CANMAT MDD 2023

Depression Guidelines

Slides: B Chow
Updates: A Chhabra 2026

Contents

1 What are Important issues for Assessment and Diagnosis?

(2016 Guidelines) Disorder Classification

- DSM-IV-TR
  - Bereavement exclusion **eliminated**

- DSM-5
  - **Persistent Depressive Disorder**
    - Includes chronic MDE + dysthymic disorder
  - **Disruptive Mood Dysregulation Disorder**
    - Age 6-18, severe + recurrent temper outbursts, uncontrollable, irritability
  - **Premenstrual Dysphoric Disorder**
    - Serious form of PMS (intense emotional sxs, final week before menses)

(2016 Guidelines) Disorder Classification

Table 3. Summary of Changes from DSM-IV-TR to DSM5	
DSM-IV-TR	*DSM-5*
Old MDD episode specifiers • With postpartum onset	New MDD episode specifiers • **With anxious distress** • **With mixed features** • **With peripartum onset** • **Suicidality**
Bereavement • Bereavement exclusion	Bereavement • **No bereavement exclusion**
Premenstrual dysphoric disorder • In the appendix	Premenstrual dysphoric disorder • **Now included** as diagnosis
Dysthymia, "double depression" • MDE superimposed on dysthymia	Persistent depressive disorder • **Can have full MDE criteria** • **Dysthymia when full MDE not met**

1.a. Risk Factors

Table 1.1. Examples of Risk Factors for Major Depressive Disorder	
Static, nonmodifiable risk factors	*Dynamic, potentially modifiable risk factors*
• **Female sex** • **Family history of mood disorders** • **History of adverse childhood events/maltreatment** • **Death of a spouse**	• **Chronic and nonpsychiatric medical illnesses** • **Psychiatric comorbidities especially anxiety disorders** • **Alcohol and substance use disorders** • **Insomnia, night shift work** • **Periods of hormonal changes (i.e., puberty, pregnancy, perimenopause)** • **Recent stressful life events** • **Job strain/income inequality** • **Bereavement** • **Peer victimization/bullying/cyberbullying** • **Gender dysphoria** • **Sedentary lifestyle/screen time**

1.b. Screening

- Recommendation same as 2016
  - ***RECOMMENDATION***
    - **Screening pts with risk factors** in primary/secondary settings
    - If available resources + diagnostic/management services

1.c. Screening Tools

- PHQ-2
  - In past 2 weeks, score of 0-3 | score **≥ 2** = positive
  - Asks about feeling depressed/down/hopeless
  - Asks about experiencing anhedonia/lack of

- PHQ-9
  - In past 2 weeks, score of 0-3 | score **≥ 10** = positive
  - can use if PHQ-2 was positive
  - NOT diagnostic

1.d. Factors for Assessment and Diagnosis

- Comprehensive diagnostic assessment
  - Supplemented by collateral when possible
  - Screen for childhood maltreatment and/or stressful traumatic experiences in sensitive manner

1.d. Factors for Assessment and Diagnosis

- Differential
  - Should include psychiatric and non-psychiatric medical causes
  - Medical workup = CBC, TSH to rule out **anemia** and **thyroid dysfunction**
  - EEG, ECG, neuroimaging **NOT** routinely recommended
    - ECG → history of cardiovascular disease and/or using medications that prolong QTc
    - Neuroimaging →
      1) Neurologic signs, new onset or persistent cognitive impairment, or sudden changes in mood, behaviour, or personality
      2) Can also consider in new onset late-life depression to rule out cerebral events or rother structural abnormalities (i.e., tumour, metastasis)

1.e. Specifiers and Symptom Dimensions

- Episode and course specifiers
  - Several from DSM-IV-TR → melancholic, atypical, psychotic, and catatonic
  - New for DSM-V-TR → anxious distress and mixed features

- Chronic MDE
  - Now classified as a specifier for persistent depressive disorder (PDD) = 2+ depressive symptoms for 2+ years
  - Compared to episode MDEs, those with PDD show lower response rates + less likelihood of achieving remission → use DTD framework

DSM5 Specifier	Key Features
Anxious distress	Feeling keyed up or tense, restless, worried, something awful may happen, afraid of losing control
Mixed features	Elevated mood, inflated self-esteem or grandiosity, more talkative, racing thoughts, increased energy and activity, decreased need for sleep, risky and impulsive activities
Melancholic features	**Nonreactive mood,** anhedonia, **weight loss**, guilt, psychomotor retardation/agitation, morning worsening of mood, early morning awakening, excessive/inappropriate guilt
Atypical features	**Reactive mood**, oversleeping, **overeating,** leaden paralysis, interpersonal rejection sensitivity
Psychotic features	Hallucinations or delusions
Catatonic features	Catalepsy (waxy flexibility), catatonic excitement, negativism or mutism, mannerisms or stereotypes, echolalia or echopraxia
Seasonal pattern	Regular onset and remission of depressive episodes during a particular seasons (usually fall/winter onset)
Peripartum onset	Onset of depressive episode during pregnancy or within 4 weeks postpartum

Dimension	Key Features
Cognitive dysfunction	Disturbances in attention, memory, processing speed, executive functioning and emotional processing
Sleep disturbance	Insomnia or hypersomnia, circadian rhythm disturbance
Somatic symptoms	Headaches, body aches, fatigue, anergia

1.f. Access for Equity Deserving Groups

- Racialized, indigenous, gender minority, and certain religious groups
  - Lack of access and underutilization
  - Use screening, culturally competent care, collaborative care, and digital health interventions to improve access to and quality of mental health care

2 What are the Principles for Depression Management

2.a. Phases and Objectives of Treatment

- 2-phase model
  - Acute → maintenance
  - Relapse/recurrence

Table 2.1. Summary of Phases of Treatments, Objectives, and Actions

Phase	*Duration*	*Objectives*	*Actions*
Acute	• Approximately **8-16 weeks**, until **symptom remission**	• Address **patient safety**	• Assess suicide and safety risks • Define treatment settings (inpatient vs outpatient) • Develop a safety plan
		• Treat to **symptom remission** and **functional improvement**	• Establish rapport and therapeutic alliance • Psychoeducation and self-management • Select and implement evidence-based treatment(s) • Monitor tolerability, adherence, response, and side effects

2.a. Phases and Objectives of Treatment

Table 2.1. Summary of Phases of Treatments, Objectives, and Actions

Phase	*Duration*	*Objectives*	*Actions*
Maintenance	• Approximately **6-24 months** following the acute phase (or longer if clinically indicated)	• **Maintain** symptomatic **remission** • **Restore functioning** and **QOL** to premorbid levels • **Prevent recurrence** • **Consolidate gains** during treatment discontinuation	• Maintain evidence-based adjustments to treatment(s) • Address residual symptoms • Psychoeducation and self-management • Treat comorbidities • Consider addition psychosocial interventions • Psychoeducation to identify symptoms early for early intervention • Monitor for long-term side effects and adherence issues • Address barriers to care • Promote resilience • Discontinue treatments when clinically indicated • Use evidence-based approaches to stop treatments • Continue treatment when discontinuation not indicated

2.b. Importance of Symptom Remission

- Remission = crucial clinical target
  - Lower risk of relapse in those who achieve remission
  - Failure to achieve remission → **continuing symptom burden** and **poor functional outcomes**

- Persisting depressive symptoms
  - Common and important to identify + treat → **persistent residual symptoms** is a **major risk factor for recurrence**
  - For **difficult to treat depression (DTD)** → prioritize best improvement in functioning + QOL

2.c. Suicide and Safety Risks

- Risk of suicide attempts is **5x higher in MDD**
  - Suicide deaths in Canada
    - Males = 15 deaths/100,000 | Females = 5 deaths/100,000
      - 3:1 ratio for M:F for completed suicides
      - Half of those suffer with MDD

- Validated risk scales
  - Low sensitivity and predictive powers → use only alongside clinician judgement

- **High risk = i.e., experiencing suicidal ideation with intent to act and/or psychotic symptoms**
  - Inpatient setting often warranted
  - Month after initiating and stopping an antidepressant are periods of increased risk

2.c. Suicide and Safety Risks

Table 2.2. Potentially Modifiable Risk factors for Suicide in Major Depressive Disorder (MDD)

Symptoms & Life Events

- **Active SI**
- **Hopelessness**
- **Anxiety**
- **Impulsivity**
- **Psychotic symptoms**
- **Stressful life events** (finance, victimization)

Comorbidities

- **PTSD**
- **SUD** (esp AUD)
- **Personality disorders** (esp cluster B)
- **Sleep disorders**
- **Chronic pain** conditions (migraines, arthritis)

2.c. Suicide and Safety Risks

Table 2.3. Suicide Safety Plan (Adapted from Hawton et al., 2022).

Step 1. Identify warning signs – e.g., thoughts, feelings, and circumstances.

Step 2. Enlist personalized coping strategies – e.g., self-management.

Step 3. Enable distraction and connect with people – e.g., go for a walk with a friend, go to a cafe or movie, use support groups or online forums.

Step 4. Engage with social and community supports – e.g., involve personal contacts in contingency plans.

Step 5. Identify professional contacts – e.g., crisis lines (9-8-8 in Canada and USA), mental health providers, urgent care clinics, and hospital emergency rooms.

Step 6. Make the environment safe – e.g., remove excess medications, firearms, sharp objects, or ropes; avoid busy streets and heights.

2.d. Role of Patient Preference

- Strong therapeutic alliance = key
  - Follow shared-decision making (SDM) model
  - Psychoeducation is important about broad range of treatment options, achieving symptom remission, and promoting long-term mental wellness

- Clinician + patient should contribute mutually to decision-making process
  - Meta-analyses found that while SDM may not significantly improve treatment adherence or symptom change → increases **patient knowledge, communication, and satisfaction**

2.e. Role of Treatment Cost and Access

- Cost and health insurance coverage
  - Can play significant roles in available options
  - Clinicians should be familiar with cost of treatments and patient's insurance coverage and ability to pay

2.f. Lifestyle Interventions

- Cigarette smoking and depression = bidirectional relationship
  - Individuals may smoke to alleviate depressive symptoms which can increase susceptibility to depressive symptoms

- Exercise
  - Medium to large effects for MDD
  - Can also reduce suicidal ideation
  - Low to moderate intensity for 30-40 mins/time, 3-4 times a week for a minimum of 9 weeks

  - ***RECOMMENDATION***
    - **Exercise is FIRST-LINE monotherapy** for mild MDD
    - **Exercise is SECOND-LINE adjunct** for mod MDD

2.f. Lifestyle Interventions

- Sleep and depression = bidirectional relationship
  - Insomnia and hypersomnia can be common symptoms of depression, but disturbed sleep can also increase risk of developing MDD
    - CBT-I has promising effects in MDD
  - Insomnia can also be a common residual symptom
  - Sleep deprivation (aka wake therapy) = rapid but transient antidepressant effects
    - **Caution:** can precipitate manic/hypomanic episodes in susceptible individuals

  - ***RECOMMENDATION***
    - **Sleep hygiene and CBT-I are SECOND-LINE adjunct** MDD
    - **Sleep deprivation (wake therapy) is THIRD-LINE adjunct** for MDD

2.f. Lifestyle Interventions

- Light therapy
  - Typical protocol = 10,000 lux fluorescent white light x 30 mins in the morning, shortly after awakening
    - 2016 protocol details (nothing mentioned in 2023)
      - **30 mins per day for 6 weeks**
      - **Response within 1-3 weeks**

  - ***RECOMMENDATION***
    - **LT** as **FIRST-LINE** **monotherapy** for seasonal depression
    - **LT** as **SECOND-LINE** **monotherapy** for mild nonseasonal MDD
    - **LT** as **SECOND-LINE** **adjunct** for mod nonseasonal MDD

2.f. Lifestyle Interventions

- Diet
  - Unhealthy diet has **increased prevalence and severity** of depressive symptoms
    - High content of refined carbohydrates and saturated fats with low content of fruits and vegetables, aka “Western diet”
  - Mediterranean diet has limited data but modest effect
  - Probiotics = insufficient evidence

  - ***RECOMMENDATION***
    - Healthy diet as **THIRD-LINE** **adjunct** for MDD
    - Mediterranean diet as **THIRD-LINE** **adjunct** for MDD
    - Probiotics are **INSUFFICIENT EVIDENCE**

2.f. Lifestyle Interventions

Table 2.4. Summary of Recommendations for Lifestyle Interventions

Line of treatment	*Intervention*	*Indication*	*Level of evidence*
FIRST LINE	**Supervised exercise (low to moderate intensity, 30-40 mins, 3-4 times/week, min of 9 weeks**	**Mono for mild MDD**	**Level 1**
FIRST LINE	**Light therapy (10k lux white light x 30 mins daily)**	**Mono for Seasonal (winter) MDD**	**Level 1**
SECOND LINE	**Light therapy**	**Mono for mild nonseasonal MDD**	**Level 2**
SECOND LINE	**Exercise**	**Adjunct for mod MDD**	**Level 2**
SECOND LINE	**Light Therapy**	**Adjunct for mod nonseason MDD**	**Level 2**
SECOND LINE	**Sleep hygiene and CBT-I**	**Adjunct**	**Level 3**
THIRD LINE	**Healthy diet (varied with high fruit content, veggies, and fibre, low saturated fats and carbs)**	**Adjunct**	**Level 3**
THIRD LINE	**Mediterranean diet**	**Adjunct**	**Level 3**
THIRD LINE	**Sleep deprivation (wake therapy)**	**Adjunct**	**Level 2**
Insufficient Evidence	**Probiotics**		**N/a**

3 How are Treatments Selected?

Table 1. Criteria for Level of Evidence and Line of Treatment	
Level of evidence	
1	• High-quality meta-analysis with **narrow** confidence intervals and/or **2 or more** RCTs with adequate samples size, preferably placebo-controlled
2	• Lower-quality meta-analysis with **wide** confidence intervals and/or **1 or more** RCTs with adequate sample size
3	• Small-sample RCTs • Non-randomized, controlled prospective studies • High-quality retrospective studies
4	• Expert opinion/consensus
Line of treatment	
First-line	• Level 1/2 evidence, plus clinical support
Second-line	• Level 3+ evidence, plus clinical support
Third-line	• Level 4+ evidence, plus clinical support

3.a. Initial Treatment Selection

MDE severity	Initial treatments

Mild with low safety risk	• **Psychotherapy preferred due to fewer risks, similar in benefits**
	• **Exercise, certain CAM treatments, or guided DHIs can be considered as monotherapy**
	• Can consider pharmacotherapy IF:
	  • **Patient preference**
	  • **Previous response to ADs**
	  • **Lack of response to non-pharm**

Moderate, with low moderate safety risk	• **Pharmacotherapy slightly more efficacious in reducing mood, guilt, SI, anxiety, and somatic symptoms** • **Psychotherapy (specifically CBT) slightly more efficacious in medium term (6-12 months)** • **Can consider combo (pharm + therapy)** • **Exercise, certain CAM treatments, or guided DHIs can be considered as adjuncts**
Severe, with moderate to high safety risk	• **Severe without psychotic symptoms → combo (pharm + therapy)** • **Severe with psychotic symptoms → antidepressants + antipsychotics** • **Very severe and/or life threatening → consider ECT**

3.b. When to Combine Pharm + Therapy?

