CANMAT MDD 2016

Depression Guidelines

Slides: B Chow
Updates: L Jia 2021

Contents

1 Disease Burden & Principles of Care

1.1 Depressive 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)

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**

1.2 Clinical Specifiers

- **Peripartum onset**
  - Postpartum depressive episodes → **50% onset PRIOR to delivery**

- **Anxious distress**
  - Even if without comorbid anxiety disorder
  - **Increases SUICIDE rates**
  - Poor response to treatment
  - Increase risk of chronicity, recurrence

- **Mixed features**
  - Up to 1/3 of MDE pts (prevalence varies depending on criteria)

1.2 Dimensions of MDE

- Cognitive symptoms
  - Attention, memory, processing speed, executive function
  - Evidence on neuropsychological tests during acute MDE
  - **Common residual sx** → may continue after mood sx remitted

- Sleep disturbances
  - In acute MDD, residual sx, medication side effects
  - Bidirectional relationship with depression

- Somatic symptoms
  - Pain, fatigue → common
  - Associated poor outcomes in depression

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

1.3 Prevalence and Incidence

- Prevalence of MDE (Canada)
  - Annual = 4.7% → NO changes since 2002
  - Lifetime = 11.3%

- Prevalence of MDD (not bipolar)
  - **Annual = 4%** → female 4.9%, male 2.8%
  - **Lifetime = 10%** → inverse relationship with age

- Incidence of MDE (Canada)
  - 2 years = 3%
  - 4 years = 6%

- **50% of MDE = brief** → resolution in 3 months

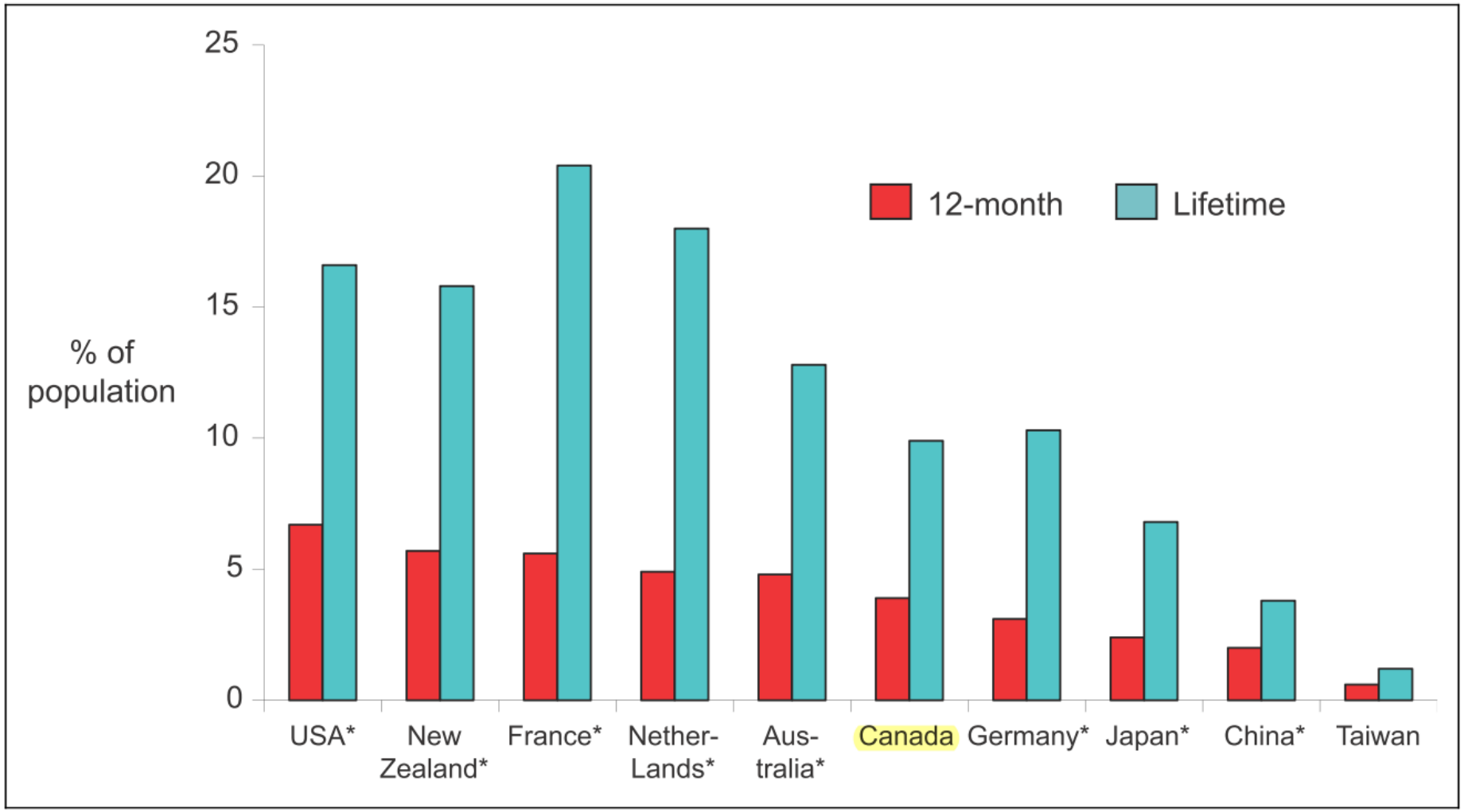
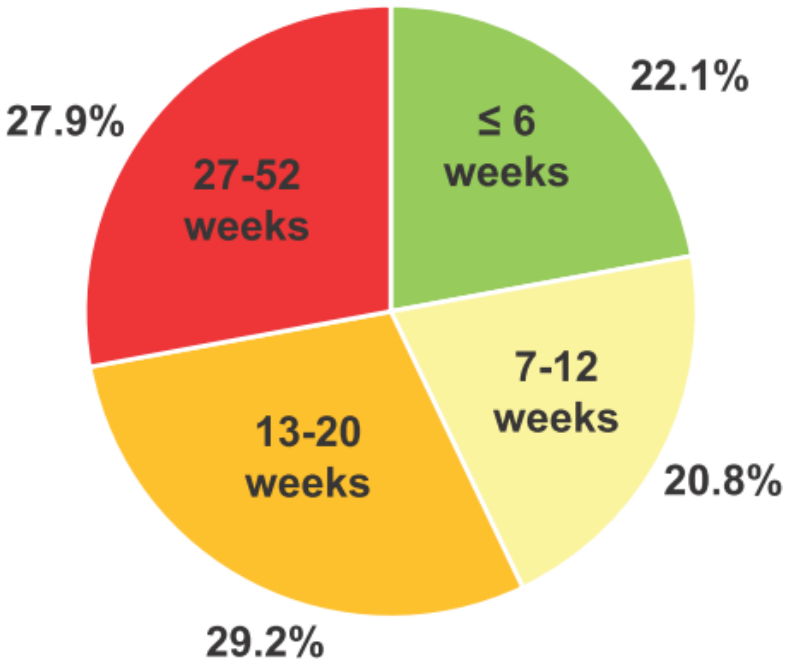


Figure 1. Prevalence of major depressive disorder by world region. *WMH, World Health Organization's World Mental Health Surveys, Canada, CCHS[113]; Taiwan Psychiatric Morbidity Survey.[114]

In the past 12 months:

MDD prevalence	3.9%
Sought treatment	63%
Taking an antidepressant	33%
With generalized anxiety disorder	25%
Suicide attempts	6.6%
With alcohol abuse & dependence	4.8% 4.5%

Number of weeks depressed in past year



1.4 Risk of Relapse & Recurrence

- Chronicity
  - 26.5% chronic episode >2 years (US)
  - 15.1% chronic course during 3-year follow-up (US)

- Recurrence
  - 35% recurrent MDE in 3-year follow-up (US)
  - Netherlands, after remission for 3 months in 2-year follow-up
    - Primary care = 26.8% recurrence
    - Specialized mental health care = 33.5% recurrence

1.5 Disease Burden

- Disease burden metrics
  - Early mortality + loss of function
  - **DALYs** (disability-adjusted life years)
  - **HALYs** (health-adjusted life years)

- Depressive disorders = **2nd leading cause of disability**
- MDD = **2.5% of global DALYs**

1.6 Occupational Impact

- Major productivity losses due to depression
  - Absenteeism (away from work), presenteeism (while at work)
  - MDD 5% of population illness-related productivity loss
  - Mean 34.4 "days out of role"
  - **Twice as likely to leave work** during 10-year follow-up (Canada)

- Higher degree of work disability
  - Illness severity, medical comorbidities, anxiety disorders

- Workplace performance
  - Concentration, mood, fatigue, insomnia
  - **Cognitive dysfunction** = more strongly assoc with productivity loss
  - **Depression treatment** → sig positive effect on productivity

1.7 Impact on Other Domains

- Social impairment
  - Mood, anhedonia, concentration, self-blame

- Perinatal maternal depression → adverse outcomes in child
  - Emotional regulation
  - Internalizing disorders
  - Behavioral disorders
  - Hyperactivity
  - Decr social competence
  - Insecure attachment
  - Adolescent depression
  - Cognitive development

- Effective treatment of maternal depression
  - Improved parenting
  - **Reduced psychiatric symptoms in offspring**

1.8 Impact on Physical Health

- MDD in chronic medical illness → worse disability, QoL
  - Heart disease, HTN, asthma, COPD, migraine, back pain, arthritis
  - Reduced adherence to treatment
  - Interferes with participation in preventative health care

- MDD = independent risk factor for **ischemic heart disease** + **cardiovascular mortality**
  - Vascular risk factors → assoc with depression in later life

- Bidirectional relationship with obesity + metabolic problems
  - Immune-inflammatory dysfunction
  - Neural plasticity, neuroprogression

1.9 Typical MDD Presentation

- Broad range of presentations
  - Often presenting with physical symptoms (high comorbidity)
  - Screening more effective if additional supports available

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

1.10 Clinical Management

- Stepped care + chronic disease management models
  - **Significant improvements** in depression outcomes
  - Systematic monitoring of outcomes
  - Patient education
  - Evidence-based treatment decisions

- Strategies to improve treatment adherence
  - Patient education
  - Supported self-management
  - Collaborative care
  - Discuss early, monitor frequently

1.10 Clinical Management

- Self-management
  - Manage depression, assoc tx, physical + psychosocial sequelae
  - Action planning to change behavior
    - Behavioral activation, communication skills, coping with emotion
    - Patient education, healthy lifestyle, relapse-prevention planning
    - Skill development, self-monitoring
  - Decrease reliance on HCPs
  - **Increase empowerment + self-efficacy**

Table 6. Principles of Clinical Management (Level 4 Evidence, Unless Indicated).

- Conduct a thorough biopsychosocial assessment, using clinical scales.
- Obtain collateral information whenever possible.
- Formulate a diagnosis and differential diagnosis.
- Establish a therapeutic alliance.
- Support education and self-management (Level 2 Evidence).
- Engage the patient as a partner to determine treatment goals.
- Construct a comprehensive management plan, including safety, together with the patient and his or her family (or other supports) if possible.
- Deliver evidence-based treatments.
- Monitor outcomes with measurement-based care (Level 2 Evidence).

1.11 Suicide Risk

- **History of suicide attempt** = STRONGEST RISK FACTOR

- Suicide risk assessment tools **NOT RELIABLE** predictors of SA
  - SADPERSONS
  - Columbia Suicide Severity Rating Scale

Table 7. Risk Factors for Suicide During a MDE (Level 3 Evidence)

Non-Modifiable	*Modifiable*	
• **Past suicide attempt** • **Family hx of suicide** • Hx of **self-harm** • Hx of **legal problems** • **Older men** • **Sexual minority**	<u>Symptoms & Life Events</u> • **Active SI** • **Psychotic symptoms** • **Hopelessness** • **Anxiety** • **Impulsivity** • **Stressful life events** (finance, victimization)	<u>Comorbidities</u> • **SUD** (esp AUD) • **PTSD** • **Personality disorders** (esp cluster B) • **Chronic pain** conditions (migraines, arthritis) • **Cancer**

1.12 Measurement-Based Care

- Validated rating scales
  - Monitor outcomes → depressive sx, function, QoL
    - Can improve symptom remission, adherence
  - Support clinical decision-making

- Patient-rated questionnaires
  - Highly corelated with clinician-rated scales
  - **Simpler to use**
  - **More efficient**

Table 8. Examples of Validated Outcomes Scales

Outcome	*Clinician Rated*	*Patient-Rated*
Symptoms	• **HAM-D** (Hamilton Depression Rating Scale) • **MADRS** (Montgomery-Asberg Depression Rating Scale) • **IDS** (Inventory for Depressive Symptomatology)	• **PHQ-9** (Patient Health Questionnaire) • **QIDS-SR** (Quick Inventory for Depressive Symptomatology, Self-Rated) • **CUDOS** (Clinically Useful Depression Outcome Scale)
Functioning	• **MSIF** (Multidimensional Scale of Independent Functioning) • **WHO-DAS** (WHO Disability Assessment Scale) • **SOFAS** (Social and Occupational Functioning Assessment Scale)	• **SDS** (Sheehan Disability Scale) • **WHO-DAS, self-rated** • **LEAPS** (Lam Employment Absence and Productivity Scale)
Side Effects	• **UKU Side Effect Rating Scale**	• **FIBSER** (Frequency, Intensity and Burden of Side Effects Rating)
Quality of Life	• **QOLI** (Quality of Life Interview)	• **QLESQ** (Quality of Life, Enjoyment and Satisfaction Questionnaire) • **EQ-5D** (EuroQoL-5D)

1.13 Phases of Treatment

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

Table 9. Phases of Treatments and Activities

Phase	*Goals*	*Activities*
Acute (8 – 12 weeks)	• **Remission** of symptoms • **Restoration** of functioning	• Establish **therapeutic alliance** • **Psychoeducation** • Support **self-management** • Deliver **evidence-based tx** • **Monitor progress**
Maintenance (6 – 24 mos, or longer)	• **Return** to full functioning and quality of life • **Prevention** of recurrence	• **Psychoeducation** • Support **self-management** • **Rehabilitate** • Treat **comorbidities** • **Monitor for recurrence**

1.14 Goals of Acute and Maintenance Treatment

- Acute Treatment
  - **Achieve remission**
    - No longer meeting criteria
    - Restoration of premorbid psychosocial function
  - **Reduce residual depressive sx**
    - Risk factor for relapse
    - Negative predictors of long-term outcome

- Maintenance Phase
  - **Prevention of recurrence**
    - Healthy life strategies, personality vulnerabilities, long-term self-management
    - Pharmacological, psychological, neurostimulation, CAM

1.15 Longer Term Treatment

- Chronic or recurrent course → **half of MDD pts**

Table 10. Risk Factors for Chronic or Recurrent Episodes (Level 3 Evidence)
• **Earlier age of onset** • More **previous episodes** • **Initial episode severity** (# symptoms, SI, psychomotor agitation) • **Comorbid psychopathology** (PDD, dysthymia) • **Family hx of psychiatric illness** • Presence of **negative cognitions** • **High neuroticism** • **Poor social support** • **Stressful life events**

2 Psychological Treatments

2.1 Indication for Psychological Treatments

- Low to moderate severity cases
  - Can balance preferences + availability
    - Availability of high-quality evidence-based psychological tx
    - Risk of delay in treatment initiation

- Severe + high-risk cases
  - Need to start immediately → consider all modalities

- Pregnancy/wanting to conceive
  - May preferentially consider psychological treatment

- **NOT indicated for psychotic depression**
  - Requires pharmacotherapy +/- ECT

