Managing Depression

Remission as the Treatment Goal

John D. Matthews, M.D., M.Sc.
Epidemiology of Depression

- Lifetime prevalence of a major depressive episode (MDE): 17%
  - Male: 13%
  - Female: 21%
- Trends
  - Age at onset: younger
  - Incidence: increasing
  - Etiology: biologic vs psychologic

### DSM-IV Criteria for Major Depressive Episode

≥5 symptoms in the same 2-week period

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sleep</strong></td>
<td>insomnia or hypersomnia</td>
</tr>
<tr>
<td><strong>Interest</strong></td>
<td>depressed mood,* loss of interest or pleasure*</td>
</tr>
<tr>
<td><strong>Guilt</strong></td>
<td>feelings of worthlessness</td>
</tr>
<tr>
<td><strong>Energy</strong></td>
<td>fatigue</td>
</tr>
<tr>
<td><strong>Concentrate</strong></td>
<td>diminished ability to think or make decisions</td>
</tr>
<tr>
<td><strong>Appetite</strong></td>
<td>weight change</td>
</tr>
<tr>
<td><strong>Psychomotor</strong></td>
<td>psychomotor retardation or agitation</td>
</tr>
<tr>
<td><strong>Suicidality</strong></td>
<td>preoccupation with death, hopelessness</td>
</tr>
</tbody>
</table>

*Must include 1 of these.

Common Presenting Somatic Symptoms in Patients with Depression

- Tired all the time, “blahs”
- Headache
- Malaise
- Vague abdominal or joint pains
- Disturbed sleep
- Sexual dysfunction or loss of sexual interest
- “Stressed out”
- GI complaints (eg, constipation, diarrhea)

Common Presenting Psychological Symptoms in Patients with Depression

• Hopelessness
• Low self-esteem
• Impaired memory
• Difficulty concentrating
• Anhedonia
• Anxiety
• Preoccupation with negative thoughts

Depression Guideline Panel. Depression in Primary Care: Volume 1. Detection and Diagnosis.
Clinical Practice Guideline, Number 5. AHCPR publication no. 93-0550. April 1993.
Depression and Suicide

- 8% to 19% of patients with MDD severe enough to require hospitalization eventually commit suicide\(^1,2\)
- Suicide is the 8th leading cause of death in the US\(^3\)

Etiology of Major Depressive Disorder

- Genetics
- Biopsychosocial stress
Etiology (Stress/Vulnerability): Twin Studies in Major Depressive Disorder

Identical

Non-Identical

70% Concordance

25% Concordance
Depression and Stress

• Major depressive disorder (MDD) is expressed by the interaction of genes and environment
  – 80% of new onset episodes of MDD are triggered by significant stressors in the previous 6-month period
  – Childhood trauma increases the risk of developing MDD in adulthood
  – Prolonged stress increases risk for relapse/recurrence of MDD

• Treatment must target both genetic vulnerability (biological) and stress (psychosocial)
Interventions for Major Depressive Disorder

- Pharmacological
- Somatic interventions: electroconvulsive therapy (ECT), trans-magnetic stimulation (rTMS), vagal nerve stimulation (VNS), deep brain stimulation (DBS)
- Cognitive Behavioral Therapy (CBT)
- Acceptance and Commitment Therapy (ACT)
- Mindfulness-Based Cognitive Therapy (MBCT)
- Stress management
- Nutrition (gut-brain connection)
- Exercise
Pharmacological Interventions
How does the Synapse carry the signal?

1. Electrical current travels down the axon
2. Vesicles with chemicals move toward the membrane - what is that called?
3. Chemicals are released and diffuse toward the next cell’s plasma membrane
4. The chemicals open up the transport proteins and allow the signal to pass to the next cell - what type of diffusion is this?
Close up look at your synapse

The synapse - where the action happens

The next cell's plasma

Transport protein
Neurotransmitter Specificity

- **Norepinephrine** - motivation, energy, interest, concentration
- **Serotonin** - impulsivity, sexual function, appetite, aggression
- **Norepinephrine and Serotonin** - mood, sleep, emotion, cognitive function
- **Dopamine** – motivation, interest

Healy et al. 1997;11(4 suppl):S25-S31
Classes of Antidepressants and Targeted Neurotransmitters

- **Tricyclic antidepressants**
  - Nortriptyline, desipramine, imipramine, amitriptyline, doxepin, clomipramine, protriptyline

- **MAOI inhibitors**
  - Phenelzine, tranylcypromine, selegline, selegline patch

- **Selective Serotonin Reuptake Inhibitor**
  - Fluoxetine, paroxetine, sertraline, citalopram, escitalopram, vortioxetine