- Benefits
  - Combining = more effective than either alone
  - Combined = reduced risk of recurrence

- Sequential treatment: **pharmacotherapy THEN psychotherapy**
  - Strongest evidence = in-person CBT **sequentially AFTER** treatment with antidepressant is established
  - Planned sequentially treatment = especially useful in **recurrent/more severe forms of depression with high risk of relapse**

- Sustained recovery
  - Psychological treatment is effective regardless of continuing antidepressant BUT highest chance of sustained recovery = when continued

3.c. How to Select Psychological Treatment?

- Initial psychotherapy
  - Consider efficacy, availability, and patient preference
  - Psychotherapy similarly effective across most demographic factors

- Outcomes
  - Severity of MDE does NOT predict outcomes in CBT vs pharmacotherapy but combo = more effective than either alone
  - CBT **reduces suicide attempts by 50%** in those who attempted suicide in past 6 months → consider in those with recent history of suicide

- CBT
  - Efficacious across all formats → individual, group, telephone/digital

- **Eclectic use** of different models = **NOT RECOMMENDED**

3.c. How to Select Psychological Treatment?

Table 3.2. Summary Recommendations for Psychological Treatments

Line of Treatment	*Psychological Treatment*	*Level of evidence*
FIRST LINE	**CBT** (cognitive behavioral therapy)	**Level 1**
FIRST LINE	**IPT** (interpersonal therapy)	**Level 1**
FIRST LINE	**BA** (behavioral activation)	**Level 1**
SECOND LINE	**CBASP** (cognitive-behavioral analysis system)	**Level 2**
SECOND LINE	**MBCT** (mindfulness-based cognitive therapy)	**Level 2**
SECOND LINE	**PST** (problem-solving therapy)	**Level 2**
SECOND LINE	**STPP** (short-term psychodynamic psychotherapy)	**Level 2**
SECOND LINE	**Transdiagnostic psychological treatment of emotional disorders**	**Level 2**
THIRD LINE	**ACT** (acceptance & commitment therapy)	**Level 3**
THIRD LINE	**PDT** (long-term psychodynamic psychotherapy)	**Level 3**
THIRD LINE	**MCT** (metacognitive therapy)	**Level 3**
THIRD LINE	**MI** (motivational interviewing)	**Level 4**

3.c. How to Select Psychological Treatment?

Summary Table. Psychological Treatments for Acute and Maintenance Tx of MDD		
Treatment	*Acute Tx*	*Maintenance Tx*
CBT (cognitive behavioral therapy)	**First-line**	**First-line**
IPT (interpersonal therapy)	**First-line**	**First-line**
BA (behavioral activation)	**First-line**	Not described
CBASP (cognitive-behavioral analysis system)	**Second-line**	**First-line**
MBCT (mindfulness-based cognitive therapy)	**Second-line**	**First-line**
PST (problem-solving therapy)	**Second-line**	**First-line**
STPP (short-term psychodynamic psychotherapy)	**Second-line**	Not described
Transdiagnostic psychological treatment of emotional disorders	**Second-line**	Not described
Internet-/computer-assisted therapy	**Second-line**	Not described
ACT (acceptance & commitment therapy)	**Third-line**	Not described
PDT (long-term psychodynamic psychotherapy)	**Third-line**	Not described
MCT (metacognitive therapy)	**Third-line**	Not described
MI (motivational interviewing)	**Third-line**	Not described

3.d. Number of Psychotherapy Sessions

- Relationship remains unclear
  - Recommendation based on number of sessions in which at least 50% respond
  - Optimal dose for a **FIRST LINE** psychotherapy is **12-16 sessions**

- Increased frequency = better outcomes
  - Twice weekly shows better outcomes than once weekly
  - Little support for less than once per week

3.e. Selecting an Antidepressant

- Cipriani et al. 2018
  - **Escitalopram, Vortioxetine, Agomelatine** (EVA) → superior in **efficacy and acceptability**

- 8 Antidepressants = evidence for **superior response**
  - **Bupropion, Escitalopram, Vortioxetine, Venlafaxine, Agomelatine, Mirtazapine, Paroxetine, Sertraline**
  - Small differences (5-10%)

3.e. Selecting an Antidepressant

- DDI
  - **Fluoxetine, fluvoxamine, paroxetine** → clinically relevant
- QTc prolongation
  - **Citalopram** (escitalopram does NOT carry same risk)
- LFT monitoring
  - **Agomelatine** requires regular monitoring of LFTs
- Sexual dysfunction
  - **Desvenlafaxine, Bupropion, Mirtazapine, Vilazodone, Vortioxetine, Agomelatine** → lower rates of sexual side effects
- Age
  - > 65 → **SNRIs > SSRI**
  - < 25 → **Fluoxetine or Agomelatine** > others

3.e. Selecting an Antidepressant

- **FIRST-LINE**
  - **SSRIs, SNRIs, bupropion, mirtazapine, vortioxetine, agomelatine, levomilnacipran, milnacipran, mianserin, vilazodone**

- **SECOND-LINE**
  - **TCAs, quetiapine, trazadone** → higher SE burden
  - **Moclobemide, selegiline** → potential serious drug interactions
  - **Dextromethorphan-bupropion** → limited evidence, potential for misuse, lack of long-term safety data

- **THIRD-LINE**
  - **MAO inhibitors** → higher SE burden, drug interactions, diet
  - **Reboxetine** → lower efficacy

Table 3. Summary Recommendation of Antidepressants

Line of Treatment	*Antidepressant*	*Mechanism*	*Dosing*
FIRST LINE	**Citalopram**	SSRI	20-40 mg
	Escitalopram	SSRI	10-20 mg
	Fluoxetine	SSRI	20-60 mg
	Fluvoxamine	SSRI	100-300 mg
	Paroxetine	SSRI	20-50 mg
	Sertraline	SSRI	50-200 mg
	Venlafaxine	SNRI	75-225 mg
	Desvenlafaxine	SNRI	50-100 mg
	Duloxetine	SNRI	**60-120 mg**
	Levomilnacipran	**SNRI**	**40-120 mg**
	Milnacipran	SNRI	**50-120 mg**
	Bupropion	NDRI	**150-450 mg**
	Mirtazapine	α2-agonist, 5HT2 antagonist	15-45 mg
	Mianserin	α2-agonist, 5HT2 antagonist	60-120 mg
	Vortioxetine	Multimodal	10-20 mg
	Agomelatine	MT1/MT2 agonist, 5HT2 antagonist	25-50 mg
	Vilazodone	**SRI, 5HT1A partial agonist**	**20-40mg**

RED = updated medication dose range from 2016

BLUE = new level of evidence from 2016

Table 3. Summary Recommendation of Antidepressants

Line of Treatment	*Antidepressant*	*Mechanism*	*Dosing*
SECOND LINE	Amitriptyline	TCA	75-300 mg
	Clomipramine	TCA	150-300 mg
	Desipramine	TCA	100-300 mg
	Doxepin	TCA	75-300 mg
	Imipramine	TCA	75-300 mg
	Nortriptyline	TCA	75-150 mg
	Protriptyline	TCA	30-60 mg
	Trimipramine	TCA	75-300 mg
	Moclobemide	RIMA	150-450 mg
	Trazodone	SR; 5HT2 antagonist	**150-400 mg**
	Quetiapine	Atypical antipsychotic	150-300 mg
	Dextromethorphan-bupropion	**NMDA antagonist, NDRI, sigma-1 agonist**	**45 mg/105-90 mg/210 mg**
	Nefazodone	**SRI, 5HT antagonist**	**300-600 mg**
	Selegiline transdermal	MOA-B inhibitor	6-12 mg
THIRD LINE	Phenelzine	MAO inhibitors (irreversible)	45-90 mg
	Tranylcypromine	MAO inhibitors (irreversible)	**30-60 mg**
	Reboxetine	NRI	**8-12 mg**

RED = updated medication dose range from 2016

BLUE = new level of evidence from 2016

Table 3.4. Frequency of Adverse Effects of First-Line Antidepressants.

	Nausea	Vomiting	Constipation	Diarrhea	Dry mouth	Headaches	Dizziness	Somnolence	Nervousness	Anxiety	Agitation	Insomnia	Fatigue	Sweating	Asthenia	Tremor	Anorexia	Incr. appetite
SSRIs																		
Citalopram	21	4		8	19			17	4	3	2		5	11		8	4	
Escitalopram	15		4	8	7	2	6	4	2	2		8	5	3		2	2	2
Fluoxetine	21				10			13	14	12		16		8	9	10	11	
Fluvoxamine			18	6	26	22	15	26	2	2	16	14		11	5	11	15	
Paroxetine	26	2	14	12	18	18	13	23	5	5	2	13		11	15	8	6	1
Sertraline	26	4	8	18	16	20	12	13	3	3	6	16	11	8		11	3	1
SNRIs																		
Desvenlafaxine[1]	22	3	9	11	11	20	13	4	<1	3	0	9	7	10		2	5	2
Duloxetine	20	5	11	8	15		9	7		3		11	8	6		3	8	
Levomilnacipran	17	5	9		10	17	8			2		6		9			3	
Milnacipran[2]	37	7	16		5	18	10			4		12		9		2	2	
Venlafaxine-IR		6	15	8	22	25	19	23	13	6	2	18		12	12	5	11	
Venlafaxine-XR	31	4	8	8	12	26	20	17	10	2	3	17		14	8	5	8	
Others																		
Agomelatine	≤9	≤9	≤9	≤9		≥10	≤9	≤9		≤9	<1	≤9	≤9	<1			<1	≤9
Bupropion SR[3]	11		≥10	4	≥10	≥10	7	3	5	5		≥10		2	2	3		
Bupropion XL	15	2	10		19		8			5		10		2		4	5	
Mirtazapine			13		25		7								8	2		17
Vilazodone[4]	24	5		29	7	14	8	5				6	3					3
Vortioxetine[5]	23	4	4	5	6		5	3				3	3	2			1	

Table 3.5. Summary of Comparative Favourability Ratings for First-Line Antidepressants: Efficacy, Acceptability, Drug Interactions, Discontinuation Effects, and Tolerability Issues.

	Efficacy and drug-specific issues[1]					Tolerability issues			
Antidepressant	**Efficacy**	**Acceptability[2]**	**Drug interactions**	**Discontin-uation**		**Sedation**	**Weight gain**	**Sexual dysfunction**	**Other Tolerability[2]**
SSRIs									
Citalopram			QTc[3]						
Escitalopram									
Fluoxetine									
Fluvoxamine									
Paroxetine									
Sertraline									
SNRIs									
Desvenlafaxine									
Duloxetine									
Levomilnacipran									
Venlafaxine-XR									
Others									
Bupropion									
Mirtazapine									
Vilazodone									
Vortioxetine									
Not available in Canada									
Agomelatine			LFTs[4]						
Mianserin									
Milnacipran									

	More favourable
	Less favourable
	Neutral[5]

3.f. Which Treatments have New Evidence?

- Psychological treatments
  - **FIRST LINE** psychotherapies (**CBT, IPT, BA**) continue to show strong evidence
  - Most **SECOND-LINE** therapies continue to build evidence base
  - 2 new psychological treatments
    1) **Transdiagnostic or "unified" psychological treatment of emotional disorders**
       - Incorporates multiple aspects of different treatments
       - **SECOND-LINE** recommendation
    2) **Metacognitive therapy (MCT)**
       - Focuses on awareness and understanding of thoughts and feelings of oneself and others
       - **THIRD-LINE** recommendation

3.f. Which Treatments have New Evidence?

