Rapid-Acting Antidepressants: Efficacy and Mechanisms of Action

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Learning Objective

Critique the latest evidence for rapid-acting treatment options in patients with major depressive disorder
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Disclosures

- **Research/Grants:** None
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- **Consultant:** None
- **Stockholder:** None
- **Other Financial Interest:** None
- **Advisory Board:** None
An Urgent Therapeutic Need

- **Long-standing challenge** in psychiatry: development of rapid-acting antidepressant strategies for mood disorders (within 24 hours)
- **Current antidepressant treatments** typically require 2-8 weeks for full clinical response
- During this time, patients
  - Continue to suffer from their symptoms
  - Continue to be at significant risk for suicide
  - Experience harm to their personal and professional lives
- **Rapid-acting antidepressant strategies** would have a significant impact with major healthcare implications
Rapid-Acting Antidepressant Strategies

Outline

A. Ketamine treatment
B. DBS treatment
C. Sleep deprivation
   1. Potential brain imaging biomarkers to predict response to sleep deprivation
   2. Circadian abnormalities and circadian treatment manipulations in mood disorders
   3. Regulation of circadian rhythms by clock genes
   4. Potential genetic biomarkers
   5. Recent study showing rapid, robust, and sustainable clinical response to combined chronotherapeutic treatments
D. Future studies

DBS = deep brain stimulation
Ketamine
Ketamine

- Ketamine is a nonselective NMDA antagonist
  - Utilized in high doses as an anesthetic for children for many decades
Low-Dose Ketamine Infusion
Rapid Antidepressant Actions

**Study** | **N** | **Design** | **Finding**
--- | --- | --- | ---
Berman 2000\(^1\) | 7 MDD | Randomized double-blind | Improvement within 2-4 hrs
Zarate 2006\(^2\) | 18 treatment-resistant MDD | Randomized double-blind, placebo-controlled crossover | Improvement within 4 hrs [12/17 ketamine vs. 0/14 placebo]
Correll and Futter 2006\(^3\) | 2 MDD | Open | Improvement in 48 hrs
Phelps 2009\(^4\) | 23 treatment-resistant MDD with family history of alcoholism 3 MDD w/o family history | Open | Improvement within 4 hrs Higher response rate in the family history positive group (67%) than in subjects without family history (18%)
Salvadore 2009\(^5\) | 11 MDD | Open | Improvement within 4 hrs
**TOTAL** | 61 MDD | | 4/5 studies report improvement in 2-4 hrs

MDD = major depressive disorder

Current Treatment Strategies to Extend Rapid Response to Ketamine

1. Utilize multiple IV infusions of ketamine
2. Utilize ketamine as adjunctive therapy to a standard antidepressant to rapidly accelerate clinical response
Deep Brain Stimulation
Sleep Deprivation
Sixty studies involving > 1,700 patients over last 4 decades
- One night total sleep deprivation can reverse depressive symptoms within 24 hours in 40% to 60% of severely depressed patients

Relapse often occurs after next night of sleep
47-Year-Old MDD Male, Severely and Continuously Depressed for 30 Days

- Responded within 24 hrs to one night of sleep deprivation; relapsed following next night of sleep
- Symptoms changed from psychotic suicidal depression to mild euphoria and talkativeness following sleep deprivation
32-Year-Old Female with Severe Depression Over 2 Months

Depression Ratings

Worse

Better

Days

Total sleep deprivation

EEG recording of 90 sec nap

Immediate return of depression and psychosis
Accused nursing staff of giving her a poison

Smiling and telling jokes to the staff

EEG = electroencephalogram
Potential Brain Imaging Biomarkers
Method

- 36 MDD patients (responders n = 12; nonresponders n = 24); 26 controls
- PET scans day before and day after sleep deprivation
- Behavioral Ratings: HRSD

HRSD = Hamilton Rating Scale for Depression
Sleep Deprivation Response and Relapse Following a Night of Recovery Sleep

Effect of Sleep Deprivation

Baseline Group Differences

Higher rate in responders in medial prefrontal cortex and vent. anterior cingulate
Lower rate in non-responders in medial prefrontal cortex and ventral anterior cingulate
No change in rate in medial prefrontal cortex

Effects of Sleep Deprivation

Rate decreased in medial prefrontal cortex
No change in rate in medial prefrontal cortex
No change in rate in medial prefrontal cortex

Increased metabolic glucose rate in ventral anterior cingulate and medial prefrontal cortex could predict patients who respond to sleep deprivation vs. those who do not

Possible Role of Clock Genes in Mood Disorders

- Circadian abnormalities in mood disorders
- Circadian treatment manipulations in mood disorders
- Regulation of all circadian rhythms by clock genes
Summary of Abnormal Circadian Rhythms in Subgroup of Mood Disorder Patients

1. Marked circadian variation in clinical depressive symptoms
   - Severe symptoms during early morning hours with marked improvement in late afternoon

2. Abnormal temperature curve
   - Increase in nocturnal core body temperature and flattening of diurnal curve

3. Abnormal cortisol cycles
   - Elevation of 24-hour cortisol levels with absence of late day trough

4. Sleep abnormalities
   - Abnormal sleep patterns including shortened REM latency and early morning awakening, which could reflect phase change in the rest/activity cycle

REM = rapid eye movement
Nocturnal Temperatures
(Depressed Patients and Controls)

<table>
<thead>
<tr>
<th>Temperature (°C)</th>
<th>Depressed Patients</th>
<th>Controls</th>
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<tbody>
<tr>
<td>6:00 pm</td>
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Sleep Period
Circadian Rhythm of Cortisol
*(Depressed Patients vs. Controls)*

Composite Graph of Over 150 Patients and 1080 Cortisol Assays
Stable and Marked Diurnal Mood Changes in Subgroups of Depressed Patients

Graph showing depression ratings over 12 hours from 1 PM to 1 AM. The graph has two lines, one for 13 patients and another for 11 patients. The x-axis represents hours from 1 PM to 1 AM, and the y-axis represents depression ratings from 0 to 15. The line for 13 patients shows a peak around 4 PM and drops sharply by midnight, while the line for 11 patients shows a peak around 8 PM and drops more gradually.
Two Subtypes of Depressed Patients

Marked Diurnal Mood Changes

Stable Diurnal Mood
Are these circadian abnormalities central components of mood disorders or epiphenomena?