2.2 Who is Most Likely to Benefit?

- Demographics
  - **Equal benefit** M=F, all ages, education levels, cultures, ethnicities
  - **CBT = equal for all subtypes** of depression
  - **PDD → meds or combo BETTER** (than psychological tx alone)

- Severity
  - Does NOT predict outcomes with meds vs CBT
  - **More severe → greater benefit** from psychological tx
    - May be beneficial for subthreshold depressive sx
    - But **faster improvement with pharmacological tx**

2.3 Comorbidities

- Psychiatric Comorbidities (insufficient evidence, no formal recommendations)
  - Anxiety → conflicting/insufficient evidence
  - SUD → **CBT effective**
  - AUD → **integrated psychosocial tx** (level 2)
  - ADHD → **CBT improves both** depressive + ADHD sx
  - Personality disorder → **neg impact** on tx outcomes

- Medical Comorbidities (insufficient evidence, no formal recommendations)
  - CVD → **CBT, IPT, PST (problem-solving therapy)**
  - Cancer → various interventions, phase of cancer tx
  - HIV → **CBT**, improved adherence , improved depression
  - Neurological → **CBT** for MS, PD (also epilepsy, migraines)
  - Hep C → **CBT, IPT**

Table 2. Impact of Comorbid Psychiatric Disorders on Psychological Treatments in MDD		
Comorbidity	*Summary of Findings*	*Evidence*
Anxiety	• May NOT complicate/reduce response to psychological tx • **CBT = MORE beneficial** than other psychological tx	Conflicting Level 2
SUD	• **CBT = improves BOTH** depressive + substance abuse sx • **Integrated tx = EFFECTIVE** (small effect size)	Level 2 Level 2
PDs	• PDs → NEGATIVE impact on depression tx outcomes	Level 2
ADHD	• **CBT = helps BOTH** depressive + ADHD sx (adjunct to meds)	Level 2

Table 3. Impact of Comorbid Medical Disorders on Psychological Treatments in MDD		
Comorbidity	*Summary of Findings*	*Evidence*
Cancer	• Evidence varies by psychological tx, phase of cancer tx • Multiple small positive RCTs	Level 2
CVD	• **CBT, IPT, PST = effectiveness shown** (alone, with meds)	Level 2
MS	• **ALL BENEFICIAL** (various tx studied, mainly CBT)	Level 2
HIV	• **CBT = EFFECTIVE** (mostly delivered in group) • **IPT = EFFECTIVE** (limited studies)	Level 1 Level 2
Epilepsy	• **CBT = moderate benefit** for depressive sx (limited data)	Level 3
Migraines	• **Various tx = moderate benefit** for depressive sx	Level 3
Parkinson's	• **CBT = EFFECTIVE** for depressive sx	Level 2
Hepatitis C	• Psychological tx may be useful	Level 3

2.4 Gender & Age

- Perinatal, childbearing age
  - Mild-moderate depression → **psychological tx = FIRST LINE**
  - May be preferred (potential adverse effects of antidepressants)

- Elderly
  - May be relevant → med SE, drug interactions

2.5 Therapist Factors

- Therapy relationships
  - 3 common factors predicting positive outcomes
    - Establishing **strong therapeutic alliance**
    - **Using empathy**
    - Collecting **client feedback**

- Factors improving outcomes
  - Therapist supervision + feedback
  - Therapist experience, adherence, responsiveness

Table 4. Evidence-based Therapy Relationships: Therapist Factors That Improve Clinical Outcomes	
Efficacy	*Elements of a Therapeutic Relationship*
Demonstrably effective	• **Alliance** • **Empathy** • **Collecting patient feedback**
Probably effective	• **Goal consensus** • **Collaboration** • **Positive regard**
Promising, but insufficient data	• **Congruence/genuineness** • **Repairing alliance ruptures** • **Managing countertransference**

2.6 Choosing a Psychological Treatment

- Consider treatment efficacy, quality, availability

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

2.7 Comparison of Psychological Treatments

- "Bona-fide therapy"
  - Trained therapists, psychological principles, designed to be viable tx
  - CBT > other psychotherapies as a group
  - **CBT = IPT = PDT**
  - **Supportive therapy LESS effective** than other types
  - **Short-term PDT → slightly WORSE** outcomes on some measures

- CBT = MOST evidence + established
  - Efficacy even in **severe illness, non-responders to ADs**
  - **FIRST-LINE** for acute treatment
  - **FIRST-LINE** for maintenance

- IPT → certain populations (adult, adolescents, perinatal)
  - **FIRST-LINE** for acute treatment
  - **SECOND-LINE** for maintenance

Table 5. 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**	**Second-line**
BA (behavioral activation)	**First-line**	**Second-line**
MBCT (mindfulness-based cognitive therapy)	**Second-line**	**First-line**
CBASP (cognitive-behavioral analysis system)	**Second-line**	**Second-line**
PST (problem-solving therapy)	**Second-line**	Insufficient evidence
STPP (short-term psychodynamic psychotherapy)	**Second-line**	Insufficient evidence
Telephone-delivered CBT/IPT	**Second-line**	Insufficient evidence
Internet-/computer-assisted therapy	**Second-line**	Insufficient evidence
PDT (long-term psychodynamic psychotherapy)	**Third-line**	**Third-line**
ACT (acceptance & commitment therapy)	**Third-line**	Insufficient evidence
Videoconference psychotherapy	**Third-line**	Insufficient evidence
MI (motivational interviewing)	**Third-line**	Insufficient evidence

2.8 Group vs Individual Format

- Group therapy vs individual therapy
  - Less effective at end of treatment, higher dropout
  - **But NO difference found at follow-up**
  - Availability, cost, patient preferences

2.9 Number of Sessions

- Brief interventions can be EFFECTIVE
  - **# of session/hours** vs clinical improvement → NO ASSOCIATION
  - **Frequency** vs clinical improvement → **STRONG POSITIVE ASSOC**

- *Recommendation* = **more frequent sessions, esp early**

2.10 CBT Efficacy

- Intensive, time-limited, symptom-focused
  - Depression maintained by unhelpful behaviors
  - Inaccurate thoughts/beliefs about oneself, others, future

- Behavioral interventions
  - Promote sense of pleasure + achievement → lift mood
  - Assess impact of various behaviors on mood
  - Evaluate accuracy of negative thoughts/beliefs
  - **Homework is crucial** for effectiveness

2.10 CBT Efficacy

- Acute treatment (evidence from several meta-analyses)
  - **CBT as effective as antidepressants**
  - **Combination = MORE effective** than either alone
  - Effective for **treatment-resistant depression**
    - **Sustained effects** at 3 yr follow-up
  - *Recommendation* = **CBT is FIRST-LINE** for acute treatment

- Maintenance treatment
  - CBT in acute phase → decr relapse risk by 21% (1st yr), 28% (2nd yr)
    - Better vs pharmacotherapy only in acute phase (discontinued)
    - **No difference vs continued pharmacotherapy** at 1 yr follow-up
  - CBT during remission → decr relapse by 32%
    - **No difference vs pharmacotherapy** during remission
  - *Recommendation* = **CBT is FIRST-LINE** for maintenance treatment

2.11 MBCT Efficacy

- Mindfulness meditation + CBT techniques
  - **Disengage** from maladaptive cognitive processes
  - Mindfulness, rumination, worry, compassion, meta-awareness
  - Originally developed to prevent relapse (in remitted pts)

- May only be efficacious/superior in more vulnerable pts
  - Recurrent depression, unstable remission, hx of childhood trauma
  - Efficacy as **adjunct to TAU** (in both depressed/remitted outpts)
  - **Superior to psychoeducation control**
  - **Comparable to group CBT**

- *Recommendation*
  - **MBCT is SECOND-LINE adjunctive** for acute treatment
  - **MBCT is FIRST-LINE** for maintenance treatment

2.12 IPT Efficacy

- Losses, changes, disagreements, interpersonal sensitivity
  - Grief, role transitions, role disputes, interpersonal deficits
  - Alleviate suffering, remit sx, improve functioning

- Acute MDD
  - IPT vs CBT → NO DIFFERENCE in acute MDD
  - *Recommendation* = **IPT is FIRST-LINE** for acute treatment

- Maintenance
  - IPT + pharmacotherapy → better than pharmacotherapy alone
    - But lower level evidence
  - *Recommendation* = **IPT is SECOND-LINE** for maintenance treatment

2.13 PDT, STPP Efficacy

- Careful attention to the therapist/patient interaction
  - Interpretation of transference + resistance
  - Sophisticated appreciation of therapist's contribution

- **Short-term PDT** → **SECOND-LINE** for acute tx
  - More effective than waitlist/TAU
  - Less effective than other psychotherapies at post-tx
  - **No evidence** for STPP as **maintenance**

- **Long-term PDT** → **THIRD-LINE** for acute tx
  - May be useful in MDD with comorbid personality disorder
  - Weak evidence → **THIRD-LINE** for maintenance tx

2.14 Motivational Interviewing Efficacy

- Engaging + treating pts with SUDs
  - Pts approach change with ambivalence, continuum of readiness

- No trials of MI as stand-alone tx for MDD
  - **Used in conjunction** with CBT, IPT, medications
  - Worth considering

- *Recommendation* = **MI is THIRD-LINE** for acute treatment

2.15 CBASP

- Cognitive-Behavioral Analysis System of Psychotherapy
  - Specific developed for tx of chronic depression
  - Involves **cognitive, behavioral, interpersonal strategies**
  - How maladaptive cognitions + behaviors influence each other
  - Lead to + perpetuate negative outcomes

- Mixed results
  - Monotherapy or combination with antidepressants
  - For partial-responding/non-responding pts
  - Persistent depressive disorder

- *Recommendation*
  - **CBASP is SECOND-LINE** for acute treatment
  - **CBASP is SECOND-LINE** for maintenance

2.16 ACT

- Acceptance + Commitment Therapy
  - Mindfully incr acceptance of distressing experiences
  - Take observer perspective, orienting behavior towards values

- 3 meta-analyses
  - Improvement in depression, anxiety → less than CBT
  - May have particular value **if comorbid medication conditions**

- *Recommendation* = **ACT is THIRD-LINE** for acute tx

2.17 Behavioral Activation

- **Avoidance of aversive emotions** → depression
  - Prevents positive reinforcement of non-depressive behavior
  - Longstanding patterns of inertia, avoidance, social withdrawal

- Similar effect to CBT in meta-analysis
  - **BA is FIRST-LINE** for acute tx
  - **BA is SECOND-LINE** for maintenance tx

2.18 Peer Interventions

- Self-help groups, peer-run organizations/services
  - Either alone or complement to clinical care
  - Mixed results

- *Recommendation*
  - **Peer interventions = SECOND-LINE adjunctive** for acute tx

2.19 Problem-Solving Therapy

- Adaptive problem-solving attitudes + skills
  - Structured, brief, empirically tested
  - Both positive problem orientation + solving skills

- Clear efficacy in reducing depressive sx
  - Late life depression → significant decr in depressive sx/disability

- *Recommendation*
  - **PST is SECOND-LINE** for acute tx in **primary care & elderly**

2.20 Bibliotherapy

- Reading + use of self-help materials
  - Practical, ease of use, low cost, useful for waitlist

- *Recommendation*
  - **Bibliotherapy is SECOND-LINE** treatment alone or as adjunct
    - (doesn't specify acute or maintenance)

2.21 Internet/Computer-Delivered Therapy

- Usually use adaptations of CBT, also self-guided IPT
  - **If clinician-guided** → better adherence + efficacy
  - 1 study → no difference vs face-to-face CBT

- *Recommendation*
  - **Internet/computer-CBT/IPT is SECOND-LINE** for acute tx

2.22 Remote Interactive Psychological Tx

- Phone, video, internet (vs live therapist)
  - **Telephone** → **SECOND-LINE** for acute tx
  - **Video** → **THIRD-LINE** for acute tx
  - Insufficient evidence for maintenance

2.23 Combined Tx vs Psychological Alone

- Most studies → CBT/IPT + SSRIs/TCAs
  - **Combined tx more effective** than psychological tx alone
  - Small-moderate effect size
  - Should offer to **pts with moderate-severe depression**
  - Consider benefit-burden balance, pt preference

2.24 Combined Tx vs Medication Alone

- Most studies → CBT/IPT + SSRIs/TCAs
  - **Combined tx more effective** than antidepressants alone
  - Moderate effect size
  - Should offer to **pts with moderate-severe depression**

2.25 Sequential Treatment vs Monotherapy

- CBT, MBCT after antidepressant therapy
  - **Decr relapse risk** by 20% (vs TAU, AD discontinuation)

- CBT adjunct to pharmacotherapy (large pragmatic trial)
  - Decr depressive sx
  - Incr likelihood of therapeutic **response to AD in TRD**

- Group MBCT + maintenance AD
  - **Time to relapse = no sig diff**
  - Greater relapse risk if prematurely stopped AD

- PDT → did not incr likelihood of remission

- *Recommendations*
  - **CBT, MBCT = FIRST-LINE sequential tx** after course of AD
  - **MBCT = SECOND-LINE alternative to maintenance AD**

3 Pharmacological Treatments

Table 1. Criteria for Level of Evidence and Line of Treatment	
Level of evidence	
1	• Meta-analysis with narrow confidence intervals • 2 or more RCTs with adequate samples size, preferably placebo-controlled
2	• Meta-analysis with wide confidence intervals • 1 or more RCTs with adequate sample size
3	• Small-sample RCTs • Non-randomized, controlled prospective studies • Case series • 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

3.1 Treatment with Pharmacotherapy

MDE severity	First-line treatments

Mild	• **Psychoeducation = FIRST-LINE**
	• **Self-management = FIRST-LINE**
	• **Psychological treatments = FIRST-LINE**
	• Can consider pharmacotherapy IF:
	  • **Patient preference**
	  • **Previous response to ADs**
	  • **Lack of response to non-pharm**

Moderate	• **Most 2nd generation antidepressants = FIRST-LINE**
Severe	

3.2 Newly Approved Antidepressants

- Levomilnacipran → **NSRI** (active enantiomer of milnacipran)
  - Greater selectivity for NE reuptake inhibition (vs other SNRIs)
  - No meta-analyses, no comparison studies
  - Placebo controlled RCTs → no difference vs placebo

- Vilazodone → **multimodal AD** (SRI, 5HT1A partial agonist)
  - Lacking meta-analyses, mixed results
  - Must be taken with food, slow titration to avoid GI side effects

- Vortioxetine → **multimodal AD**
  - SRI, 5HT1A agonist, 5HT2A partial agonist, 5HT1D/3A/7 antagonist
  - **Superior to placebo** (response, remission, relapse prevention)
  - Positive **neuropsychological/cognitive effects**

Table 3. Summary Recommendation of Antidepressants

	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 mg
	Milnacipran	SNRI	100 mg
	Bupropion	NDRI	150-300 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
SECOND LINE	Levomilnacipran	NSRI	40-120 mg
	Amitriptyline, clomipramine, etc.	TCAs	various
	Quetiapine	Atypical antipsychotic	150-300 mg
	Trazodone	SRI, 5HT2 antagonist	150-300 mg
	Vilazodone	SRI, 5HT1A partial agonist	20-40 mg
	Moclobemide	MAO-A inhibitor (reversible)	300-600 mg
	Selegiline (transdermal)	MAO-B inhibitor (irreversible)	6-12 mg
THIRD LINE	Phenelzine, tranylcypromine	MAO inhibitors (irreversible)	45-90 mg, 20-60 mg
	Reboxetine	NRI	8-10 mg

3.3 Selecting and Antidepressant

- **FIRST-LINE**
  - **SSRIs, SNRIs, bupropion, mirtazapine, vortioxetine, agomelatine**

- **SECOND-LINE**
  - **TCAs, quetiapine, trazadone** → higher SE burden
  - **Moclobemide, selegiline** → potential serious drug interactions
  - **Levomilnacipran** → lack of comparative/relapse-prevention data
  - **Vilazodone** → lack of comparative/relapse-prevention data, need to titrate, take with food

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

3.4 Clinical Factors Affecting Selection

- Predictive factors
  - Poorer response to meds → **incr age, anxiety, longer episode**
  - (age, sex, race, ethnicity do NOT predict outcomes with specific AD)
  - Some evidence for specific ADs for depressive subtypes

- Melancholic, atypical, anxious subtypes
  - No differences

- Psychotic depression
  - **AD+AP combo** better (vs AD or AP alone)

- Mixed features
  - **Lurasidone, ziprasidone** monotherapy (vs placebo)

3.4 Clinical Factors Affecting Selection

- Cognitive dysfunction
  - **Vortioxetine** → largest effect on processing speed, executive control, cognitive control
  - **Duloxetine** → largest effect on delayed recall
  - SSRIs, bupropion, duloxetine, moclobemide → may improve learning, memory, executive function

- Sleep disturbance
  - **Agomelatine, mirtazapine, trazadone, quetiapine** → benefits
  - BUT mirtazapine, trazadone, quetiapine → most sedation SEs

- Somatic symptoms
  - Pain (neuropathic, fibromyalgia) → **SNRIs, esp duloxetine**
  - No comparative studies on fatigue, low energy

Table 2. Principles of Pharmacotherapy Management.