- **Serootonin and Norepinephrine Reuptake Inhibitor**
  - Venlafaxine, desvenlafaxine, duloxetine, levomilnacipran

- **Atypical antidepressants**
  - Bupropion, mirtazapine
Classes of Antidepressants and Targeted Neurotransmitters

- **Tricyclic antidepressants**
  - Norepinephrine or norepinephrine + serotonin (uptake blockers)

- **MAOI inhibitors**
  - Norepinephrine + serotonin + dopamine (inhibit metabolism)

- **Selective Serotonin Reuptake Inhibitor**
  - Serotonin (uptake blockers)

- **Serotonin and Norepinephrine Reuptake Inhibitor**
  - Norepinephrine + serotonin (uptake blockers)

- **Atypical antidepressants**
  - Norepinephrine + dopamine (uptake blocker); norepinephrine + serotonin (transmitter releaser)
Response in Major Depressive Disorder: 50-70%

≥50% decrease from baseline HAM-D scores

Improvement, but not necessarily complete relief of symptoms

Remission in Major Depressive Disorder: 35-40%

• Minimal or no symptoms
  – No longer meets diagnostic criteria
  – HAM-D$_{17}$ ≤7

• Return to “functional normality”
  – Usually associated with restoration of daily functioning
  – Typically, cannot be distinguished from those without depression
Potential Consequences of Failing to Achieve Remission

• Increased risk of relapse and treatment resistance\(^1\)-\(^3\)

• Continued psychosocial limitations\(^4\)

• Decreased ability to work and decreased workplace productivity\(^5,6\)

• Increased cost for medical treatment\(^6\)

• Sustained depression may worsen morbidity/mortality of other conditions\(^7\)-\(^9\)

Remission (HAM-D$_{17} \leq 7$) Decreases Risk of Relapse

* $P<0.001$.

Depression May Worsen Outcome of Many General Medical Conditions

• Depression may worsen morbidity and mortality after myocardial infarction\(^1,2\)

• Depression increases morbidity and mortality in patients with congestive heart failure CHF\(^3,4\)

• Depression increases risk of mortality in patients in nursing homes\(^5\)

• Depression worsens morbidity post-stroke\(^6\)

• Depression may worsen outcomes of cancer, diabetes, AIDS, and other disorders\(^7\)

7. Petitto JM, Evans DL. *Depress Anxiety*. 1998;8(suppl 1):80-84.
Potential Obstacles to Attaining Remission in Clinical Practice

- Patients and clinicians are satisfied with partial improvement in symptoms (i.e., response but not remission)
- Treatments may not be well tolerated
- Underdosing and inadequate duration of trial
- Failure to recognize residual symptoms
- Continued psychosocial stressors
Strategies for Achieving Remission

- Recognize/diagnose depression
- Aggressively treat depression at diagnosis
- Ensure adequate medication doses
- Ensure adequate duration of treatment
- Select optimal treatment(s)
  - Combination pharmacotherapy and psychotherapy
  - Combination pharmacotherapy
  - Augmentation strategies (e.g., lithium, quetiapine, aripiprazole)
- Ensure patient adherence
- Educate patients that remission is the goal

Somatic Therapies

- **ECT** = Electroconvulsive Therapy
- **VNS** = Vagus Nerve Stimulation
- **rTMS** = Repetitive Transcranial Magnetic Stimulation
- **DBS** = Deep Brain Stimulation
ECT: Electroconvulsive Therapy

- Oldest, most effective treatment for depression; > 80% remission
- Mechanism of action unknown
- Seizure a necessary component of treatment
- General anesthesia required
- Confusion/memory loss potential side effects
- Maintenance ECT maybe necessary + medications
rTMS: repetitive Transcranial Magnetic Stimulation

- Powerful magnetic field over the surface of the left frontal cortex to affect brain functioning
- Magnetic field affects neuronal activity in this part of the brain
- Efficacy < ECT, but better tolerated

From www.neuronetics.com
Psychotherapy Interventions

• Cognitive Behavioral Therapy
• Acceptance and Commitment Therapy
Two States of Mind

• **Thinking Mind**
  – Solves problems and makes decisions
  – Evaluates and plans for the future
  – Creates
  – Communicates through language
  – Creates stories through language for survival and attachment

• **Observing Mind**
  – Awareness
  – Descriptive, non-judgmental, observer of experience
  – The perspective from which one perceives, speaks, acts, and lives; perspective of I/you, here/there, now/then
### Daily Record of Dysfunctional Thoughts

