An Update on the Diagnosis, Treatment, and Research of Mood Disorders

NAMI
June 30, 2017

Carlos A. Zarate, Jr., M.D
Section Neurobiology and Treatment of Mood Disorders
Division of Intramural Research Program
National Institute of Mental Health
Overview
Major depressive disorders: a major cause of disability

- >10% of the American population suffer from a mood disorder each year
- Depression is one of THE leading causes of disability worldwide, ranking ahead of ischemic heart disease, cerebrovascular disease, cancers, infectious diseases, etc.
- An increase in the death rate at any age, independent of suicide, smoking, or other risk factors
- > 44,000 deaths from suicide/yr (cf ~ 18,000 homicides)
- Individuals with major depression sometimes describe an emotional pain much worse than any physical pain that they have experienced
U.S. Burden of Diseases: 291 diseases and injuries

Leading Categories of DALYs 2010

1. Neuropsychiatric Disorders
   - Mental and Behavioral Disorders: 13.6
   - Neurological Disorders: 5.1
   - Total: 18.7

2. Cardiovascular and Circulatory Diseases
   - Total: 16.8

3. Neoplasms
   - Total: 15.1

4. Musculoskeletal Disorders
   - Total: 11.8

5. Diabetes, Urogenital, Blood, and Endocrine Diseases
   - Total: 8.0

6. Chronic Respiratory Diseases
   - Total: 6.5

7. Other Non-communicable Diseases
   - Total: 5.1

Percent of Total U.S. DALYs

Excess deaths in bipolar disorder

Osby et al. Arch Gen Psych 2001
The McLean-Harvard First-Episode Mania Study: Prediction of Recovery and First Recurrence at 24-Months (N=166)

Diagnosis
Depressive Disorders

- Disruptive Mood Dysregulation Disorder (<12 Yrs)
- Major Depressive Disorder
- Persistent Depressive Disorder (Dysthymia)
- Premenstrual Dysphoric Disorder
- Substance/Medication Induced Depressive Disorder
- Depressive Disorder Due to Another Medical Condition
- Other Specified or Unspecified
Major Depressive Disorder

✓ A. Five of the 9 SXS of depression with either depressed mood or anhedonia as one of the SXS, for a 2 week period most of the day nearly everyday.
  - Depressed mood
  - Anhedonia
  - Weight (5% in one month) or appetite changes
  - Sleep changes
  - Psychomotor changes (observable by others, not just subjective)
  - Fatigue or energy loss
  - Worthlessness/inappropriate guilt
  - Diminished ability to concentrate/ think / make decisions
  - Recurrent thoughts of death or dying/ suicidality

✓ B. Significant distress or impairment in functioning
✓ C. Not due to substance or another medical condition
✓ D. Not better explained by another psychotic disorder
✓ E. There has never been a manic or hypomanic episode
Depression: A Brain and Systemic Medical Illness

- **Inflammation**
  - ↑ IL-1, ↑ IL-6, ↑ TNF-α

- **Migraines**
  - Thyroid Diseases
  - Diabetes, GI problems

- **Stress Related Factors**
  - CRH, Cortisol, ACTH

- **BMI, ↑↓ Adipokines**
  - (adiponectin, resistin & leptin)

- **Osteoporosis**
  - ↑RANKL, ↓OPG-RANK, ↓OPN

- **Migraines**
  - Thyroid Diseases
  - Diabetes, GI problems

- **BMI, ↑↓ Adipokines**
  - (adiponectin, resistin & leptin)

- **Impairment of synaptic homeostasis**
  - MEG sensory task
  - DTI and MRS
  - rsFMRI

- **↑ MI risk of death by 3.5 x compared to non-depressed patients**
Diagnostic Statistical Manual (DSM) & Research Domain Criteria (RDoC)

**DSM diagnosis**
- Common language for describing psychopathology
- Significant overlap in symptoms across disorders
- Symptoms do not overlap with pathophysiology

**RDoc**
- Focus is on understanding pathophysiology, e.g., neural circuitry, with levels of analysis
Defining Depression Circuits
Response Pathways

Cognition
(attention-appraisal-action)