Recommendations (Level 4 Evidence)
• Conduct a detailed clinical assessment, including evaluation of suicidality, bipolarity, comorbidity, concomitant medications, and symptom specifiers/dimensions. • Discuss evidence-based pharmacologic and nonpharmacologic treatment options. • Elicit patient preference in the decision to use pharmacological treatment. • Evaluate previous treatments, including dose, duration, response, and side effects of antidepressant and related medications. • Where clinically indicated, refer for laboratory testing, including lipids, liver function tests, and electrocardiograms. • Reassess patients for tolerability, safety, and early improvement no more than 2 weeks after starting a medication. Further follow-up may be every 2 to 4 weeks. • Follow measurement-based care by using validated rating scales to monitor outcomes and guide clinical decisions.

Table 4. Factors to Consider in Selecting an Antidepressant	
Patient Factors	*Medication Factors*
• **Clinical features** & dimensions • **Comorbid** conditions • Response & SE of **previous ADs** • **Patient preference**	• Comparative **efficacy** • Comparative **tolerability** (potential SE) • Potential **drug interactions** • **Simplicity** of use • **Cost & availability**

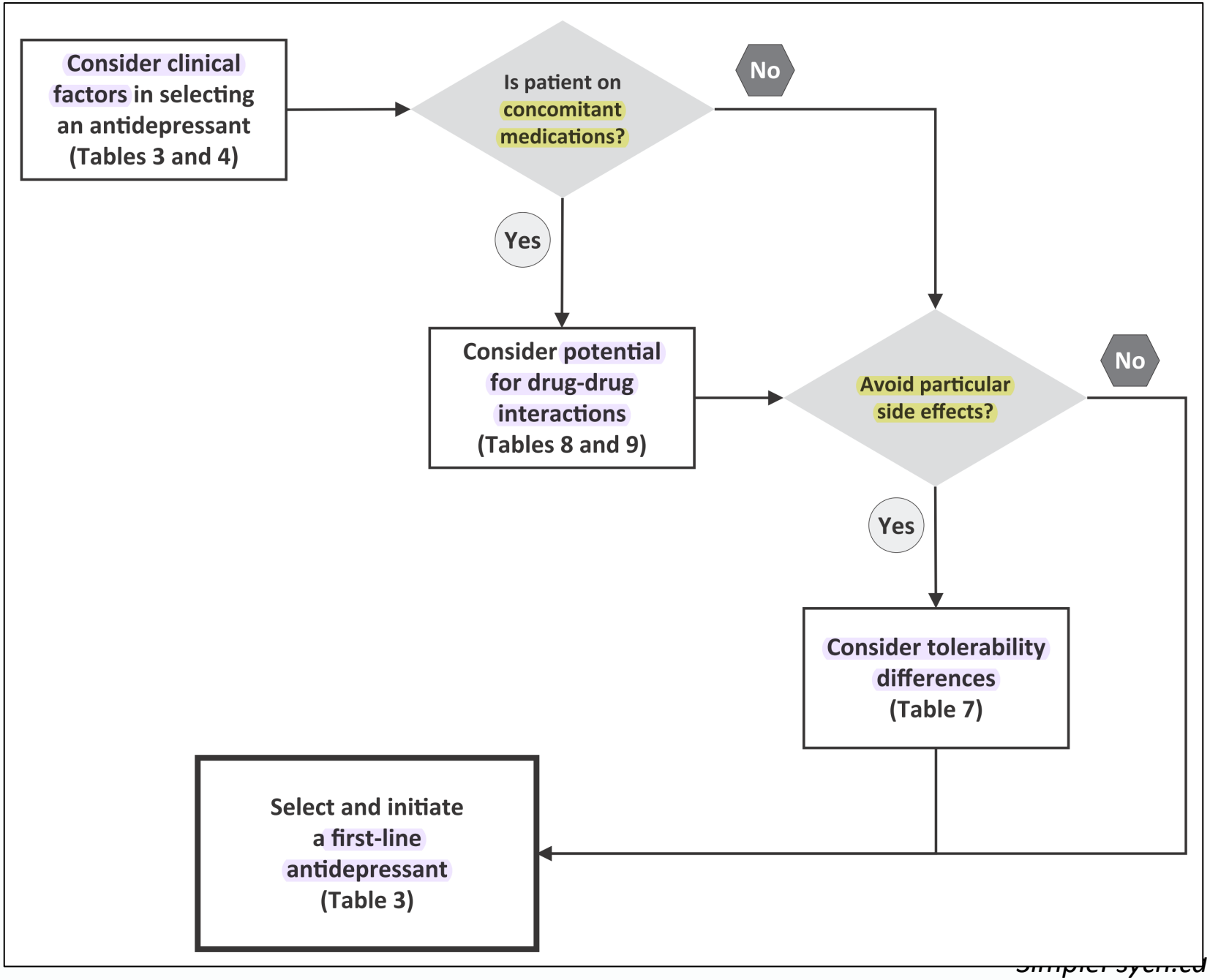

Consider clinical factors in selecting an antidepressant (Tables 3 and 4)
Is patient on concomitant medications?
No
Yes
Consider potential for drug-drug interactions (Tables 8 and 9)
Avoid particular side effects?
No
Yes
Consider tolerability differences (Table 7)
Select and initiate a first-line antidepressant (Table 3)

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

3.5 Psychiatric & Medical Comorbidities

- Limited evidence to guide antidepressant choice
  - CANMAT 2012

3.6 Comparison of 2nd Generation ADs

- Some ADs had superior efficacy
  - **Escitalopram, sertraline, venlafaxine, mirtazapine** (level 1)
  - Agomelatine, citalopram (level 2)
  - Small differences (5-6%)

Table 6. Antidepressants with Evidence for Superior Efficacy Based on Meta-Analyses.

Antidepressant	Level of Evidence	Comparator Medications
Escitalopram	Level 1	Citalopram, duloxetine, fluoxetine, fluvoxamine, paroxetine
Mirtazapine	Level 1	Duloxetine, fluoxetine, fluvoxamine, paroxetine, sertraline, venlafaxine
Sertraline	Level 1	Duloxetine, fluoxetine, fluvoxamine, paroxetine
Venlafaxine	Level 1	Duloxetine, fluoxetine, fluvoxamine, paroxetine
Agomelatine	Level 2	Fluoxetine, sertraline
Citalopram	Level 2	Paroxetine

3.7 Functional Outcomes

- Few studies of ADs assess functional outcomes
  - Not conclusive that improved cognition leads to improved function
  - **NO medication that shows superior functional improvement**

3.8 Comparative Tolerability of 2nd Gen ADs

- Few differences in tolerability
  - Based on product monographs
  - Not placebo-adjusted or direct comparisons

- Sexual side effects
  - **Bupropion** → **lower rates**
  - Mirtazapine, agomelatine, vilazodone, vortioxetine → lower rates
  - **Escitalopram, paroxetine** → **higher rates** (vs other ADs)

3.9 Suicidality

Adolescents	
• **SSRI → double risk of suicide/SA** (OR 1.92) • "Black box" warnings in 2004 • No specific ADs **(caution with all)**	
Adults	**Elderly**
• ADs **decr SI/SA** • SSRIs **decr risk by >40%**	• ADs **decr SA** • SSRIs **decr risk by >50%**

3.10 Serious Adverse Effects

- QTc Prolongation/TdP (idiosyncratic, unclear associations)
  - **Citalopram, escitalopram, quetiapine**
  - Systematic review → can occur at therapeutic dose, normal QTc
    - Most cases had **additional risk factors** (not just ADs)
    - Without additional risk factors → very low risk with SSRIs/ADs

- Long-term SSRI use
  - **Incr falls** (not due to postural hypotension)
  - **Incr fractures** → highest risk in first 6 weeks of exposure
  - **Hyponatremia** → esp elderly pts with other risk factors
  - **Incr GI bleeding (2x with NSAIDs)** → inhibited platelet aggregation
    - Acid-suppressing drugs sig reduce risk of GI bleeding

- Liver enzyme elevation → uncommon, no routine testing
  - **Agomelatine** → regular LFTs (can incr LEs, sporadic toxic hepatitis)

Table 7. Prevalence of Adverse Events among Newer Antidepressants: Unadjusted Frequency (%) of

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

Table 7. Pre\ Common Adverse Events as Reported in Product Monographs.

	Agitation	Insomnia	Fatigue	Sweating	Asthenia	Tremor	Anorexia	Increased Appetite	Weight Gain	Male Sexual Dysfunction
Citalopram	2		5	11		8	4			9
Escitalopram		8	5	3		2		2	2	10
Fluoxetine		16		8	9	10	11			2
Fluvoxamine	16	14		11	5	11	15			1
Paroxetine	2	13		11	15	8		1		16
Sertraline[a]	6	16	11	8		11	3	1		16
Desvenlafaxine[b]		9	7	10		2				6
Duloxetine		11	8	6		3				10
Levomilnacipran		6		9						11
Milnacipran		7	3	4		3				
Venlafaxine IR	2	18		12	12	5	11			18
Venlafaxine XR	3	17		14	8	5	8			16
Agomelatine[c]		C	C	C						
Bupropion SR[d]	2	8		2	2	3				
Bupropion XL	2	16				3				
Mirtazapine					8	7		17	12	
Moclobemide	5	7	3	2	1	5				
Vilazodone[e]		6	3					3	2	5
Vortioxetine[f]		3	3	2						<1

3.11 Formulation of Specific ADs

- Extended vs Immediate Release formulations
  - **NO differences in efficacy or tolerability**
  - May consider ER if adherence/compliance issues

- Generic vs Branded
  - CAN/US regulation → **80-125% bioequivalence**
  - Generic → **safe + reliable for most pts**
  - Risk-benefit for switching pt who it benefiting from branded

3.12 Clinically Relevant Drug-Drug Interactions

- Cytochrome P450 enzyme metabolic pathway

- No evidence of relevant P-glycoprotein interactions

- Serotonin Syndrome/Hypertensive Crisis
  - Serotonergic/sympathomimetic drugs + MAO inhibitors
    - **Moclobemide** (reversible MAOI)
    - **Selegiline** (irreversible MAOI)
  - SS → rare, except in overdose or multiple serotonergic medications

Table 8. Some Clinically Significant Drug-Drug Interactions Resulting from Inhibition of Cytochrome P450 (CYP) Isoenzymes.

Cytochrome P450 Inhibition of	Increases Serum Levels of These CYP Substrates	
CYP1A2	• **Agomelatine** • Caffeine • **Clozapine** • **Duloxetine** • Mexiletine	• Naproxen • **Olanzapine** • **Risperidone** • Tacrine • Theophylline • Warfarin
CYP2C19	• Antiarrhythmics • Antiepileptics (diazepam, phenytoin, phenobarbital) • Indomethacin	• Omeprazole • Primidone • Propanolol • Warfarin
CYP2D6	• Tricyclic antidepressants • Beta-blockers (metoprolol, propranolol) • Codeine and other opioids (reduces effect) • **Olanzapine**	• **Risperidone** • **Vortioxetine** • Tamoxifen (reduces effect) • Tramadol
CYP3A4	• Amiodarone • Antiarrhythmics (quinidine) • Antihistamines (astemizole, chlorpheniramine) • Calcium channel antagonists (e.g., diltiazem, verapamil) • **Haloperidol** • HIV protease inhibitors • Statins • Immune modulators (cyclosporine, tacrolimus)	• **Levomilnacipran** • Macrolide antibacterials (clarithromycin, erythromycin) • **Methadone** • **Phenothiazines** • **Quetiapine** • Sildenafil • Tamoxifen • **Vilazodone**

Table 9. Potential Drug-Drug Interactions Involving Newer Antidepressants and Atypical Antipsychotics.

Potential for Drug-Drug Interaction	Antidepressants	Atypical Antipsychotics
Minimal or low potential	• Citalopram • Desvenlafaxine • Escitalopram • Mirtazapine • Venlafaxine	• Paliperidone
Moderate potential	• Agomelatine (1A2 substrate[a]) • Bupropion (2D6 inhibitor) • Duloxetine (2D6 inhibitor; • 1A2 substrate[a]) • Levomilnacipran (3A4 substrate) • Sertraline (2D6 inhibitor) • Vilazodone (3A4 substrate) • Vortioxetine (2D6 substrate)	• Aripiprazole (2D6, 3A4 substrate) • Olanzapine (1A2 substrate[b]) • Risperidone (2D6, 3A4 substrate)
Higher potential	• Fluoxetine (2D6, 2C19 inhibitor) • Fluvoxamine (1A2, 2C19, 3A4 inhibitor) • Moclobemide (MAO inhibitor precautions[c]) • Paroxetine (2D6 inhibitor) • Selegiline (MAO inhibitor precautions[c])	• Clozapine (3A4, 1A2 substrate) • Lurasidone (3A4 substrate) • Quetiapine (3A4 substrate)

Moderate and higher potential interactions are noted in parentheses. MAO, monoamine oxidase.

[a]Coadministration with CYP1A2 inhibitors (e.g., cimetidine, ciprofloxacin and other fluoroquinolone antimicrobials, ticlopidine) should be avoided because serum antidepressant levels will be higher, leading to increased potential for side effects.

[b]Also metabolized through the uridine diphosphate glucuronosyltransferase (UGT) pathway.

[c]Precautions similar to those of older MAO inhibitors. Avoid coadministration of other antidepressants, serotonergic drugs (e.g., meperidine), and sympathomimetic drugs (e.g., pseudoephedrine, stimulants).

