Major Depression in Primary Care

Diagnosis and Treatment: What the Current Guidelines Tell Us

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Disclosure

I have no financial interests or relationships to disclose.

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Learning Objectives

As a Result of Participating in This Activity, Learners Will Be Able to:

1. Apply current guideline recommendations for screening, diagnosis, and risk assessment of major depression in adults
2. Select an initial treatment matched to severity, comorbidity, and patient preference
3. Use measurement-based care to recognize early non-response and choose among optimizing, switching, and augmenting

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The Evidence Base for This Talk

Four Recent Guidelines and Reviews

Source	Type	What it adds
CANMAT 2023 update (Lam et al., Can J Psychiatry 2024)	Comprehensive clinical guideline	Treatment recommendations across lifestyle, psychotherapy, medications, digital tools, neuromodulation, and maintenance treatment
ACP living guideline (Qaseem et al., 2023)	Systematic review–based clinical guideline	Initial and second-line treatment of the acute phase of treatment
VA/DoD guideline synopsis (McQuaid et al., 2022)	36 graded recommendations	Collaborative care, measurement-based care, what not to use, special patient populations
JAMA review (Simon et al., 2024)	Narrative review	Effect sizes for every major treatment; treatment gaps

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PART 1

Burden, Course, and Who Is at Risk

Depression Is Common, Recurrent, Costly, and Commonly Undertreated

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PART 1 · EPIDEMIOLOGY

Simon 2024 (JAMA) · Malhi 2026 (Lancet)

Depression: Epidemiology

Common at Every Age; Roughly 2x as Common in Women; Onset Typically in the 2nd Decade

7% / 10.4%
US adults (men/women) experience depression each year

17% / 30%
Lifetime prevalence of depression in US adults (men/women)

27%
Prevalence of depression in medical settings

Course of illness

- Nearly 40% have their first episode before age 25
- About a quarter have another episode within 5 years; risk rises with each recurrence

Recent trends

- Risk rose during the COVID-19 pandemic:
  - +13% in ages 18–24
  - +10% in ages 25–34
- The 2:1 female-to-male ratio is consistent from puberty onward

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PART 1 · RISK FACTORS

Malhi 2026 (Lancet) · Lam 2024 (CANMAT)

Who Is at Risk? Vulnerability Factors

A High Index of Suspicion Is Warranted When These Are Present

Biological & physical

- Family history of mood disorder or substance misuse
- Chronic medical illness: cardiovascular, neurological, metabolic (diabetes, hypothyroidism)
- Head injury, epilepsy
- Unbalanced diet, inactivity, poor or non-restorative sleep, tobacco, alcohol, drugs

Psychological

- Personal history of mood disorder
- Anxiety, psychosis, eating or substance use disorders
- Negative self-concept, rejection sensitivity, perfectionism, rumination, low resilience

Social & economic

- Stressful life events; bereavement, loss
- Childhood maltreatment; current or past partner abuse; bullying or harassment
- Low social support, social exclusion, unemployment, low income, unstable housing
- Female sex; gender dysphoria; shift work

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PART 1 · CONSEQUENCES

Egede 2007 (Gen Hosp Psychiatry)

Major Depression: Consequences

Comorbid Depression Amplifies Utilization, Disability, and Cost

Outcome (adjusted odds vs adults with no CMD)	**CMD alone** (n=9,585)	**CMD + major depression (n=975)**
≥1 ambulatory visit	**1.50 (1.28–1.77)**	**1.73 (1.32–2.27)**
≥1 emergency department visit	1.14 (0.99–1.33)	**1.94 (1.55–2.45)**
Functional disability	1.06 (0.91–1.24)	**2.48 (1.96–3.15)**

Adjusted for age, sex, race/ethnicity, education, income, region, BMI, employment, health status, smoking, marital status, and chronic medical conditions.

Increased morbidity

- Cognitive decline
- Higher functional impairment

Higher mortality

- Across chronic medical disorders

Increased cost

- Increased length of stay

More admissions

- More preventable admissions
- Increased readmissions

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PART 1 · BURDEN

Simon 2024 (JAMA) · Coles 2025 (AFP)

Why It Matters: Burden and the Treatment Gap

Depression Multiplies the Risk of Adverse Events; Patients Often Never Reach Remission

The gap is in delivery, not in the science

- Only an estimated 20% of patients with major depressive disorder receive adequate treatment (CANMAT)
- Effective first-line treatments exist
  - >20 antidepressants and at least 6 specific psychotherapies with medium ESs
- "Despite 30 years of practice guidelines aiming to improve care“ the bottleneck is initiation, adherence, follow-up, and treatment adjustment
  - Close monitoring and organized follow-up are the interventions that most reliably improve the odds of success

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PART 2

Screening and Diagnosis

Find It, Confirm It, Grade It, and Determine When to Change the Plan

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PART 2 · SCREENING

Simon 2024 (JAMA) · Lam 2024 (CANMAT) · McQuaid 2022 (VA/DoD)

Screening: What the Guidelines Say

Guidelines Differ on Universal vs Targeted Screening; All Agree Screening Is Only Useful When Linked to Assessment and Treatment