PF9/46  PM6  Par40  hc
MCC  PCC

mF9/10  pACC24  na-vst  thal
oF11  pACC24  amg  mb-vta

sACC25  a-ins  hth  bstem

Self-awareness insight

Arch Gen Psych 61:34-41-2004

Interoception
(drive-autonomic-circadian)

Mood state

MEDS

CBT

Meds
Course of Illness
Bipolar Disorder: Course of illness, Comorbidity, Life Impact, Disability, and Neurobiological Insults

- Disruption to:
  - Personal life
  - Familial life
  - Occupation
  - Social life
  - Economic well-being
- Risk for suicidal behavior

Risk for suicidal behavior

Course of Illness

- Cycling/mixed symptoms
- Manic/hypomanic symptoms
- Depressive symptoms
- Symptomatically Ill

Follow-up wks

0 10 20 30 40 50

% Follow-up wks

Merikangas et al. Arch Gen Psychiatry 2007

- > 3 Disorders: 70%
- 1 Other Disorder: 18%
- > 2 Other Disorders: 9%

Anhedonia
Suicidal ideation
Normal Sleep/Cognition
Treatment
Depressive Disorders: Treatment Goals

Reduce/Remove Signs, Symptoms

Restore Role/Function

Minimize Relapse/Recurrence Risk

Adapted from WPA/PTD Educational Program on Depressive Disorders
Indications for Formal Psychotherapy as Monotherapy

Psychotherapy only if

- Mild disorder
- Psychotic or melancholic features are absent
- History of chronic psychosocial problems

Adapted from WPA/PTD Educational Program on Depressive Disorders
### Antidepressants

#### SSRIs
- Fluoxetine (Prozac)
- Citalopram (Celexa)
- Fluvoxamine (Luvox)
- Paroxetine (Paxil)
- Sertraline (Zoloft)
- Escitalopram (Lexapro)

#### SNRIs
- Venlafaxine (Effexor)
- Duloxetine (Cymbalta)

#### Tricyclics/Tetracyclics
- Nortriptyline (Pamelor)
- Amitriptyline (Elavil)
- Desipramine (Norpramin)
- Imipramine (Tofranil)
- Doxepin (Sinequan)
- Protriptyline (Vivactil)
- Trimipramine (Surmontil)
- Maprotiline
- Clomipramine
- Amoxapine
- Dothiepin

#### DNRIs
- Bupropion (Wellbutrin)

#### MAOIs
- Phenelzine (Nardil)
- Tranylcypromine (Parnate)
- Selegilene transd (EMSAM)

#### Newer
- Vortioxetine (Brintellix)
- Vilazadone (Viibryd)
- Levomilnacipran transd (Fetzima)
All Antidepressants Are Efficacious

- 70 - 80% efficacy with any marketed antidepressant
- SRI’s or Bupropion are excellent first line choices
- TCA’s may be superior for some “severe” depressions
- MAO-I’s may be preferred for some atypical depressions
Response Rate After Pharmacologic Treatment Of Depression

- Normal Mood
- Depression
- Medication Started
- 67% Responders
- 33% Nonresponders
- 8 weeks
Diagnostic Challenges:

1. Specific Depressive Subtypes may suggest specific treatment modifications

A. Depression with anxiety or Anxious Depression (PTSD, Social anxiety disorder, GAD, panic disorder, OCD)

B. Depression with psychotic features

C. Atypical depression

D. Depression with substance abuse

E. Bipolar depression

F. Depression with personality disorder
Pharmacotherapy of Treatment Resistant Depression: Next Step

- Optimize
- High Dose Therapy
- Switch
- Augment/Co-prescribe
- Neuromodulation (e.g., ECT, TMS)
- Psychotherapy
Antidepressant “Augmenters”

- Augmenters with established effectiveness:
  - Lithium carbonate
  - Triiodothyronine

- Co-prescribing strategies:
  - SSRI + TCA
  - Antidepressant + Bupropion
  - Antidepressant + Mirtazapine

- With possible effectiveness:
  - Stimulants
  - Dopaminergic agonists
  - Pindolol
  - Buspirone
  - Atypical antipsychotic

- Other proposed augmentations strategies:
  - Modafinil (Provigil)
  - Estrogen
  - Testosterone
  - Lamotrigine
  - Folate
  - Dexamethasone
  - Ketoconazole
  - Inositol
Neuromodulation: Devices for Depression