3.13 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**
  - 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**

3.14 Waiting for a Response

- Early improvement
  - **>20-30% reduction**, **after 2 – 4 weeks** (baseline rating scales)
  - Correlated with **response + remission at 6 – 12 weeks**

- Lack of early improvement (after 2 – 4 weeks)
  - Predictor of non-response/non-remission
  - BUT low-quality evidence for early switching (after 2 – 4 weeks)

- Recommendation for non-improvers at 2 – 4 weeks
  - **If medication tolerated → increase dose**
  - **If not tolerated → switch to another AD**

3.15 Duration of Continuation

- Acute Phase (getting to symptomatic remission)

- Maintenance Phase (preventing relapse/recurrence)
  - After symptomatic remission → continue for **6 – 9 months**
    - High risk of relapse/recurrence if AD stopped within 6 months
  - If risk factors for recurrence → continue for **at least 2 years**

Table 10. Risk Factors to Consider Longer Term (2 Years or Longer) Maintenance Treatment with Antidepressants (Level 3 and 4 Evidence).

- Frequent, recurrent episodes
- Severe episodes (psychosis, severe impairment, suicidality)
- Chronic episodes
- Presence of comorbid psychiatric or other medical conditions
- Presence of residual symptoms
- Difficult-to-treat episodes

3.15 Duration of Continuation

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

- Generally **mild + transient**
  - Most likely → **paroxetine, venlafaxine**
  - Least likely → **fluoxetine, vortioxetine** (longer half-life agents)

- *RECOMMENDATION* = **slowly taper dose over several weeks**

3.16 Inadequate Response to Antidepressants

- Ensure treatment optimization if:
  - **Partial response → 25 – 49% reduction** in symptom scores
  - **No response → <25% reduction** in symptom scores
  - Re-evaluate dx, consider treatment issues
    - Subtherapeutic doses, inadequate tx duration, poor adherence
    - Consider psychotherapy, neurostimulation approaches

- Treatment-Resistant Depression (TRD)
  - **"Inadequate response to ≥2 antidepressants"** (most common defn)
  - Does not consider adjunctive strategies, or partial vs no response

- Strategies for Inadequate Response (AHRQ 2012)
  - Insufficient evidence: for switch within SSRI class vs non-SSRI
  - Low quality evidence: that AAP augmentation > AD monotherapy
  - Insufficient evidence: benefits of individual AAPs, other adjuncts

3.17 Efficacy of Switching Strategies

- Switching non-responders → good response + remission
  - Switch *vs placebo* → BETTER response + remission rates
  - Switch *vs continuing* → NO difference in response/remission rates
  - Switch *within class* → NO difference in efficacy

- Switching *between* vs *within* classes
  - Controversial
  - *Recommendation* = **switch to AD with evidence of superior efficacy**

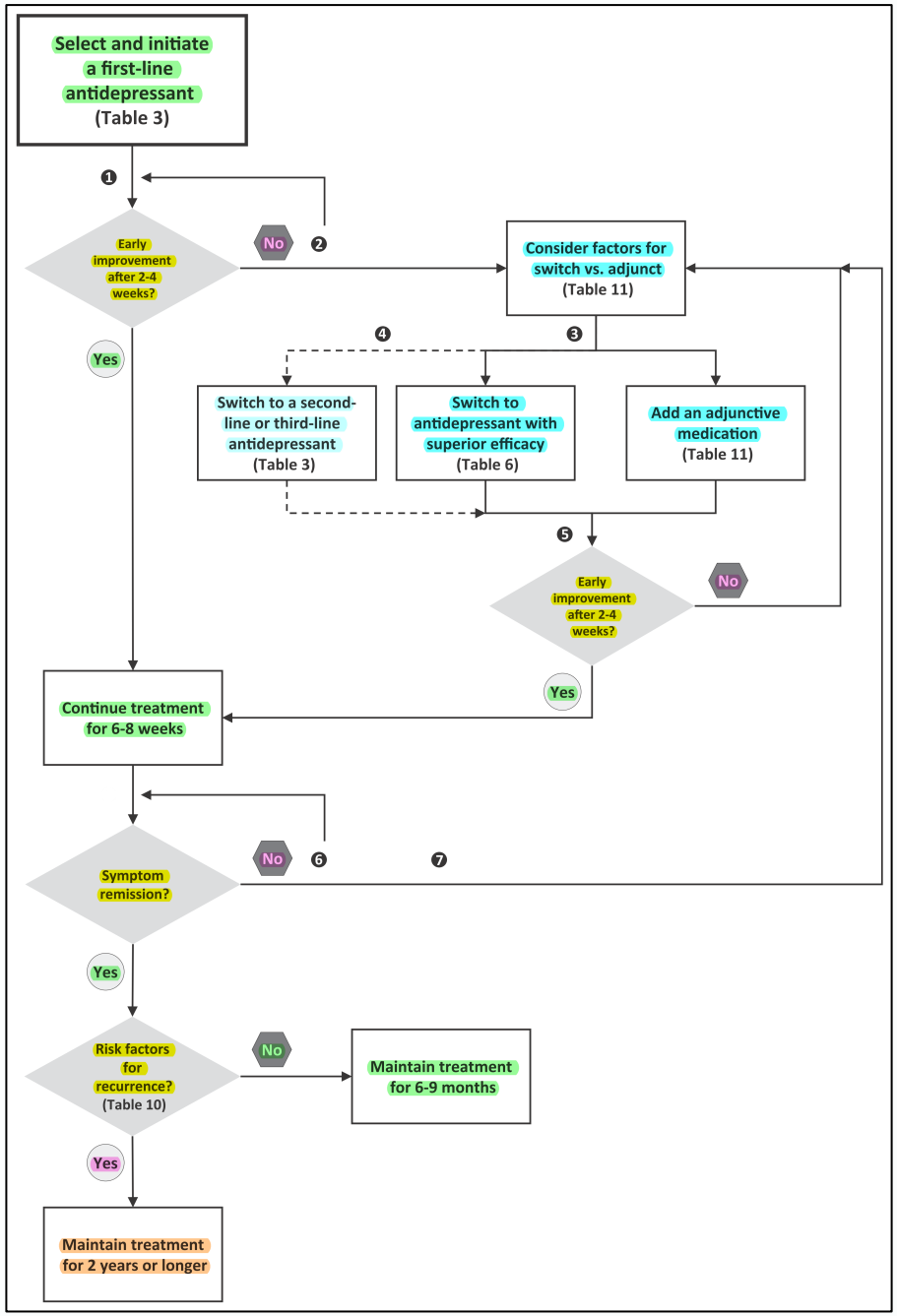

Select and initiate a first-line antidepressant (Table 3)
1
Early improvement after 2-4 weeks?
No
2
Consider factors for switch vs. adjunct (Table 11)
Yes
4
3
Switch to a second-line or third-line antidepressant (Table 3)
Switch to antidepressant with superior efficacy (Table 6)
Add an adjunctive medication (Table 11)
5
Early improvement after 2-4 weeks?
No
Yes
Continue treatment for 6-8 weeks
Symptom remission?
No
6
7
Yes
Risk factors for recurrence? (Table 10)
No
Maintain treatment for 6-9 months
Yes
Maintain treatment for 2 years or longer

Table 11. Summary Recommendation of Adjunctive Medications			
	Antidepressant	*Evidence*	*Dosing*
FIRST LINE	**Aripiprazole**	Level 1	2-15 mg
	Risperidone	Level 1	1-3 mg
	Quetiapine	Level 1	150-300 mg
SECOND LINE	Brexpiprazole	Level 1	1-3 mg
	Olanzapine	Level 1	2.5-10 mg
	Lithium	Level 2	600-1200 mg (therapeutic levels)
	Bupropion	Level 2	150-300 mg
	Mirtazapine/mianserin	Level 2	30-60 mg
	Modafinil	Level 2	100-400 mg
	Triiodothyronine	Level 2	25-50 mcg
THIRD LINE	TCAs	Level 2	Various
	Other antidepressants	Level 3	Various
	Other stimulants	Level 3	Various
	Ziprasidone	Level 3	20-80 mg BID
Experimental	Ketamine	Level 1	0.5 mg/kg (single IV dose)
NOT Recommended	Pindolol	Level 1 (neg)	

3.18 Efficacy of Adjunctive Strategies

- Adjunctive strategy (preferred term)
  - **Adding 2nd medication to initial medication**
  - *Combination* = adding 2nd antidepressant
  - *Augmentation* = adding non-antidepressant

- Network meta-analysis of 48 RCTs
  - **Only aripiprazole, quetiapine, lithium, T3** more effective vs placebo
  - Stronger efficacy for aripiprazole, quetiapine

3.18 Efficacy of Adjunctive Strategies

- Atypical Antipsychotics as Adjuncts
  - **Most consistent evidence for efficacy in TRD**
    - **Aripiprazole, olanzapine, quetiapine, risperidone** (vs placebo)
      - Network meta-analysis → small-medium effect sizes
    - Brexpiprazole, ziprasidone → RCT efficacy
  - **NO differences between AAPs**
  - **Worse tolerability vs placebo**

- Antidepressants
  - Adjunctive AD → **incr SE vs monotherapy** (esp mirtazapine)
  - *Recommendation* = **do NOT combine AD at initiation of treatment**

3.18 Efficacy of Adjunctive Strategies

- Lithium
  - Mostly small studies, combo with TCAs → **EFFECTIVE**
  - Combo with SSRI → sig, but **wide confidence intervals** (Level 2)

- T3 (triiodothyronine)
  - Only 2 placebo-controlled RCTs (none since 2008)
  - STAR*D → **T3 better tolerated, lower dropout rates (vs lithium)**

- Stimulants
  - **Modafinil → marginal evidence** for efficacy, SE similar to placebo
  - Other stimulants, lisdexamfetamine, methylphenidate → NEGATIVE

- IV Ketamine
  - Rapid antidepressant effects in TRD
  - Risk psychosis + abuse, limited long-term data (safety, efficacy)
  - Recommendation = **experimental still, limit to academic centres**

- Pindolol (beta-blocker) = **NOT RECOMMENDED**

3.19 Switching vs Adjunctive Strategies

- Some evidence adjunctive better than switching
  - STAR*D, adjunctive studies, RCTs
  - **No specific adjunctive agents** to target specific symptoms/SE

- *Recommendation* = **individualize tx based on clinical factors**
  - Given limited evidence
  - Diagnostic re-evaluation, consider previous med trials
  - Rational use of adjunctive meds
  - Discontinue non-beneficial meds
  - Monitor symptoms, SE, functional outcomes

3.19 Switching vs Adjunctive Strategies

Table 12. Factors to Consider between Switching to Another Antidepressant Monotherapy or Adding an Adjunctive Medications (Level 3 Evidence)	
Consider switching	*Consider adjunctive*
• **First trial** of antidepressant • Initial AD **poorly tolerated (SE)** • **No response (<25%)** to initial AD • **More time available** to wait for response (less severe, less impairing) • **Patient prefers** to switch	• **≥2 past trials** of antidepressants • Initial AD **well-tolerated** • **Partial response (>25%)** to initial AD • **Less time available** to wait for response (more severe or impairing) • **Patient prefers** to add on • **Specific residual symptoms/SE** from initial AD that can be targeted

3.20 Persistent + Chronic Depression

- Persistent Depressive Disorder
  - Meta-analysis → **most studied drugs MORE effective** (vs placebo)
    - No differences in acceptability
    - Differences = **sertraline** > imipramine, **moclobemide** > fluoxetine
  - SSRIs vs TCAs → **similar efficacy, better tolerated**
  - Dysthymia vs chronic MDD → may be **heterogeneous tx response**

- Chronic disease management approach
  - Greater emphasis on improving function, quality of life
  - Greater use of psychotherapy, non-pharm tx

3.21 Novel Treatments

- Glutamate system
  - Ketamine, esketamine, lanicemine, memantine
  - CERC-301, GLYX-13, basimlurant

- Endocannabinoid system, neuroplastic mechanisms

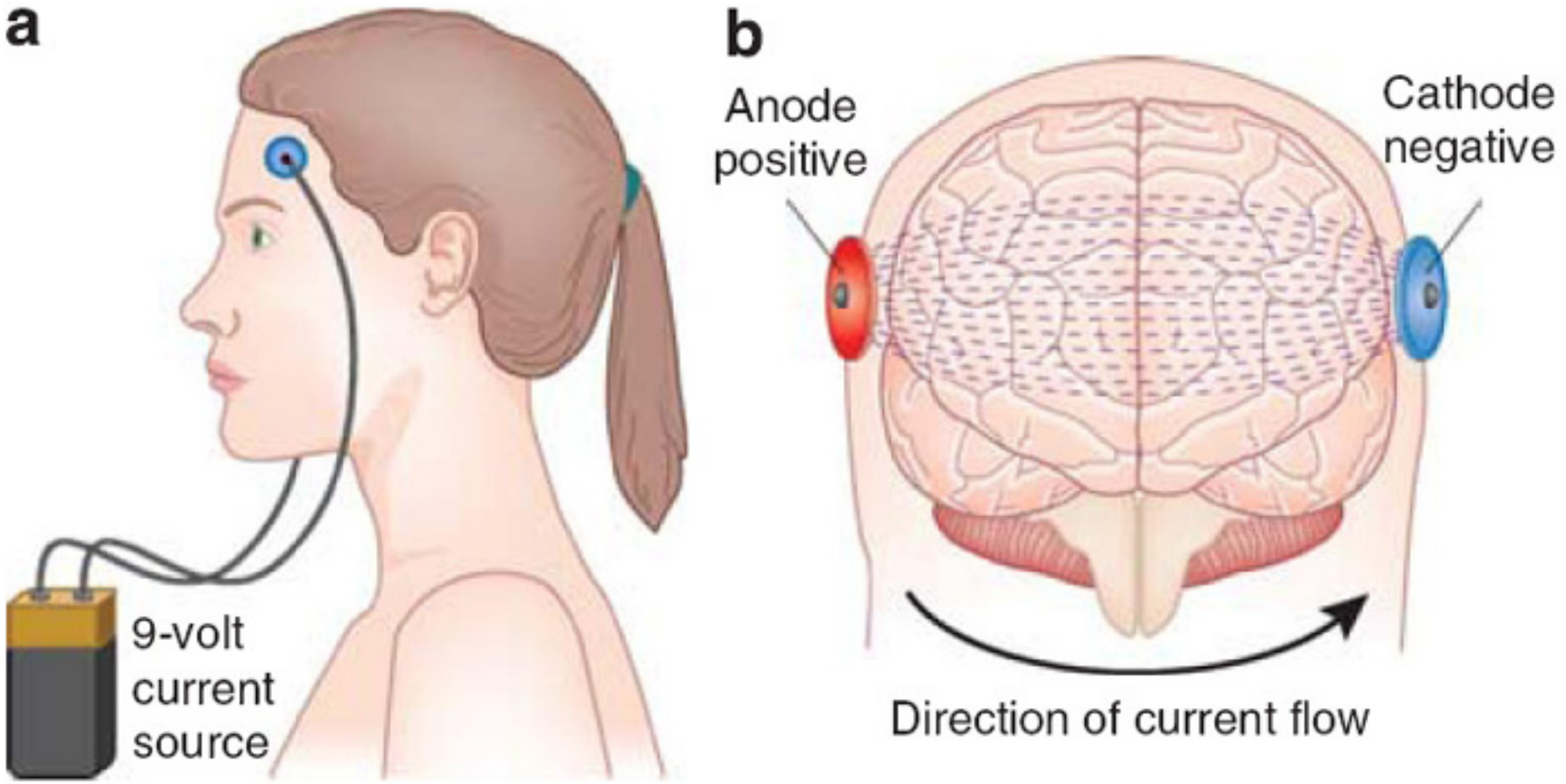
- Adjunctive celecoxib (NSAID) → MDD
- Pramipexole (dopamine agonist) → bipolar depression
- Cariprazine (novel AAP) → MDD