Guideline	Who to screen	Strength
USPSTF (2023)	All adults, including pregnant, postpartum, and older adults	Grade B; moderate net benefit; insufficient evidence for suicide-risk screening
VA/DoD (2022)	All patients not currently receiving treatment for depression	Weak
CANMAT (2023)	Adults with risk factors, when resources exist for diagnostic follow-up and treatment	Level 2 Potential harms: stigma, occupational effects, unnecessary treatment

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PART 2 · SCREENING

Simon 2024 (JAMA) · Lam 2024 (CANMAT) · McQuaid 2022 (VA/DoD)

Screening: How, and the Catch

How: PHQ-2, then PHQ-9

- Two items (over the past 2 weeks)
  1. little interest or pleasure
  2. feeling down, depressed, or hopeless
- Positive PHQ-2 (score ≥3) followed by PHQ-9 (score ≥10) has similar sensitivity and better specificity than PHQ-9 alone

The catches

- Screening that is not linked to effective treatment has no clear benefit
- Screening tools alone can both miss and over diagnose depression
- A positive screen is the start of a diagnostic conversation, NOT a diagnosis

Up to 60% of MDD is unrecognized or misidentified in primary care

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PART 2 · SCREENING

Simon 2024 (JAMA) · Lam 2024 (CANMAT)

The PHQ-9: Screen, Severity, and Outcome Measure

One Instrument Carries You from Detection Through Remission

≥10

identifies major depression with 88% sensitivity and 88% specificity

≥20%

reduction by 2–4 weeks = early improvement; absence of reduction predicts non-response

≤4

= remission
Response: ≥50% reduction or score <11

Look at item scores, not just the total; they speak to symptom(s) burden

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PART 2 · SCREENING

Simon 2024 (JAMA) · Lam 2024 (CANMAT)

PHQ-9 Severity and What It Implies for Treatment

PHQ-9 score	Severity	Typical initial-treatment implication (see Part 3)
0–4	None / remission	Monitor; treat residual symptoms
5–9	Mild	Psychotherapy, exercise, guided digital tools; antidepressants are usually not indicated
10–14	Moderate	Psychotherapy OR antidepressant; combination may be superior
15–19	Moderately severe	Combination of psychotherapy and antidepressant
20–27	Severe	Combination treatment; consider early consultation, ECT if life-threatening

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PART 2 · DIAGNOSIS

American Psychiatric Association. DSM-5 TR. 2022.

Diagnosis of Major Depression: DSM-5-TR Criteria

Five (or More) of the Following Present During the Same 2-week Period; At Least One Is Either (1) Depressed Mood or (2) Loss of Interest or Pleasure

Core symptoms (≥1 required)

Depressed mood		Markedly diminished interest or pleasure	
Appetite / weight disturbance	Sleep disturbance	Psychomotor agitation or retardation	Fatigue or loss of energy
Feelings of worthlessness or excessive guilt	Diminished ability to concentrate	Thoughts of death, suicide, or attempt	Symptoms must cause impairment

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PART 2 · DIAGNOSIS

Lam 2024 (CANMAT) · Simon 2024 (JAMA)

The Medical Workup: What to Order (and Not Order)

Routine Testing Is Not Needed; Targeted Testing to Rule Out Treatable Causes

Reasonable in most patients

- Detailed medical history and targeted physical examination
- CBC and TSH
- Medication review

Only when indicated

- Other labs when history or exam suggests another condition, or in medical comorbidity, substance use, or older adults
- ECG when using QTc-prolonging drugs in patients with CV disease
- Neuroimaging for neurologic signs, new or persistent cognitive impairment

Not recommended routinely

- Routine ECG, EEG, or neuroimaging to diagnose depression
- Inflammatory or EEG biomarkers to select an antidepressant (CANMAT: not recommended)
- Routine pharmacogenetic testing (see Part 5)

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PART 2 · DIAGNOSIS

Simon 2024 (JAMA)

Screen for What Changes the Plan

Complicating Factors that May Require Consultation or Alter Management

Factor	Prevalence in depression	Quick screen	Implication
Bipolar I or II	5% (≥7% unrecognized in primary care)	MDQ In primary care, sensitivity was low (0.28–0.43), while specificity remained high (>0.90)	Antidepressant without a mood stabilizer can precipitate mania
Psychotic symptoms	—	Strange experiences you cannot explain? Hearing or seeing things others cannot?	Referral; antidepressant plus antipsychotic (or ECT)
Suicidal ideation	5%	PHQ-9 item 9 score 2–3	Structured risk assessment; safety plan; urgent consultation if intent

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PART 2 · DIAGNOSIS

Simon 2024 (JAMA)

Screen for What Changes the Plan (Cont.)

