Depressive Disorders
A clinical overview

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Depressive Disorders

• What is depression?
  – Complex series of conditions
  – Physical component
  – Emotional component
  – Treatments aimed at both components
History of concept of depression

• First concept of depression: Mesopotamia, second millennium BC

• Causes: spiritual passion; demonic possession

• Problems to be addressed by priests; not “medically” oriented
  – Greeks, Romans, Babylonians, Chinese and Egyptians similar ideas

• Early Treatments include beating, starvation, physical restraint
  – Represents early stigma of mental illness
Progression of thought on depression

- Greeks and Romans – post CE; initial conception of depression as physical
- Notion that toxic “humors” may be harbored within body and cause mood change
- Newer Treatments
  - Gymnastics, massage, diet, baths, poppy extract and donkey milk
More contemporary thoughts on depression

• 1895 - Emil Kraepelin differentiated manic depression from depression
  - Foundational concept that schizophrenia and mood are distinct

• 1917 - Sigmund Freud introduced concept of the “unconscious”
  - Depression was anger turned inward
  - Self loathing
  - Psychoanalysis: Form of treatment to bring unconscious thoughts and emotions to conscious awareness. Depression has “nurture” roots.
Early thoughts on depression

Freudian analysis mainstay of treatment – early 20\textsuperscript{th} century

- Helpful for certain types of patients
- Lengthy and expensive
- Seen more as treatment for the elite. Not “The Peoples” therapy.
- Sigmund did not take kindly to the Prior Authorization process
Rapid changes in concept of mental illness and depression

- Post WWII- state of psychiatric diagnoses was chaotic
- DSM system introduced 1952; solve “Tower of Babel” crisis of psych
- Most profound change – 1980 DSM III
  - Change from cause bases diagnoses to measurable observation
  - Endogenous depression vs exogenous depression – eliminated
- Washington University (St. Louis); “Dust Bowl Empiricism”
- Goodwin, Guze, Winnuker, Clayton, Andreason
- Primary Principle – Psychiatric diagnoses are atheoretical
Depression and current DSM

- DSM 5 introduced 2013
- There are currently 7 specific depressive disorders
- Each disorder has unique set of criteria
- Each disorder has its own epidemiology associated with it
- Current DSM 5 represents consolidation of previous editions
  - No longer a distinct post-partum depression
DSM 5 classification of Depressive Disorders

- Major Depressive Disorder
- Persistent Depressive Disorder (dysthymia or minor depression)
- Premenstrual Dysphoric Disorder
- Substance/Medication-Induced Depressive Disorder
- Depressive Disorder due to Another Medical Condition
- Other Specified Depressive Disorder (brief depression)
- Other Unspecified Depressive Disorder
Criteria Major Depression

- Need 5 out of 9; 1 must be depressed mood or loss of pleasure
  - Depressed mood
  - Loss of pleasure
  - Weight loss
  - Insomnia
  - Suicidal
  - Poor concentration
  - Fatigue
  - Poor concentration
  - Motor agitation
Prevalence of Major Depressive Episode


Data courtesy of SAMHSA

*NH/OPI = Native Hawaiian/Other Pacific Islander
**AI/AN = American Indian/Alaska Native
Major depressive disorder: Unipolar depression

• Epidemiology
  - Sex: Twice as often in men than women
  - Age: Most common onset is between ages of 20-40
  - Lifetime prevalence: 5-12% in males; 10-25% in females
  - Annual incidence: 1.5% in entire population
  - Marital status
  - Socioeconomic status
Biology of depression

- 1950’s and Introduction of Biological Psychiatry
- Ipronizid – first antidepressant
  - Accident; looking for tuberculosis cure
- Imipramine – discovered 1953
  - Accident; thought was antipsychotic
- Led to monoamine theory of depression
- 1960’s – concept that depression linked to brain chemicals called monoamines
  - Monoamines released from one nerve cell, attach to adjacent nerve cell
Monoamines and depression

- Neurotransmitters
- Receptors
- Akin to key and lock
- Serotonin
- Norepinephrine
- Dopamine

**BIOCHEMICAL BASIS OF DEPRESSION**

**Monoamine Hypothesis:** depression was due to a deficiency of monoamine neurotransmitters, notably nor-epinephrine (NE) and serotonin (5-hydroxytryptamine [5HT])
Biological theory of depression

- Normal neurotransmitter flow
- Abnormal absence of transmitter flow
- Treatment aimed at restoring normal balance
Depression—the role of serotonin
Depression—other neurotransmitters

Dopamine

Norepinephrine

Epinephrine
Serotonin – most common neurotransmitter

- Over 90 serotonin types of receptors
- Most serotonin receptors do not pertain to mood
- Sleep, sex, appetite, blood clotting, digestion all under prominent serotonin regulation
- In brain, most serotonin is concentrated in area called Dorsal Raphe Nucleus; synthesized from amino acid tryptophan
Norepinephrine—second most common

- Adrenaline like
- Not as widely distributed
- Plays role in anxiety
- Plays role in depression, especially agitated depression
- Located in adrenal glands also
- Synthesized from amino acid called Tyrosine
Dopamine—another big player

- Active in pleasure and reward behavior
- Enhances energy levels
- Cocaine’s effect as an antidepressant is mediated via dopamine
Psychometric tests – depression