4 Neurostimulation

Summary of Neurostimulation Recommendations

Table 2. Summary of Neurostimulation Treatment Recommendations for MDD				
Modality	*Overall Recommendation*	*Acute Efficacy*	*Maintenance Efficacy*	*Safety & Tolerability*
rTMS	**First-line** (if failed at least 1 AD)	Level 1	Level 3	Level 1
ECT	**Second-line** (first-line in some situations)	Level 1	Level 1	Level 1
tDCS	**Third-line**	Level 2	Level 3	Level 2
VNS	**Third-line**	Level 3	Level 2	Level 2
DBS	Investigational	Level 3	Level 3	Level 3
MST	Investigational	Level 3	Unknown	Level 3

Transcranial Direct Current Stimulation



4.1 Transcranial Direct Current Stimulation

- Using scalp electrodes, to specific cortical region
  - Continuous, low-amplitude electrical current
  - Anodal stimulation → incr cortical excitability (depolarization)
  - Cathodal stimulation → decr cortical excitability (hyperpolarization)

- Repeated tDCS → may lead to neuroplasticity effects
  - Similar to long-term potentiation/depression (?NMDA mechanism)

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

4.2 tDCS Delivery Parameters

- No cohesive review of optimal parameters
  - Left dorsolateral prefrontal cortex (DLFPC), anodal stim
  - Left (anodal) + right (cathodal) DLFPC

- May have enhancing effects
  - RCT → higher remission rates with sertraline (vs sertraline alone)
  - May enhance psychotherapeutic modalities

4.3 tDCS Efficacy

- Acute MDD
  - Meta-analysis → tDCS superior to sham
  - Hx treatment resistance → poorer responses to tDCS

- Maintenance/relapse prevention → no controlled studies

- *Recommendation* = **tDCS as THIRD-LINE tx**

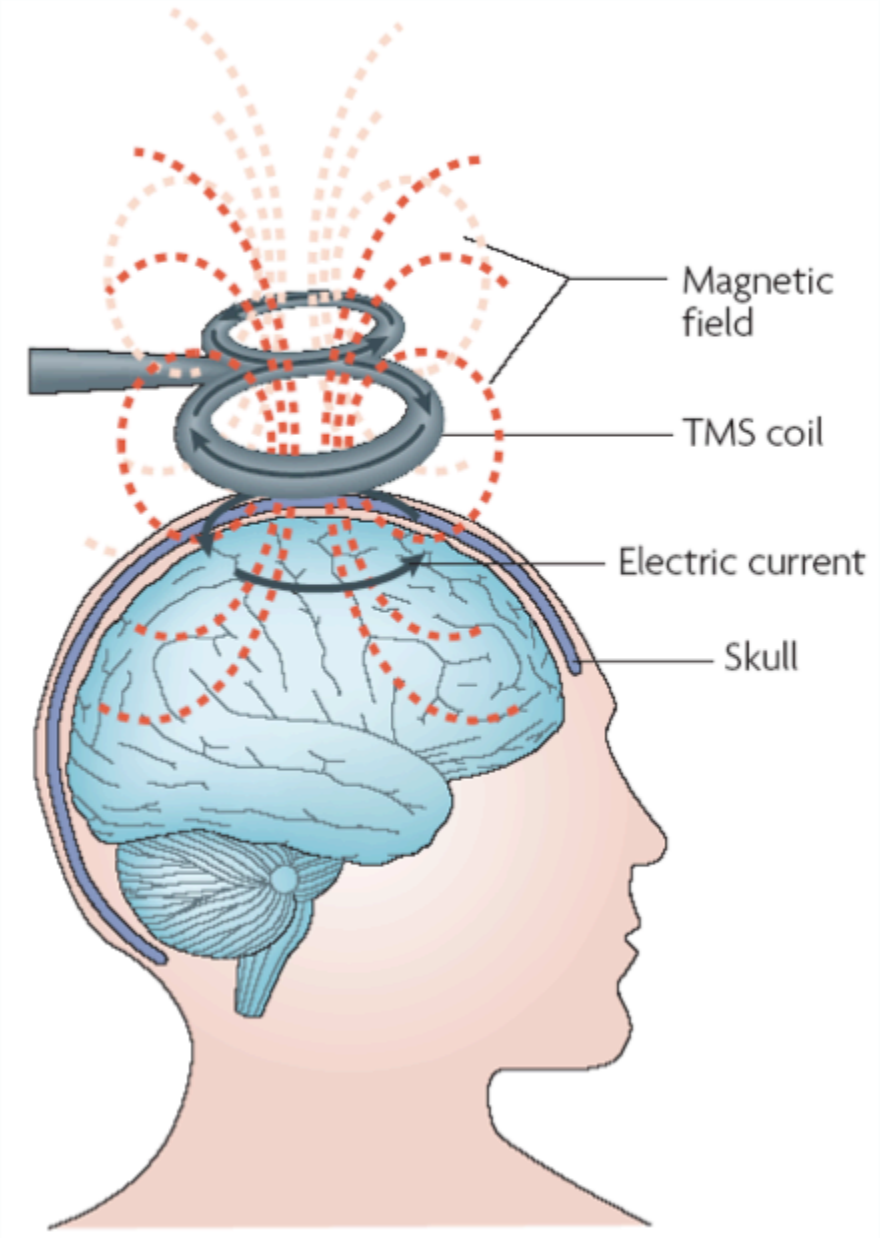
4.4 tDCS Side Effects

- 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

Repetitive Transcranial Magnetic Stimulation



4.5 Repetitive Transcranial Magnetic Stimulation

- Inductor coil placed against scalp
  - Focused magnetic field pulses (powerful 1.0 – 2.5 Tesla)
  - Induces electrical currents in neural tissue, non-invasively
  - Delivered by trained tech/nurse, under physician supervision
  - **No anesthesia required**

- Protocols
  - Standard → **once daily, 5 days/week**
  - 3x weekly → similar efficacy, slower improvement, same # overall
  - Accelerated → multiple daily sessions (under research)

- Therapeutic effects → can last several months
  - **Max effect at 26 – 28 sessions**
  - 20 sessions before "tx failure" (can extend to 25-30 if improving)
  - No validated biomarkers to predict rTMS outcomes

4.6 rTMS Delivery Parameters

- Stimulation intensity, frequency, pattern, site
  - Conventional figure-8 or circular coils → target regions 1-4 cm deep
  - Helmet-shaped "deep" rTMS coils → slightly deeper
  - Coil navigation → MRI most precise, scalp-based most common

- Stimulus intensity → based on resting motor threshold
  - Minimum intensity to elicit muscle twitches (visual or EMG)
  - 110% RMT → most common intensity
  - Newer **theta-burst stimulation (TBS)** → lower intensity (70-80%)

- Different frequency/patterns → different effects
  - Conventional 15-45 min sessions, **TBS 1-3 min sessions**
  - **High freq excitatory**, low freq inhibitory
  - **Intermittent TBS excitatory**, continuous TBS inhibitory

4.6 rTMS Delivery Parameters Recommendation

Table 3. Summary of Treatment Parameters for rTMS
Intensity, frequency and site
• Stimulate at **110-120% of resting motor threshold** • **70-80% of RMT for theta-burst stimulation** • Select stimulation frequency and site
Treatment course
• Stimulation **5 times weekly** • Delivery **initial course until sx remission**, up to **20 sessions** • Extend course **to 30 sessions** if partial response
Maintenance course
• Use rTMS as needed to **maintain response**

4.6 rTMS Protocol Recommendations

Table 4. Recommendation for rTMS Stimulation Protocols	
Recommendation	*Evidence*
First-line	
• **High-frequency, to left DLPFC**	Level 1
• **Low-frequency, to right DLPFC**	Level 1
Second-line	
• **Bilateral DLPFC** (left high-freq, right low-freq)	Level 1
• **Switching first-line options** (initial non-responders)	Level 3
• **TBS protocols** (intermittent TBS to left DLPFC, left intermittent + right continuous TBS to DLPFC, intermittent TBS to bilateral DMPFC)	Level 3
Third-line	
• **High-frequency, bilateral DLPFC**	Level 3

4.7 Efficacy of rTMS

- Unilateral rTMS = **FIRST-LINE** (for pts who failed ≥1 AD)
  - **High-frequency left DLPFC**
  - **Low-frequency right DLPFC** (shorter tx time)
  - Both have efficacy in meta-analyses, no differences in outcomes
  - Switch protocols in non-responders = **SECOND-LINE**

- Bilateral stimulation = **SECOND-LINE rTMS protocol**
  - High-freq left + low-freq right DLPFC
  - Not superior to unilateral rTMS, more intensive, not safer

- Efficacy in TRD
  - Left DLPFC → **superior response + remission rates** (vs sham)

4.7 Efficacy of rTMS

- Excitatory rTMS of dorsomedial prefrontal cortex (DMPFC)
  - May be slightly better than DLPFC, not different than iTBS
  - Recommendation = **DMPFC as THIRD-LINE rTMS protocol**

- Theta-burst protocols (intermittent, continuous)
  - DLPFC → **left iTBS > sham** (right iTBS not superior)
    - Mixed results for bilateral iTBS
  - DMPFC → **iTBS = conventional** (10 Hz)
  - Ongoing conventional rTMS vs TBS studies
  - Recommendation = **TBS as SECOND-LINE rTMS protocol**

4.8 Maintenance Treatment after rTMS

- Following successful rTMS
  - Without maintenance rTMS → **relapse common**
  - With maintenance rTMS → **more sustained remission**

- rTMS maintenance schedules
  - **Insufficient evidence** for any one schedule

4.9 rTMS vs ECT

- May be best understood as complementary techniques
  - rTMS consistently **LESS EFFECTIVE than ECT** (esp for **psychosis**)
    - ECT > left DLPFC rTMS

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

4.10 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**

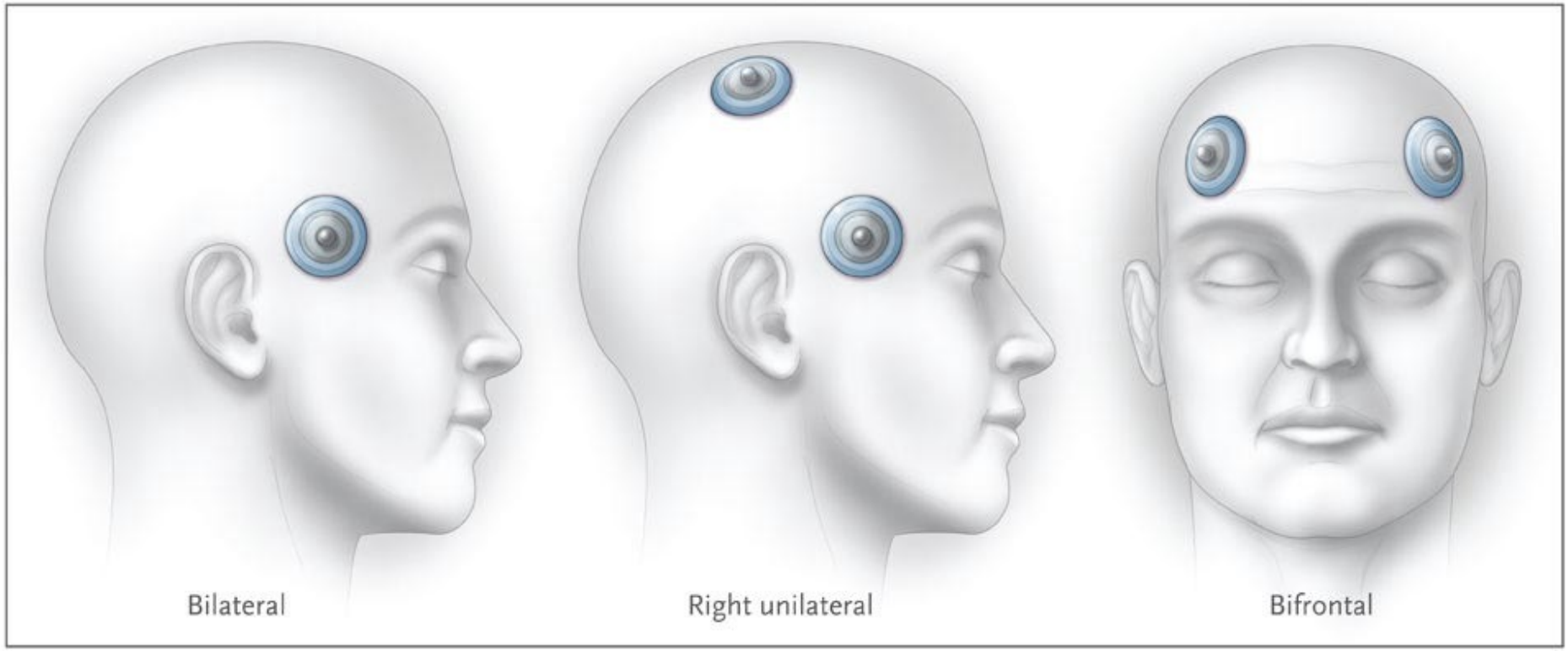
4.10 rTMS Adverse Effects

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)

4.11 rTMS Combination with Antidepressants

- <u>rTMS as add-on to pre-existing AD in most studies</u>
  - Discontinuing AD prior to rTMS → NO evidence
  - New AD + rTMS → **higher response/remission** (vs rTMS alone)

Electroconvulsive Therapy



4.12 ECT – Electroconvulsive Therapy

- Induction of seizure via electrical stimulus to brain
  - Controlled clinical setting, general anesthesia, muscle relaxant
  - Effective + well-established tx for depression, other disorders

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

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

4.12 ECT – Electroconvulsive Therapy

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

- Delivery recommendations
  - Placements: bitemporal, bifrontal, right unilateral
  - Intensity: seizure threshold (BT/BF = 1.5-2.0x ST, RUL = 5-8x ST)
  - BT, BF, RUL = same efficacy, but different cognitive effects

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

4.12 ECT Clinical Indications

Table 5. Clinical indications for ECT as first-line treatment for MDD	
• **Acute suicidal ideation**	Level 1
• **Psychotic features**	Level 1
• **Treatment-resistant depression**	Level 1
• Repeated medication intolerance	Level 3
• Catatonic features	Level 3
• Prior favorable response to ECT	Level 3
• Rapidly deteriorating physical status	Level 3
• **During pregnancy**, any of the above indications	Level 3
• Patient preference	Level 4

4.12 ECT Delivery

- Ultrabrief pulse width (vs conventional brief pulse width)
  - UBP → **less short-term cog impairment** (esp autobiographical)
    - But may have slower improvement, require more tx than BP
  - Systematic review → **no advantage** of UBP vs BP in RUL/BT/BF ECT
    - BP RUL more effective, fewer tx (vs UBP) → but more cog AE
  - **UBP RUL = SECOND-LINE ECT tx** (minimize short-term cog impair)

- Number of ECT treatments
  - **Index course = 6-15 treatments, 2-3x per week**
    - 2x weekly similar efficacy, but longer tx duration (vs 3x)
    - >3x weekly → higher rates of cognitive side effects

4.12 ECT Delivery

Table 6. Recommendations for Delivery of ECT	
Recommendation	*Evidence*
First-line	
• **BP RUL** (5-6x ST)	Level 1
• **BP BF** (1.5-2.0x ST)	Level 1
Second-line	
• **UBP RUL** (up to 8x ST)	Level 1
• **UBP BF** (1.5-2.0x ST)	Level 1
• **2x-weekly ECT similar efficacy** to 3x-weekly, but longer duration of treatment	Level 2
• If no response to RUL (after 4-6 treatments), **switch to bilateral ECT** (BT or BF)	Level 3
• For maintenance pharmacotherapy post-ECT, use an **untried antidepressant**, or **nortriptyline + lithium**, or **venlafaxine + lithium**	Level 2
• **Maintenance ECT is as effective as pharmacotherapy** (preventing relapse/recurrence)	Level 2