- Pharmacological Treatments

1) **Dextromethorphan-bupropion**
   - Approved by FDA in 2022 → not available in Canada
   - NMDA receptor antagonist, SNRI, and opioid sigma-1 receptor agonist
   - Bupropion works to inhibit 2D6 and increase Dextromethorphan bioavailability (used in cough and cold medications)
   - limited evidence, potential for misuse, lack of long-term safety data → **SECOND-LINE**

2) Allopregnanolone agonists i.e. **Brexanolone** and **Zuranolone**
   - Approved in US for postpartum depression
   - Will be included in updated CANMAT perinatal mood and anxiety disorders

3.g. DSM Specifiers and Medication Selection

- Melancholic, atypical, anxious subtypes
  - No differences
  - Anxious → Poorer response to standard treatments, but evidence for preferred treatment options

- Mixed features
  - **Lurasidone** recommended as a **SECOND-LINE** agent
  - Close monitoring needed for **activating side effects** (i.e. agitation and increase in SI) as well as **risk of potential manic/hypomanic switch**

- Psychotic depression
  - **AD+AP combo**

- Catatonic features
  - **BZD+AD combo**

3.g. DSM Specifiers and Medication Selection

- Cognitive dysfunction
  - Concentration/memory/executive function
  - **Vortioxetine** → remains **FIRST LINE**
  - **Duloxetine/Bupropion/other SSRIs** → **SECOND-LINE**

- Sleep disturbance
  - **Agomelatine** → **FIRST LINE**
  - **Mirtazapine, Trazadone, Quetiapine** → **SECOND-LINE**

- Somatic symptoms
  - Pain → **Duloxetine FIRST LINE**, with **other SNRIs SECOND-LINE**
  - Fatigue → **Bupropion FIRST LINE** with **Duloxetine** and **other SSRIs SECOND-LINE**
    - Energy, fatigue, motivation → **SNRIs** > **SSRIs**

- Anhedonia
  - Reported in up to 70% of patients
  - Associated with reduced likelihood of remission with SSRI treatment, ? Related to dopamine
  - Promising symptom dimension for future clinical trials

3.h. Antidepressants and Suicidality

- Collective risk
  - Reduced suicidal thoughts and behaviours
  - Greater effect on suicidal ideation than on prevention of suicide attempts and death

- Increased risk may be associated with **patient age** and **time period of antidepressant use**
  - Patient age
    - **< 25** → increased risk | **25-65** → no effect | **> 65** → decreased risk
  - Time period
    - Highest in the month before antidepressant initiation, **remains highest in month after initiation** → then declines

- CANMAT recommends routine monitoring in all patients
  - With enhanced attention in **1st 4 weeks of new medication** AND **after stopping medication**

- Psychoeducation
  - Important to provide psychoeducation about risk of increased suicidal thoughts/behaviours
    - Understand the increase as a side effect of the medication
    - Indicate need for urgent action
    - Implement safety plan

3.i. Differences in Formulation

- No difference in efficacy between XR vs IR

- Generic vs brand
  - Differences in bioavailability have been reported, especially for XR formulations
  - Not well studied

- CANMAT recommends continuing same formulation and/or brand when effective, and minimize changes

3.j. Safety Concerns and Drug Interactions

- SSRIs
  - Modest increased risk of #s, especially in older adults
  - Most have few clinically relevant DDI
    - **Fluoxetine** and **Paroxetine** → potent inhibitors of CYP2D6
    - **Fluvoxamine** → potent inhibitor of CYP1A2, CYP2C19, and CYP3A4
  - SSRIs + NSAIDs
    - Increased risk of GI bleeding → can be mitigated with PPIs
  - SSRIs + Diuretics
    - Increased risk of hyponatremia, especially in older adults
    - **Mianserin** and **Agomelatine** = only antidepressants NOT associated with hyponatremia

- SNRIs
  - Can cause increases in BP
  - SNRIs + NSAIDs
    - Increased risk of GI bleeding → can be mitigated with PPIs
  - SNRIs + Diuretics
    - Increased risk of hyponatremia, especially in older adults

3.j. Safety Concerns and Drug Interactions

- Mirtazapine
  - Excellent short-term safety profile BUT significant increases in appetite, weight gain, and long-term metabolic risks

- TCAs
  - Higher risk of life-threatening effects in overdose → altered mentation, cardiac toxicity, seizures
    - SSRIs preferred if significant risk of overdose

- MAOI
  - Life threatening interactions → **SS** and **hypertensive crisis**
  - Require detailed guidance on **avoiding interacting medications and foods**

3.j. Safety Concerns and Drug Interactions

- Drug induced liver injury
  - Can occur up to 6 months after initiation
  - Agomelatine, Bupropion, Duloxetine, and Nefazodone → higher risk
  - Escitalopram and Citalopram → lower risk

- Age
  - SSRIs and SNRIs associated with increased risk of akathisia, agitation, and aggression in < 25
  - Risks of GI bleeding, hyponatremia, liver damage, and QTc prolongation most prominent in > 65

3.k./3.i. Pharmacogenetic Testing, Drug-Levels

- Pharmacogenetic testing available for CYP enzymes
  - **Routine pharmacogenetic testing NOT recommended**

- Drug-level monitoring for 2nd generation ADs
  - **Routine monitoring NOT recommended**
    - **Except for select TCAs**
  - Poor correlation between blood levels vs clinical response

- May be helpful in certain circumstances
  - Inability to tolerate minimum doses → **? poor metabolizer**
  - Repeated failure to respond to high doses → **? rapid metabolizer**
  - **Detect non-adherence**

- EEG
  - Some biomarkers associated with better response → **stronger loudness dependence of the auditory evoked potentials**
    - Early state of evidence modest effect size, and lack of evidence with better response to alternative treatments
  - **Routine EEG testing NOT recommended**

3.m. CAMs

- Varying quality of RCTs
  - Major limitation to systematic evaluation
  - Variations within interventions, blinding, publication bias

- Evidence-based pharmacological + psychological tx FIRST
  - No CAM treatments with enough evidence to make it comparable to **FIRST LINE** pharmacological or psychotherapy
  - Consider CAM monotherapy in mild MDE → can be used as adjuncts in mod severity MDE

3.m. CAMs

- St. John's Wort
  - Uncertain risk of SS
  - Is a potent CYP3A4 inducer → can interact with OTC meds
  - **FIRST LINE** for mild MDE, **SECOND-LINE** for mod MDE

- Herbs
  - Saffron (*Crocus sativus*), Lavender (*Lavandula*), and Roseroot (*Rhodiola*) have modest evidence but major limitations in RCTs
  - **THIRD-LINE** for mild MDE

- Nutraceuticals and unregulated products
  - L-methyl folate (folic acid) → has evidence but small effect size
    - **SECOND-LINE** as adjunct for mild-mod MDE
  - SAM-e
    - Previously **SECOND-LINE** → mixed recent findings so now **THIRD-LINE** adjunct for mild-mod MDE
  - Omega-3
    - Previously **SECOND-LINE** → mixed recent findings so now **THIRD-LINE** monotherapy for mild MDE
  - DHEA (dehydroepiandrosterone)
    - Modest evidence → **THIRD-LINE** monotherapy for mild MDE

(2016 Guidelines) St. John's Wort

- *Hypericum perforatum* → perennial plant
  - Proposed mechanisms
    - Direct effect of serotonin receptors
    - Monoamine oxidase inhibition
    - Neuroendocrine + ion channel modulation
  - Widely varying doses (500 – 1800 mg/day)

- Better tolerated than many first-line ADs
  - GI upset, headaches, skin irritation, photosensitivity, dry mouth
  - Risk of **P450 drug interactions**
  - Reports of serotonin syndrome, hypomania if concurrent ADS

(2016 Guidelines) Omega-3 Fatty Acids

- <u>EPA, DHA most studied</u>
  - 1 – 2 grams of EPA + DHA, or 3 – 9 grams total
  - Inconsistent findings due to study design/methodology

- <u>Generally well tolerated</u>
  - Diarrhea, nausea, fishy aftertaste
  - If on **anticoagulant or antiplatelet** meds → additional monitoring
  - Reports of manic induction in a few cases

(2016 Guidelines) SAM-e

- Natural substrate in body (methyl donor)
  - Proposed modulation of monoaminergic neurotransmission
  - Prescribed in Europe for MDD
  - OTC in US/Canada → 800 – 1600 mg PO/day, 4 – 12 weeks

- Generally well-tolerated
  - GI upset, tachycardia, sweating, headache
  - Irritability, restlessness, anxiety, insomnia, fatigue

(2016 Guidelines) DHEA

- Adrenal cortex hormone → converted to sex hormones
  - Modulates neuroendocrine + immune homeostasis
  - Influences monoaminergic + glutaminergic neurotransmission
  - Dosing → 30 – 450 mg/day, 6 – 8 weeks

- Side effects
  - Hirsutism, acne, hypertension, liver damage, **manic induction**
  - Higher doses → worsening prostatitis, incr risk of breast cancer

Table 3. Summary of Recommendations for Natural Health Products				
Line of Treatment	*CAM Treatment*	*Type*	*Indication*	*Level of Evidence*
FIRST LINE	**St. John's Wort**	**Monotherapy**	**Mild MDE**	**Level 1**
SECOND LINE	**Acupuncture**	**Monotherapy**	**Mild MDE**	**Level 2**
SECOND LINE	**St. John's Wort**	**Monotherapy**	**Mod MDE**	**Level 2**
SECOND LINE	**Acupuncture**	**Adjunct**	**Mod MDE**	**Level 2**
SECOND LINE	**L-Methyl Folate**	**Adjunct**	**Mild-Mod MDE**	**Level 2**
THIRD LINE	**SAM-e**	**Adjunctive**	**Mod-severe MDE**	**Level 2**
THIRD LINE	**DHEA**	**Monotherapy**	**Mild MDE**	**Level 3**
THIRD LINE	**Omega-3 Fatty Acids**	**Monotherapy**	**Mild MDE**	**Level 3**
THIRD LINE	**Saffron, Lavender, or Roseroot**	**Monotherapy**	**Mild MDE**	**Level 3**

3.n. Comorbid Conditions

- High rates of comorbidities
  - **10-30% for many disorders i.e. ADHD, SUD, PDs**
  - **40-60% for Anxiety Disorders**
  - **10-30% for nonpsychiatric medical conditions i.e. DM, CVD, Cancer, Chronic Pain, among others**

- Presence of comorbidity
  - Generally more difficult to treat and have worse treatment response to antidepressants
  - Respond similarly to psychological treatments as those without
    - CBT and BA has good support → CVD and neurological conditions

- Considerations
  - Important to distinguish side effects of depression treatment from side effects of concomitant meds
  - Minimize polypharmacy and avoid iatrogenic adverse effects

- CANMAT 2016 update
  - Previously was some evidence that PDs reduced benefit of psychotherapy → no longer the case
  - CBT (16-20 sessions) recommended for patients with depression and concurrent PDs

3.o. Cultural and Religious practices

- CANMAT recommends cultural and religious adaptations of evidence-based psychotherapies where available and appropriate

4 What is the Role of DHIs?

4.a. What are DHIs?

- DHI = digital health intervention
  - Usage includes **disease screening, monitoring, treatment, and prevention of recurrence**

- Depression severity → for mild to moderate
  - Can be useful for **mild to moderate severity** of depressive symptoms → **severe depression may interfere** with ability to use DHIs

- Advantages
  - Accessibility and customization (i.e. different languages)

- Challenges
  - Limited data around efficacy and safety
  - User engagement challenges
    - < 1/3 still using after 6 weeks
    - Digital inequity factors → low digital literacy, inability to purchase a computer/mobile device, lack of internet access

4.b. Best Practices for Evaluating DHIs?

