L Jia 2021

DEPRESSION GUIDELINES 2016

SECTION 1: DISEASE BURDEN AND PRINCIPLES OF CARE

- Tidbits:
  - 50% of postpartum depression have onset prior to delivery
  - Mixed features found in ⅓ of patients with MDE - more common in younger pt
  - Cognitive dysfunction - disturbed attention, memory, processing speech, EF
  - Specifiers: ESP. MAPS CAMP; Catatonia: 3 SWAMP SEMEN CG (cataplexy grimace)
- MDE - Annual prevalence 4.7%, lifetime prevalence 11.3% (4% and 10% if bipolar excluded)
  - W2 : M1 and prevalence has INVERSE relationship with age; 50% brief (< 3 mo)
- Chronic and episodic course - ⅓ of those in remission will experience recurrence in 3 yrs
- ***Disease burden*** - 2nd leading cause of disability worldwide
  - Loss of productivity due to absenteeism and presenteeism (illness-related loss of productivity while at work)
- ***Medical burden*** **-** MDD associated with heart disease, arthritis, asthma, back pain, COPD, HTN, migraines
  - Depression = independent risk factor for ischemic HD and CV mortality
  - Decreased med adherence and participation in preventative healthcare
  - MDD associated with immune-inflammatory dysfunction → reduced neuroplasticity
- ***Screening*** - inconsistent recommendation - more effective when additional supports are available
  - Recommendation: screening in primary and secondary care setting in individuals with **risk factors**
  - ***PHQ-9 = pt, screen, mild 10, mod 20, severe 30***
  - ***BDI = pt, severity, N 0-7, mild 8-13, mod 14-18, severe 19-22, 23+ very severe***
  - ***HAM-D = clinician, severity; <21 mild, 21-30 mod, 31-40 severe, 41+ extreme***
- ***Basic principles*** - stepped care and chronic disease management model associated with significant improvements in depression outcomes
  - Enhance adherence thru patient education, supported self-management (including behavioural activation, coping skills), and collaborative care systems
  - Further research needed on peer-support service delivery models
- ***Suicidality risk assessment*** **-** every clinical encounter
  - Tools - SADPERSONS, CSSRS (columbia suicide severity rating scale, 6 Qs re: SI, plan, past SA) - **not** reliable in predicting suicide attempts
- ***Measurement-based care*** (sx, fn, SE, QOL) - can improve outcomes, i.e. sx remission, adherence

Clinician-rated	Patient-rated
HAM-D (hamilton depression rating scale) MADRS (montgomery-asberg depression rating scale) WHO-DAS (WHO disability assessment scale) QOLI (quality of life interview)	PHQ-9 (pt health questionnaire) Beck Depression Inventory QIDS-SR (quick inventory for depressive sx, self-rated) SDS (sheehan disability scale)

  - Routine monitoring must include ongoing evaluation of functional impair and QoL
    - Can vary independent of sx
- ***Treatment phases*** - Acute (8-12 weeks) → goal of sx remission and restoration of fn
  - Maintenance (6-24+ months) → goal to return to full functioning, QoL, and prevent recurrence
  - Risk factors for chronic/recurrent episodes:
    - Earlier age of onset, greater # of previous episodes
    - Severity of initial episode (more sx, SI, psychomotor agitation)
    - **Sleep-wake disruption**
    - Comorbid psychopathology (esp PDD/dysthymia)

Table 5. Risk Factors for Depression Screening (Level 3 and 4 Evidence).

Clinical Factors	Symptom Factors
• History of depression • Family history of depression • Psychosocial adversity • High users of the medical system • Chronic medical conditions (especially cardiovascular disease, diabetes, and neurological disorders) • Other psychiatric conditions • Times of hormonal challenge (e.g., peripartum)	• Unexplained physical symptoms • Chronic pain • Fatigue • Insomnia • Anxiety • Substance abuse

Table 7. Risk Factors for Suicide During a Major Depressive Episode (Level 3 Evidence).

Nonmodifiable Risk Factors	Modifiable Risk Factors
• Older men • Past suicide attempt • History of self-harm behaviour • Being a sexual minority • Family history of suicide • History of legal problems	Symptoms and life events • Active suicidal ideation • Hopelessness • Psychotic symptoms • Anxiety • Impulsivity • Stressful life events such as financial stress (e.g., bankruptcy) and victimization Comorbid conditions • Substance use disorders (especially alcohol use disorder) • Posttraumatic stress disorder • Comorbid personality disorders (especially cluster B personality disorders) • Chronic painful medical conditions (e.g., migraine headaches, arthritis) • Cancer

- Family hx psychiatric illness
- Negative cognitions, high neuroticism, poor social support, stressful life events

SECTION 2: PSYCHOLOGICAL TREATMENTS

- Shared components:
  - 1) Goal of tx = alleviation of core sx of depression
  - 2) Careful attention to a specific method to delivery therapy (usually a manual)
  - 3) Focus on the current problems of the pt
  - 4) High levels of activity are expected from the therapist and patient
  - 5) Careful sx monitoring expected (i.e. rating scales)
  - 6) Psychoeducation about illness = frequent component
  - 7) Tx generally time-limited

Indications - depends on:

- Patient attitude and preferences
- Availability of high-quality treatment
- Patients most likely to benefit:
  - M=F, suitable for all ages/education/cultures, depression subtypes
  - In PDD: COMBO and MEDS ONLY are both **>** psychological tx alone
  - Severity of MDD does NOT predict outcomes of tx with meds vs. CBT
    - Magnitude of benefit for psychological tx increases with increased severity
    - Time-course with meds is faster - generally preferred in severe/high risk cases