4.13 Efficacy of ECT as Acute Treatment

- ECT is one of the most effective treatments for MDD
  - **Response rates 70-80%** → **remission rates 40-50%**
  - Strongest predictor of non-response = **resistance to previous tx**
  - Higher response rates
    - **Older pts, psychotic features, shorter episode, less severity**

- High rates of relapse/recurrence after acute ECT course
  - Even if receiving maintenance treatment
    - Highest relapse rates **within 6 months post-ECT**
    - Relapse rate **~50% at 1 & 2 years**
  - Baseline med resistance → NOT associated with relapse
  - **Cohorts with older pts, psychotic pts** → **lower relapse rates**

4.14 Maintenance Treatment Post-ECT

- Antidepressants post-ECT → **decr relapse rates by half**
  - Little data on specific medication strategies, ADs or AD class
  - **Combo nortriptyline + lithium** → superior to nortriptyline alone
  - **Combo venlafaxine + lithium** → equal to nortriptyline + lithium
  - *Recommendation* = **use AD not tried before ECT**
    - Or **nortriptyline + lithium**, or **venlafaxine + lithium**

- Continuation/maintenance ECT
  - Safe + effective → **reduces relapse/recurrence**
    - Similar effect as medications at 6 months
  - No studies on optimal frequency of mECT
    - Most common = weekly x 4 wks, biweekly x 8 wks, then monthly

- Psychotherapy post-ECT
  - **Insufficient evidence** to recommend maintenance psychotherapy

4.15 ECT Adverse Effects

- 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%)**

4.15 ECT Adverse Effects

- Cognitive impairment
  - Mild, short-term impairment during + immediately after ECT
    - Transient disorientation (recovery, postictal, effects of GA)
    - **Retrograde amnesia, anterograde amnesia**
  - Greater impairment → **pre-existing cog imp, older age, bitemporal**
    - Less impairment → **UBP RUL ECT**
  - Usually transient → **recovery weeks-months after acute course**
    - No eventual differences between ECT parameters
    - May have subjective self-reports → correlated with depressive sx

4.15 ECT Adverse Effects

Table 7. Factors Associated Short-Term Adverse Cognitive Effects of ECT		
Higher Rates	*Lower Rates*	*Evidence*
• Bitemporal	• **Bifrontal, unilateral**	Level 1
• Brief pulse width	• **Ultrabrief pulse width**	Level 2
• Suprathreshold stimulation	• **Lower electrical dose**	Level 2
• 3 times per week treatment	• **2 times per week** treatment	Level 2
• Concomitant use of lithium or agents with independent adverse cognitive effects	• **Reduce doses or discontinue** agents with adverse cognitive effects	Level 3
• High doses of anesthetic medications	• **Lower doses** of anesthetic medications	Level 4

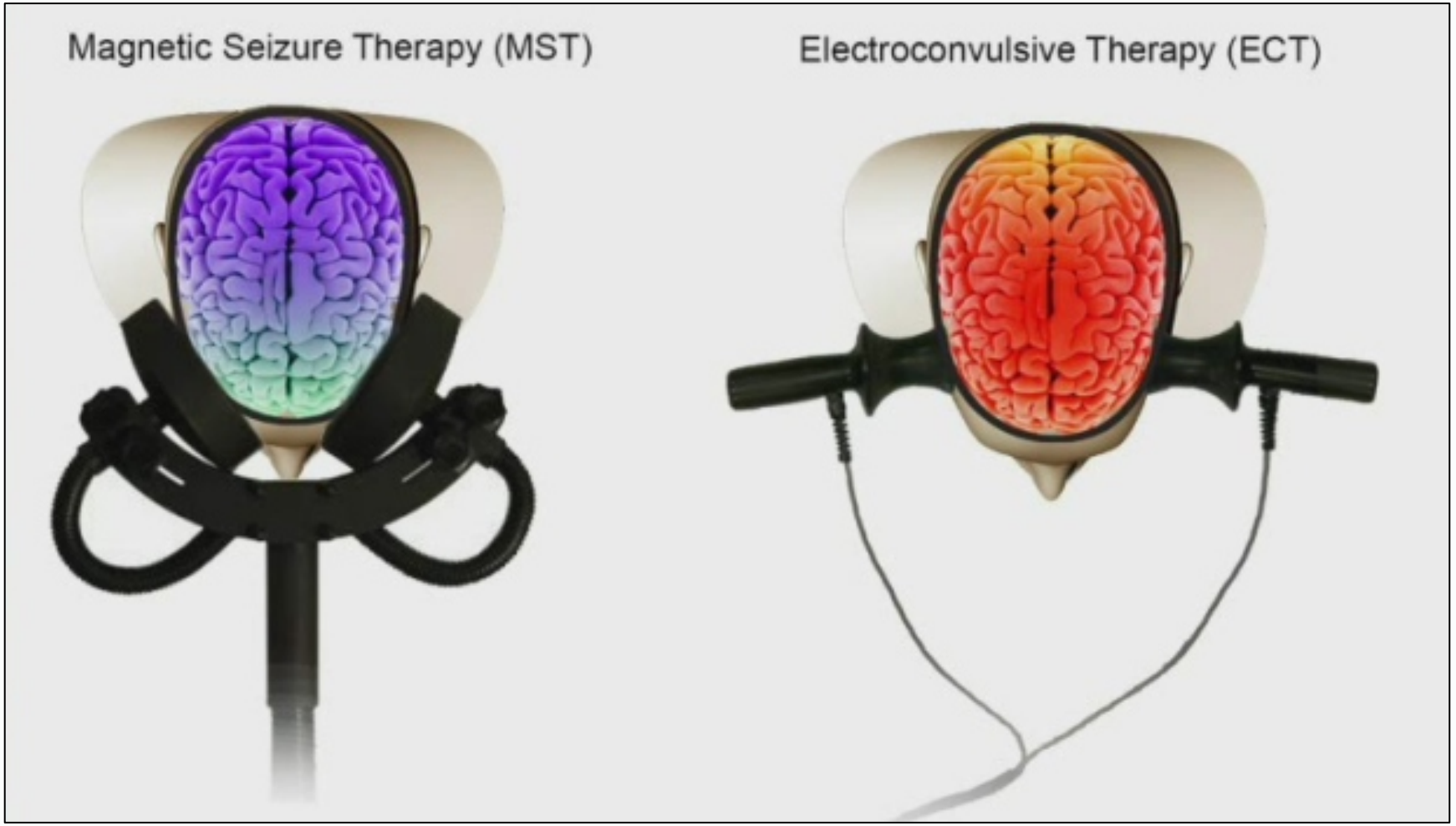
4.16 ECT Combination with Antidepressants

- Concurrent antidepressants during ECT course
  - **Lower relapse rates** (vs sequential ADs after ECT)

- Concomitant lithium
  - May incr SE → **cognitive sx, encephalopathy, spontaneous seizures**

- Concomitant benzos + anticonvulsants
  - May raise seizure threshold → **decr seizure efficacy**
  - Lamotrigine may be less problematic

Magnetic Seizure Therapy



4.17 Magnetic Seizure Therapy (MST)

- Non-invasive convulsive neurostimulation
  - Electromagnetic induction to elicit **generalized tonic-clonic seizure**
    - Neurostimulator + coil → direct contact with skull
  - Requires GA, assisted ventilation, EEG monitoring
  - Investigated as alternative to ECT → ? fewer SE (cognitive)

4.18 MST Delivery Parameters

- Optimal delivery parameters → under investigation
  - Vertex coil placement common

- Similar schedule to ECT
  - Index course = 12 treatments, 2-3 times per week

4.19 MST vs ECT

- MST vs RUL ECT → **no sig differences** in response/remission
  - Case series → similar rates to ECT

- No studies comparing MST vs sham
- No studies on relapse after MST or relapse prevention

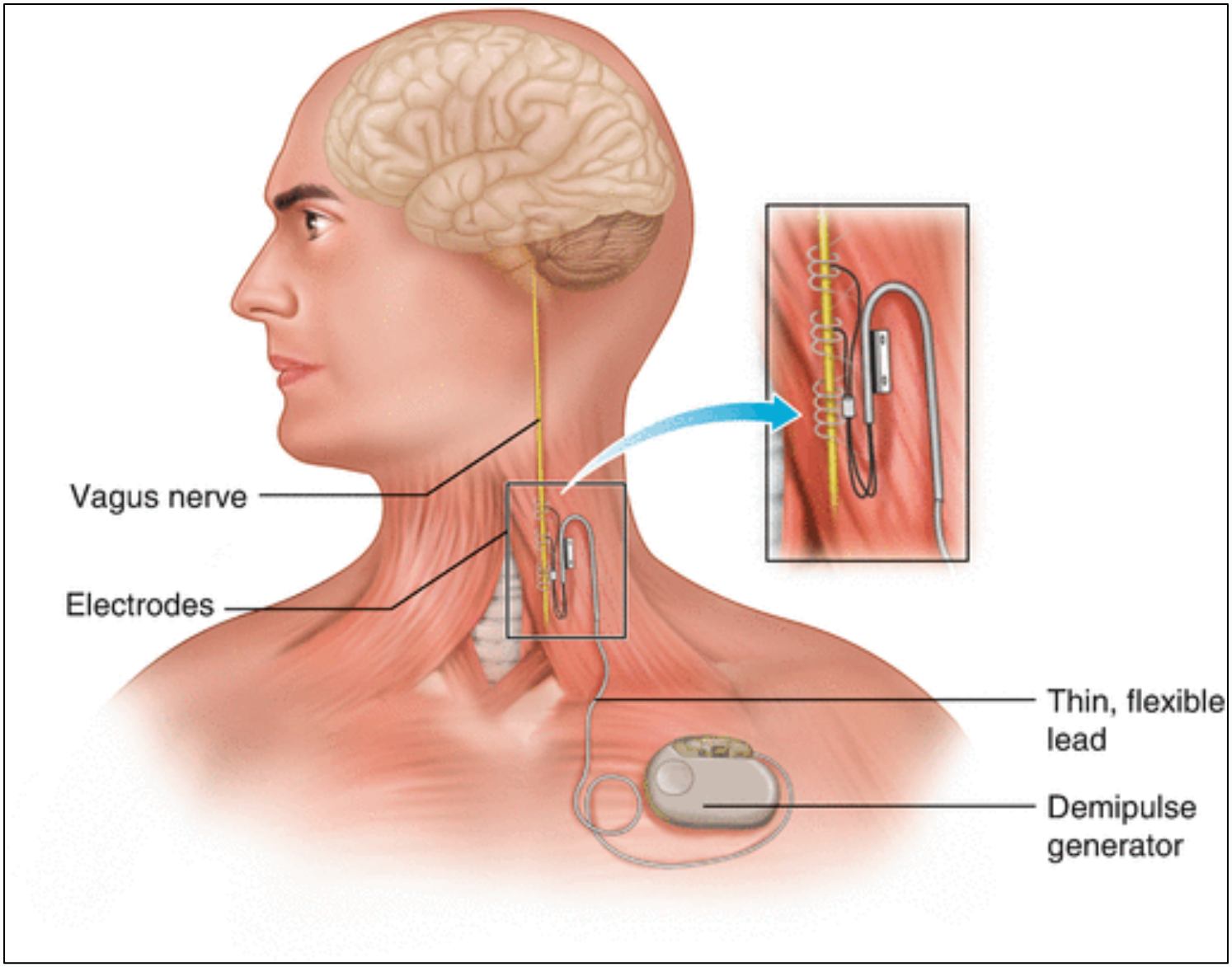
- *Recommendation* = **investigational tx alternative to ECT**

4.20 MST Adverse Effects

- 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

Vagus Nerve Stimulation



4.21 Vagus Nerve Stimulation (VNS)

- Implantable pulse generator, electrode into vagus nerve
  - Originally for drug-resistant epilepsy
  - Stimulation to **nucleus tractus solitarius** → sub/cortical regions

4.22 VNS Delivery Parameters

- Optimal treatment parameters → under investigation

4.23 VNS Efficacy in Acute Treatment

- Approved by US FDA
  - **Adjunct long-term tx of chronic/recurrent depression**
  - Failure to respond to ≥4 adequate antidepressant treatments

- VNS vs sham RCT → no significant differences at 12 weeks

- *Recommendation* = **THIRD-LINE acute treatment**

4.24 VNS Efficacy in Extended Treatment

- Antidepressant effects → **may accrue over time**
  - Median time to response → 3-9 months
  - Effects may be maintained at 12-24 months

- VNS can be considered for chronic depression
  - Particularly if **treatment adherence issues**

4.25 VNS Adverse Effects

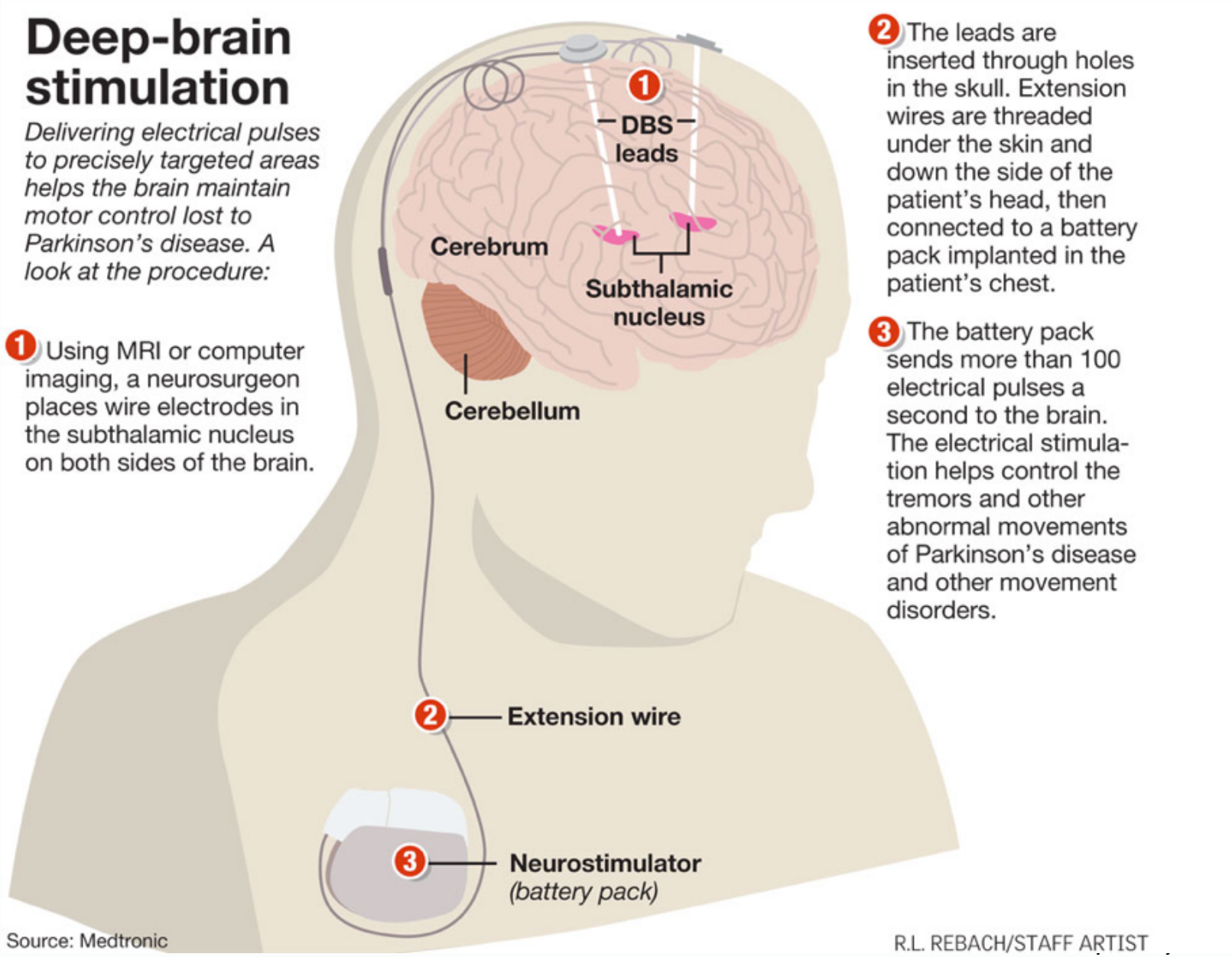
- Most VNS pts also on AD → combined tx SE

