MAJOR DEPRESSIVE DISORDER (MDD): defined by APA as
- Common & serious medical illness that negatively affects how one feels, thinks and acts
- Depressed individual feels sadness and/or loss of interest in activities once enjoyed
- Leads to variety of emotional & physical problems that decreases person’s ability to function at work and at home

SX: DSM-5 indicates 5 of the following depression sx required for diagnosis for a minimum of 2 continuous weeks (one sx MUST be from the first 2 listed)
1. Feeling sad or having a depressed mood
2. Loss of interest or pleasure in activities once enjoyed
3. Appetite changes – weight loss/gain unrelated to dieting
4. Sleep issues (trouble sleeping or sleeping too much)
5. Increased fatigue, lack of energy
6. Changes in speech or other motor activities; increase in purposeless physical activity (ex// hand-wringing or pacing) or slowed movements & speech (actions observable by others)
7. Feeling a sense of guilt or worthlessness
8. Cognitive impairment, concentration, and decision making
9. Recurring thoughts of death or suicide

NOTE: certain medical conditions (ex// thyroid problems, brain tumor, vitamin deficiency) may mimic above sx

NOTE: sadness of depression differs from sadness of grief

<table>
<thead>
<tr>
<th>Mood/Interest</th>
<th>Depression</th>
<th>Bereavement</th>
</tr>
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<tbody>
<tr>
<td>Constantly low</td>
<td>“Painful” waves occur intermixed with positive memories of deceased</td>
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Self esteem
- Feelings of worthlessness & self-loathing
- Usually maintained

Sudden loss of loved one
- Can intensity existing MDD
- Can precipitate MDD

SUICIDE: 2nd leading cause of death among Young Canadians (25% deaths aged 15-24)

RISK FACTORS:
- Completion
  - Elderly men
  - Depression
  - Alcohol/substance abuse
  - Psychiatric dx
  - Recent severe stresses
  - Job loss
  - Death of someone close
  - Financial difficulties
  - Social isolation / lack of support / peer network
  - Past suicide attempts

- Suicide Attempts
  - Female
  - < 30 yrs
  - Relationship difficulties
  - Mood/personality disorder
  - Substance abuse

SUICIDAL PATIENT: Urgency is based on suicide risk:
- Intent to die, expressed with plan
- Extreme despair, hopelessness, pessimism
- Involvement of illicit drugs/alcohol is likely

ACTION: REFER IMMEDIATELY
- Communicate your commitment to help the patient
- Accompany patient (ex// staff, family member)
- Call paramedics, nurse or physician to the situation
- ER for psychiatric assessment ASAP

IMPACT:

SOCIETAL IMPACT:
- 2nd largest cause of disability
  - Women (15-44 yo) bear greatest burden
  - Most disabling disease (years lost of healthy, productive life)
  - Economically, $14 billion annually in Canada (txt, loss productivity, premature death)

PERSONAL IMPACT:
- Relationships
  - Work/school (loss of productivity or job)
  - Comorbidity (66%) – anxiety disorder, substance abuse
  - Suicidal thinking, attempts, completions
    - 35% of depressed pts have or will make a suicide attempt
    - 2-8% commit suicide over a 10 yrs

EPIDEMIOLOGY:
- Depression can strike any time, but usually late teens to mid-20s
  - Women > men
  - 5% (1/20) Canadians suffer from clinical depression
  - 17% (1/6) will experience depression at some time in life

RISK FACTORS:
- Neuro-chemistry/physiology: overactive HPA; biogenic amine theory
  - Genetics: 40% chance second twin also experiences depression
  - Personality: low self-esteem, pessimistic, “stressed out” are more prone
  - Environment: continuous exposure to violence, neglect, abuse or poverty

MDD AS A PROGRESSIVE ILLNESS:
- MDD = episodic illness; re-occurrence is norm rather than exception
  - Majority of patients experience recurrent episode with each subsequent episode
    - Increases probability of further episodes
    - “Kindling” process = depressive episodes more easily triggered over time
  - As duration of depressive episodes increases, probability of recovery decreases
- Residual symptoms = “vulnerability” that may be due to an active disease state
  - Patients experiencing sub-threshold sx following MDD episode had higher risk of re-occurrence & increased propensity for faster onset of next episode compared to full remissions
  - Treatment outcome shifted from sx reduction to remission (absence of sx) or recovery (extended remission)

- Recovery infers restoration of underlying (patho)physiology associated with depression