Impact of comorbid psychiatric and medical conditions on psychological treatments

- Insufficient evidence for formal tx recommendations
- Evidence summary (level 2):
  - Comorbid PD = NEGATIVE prognostic impact on treatment
  - Anxiety = unclear if +/- impact on outcomes, but **CBT** may be more effective than other psychological treatments
  - SUDs = CBT also effective for depressive sx
  - ADHD = CBT can improve depressive and ADHD sx
- Evidence summary:
  - Cancer - depends on type of psychological tx/cancer phase; overall +
  - CV disease - CBT, IPT, PST effective alone or w/ antidepressants
  - MS - all psychological tx effective, esp CBT
  - HIV - CBT (usually group) and IPT
  - Epilepsy, Parkinson's - CBT helpful for depressive sx
  - Migraines - various psychological tx helpful for depressive sx
  - Hep C - psychological tx helpful

Impact of Gender/Age

- More women than men prefer psychological tx over meds
- Psychological tx first-line for **perinatal women** with mild-moderate depressive illness

Therapist factors ("evidence-based therapy relationships", level 3 evidence but **first-line**)

- *Demonstrably effective:* alliance, empathy, collecting pt feedback (standardized scales) ACE

- *Probably effective:* goal consensus, collaboration, positive regard (pt feels respected/appreciated)
- *Promising, insufficient research*: congruence/genuineness, repairing ruptures, managing countertransference
- Also important - therapist supervision/feedback, experience, adherence, ability to be responsive to individual patient differences
    - *Second-line recommendation*: psychological tx delivered by trained/proficient therapists

Choosing a psychological treatment

	First-line	**Second-line**	**Third-line**
Acute	CBT, IPT, BA	MBCT, CBASP Short-term psychodynamic therapy Problem-solving therapy Telephone-delivered CBT/IPT Internet/computer-assisted therapy	ACT, MI Psychodynamic psychotherapy Videoconference psychotherapy
Maintenance	CBT, MBCT	IPT, BA, CBASP	Psychodynamic therapy

- *Summary*: CBT = most established, evidence-based, first-line treatment
    - IPT = alternative first-line in acute MDD
    - MBCT = first-line maintenance tx *adjunctive* to medications
- Individual > group therapy (slightly) for efficacy - but group more available/lower cost
- Level 1 evidence that BRIEF interventions can be effective (i.e. 8 sessions = 16 sessions)
    - No minimum dose
- Select a tx, and follow specific manual
    - Level 3 evidence that more FREQUENT tx sessions (especially at beginning) should be considered

- **CBT**: as effective as antidepressants, and effective for tx-resistant depression
    - CBT + antidepressant **>** either alone
    - Adding CBT to meds increases recovery rate
    - Those who received CBT in acute phase had lower relapse rate than those who d/c meds
        - No difference between CBT vs. those who CONTINUED meds at 1 yr f/up
        - To prevent relapse/recurrence, **CBT** delivered during acute phase offers **BETTER protection than meds** (*i.e. if the patient wants to NOT TAKE meds long-term, offer CBT during acute phase to PREVENT recurrence!*)
    - In maintenance phase, **CBT = meds** for relapse prevention
- **MBCT**: 8-week group tx, teaches pts to disengage from maladaptive cognitive processes
    - Change mindfulness, rumination, worry, compassion, meta-awareness
    - Evidence to support MCBT as **adjunct** to tx as usual, comparable to meds in maintenance
    - May only be efficacious for those w/ <u>greater vulnerability</u> (recurrent depression, unstable remission, hx childhood trauma)
- **IPT**: goal to alleviate suffering, remit sx, and improve functioning
    - In acute phase, IPT = CBT
    - In maintenance phase, IPT + meds > IPT alone
- **Psychodynamic** (short-term and long-term): particular utility if comorbid personality d/o
- **MI:** for pts less likely to engage in or respond to unmodified tx, consider integration of MI
    - Used in conjunction w/ CBT, IPT, or meds to improve engagement/adherence

- **CBASP** (cognitive behavioural analysis system of psychotx)**:** developed specifically for **chronic** depression (*think of this as CBT+IPT*)
    - Cognitive, behavioural and interpersonal strategies to help pts recognitize how maladaptive cognitions/behaviours influence each other, and → negative outcomes
- **ACT:** mindfully increase acceptance of distressing experiences
    - Take an observer perspective, clarify and orient behaviour towards VALUED directions
    - NOT struggle against/control perceived suffering
    - Particular value if comorbid MEDICAL condition
- **BA:** rationale - depression is caused/maintained by escape and avoidance of aversive emotions/stimuli
    - → self-reinforced, prevents positive reinforcement of non-depressive behaviour
    - → longstanding inertia, avoidance, social withdrawal
- **Peer interventions:** self-help groups, peer support
    - SECOND-LINE ADJUNCT (not in chart)
- **PST:** structured, brief, adopt problem-solving attitude and skills to tx MDD
    - Tested mostly in primary care
    - SECOND-LINE acute tx in primary care and geriatric depression
- **Bibliotherapy**: practical utility, useful for those on wait-list, alone or adj, ideally w/ clinician monitoring
- **Internet/computer-delivered therapy**: adherence and efficacy improved if clinician-guided
- **Remote interactive (phone/video/internet) vs. face-to-face** = comparable
- **Combination treatment =** MORE effective than meds/psychological tx alone
    - Offer to those with moderate-severe depression
- **Sequential treatment:** psychological tx AFTER antidepressant tx reduces relapse by 20%
    - Evidence for CBT and MBCT (*note both first-line maintenance!*)
    - CBT or MBCT = FIRST-LINE TX after course of meds (sequential)
    - MBCT = SECOND-LINE **alternative** to long-term maintenance meds

