DSM-5 CRITERIA FOR MDD:

- 5 (or more) of the following symptoms present during same 2-week period and represent a change from previous functioning
- At least 1 of the symptoms is either #1 or #2

1. Depressed Mood
2. Loss of interest/pleasure
3. Weight/appetite changes
   - Change = > 5% of body weight/month
4. Insomnia or hypersomnia
5. Psychomotor agitation/retardation
6. Fatigue/loss of energy
7. Feelings of guilt/worthlessness
8. Diminished concentration or indecisiveness
9. Suicidal ideation/attempt

- Pneumonic: MSIGECAPS
- Symptoms → significant distress or impairment in daily function
- Symptoms are not secondary to substance use or a general medical condition

MEDICATION CAUSES:

- Acyclovir
- Phenytoin
- BZDs
- BBs
- Anti-histamines
- CCBs
- Isotretinoin
- Opioids
- Varenicline

DISEASE CAUSES:

- Hypothyroidism
- Substance-Use Disorder
- Chronic Illness (diabetes, CVD, arthritis, kidney disease, HIV, lupus, MS)
- Chronic pain

STANDARDIZED RATING SCALES: HAM-D, MADRS, QIDS, **PHQ-9,** BDI

PATIENT HEALTH QUESTIONNAIRE 9:

- 9 item, self-administered scale based on DSM-5 criteria and patient report of sx frequency over **previous 2 weeks**
- Diagnostic Tool and to monitor symptom severity and determine the need for treatment
- Scoring: 20 – 27 = severe depression; 15 – 19 = moderately severe depression; 10 – 14 = moderate depression; 5 – 9 = minimal symptoms; < 5 = symptoms absent

CLINICAL COURSE OF DEPRESSION:

- Symptoms can develop over days to weeks, but may develop suddenly
  - Untreated episodes last ≥ 6 months
- Median time to recovery is 20 weeks with ADEQUATE TXT (4 psychotherapy sessions + 12 weeks Rx)
- 50% will have a chronic or recurrent course of depression; 2 episodes = 70%; ≥ 3 episodes = 90%
- Suicide (lifetime risk untreated = 20%), with each episode the risk of suicide becomes greater
  - Risk factors: IS PATH WARM (ideation, substance use, purposelessness, anger, trapped, hopelessness, withdrawal (social), anxiety, recklessness, mood change (dramatic)

TREATMENT: INITIAL EVALUATION → WEEKS 2-4 (response, adherence, SEs) → WEEKS 4-8 (response) → WEEKS 9-12 (continuation) → MAINTENANCE

ACUTE PHASE (WEEK 0):

- Initial evaluation:
  - Medical, family, and psychiatric hx, previous hospitalizations, suicide attempts
  - Current medications, previous txts
  - Labs (CBC, serum chemistries, thyroid)
  - Psych evaluation (exclude other dx)
  - Safety plan
- Treatment:
  - Pharmacotherapy
  - Psychological Therapies (CBT, IPT)
  - ECT, VNS, rTMS, Bright Light Therapy

ASSESSMENT AT WEEKS 2-4: response, adherence, SEs

- Full response (>50% reduction of sx) = maintain treatment if no tolerability issues
- Partial or no response = increase dose if no issues with tolerability or switch antidepressant

ASSESSMENT AT WEEKS 4-8: response

- Full response: move to continuation phase
- Partial or no response: increase dose or switch or adjunct (continue to assess q2-4 weeks)

CONTINUATION PHASE AT WEEKS 9-12

- Sx remission and no risk factors for reoccurrence = maintain treatment for 6-9 months
- Sx remission with risk factors for reoccurrence = maintain treatment for 2 years
- No sx remission = keep trying to optimize therapy

MAINTENANCE PHASE: duration of therapy indefinite

- Risk of relapse (20-85%)
- Risk factors for re-occurrence:
  - Residual depressive sx
  - Severity of eps
  - Early age of onset
  - Psychosocial stressors
  - Family hx
- 3 or more depressive episodes = life-long treatment

DISCONTINUATION SYNDROME: may occur when suddenly d/c or lower dose; sx = **FINISH:**

- Flu-like symptoms, insomnia, nausea, irritability, sensory changes, headache

NON-RESPONDERS:

- Predictors of remission
- After 2 adequate medication trials, possibility of responding to future trials significantly declines
- Over 30% of pts will have less than satisfactory response to 4 courses of antidepressant pharmacotherapy

RISK FACTORS:

- Comorbid disorders (including substance abuse)
- Inadequate dosage
  - At week 2-4, if pt is tolerating but not responding to med, consider increasing dosage
  - Maximize dosage (SE permitting) before switching
- Inadequate duration
- Incorrect diagnosis
- Non-adherence
- Persistent AE's
- Drug interactions
- Unaddressed psychosocial stressors

ALGORITHM FOR INADEQUATE RESPONSE:

1st line antidepressant
↓
Improvement after 2-4 weeks? → Yes
↓ No

1) Switch to 2nd line agent
2) Switch to AD with superior efficacy
3) Add adjunctive therapy

SWITCH WHEN:

- It is the first antidepressant trial
- Poorly tolerated SEs to initial AD
- No response (< 25% improvement) to initial anti-depressant
- More time to wait for a response (less severe, less functional impairment)
- Patient prefers to switch to another AD

HOW:

- CANMAT guidelines recommends switching to one of the antidepressant with evidence of superior efficacy
- No clear benefit on switching within class or to agent with different MOA
- Cross-tapering (good with novel MOA)
- Direct switch (b/w SSRIs, watch $T_{1/2}$)
- SwitchRx program

ADD ADJUNCTIVE MED WHEN:

- ≥ 2 antidepressant trials
- Initial antidepressant is well-tolerated
- Partial response (>25% improvement) to initial antidepressant in 4-8 weeks
- Specific residual sx or SEs to initial antidepressant that can be targeted
- Less time to wait for a response (more severe, more functional impairment)
- Patient prefers to add on another med

1st line:

- Aripiprazole 2 – 15 mg
- Quetiapine 150 – 300 mg
- Risperidone 1 – 3 mg

2nd line:

- Bupropion 150 – 300 mg
- Lithium 600 – 1200 mg
- Olanzapine 2.5 – 10 mg

TREATMENT OPTIONS:

CHOICE OF AGENT:

- Patient preference
- Prior response
- Safety, tolerability, and adverse effects
- Comorbid disorders
- Potential drug-drug interactions
- PK parameters
- Cost

TREATMENTS WITH SUPERIOR EFFICACY:

Antidepressants that had a 5-6% improvement in treatment response in head-to-heads

Antidepressant	Comparator
Escitalopram	Citalopram Duloxetine Fluoxetine Paroxetine
Mirtazapine	Duloxetine Fluoxetine Fluvoxamine Paroxetine Sertraline Venlafaxine
Sertraline	Duloxetine Fluoxetine Fluvoxamine Paroxetine
Venlafaxin	Duloxetine Fluoxetine Fluvoxamine Paroxetine

TREATMENT OPTIONS:

First-line options		
Class	**Anti-depressant**	**Dose Range**
SSRIs	Citalopram (Celexa)	20 – 40 mg
	Escitalopram (Cipralex)	10 – 20 mg
	Fluoxetine (Prozac)	20 – 60 mg
	Fluvoxamine (Luvox)	100 – 300 mg
	Paroxetine (Paxil)	20 – 50 mg; 25 – 62.5 mg CR
	Sertraline (Zoloft)	50 – 200 mg
SNRI	Desvenlafaxine (Pristiq)	50 – 100 mg
	Duloxetine (Cymbalta)	60 mg
	Venlafaxine (Effexor)	75 – 225 mg
Other	Bupropion (Wellbutrin)	150 – 300 mg
	Mirtazapine (Remeron)	15 – 45 mg
	Vortioxetine (Trintellix)	10 – 20 mg
Second-line options		
TCA	Amitriptyline, clomipramine, others	Varies
SNRI	Levomilnacipran (Fetzima)	40 – 120 mg
MAO_AI	Moclobemide (Manerix)	300 – 600 mg
MAO_BI	Selegiline	
AAP	Quetiapine (Seroquel)	150 – 300 mg
SRI, 5-HT_2 agonist	Trazodone (Desyrel)	150 – 300 mg
SRI, 5-HT_{1A} partial agonist	Vilazodone	
Third-line options:		
MAOI	Phenelzine	
	Tranylcypromine	
MRI	Reboxetine	