Factor	Prevalence in depression	Quick screen	Implication
Alcohol use disorder	up to 20%	AUDIT-C ≥4	Treat both; do not delay depression treatment
Drug use	up to 12%	"How many times in the past year have you used an illegal drug or a prescription for nonmedical reasons?"	Treat both; do not delay depression treatment
Anxiety disorder	~40%	GAD-2 ≥3 → GAD-7	Combined psychotherapy and medication preferred

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PART 3

Principles of Management

Phases, Treatment Goals, and Measurement

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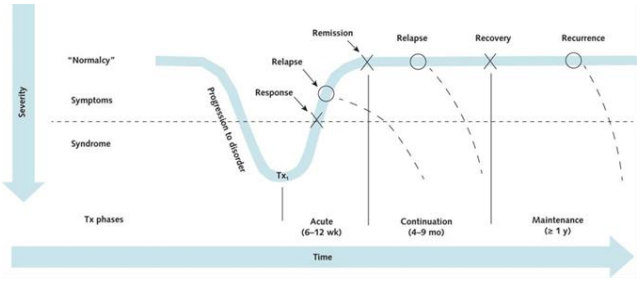
PART 3 · GOALS AND PHASES

Major Depression: Goals and Phases of Treatment

Aim for Remission, Not Just Response



Response:

- Clinically significant improvement in depressive symptoms (usually ≥50%)

Remission:

- Absence of or minimal symptoms

Recovery:

- Sustained remission and restoration of the prior level of functioning

Phase	Duration	Goal
Acute	6–12 weeks	Achieve response, then remission
Continuation	4–9 months	Prevent relapse
Maintenance	≥1 year	Prevent recurrence (recurrent or high-risk illness)

Qaseem A, et al. Ann Intern Med. 2023;176(2):239-252. | Kroenke K, et al. J Gen Intern Med. 2001;16(9):606-613.

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PART 3 · SHARED DECISION-MAKING

Lam 2024 (CANMAT) · Malhi 2026 (Lancet)

Shared Decision-Making and Psychoeducation

Complementary Strategies and the Patient Chooses Among Them with You

Psycho-education	Lifestyle modification	Psychological interventions	Pharmaco-therapy	Neuro-modulation

What patients should hear at the outset

- Depression is a medical illness
- Recovery is the goal; an effective treatment can be found for nearly all patients
- Lots of treatment options
- Time course to benefit, likely adverse effects, and the plan if the first choice does not work
- Warning signs of worsening illness
- CANMAT's free CHOICE-D patient and family guide (canmat.org)

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PART 3 · MEASUREMENT-BASED CARE

Lam 2024 (CANMAT) · McQuaid 2022 (VA/DoD)

Measurement-Based Care

Clinicians and Patients Often Fail to Recognize Non-Response by Impression Alone, So Measure It

Recommendations

- VA/DoD: use a quantitative measure in initial planning and at regular intervals to guide decisions
- CANMAT: use validated scales for measurement-based care
- Measure every 2–4 weeks during acute treatment when decisions are being made; less often in maintenance
- Can also measure function (Sheehan Disability Scale), quality of life (EQ-5D), and side effects (FIBSER)

Use free, brief scales	Send it before the visit	Build it into the EMR	Use it to act	Use discrepancies
PHQ-9, GAD-7, QIDS-SR	Portal, email, app, or waiting room	Trend scores the way you trend HbA1c	No improvement → change the plan	When your impression differs, explore why

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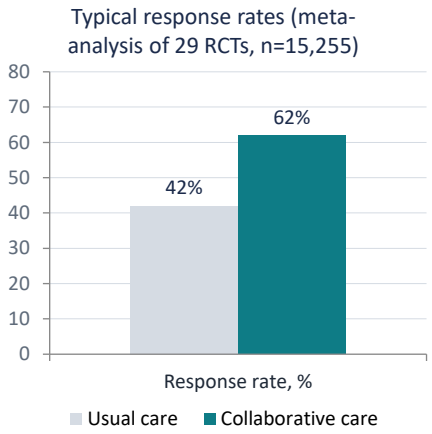
PART 3 · COLLABORATIVE CARE

Simon 2024 (JAMA) · McQuaid 2022 (VA/DoD) · Lam 2024 (CANMAT)

Collaborative Care: Strongest System-Level Evidence

Systematic Follow-up, Outcome Measurement, Care Management, and Psychiatric Consultation Are All Built Around the Primary Care Visit



Components

- Care manager for systematic follow-up and adherence
- Routine outcome measurement (PHQ-9)
- Evidence-based algorithms to adjust or intensify treatment
- Consulting psychiatrist collaborating with the PCP

Guideline positions

- VA/DoD: strong recommendation (one of few)
- CANMAT: reduces symptoms and suicidal ideation; especially effective with medical comorbidity; reduces racial and ethnic disparities (2 systematic reviews)
- SMD 0.42 (95% CI 0.23–0.61) vs usual care without systematic follow-up

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PART 4

Choosing Initial Treatment

Lifestyle, Psychotherapy, Medication, or a Combination

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PART 4 · THE CHOICE

Medication Choice: What Drives the Decision

- Co-occurring psychiatric or general medical conditions
- Pharmacologic properties of the medication
- Patient preference
- Nature of prior response to medication (patient or first-degree relative)
- Cost and access

Overall, all available antidepressants are considered roughly equally effective; consider the above

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PART 4 · THE CHOICE

Pharmacodynamic Considerations

Receptor Effects Predict Adverse Effects and Can Be Deliberately Chosen

Norepinephrine	Serotonin	Dopamine	Histamine-1 antagonism	α1 antagonism	Muscarinic antagonism
Anxiety	Sexual side effects	Psychomotor activation	Sedation	Postural hypotension	Blurred vision
Tachycardia	GI disturbance	Anxiety	Weight gain	Dizziness	Urinary retention
Hypertension	Serotonin toxicity	Nausea			Constipation
Insomnia					Cognitive impairment