- 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)

Deep Brain Stimulation



4.26 Deep Brain Stimulation

- 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)**

4.27 DBS Efficacy in Acute Treatment of TRD

- Still experimental treatment → refractory depression
  - Anatomical targets for TRD
    - **SCC (subcallosal cingulate white matter)**
    - **VC/VS** (ventral capsule, ventral striatum)
    - **NA** (nucleus accumbens)
    - **MFB** (medial forebrain bundle)

- Efficacy results conflicting
  - At 3/6 months → response 30/60%, remission 20/40%
  - MFB DBS study → response 86%, remission 57%
  - Sham-controlled RCTs → discontinued early due to lack of efficacy

- **Lack of data for VC/VS/SCC DBS in acute tx of TRD**

4.28 DBS Efficacy in Extended Treatment

- SCC DBS → reduced depression severity at 12 months
  - May have higher response rates beyond 1 year (open-label)
  - **Antidepressant effects continue to accrue over months-years**
    - Improved clinical + functional outcomes beyond 1 year

4.29 DBS Maintenance Tx

- **Ongoing DBS required to maintain remission**

4.30 DBS Adverse Effects

- Many possible factors
  - Surgical procedure itself, perioperative risks
  - Stimulation of discrete brain regions, changes in DBS parameters

- Generally well-tolerated
  - 1 year of SCC DBS → 11% dropout
  - No evidence of worsening neuropsych performance (may improve)
  - **Oculomotor AE (MFB DBS)** → blurred vision, strabismus

- Psychiatric AE
  - **Psychosis, hypomania (NA DBS)** → transient, reversible
    - No hypomania with SCC DBS (even in bipolar pts)
  - Reports of suicidality, completed suicide → unclear association

4.31 DBS Combination with Antidepressant Tx

- Largely used as augmentation to AD
  - Optimal combination unknown

5 Complementary & Alternative Medicine Treatments

5.1 General Caveats + Limitations of CAM Tx

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

- Evidence-based pharmacological + psychological tx FIRST

Physical & Meditative Treatments

Table 2. Summary of Recommendations for Physical and Meditative Treatments				
Intervention	*Type*	*Indication*	*Recommendation*	
Exercise	**Monotherapy**	**Mild-mod MDD**	First-line	Level 1
Light therapy	**Monotherapy**	**Seasonal (winter) MDD**	First-line	Level 1
Exercise	Adjunctive	Mod-severe MDD	Second-line	Level 1
Light therapy	Mono/adjunctive	Mild-mod nonseasonal MDD	Second-line	Level 2
Yoga	Adjunctive	Mild-mod MDD	Second-line	Level 2
Acupuncture	Adjunctive	Mild-mod MDD	Third-line	Level 2
Sleep deprivation	Adjunctive	Mod-severe MDD	Third-line	Level 2

5.2 Light Therapy (LT)/Phototherapy

- Daily exposure to bright light
  - Typically with fluorescent light box

- Standard protocol
  - **10,000 lux during early morning**
  - **30 mins per day for 6 weeks**
  - **Response within 1-3 weeks**

- Proposed mechanisms
  - Alteration of circadian rhythm
  - Modulation of serotonin + catecholamine systems

5.2 Light Therapy (LT)/Phototherapy

- Generally well-tolerated
  - Common SE → eye strain, headache, agitation, nausea, sedation

- *Recommendation*
  - LT as **FIRST-LINE** **monotherapy** for seasonal depression
  - LT as **SECOND-LINE** **monotherapy** for mild-mod non-seasonal MDD
  - LT as **SECOND-LINE** **adjunct** for mild-mod non-seasonal MDD

5.3 Sleep Deprivation (SD)

- Keep pts awake for extended periods of time
  - **2 – 4 times over 1 week**
    - Total SD → up to 40 hrs
    - Partial SD → 3 – 4 hrs of sleep per night
    - Total SD often mixed with partial SD or normal (recovery) sleep

- Rapid antidepressant effects
  - Proposed mechanisms
    - Incr activity of all neurotransmitter systems
    - Incr synaptic potentiation + glial signaling

- Practical limitation
  - **Difficult to maintain use** for more than a few weeks
  - Often **rapid relapse** after discontinuation

5.3 Sleep Deprivation (SD)

- Combined SD + chronotherapy
  - Rapid onset of efficacy, greater clinical utility + sustained response
  - Combination SD + **sleep-phase advance (SPA)**
    - Schedule bedtimes earlier than usual
    - Then keep advancing (earlier) until normal bedtime reached

- Most common SE = **DAYTIME SLEEPINESS**
  - May have recurrence of panic attacks
  - Low rates of SD-induced mania

- CONTRAINDICATION = **EPILEPSY**
  - High risk of seizure induction

- *RECOMMENDATION*
  - **SD is THIRD-LINE adjunctive** for mod-severe/refractory MDD

5.4 Exercise

- Supervised, moderate intensity exercise
  - Both aerobic + anaerobic exercise effective → **no superior form**
  - **30 mins, 3 times per week, for 9 weeks**
  - Rarely adverse events reports in trials (but consider physical fitness)

- Potential mechanisms
  - Biological (incr NT turnover, endorphins, BDNF, decr cortisol levels)
  - Psychological (incr self-efficacy)
  - Long-term benefits in MDD less clear (mostly short-term studies)

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

5.5 Yoga

- Ancient Indian practice
  - "Asana" postures, "Pranayama" breathing, "Dhyana" mediation
  - Proposed mechanisms
    - Incr turnover of dopamine + GABA
    - Regulation of HPA axis, normalization of HR variability

- Duration varies
  - **2 – 4 sessions per week, for 2 – 3 months**
  - Rarely SE (consider level of fitness)
    - Case reports of meditation-induced mania/psychosis
    - Excessive/incorrect practice → artery occlusion, neuropathy

- *Recommendation*
  - **Yoga is SECOND-LINE** adjunct for mild-mod MDD

5.6 Acupuncture

- Inconsistent findings due to methodological issues
  - Generally **well-tolerated** if trained + regulated practitioner
    - Mild SE → headache, syncope
      - At insertion sites → transient bleeding, bruising, skin irritation

- *Recommendation*
  - **Acupuncture is THIRD-LINE adjunctive** for mild-mod MDD

Table 3. Summary of Recommendations for Natural Health Products				
Intervention	*Type*	*Indication*	*Recommendation*	
St. John's Wort	**Monotherapy**	**Mild-mod MDD**	First-line	Level 1
St. John's Wort	Adjunctive	Mod-severe MDD	Second-line	Level 2
Omega-3	Mono/adjunctive	Mild-mod MDD	Second-line	Level 1
Omega-3	Adjunctive	Mod-severe MDD	Second-line	Level 2
SAM-e	Adjunctive	Mild-mod MDD	Second-line	Level 1
SAM-e	Adjunctive	Mod-severe MDD	Second-line	Level 2
Acetyl-L-carnitine	Monotherapy	Mild-Mod MDD	Third-line	Level 2
Saffron	Mono/adjunctive	Mild-Mod MDD	Third-line	Level 2
DHEA	Monotherapy	Mild-Mod MDD	Third-line	Level 2
Folate	Adjunctive	Mild-Mod MDD	Third-line	Level 2
Lavender	Adjunctive	Mild-Mod MDD	Third-line	Level 3
Inositol		Mild-Mod MDD	NOT REC	Level 2
Tryptophan		Mild-Mod MDD	NOT REC	Level 2
Roseroot		Mild-Mod MDD	NOT REC	Insufficient

5.7 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

- *Recommendation*
  - **St. John's Wort is FIRST-LINE monotherapy** for mild-mod MDD
  - **St. John's Wort is SECOND-LINE adjunct** for mod-severe MDD

5.8 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

- *Recommendation*
  - **Omega-3s are SECOND-LINE monotherapy** for mild-mod MDD
  - **Omega-3s are SECOND-LINE adjunct** for mod-severe MDD

5.9 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

- *Recommendation*
  - **SAM-e SECOND-LINE adjunct** for mild-mod MDD

5.10 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

- *Recommendation*
  - **DHEA is THIRD-LINE monotherapy**
  - **DHEA is THIRD-LINE adjunctive**

5.11 Tryptophan

- Precursor of **serotonin**
  - Must be supplied through DIET (cannot make *de novo*)
  - May potentiate serotonergic neurotransmission (precursor loading)
  - Dosing → 2 – 4 grams/day, 3 – 4 months

- Mild SE
  - Sedation, dry mouth, GI distress
  - May have risk of serotonin syndrome
  - Potential for lithium toxicity if combined

- **Tryptophan is NOT RECOMMENDED** for treatment of MDD

6 Special Populations

Child & Adolescence

- Major depressive episodes in youth
  - American age 12-17 → 11% report ≥1 MDE past year
  - Canadian age 15-24 → 8.2% report mood disorders

6.1 Suspected Depression in C&A

- Semistructured approach for those who screen positive
  - **K-SADS** (Kiddie Schedule for Affective Disorders)
  - Various sources (clinical interview, auxiliary information)

- Symptoms in adolescents may differ (vs children)
  - **More HYPERsomnia**
  - **Fewer appetite/weight changes**
  - **Fewer psychotic symptoms**

- Supportive clinical care may be sufficient for mild MDE
  - Psychoeducation, active/empathetic listing
  - Lifestyle advice (sleep hygiene, eating habits, exercise)

6.2 Psychotherapy for Depressed C&A

- CBT → **modest effects** in depressed C&A (vs control)
  - More evidence in adolescents
- IPT → **superior in short + long term** (vs control)
- Internet-based psychotherapy → **mixed results**
  - Promising treatment alternative (when in-person not possible)
  - Usually parental/teacher involvement, therapist guidance

6.2 Psychotherapy for Depressed C&A

- Psychotherapy + medications in age 6-18
  - No sig differences in achieving remission, preventing relapse
    - **Combination reduced functional impairment** in short-term
    - CBT for suicide prevention + pharmacotherapy for recent SA
  - **No clear advantage** for pharmacotherapy or psychotherapy

- *Recommendation*
  - **Psychotherapy is FIRST-LINE** for mild-moderate MDD
  - Consider **CBT or IPT ahead** of other psychotherapies

6.3 Antidepressant Medications in C&A

- SSRIs most extensively studied in C&A
  - Lower depression severity scores, higher response/remission rates
  - **Fluoxetine = first choice** (superior to placebo)
  - **Escitalopram** → superiority on function + depression scores
  - **Sertraline** → some evidence superior to placebo, small effects
  - Citalopram → little evidence in C&A, higher remission rates
  - Paroxetine → no efficacy shown in C&A

- Caution with SSRIs
  - If **congenital long QT syndrome** → **avoid citalopram**
  - If congenital heart defect, hepatic impairment → use with caution

6.3 Antidepressant Medications in C&A

- **TCAs → NOT useful** in children, marginal evidence in adols
- **MAOIs → NOT recommended** in C&A (limited data, safety)

- *Recommendations*
  - Moderate MDE → consider medication if psychotherapy n/a
  - **Severe MDE** → pharmacotherapy is **FIRST-LINE**
  - **Fluoxetine → first choice** antidepressant in C&A
    - **Escitalopram, sertraline, citalopram** → second choice
    - **Paroxetine → NOT recommended**
  - TCAs, MAOIs → only in TRD

6.3 Antidepressant Medications in C&A

Table 2. Treatment of MDD in Children/Youth			
	Standard MDD	*Minimal or Non-Response*	*Treatment Resistant*
First Line	• **CBT or IPT** • **Internet-based psychotherapy** (milder severity, in-person n/a)	• **SSRI + psychotherapy**	
Second Line	• **Fluoxetine** • Escitalopram, sertraline • Citalopram	• **Switch to other SSRI** (if unresponsive to fluoxetine)	
Third Line	• Venlafaxine • TCA	• Venlafaxine • TCA	• Venlafaxine • TCA • ECT or rTMS

- *Citalopram not recommended if congenital long QT, congenital heart disease, hepatic impairment*
- *Venlafaxine, TCAs, ECT, rTMS only recommended for adolescents (age >12)*

6.4 Monitoring Initiation of Pharmacotherapy

- USFDA → to monitor SE + suicidality
  - Weekly 1st month, then q2weeks 2nd month, then after 12 weeks
  - Especially for **more severely depressed pts, high SI, family conflict**

- CPA → weekly 1st month

- Dosing
  - Initial low dose for **at least 4 weeks** → before considering increase
  - If only **partial response after 12 weeks** → change treatment

6.5 Duration of Pharmacotherapy

- Little known about AD maintenance strategies in C&A
  - Based on adult research

- *Recommendation in C&A*
  - If no MDD hx → tx for **6 – 12 months**
  - If hx ≥2 MDEs, or 1 severe/chronic MDE → tx for **≥1 year**
  - Discontinue with **slow taper during stress-free time**

6.6 TRD & Comorbidity

- If unresponsive to first-line tx → consider before switch
  - **?misdiagnosis** (bipolar, comorbid medical/psychiatric disorder)
  - **?treatment adherence**
  - **?psychosocial factors** (bullying, sexual identify, family)

- TORDIA (Treatment of Resistant Depression in Adolescents)
  - If <20% response after initial SSRI → should **switch to another SSRI**
  - **Venlafaxine → LESS preferable** (equal response, more SH events)
  - SSRI-resistant depression → **combo meds + psychotherapy**
    - Decr number depression days, may be cost-effective

6.6 TRD & Comorbidity

- Neurostimulation → limited evidence
  - **ECT** → effective in case series, may have long-term cognitive imp
    - **NOT recommended in children age <12**
    - Use with **extreme caution in adolescents** (severe MDD, TRD)
  - **rTMS** → may be promising

- Psychiatric comorbidity → may complicate tx
  - **Fluoxetine** → for mild-mod AUD, oppositional symptoms
  - (TORDIA) **remission from depression** → may reduce comorbid sx
    - Anxiety, ADHD, oppositional symptoms

6.7 Medication Safety Concerns

- Regulatory approval
  - Health Canada → **no approved AD for C&A (age <18)**
  - US FDA → fluoxetine for age ≥8, also escitalopram for age ≥12

- Black-box warning (US FDA, Health Canada)
  - SSRI use in age <24 → **incr suicidal behavior + ideation**
    - **4% vs baseline 2.5%** (Cochrane)
    - **1.5 – 2x risk** (FDA meta-analysis)
    - **OR 1.92** (systematic review)
  - Observational studies → ? these adolescents more depressed
  - **Appropriate monitoring** with SSRIs (vs risk of untreated depression)