- If one manipulates circadian rhythms, will depressive symptomatology show profound improvement?
- If so, it would argue that circadian rhythms, which are under the regulation of clock genes, may be etiologically linked to mood disorders.
3 nonpharmacological treatment approaches documented to produce striking and often rapid treatment responses in subgroup of mood disorder patients

- Sleep deprivation, sleep phase advance, bright light therapy
- Each involves circadian manipulations

Thus, identification of abnormalities in clock genes could lead to new knowledge concerning one of the core pathophysiological elements of mood disorders
Clock Genes

- One of most pervasive epigenetic influences in evolutionary process from single-cell organisms to man has been 24-hour light/dark cycle
- Virtually all body processes and circadian rhythms systematically fluctuate during the 24-hour period
- Mechanisms have developed through evolution to accomplish these processes
Positive gene activators turn on clock genes that make mRNAs, which move out into cytoplasm and make proteins. Proteins move back into nucleus and shut off own genes over a 24-hour cycle.

Potential Genetic Biomarkers
1. A growing body of literature has demonstrated utility of using blood-based markers to assess genome expression abnormalities in psychiatric and neurological disorders:
   1. Whole blood
   2. Transformed lymphocytes
   3. Peripheral blood mononuclear cells
   4. Lymphoblastoid cell lines

2. Blood-based markers have been reported in schizophrenia, Huntington’s disease, Alzheimer’s disease, and PTSD

PTSD = post-traumatic stress disorder
Timing of Blood Sample Collection

- Lymphocytes for microarray profiling and QPCR of clock genes
- Total sleep deprivation treatment

QPCR = qualitative polymerase chain reaction
Pilot Study: Prolongation of Rapid Antidepressant Response to Sleep Deprivation with Chronobiological Augmentation

Study Authors

UC Irvine
- Joe Wu
- Steve Potkin
- Carol Schachat
- Blynn Bunney

UC San Diego
- John Kelsoe
- Chris Gillin (deceased)
- Anna Demodena

(Funding: Stanley Foundation and Penzner Foundation)
Nonpharmacological Manipulation of the Circadian Sleep/Wake Cycle
Sleep phase advance treatment involves shifting onset and offset times of the sleep period 4-6 hours earlier than usual.

- Then progressively moving sleep period back toward normal sleep time over next 3 days.
Bright Light Treatment in Non-Seasonal Depression

Randomized, controlled trials of bright light therapy

- 11 randomized, controlled trials of bright light therapy have been conducted in non-seasonal depression
- A number of studies have shown very positive results; however, other studies were unable to confirm these findings

References available in supplemental bibliography.
METHOD

Chronotherapeutic treatment

1. Total sleep deprivation for one night
2. 3 nights of phase advance of sleep after total sleep deprivation
   - Day 1: sleep: 6pm to 1am (plus morning light therapy*)
   - Day 2: sleep: 8pm to 3am (plus morning light therapy*)
   - Day 3: sleep: 10pm to 5am (plus morning light therapy*)
   (* light therapy = 5000 lux for 2 hours)

Medications

Selective serotonin reuptake inhibitors (SSRIs)
(sertraline, paroxetine, or fluoxetine)
Mood stabilizer (lithium) began one week prior to chronotherapeutic augmentation
There was not a statistically significant over-representation of any of the drugs or doses in any of the patient subgroups

Methodology-Timeline for Chronotherapeutic Augmentation

* Hamilton Depression Rating Scale; SD = sleep deprivation
Sleep deprivation followed by bright light plus sleep phase advance

CAT = chronotherapeutic augmentation therapy
MED = “treatment as usual” medicated only
Clinical Use of Sleep Deprivation Therapy

Quotes from F. Benedetti in the Department of Neuropsychiatric Sciences, Scientific Institute and University Milan, Italy

- Sleep deprivation has reached the status of a powerful and affordable clinical intervention for everyday treatment of depressed patients
- Its rapid and safe administration should be tested as a first-line treatment strategy in the majority of depressive syndromes
Future Studies

- **Brain imaging biomarkers** utilizing HRRT-PET to identify hypothesized brain regions associated with rapid antidepressant response
- **Genetic biomarker** studies to identify responder potential
- **Circadian evaluation of clock genes in postmortem human brain**
- Evaluate ketamine and sleep deprivation ability to reverse animal models of depression
- **Study mechanism of action of ketamine and sleep deprivation in animal models**, including epigenetic changes
- Study strategies to extend and sustain rapid therapeutic effects of ketamine and sleep deprivation
Three Manipulations that Acutely Relieve Depression Operate at Different Brain Regions of the Same Well-Established Network

Hab = habenula; PV = paraventricular nucleus of the thalamus; SCN = suprachiasmatic nucleus; BA25 = subgenual
Example: The HRRT PET Images Show Decreased Glucose Utilization in AnCg, SCN, PVT and Habenula in a Responder Before and After Sleep Deprivation.
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Zarate CA Jr. A randomized trial of an N-methyl-D-aspartate antagonist in treatment-resistant major depression. *Arch Gen Psychiatry* 2006;63:856-864.
Supplemental Bibliography for:

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