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SECTION 3: PHARMACOLOGICAL TREATMENTS

- Mild MDE - psychoeducation, self-management, psychological treatments
    - Meds can be considered for mild MDD if - patient preference, previous response to AD, or lack of response to non-pharmacological interventions
- Moderate to severe MDE - most 2nd generation AD are first-line
- New meds:
    - Levomilnacipran (S**N**RI - N>S)
    - Vilazodone ("multimodal AD" - SRI, 5-HT1A agonist) - take with food
    - Vortioxetine ("**multi**modal AD" - SRI, 5-HT1A/1B agonist, 5HT1D/3A/7 antagonist)
- ANTI-Depressant effects: 5HT2 ANTAGONIST + Alpha2 AGONIST (*note: this is what mirtazapine does*)

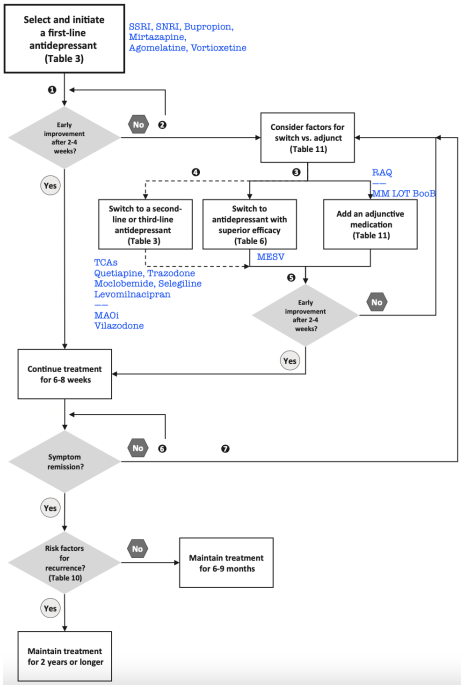
First-line	**Second-line**	**Third-line**
SSRIs: Citalopram, Escitalopram, Fluoxetine, Fluvoxamine, Paroxetine, Sertraline SNRIs: Desvenlafaxine, Duloxetine, Milnacipran, Venlafaxine MT agonists: Agomelatine NDRIs: Bupropion NaSSA: Mirtazapine, Mianserin SRI/multimodal: Vortioxetine	TCAs SNRI: Levomilnacipran AAP: Quetiapine SRI: Trazodone, Vilazodone MAOBi: Selegiline RIMA: Moclobemide	MAOi: Phenelzine, Tranylcypromine NRI: Reboxetine

- **Superior efficacy for mirtazapine, escitalopram, sertraline, venlafaxine (MESV - in this order!)**
  - Agomelatine > Sertraline
  - Citalopram > Paroxetine, Reboxetine
  - **E**scitalopram > Citalopram
  - Fluoxetine > Milnacipran
  - **M**irtazapine > SSRI, venlafaxine
  - Paroxetine, **S**ertraline, **V**enlafaxine > Fluoxetine
- **Summary**: Mirtazapine > Escitalopram > Citalopram > Paroxetine, Sertraline, Venlafaxine > Fluoxetine
- NO evidence that age, sex, race or ethnicity predicts outcomes
- NO differences in efficacy re: escitalopram, sertraline and venlafaxine for melancholic/atypical/anxious ft
- **Psychotic depression**: antidepressant + antipsychotic > monotherapy
  - No evidence re: duration of combination once psychosis resolved
- **Mixed features**: lurasidone or ziprasidone monotx > placebo
  - (*memory aid - these are in the bipolar guidelines!)*
- **Cognitive dysfunction:** SSRIs, bupropion, duloxetine, moclobemide may improve **learning/memory/EF**
  - Vortioxetine had largest effect on processing speed, executive control, and cognitive control
  - Duloxetine had largest effect on delayed recall
- **Sleep:** Agomelatine, mirtazapine, trazodone, quetiapine
- **Somatic sx:** SNRIs
- **Function:** NO meds demonstrate superior functional improvement
- **Tolerability:** clinical data NOT reliable for sexual dysfunction
  - Bupropion less than other AD
  - Generally lower in agomelatine, bupropion, mirtazapine, vilazodone and vortioxetine
- **Suicidality:** REDUCED risk of SI/acts in those age 25-64
  - **OR 1.92** for SI and attempts among adolescents → suggest close monitoring
- **Serious adverse effects**:
  - Generally low risk of TdP
  - Falls and #: Long-term use of SSRI (highest risk of # in first 6 weeks)
  - HypoNa+: SSRI, esp elderly with other RF
  - Inhibit platelet aggregation: SSRIs alter platelet 5HT receptors
    - Increase risk of GI bleed, esp with NSAIDs (risk x2)
    - Acid-suppressing drugs can reduce GI bleed risk
  - Elevated liver enzymes: for agomelatine
- **Formulations: NO** difference in tolerability; possibly lower adherence with IR
- **Drug-drug interactions:**
  - SUBSTRATES:

Table 5. Recommendations for Clinical Specifiers and Dimensions of Major Depressive Disorder.