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PART 4 · BY SEVERITY

Simon 2024 (JAMA) · Lam 2024 (CANMAT)

First-Line Treatment by Severity

Mild → Psychotherapy; Moderate → Either; Moderately Severe or Severe → Combination

Guideline	Mild (PHQ-9 <10)	Moderate (10–14)	Moderately severe/severe (≥15)
ACP 2023	CBT	CBT OR second-generation antidepressant; CBT AND antidepressant	Same as moderate
VA/DoD 2022	Clinician-guided internet CBT ± antidepressant	Psychotherapy OR antidepressant	Evidence-based psychotherapy AND antidepressant
CANMAT 2023	Psychotherapy preferred if accessible; exercise, guided digital tools if preferred	Psychotherapy or pharmacotherapy; medication slightly better acutely, CBT slightly better at 6–12 months; combination may be considered	Combination of pharmacotherapy and psychotherapy; add antipsychotic if psychotic; ECT if life-threatening
APA 2019	Psychotherapy	Psychotherapy OR second-generation antidepressant	Same as moderate

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PART 4 · ACP 2023

Qaseem 2023 (ACP)

ACP Living Guideline 2023: Acute-Phase Treatment

1a · Strong; moderate certainty	Monotherapy with either CBT or a 2nd generation antidepressant as initial treatment for moderate to severe MDD
1b · Conditional; low certainty	Combination therapy with CBT and a 2nd generation antidepressant as initial treatment for moderate to severe MDD
2 · Conditional; low certainty	Monotherapy with CBT as initial treatment for mild MDD
3 · Conditional; low certainty	Non-response to an adequate dose of a 2nd antidepressant: switch to or augment with CBT, OR switch to a different 2nd generation antidepressant or augment with a second pharmacologic treatment of a different mechanism

Personalize based on benefits, harms, cost, feasibility, specific symptoms (insomnia, hypersomnia, appetite), comorbidities, and preferences. CBT access and cost are barriers in the US.

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PART 4 · VA/DOD 2022

McQuaid 2022 (VA/DoD)

VA/DoD Guideline 2022

36 Recommendations

Strong recommendations for

- Collaborative/integrated care models in primary care
- Psychotherapy OR pharmacotherapy as monotherapy, based on patient preference
- ECT (± psychotherapy) for severe MDD with catatonia, psychosis, severe suicidality, prior good response, need for rapid response, or when other treatments are riskier
- Continue antidepressants at therapeutic dose ≥6 months after remission
- Evidence-based psychotherapy first-line for mild–moderate MDD in pregnancy or breastfeeding

Weak for (selected)

- Screen all patients not in treatment; measure severity quantitatively
- Initial drug: bupropion, mirtazapine, SNRI, trazodone/vilazodone/vortioxetine, or SSRI (not rank ordered)
- Guided computer/internet CBT for mild–moderate MDD; exercise as adjunct; CBT bibliotherapy; St. John's wort for mild MDD if patient prefers herbal
- Non-response: switch drug, switch to or add psychotherapy, or add a second-generation antipsychotic; rTMS after ≥2 failed trials; ketamine/esketamine after several

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PART 4 · VA/DOD 2022

McQuaid 2022 (VA/DoD)

VA/DoD Guideline 2022

36 Recommendations

Strong against

- Given the limited information on the safety and efficacy of psilocybin, MDMA, cannabis, and other unapproved pharmacologic treatments, we recommend against using these agents for MDD outside a research setting
- For patients with MDD, we recommend against using deep-brain stimulation outside a research setting

Weak against

- When choosing an initial pharmacotherapy, we suggest against using:
  - Esketamine
  - Ketamine
  - MAOIs
  - Nefazodone
  - TCAs
- For patients with MDD, we suggest against using VNS outside a research setting
- We suggest against using omega-3 fatty acids or vitamin D for the treatment of MDD

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PART 4 · CANMAT 2023

Lam 2024 (CANMAT)

CANMAT 2023: Selecting the Initial Treatment

Mild, low	• Psychotherapy and pharmacotherapy show similar benefit; psychotherapy preferred if readily accessible (Level 1) • Exercise (Level 1) • Guided digital interventions, especially if preferred (Level 2–3)
Moderate, low–moderate	• Choice is between pharmacotherapy and structured psychotherapy (Level 1) • Medication slightly more effective acutely; CBT slightly more effective at 12m • Combination may be considered; exercise, CAM, digital tools as adjuncts
Severe, moderate–high	• Without psychosis: combination of pharmacotherapy and psychotherapy (Level 2) • With psychosis: antidepressant + atypical antipsychotic • Very severe or life-threatening: consider ECT

Planned sequential treatment (adding CBT or MBCT) after response to medication carries the strongest evidence for durable recovery

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PART 4 · LIFESTYLE

Lam 2024 (CANMAT) · Coles 2025 (AFP)

Lifestyle Interventions: Now First-Line for Mild Depression

Supervised Exercise and Light Therapy Have Guideline-level Evidence; Sleep, Diet, and Smoking Cessation Support the Rest

