overnight Timecourse

Baseline
PSG: Experimental Procedures SWA & BDNF: Acute Changes (N=30)

- 2 Sleep recordings (Baseline/Post Treatment night)
- 4 mood ratings (MADRS) and sample collection:
  - 1 hour Pre infusion (BDNF, VEGF plasma)
  - 4 hours Post infusion (BDNF, VEGF plasma)
  - After a night of sleep in the morning (Day 1)
  - After a second night of sleep in the morning (Day 2)

Ketamine hydrochloride 0.5 mg/Kg i.v. x 40 min

SWA analysis:
- SWA (0.6-4 Hz) calculated as FFT averages over consecutive 5 sec epochs
- Average of the 2 channels
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: $r = -0.73, p = 0.024$
Gamma rhythms are involved in many aspects of cognitive function from sensory representation through selective attention and short-term memory.

They possess the ability to facilitate synchrony of neuronal activity occurring in many, anatomically distant areas at the same time.

Using ketamine in rodents produces an increase in gamma rhythm generation (frontoparietal, hippocampus).

Cornwell et al. Biol Psych 2012
Gamma Power Following a Somatosensory Task is Associated with Response to Ketamine

Contralateral (right) stimulation

Cornwell et al. Biol Psych 2012
Activation Studies Implicate Anterior Cingulate in Cognitive & Affective Processing

Experiment 1 (affective task): rostral ACC activity is positively correlated with ketamine response

Experiment 2 (a cognitive task): rostral ACC activity is negatively correlated with ketamine response

Salvadore et al., Biol Psychiatry 2010

Salvadore et al. Neuropsychopharmacology 2010
Depression: A Dimensional Approach
RDoC

Anhedonia

• The inability to experience pleasure from activities usually found enjoyable
• Occurs in the context of major depressive disorder (MDD), bipolar disorder (BD), and schizophrenia
• A common residual symptom after antidepressant treatment
Change of MADRS and SHAPS Scores over 14 days following a Single Infusion of Ketamine in BP TRD

A Scale for the Assessment of Hedonic Tone
The Snaith–Hamilton Pleasure Scale

Anhedonia levels following ketamine infusion relative to placebo

Níall Lally
Anti-hedonic Effects of Ketamine and Metabolic Correlates of Symptomatic Change

ROI Analysis of Regions Involved in Reward Processing – Ventral Striatum

Voxel-wise Analysis Controlling for MADRS score

Lally, et al., Trans Psych 2014
What is Suicide?
Survivors can include family, friends and providers.

American Foundation for Suicide Prevention, 2012
FIGURE 1. Public health burden of suicidal behavior among adults aged ≥18 years — United States, 2008

- 35,045 deaths* rate:† 15.2
- 197,838 hospitalizations§ rate: 86.0
- 323,342 emergency departments visits¶ rate: 140.6

CDC, 2011
Definitions
Suicide Attempt

- A self-injurious act committed with at least some intent to die, as a result of the act
- Any non-zero intent to die – it does not have to be 100%
- There does not have to be any injury or harm, just the potential for injury or harm
- Intent can sometimes be inferred clinically from the behavior or circumstances

Self Injurious Behavior without Suicidal Intent

- Behavior PURELY (100%) for reasons other than to die:
  - Either to affect internal state (feel better, relieve pain etc.) “self-mutilation” or
  - External circumstances (get sympathy, attention, make angry, etc.)
Risk factors for suicide
Multifactorial

- Previous suicide attempts
- Major depression or bipolar disorders
- Comorbid abuse of alcohol or drugs
- Multiple comorbidity
- Losses, deaths, shame, poverty, disability
- Social isolation, unmarried
- Lack of access to clinical care
- Access to firearms, toxins, medicines
Case Vignette ("Jane")

59 y.o. divorced female, on disability with a 47 year history of severe refractory major depressive disorder and co-morbid panic disorder, social phobia, generalized anxiety disorder and past history of alcohol dependence. She reported “pretty constant depression most of my life.” She had a total of 10 hospitalizations for depression; 6 suicide attempts, the first was at 25 years of age following her sister’s suicide (by hanging). Her mother had depression, a paternal uncle was an alcoholic, and a maternal cousin attempted to kill herself by crashing a car. She lived alone with a cat.

Six months prior to admission, she experienced significant depression, agitation, and suicidal thinking. During her admission to 7SE CC/NIH, she reported “feeling nearly the worst I’ve ever felt, “having intermittent moderate to strong thoughts of wanting to hang herself, and images of “killing myself by shooting myself in the head with a gun.” “At some point in the future, I can see myself making another suicide attempt.”
Current Treatments

• Only FDA approved medication for suicidal behavior: clozapine for patients with schizophrenia

• No FDA approved medication for suicidal thoughts

• Lithium not FDA approved but evidence of reducing suicidal behaviors

• Black box warning on SSRIs may have led to decreased depression treatment in adolescents and adults

Critical Windows of Suicide Risk

- Week after psychiatric admission and week after psychiatric discharge
- First 9 days of starting an antidepressant

Qin et al., 2005; Olfson et al., 2014
Putative targets to be explored in the neurobiology of suicide

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Mathews et al. 2013
Rapid Decreases in Suicidal Ideation (SI) with Ketamine in MDD and BD

Zarate et al., Biological Psychiatry 2012

Potential to revolutionize management of acute suicidality

***p<0.001, **p<0.01, *p<0.05
Ketamine’s impact on suicidal thoughts is independent of depression

Change in depression scores only accounts for 19% of variance in suicide ideation change.

Ketamine is associated with a reduction in suicidal thoughts, when controlling for the effect of ketamine on depression, $p = .001$.

Ketamine’s effect on suicidal thoughts is also independent of anxiety, $p = .004$.

Potential Biomarkers for Suicide and Treatment Response

- Glucose metabolism in infralimbic cortex
- Fear-Potentiated Startle
- Polysomnography: Wakefulness after sleep onset
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 ($p = .69$)