Specifiers/ Dimensions	Recommendations (Level of Evidence)	Comments
With anxious distress[a]	• Use an antidepressant with efficacy in generalized anxiety disorder (Level 4)	• No differences in efficacy between SSRIs, SNRIs, and bupropion (Level 2)
With catatonic features[a]	• Benzodiazepines (Level 3)	• No antidepressants have been studied
With melancholic features[a]	• No specific antidepressants have demonstrated superiority (Level 2)	• TCAs and SNRIs have been studied
With atypical features[a]	• No specific antidepressants have demonstrated superiority (Level 2)	• Older studies found MAO inhibitors superior to TCAs
With psychotic features[a]	• Use antipsychotic and antidepressant cotreatment (Level 1)	• Few studies involved atypical antipsychotics
With mixed features[a]	• Lurasidone[b] (Level 2) • Ziprasidone[b] (Level 3)	• No comparative studies
With seasonal pattern[a]	• No specific antidepressants have demonstrated superiority (Level 2 and 3)	• SSRIs, agomelatine, bupropion, and moclobemide have been studied
With cognitive dysfunction	• Vortioxetine (Level 1) • Bupropion (Level 2) • Duloxetine (Level 2) • SSRIs (Level 2)[b] • Moclobemide (Level 3)	• Limited data available on cognitive effects of other antidepressants and on comparative differences in efficacy
With sleep disturbances	• Agomelatine (Level 1) • Mirtazapine (Level 2) • Quetiapine (Level 2) • Trazodone (Level 2)	• Beneficial effects on sleep must be balanced against potential for side effects (e.g., daytime sedation)
With somatic symptoms	• Duloxetine (pain) (Level 1) • Other SNRIs (pain) (Level 2) • Bupropion (fatigue) (Level 1) • SSRIs[b] (fatigue) (Level 2) • Duloxetine[b] (energy) (Level 2)	• Few antidepressants have been studied for somatic symptoms other than pain • Few comparative antidepressant studies for pain and other somatic symptoms

        - 1A2 - Agomelatine, Clozapine, Duloxetine, Olanzapine, Risperidone CARD OR
            - Avoid inhibitors - Cimetidine, Ciprofloxacin
        - 2D6 - Aripiprazole, Olanzapine, Risperidone, Vortioxetine A OR
        - 3A4 - Aripiprazole, Clozapine, Lurasidone, Haldol, Levomilnacipran, Quetiapine, Vilazodone, Tamoxifen, MMT, HIV meds CHALQ
            - Avoid inhibitors - Ketoconazole
    - INHIBITORS:
        - Fluoxetine and Paroxetine are POTENT (-) of 2D6
        - Fluvoxamine is POTENT (-) of 1A2, 2C19, 3A4
        - 1A2 - Fluvoxamine
        - 2D6 - Bupropion, Fluoxetine, Paroxetine, Duloxetine, Sertraline = Big Friggin Problem DudeS
        - 2C19, 3A4 - Fluvoxamine
    - P-gp is part of BBB - NO evidence of clinically relevant interactions



- **Pharmacogenomics:** not routinely recommended
    - Helpful to detect poor/ultrarapid metabolizers
- Early improvement (20-30+% reduction from baseline, rating scale, after 2-4 weeks) → correlated with response and remission at 6-12 weeks
    - Lack of early improvement → predicts non-response/remission
- **Treatment duration:** Cont meds for 6-9 mo after achieving remission
    - If + risk factors for recurrence, **extend tx to 2+ years**
        - Frequent, recurrent, difficult to treat, severe, or chronic episodes
        - Presence of comorbid psych/medical issues or residual sx
- **Discontinuation** = FINISH (flu-like sx, Insomnia, Nausea, Imbalance, Sensory disturbance, Hyperarousal)
    - Occur in 40% when AD stopped abruptly, worse in IR meds (paroxetine, venlafaxine, FLUVOX)

Algorithm:

First line	Second line	Third line
Risperidone Aripiprazole Quetiapine RAQ	Brexpiprazole Olanzapine Bupropion Mirtazapine Lithium Modafinil T3 MM LOT BooB	TCAs Ziprasidone Stimulants Ketamine = experimental Pindolol = NR

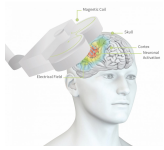
- INSUFFICIENT evidence to differentiate between monotx switch within SSRI or to non-SSRI
    - Augmenting with atypical antipsychotic MORE effective than antidepressant monotx
- **Adjuncts:**
    - **AAP** had most consistent evidence for efficacy in TRD
    - Combo of antidepressants at initiation of tx NOT recommended
    - Single doses of IV ketamine have rapid antidepressant effects in TRD
    - Patients who tolerated citalopram with partial response MORE likely to benefit from adjunct vs. switch -
    - **NO evidence to support specific adjuncts for specific sx/side effects**

- **SWITCH vs ADJUNCT**
    - **Switch** → first AD trial, initial AD not well tolerated/no response, more time to wait for response (less severe), patient preference
    - **Adjunct** → 2+ AD trials, initial AD well-tolerated/partial response, specific residual sx/SE of the initial AD that can be targeted, less time (more severe), pt preference
- **For TRD:** dx re-evaluation, consideration of past med trials, rational use of adjuncts, d/c meds that are not helpful, careful monitoring of sx/SE/function