Line	Intervention	Evidence
First line	Supervised exercise — low to moderate intensity, 30–40 min, 3–4 times/week, for at least 9 weeks for **mild MDE**	Level 1
	Light therapy (10,000 lux white light, 30 min daily in the morning) for **MDE with seasonal pattern**	Level 1
Second line	Light therapy for mild non-seasonal MDE; adjunctive light therapy for moderate non-seasonal MDE	Level 2
	Adjunctive exercise for moderate MDE	Level 2
	Adjunctive sleep hygiene/CBT for insomnia (CBT-I)	Level 3
Third line	Adjunctive healthy diet or Mediterranean diet	Level 3
Insufficient	Probiotics	—

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PART 4 · LIFESTYLE

Lam 2024 (CANMAT) · Coles 2025 (AFP)

Lifestyle Interventions: Now First-Line for Mild Depression

Why it matters

- Exercise reduces depressive symptoms with medium-to-large effects
- Exercise also reduces suicidal ideation
- No concern about drug interactions with antidepressants
- Smoking cessation improves, not worsens, mood in the following months
- Reducing drinking often reduces depressive symptoms
- Insomnia both predicts episodes and persists as a residual symptom

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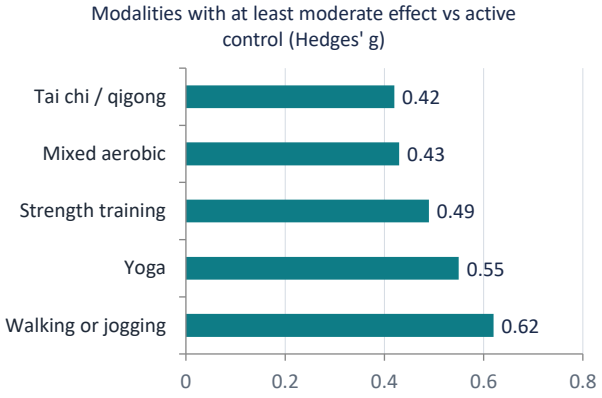
PART 4 · EXERCISE

Noetel 2024 (BMJ)

Physical Exercise: What to Prescribe

Network Meta-Analysis of 218 Trials, 14,170 Participants with Major Depression



Age differences

- Yoga and aerobic exercise alongside psychotherapy appeared more effective for older participants
- Strength training appeared more effective in younger participants

Sex differences

- Effects appeared larger for women with strength training and cycling
- Effects appeared larger for men with yoga, tai chi, and aerobic exercise

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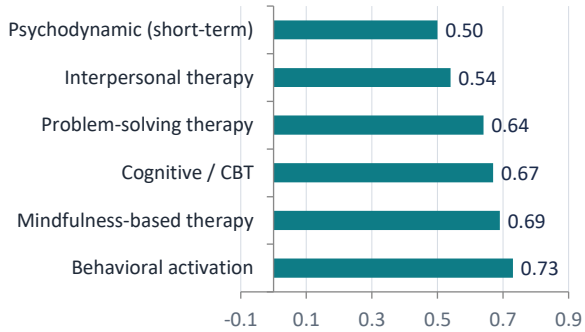
PART 4 · PSYCHOTHERAPY

Simon 2024 (JAMA) · Lam 2024 (CANMAT)

Psychotherapy: First-Line Options

Six Specific Therapies All Outperform Usual Care with At Least Medium Effects

Network meta-analysis: 331 RCTs, n=34,285 (SMD; 0.5 = medium, 0.8 = large)



CANMAT lines of treatment

- **First: CBT, interpersonal therapy (IPT), behavioral activation (BA)**
- Second: mindfulness-based cognitive therapy (MBCT), problem-solving therapy, short-term psychodynamic therapy
- Third: acceptance and commitment therapy, long-term psychodynamic therapy, metacognitive therapy, motivational interviewing

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PART 4 · BRIEF COUNSELING

Simon 2024 (JAMA)

Brief Counseling Strategies You Can Use

Elements of Effective Psychotherapies, Adapted for Primary Care

Behavioral activation	"Can we identify one or two positive things you could plan over the next week? When would you do them — can we write that down? What might get in the way, and how could you manage that?"
Cognitive: interrupting negative thoughts	"What negative or self-critical thoughts do you get stuck in? How can you recognize when you're stuck? What would help you step back and look at the evidence?"
Mindfulness	"Instead of fighting negative thoughts, try disconnecting from them by focusing on the present — your breathing, what you hear. Try a few exercises or apps; groups can help."
Problem-solving: small steps	"Plan your day the evening before. Set 1 to 3 small, achievable goals. If you miss them, treat it as learning — and congratulate yourself for any goal met."
Interpersonal: social support	"Is there someone you feel comfortable talking with? Someone you'd like to spend a little time with — even coffee or a movie?"