- Safety Concerns
  - Commercially available DHIs often fail to disclose criteria for efficacy, safety, privacy, and security

- Potential harms
  - Mental DHIs can have unwanted effects in vulnerable individuals →i.e. daily mood monitoring and reminders for depression may exacerbate depressive symptoms in some

- Practice factors
  - Access, cost, and ease of use → especially for users with disability or language/literacy issues

4.c. Guided vs Unguided DHIs

- Unguided = self-directed

- Guided = facilitated
  - Guidance can be synchronous (real-time) or asynchronous (i.e. email or text after)

- In general, **guided DHIs are more effective than self-directed**

4.d. Examples of Guided DHIs

- **Internet CBT = iCBT**
  - Most studied guided DHI
  - Medium to large effect sizes → level 1 evidence

- **Internet behavioural activation = iBA**
  - Inconsistent data
    - Some studies show superior to psychoeducation or treatment as usual and noninferior to other behavioural therapy and mindfulness formats → level 2 evidence
    - 1 RCT shows no differences compared to WL control

- ***Recommendation***
  - **Guided iCBT FIRST-LINE monotherapy** for mild MDD
  - **Guided iCBT** is **FIRST-LINE adjunctive** for mild-mod MDD
  - **Guided iBA** is **SECOND-LINE adjunctive** for mild-mod MDD

4.e. Examples of Unguided DHIs

- Limited evidence for most self-directed DHIs → low level of evidence

- CANMAT does not recommend routine use of self-directed DHIs as monotherapy, except in cases of mild severity when other resources not available → level 3 evidence
  - Can consider as **SECOND-LINE** adjuncts with support by clinicians

- **Artificial intelligence and chatbots** → currently insufficient evidence to recommend chatbots and conversational agents for treatment of MDD
  - Still at early stage and little known about potential risks

- ***Recommendation***
  - **Self-directed DHIs SECOND-LINE adjunctive** for mild-mod MDD ***when supported with guidance by clinicians***
  - **Self-directed DHIs THIRD-LINE monotherapy** for mild MDD ***when no other clinical interventions are available***
  - Chatbots and conversational agents have **INSUFFICIENT EVIDENCE**

Table 4.3. Summary Recommendations for DHIs

Line of treatment	*Intervention*	*Indication*	*Level of evidence*
FIRST LINE	**Guided iCBT**	**Mono for mild MDD**	Level 1
FIRST LINE	**Guided iCBT**	**Mono for mild-mod MDD**	Level 2
SECOND LINE	**Self-directed DHIs, *when supported with guidance from clinicians***	**Adjunct for mild-mod MDD**	Level 3
SECOND LINE	**Guided iBA**	**Adjunct for mild-mod MDD**	Level 3
THIRD LINE	**Self-directed DHIs *when no other clinical interventions are available***	**Mono for mild MDD**	Level 3
Insufficient Evidence	Chatbots and conversational agents		N/a

5 What are Important issues for Assessment and Diagnosis?

5.a. Measurement-Based Care (MBC)

- 3 components:
  1) Validated outcome scales
  2) Reviewing scale scores with patients
  3) Using scale scores alongside clinical assessment to support collaborative decision-making

- Supported by research
  - Several high-quality trials and systematic reviews supporting medical adherence and outcomes → level 2 evidence

- Validated rating scales
  - Monitor outcomes → depressive sx, function, QoL
    - Can improve **enhanced patient engagement, higher intervention accuracy, and shorter treatment duration**
    - Can also **enhance therapeutic alliances and facilitate SDM**
  - Support clinical decision-making

5.a. Measurement-Based Care (MBC)

- Patient-related scales = patient-related outcome measurements (PROMs)
  - **Simpler to use**
  - **More efficient**

- Suicidality
  - Clinician rated → Columbia Suicide Severity Rating Scale (C-SSRS)
  - Patient rated → Suicide Scale
  - Some patients find it easier to endorse on questionnaire than face to face
  - NB: scales **can help with assessment**, but **cannot reliability predict suicide attempts or behaviours**

5.a. Measurement-Based Care (MBC)

- Insight into subjective experiences
  - Can prompt discussions that inform about patients' cognitive schemas and enhance rapport

- Component of assessment
  - Should **COMPLEMENT** not **REPLACE** clinical interview and comprehensive understanding of patient

5.b. Operational Definitions for Outcomes

- Early Improvement = reduction in score of 20% or greater from baseline (within 2-4 weeks)
  - Lack of early improvement **strongly associated** nonresponse and nonremission at later points
  - ∴ at 4 weeks → consider dose optimization vs switch

- Response = reduction in score of 50% or greater from baseline

- Remission = subthreshold score (varies per scale)
  - DSM-5-TR defines remission as **absence or near absence** of **symptoms** for **at least 2 months**

5.b. Operational Definitions for Outcomes

- Functional outcomes and QOL
  - Few consensus definitions here → can use appropriate scales (table 5.2 on next slide)

5.b. Operational Definitions for Outcomes

Table 5.2. Examples of Validated Rating Scales for MBC

Outcome	*Clinician Rated*	*Patient-Rated*
Symptoms/ Severity	• **HAM-D, HAM-7** (Hamilton Depression Rating Scale) • **MADRS** (Montgomery-Asberg Depression Rating Scale) • **IDS** (Inventory for Depressive Symptomatology) • **C-SSRS** (Columbia Suicide Severity Rating Scale) • **DARS** (Dimensional Anhedonia Rating Scale)	• **BDI-II** (Beck Depression Inventory-II) • **CUDOS** (Clinically Useful Depression Outcome Scale) • **PHQ-9** (Patient Health Questionnaire) • **PROMIS** (Patient Rated Outcome Measurement Information System) • **QIDS-SR** (Quick Inventory for Depressive Symptomatology, Self-Rated) • **Suicidality Scale**
Functioning	• **MSIF** (Multidimensional Scale of Independent Functioning) • **SOFAS** (Social and Occupational Functioning Assessment Scale) • **WHO-DAS** (WHO Disability Assessment Scale)	• **LEAPS** (Lam Employment Absence and Productivity Scale) • **SDS** (Sheehan Disability Scale) • **WHO-DAS, self-rated** • **WSAS** (Work and Social Adjustment Scale)
Side Effects	• **QOLI** (Quality of Life Interview)	• **EQ-5D** (EuroQoL-5D) • **QLESQ** (Quality of Life, Enjoyment and Satisfaction Questionnaire)
Quality of Life	• **UKU Side Effect Rating Scale** • **Toronto Side Effects Scale**	• **FIBSER** (Frequency, Intensity and Burden of Side Effects Rating)

5.c. How to Implement MBC

- Barriers
  - Clinician concerns
    - Often feel takes time away from clinical encounter
    - Worries that it may not capture important aspects of clinical situation
  - Insufficient training on usage and workflow
  - Misbeliefs about feasibility and efficacy
  - Language and cultural barriers
  - Costs associated with changing workflow

- Addressing barriers
  - Simple PROMs are free → can email prior to appointment or while in waiting room
  - Can use mobile apps → Apple has integrated PHQ-9 and GAD-7 in health mobile app
  - Can track in progress note and EMR

- Phase of treatment
  - Acute → can administer q2-4 weeks
  - Maintenance → less frequently to avoid frustrating/overwhelming patient

5.d. Laboratory Test for Monitoring

- Routine lab tests not necessary for most clinical situations
  - **Pre-existing liver disease:** LFTs at baseline → then q6-12 months
  - **Older adults (≥ 60):** serum electrolyte monitoring
  - **Adjunctive agents** → tailor to med
    - **Lithium:** lithium levels, electrolytes, calcium, Cr/eGFR, and TSH at baseline and q6-12 months or when clinical status or dose changes
    - **Ketamine/esketamine:** periodic urinalysis to check for cystitis
  - **Medications associated with weight gain** → weight, glucose, and lipid profiles

5.d. Laboratory Test for Monitoring

Table 5.1. Summary Recommendations for Monitoring Treatment	
Recommendation	*Level of Evidence*
• **Use validated rating scales for MBC**	**Level 2**
• **Obtain lab and imaging tests only *when clinically indicated***	**Level 4**
• **Monitor weight, glucose, and lipids at *baseline* and *q6 months* when prescribing meds associated with weight gain**	**Level 2**

6 What Should be Done When a Patient is Better?

6.a. Remission

- Goal = maintain remission as risk of recurrence increases with each subsequent depressive episode

- Psychological treatments
  - Scheduler regular booster sessions

- Pharmacotherapy
  - Optimize on lowest effective dose
  - Monitor side effects
  - Use MBC to monitor symptoms and side effects

- Address modifiable risk factors
  - Exercise, avoiding substance misuse, quality sleep, healthy diet

- Peer support = “giving and receiving help from individuals with lived experiences of mental illness”
  - Small but positive effect

6.b. Preventing Recurrence

- Maintenance pharmacotherapy and psychotherapy = both effective
  - Pharmacotherapy
    - Can **reduce relapse rates by 50%** → flexible doses adjustments > fixed dose adjustments
    - **Lower rates of recurrence at 1-/3-year with OR without CBT**
    - 2016 guidelines recommended meds for 6-9 months after remission → new evidence suggests **6-12 months after remission**
  - Psychotherapy
    - Can prevent relapse and recurrence
    - Evidence for **CBT, MBCT, PST, IPT, and CBASP** (**no BA**) for **maintenance** → comparable effects amongst these
    - Evidence also suggests booster sessions at regular intervals (no clear definition, example = "i.e. 4 sessions over 12 months"
    - Psychotherapy = medications for preventing recurrence, and may have longer lasting benefits

6.b. Preventing Recurrence

Summary Table. Psychological Treatments for Acute and Maintenance Tx of MDD		
Treatment	*Acute Tx*	*Maintenance Tx*
CBT (cognitive behavioral therapy)	**First-line**	**First-line**
IPT (interpersonal therapy)	**First-line**	**First-line**
BA (behavioral activation)	**First-line**	Not described
CBASP (cognitive-behavioral analysis system)	**Second-line**	**First-line**
MBCT (mindfulness-based cognitive therapy)	**Second-line**	**First-line**
PST (problem-solving therapy)	**Second-line**	**First-line**
STPP (short-term psychodynamic psychotherapy)	**Second-line**	Not described
Transdiagnostic psychological treatment of emotional disorders	**Second-line**	Not described
Internet-/computer-assisted therapy	**Second-line**	Not described
ACT (acceptance & commitment therapy)	**Third-line**	Not described
PDT (long-term psychodynamic psychotherapy)	**Third-line**	Not described
MCT (metacognitive therapy)	**Third-line**	Not described
MI (motivational interviewing)	**Third-line**	Not described

6.b. Preventing Recurrence

- Sequential treatment model
  - "Adding or switching to psychotherapy after response to acute phase pharmacotherapy"
  - Evidence for prevention of recurrence **even when antidepressants are stopped**

- ***Recommendation***
  - **Sequential treatment model is FIRST-LINE** for recurrent or severe MDEs

6.c. Preventing Recurrence

Table 6.2. Risk Factors for Recurrence of Depressive Episodes.

- Persistent residual symptoms* (e.g., anhedonia, sleep problems, and cognitive dysfunction)
- History of childhood maltreatment*
- Greater severity of depressive episodes
- Chronic depressive episodes
- Presence of medical comorbidities (psychiatric or nonpsychiatric)
- Greater number of previous episodes
- Poor social support
- Persistent stressful life events

* These have robust evidence as risk factors for recurrence.

6.c. Longer Term Treatments When?

- Without risk factors = 6-12 months of maintenance pharmacotherapy

- With risk factors (table 6.2, previous slide) = 2 years or more
  - **Persistent residual symptoms (i.e. anhedonia, sleep problems, cognitive dysfunction)** and **history of childhood maltreatment** = robust risk factors

- Support tools to estimate risk of recurrence
  - Look promising but need further validation before clinical use

6.d. How to Discontinue Pharmacotherapy?

- Discontinuation symptoms (FINISH)
  - **Flu-like** symptoms
  - **Insomnia**
  - **Nausea**
  - **Imbalance**
  - **Sensory** disturbance
  - **Hyperarousal**

Table 6.3. Risk of Antidepressant Discontinuation Symptoms.*

Risk of discontinuation symptoms	Antidepressant
High risk	• Paroxetine • Venlafaxine
Moderate risk	• Citalopram • Desvenlafaxine • Duloxetine • Escitalopram • Fluvoxamine • Levomilnacipran • Milnacipran** • Sertraline • Vilazodone • Tricyclic antidepressants • Monoamine oxidase inhibitors
Low or minimal risk	• Agomelatine** • Bupropion • Fluoxetine • Mirtazapine • Vortioxetine

*The risk categories are based on clinical studies, but the risk and severity of discontinuation symptoms may vary for individual patients and specific medications.
**Not available in Canada.

- Typical course
  - Up to 50% may experience
    - Few days after decreasing/stopping
    - Mild to moderate in severity
    - Resolve within a few weeks
    - Gradual tapering may NOT prevent but can decrease severity/frequency
  - Shorter half lives = greater incidence/severity + quicker onset of discontinuation symptoms
    - **Paroxetine and venlafaxine** = high risk

6.d. How to Discontinue Pharmacotherapy?

- <u>Differentiate discontinuation symptoms from early recurrence</u>
  - Discontinuation symptoms:
    - Generally, have earlier onset (days to weeks)
    - Characterized by somatic symptoms → nausea, dizziness, shock-like sensations
    - Improve rapidly once dose restored

- <u>Adding psychotherapy</u>
  - May allow patient to stop medication without increasing risk of relapse and may have mitigate discontinuation symptoms

6.d. How to Discontinue Pharmacotherapy?

- <u>Discontinuation strategies</u>
  - Taper gradually over several weeks or months (except for fluoxetine which doesn't need to be tapered)
  - Extending time between dose reductions towards end of taper
  - If medications used for < 4 weeks → can use fast tapering schedule over 2 weeks or less
  - Use psychological treatments DURING or PRECEEDING discontinuation
  - If symptoms are severe → return to previous higher dose + slow taper
    - Alternatively, can switch to long-acting medication and then taper
  - Can use validated measure i.e. Discontinuation-Emergent Signs and Symptoms (DESS) Scale

Table 6.1. Summary of Recommendations for Maintenance Antidepressant Treatment

Line of treatment	*Summary Recommendations*	*Level of evidence*
FIRST LINE	**For patients who have achieved symptom remission, using maintenance pharmacotherapy and/or psychotherapy can prevent recurrence**	**Level 1**
FIRST LINE	**All patients treated with antidepressants should continue medication treatment for a minimum of 6 to 12 months after achieving symptomatic remission**	**Level 1**
FIRST LINE	**Patients with risk factors for recurrence (see Table 6.2 – next slide) should continue antidepressant treatment for 2 years or more**	**Level 3**
FIRST LINE	**Patients with recurrent and severe MDEs should use sequential treatment (adding psychotherapy after stabilizing on medications) to prevent recurrence**	**Level 1**
FIRST LINE	**When a decision is made to stop the antidepressant, it should be tapered gradually, whenever possible, for several weeks or months with more time between dose reductions near the end of the taper**	**Level 3**
FIRST LINE	**For patients treated with medication for less than 4 weeks, the antidepressant can be tapered and discontinued quickly, over 2 weeks or less**	**Level 3**
FIRST LINE	**Psychological treatments can be added before or during antidepressant discontinuation to help patients stop the antidepressant**	**Level 2**

6.d. How to Discontinue Pharmacotherapy?