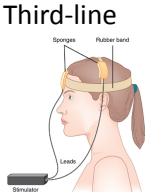
- **Persistent/chronic depression:** sertraline > imipramine, moclobemide > fluoxetine
    - Chronic course may require chronic disease management approach (less emphasis on remission, more on function and QoL with non-med strategies)

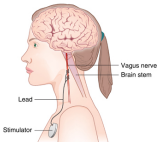
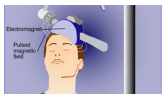
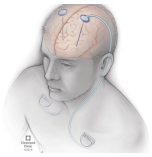
SECTION 4: NEUROSTIMULATION TREATMENTS

	Description	Treatment parameters	Effectiveness and SE

Repetitive transcranial magnetic stimulation (rTMS) First-line (pts who have failed 1+ AD) 	• Powerful, focused magnetic field pulses → electrical current in neural tissue via inductor coil on scalp
	• Mechanism unclear
	• Usually added to antidepressant regimen
	
	• Daily, 5x/week
	• Initial course 20 to 30 sessions
	• Maintenance rTMS PRN to maintain response
	• High frequency 5-10 Hz (excitatory)
	• Low frequency 1-5 Hz (inhibitory)
	• 2-10 second trains at 10-60 second intervals, in 15-45 min sessions
		Site:
		• MRI most precise for coil navigation, scalp-based most common
		  ○ High F to Lt-DLPFC
		  ○ Low F to Rt-DLPFC
		  ○ 2nd line: B/L, TBS
		  ○ 3rd line: High F B/L DMPFC
		Intensity:
		• Based on resting motor threshold (minimum to elicit muscle twitches at relaxed upper/lower extremity visually or by EMG)
		• 110-120% RMT, 70-80% for theta-burst stimulation
		"Left-side depressed, want high F"
			Effectiveness:
			• Acute: ½ respond, ⅓ remit
			• Without maintenance tx, relapse is common - avg 120 days
			• Insufficient evidence for spp schedule
			• LESS effective than ECT
			
			Side effects:
			• Scalp pain, transient headache
			• Most serious - seizure induction
			
			Contraindications:
			• Hx Seizure
			• Metallic hardware (except PO)
			• Relative - Cardiac pacemaker, ICD, hx epilepsy, brain lesion

Electroconvulsive therapy (ECT) First-line in some situations, second-line	• Mechanism unclear, likely sz → change in NT, neuroplasticity, connectivity, increased BDNF
	• BF/RUL 1st line, BT 2nd line
	• Index course: 2-3x/week, 6-15 tx
	
	Indications for first-line tx in MDD:
	• Acute SI, psychotic ft, TRD
	• Repeat med intolerance
	• Catatonia, pregnancy
	• Rapidly declining physical status
	• Pt preference, past good response
	
	• NON-response predicted by degree of resistance to previous treatments
	• HIGHER response in pts who are older, psychotic ft, shorter episode duration, less severe MDD
	• Maintenance: meds commonly used after acute tx course
	• Continuation ECT is safe and effective - usually weekly x 4 weeks (4 tx) → biweekly x 8 weeks (4 tx) → monthly
	• Insufficient evidence for post-ECT psychotherapy
		Site: BT, BF, RUL
		Intensity:
		• BL 1.5-2x ST, RUL 5-6x ST
		• Brief pulse first-line
		• Ultra brief pulse second line; less short-term cognitive impair but slower speed of improvement
		
		• 1st line - BP RUL, BP BF
		• 2nd line (if no response after 4-6 treatments) - UBP RUL, BP BT
		
		Meds during ECT:
		• Concurrent meds may IMPROVE outcomes
		• Lamotrigine least problematic of the anticonvulsants
		
		Maintenance meds post-ECT:
		• Use an antidepressant that has NOT been tried prior to ECT
		• OR nortriptyline + Li
		• OR venlafaxine + Li
			Effectiveness:
			• Acute: 70-80% respond
			• High relapse/recurrence after acute course
			
			Side effects:
			• Headache, muscle soreness, nausea, manic switch
			• Transient disorientation, retrograde and anterograde amnesia
			• Higher risk of cognitive issues:
			  ○ Pre-existing cog impair, older
			  ○ BT, brief pulse, suprathreshold
			  ○ 3x a week
			  ○ Concomitant Lithium
			  ○ High doses of GA
			• Mortality **1/73 000**
			
			Contraindications:
			• No absolute
			• Riskier - space-occupying lesion, recent cerebral hemorrhage, increased ICP, unstable vascular aneurysm/malformation, pheochromocytoma, Class 4 or 5 anesthesia risk

Transcranial direct current stimulation (tDCS) Third-line 	• Continuous low-amplitude electric current to specific cortical region w/ scalp electrodes • Repeat use → neuroplasticity, long-term potentiation/depression • + = ease, low cost, portable, can combine with other tx, low SE	• Minimum 2mA x 30min/d x 2 weeks • May enhance antidepressants or psychotherapy	Effectiveness • Mixed results - third-line Side effects • Well-tolerated; skin reddening, itching, burning, heat, tingling