SIDE EFFECTS: TABLE ON SLIDE 35

- Sexual dysfunction
- Sedation
- GI (N/V, constipation, dry mouth)
- Increased BP (NE)
- Insonnia
- Urinary hesitancy (NE)
- Anticholinergic (NE, TCA)
- Mania

REVIEW OF CONCOMITANT MEDICATIONS:

- Clinically relevant drug-drug interactions are usually caused by agents that are potent CYP inhibitors
  - Fluoxetine (CYP2D6), paroxetine (CYP2D6), fluvoxamine (CYP1A2, 2C19, 3A4)
- Drug-drug interactions with moderate CYP inhibitors rarely clinically relevant except at higher doses
  - Bupropion, duloxetine, sertraline (CYP2D6)
- Example: duloxetine = metabolized primarily via CYP1A2 pathway
  - Should not be co-administered with drugs that potently inhibit CYP1A2 (cimetidine, ticlopidine, ciprofloxacin)

OTHER TREATMENT OPTIONS:

VAGAL NERVE STIMULATION:

- Adjunctive long-term chronic or recurrent depression for at least 2 years, not responding to at least 4 trials of antidepressants
- Procedure = mild electrical pulses sent to vagus nerve which travels to brainstem → improved mood
- 10 weeks time to response
- Mixed results, invasive, side effects

TRANSCRANIAL MAGNETIC STIMULATION (TMS):

- Treatment for refractory depression
- Magnetic fields used to stimulate regions of the brain involved in mood regulation and depression
- Treatment 5 days a week for 4-6 weeks
- Appears to be effective, however lasting effects are questionable

ELECTROCONVULSIVE THERAPY (ECT):

- 80-90% effective for MDD, with older pts having better outcomes
- Electrodes placed on scalp induce a 1 minute seizure
- Treatment of choice for severe suicidal ideation or food refusal
- SEs include confusion and impaired memory immediately after procedure

SPECIAL POPULATIONS: Pregnancy and Lactation

PREGNANCY:

- Untreated maternal depression is associated with adverse pregnancy outcomes
  - Children of untreated mothers are more likely to require psychiatric care
- Risks of antidepressant medications (although risks are not clearly defined)
  - Paroxetine associated with septal wall defects
  - St. John's Wart contraindicated in pregnancy
- Antidepressant therapy recommended for pregnant patients with mod-severe sx and those with recurrent, severe depression
  - Single medication, at lowest effective dose
  - Fewer metabolites, higher protein binding, fewer drug interactions

LACTATION:

- Risk of untreated post-partum depression must be weighed against infant exposure to breast milk
- Non-pharm therapy recommended for mild-mod depression if possible
- Monotherapy with sertraline or paroxetine (at lowest effective dose)
  - Fluoxetine (long $T_{1/2}$) not recommended

SPECIAL POPULATIONS: Pediatrics and elderly

PEDIATRICS:

- Adult diagnostic criteria applied to children
- May not verbalize feelings of depression
- Present with fewer melancholic symptoms and suicide attempts
- Most predictive factor is a strong family history of MDD
- Risk of depression increases 2-4 fold after puberty (esp. in females)

TREATMENT:

- 2-3 months of supportive psychotherapy
  - If no response, then antidepressants are indicated
- SSRI (**fluoxetine**, citalopram, or sertraline)
  - Fluoxetine has most robust evidence demonstrating that benefits > risks for children aged 8-18 years old
  - Escitalopram is FDA-approved in children with depression older than 12 y/o
- Medication switches happen faster
  - Within 6 weeks instead of usual 8-12 weeks
- Monitor for suicidality (black box warning for adolescents)
  - Safety plans should be developed

ELDERLY:

- May not manifest as sadness!
- Cognitive changes include memory problem and confusion
- Often overlooked in elderly – 25% prevalence in those ≥ 60 yrs
- Disproportionate rate of completed suicides
- Take longer to respond than younger patients

TREATMENT:

- Antidepressants started at lower doses and titrated more slowly
- Medications chosen carefully to minimize drug interactions and side effects
- Monotherapy > polypharmacy
  - Switch instead of augment
- SSRIs = treatment of choice
  - Note risk of SIADH and hyponatremia
- TCAs not recommended due to risk of orthostatic hypotension, anticholinergic effects and drug interactions