- Persistent discontinuation syndromes = severe, potentially irreversible symptoms persisting beyond 6 weeks
  - Heterogenous presentations often occurring with overlapping conditions → require individual attention and assessment
  - Some have recommended at lower end of dose range, use "hyperbolic dose reduction" targeting fixed percentage vs by fixed dose
    - Not been evaluated in RCTs

- ***Recommendation***
  - **Hyperbolic dose reduction has INSUFFICIENT EVIDENCE**

7 What Should be Done When a Patient is not Better?

7.a. Contributors to Poor Response to Treatment?

- Response = >50% reduction in symptom severity
  - In real world:
    - ≈ 1/2 achieve response
    - ≈ 1/3 attain full symptom remission
    - ≈ 1/4 of nonremitters who get a 2nd treatment will achieve remission
  - First treatment patients
    - Remission rates are higher BUT almost 1/2 will not achieve remission with antidepressants after 6 months

- Contributing factors → table 7.1 (next slide)
  - Clinical factors, comorbidity, medication factors

7.a. Contributors to Poor Response to Treatment?

Table 7.1 Factors Contributing to Poor Response to Initial Treatment

Clinical	*Treatment Factors*
• **Incorrect diagnosis** (i.e. bipolar disorder) • **Demographic and illness characteristics** (i.e older age, female sex, younger age of onset, higher severity, increased number/duration of episodes, and trauma history) • **Psychiatric comorbidities** (i.e. anxiety disorders, ADHD, PTSD, personality disorders, etc.) • **Nonpsychiatric medical comorbidities** (i.e. anemia, obesity, thyroid disease, etc.) • **Acute or chronic stressors**	• **Inadequate dose of treatment** • **Inadequate duration of treatment** • **Side effects masking symptoms** • **Poor adherence to treatment** • **Pharmacogenetic variability** (i.e. rapid or slow metabolizers)

7.b. TRD vs DTD

- Treatment-Resistant Depression (TRD)
  - No universal consensus
  - Most frequently used definition:
    - "Failure to respond to 2 or more antidepressant trials at the therapeutic dose and adequate duration"
  - Criticisms:
    - "failure" has variable definitions
    - Neglecting psychological and neurostimulation treatments
    - "resistant" = negative connotation that suggests futility and can discourage patients/clinicians

- Difficult to Treat Depression (DTD)
  - "Persistent depression that has failed numerous standard treatments… and is further along the treatment trajectory"
  - DTD model shifts focus away from **symptom remission** → **symptom management**

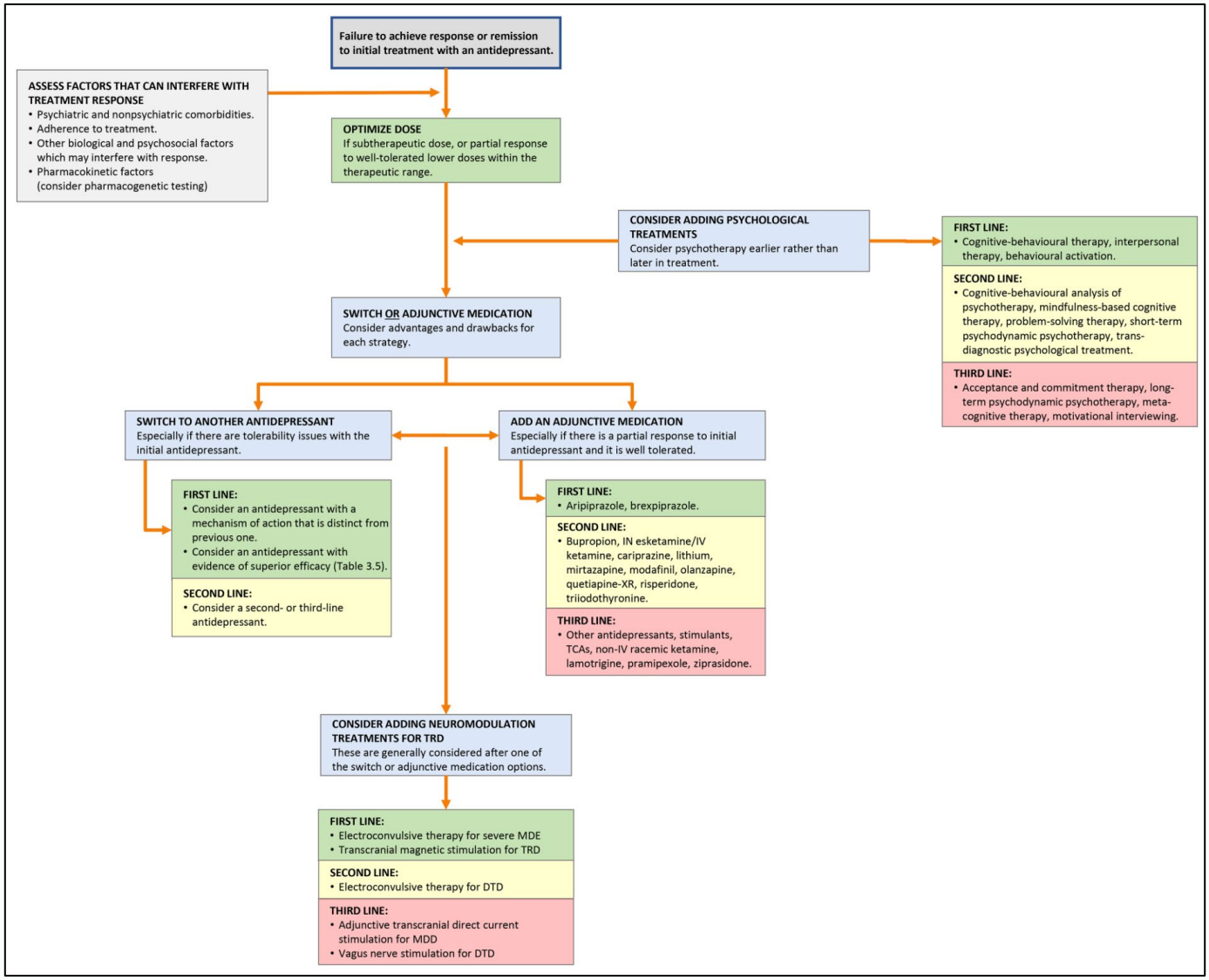
7.c. Assessment of Poor Response

- First step = clinical assessment
  - Re-evaluate the diagnosis, co-morbidities, and adherence
  - Lab investigations to rule out medical causes
  - Consider pharmacogenetic testing to identify rapid/slow metabolizers → impacting response or severity of side effects

- Systematic, sequential, and MBC may enhance outcomes when initial treatments are not fully effective

- Strategies
  - Optimize dose
  - Switch
  - Add adjunct
  - Incorporate psychological and/or neuromodulation

7.c. Assessment of Poor Response



7.c. Assessment of Poor Response

- Collaborative approach that integrates prior treatment history, strength of evidence, potential for adverse events, and patient preference

- Psychological treatments
  - Low potential for side effects ∴ consider early in treatment course

- Neuromodulation treatments
  - Have good evidence in TRD and DTD → but less likely to be considered early because of limited accessibility and patient burden

7.c. Assessment of Poor Response

- Optimize dose = often first step
  - If subtherapeutic dose or partial response to well-tolerated lower doses within therapeutic range

- Switch vs adjunct = next step
  - Evidence for switch = inconsistent
    - Switch *vs continuing* → NOT SUPERIOR + diminishing response rates beyond first switch
  - Adjunct (especially with AAP) → GREATER evidence for efficacy and SHORTER time to response or remission
    - Adjunct shown to have SUPERIOR OUTCOMES and SIMILAR TOLERABILITY to switch
  - ***Recommendation*** = adjunctive strategies be considered earlier

- Summary
  - Consider **SWITCH** when no response or significant tolerability concerns
  - Consider **ADJUNCT** when partial response and minimal or no tolerability concerns

7.d. When and How to Switch Antidepressants

- Early improvement
  - **20% reduction within first 4 weeks**
  - Predicts later response → if no response by 4 weeks = low likelihood of response/remission at 8-12 weeks

- Switching options
  - Switch *within class* vs *different class* → NO difference in outcome
  - ***Recommendation*** = select another **FIRST LINE** antidepressant with evidence for superior efficacy and a favourable tolerability profile (Table 3.5)
  - **TCAs** and **MAOIs** may be useful if poor response to first and/or **SECOND-LINE** antidepressants → efficacious treatments but downgraded due to side effect and safety profiles

7.d. When and How to Switch Antidepressants

- Switching strategies
  - Influenced by **1) discontinuation effects, 2) urgency of situation and 3) potential drug interactions**
  - **Crossover "X"** = slowly taper first med while slowly titrating second med
    - For most situations with low risk of drug interactions and side effects
  - **Washout "V"** = tapering and discontinuing first before staring second
    - For use when less urgency for switch, history of problems with discontinuation symptoms, or avoid conflating discontinuation symptoms with new side effects

- MAOIs → require at least 2 weeks' washout from other serotonergic drugs (5 weeks if fluoxetine)

- Online tools can help = SwitchRx.com

7.e. Benefits and Drawback of Adjuncts

- Benefit
  - Retains partial treatment gains from initial antidepressant
  - Avoids discontinuation symptoms
  - Complementary medication may have faster onset of response
  - Can target specific residual symptoms or side effects

- Drawbacks
  - Additive side effects
  - Increased cost of treatment
  - Potential for drug-drug interactions
  - Multiple medications can contribute to DECREASED adherence
  - Little evidence about maintenance → unclear how long adjunct meds should be continued for

7.f. Choosing an Adjunct

- Factors to consider
  - Efficacy and tolerability
  - Drug-drug interactions
  - Pharmacogenetic testing if available (especially in DTD)
  - Can try to target specific residual symptoms (little evidence to support this strategy)

- Minimize polypharmacy where possible → ongoing reassessment of concurrent meds and discontinue those with unclear benefits

7.g. Risks and Benefits of Specific Adjuncts

- Serotonin-dopamine activity modulators (low-dose AAP)
  - Most consistent evidence in DTD
  - Using lower doses than in bipolar disorder/schizophrenia
  - Common side effects to **FIRST-LINE** meds (**Aripiprazole** and **Brexpiprazole**) = akathisia and wt gain
  - **Olanzapine**/**Risperidone**/**Quetiapine-XR** have level 1 evidence but **SECOND-LINE** due to side effects
  - Long term risks
    - Tardive dyskinesia, although risk is lower with lower dosing
    - Increased mortality in older adults
    - Slightly increased risk of breast cancer but inconsistent reports → may be mitigated by lower dosing + using prolactin-sparing agents

- Second antidepressant
  - Less side effects compared to AAP but also less evidence for efficacy → **THIRD-LINE**

7.g. Risks and Benefits of Specific Adjuncts

- Glutamate modulators
  - Glutamate is implicated in pathophysiology of MDD and potential for **rapid onset of antidepressant effects**

  - Ketamine
    - IV racemic ketamine = extensive evidence for single dose, recent studies show effectiveness + safety for repeat infusions
    - IN esketamine approved as add-on for **TRD (≥ 2 failed med trials)**
    - IV racemic ketamine and IN esketamine BOTH have shown **mood-independent reductions in suicidal ideation**
      - IV anti-suicidal effects extending as long as 1 week post single infusion
    - Growing evidence for relapse prevention → maintenance doses every 1-4 weeks
    - Side effect potential and feasibility concerns → IV racemic ketamine and IN esketamine downgraded to **SECOND-LINE** due to required monitoring of BP and dissociative side effects
    - Variability in treatment protocols for non-IV racemic ketamine → downgraded to **THIRD-LINE**

  - Lamotrigine
    - Glutamate modulator as well
    - Well tolerated and effective as adjunct BUT risk of SJS → **THIRD-LINE**

7.g. Risks and Benefits of Specific Adjuncts

- Stimulants
  - Methylphenidate + other stimulants = mixed results
  - Side effects = anxiety, irritability, jitteriness and tremors, headaches, insomnia, appetite/weight loss
  - Can develop tolerance
  - Recommended **THIRD-LINE**
  - Modafinil has more consistent evidence but small effect sizes → **SECOND-LINE**
    - Potential for pro-cognitive effects and improvement in executive function

- Other medications
  - Lithium and T3 → old data with small sample sizes, requires serum monitoring → **SECOND-LINE**
  - Pramipexole (non-ergot based dopamine agonist) → **THIRD-LINE**
    - Shown to have acute and longer-term antidepressant effects in MDD and Bipolar Disorder (used in adjuncts for both)
    - Acceptability and tolerability were good, most common side effect = nausea
  - Cannabinoids → no evidence but cannabis shown to worsen depression → **NOT RECOMMENDED**

7.h. Psychological Tx AFTER Poor Med Response

- Moderate quality evidence for CBT
  - Reducing depressive symptoms and increasing response and remission rates
  - ***Recommendation*** = **SECOND-LINE** adjunct with meds for DTD