- Beck Depression (BDI)
- HAM-D
- PHQ-2
- SCID - research
Medication treatments - depression

- SSRI – Selective Serotonin Reuptake Inhibitors
- SNRI – Serotonin Norepinephrine Reuptake Inhibitors
- Serotonergic Agents
- Tricyclics
- MAOI – Monoamine Oxidase Inhibitors
- Bupropion
- Mirtazapine
Medication treatments - depression

• SSRI – Selective Serotonin Reuptake Inhibitors
  – Fluoxetine (Prozac) first of these agents (1986)
  – Revolutionized depression therapy
  – Still widely used
  – Safer in overdoses
  – Long half life – stays active in body for several weeks
Medication treatments - depression

• SSRI – Selective Serotonin Reuptake Inhibitors
  - Sertraline (Zoloft) introduced 1991
  - Shorter half life
  - Less agitation
  - Excellent for anxiety and irritability
  - Fewer drug interactions
Medication treatments - depression

- SSRI – Selective Serotonin Reuptake Inhibitors
  - Paroxetine (Paxil) 1993
  - Shortest half life
  - Good for anxiety
  - Sexual side effects are problematic
  - Severe discontinuation
  - Mildly sedating
Medication treatments - depression

• SSRI – Selective Serotonin Reuptake Inhibitors
  – Citalopram and Escitalopram
  – Formerly Pfizer compounds
  – Heavily marked to PCP
  – Studies least robust – approved when pharma allowed to “sunset” negative studies
  – FDA studies not designed to assess whether one antidepressant is better than another but whether a drug is effective
Medication treatments - depression

- **SNRI**
  - Venlafaxine (Effexor)
  - Duloxetine (Cymbalta)
  - Act like SSRI at lower doses
  - Invoke norepinephrine at higher doses
  - Venlafaxine - has severe discontinuation syndrome
  - Duloxetine – shown to be helpful in chronic pain
Medication treatments - depression

- Bupropion
  - Wellbutrin
  - Energy enhancing
  - Easily added to combinations of medications
  - Few side effects
  - Can impair sleep
  - Associated with seizures in patients with bulimia
  - Primary mechanism via dopamine
Medication treatments—depression

- Mirtazapine
  - Remeron
  - Unique direct effect of serotonin and norepinephrine
  - Increases appetite
  - Can be sedating
  - Useful in geriatric depression with features of anorexia
Medication treatments—depression

- Tricyclics (TCA’s)
  - Had been mainstay
  - Side effects as are “dirty” drugs
  - Risky in OD – cardiac dysrhythmia and seizures
  - Low doses helpful for sleep and headache prophylaxis
  - Common agents
    - Amitriptyline; Imipramine
    - Nortriptyline; Despiramine
Medication treatments - depression

- **MAOI**
  - Inhibit the breakdown of all monoamines
  - Effective
  - Among earliest antidepressants
  - Not widely used due to dietary restrictions
  - Cannot consume foods with tyramine as can cause hypertensive crisis
Medication treatments - depression

- Newer antidepressants
  - Last 5 years
  - Trintellix (Vortioxetine)—supercharged SSRI
  - Vybriid (Vilazodone)—Trazodone-like but not as sedating
  - Fetzima (Levomilnacitran)—SNRI with possibly fewer side effects
  - Most health plans either not on formulary or require step therapy
Medication treatments—depression

- Adjunctive and novel agents
  - Lithium
  - Aripiprazole/Lurasidone/Quetiapine
  - Thyroid hormone
  - Estrogen
  - Lamotrigine
  - SAM-e—regulates hormones/natural
  - Ketamine—
    - Controversial
    - Old animal sedative
    - Repair from cortisol damage
Non-medication biologic treatments - depression

- Electroconvulsive therapy
  - Used since 1930’s
  - Controlled seizure induced under anesthesia and muscle relaxant
  - Can be performed either one sided or two sided
    - One sided may leave fewer memory problems
    - No absolute contraindications for ECT
    - Some psychiatrists quick to pull the trigger
    - Helpful for elderly with weight loss and agitation
    - Mechanism unknown—phosphinositol in neuron membranes
Non-medication biologic treatments - depression

- rTMS—Reverse transcranial Magnetic Stimulation
  - Less invasive than ECT
  - Office based
  - Placing brain in magnetic field
  - Data is weak—strongest data is from Neurostar, its inventor
  - Equipment cost $75K, so some may be anxious to reap ROI
  - Strict criteria for authorization from CMS
Non-medications biologic treatments - depression

- Vagal Nerve Stimulation (VNS)
- Surgical procedure
- Like a pacemaker in upper chest
- Delivers pulses to vagus nerve (1-12 cranial nerves)
- Unknown reason why alleviates depression
- Many Commercial plans have authorized as last report
- New CMS NCS 18-002 provides avenue for use in MC
Psychotherapy

• Very valuable tool
• Studies show that psychotherapy together with medications yield best results
• School of therapeutic thought less important than ability to build rapport
• Some therapies more structured than others
• Types of therapy
  – Psychodynamic—requires motivation and capacity for insight
  – CBT—more like rote memorization
  – Interpersonal therapy—a riff on CBT in certain ways