Perinatal Depression

- Unipolar MDE during pregnancy + 1st year postpartum
  - Common comorbidity during perinatal period
  - *"with peripartum onset"* → within 4 weeks of delivery (DSM5)
  - But postpartum MDE → **40% begin during pregnancy**

- Epidemiology of unipolar MDE during pregnancy
  - **During pregnancy → 7.5%**
  - First **3 months postpartum → 6.5%**
  - Higher rates of minor depressive disorder

- Untreated perinatal MDE
  - Infant development, future depression risk
  - Family + vocational functioning

6.8 Management of Perinatal Depression

- Up to 50% of pregnancies are unplanned
  - In depressed women of childbearing age, discuss **intent to become pregnant** + **safety of treatment if pregnancy occurs**

- Challenges of treatment of perinatal MDD
  - **Risks of fetal + infant exposure (pregnancy, lactation)**

6.9 Depression Treatment During Pregnancy

- Risks of untreated MDE during pregnancy
  - Poorer nutrition + prenatal medical care
  - Smoking, recreational substance misuse
  - Significant suffering for women

- Poorer obstetrical outcomes (untreated MDE)
  - **SGA, NICU admission, neonatal complications**
  - Mother-infant bonding, infant sleep difficulties
  - Mild developmental delays
  - Cognitive, behavioral, emotional problems in offspring

6.9 Mild-Moderate Perinatal Depression Tx

- Preferred treatment for mild-moderate depression
  - **CBT, IPT** (individual or group) = **FIRST-LINE**
  - **Citalopram, escitalopram, sertraline** = **SECOND-LINE**
  - **Combo SSRI + CBT/IPT** = **THIRD-LINE**

- Less preferred
  - Other SSRIs, newer AD → less data
  - **Paroxetine, clomipramine → risk of fetal cardiac defects**
    - Only consider if previous good response, ongoing stability

- **NOT RECOMMENDED**
  - **Doxepin** → high levels in breast milk
  - **MAOIs** → interactions with analgesic, anesthetics

6.9 Mild-Moderate Perinatal Depression Tx

- Other treatments
  - Neurostimulation, CAM = **THIRD-LINE**
  - If need rapid tx → **previous effective tx = SECOND-LINE**

- Duration of treatment
  - If low-risk → continue for **6 – 12 months** after remission
  - If high-risk → longer duration

6.9 Mild-Moderate Perinatal Depression Tx

Table 3. Treatment of Mild-Moderate MDD during Pregnancy		
	Treatment	*Evidence*
First Line	• **CBT or IPT** (individual or group)	Level 1
Second Line	• **Citalopram, escitalopram, sertraline**	Level 3
Third Line	• **Structured exercise, acupuncture** (depression-specific)	Level 2
	• **Bright-light therapy**	Level 2
	• Fluoxetine, fluvoxamine, SNRIs, bupropion, mirtazapine	Level 3/4
	• TCAs (caution with clomipramine)	Level 3/4
	• ECT (severe, psychotic or TRD)	Level 3
	• rTMS	Level 4
	• Therapist-assisted Internet CBT	Level 4
	• MBCT, PDT, supportive psychotherapy, couples therapy	Level 4
	• Combination SSRI + CBT/IPT	Level 4

- ***For severe MDD,*** *pharmacotherapies move up one recommendation line, psychotherapy & CAM monotherapy NOT recommended, ECT still third-line*

6.10 Severe Perinatal Depression Tx

- **FIRST-LINE**
  - **Citalopram, escitalopram, sertraline**
  - **Combo above SSRIs + CBT/IPT**

- **SECOND-LINE**
  - Other SSRIs (except paroxetine), newer ADs, TCAs

- **THIRD-LINE**
  - Can consider ECT

- Combination pharmacotherapy → consider cautiously
  - Little known about short/long-term risks to fetus

6.11 Risks of Antidepressants During Pregnancy

- Major congenital malformations (MCM)
  - **Paroxetine in 1st trimester** → incr risk of cardiac defects (OR 1.5)
  - **Fluoxetine early** → small incr in congenital malformations
  - **Clomipramine** → incr risk of cardiac defects
  - Other SSRIs, bupropion, mirtazapine, SNRIs, TCAs → no sig risk

- Gestational SSRI use
  - Very modest link with **spontaneous abortion** (OR 1.5)
  - **Shortened gestational duration** (by 4 days)
  - **Decr birth weight** (by 74 grams)

6.11 Risks of Antidepressants During Pregnancy

- Neonatal Adaptation Syndrome (NAS)
  - Jitteriness, irritability, tremor, resp distress, excessive crying
  - SSRI exposure during **3rd trimester → 15-30% of infants**
    - Usually time-limited (2-14 days)
    - No assoc with incr mortality or long-term neurodev problems
  - Highest risk → **paroxetine, fluoxetine, venlafaxine**

- Persistent Pulmonary Hypertension of Newborn (PPHN)
  - SSRIs taken **late in pregnancy** (not early) → limited data
  - Absolute risk = 2.9 – 3.5 per 1000 (0.29-0.35% vs 0.20% gen pop)

6.12 Mild-Moderate PPD Treatment

- Untreated postpartum depression (PPD)
  - Mother-infant attachment
  - Cognitive, emotional, behavioral problems in offspring
  - **Breastfeeding NOT contraindicated** with AD

- Mild-moderate PPD + breastfeeding
  - **CBT or IPT = FIRST-LINE**
  - **Citalopram, escitalopram, sertraline = SECOND-LINE**
    - Efficacy postpartum, minimize lactation risk, childbearing risk
  - Structured exercise, acupuncture → some evidence
  - Therapist-assisted internet-based BA/CBT → some evidence
  - Unsupported internet-based psychotherapy → not established
  - MBCT, supportive, couples, PDT → may have role

6.12 Mild-Moderate PPD Treatment

Table 4. Treatment of Mild-Moderate MDD during PPD with Breastfeeding		
	Treatment	*Evidence*
First Line	• **CBT or IPT** (individual or group)	Level 1
Second Line	• **Citalopram, escitalopram, sertraline** • **Combination SSRI + CBT/IPT**	Level 3
Third Line	• **Structured exercise, acupuncture** (depression-specific) • **Therapist-assisted Internet CBT** • **Behavioral activation** • **Fluoxetine, fluvoxamine, paroxetine, TCAs** (not doxepin) • SNRIs, bupropion, mirtazapine • Bright-light therapy • ECT (severe, psychotic or TRD) • rTMS • MBCT, PDT, supportive psychotherapy, couples therapy	Level 2 Level 2 Level 2 Level 2 Level 3 Level 3 Level 3 Level 3 Level 4

- ***For severe PPD,*** *pharmacotherapies move up one recommendation line, psychotherapy & CAM monotherapy NOT recommended.*

6.12 Mild-Moderate PPD Treatment

- Less preferred treatments
  - **Fluoxetine = THIRD-LINE** (long half-life, more minor AE in breastfed)
  - **Paroxetine = THIRD-LINE** (cardiac defect risk in subsequent preg)
  - **Second-generation AD = THIRD-LINE**
  - TCAs → **nortriptyline** most evidence postpartum, OK in lactation
  - **ECT = THIRD-LINE** (SE profile)

- **AVOID DOXEPIN** → sig AE in breastfeeding infants

- rTMS, BLT → may be effective for mild-mod PPD

6.13 Severe PPD Treatment

- Pharmacotherapy
  - **Citalopram, escitalopram, sertraline = FIRST-LINE**
  - Other antidepressants = **SECOND-LINE**

- **ECT** = can be **FIRST-LINE** (esp **with psychosis**)
  - Can continue breastfeeding during ECT

6.14 Risks of AD during Breastfeeding

- Antidepressant exposure in breastfed infants
  - 5-10x lower than *in utero* exposure
  - Higher levels in preterm infants, liver/kidney impairment
  - No evidence of long-term neurodev effects

- Relative infant doses (RID) → <10% generally safe
  - All SSRIs/SNRIs meet this criterion
  - Lowest RID, M:P ratio → **sertraline, paroxetine, fluvoxamine**
    - Minor reactions with sertraline, paroxetine
  - Highest rates of infant reactions (4-5%) → **citalopram, fluoxetine**
    - Irritability, restlessness, sedation, insomnia (reversible, short)
  - If needing TCA → **nortriptyline** (low RID)
  - MAOI → limited data during lactation

Perimenopausal Depression

- Perimenopause = beginning of ovarian failure
  - Menstrual cycles become 7 days longer/shorter than usual

- Incr risk of depression (vs premenopausal years)
  - **Incr depressive symptoms**
  - **Incr risk of recurrence + new-onset MDE**

- Menopausal symptoms → may negative affect mood
  - **Hot flashes, night sweats** → ind predictor of perimenopausal dep
  - Decr libido, vaginal dryness
  - Sleep disturbances, memory complaints

6.15 Antidepressants during Menopause

- **Desvenlafaxine** → only AD specifically studied in RCT
  - **Superior to placebo**
  - No difference between perimenopause vs postmenopause

- Benefit from other ADs → smaller, open-label studies
  - Citalopram, escitalopram, duloxetine, venlafaxine XR
  - Mirtazapine, quetiapine XR
  - No comparative data

- *Recommendation* = **same as general adult population**
  - (due to limited data)

6.15 Antidepressants during Menopause

Table 5. Treatment of Perimenopausal Depression		
	Treatment	*Evidence*
First Line	• **Desvenlafaxine**	Level 1
	• **CBT**	Level 2
Second Line	• **Transdermal estradiol**	Level 2
	• **Citalopram, escitalopram, venlafaxine, duloxetine**	Level 3
	• **Mirtazapine**	Level 3
	• **Quetiapine**	Level 3
	• Fluoxetine, paroxetine, sertraline	Level 4
	• Nortriptyline	Level 4
	• Omega-3 fatty acids	Level 4
Third Line	• MBCT, supportive psychotherapy	Level 4

- *If using transdermal estradiol with intact uterus, also prescribe progesterone*

6.16 Hormonal Agents

- HRT as augmentation
  - Perimenopause → estrogen superior to placebo
  - Postmenopause → transdermal estradiol NOT superior
  - Postmenopause → methyltestosterone superior to placebo

- *Recommendation*
  - **Hormonal agents are SECOND-LINE**
    - For women who understand risks, no contraindications

6.17 Menopause – Non-Pharmacological Tx

- Group CBT = **FIRST-LINE**
  - **Effective** in decr depressive sx (vs waitlist)
  - No differences between pre/peri/postmenopause

- Adjunctive acupuncture → NO advantage (hot flashes, dep)

Late-Life Depression

- Late-life depression (LLD) → MDD in age ≥60
  - Worse prognosis, more chronic course, higher relapse rates
  - More medical comorbidity, cognitive impairment, mortality
  - May be **dementia prodrome**

- Vascular depression hypothesis
  - **Cerebrovascular disease** = predisposing/precipitating/perpetuating
  - Affect **frontostriatal circuitry** → depression + cog imp (executive!)

6.18 Non-pharmacological Tx in LLD

- Psychotherapies → large effect size (vs control)
  - Small-moderate effect vs supportive therapy/TAU

- **Problem-Solving Therapy (PST)**
  - **STRONGEST EVIDENCE** (vs supportive therapy)
  - Sig decr depression scores, decr disability
  - Studied in elder with cognitive + executive impairment

6.19 Principles of LLD Pharmacotherapy

- "Start low and go slow (and keep going)"
  - **Young-old (age <75)** vs **old-old (age ≥75)**
  - Comorbidities, polypharmacy → drug interactions
  - **Suggest longer AD trials (10-12 weeks)**

- Pharmacokinetic changes with aging
  - Decr absorption rate, bioavailability
  - Incr half-life for lipid-soluble drugs
  - Incr concentration for water-soluble drugs/metabolites

- Antidepressant SE
  - Bone loss, serotonin syndrome, NMS, EPS → more common
  - Falls, hyponatremia, GI bleeding (SSRIs)
  - QTc prolongation (citalopram)

6.20 Pharmacotherapy Approach in LLD

- Dissonance between clinical practice vs RCT evidence!
  - Treatment recommendations = **evidence-informed** (vs based)

- Citalopram/escitalopram
  - **Clinically FIRST-LINE** (better tolerability, fewer drug interactions)
  - RCTs → **no superiority over placebo in elderly**
    - Evidence for citalopram in old-old with severe depression

- Paroxetine/fluoxetine
  - **Clinically avoided**
    - Paroxetine anticholinergic
    - Fluoxetine drug interactions
  - RCTs → **positive evidence in LLD**

6.20 Pharmacotherapy Approach in LLD

- No differences between SSRIs & SNRIs
  - Efficacy in LLD, recurrence of adult-onset MDD in late-life
  - Modest drug-placebo differences for age >65
    - Network meta-analysis → sertraline, paroxetine, duloxetine

- Moderators of treatment response in LLD
  - **Longer illness duration, mod-severe depression** → benefit from AD
  - Shorter illness duration → no AD response
  - Executive dysfunction → poor AD response
  - Vascular depression → may be more resistant (?dementia)

6.20 Pharmacotherapy Approach in LLD

- New antidepressants
  - **Vortioxetine, duloxetine** → sig decr depressive scores (vs placebo)
    - Both improved verbal learning
    - Vortioxetine also improved processing speed
  - **Agomelatine** → improved depressive sx, better tx response
    - Not better for remission (vs placebo)

- Continuation/maintenance tx in LLD
  - **AD effective in preventing relapse + recurrence** in elderly
  - Similar tolerability for SSRIs + TCAs

6.21 Atypical Antipsychotics in LLD

- **Adjunctive aripiprazole + AD**
  - EFFECTIVE (large effect size vs placebo)
  - Most common SE → akathisia, dizziness, Parkinsonism

- Quetiapine XR monotherapy
  - EFFECTIVE in depression scores, response, remission (vs placebo)
  - Less effect on age ≥75, higher dropout rates

- Antipsychotics for dementia
  - **Incr risk of all-cause mortality**
  - **Higher risk in typical** (vs atypical)
  - Risk less clear in cognitively intact elderly

6.22 Sequential Pharmacotherapy in LLD

- Stepwise algorithmic approach → **RECOMMENDED**
  - Improves depressive sx → IMPACT (OR 3.45), PROSPECT (OR 2.13)
  - Little evidence for tailoring of AD to sx clusters or leveraging SE
  - No evidence that sedating med for sleep improves overall outcomes

- TRD in age >55 (meta-analysis)
  - 50% respond to **switch or augmentation**
  - **Lithium augmentation** → most consistent data
  - **Sequential treatment strategy** → highest response rates

6.22 Sequential Pharmacotherapy in LLD

Table 6. Algorithmic Pharmacological Treatment of Late-Life Depression		
	Treatment	*Evidence*
First Line	• **Duloxetine, mirtazapine, nortriptyline**	Level 1
	• **Citalopram, escitalopram, sertraline, vortioxetine**	Level 2
	• **SNRIs**	Level 2
	• **Bupropion**	Level 2
Second Line	Switch to:	
	• **Nortriptyline**	Level 1
	• Moclobemide, phenelzine, quetiapine, trazadone	Level 2
	• Bupropion	Level 3
	Combine with:	
	• **Aripiprazole, lithium**	Level 1
	• Methylphenidate	Level 2
Third Line	Switch to:	
	• Amitriptyline, imipramine	Level 2
	Combine SSRI/SNRI with:	
	• Bupropion, SSRI	Level 3