- Psychedelic assisted psychotherapy → review CANMAT Task Force Report
  - Several RCTs show efficacy
  - Promising results BUT ongoing methodological issues
  - Currently considered **INVESTIGATIONAL TREATMENT**

8 When Should Neuromodulatation Treatments be Used?

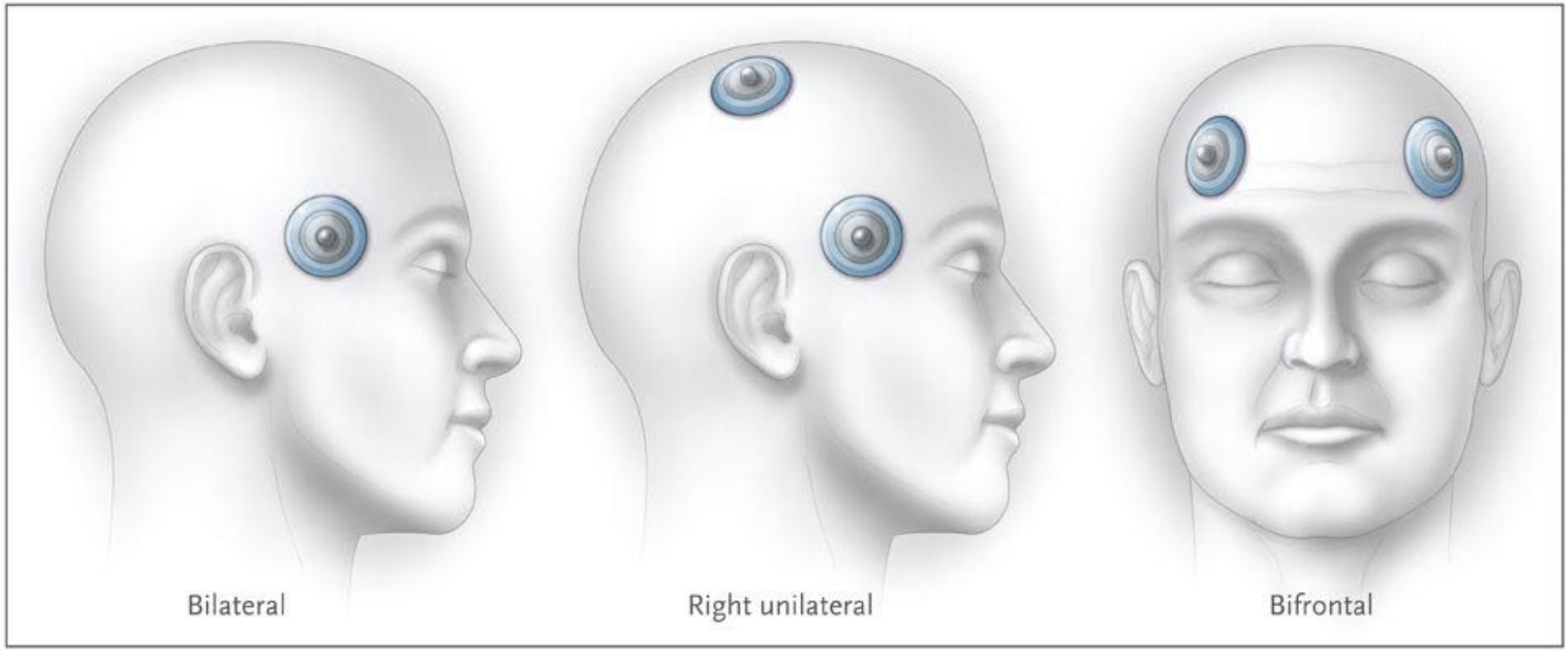
8.a. What Are Neuromodulation Treatments

- Neuromodulation = "Treatments that alter central nervous system activity through the application of electrical or magnetic stimulation of the brain"

- Non-invasive
  - ECT
  - rTMS
  - tDCS
  - MST (investigational)

- Invasive
  - VNS
  - DBS (investigational)

8.b. Non-invasive Treatment Modalities - ECT



8.b. Non-invasive Treatment Modalities - ECT

- Induction of seizure via electrical stimulus to brain
  - Controlled clinical setting, general anesthesia, muscle relaxant

- Limiting factors
  - Stigma
  - Need for general anesthesia
  - Cognitive concerns
  - High rates of relapse after acute treatment

- Recommendations in MDD
  - Due to adverse effects → **generally SECOND-LINE treatment**
  - Some clinical situations → can be **FIRST-LINE treatment**

- **BF, RUL** = **FIRST-LINE** (less cognitive AE)
- **BT** = **SECOND-LINE** (higher rates of short-term cognitive AE)

- ***Recommendation*** within Neuromodulation as a whole
  - **ECT as FIRST-LINE for severe MDD**
  - **ECT as SECOND-LINE for DTD**

8.b. Non-invasive Treatment Modalities - ECT

- Number of ECT treatments
  - Acute course = 6-12 sessions
  - No difference in response with 2x/week vs 3x/week

- Delivery recommendations
  - Placements: bitemporal, bifrontal, right unilateral
    - BT, BF, RUL → RUL fewer cognitive side effects + superior QOL outcomes, bitemporal greater efficacy but also greater cognitive burden
  - Waveforms: Brief pulse ≈ 1.0 ms vs Ultrabrief pulse ≈ 0.3 ms
  - Intensity: seizure threshold (BT/BF = 1.5x ST, RUL = 6x ST)

- ECT is one of the most effective treatments for MDD and specifically TRD
  - **Response rates 65-75%**
  - Especially effective in **1) older patients, 2) psychotic or catatonic features, and 3) more severely depressed patients**
  - **Benefits > risks** among hospitalised MDD patients
  - ECT **significant reduced risk of suicide in year after** discharge from hospital

8.b. Non-invasive Treatment Modalities - ECT

- Antidepressants and other medications
  - Can usually be continued during ECT treatment
  - Concurrent use of antidepressants during ECT shown to have **improved outcomes**
  - **Ketamine** has **NOT** been shown to improve outcomes (either as single dose infusion or as anesthetic)
  - Certain meds can interfere → **benzodiazepines, AED**
  - Certain meds can worsen cognitive side effects → **lithium and cannabis**

8.b. Non-invasive Treatment Modalities - ECT

- Side effects
  - ECT generally safe and well tolerated → rates of cardiac events and mortality = very low
  - Cognitive effects immediately after ECT include: transient disorientation, confusion, and memory lapses → particularly anterograde amnesia
    - Typically resolve in days to weeks, retrograde amnesia can persist for longer
    - Cognitive performance at 1 month post ECT is **unchanged or improved**
    - May still experience significant and distressing gaps in memory long after ECT

(2016 Guidelines) ECT

- Mortality rate → <1 per 73,440 treatments (0.0014%)

- Most common AE → transient, symptomatic tx
  - **Headache (45%),** muscle soreness (20%), nausea (1-25)

  - **Switch to manic/mixed state (7%)**

8.b. Non-invasive Treatment Modalities - ECT

- High rates of relapse/recurrence after acute ECT course
  - Relapse rate **60-80% of patients at 6-months**
  - Maintenance strategy recommended → continuation ECT or maintenance pharmacotherapy

- Continuation ECT
  - Continuation ECT = administered at increasing intervals from once a week to once a month
  - **Continuation ECT > maintenance pharmacotherapy** in preventing recurrence

- Maintenance pharmacotherapy
  - Little data on specific medication strategies, ADs or AD class
  - **Combo nortriptyline/venlafaxine + lithium** → superior for relapse prevention compared to either antidepressants alone

- Cognitive outcomes
  - Equal with maintenance ECT vs maintenance pharmacotherapy

(2016 Guidelines) ECT

- Hypothesized mechanism → seizure-induced changes
  - Neurotransmitters, neuroplasticity, functional connectivity
  - Can ↑ BDNF → may have antidepressant effect

- Safety risk factors **(NO absolute contraindications)**
  - Space-occupying cerebral lesions, ↑ intracranial pressure
  - Recent cerebral hemorrhage, unstable vascular aneurysm or AVM
  - Recent MI, pheochromocytoma, class 4/5 anesthesia risk

8.b. Non-invasive Treatment Modalities - ECT

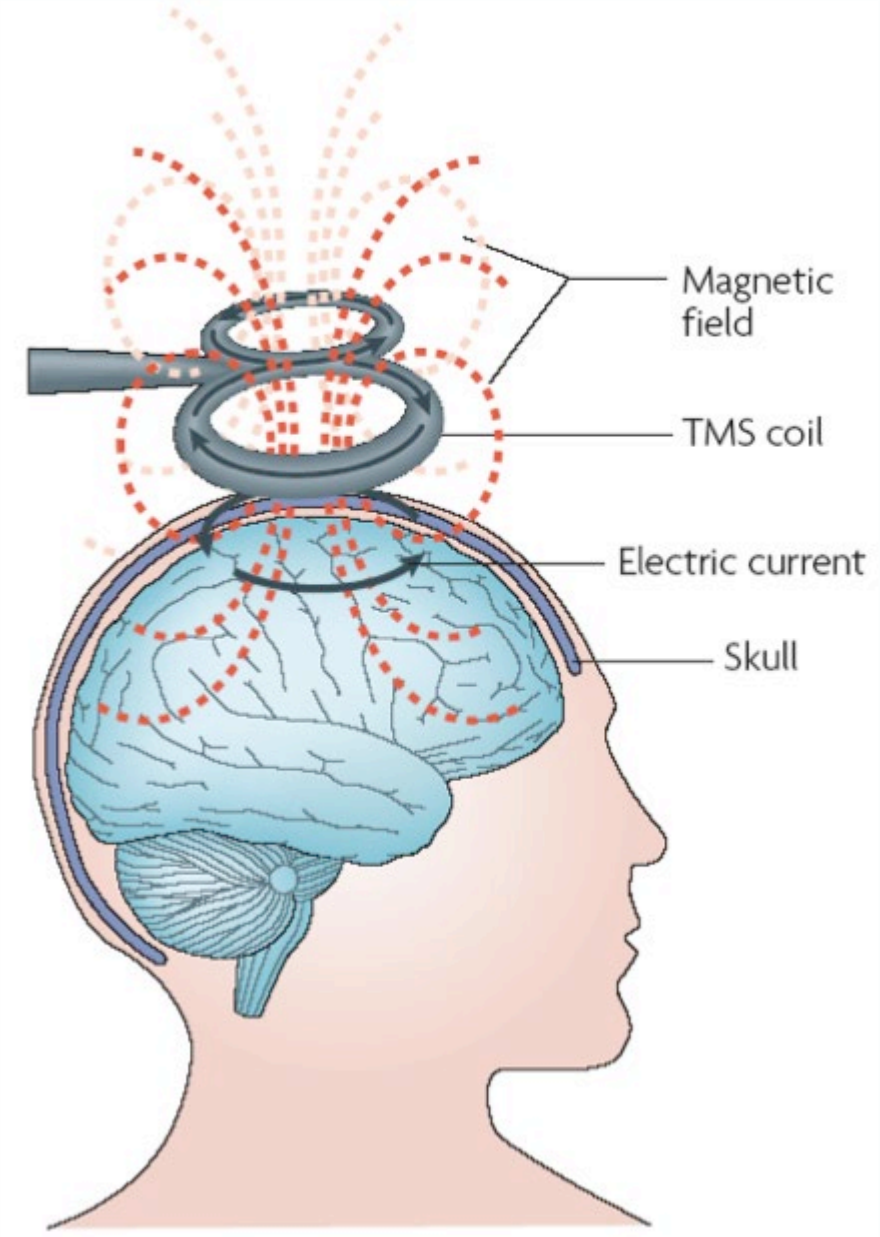
Table 8.1. Recommendations for Electroconvulsive Therapy (ECT) Protocols.

Line of treatment	ECT protocol	Level of evidence
First Line	Brief Pulse, bifrontal (at 1.5 times seizure threshold)	●
	Brief Pulse, right unilateral (at 6 times seizure threshold)	●
	Ultrabrief Pulse, right unilateral (at 6 times seizure threshold)	●
Second Line	Brief Pulse, bitemporal (at 1.5 times seizure threshold)	●
	Ultrabrief Pulse, bifrontal (at 1.5 times seizure threshold)	●

● Level 1; ◔ Level 2; ◐ Level 3; ◕ Level 4.

Note. By convention, treatments are listed within each line of treatment by level of evidence, then alphabetically.