- Electroconvulsive Therapy (ECT)
- Repetitive Transcranial Magnetic Stimulation (rTMS)
- Vagus Nerve Stimulation (VNS)
- Transcranial Electrical Stimulation (tES)
Electroconvulsive Therapy (ECT)

- Developed in 1930s
- FDA- Approved Device in 1979 (grand-fathered)
- Brief electrical pulse passed through scalp
- Patient under anesthesia
- Produce seizure on EEG
- Muscle paralysis prevents convulsive movement
- Bilateral or unilateral
- 6 - 12 treatments
- 2 - 3 treatments per week

Limitations:
- Headache, muscle aches
- Cognitive Side Effects: Memory
- Access: Hospital, Often Inpatient
- Stigma
- Anesthesia Risks
- Cost
- Maintenance: ECT v. meds

1. Seiner and Henry 2003
Repetitive Transcranial Magnetic Stimulation (rTMS)

Non-invasive technique

USA: Approved (NeuroStar TMS Therapy®)

Approved: Canada and Israel

Strong, pulsed magnetic fields pass through skull

Coil placed on head in awake patient

Induces electrical current in cortex which depolarizes neurons

Control over site and intensity of stimulation

Limitations:

Need more controlled trials for efficacy/maintenance data

Higher intensity stimulation leads to higher risk of motor convulsion

Best stimulation parameters not known

Noisy; high-freq clicking

Neuronal depolarization only extends 2 cm below scalp - effects limited to cortex
Vagus Nerve Stimulation (VNS)

- FDA approved for epilepsy; FDA approved for TRD 2005
- Implanted in over 30,000 patients worldwide
- Pulse generator implanted in left chest wall area, connected to leads attached to left vagus nerve
- Mild electrical pulses applied to CN X for transmission to the brain

Limitations

Efficacy data from nonrandomized study
Surgical procedure
Limited acute antidepressant effect
MRI contraindication
Battery Life (3-8 yrs)
Side effects: cough, site infection, hoarseness, trouble swallowing, shortness of breath

Deep Brain Stimulation (DBS)

- FDA Approved for Parkinson’s and Tremor
- Investigational for OCD, TRD
- Stereotactic Target from MRI
- Two chest-wall Internal Pulse Generators
- Burr holes in skull for electrode placement
- Stimulation parameters programmed by computer

Limitations

- Limited, short-term, open-label data in psychiatry
- Considerable Surgical Risk
- Targets and stimulation parameters not established
- MRI contraindication
- Battery Life

This information concerns a use that has not been approved by the U.S. Food and Drug Administration
Low Field Magnetic Stimulation

- Initial Observation
  - BP depressed SS undergoing EP-MRSI had immediate relief
- Early POC trial
- Animal study (FST)
- $^{18}$FDG PET healthy volunteer study
- Prototype Development
- 20 minute session

- Positive Scale
  - interested*
  - excited
  - strong
  - enthusiastic*
  - proud*
  - alert*
  - inspired*
  - determined
  - attentive*
  - active

- Negative Scale
  - distressed*
  - upset*
  - guilty
  - scared
  - hostile
  - irritable
  - ashamed
  - nervous
  - jittery
  - afraid
Transcranial Electrical Stimulation

- tDCS: direct current
- tACS: alternating current
- tRNS: random noise
- tPCS: pulsed current
Milan et al., Eur. Neuropsychopharmacol 2015

Major depression

- 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)

Available Treatments for Mood Disorders are less than Optimal
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

Euthymic
Depressed

Initiate Treatment

Lag of onset: 10-14 weeks
Standard antidepressant (Monoaminergic)

Major Depressive Episode
Neuroimaging & Postmortem Findings in Severe Recurrent Mood Disorders

- Non mood disorder
- Severe recurrent Mood Disorders

- Volume of specific areas
- Neuron -- mainly atrophy (neuropil reduction)

- Anhedonia
- Suicidal ideation
- Normal Sleep/Cognition
Site of Action of Ketamine: Binds to Open Channel at PCP Site to Block NMDA Receptor

