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

J.J. Rasimas, M.D., Ph.D.

Associate Professor, Psychiatry & Emergency Medicine
Staff Clinician, National Institute of Mental Health
Experimental Therapeutics & Pathophysiology Branch
Disclosure

The speaker and his family have no relevant financial relationships with industry or other agencies holding stake in providing goods or medical services that would represent a conflict of interest.
Disclaimer

The views presented herein are my own and do not reflect the position or policy of the National Institutes of Health, the Public Health Service, or the Department of Health and Human Services.
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

• > 30,000 U.S. 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
DSM-IV Criteria for Major Depressive Episode

> 5 of the following symptoms present nearly every day during the same 2-wk period:

- Depressed mood (in children and adolescents, irritable mood)
- Markedly diminished interest or pleasure in most or all activities
- Significant decrease or increase in appetite or weight
- Insomnia or hypersomnia
- Psychomotor retardation or agitation
- Fatigue or loss of energy
- Feelings of worthlessness or excessive or inappropriate guilt
- Diminished ability to think, concentrate, or make decisions
- Recurrent thoughts of death, suicidal ideation, specific suicide plan, or suicide attempt
Diseases with Greatest Global Burden:
% Total Disability Adjusted Life Years

- Major Depression
- Heart Disease
- Stroke
- Chronic Obstr. Pulmonary
- Alcohol Use Dx
- Diabetes
- Schizophrenia
- Bipolar
- Lung Cancer
- Alzheimer's

World Health Report, 2004
Depression: A Brain and Systemic Medical Illness

Greater risk of osteopenia, osteoporosis in women

Depression after MI increases risk of death by 3.5 x compared to non-depressed patients

Higher rates of:
- Migraines
- Thyroid disease
- GI problems
- Diabetes

Late Life Onset Frequently Heralds Dementia
Depression Increases Risk of Cardiac Mortality

![Graph showing the risk of cardiac mortality with and without pre-existing cardiac disease, comparing nondepressed, minor depression, and major depression groups.](image)
Mood Disorders: Subtypes

A. Major Depression
B. Recurrent Depression
C. “Double Depression”
D. Dysthymic Disorder
E. Bipolar Disorder
INCIDENCE OF RECURRENT MAJOR DEPRESSION

• 50% or more of depressed patients will have at least one subsequent episode of depression during their lifetime

• Even when treated, the risk of recurrence of major depression is significant
  ▪ 50% after 1 episode
  ▪ 70% after 2 episodes
  ▪ 90% after 3 episodes

Kupfer, 1991
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 absent
- History of chronic psychosocial problems

Adapted from WPA/PTD Educational Program on Depressive Disorders
PSYCHOTHERAPY OF DEPRESSION

Response Rates

Mild depression

Moderate depression
  – Cognitive-behavioral
  – Interpersonal
  – Antidepressants

Moderate-severe depression

Placebo = medication

Mild depression

Moderate depression
  – Cognitive-behavioral
  – Interpersonal
  – Antidepressants

Antidepressant > psychotherapy

~ 70%
Consider for Medication Referral:

- 2 or more episodes
- Previous positive response to medications
- Moderate to severe vegetative symptoms
- Psychotic or bipolar features
- Significant residual symptoms after 6 weeks of psychotherapy
Response Rate After Pharmacologic Treatment Of Depression

- Normal Mood
- Medication Started
- Depression
- 67% Responders
- 33% Nonresponders
- 8 weeks
Selecting a Safe and Effective Antidepressant Medication

- 1) Efficacy
- 2) Side effect profile relative to individual patients’ needs
- 3) Drug interaction potential
  - Cytochrome P450 system
- 4) Cost-effectiveness
Antidepressants

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

SNRIs
- Venlafaxine (Effexor)
- Duloxetine (Cymbalta)
- Milnacipran (Savella)

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

NDRI
- Bupropion (Wellbutrin)

MAOIs
- Phenelzine (Nardil)
- Tranylcypromine (Parnate)
- Isocarboxazid (Marplan)
- Selegiline transdermal (EMSAM)

Others
- Mirtazapine (Remeron)
- Nefazodone (Serzone)
- Vilazodone (Viibryd)
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
“ABCD” Evaluation Approach to Antidepressant Treatment Resistance

- **Adequacy of prior treatment**
  - Duration of treatment
  - Dosage of medication

- **Behavioral / Environmental factors**
  - Personality disorder
  - Psychosocial stressors

- **Compliance/Adherence**
  - Patient education
  - Treatment intolerance

- **Diagnosis**
  - Missed medical diagnosis
  - Missed psychiatric diagnosis
Diagnostic Challenges: 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
ANXIOUS MAJOR 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
  ▪ Increased risk of suicidality
  ▪ Higher social distress and higher incidence of alcohol and drug abuse
  ▪ Less likely to respond to medications (alone…)
Pharmacotherapy of Treatment Resistant Depression: Next Steps

- Optimize
- High Dose Therapy
- Switch
- Augment / Co-prescribe
- ECT
- Psychotherapy
Antidepressant “Augmenters”

- Augmenters with established effectiveness:
  - Lithium carbonate
  - Triiodothyronine

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

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

- Other proposed augmentation strategies
  - Modafinil (Provigil)
  - Cycloserine
  - Pramipexole (Mirapex)
  - Estrogen
  - Testosterone
  - Lamotrigine (Lamictal)
  - Folate
  - Dexamethasone
  - Ketoconazole
  - Inositol
  - Supplements
  - ...
**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 blow scalp - effects limited to cortex
Bipolar disorder