8.b. Non-invasive Treatment Modalities - rTMS



8.b. Non-invasive Treatment Modalities - rTMS

- Inductor coil placed against scalp
  - Powerful, focused magnetic field pulses
  - Induces electrical currents in neural tissue, non-invasively
  - **No anesthesia required + no cognitive side effects**

- Protocols
  - Conventional → **20-40 mins once daily, 5 days/week, for 4-6 weeks**

- ***Recommendation*** within Neuromodulation as a whole
  - **rTMS as FIRST-LINE for TRD**

8.b. Non-invasive Treatment Modalities - rTMS

- Parameters
  - Type of coil, location of scalp where coil is placed (direct pulses towards specific cortical brain region), frequency of stimulation, and number and duration of magnetic pulses aka “trains”
    - Frequency: low = 1 Hz or lower | high = 5 Hz or higher

- ***Recommendation*** for rTMS protocols
  - **High-frequency rTMS to left DLPFC** is **FIRST-LINE**
  - **Low-frequency rTMS to right DLPFC** is **FIRST-LINE**

8.b. Non-invasive Treatment Modalities - rTMS

- Parameters
  - Accelerated → newer protocols, use individualized functional MRI, multiple daily sessions to reduce overall duration of treatment to as short as 5 days

- Theta burst stimulation (TBS)
  - Theta burst stimulation = delivers trains of 3 pulses at very high frequency (50 Hz)
    - Convention delivers single pulse up to frequency of 20 Hz
  - Intermittent TBS (iTBS) = 2s trains of TBS repeated every 10s for a total of 190s (just over 3 mins)
  - **Intermittent** thought to **increase** excitability | **continuous** thought to **decrease** excitability
  - Research shows no differences between accelerated bilateral TBS vs high frequency rTMS

- ***Recommendation*** for rTMS protocols
  - **iTBS to left DLPFC** is **FIRST-LINE**
  - **Accelerated iTBS to left DLPFC** is **SECOND-LINE**

8.b. Non-invasive Treatment Modalities - rTMS

- Unilateral rTMS = **FIRST-LINE**
  - **High-frequency left DLPFC**
  - **Low-frequency right DLPFC**
  - **iTBS to left DLPC**

- Bilateral stimulation
  - Low-freq right THEN high-freq left to DLPFC
  - Continuous right TBS + intermittent left TBS to DLPFC

- ***Recommendation***
  - **Sequential Bilateral rTMS to DLPFC (right low then left high)** as **FIRST-LINE**
  - **Sequential Bilateral TBS to DLPFC (right continuous then left intermittent)** as **SECOND-LINE**

8.b. Non-invasive Treatment Modalities - rTMS

Table 8.2. Summary Recommendations for Repetitive Transcranial Stimulation (rTMS) Protocols.

Line of treatment	Transcranial magnetic stimulation protocol	Level of evidence
First Line	iTBS to left DLPFC.	
	High-frequency rTMS to left DLPFC.	
	Low-frequency rTMS to right DLPFC.	
Second Line	Sequential Bilateral rTMS to DLPFC (right low frequency then left high frequency).	
	Accelerated iTBS to left DLPFC.	
	Sequential bilateral TBS to DLPFC (right continuous TBS then left intermittent TBS).	

8.b. Non-invasive Treatment Modalities - rTMS

- rTMS as add-on to pre-existing AD in most studies
  - Concurrent antidepressants may **augment response rates**
  - Specific meds such as benzodiazepines may negatively affect response rates

(2016 Guidelines) rTMS

- rTMS where ECT has failed → **poor response rates**
  - Consider **rTMS before ECT**
  - If no response to ECT → **unlikely to respond to rTMS**

(2016 Guidelines) rTMS Adverse Effects

- Scalp pain during (40%), transient headache after (30%)
  - Most common, **diminish steadily** over treatment
  - Respond to **OTC analgesia**, cause **low rates of discontinuation**

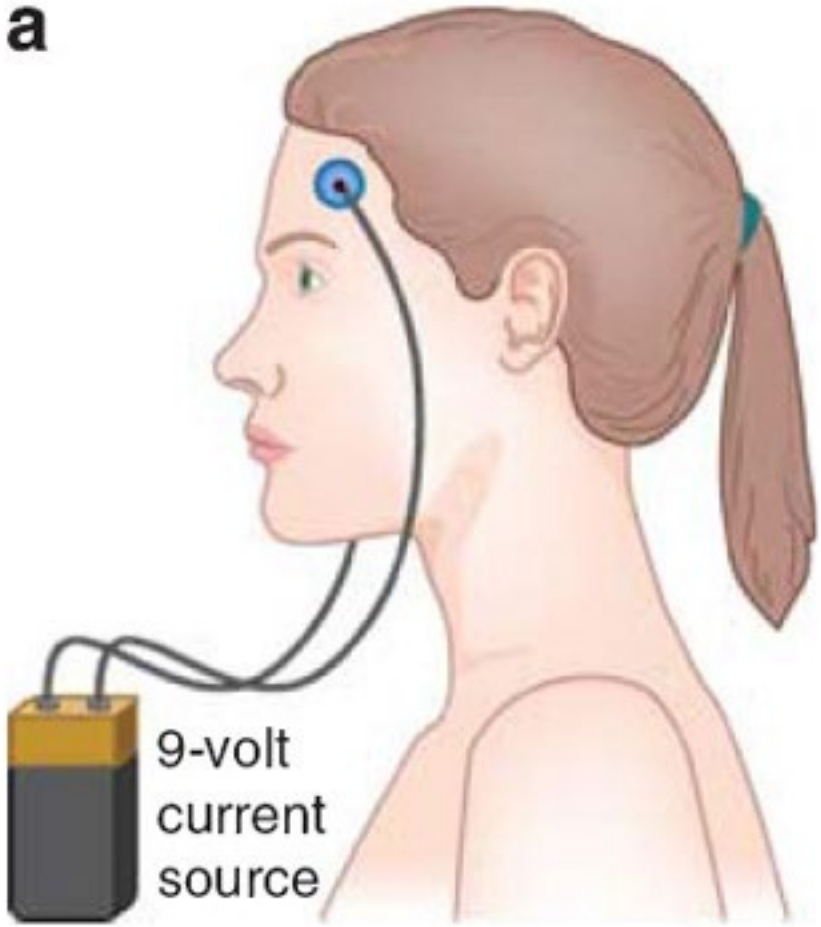
- Cognitive domains = no worsening (no difference vs sham)

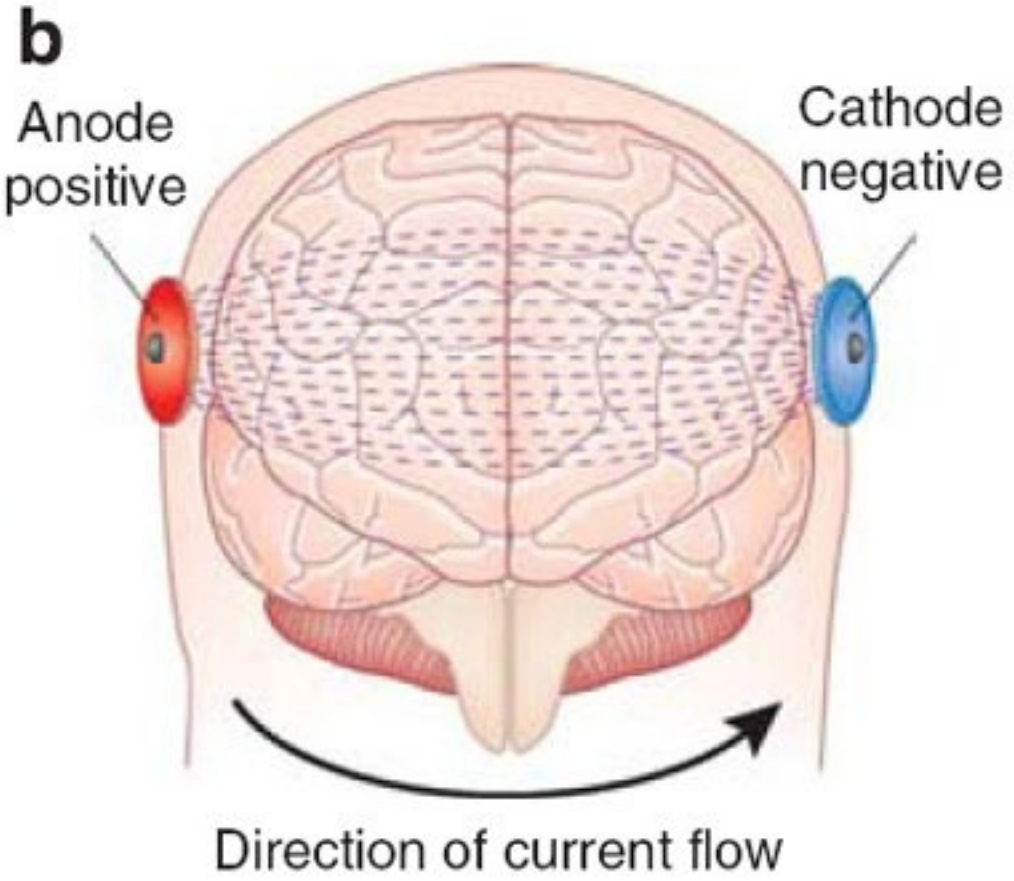
- **Seizure induction** = most serious rTMS adverse event
  - <25 cases worldwide
  - Incidence **0.01 – 0.1% rTMS** (0.1 – 0.6% AD, 0.07 – 0.09% spont)
  - If hx seizures → **high-freq rTMS CONTRAINDICATED**
  - In epilepsy → **low-freq rTMS safe** (not specifically seizures + dep)
  - Most practitioners → hx seizures = **CONTRAINDICATION**

(2016 Guidelines) rTMS Adverse Effects

Contraindications to rTMS	
Absolute Contraindications	**Relative Contraindications**
• **Metallic hardware** in head (except mouth) • (many consider hx **seizures**)	• **Cardiac pacemaker** • **Implantable defibrillator** • Hx **epilepsy** • **Brain lesion** (vascular, traumatic, neoplastic, infectious, metabolic)

8.b. Non-invasive Treatment Modalities - tDCS





8.b. Non-invasive Treatment Modalities - tDCS

- Using scalp electrodes, to specific cortical region
  - Continuous, weak electrical current

- Advantages
  - Ease of use, low cost, portability, potential for home-use
  - Ability to combined with other tx
  - Low potential for AE

- More effective than sham in mild-moderate depression
  - Shown in meta-analyses
  - Especially when combined with antidepressant
  - However significant heterogeneity in stimulation parameters + patient population, high sham responses, and some negative results from recent + large RCTs
  - Use in severe depression or DTD not supported

- ***Recommendation*** within Neuromodulation as a whole
  - **tDCS as SECOND-LINE adjunct for mild-moderate MDD**

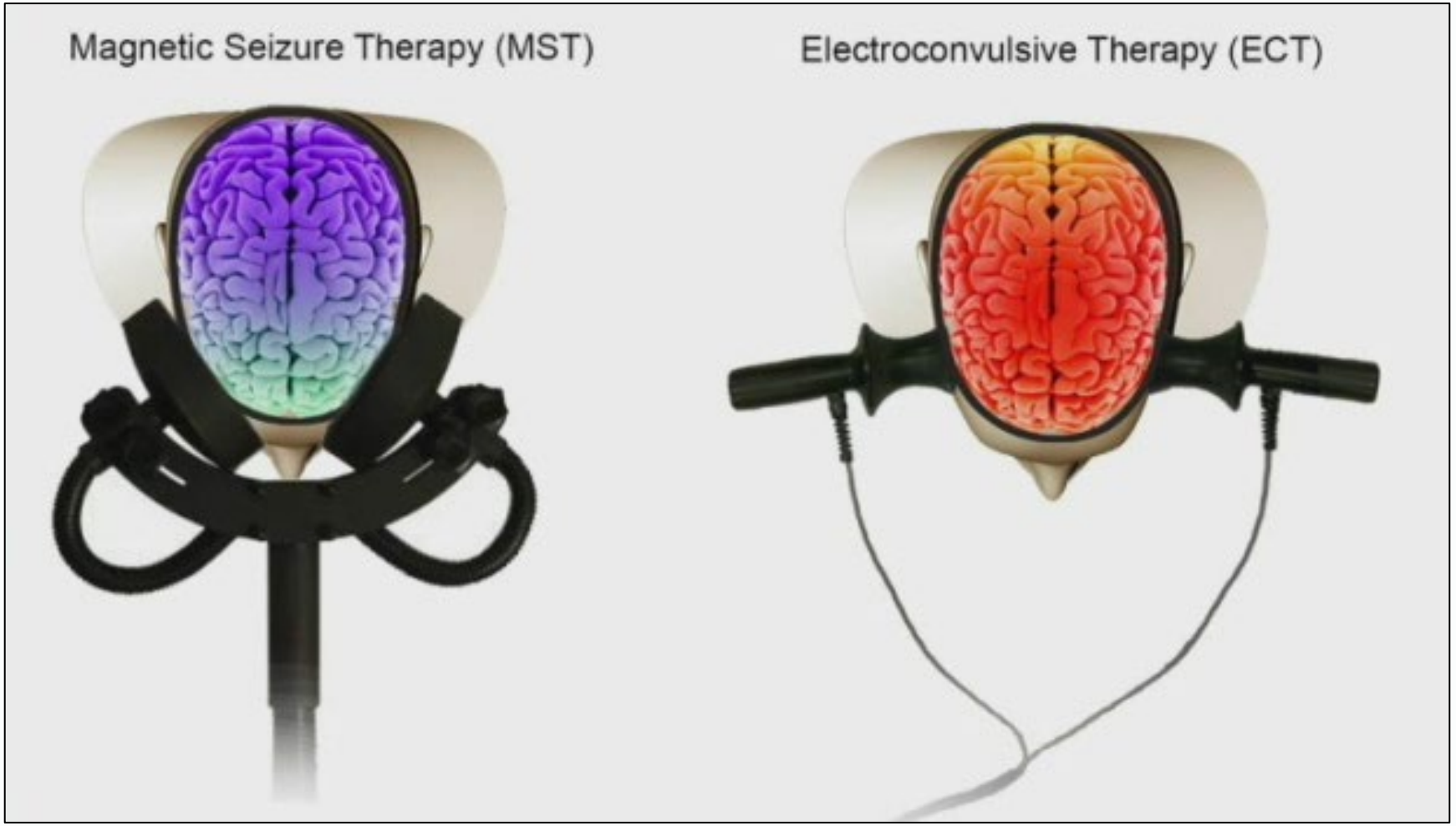
(2016 Guidelines) tDCS

- Well-tolerated in most studies
  - **Most common (>50%) → regional effects at skin**
    - Redness, itching, burning, heat, tingling
  - Low rates (minimal difference vs sham)
    - Headaches, blurred vision, ear ringing, brighter or illuminated vision, fatigue, nausea, mild euphoria, reduced concentration, disorientation, insomnia, anxiety