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PART 5

Pharmacotherapy

Which Drug, at What Dose, and for Whom

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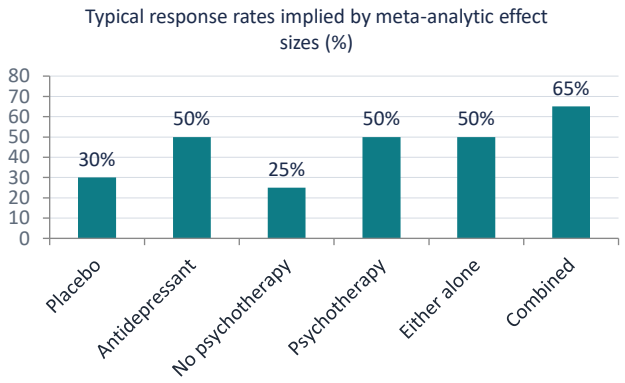
PART 5 · EFFICACY

Simon 2024 (JAMA) · Lam 2024 (CANMAT)

How Well Do Antidepressants Work?

All 21 First-Line Agents Beat Placebo with Small-to-medium Effects; the Advantage Grows with Severity



Severity matters

- SMD ≈0.15 in mild symptoms vs ≈0.38 in severe
- One reason AD are usually not indicated for mild depression

Durability

- Psychotherapy or combination yields more durable benefit:
  - Sustained 12-month response OR 1.53 (therapy vs drug) and 2.52 (combination vs drug)

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PART 5 · FIRST-LINE AGENTS

Lam 2024 (CANMAT) · Coles 2025 (AFP)

CANMAT First-Line Antidepressants

17 First-Line Agents, All with Robust Placebo-controlled Evidence; TCAs Are Second Line, MAOIs Third Line

Class	Agent (daily dose)	Notes
SSRI	Citalopram 20–40 mg; escitalopram 10–20; fluoxetine 20–60; paroxetine 20–50; sertraline 50–200	Most prescribed, best tolerated class; citalopram QTc monitoring; fluoxetine/paroxetine 2D6 and fluvoxamine 1A2/2C19/3A4 inhibition
SNRI	Desvenlafaxine 50–100 mg; duloxetine 60–120; levomilnacipran 40–120; venlafaxine-XR 75–225	Preferred for comorbid pain and fatigue; may raise blood pressure; may be more effective than SSRIs after age 65
NDRI	Bupropion 150–450 mg	No sexual dysfunction or weight gain; helps fatigue and cognition; lowers seizure threshold
α2 / 5-HT2 antagonist	Mirtazapine 30–60 mg	Sedation, appetite, and weight gain — useful with insomnia and weight loss; low risk of sexual dysfunction and drug interactions

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PART 5 · FIRST-LINE AGENTS

Lam 2024 (CANMAT) · Coles 2025 (AFP)

CANMAT First-Line Antidepressants (Cont.)

Class	Agent (daily dose)	Notes
Serotonin modulators	Vilazodone 20–40 mg; vortioxetine 10–20 mg	Lower sexual dysfunction; vortioxetine for cognitive symptoms; nausea common
Second line	TCAs, trazodone, quetiapine, dextromethorphan-bupropion, nefazodone, selegiline transdermal	
Third line	Phenelzine, tranylcypromine, reboxetine	—

Generic formulations are equally effective
Once effective, try to keep the same formulation and brand

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PART 5 · CHOOSING AMONG AGENTS

Lam 2024 (CANMAT) · Simon 2024 (JAMA) · Coles 2025 (AFP)

Are Some Antidepressants Better?

Differences Are Small (5–10 Percentage Points in Response); Tolerability and Patient Factors Should Decide

Superior efficacy (CANMAT)	Better acceptability (lower all-cause dropout)
Bupropion Citalopram Mirtazapine Sertraline Venlafaxine-XR Escitalopram Paroxetine Vortioxetine	Escitalopram Sertraline Fluoxetine Vortioxetine

In the real-world (i.e., primary care), antidepressants achieve small-to-medium effectiveness with moderate-to-high tolerability.
This is why SSRIs dominate first-line use.

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PART 5 · SSRIS

Simon 2024 (JAMA)

First-Line Pharmacotherapy: SSRIs

Drug	Start	Usual range	Other FDA indications	Common adverse effects / precautions
Citalopram	10 mg	20–40 mg	—	Dry mouth, nausea, somnolence, insomnia, sexual dysfunction; may prolong QT
Escitalopram	5 mg	10–20 mg	GAD	Headache, nausea, insomnia, sexual dysfunction
Fluoxetine	10 mg	20–60 mg	Panic, OCD, PMDD, bulimia	Insomnia, nausea, headache, diarrhea, nervousness, tremor, sexual dysfunction; long half-life; 2D6/2C19 inhibitor
Paroxetine	10 mg	20–50 mg	Panic, social anxiety, OCD, GAD, PTSD, PMDD, vasomotor symptoms	Nausea, insomnia, dry mouth, constipation, sexual dysfunction; anticholinergic; avoid in elderly; 2D6 inhibitor; discontinuation symptoms
Sertraline	50 mg	100–200 mg	Panic, social anxiety, OCD, PTSD, PMDD	Nausea, diarrhea, insomnia, dry mouth, fatigue, dizziness, sexual dysfunction

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PART 5 · BEYOND THE SSRIS

Simon 2024 (JAMA)

