

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

	Depression	Bereavement
Mood/ Interest	Constantly low	"Painful" waves occur intermixed with positive memories of deceased
Self esteem	Feelings of worthlessness & self-loathing	Usually maintained
Sudden loss of loved one	Can intensify existing MDD	Can precipitate MDD

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

RISK FACTORS:

Completion	Suicide Attempts
<ul style="list-style-type: none"> • 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 	<ul style="list-style-type: none"> • 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:	PERSONAL IMPACT:
<ul style="list-style-type: none"> • 2nd largest cause of disability • Women (15-44 yo) bear greatest burden • Most disabling disease (years lost of <u>healthy, productive</u> life) • Economically, \$14 billion annually in Canada (txt, loss productivity, premature death) 	<ul style="list-style-type: none"> • Relationships • Work/school (loss of productivity of job) • Comorbidity (66%) – anxiety disorder, substance abuse • Suicidal thinking, attempts, completions <ul style="list-style-type: none"> ◦ 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, methyl dopa, procainamide, hydralazine, digoxin
CNS & drugs of abuse	Alcohol, amphetamines, BZDs, barbiturates, cocaine, narcotics, marijuana, phenytoin
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	Psychotherapy
<ul style="list-style-type: none"> • 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) • Tricyclic antidepressants (TCAs) • Reversible inhibitors of monoamine oxidase (RIMA) • Monoamine oxidase inhibitors (MAOIs) • Other: ketamine, herbals/NHPs 	<ul style="list-style-type: none"> • Cognitive behavioral • Interpersonal • Dialectical behavior • Acceptance and commitment <p><i>Also combined with pharmacotherapy</i></p>

ELECTROCONVULSIVE THERAPY:

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

BARRIERS TO ECT:

- Fear of electricity
- Unreasoned prejudice
- Legislative restrictions
- Limited availability of trained professionals and adequate facilities

THERAPEUTIC EFFECTS:

EFFECT ON BRAIN:

- Increase in neurotrophic signalling
- Increase in hippocampal volume

EFFECT ON DEPRESSION:

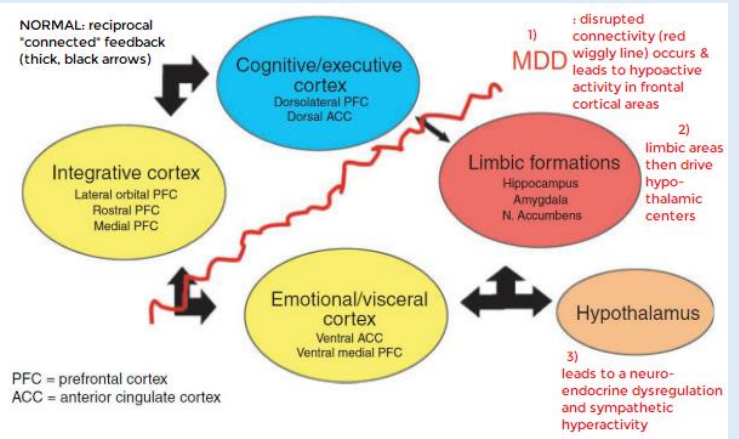
- Rapid relief of severe depression
- Rapid reduction in suicide drive

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

MONOAMINE THEORY OF DEPRESSION:

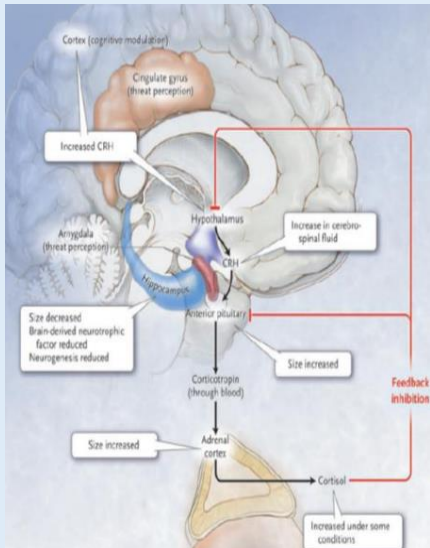
- Abnormality in monoamine NT receptors leads to depression
 - Depletion of monoamine NTs
 - Abnormalities in monoamine NT receptors
 - Problem with signal transduction of NT's message from receptor to other downstream events
- Stems from 3 significant findings:
 - Drugs that deplete biogenic amines (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

CHANGES IN BRAIN FUNCTION & STRUCTURE IN MDD:



- Hyperactivity in VMPFC & LOPFC = ↑ pain, anxiety, tension
- Hypoactivity in DLFC = apathy, ↓ attention, memory & psychomotor activities
- Decreased connectivity between ACC & amygdala
- Hippocampal volume decreased

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

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