Depression is a Brain Disease

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- **Board of Directors:** AFSP, Gratitude America
Canst thou not minister to a mind diseased? 
Pluck from the memory a rooted sorrow, 
Raze out the written troubles of the brain, 
And with some sweet oblivious antidote 
Cleanse the stuffed bosom of that perilous 
Stuff which weighs upon the heart?

MACBETH
All his life he suffered spells of depression, sinking into the brooding depths of melancholia, an emotional state which, though little understood, resembles the passing sadness of the normal man as a malignancy resembles a canker sore.

William Manchester,
Major Depressive Episode: DSM-IV Diagnostic Criteria

• Characterized by clinically significant distress and/or impairment in social, occupational, or other important areas of functioning
• Symptoms must persist for most of day, nearly every day, for ≥ 2 consecutive weeks
DSM-IV Diagnostic Criteria for Major Depression

- ≥ 5 symptoms including depressed mood and/or anhedonia
  - Other symptoms may include:
    - Significant weight change
    - Psychomotor agitation/retardation
    - Pervasive loss of energy/fatigue
    - Feelings of worthlessness/excessive or inappropriate guilt
    - Difficulty concentrating
    - Sleep disturbance
    - Recurrent thoughts of death/suicide
- Symptoms present for ≥ 2 weeks
Prevalence of Depression in United States

# Depression—A Major Cause of Disability Worldwide

**DALYs—2000 and 2020**

<table>
<thead>
<tr>
<th>Rank</th>
<th>2000</th>
<th>2020 (Estimated)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Lower respiratory infections</td>
<td>Ischemic heart disease</td>
</tr>
<tr>
<td>2</td>
<td>Perinatal conditions</td>
<td><strong>Unipolar major depression</strong></td>
</tr>
<tr>
<td>3</td>
<td>HIV/AIDS</td>
<td>Road traffic accidents</td>
</tr>
<tr>
<td>4</td>
<td><strong>Unipolar major depression</strong></td>
<td>Cerebrovascular disease</td>
</tr>
<tr>
<td>5</td>
<td>Diarrheal diseases</td>
<td>Chronic obstructive pulmonary disease</td>
</tr>
</tbody>
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DALYs = disability-adjusted life-years.
Depression is Often Under Diagnosed and Inadequately Treated

- Less than 1/2 of patients with major depression are explicitly recognized as being depressed\(^1\)
- Only about 1/2 of all depressed patients receive some form of therapy for their illness\(^2\)
- Only about 1/4 of depressed patients receive an adequate dose and duration of antidepressant treatment\(^3\)

The Mood-Disorders Spectrum

- Bipolar I Disorder
- Bipolar II Disorder
- Unipolar Depression
- Cyclothymia
- Dysthymia
- Normals
Suicide Rate over 15 Years

Rate per 100,000
Comorbidity

Lifetime comorbidity of mood and anxiety disorders

48% of patients with PTSD\(^1\)

Up to 65% of patients with Panic Disorder\(^2\)

Up to 70% of patients with Social Anxiety Disorder\(^5\)

67% of patients with Obsessive–Compulsive Disorder\(^4\)

42% of patients with Generalised Anxiety Disorder\(^3\)

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Outcome of Depression Treatment

The Five Rs

Etiology of Major Depression

- Over a third of the liability for developing MDD comes from genetic factors
- Genes likely mediate risk as well as resilience
- Environmental stressors interact with genes to influence the likelihood of developing MDD
Studies of identical twins have revealed that some conditions, such as psoriasis, have a strong genetic component and are less influenced by environmental and lifestyle factors—identical twins are more likely to share these diseases; but other conditions, such as MS, are only weakly influenced by genetic makeup and therefore twins may show differences depending on their exposure to various environmental factors.

“We used to think our fate was in our stars. Now we know, in large measure, our fate is in our genes.”

—J. D. Watson

Depression and anxiety are ultimately about how the brain responds to the environment.

Genes:
- sequence
- variants and
- variable gene
- processing

Cells:
- molecular
- pathways

Systems:
- activity in emotion
- processing circuitry

Behavior:
- Clinical phenotype
Risk Factors for Depressive Disorders

- Family History of depressive disorders
- Prior personal history of a depressive disorder
- Female gender
- Life stressor (e.g., bereavement, chronic financial problems)
- Certain personality traits
- Loss of parents at an early age
- Childhood abuse
- Alcohol or drug abuse
- Anxiety disorders
- Neurologic disorders (e.g., Parkinson’s, Alzheimer’s, stroke)
- Primary sleep disorders

Depression Guideline Panel. Depression in Primary Care: Volume 1. Detection and Diagnosis. 1993: 1-65
Depressive Disorders: The Essentials

- Stress is an important risk factor for depression
- Early life stress is an important risk factor
- Genes account for a substantial variation in risk
- Brain systems related to the regulation of emotion are functionally impaired during an episode
- Monoaminergic drugs are therapeutic
Neurotransmitters and Depression

• There are disturbances in the monoamine systems
  – Serotonin (5-hydroxytryptamine, 5-HT)
  – Norepinephrine (NE)
  – Dopamine (DA)

• There are also disturbances in other neurotransmitter systems (e.g., corticotropin-releasing factor [CRF] and substance P)