<table>
<thead>
<tr>
<th>Situation: Describe context</th>
<th>Emotions:</th>
<th>(-) AT: -Thought -Belief (0-100)</th>
<th>Rational Response: -Belief (0-100)</th>
<th>Outcome: -Re-rate belief in (-) AT (0-100)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>-Type</td>
<td>“what went through your mind”</td>
<td>“evidence against; another way of looking at it”</td>
<td></td>
</tr>
<tr>
<td></td>
<td>-Intensity (0-100)</td>
<td></td>
<td></td>
<td></td>
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**Rational Response:**

- Belief (0-100)

**Outcome:**

- Re-rate belief in (-) AT (0-100)
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<td>Biochemistry test</td>
<td>Fear, anxiety 70%</td>
<td>“I will fail” 75%</td>
<td>One test does not define future 90%</td>
<td>Belief down 35%</td>
</tr>
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Errors in logic

Early Experiences
- Lovable ±
- Control ±
- Competent ±

Core Beliefs

Dysfunctional Attitudes
- Assumptions If then
- Rules

Situations (Perception of Environment)

Thoughts (automatic)

Moods

Behavioral Compensatory Strategies

Physiology

Past

Present

Behavior
Acceptance and Commitment Therapy (ACT) vs Cognitive Behavioral Therapy (CBT)

- ACT **DOES NOT** focus on changing the content of thoughts
- ACT **DOES** focus on changing one’s relationships to distressing internal experiences (thoughts, emotions, sensations, images, and memories) based on context (values – who and what is important)
ACT

- The more you engage, analyze, struggle, and attempt to control and eliminate negative internal experiences (thoughts, feelings, memories, sensations, images), the more you have them.
According to ACT: What should determine our behaviors or actions?

- Experience (“Is this action good or bad for me based on my experience”)
- Values (“Who and what is important to me”)

Values: “Who and What is Important in terms of actions/behaviors”

- Relationships
- Work
- Learning
- Healthy lifestyle
- Recreation
- Community
- Spirituality
Psychological Flexibility: The Aim of ACT

• “Being aware and willing to experience distressing thoughts, feelings, sensations, images, and memories, in the moment, while freely engaging in actions that matter and value-based” (Matthews & Doorley, 2015)
ACT Matrix
(Polk and Schoendorff, 2014) (modified)

“What Do you Do to Move Away from Unwanted Thoughts, Feelings, Memories, Sensations, and Images”

Experiential Avoidance

Away

Me Noticing (Perspective Taking)

External Experiences (ACTIONS)

“What Can You Do to Move Toward Who or What Is Important”

Values

“Who and What Are Important”

“What thoughts, feelings, memories get in the way of “Who and What is Important”

Internal Experiences
ACT Matrix - MJ
(Polk and Schoendorff, 2014) (modified)

“Avoid contact with daughters”
“I drink to numb the pain”

“Give daughters a call”
“Go to AA 4 times/wk”

Me Noticing (Perspective Taking)

Experiential Avoidance
“Be a good father
Keep sober”

External Experiences (Actions)

Values

“I will fall apart if my daughters reject me”
“I’m a fraud because I have not kept sober”
Summary

• The goal of treatment for depression should be remission
• Remission is associated with improved function and a better prognosis
• There are predictors of response to pharmacological interventions, but, they are limited
• The combination of antidepressants with CBT or ACT, stress management, good nutrition, and exercise increase remission rates
Bulfinch Program: Integrated Healthcare

Psychiatric Disorders

Individual State of Wellness

Medical Disorders

Hyper-reactive stress response
Amygdala co-ordinates the stress response
Normal Stress Response

Prefrontal cortex (executive function)

Parietal cortex (sensation)

Visual cortex (vision)

Auditory cortex (hearing)

Olfact/gust cortex (smell and taste)

Hippocampus (memory)

Amygdala (fear center)

Sympathetic nervous system

Cardiac/respiratory centers

Hypothalamus (HPA-axis; cortisol)

Immune System
Amygdala co-ordinates the stress response
Prolonged Stress $\rightarrow$ Amygdala Hypertrophy (Johnson et al., 2009)
Prolonged Stress $\rightarrow$ Hyper-reactive Stress Response (HRSR)

- Prolonged Stress
- Amygdala Hypertrophy
  - Increased Cortisol
  - Increased Pro-inflam. cytokines
  - Increased Adrenalin
- Insulin Resistance
  - ↓Immune Response
  - Depression
- Cancer
  - Infection
  - Autoimmune
  - Depression
- Hypertension
  - Atherosclerosis
Summary

• The life expectancy for patients with major mental illness is about 20 years shorter than the general population.

• 70% of the shortened life expectancy is due to medical disorders

• Prolonged stress contributes to the development of a hyper-reactive stress response

• The hyper-reactive stress response not only contributes to the development of cardiovascular disease, diabetes, cancer, infectious diseases, autoimmune diseases, but psychiatric disorders including depression