Vagus nerve stimulation (VNS) Third-line 	• Implantable pulse generator, connected to vagus nerve → modulates many parts of the brain • Treatment parameters unclear - medium and high stimulation better	•	• Approved by FDA as adjunct for those who have failed 4+ AD • Response rate ~30% • Longer term = better <u>Side effects:</u> • Voice alteration, dyspnea, pain, increased cough
Magnetic seizure therapy (MST) = Investigational 	• Non-invasive, uses electromagnetic induction to elicit seizure • Current via coil → magnetic field generated → reaches brain (unimpeded) → depolarize → sz • Also uses GA and ventilation; possibly less cog dysfunction than ECT • 2-3x/week x 12 treatments	• Coil placed at vertex • 100 Hz, PW 0.2-0.4 ms, stimulation for 10 seconds	• Similar effectiveness to ECT • Lower rates of headaches, muscle aches, amnesia, reorientation time
Deep brain stimulation (DBS) = Investigational 	• INvasive implant of electrodes under MRI guidance, connected to IPG • Program PW, frequency, amplitude • Indications: PD • Target: subcallosal cingulate **SCC**, ventral capsule/striatum, nucleus accumbens, medial forebrain bundle		• Response 86%, remission 57% • Antidepressant effects of SCC DBS accrue over months/years <u>Side effects:</u> • RElated to procedure • No worsening of neuropsych performance • Depend on site

SECTION 5: COMPLEMENTARY AND ALTERNATIVE MEDICINE TREATMENTS

Light therapy

- 10,000 lux x 30min daily for up to 6 weeks
    - Response seen within 1-3 weeks
- Mechanism: Alteration of circadian rhythms, and modulation of serotonin and catecholamine systems
- Well tolerated; SE = eye strain, headache, agitation, nausea, sedation
- Indicated in mild-moderate MDD (second line, mono or adj) and seasonal depression (first line)

Sleep deprivation

- Keep patient awake up to 40 hrs total, divided 2-4 times over 1 week
- Mechanism: Increased NT systems, synaptic potential, glial signalling
- Relapse after d/c is rapid
- More effective when combined w/ sleep-phase advance
- SE = daytime sleepiness; C/I = epilepsy
- Third line adjunct for moderate-severe MDD (combine with other chronotherapeutic techniques)

Exercise

- 30+ minutes supervised moderate-intensity exercise, 3+ times/week x 9+ weeks
- Unclear about long-term benefit
- First-line for mild-moderate MDD, second-line adj for moderate-severe MDD

Yoga

- Mechanism: Increased dopamine and GABA turnover, HPA axis regulation, and normalize HR variability

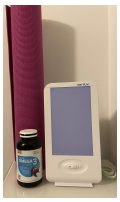
- 2-4 sessions/week x 2-3 months
- Second-line adjunct for mild-moderate MDD

Acupuncture

- Fine needs inserted in specific physiological points - modulate nervous, hormonal and immune systems
- 20-30 mins x 10-13 sessions (from daily to weekly intervals)
- Generally well-tolerated; SE = headache, bleeding, bruising, skin irritation, syncope
- Third-line adjunct for mild-moderate MDD

Natural health products

- **SJW:** direct effect on serotonin receptors, MAO inhibition, and neuromodulation
  - Comparable efficacy to antidepressants
  - SE: GI upset, headache, skin irritation, photosensitivity, dry mouth; risk of SS and hypomania when used with antidepressants
- **Omega-3 FA:** EPA > DHA; dosing 1-2g of both daily x 4-16 weeks
  - Careful if on anticoagulants or antiplatelets
- **SAM-e**: natural substrate in body, methyl donor ⟶ modulates monoamine neurotransmission
  - Well tolerated, SE: GI upset, insomnia, sweating, headache, irritable, tachycardia, fatigue
- **DHEA:** converted to sex hormones ⟶ modulates monoamine and glutaminergic neurotransmission
  - SE: hirsutism, acne, HTN, liver damage, mania, prostatitis, breast cancer

	First-line	Second-line	Third-line	NOT recommended
Mild to moderate	Monotherapy Exercise St. John's Wort 	Monotherapy Light therapy Omega 3  Adjunct Light therapy Yoga Omega 3 SAM-e 	Monotherapy Acetyl-L-carnitine Saffron DHEA Adjunct Acupuncture Saffron Folate Lavender	Inositol Tryptophan Roseroot
Moderate to severe		Adjunct Exercise St. John's Wort Omega 3 SAM-e  	Adjunct Sleep deprivation	

SECTION 6: SPECIAL POPULATIONS

CHILDREN AND YOUTH

Initial Approach

- Use standardized depression screening tool
- Use semi-structured diagnostic approach - i.e. Kiddie Schedule for Affective Disorders, K-SADS
- Presenting symptoms may differ:
    - Adolescents - More hypersomnia, less appetite/weight change, fewer psychotic sx than children
- Supportive clinical care may be sufficient - psychoeducation, active listening, lifestyle changes

	First-line	**Second-line**	**Third-line**
Initial treatment	CBT IPT Internet-based psychotherapy (if mild and in-person not possible)	Fluoxetine Escitalopram CItalopram Sertraline	Venlafaxine TCA (adolescents only)
If minimal or no response	Add SSRI to psychotherapy	Switch to another SSRI	Venlafaxine TCA (adolescents only)
Treatment resistant	SSRI + psychotherapy	Switch to another SSRI	Venlafaxine TCA (adolescents only) ECT (12+ only) rTMS

Psychotherapy

- Relapse prevention - no difference between meds vs. psychotherapy
    - CBT for suicide prevention + meds → greatest improvements in depressed youth with recent SA
- NO clear advantage for meds vs. psychotherapy in treating C&A with non-tx-resistant MDD