- **Synonyms**: Ketalar®, K, Special K, Vitamin K, Lady K,
- **Source**: Available by prescription only
- **Drug Class**: Dissociative anesthetic
- **Medical and Recreational Uses**:
  - In veterinary as a tranquilizer
  - Diagnostic and surgical procedures
  - Recreationally used
- **Bioavailability**
  - Intravenous: 100%
  - Intramuscular: 93%
  - Intranasal: 25-50%
  - Oral: 20%
- **Half-life** Ket 2 hs, Norket 3-5 hs
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<0.001, **p<0.01, *p<0.05

Monoaminergic Antidepressant 62-65%
Rapid antidepressant, antisuicidal, and antianhedonic effects of Ketamine in Treatment Resistant Depression

Major Depressive Disorder (n=17)

Zarate et al. Arch Gen Psychiatry 2006

Bipolar Depression (n=18)

Diazgranados et al. Arch Gen Psych 2010

Suicidal Ideation (n=15)

Zarate et al., Biological Psychiatry 2012

Anhedonia (n=36)

Lally et al., Translational Psychi 2014
Change in MADRS Score, by Dose Frequency, From Baseline Through Day 15 of the Double-Blind Phase in Study of I.V. Ketamine in TRD

What is Suicide?
Suicide in the News

From April 11, 2016:
Canadian First Nation Declares State Of Emergency Over Suicide Attempts
“The CBC reports that about 2,000 people live in the community. On Saturday night, according to Chief Bruce Shisheesh, 11 people attempted suicide....”

The Washington Post
November 5, 2015:
A group of middle-aged whites in the U.S. is dying at a startling rate
“The mortality rate for white men and women ages 45-54 with less than a college education increased markedly between 1999 and 2013, most likely because of problems with legal and illegal drugs, alcohol and suicide, the researchers concluded. Before then, death rates for that group dropped steadily, and at a faster pace.
An increase in the mortality rate for any large demographic group in an advanced nation has been virtually unheard of in recent decades, with the exception of Russian men after the collapse of the Soviet Union.”
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
Acute Risk Factors Before Suicide Attempt or Death

- Patients who attempted or died by suicide in STEP BD
- Suicidal ideation and loss of interest significantly increased in severity in months before suicidal behavior. Anxiety may be similarly elevated
- No change in agitation or high risk behavior

Ballard 2016
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

- **Wk after psychiatric admission and wk after psychiatric discharge**
- **First 9 days of starting an antidepressant**
- Provide treatment across “critical window” from emergency/inpatient treatment to outpatient follow-up
- Reduction in risk can allow time to connect patient to long-term resources (i.e. medication management, psychotherapy)

Qin et al., 2005; Olfson et al., 2014
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

Rapid reversal of complex behavioral phenotype

**Genes**
- Gene expression
- Metabolome
- Cellular
- Neurochemical

**Circuits**
- Rapid reversal of complex behavioral phenotype
- RDoC
Literature on Suicide and Ketamine

Murrough 2015; RCT of ketamine vs midazolam in actively suicidal pts

Price 2009, 2014; Changes on suicide implicit association test (IAT)

Ionescu 2016; Repeat dose open-label ketamine
rMRGlu in infralimbic cortex associated with suicidal ideation and its reduction in MDD

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 ($p = .69$)

Ballard, 2014
Suicide Ideation and Sleep

• Difficulties with sleep is associated with later suicide risk

• Sleep represents an important, potential modifiable acute risk factor for suicide

• Time period of 12-4:59 am may be a particularly high-risk time for suicide

Wakefulness in Depressed Patients and Healthy Controls

Wakefulness in Depressed Patients (n = 65)  
Wakefulness in Healthy Controls (n = 22)

Data collected using polysomnography
Time period of 12-4:59 am may be a particularly high-risk time for suicide (Perlis, 2014).

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

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 antisuicidal treatments
  - Evaluate ketamine and sleep deprivation in suicidal individuals
  - Identify neural correlates of antisuicidal response

Environment, psychosocial stress, personality, trauma, support systems, ...............
Research staff
7SE Unit staff
OP4
7SW sleep lab
Section on Neuroimaging
Affective Pathophysiology Lab
NCF staff
Intramural research pgm
Office of the Clinical Director/NIMH
MEG CORE facility
Anesthesia
Patient and their families

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