• Serotonin and norepinephrine have been the most extensively studied in the clinical setting
Axon Terminals of Serotonergic Neurons Project to Virtually All Portions of the Brain

- Thalamus
- Striatum
- Neocortex
- Ventral Striatum
- Amygdaloid Body
- Hypothalamus
- Olfactory and Entorhinal Cortices
- Hippocampus
- Rostral Raphe Nuclei
- Cingulum
- Cingulate Gyrus
- Cerebellar Cortex
- Intracerebellar Nuclei
- Caudal Raphe Nuclei
- To Spinal Cord

Serotonin Transporters Measured With $^{123}$I β-CIT and SPECT

Sagittal Image Through Brainstem and Basal Ganglia

Coronal Image

SPECT = single photon emission-computed tomography
Reduced Brainstem $[^{123}\text{I}]\beta$-CIT Binding in Depression

*p=0.02; V3" = [brainstem-occipital]/occipital; Malison RT et al. (1998), Biol Psychiatry 44(11):1090-1098
Influence of Life Stress on Depression

- Results of regression analysis estimating the association between childhood maltreatment (between the ages of 3-11) and adult depression (ages 18-26), as a function of 5-HTT genotype

Caspi A et al. (2003), Science 301(5631):386-389
Fig. 1. The major dopamine pathways in the human brain. The dopamine cell bodies in the substantia nigra project to the corpus striatum, and a deficiency of dopamine in the striatum is associated with Parkinson's disease. The ventral tegmental dopamine cell bodies form the mesocortical and mesolimbic dopamine pathways, which project respectively to the frontal cortex and to a variety of limbic forebrain structures including the nucleus accumbens, the olfactory tubercle, the amygdala and the entorhinal cortex. The short dopamine pathway in the hypothalamus regulates hormone release from the pituitary gland; most importantly, dopamine inhibits prolactin release.
Dopamine and Depression

- Role of dopamine neurons in behavioral and physiological areas altered in depression
- High rate of comorbidity of Parkinson’s disease and depression
- Pathophysiological involvement of DA systems in depression
  - Imaging Studies
  - Postmortem Studies
  - Biological Fluids Studies
- Role of DA circuits in the actions of antidepressants
  - MAOIs
  - Effects on the DA transporter
Dopamine transporter binding potential in bilateral striatum is lower in depressed patients. Data was analyzed using analysis of covariance with age as a covariate, examining effect of diagnosis (effect of diagnosis: $F_{1,29} = 7.1$, $p=0.01$).
Cg25-Frontal Interactions in Negative Mood Regulation

Recovery With SSRI
FDG PET

Transient Sadness
CBF PET

Depressed Patients

Healthy Volunteers

FDG = [18F] fluorodeoxyglucose; Numbers (i.e., 25, 31) are Brodmann area designations; Mayberg HS et al. (1999), Am J Psychiatry 156(5):675-82
Paroxetine (Paxil)
N=13
Age 36±10
HAM 22±3
post 6±4

CBT
N=14
Age 41±9
HAM 20±3
post 6.7±4

Different Treatments; Different Targets

HAM = HAM-D Score; P = inferior parietal; th = thalamus; hc = hippocampus; pCg = posterior cingulate; mF = medial frontal; vF = ventral prefrontal; Goldapple K et al. (2004), Arch Gen Psychiatry 61(1):34-41
Current Treatment Options for Depression

Goal = reduce symptoms of depression and return patient to full, active life

Nonpharmacologic

• Psychotherapy
  - Cognitive behavioral therapy
  - Interpersonal therapy
  - Psychodynamic therapy
• Electroconvulsive therapy
• Phototherapy

Pharmacologic

• Antidepressant medications

Binder et al (Submitted)
Optimizing current treatments

- ECT effective for depression\(^1\)
  - Limitations include side effects and high relapse rate (even with continuation ECT)\(^2\)
  - Increasingly focal ECT may be efficacious with fewer side effects\(^3,4\)

- Magnetic seizure therapy
  - Convulsive therapy with a very focal initial stimulation
  - Preliminary efficacy suggested with fewer cognitive side effects than ECT\(^5,6\)

\(^1\)The UK ECT Review Group, Lancet, 2003; \(^2\)Kellner et al., Arch Gen Psychiatry, 2006; \(^3\)Sackeim et al., Arch Gen Psychiatry, 2000; \(^4\)Bakewell et al., J ECT, 2004; \(^5\)Lisanby et al., Neuropsychopharmacology, 2003; \(^6\)White et al., Anesth Analg, 2006
Vagus Nerve Stimulation (VNS)

- FDA-approved (1997) for treatment of medication-refractory epilepsy
- FDA-approved (2005) for treatment of depression that has not responded to four or more medications
- Achieved by implanting a pulse generator attached to (usually) the left vagus nerve
rTMS

• Studied for treatment of depression since 1993
  – Multiple open and sham-controlled studies have been performed; meta-analyses support antidepressant effects for high frequency left-sided rTMS\(^1,2\)
  – Some studies have suggested a favorable comparison to ECT, but data are mixed\(^3,4\)
  – Low frequency right-sided rTMS may also have antidepressant effects\(^5,6\)

• Side effects are generally mild; serious adverse events (seizures) from TMS performed within current safety guidelines are very rare\(^7\)