Medications

- Antidepressant-treated C&A had lower depression severity scores and higher remission rates
- NO evidence for Paroxetine and MAOis
- AVOID citalopram if congenital long QT syndrome
- Marginal evidence for TCA in adolescents only
- Caution in congenital heart disease or hepatic impairment
- **Monitoring** - weekly x 4 weeks, then q2 weeks x 1 month, then after 12 weeks of tx (7x in first 3 mo)
    - Continue low dose for **4 weeks** until increase
    - If partial response at 12 weeks despite adequate dose, change treatment
- **Duration** - if no hx MDD, continue for 6-12 months
    - Continue for **1+ year** if 1+ severe/chronic episode, or 2+ depressive episodes
- **Tx-resistance**
    - TORDIA study: Adequate course with initial SSRI, if minimal response (<20%) → another SSRI
        - Venlafaxine had equal efficacy, but higher rate of self-harm in those with SI
        - If SSRI-resistant, combining meds + therapy decreases # days with depression
        - Remission from MDD associated with reduction in ADHD and ODD sx
- **Comorbidity** - treating depression may reduce comorbid disorder sx
    - Limited evidence for **fluoxetine** in depressed youth with mild-moderate ETOH u/d
- **Safety -** Health Canada: NO approved antidepressants for those <18 years
    - FDA: **Fluoxetine approved for 8+ years old; Escitalopram for 12+ years old**
    - Black box warning for those **<25 yrs** - 1.5-2x risk of increased SI/behaviours (not death)
        - Applies to newer antidepressants
        - NO relationship between AD and suicide deaths

- OR 1.92 of suicidal acts with SSRI exposure in adolescents
    - Reduced risk in older adults

PERINATAL DEPRESSION

- During pregnancy and first year postpartum
- DSM-5 def'n - during pregnancy and 4 weeks postpartum; 40% of postpartum depr begins during pregnancy
- **Principles of management**
    - Discussion about pregnancy intent and safety of treatments for all depressed women
    - Balance risk of fetal/infant exposure during pregnancy/lactation vs. risk of untx depression

Treatment in pregnancy

- Untreated MDE associated with: poorer nutrition/prenatal care, smoking, substance use
    - Poor OB outcomes, small for gestational age neonates, NICU admission, neonatal complications, impaired bonding, infant sleep difficulties, mild developmental delay, cognitive/behavioural/emotional problems in offspring
- Paroxetine and clomipramine - increased risk of fetal CV malformations
    - Only consider if hx good response or ongoing stability on these meds
    - NOT Doxepin (passes thru breast milk), MAOis (many interactions)
- Given the need for rapid tx in pregnancy, interventions previously effective worth discussing as second-line strategies as long as they are NOT C/I
- Continue meds x 6-12 months after remission in low-risk pts (longer if higher risk of relapse)
- **Risk of antidepressants in pregnancy**
    - Paroxetine - OR 1.5 for CV malformations
    - Clomipramine, Fluoxetine - small risk of congenital malformations
    - Gestational SSRI use - OR 1.5 for spontaneous abortion
    - If exposed to SSRI in 3rd ™, risk of **neonatal adaptation syndrome** (15-30% of infants)
        - Jittery, irritable, tremor, respiratory distress, excess crying
        - Highest risk with **paroxetine, venlafaxine, fluoxetine**
    - If exposed in late pregnancy, risk of **persistent pulmonary HTN of newborn (PPHN)**

Postpartum Depression

- Successful tx can reduce risk of impaired attachment, and cognitive/emotional/behavioural problems
- **Antidepressant risks:**
    - RID <10% = safe; ALL SSRI/SNRI meet this criteria
        - Sertraline, fluvoxamine, paroxetine have LOWEST RID
        - Nortriptyline has low RID, good choice if wanting TCA
    - Exposure in breastfed infants 5-10% LOWER than in utero
    - Higher serum level if preterm, liver/kidney impair
    - Specific medication risks:
        - Fluoxetine - long t1/2
        - Paroxetine - risk of CV malformations in subsequent pregnancies
        - Doxepin - adverse reactions in breastfeeding infants
- **Severe PPD:** meds FIRST line, with/without psychotherapy
    - ECT can be first line if severe and okay to breastfeed

Perimenopausal Depression

- Def'n: starts when menstrual cycles become +/- 7 days than usual → early postmenopausal years
- Increased risk of depression (recurrence and new-onset)
- Hot flashes and night sweats = independent predictors of periM depression
- **Antidepressant medications:**
  - Only Desvenlafaxine specifically evaluated through RCT
  - Recommendations do not differ from general adult population
- **Hormonal agents:** 2nd line monotx/adjunct if no C/I to hormonal therapy
- **Non-pharmacological options:** CBT