First-Line Pharmacotherapy: Beyond the SSRIs

Drug	Start	Usual range	Other FDA indications	Common adverse effects / precautions
Duloxetine	30 mg	60–120 mg	GAD, diabetic neuropathy, fibromyalgia, chronic musculoskeletal pain	Nausea, dry mouth, headache, somnolence, fatigue; avoid GFR <30; liver
Venlafaxine XR	75 mg	150–300 mg	GAD, social anxiety, panic	Headache, nausea, insomnia, sweating, sexual dysfunction; ↑ blood pressure; discontinuation symptoms
Desvenlafaxine	50 mg	50–100 mg	—	Nausea, dizziness, insomnia, sweating; ↑ blood pressure
Levomilnacipran	20 mg	40–120 mg	—	Nausea, sexual dysfunction; renal dose reduction
Bupropion XL	150 mg	300–450 mg	Seasonal affective disorder, smoking cessation	Dry mouth, nausea, appetite loss, insomnia, tremor; seizure risk

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PART 5 · BEYOND THE SSRIS

Simon 2024 (JAMA)

First-Line Pharmacotherapy: Beyond the SSRIs

Drug	Start	Usual range	Other FDA indications	Common adverse effects / precautions
Mirtazapine	15 mg qhs	30–45 mg qhs	—	Somnolence, weight gain, appetite, dry mouth, constipation
Vortioxetine	5 mg	10–20 mg	—	Nausea
Vilazodone	10 mg	20–40 mg	—	Nausea, diarrhea; take with food
Nortriptyline / desipramine	25 / 50 mg	50–100 / 100–200 mg	—	Anticholinergic, somnolence, constipation; avoid in elderly; lethal in overdose

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PART 5 · MATCHING THE DRUG

Lam 2024 (CANMAT) · Malhi 2026 (Lancet)

Matching the Drug to the Clinical Profile

Evidence for Differential Efficacy Is Limited — but Side-Effect Profiles Can Be Turned to the Patient's Advantage

Feature	First line (CANMAT)	Second line / alternatives	Comment
Cognitive dysfunction	Vortioxetine	Bupropion, duloxetine, SSRIs	Vortioxetine, bupropion, SNRIs may outperform SSRIs for cognition
Sleep disturbance	Agomelatine (not US)	Mirtazapine, quetiapine-XR, trazodone	Sedation as a benefit, not a side effect
Pain	Duloxetine	Other SNRIs; TCAs	SNRIs > SSRIs for comorbid pain
Fatigue, low energy	Bupropion	Duloxetine, SSRIs	SNRIs or bupropion improve energy
Anxiety/anxious distress	Any first-line agent (SSRIs, SNRIs)	—	Anxiety may worsen briefly on starting

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PART 5 · MATCHING THE DRUG

Lam 2024 (CANMAT) · Malhi 2026 (Lancet)

Matching the Drug to the Clinical Profile (Cont.)

Feature	First line (CANMAT)	Second line / alternatives	Comment
Weight loss, anorexia	Mirtazapine	—	Appetite stimulation
Psychotic features	Antidepressant + atypical antipsychotic	ECT	Defer psychotherapy until psychosis resolves
Tobacco dependence	Bupropion	—	Dual benefit
Sexual dysfunction concern	Bupropion, mirtazapine, vilazodone, vortioxetine, desvenlafaxine	—	Assess baseline sexual function first

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PART 5 · MATCHING THE DRUG

Lam 2024 (CANMAT) · Simon 2024 (JAMA) · McQuaid 2022 (VA/DoD) · Malhi 2026 (Lancet)

Matching the Drug to the Patient

Under 25

- SSRIs favored (efficacy, adverse reactions, discontinuation risk)
- Higher risk of akathisia, agitation, aggression, and treatment-emergent suicidality
  - Counsel and monitor closely

Over 65

- Vortioxetine may help those with complaints of cognitive dysfunction related to depression
- Avoid anticholinergic agents (paroxetine, TCAs)
  - Concern for delirium, urinary retention, constipation, etc.
- Avoid alpha-1 antagonism (TCAs)
  - Concern for orthostasis, dizziness, falls
- SSRIs associated with hyponatremia risk; GI bleeding

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PART 5 · MATCHING THE DRUG

Lam 2024 (CANMAT) · Simon 2024 (JAMA) · McQuaid 2022 (VA/DoD) · Malhi 2026 (Lancet)

Matching the Drug to the Patient

Pregnancy / breastfeeding

- Evidence-based psychotherapy is first-line for mild–moderate MDD
- If previously responsive and stable on medication: weigh the risk–benefit of continuation for the mother and fetus
- Sertraline, citalopram, escitalopram, and fluoxetine are most commonly used in pregnancy

Other

- Prior response in the patient or a first-degree relative predicts response
- Overdose risk: prefer SSRIs; TCAs are lethal in overdose
- Anhedonia: no agent is proven superior
- Cost: generics are bioequivalent

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PART 5 · SAFETY

Lam 2024 (CANMAT) · Simon 2024 (JAMA)

Safety and Drug Interactions

Most First-Line Agents Combine Safely with Common Medications

Bleeding	SSRIs/SNRIs + NSAIDs or anticoagulants increase GI bleeding; mitigated with a PPI
Hyponatremia	SSRIs/SNRIs with diuretics, especially in older adults; consider checking e'lytes at age ≥60.
Cardiovascular	Citalopram QTc (clinically low risk; escitalopram not clinically relevant); SNRIs raise blood pressure; TCAs are cardiotoxic in overdose
Liver	Rare drug-induced liver injury; consider LFTs at baseline and q6–12m with pre-existing liver disease
Metabolic	Mirtazapine: appetite, weight, long-term metabolic risk. Monitor weight, glucose, and lipids at baseline and q6m
Serotonin toxicity / MAOIs	MAOIs interact with serotonergic drugs and tyramine-rich foods; 2-week washout from serotonergic agents (5 weeks after fluoxetine)