- Combination with sertraline 50mg
  - Hypomania 10% (3 pts), mania 7% (2 pts)

- No studies on long-term safety/tolerability

8.b. Non-invasive Treatment Modalities - MST



8.b. Non-invasive Treatment Modalities - MST

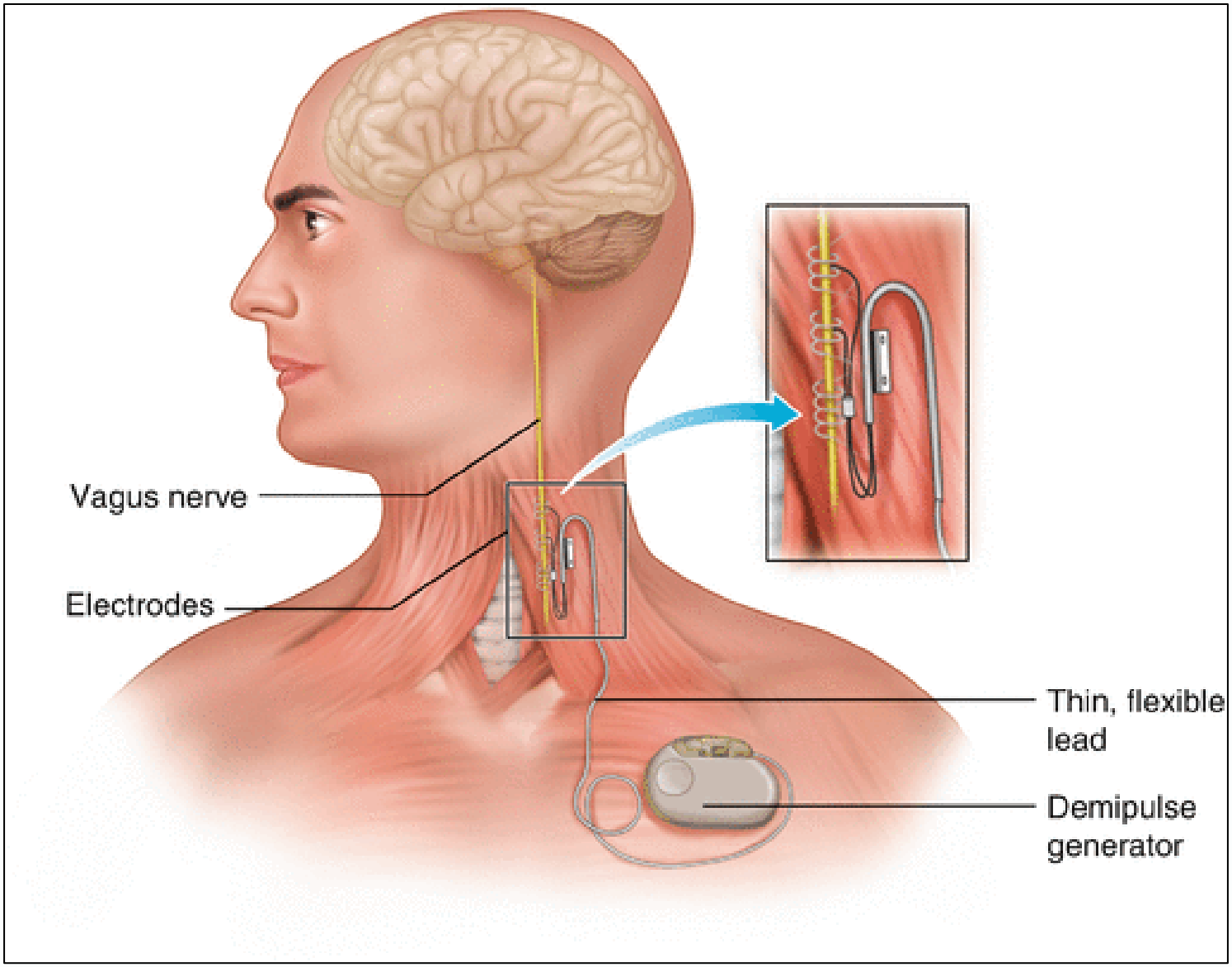
- Non-invasive convulsive neurostimulation
  - Electromagnetic induction to elicit **generalized tonic-clonic seizure**
    - Neurostimulator + coil → direct contact with skull
    - Induces an electrical field that elicits a seizure vs direct electrical current
  - Requires GA, assisted ventilation, EEG monitoring
  - Promising results in small sample RCTs → similar efficacy to RUL ECT but fewer adverse effects
  - Need more definitive studies
- ***Recommendation*** within Neuromodulation as a whole
  - **MST as INVESTIGATIONAL TREATMENT for DTD**

(2016 Guidelines) MST

- Compared to ECT
  - Lower rates of **headaches, muscle aches**
  - No sig impact on **retrograde + anterograde amnesia**
  - **Shorter reorientation time**

- MST vs RUL ECT
  - **No difference in neuropsych testing** after 12 treatments

8.c. Neurosurgical Treatment Modalities - VNS



8.c. Neurosurgical Treatment Modalities - VNS

- Implantable pulse generator, electrode into vagus nerve
  - Originally for drug-resistant epilepsy
  - Stimulation to **left vagus nerve** = stimulation of **nucleus tractus solitarius** and its **cortical/subcortical regions**

- Limited evidence
  - Few RCTs and even within these VNS vs sham RCT → no significant differences in short term
  - Some evidence that longer-term treatment (2-5 years) may result in superior response and remission compared to treatment-as-usual cohorts

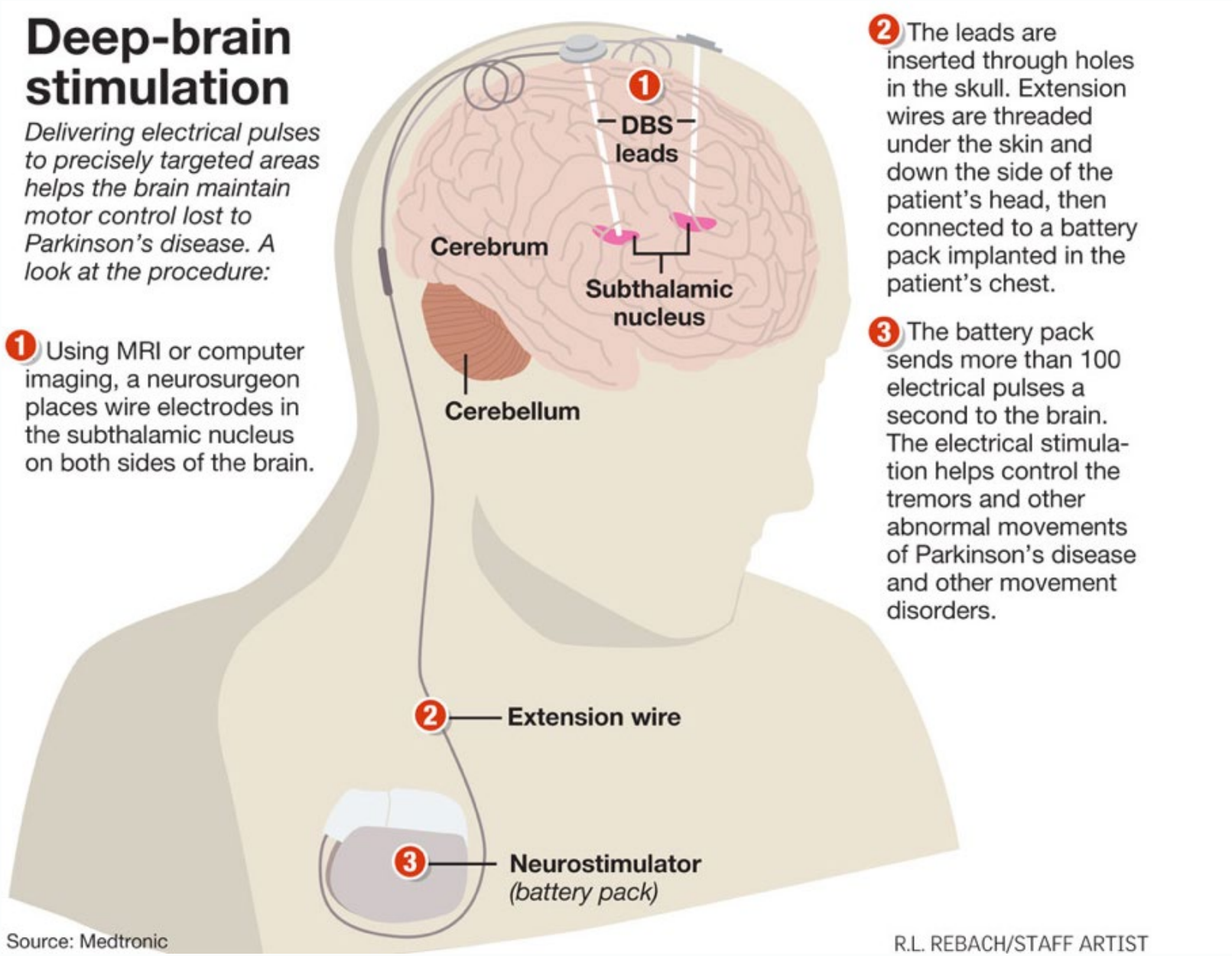
- ***Recommendation*** within Neuromodulation as a whole
  - **CNS as THIRD-LINE for DTD**

8.c. Neurosurgical Treatment Modalities - VNS

- Adverse effects
  - Most common
    - Pain related to device implantation, voice hoarseness or alteration (due to intermittent stimulation of larynx), incr cough, headache, sore throat, and neck pain

- (from 2016 guidelines)
  - Most common
    - **Voice alteration (69%),** dyspnea (30%), pain (28%), incr cough (26%)
    - Voice + cough → direct effects, improve by turning VNS off
    - Tolerability improves over time
  - Serious adverse psychiatric events
    - **Suicide + attempted suicide** (4.6%)
    - **Tx-emergent hypomania/mania** (2.7%)
  - LOWER all-cause mortality in TRD with VNS (vs TAU)

8.c. Neurosurgical Treatment Modalities - DBS



8.c. Neurosurgical Treatment Modalities - DBS

- Electrode implantation into discrete brain targets
  - **Neurosurgical**, MRI guidance, connected to IPG under R clavicle
  - DBS parameters: pulse width, frequency, amplitude
  - Most common indications → **movement disorders (Parkinson's)**

- Still experimental treatment → refractory depression
  - Anatomical targets for TRD
    - **Most frequently studied = SCC (subcallosal cingulate white matter)**
    - **VC/VS** (ventral capsule, ventral striatum)
    - **NA** (nucleus accumbens)
    - **Anterior limb of the internal capsule**
    - **MFB** (medial forebrain bundle)

8.c. Neurosurgical Treatment Modalities - DBS

- Limited patient population given nature of procedure
  - Highly refractory illness, including ECT nonresponders
  - Open label studies demonstrate high response rate in those with DTD across several targets
    - Sham-controlled RCT looking at SCC did NOT show efficacy after 6 months
- Longer term observational studies suggest (like in VNS) therapeutic effects increase over time
- Transient side effects associated with stimulation
- Serious adverse events related to neurosurgery implantation
- ***Recommendation*** within Neuromodulation as a whole
  - **DBS as INVESTIGATIONAL TREATMENT for DTD**

8.d. When to use Neuromodulation Treatments

- Generally non-invasive neuromodulation = safe and well-tolerated

- ECT is more efficacious for DTD than others BUT greater side effect burden

- rTMS typically recommended for TRD vs ECT for DTD → AFTER failure of **FIRST-LINE** psychotherapy and medication treatments
  - Because of feasibility, limited availability, patient burden, and need for specialized personnel

- Surgical neuromodulation treatments should be considered after non-invasive

8.d. When to use Neuromodulation Treatments

- Clinical situations where can be considered **FIRST-LINE**
  - **ECT as first line:**
    - Severe illness = MDD with psychotic or catatonic features
    - Severe suicidal ideation
    - Deteriorating physical condition
  - **rTMS as first line:**
    - Tolerability concerns with medications
    - History of effectiveness
  - In emergent situations → **rTMS considered BEFORE ECT**
    - Mixed evidence on **prior poor response to ECT** leading to **poor response to rTMS**

8.d. When to use Neuromodulation Treatments

Table 8.3. Summary Recommendations for Neuromodulation Treatments.

Line of treatment	Neuromodulation treatment	Level of evidence: Acute efficacy	Level of evidence: Maintenance efficacy
First line	ECT for **severe MDE.***		
	rTMS for T**RD**.		
Second line	ECT **for DTD**.		
Third line	Adjunctive use of tDCS **for mild–moderate MDE**.		
	VNS **for DTD**.		
Investigational	DBS **for DTD**.		Not known
	MST **for DTD**.		Not known