	First-line	**Second-line**	**Third-line**
Pregnancy If severe: Pharmacotherapies each move up one recommendation line; psychotherapy and CAM NR; ECT still 3rd line	Mild to moderate: CBT IPT Severe: Escitalopram Citalopram Sertraline +/- CBT or IPT	Escitalopram Citalopram Sertraline Severe: Other SSRIs Newer ADs TCAs Consider ECT	Structured exercise, acupuncture, light therapy NDRI - Bupropion SNRI - Desvenlafaxine, Duloxetine, Venlafaxine SSRI - Fluoxetine, Fluvoxamine (NOT paroxetine) TCAs - caution with clomipramine ECT (severe, psychotic, TRD), rTMS Internet CBT (therapist-supported), mindfulness-based CBT, supportive psychotherapy, couples therapy, PDT, SSRI + CBT/IPT
Breastfeeding If severe: Pharmacotherapies each move up one recommendation line; psychotherapy and CAM NR; ECT still 3rd line	CBT IPT	Escitalopram Citalopram Sertraline +/- CBT or IPT	Structured exercise, acupuncture, internet CBT (therapist-supported), behavioural activation NDRI - Bupropion SNRI - Desvenlafaxine, Duloxetine, Venlafaxine **NaSSA - Mirtazapine (a2ant->inc NE and 5HT; 5HT2A,2c,3 ant, h1 ant; moderate a1 ant)** SSRI - Fluoxetine, Fluvoxamine, Paroxetine TCAs - Nortriptyline most evidence; EXCEPT Doxepin ECT (severe, psychotic, TRD), rTMS, light therapy Mindfulness-based CBT, supportive psychotherapy, couples therapy, PDT
Perimenopausal	Desvenlafaxine CBT	Transdermal estradiol SSRI - Citalopram, Escitalopram (*lower evidence for fluoxetine, paroxetine, sertraline*) SNRI - Duloxetine, Venlafaxine NaSSA - Mirtazapine Quetiapine Omega 3 FA	Mindfulness-based CBT, supportive psychotherapy

Late life depression (Adults 60+ years old)

- Late-ONSET depression has worse prognosis, chronic course, high relapse, more medical comorbidity, cognitive impair and mortality (than earlier onset MDD that recurs in late life)
- Vascular depression hypothesis: CVD affects fronto-striatal circuitry → cognitive and executive dysfunction → predispose/ppt/perpetuates depressive sx

- **Non-pharmacological treatment -** Some evidence for **<u>problem-solving therapy</u>**
- **Pharmacological treatment**
    - Aging → decreased absorption, modified bioavailability, increased half-life of lipid-soluble drugs, and increased relative [ ] of water-soluble drugs
    - Bone loss, SS, EPS, NMS more common
    - LONGER antidepressant trials required in LLD - **10-12 weeks**
    - Executive dysfunction associated with poor antidepressant tx response
        - Vascular depression possible early manifestation of dementia
    - Antipsychotics can be considered in select elderly pts
- **Approach** - stepwise
    - IMPACT and PROSPECT studies - stepwise > usual care

	First-line	**Second-line**	**Third-line**
LLD	*Level 1 evidence:* Duloxetine, Mirtazapine, Nortriptyline *Level 2 evidence*: NDRI - Bupropion SSRI - Citalopram, Escitalopram, Sertraline SNRI - Desvenlafaxine, Duloxetine, Venlafaxine Vortioxetine	<u>Switch to:</u> Nortriptyline Moclobemide, phenelzine Quetiapine Trazodone Bupropion <u>Combine with:</u> Aripiprazole Lithium Methylphenidate	<u>Switch to:</u> Amitriptyline Imipramine SSRI + NDRI SNRI + NDRI SSRI + SNRI

Table 7. Prevalence of Adverse Events among Newer Antidepressants: Unadjusted Frequency (%) of Common Adverse Events as Reported in Product Monographs.

	Nausea	Constipation	Diarrhea	Dry Mouth	Headaches	Dizziness	Somnolence	Nervousness	Anxiety	Agitation	Insomnia	Fatigue	Sweating	Asthenia	Tremor	Anorexia	Increased Appetite	Weight Gain	Male Sexual Dysfunction
Citalopram	21		8	19				3	3	2		5	11		8	4			9
Escitalopram	15	4	8	7	3	6	4	2	2		8	5	3		2		2	2	10
Fluoxetine	21			10			13	14	12		16		8	9	10	11			2
Fluvoxamine	37	18	6	26	22	15	26	2	2	16	14		11	5	11	15			1
Paroxetine	26	14	11	18	18	13	23	5	5	2	13		11	15	8		1		16
Sertraline[a]	26	8	18	16	20	12	13	3	3	6	16	11	8		11	3	1		16
Desvenlafaxine[b]	22	9		11		13	4	<1	3		9	7	10		2				6
Duloxetine	20	11	8	15		8	7		3		11	8	6		3				10
Levomilnacipran	17	9		10	17	8			2		6		9						11
Milnacipran	12	7		9	10				4		7	3	4		3				
Venlafaxine IR	37	15	8	22	25	19	23	13	6	2	18		12	12	5	11			18
Venlafaxine XR	31	8	8	12	26	20	17	10	2	3	17		14	8	5	8			16
Agomelatine[c]	C	C	C		C	C	C		C		C	C	C						
Bupropion SR[d]	11	7	4	13	28	7	3	5	5	2	8		2	2	3				
Bupropion XL	13	9		26	34	6			5	2	16				3				
Mirtazapine		13		25		7	54							8	7		17	12	
Moclobemide	5	4	2	9	8	5	4	4	3	5	7	3	2	1	5				
Vilazodone[e]	24		29	7	14	8	5				6	3					3	2	5
Vortioxetine[f]	23	4	5	6		5	3				3	3	2						<1

When data from multiple doses were reported separately, the data from the minimum therapeutic dose were used (indicated by footnotes). Data sources and references are available in Supplemental Table S3. Clear cells represent 0% to 9%; shaded cells, 10% to 29%; and black cells, 30% and higher.
[a]Data from all indications.
[b]Data from 50-mg dose.
[c]C, common effects, ≥1% and <10%.
[d]Data from 100- to 150-mg dose.
[e]Data from 40-mg dose.
[f]Data from 10-mg dose.