“DEPRESSOGENIC” MEDICATIONS: linked with behavioral manifestation of depression sx
- Cardiac BBs, clonidine, methylodopa, procaainamide, hydralazine, digoxin
  - CNS & drugs of abuse Alcohol, amphetamines, BZDs, barbiturates, cocaine, narcotics, marijuana, phencyclidine
  - Antihistamines Diphenhydramine, brompheniramine
  - Cancer chemotherapy Tamoxifen
  - Steroids & hormones Glucocorticoid, anabolic, estrogen, oral contraceptives
  - Other Isotretinoin, interferon, efavirenz

NOTE: Assessing whether a medication has caused clinical depression (direct; altering NT levels; indirect; causing fatigue, diminished appetite, sedation) or whether relationship is coincidental (depression common in pts with medical illnesses) is challenging

TREATMENT OF MDD:
- Pharmacotherapy
  - Selective serotonin re-uptake inhibitors (SSRI)
  - Serotonin-noradrenaline re-uptake inhibitors (SNRI)
  - Noradrenaline re-uptake inhibitors (NRI)
  - NA and DA re-uptake inhibitors (NDRIs)
  - 5-HT antagonists/reuptake inhibitors (SARIs)
  - Noradrenaline and Specific 5-HT antagonists (NaSSAs)
  - Tetracyclic antidepressants (TECAs)
  - Reversible inhibitors of monoamine oxidase (RIMA)
  - Monoamine oxidase inhibitors (MAOIs)
  - Other: ketamine, herbs/NHPs

Psychotherapy
- Cognitive behavioral
  - Interpersonal
  - Dialectical behavior
  - Acceptance and commitment

Also combined with pharmacotherapy
**LECTURE 1: Neurological Basis of Depression**

**ECT PROCEDURE:**
- Reserved for MDD pts resistant to other txt options
- Performed under general anesthesia with muscle relaxant
- EEG, ECG and blood oxygen monitored during txt
- Brief pulses (800 mA) applied bilaterally over 1-6s; repeated 2-3 times/week over 2-4 weeks

**ADVERSE EFFECTS:**
- Retro*- or antero-grade amnesia * especially few weeks before txt
- Post-operative amnesia & cognitive impairment
  - Complication from repeated anesthetic exposure that increases with age

**THERAPEUTIC EFFECTS:**

**EFFECT ON BRAIN:**
- Increase in neurotrophic signalling
- Increase in hippocampal volume

**EFFECT ON DEPRESSION:**
- Rapid relief of severe depression
- Rapid reduction in suicide drive

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**THEORIES UNDERLYING PATHOPHYSIOLOGY OF DEPRESSION:** Table on pg 3 of Soja’s notes explain several theories

**MONOAMINE THEORY OF DEPRESSION:**
- Abnormality in monoamine NT receptors leads to depression
  - Depletion of monoamine NTs
  - Abnormalities in monoamine NT receptors
  - Problem with signal transduction of NTs’s message from receptor to other downstream events
- Stems from 3 significant findings:
  - Drugs that deplete biogenic amines (ex./ Reserpine) produce state of depression in mentally normal people
  - Drugs that increase biogenic amine activity at synaptic level tend to alleviate depression (TCA, MAOI)
  - Biochemical investigations in some depressed patients suggest an abnormality in amine metabolism
- Amines involved: 5-HT and NA
  - Since PD patients also suffer from MDD, DA (dopamine) also is implicated to play a role

**HYPOTHALAMIC-PITUITARY-CORTISOL SYSTEM IN MDD**
- MDD patients have high levels of stress hormone cortisol
  - alters glucocorticoid receptors (GR)
- High density of GR → hippocampal dysfunction and shrinkage
  - down-regulation of GR sensitivity
- During chronic stress, GR signalling can’t contain the stress response (GR negative feedback fails)
- Over-activity in HPA & amygdala follows → increase in sympathetic tone → cytokine & macrophage release = fatigue, ↓ appetite, libido and pain thresholds
- Cytokines diminish neurotrophic support and monoamine neurotransmission → neuronal death and glial cell damage

**CHANGES IN BRAIN FUNCTION & STRUCTURE IN MDD:**
- Hyperactivity in VMPFC & LOPFC = ↑ pain, anxiety, tension
- Hypoactivity in DLPFC = apathy, ↓ attention, memory & psychomotor activities
- Decreased connectivity between ACC & amygdala
- Hippocampal volume decreased

**NEUROTROPHIC THEORY - ROLE OF BDNF IN MDD**
- BDNF is involved in neuron survival, stimulates and controls neurogenesis
  - BDNF acts in hippocampus
- BDNF levels decrease when corticosteroid levels rise and monoaminergic transmission decreases
- BDNF levels in CSF and plasma/serum in MDD patients are lower than non-depressed individuals
  - BDNF levels appear to be lower in pts who attempt suicide
- Antidepressant treatment has been shown to increase BDNF plasma levels
- BDNF plasma levels may reflect the state of the neuronal network in patients with major depression