- Bipolar disorder is a common, recurrent, often lifelong, major psychiatric disorder
- Bipolar disorder is the 6th leading cause of disability worldwide in 1990
- Without treatment there are substantial risks of morbidity and mortality
- Bipolar disorder can be lethal: At least 25% of patients attempt suicide

**Manic Mood and Behavior**
- Euphoria
- Grandiosity
- Pressured Speech
- Impulsivity
- Excessive Libido
- Recklessness
- Diminished Need for Sleep

**Psychotic Symptoms**
- Delusions
- Hallucinations
- Sensory Hyperactivity

**Dysphoric or Negative Mood and Behavior**
- Depression
- Anxiety
- Irritability
- Hostility
- Violence or Suicide

**Cognitive Symptoms**
- Racing Thoughts
- Distractibility
- Poor Insight
- Disorganization
- Inattentiveness
Bipolar Disorder
Natural history

Severity

Elevated Mood
Subsyndromal Period
Mania Threshold
Major Depression Threshold
Depressed Mood

Bipolar Disorder

Weeks With Cycling/Mixed Symptoms
Manic/Hypomanic Symptoms
Depressive Symptoms
Symptomatically Ill

Weeks

Percent Of Follow-Up Weeks

Manning et al. 2002; Judd and Akiskal 2003
Treatments Used for Mood Disorders

- Lithium
- Anticonvulsants
  - Divalproex
  - Carbamazepine
  - Gabapentin
  - Lamotrigine
  - Topiramate
  - Tiagabine
  - Oxcarbazepine
  - Levetiracetam
  - Felbamate
- Adrenergic blocking agents
- Calcium channel blockers
  - Verapamil
  - Nimodipine
  - Amlodipine

- Atypical antipsychotics
  - Clozapine
  - Risperidone
  - Olanzapine
  - Quetiapine
  - Ziprasidone
  - Aripiprazole
  - …me, too…
- Hormonal
  - Thyroxine/estrogen
  - Tamoxifen
- Novel Antidepressants
  - Pramipexole
  - Riluzole
  - RU486
  - Genistein
  - Memantine
Psychosocial Strategies to Promote Stabilization and Enhance Coping in Patients with Bipolar Disorder
Drug Adherence Among Bipolar Patients

- 59% of patients hospitalized for a major affective episode are fully or partially nonadherent in year following discharge
- Only 21% of patients on lithium are continuously adherent to it
- Nonadherence is predicted by male gender, younger age, severe illness, substance misuse, lack of family support
Episodes of Bipolar Disorder May be Precipitated by Psychosocial Stress

- High levels of expressed emotion in relatives (Miklowitz et al. 1988)
- Life events that disrupt social rhythms
- Life events that accelerate goal-striving (Johnson et al. 1999)
Why Treat Bipolar Patients with Adjunctive Psychotherapy?

- Enhance social and occupational functioning
- Enhance capacity to manage stressors in the social-occupation milieu
- Enhance the protective effects of the family
- Decrease denial and encourage acceptance of the disorder
- Decrease the trauma associated with the disorder
- Increase adherence to medication
Drug Development in the past 50 years

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

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

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

Insel and Skolnick Mol Psychiatry 2006;11:11-17
Impaired resilience and neuroplasticity in severe recurrent mood disorders

Non mood disorder vs Severe recurrent mood disorders

Trophic Factors
Energy Supply

Glial cells

Developmental vs progressive atrophic?
BDNF
CREB
ERK
Bcl-2

Volume of specific areas
Neuron -- mainly atrophy

Stress, depression?
Glutamate
Unknown

Gr
Hyperactivation of Ca²⁺-dependent enzymes
Glucose Transporters
Oxygen Free Radicals
Energy Capacity
Trophic Support

Atrophy, Endangerment, and Death of Neurons
Inhibition of Hippocampal Neurogenesis

Derived from Duman, McEwen & Sapolsky
Ketamine is widely used nonbarbiturate, dissociative anesthetic mainly for ambulatory surgery and chronic pain.

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

Response: 50% decrease in HAMD from baseline

33% remission day 1

Ketamine: 13% 35% 53% 56% 71%
Placebo: 35% 40% 53% 56% 58%
Venlafaxine: 53% 56% 58% 53% 35%
Bupropion: 62-65%
SSRI: 62-65%

Zarate et al. Arch Gen Psychiatry, 2006
Study of ketamine’s mechanism of action from synapses through a range of systems

Synaptic Plasticity (mTOR, eEF2, GSK-3B inh)

Neurochemicals (Glx DM/DA-PFC Glx/Glu ratio)

- Glucose changes (glutamate signal)
- Circuits/connectivity

Genes

Gene expression

Cellular

Circuits

Rapid reversal of complex behavioral phenotype

Polysomnography

MRS

PET & MEG

MEG

Cortical excitability

Genes

Gene expression

Cellular

Circuits

Rapid reversal of complex behavioral phenotype

NEGE (GABA inhibition)
MEG: Activation Studies Implicate Anterior Cingulate in Cognitive & Affective Processing

Anterior Cingulate Desynchronization and Functional Connectivity with the Amygdala During a Working Memory Task Predict Rapid Antidepressant Response to Ketamine

Salvadore et al. Neuropsychopharmacology 2010
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NARSAD
Brain & Behavior Research Foundation

Patients and their families
Research studies:

http://patientinfo.nimh.nih.gov

1-877-MIND-NIH (1-877-646-3644)

e-mail – moodresearch@mail.nih.gov