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PART 5 · SAFETY

Medication Choice: Drug Interaction Potential

CYP450 Inhibition Is the Main Issue; Choose Low-Interaction Agents

Minimal or low potential

- Citalopram
- Escitalopram
- Venlafaxine / desvenlafaxine
- Mirtazapine
- Sertraline (at lower doses)

Moderate potential

- Bupropion (2D6 inhibitor)
- Duloxetine (2D6 inhibitor; 1A2 substrate)
- Levomilnacipran (3A4 substrate)
- Sertraline (2D6 inhibitor at higher doses)
- Vilazodone (3A4 substrate)
- Vortioxetine (2D6 substrate)

Higher potential

- Fluoxetine (2D6, 2C19 inhibitor; very long half-life)
- Paroxetine (2D6 inhibitor)
- Fluvoxamine (1A2, 2C19 inhibitor)

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PART 5 · STARTING

Simon 2024 (JAMA) · Lam 2024 (CANMAT) · Malhi 2026 (Lancet)

Starting, Titrating, and Following Up

Start Low, Go to the Bottom of the Range Within 2 Weeks, and Follow-Up

1. **Consider starting at one-half of the usual dose**
   Increase to the low end of the therapeutic range over 1–2 weeks; fewer early adverse effects mean fewer early dropouts
2. **Set expectations**
   Nausea and headache usually subside in 1–2 weeks; mood benefit may not appear for 2 weeks or more
3. **Ask about side effects within 2 weeks**
   CANMAT: actively inquire about side effects by 2 weeks
4. **Measure at 2–4 weeks**
   <20% improvement by 4 weeks at a dose in the recommended range → increase the dose
   Only 71% of patients refill the first prescription; communication is the intervention.
5. **Dose–response has a ceiling**
   More effective up to ~50 mg fluoxetine-equivalents, then a plateau while adverse-effect dropout keeps rising

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PART 5 · STARTING

Simon 2024 (JAMA) · Lam 2024 (CANMAT) · Malhi 2026 (Lancet)

Starting, Titrating, and Following Up (Cont.)

Adherence: five messages that work

1. Take it every day
2. It takes 2–4 weeks to notice an effect
3. Keep taking it even when you feel better
4. Don't stop without checking with me
5. Here is exactly what to do if you have questions or side effects

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PART 5 · SUICIDALITY

Simon 2024 (JAMA) · Lam 2024 (CANMAT) · Coles 2025 (AFP)

Antidepressants and Suicidality: What to Tell Patients

Antidepressants Reduce Suicidal Ideation Overall, but a Small Subset (Mostly Young Adults) Experiences Thoughts Early in Treatment

Practical points

- All antidepressants carry a US boxed warning; the signal is confined to ages <25 in RCTs
- Suicidal behavior peaks in the month BEFORE starting (it predates the drug), stays high the month after, then declines with continued treatment
- The month after stopping an AD also represents an increased risk

What to say and do

- Tell every patient: rarely, new thoughts of self-harm can appear within weeks of starting or increasing the dose; report them
- Monitor suicide risk; with enhanced attention for 4 weeks after starting or stopping
- Have a safety plan and 988 in the conversation from the start

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PART 5 · PHARMACOGENETICS

Lam 2024 (CANMAT) · Simon 2024 (JAMA) · McQuaid 2022 (VA/DoD)

Pharmacogenetic Testing and Biomarkers

Modest, Inconsistent Benefit — Not Recommended Routinely, but Useful in Specific Situations

What the evidence shows

- NEED TO ATTEND NEXT LECTURE!

Guideline	Position
CANMAT 2023	Not recommended routinely
VA/DoD 2022	Insufficient evidence for or against
JAMA review	May reduce adverse effects; no gain in sustained response
When testing may help	Severe or unusual adverse effects at low doses; poor response at therapeutic doses; results already available from another indication; difficult-to-treat depression when choosing adjuncts

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PART 5 · COMPLEMENTARY TREATMENTS

Lam 2024 (CANMAT) · Simon 2024 (JAMA) · McQuaid 2022 (VA/DoD)

Complementary and Alternative Treatments

Reasonable for Mild Depression or as Adjuncts; None Approach First-Line Psychotherapy or Medication

Line (CANMAT)	Treatment	Evidence and cautions
First	St. John's wort for mild MDE	SMD 0.49 vs placebo in mild–moderate depression; potent CYP3A4 inducer; serotonin toxicity risk with SSRIs/SNRIs; VA/DoD: option for mild MDD if patient prefers herbal treatment
Second	Acupuncture (mild; adjunct in moderate); St. John's wort for moderate MDE; adjunctive L-methylfolate	Acupuncture added to antidepressant: SMD 0.44 (16 RCTs); VA/DoD: insufficient evidence
Third	Adjunctive SAM-e; DHEA; omega-3 fatty acids; saffron, lavender, roseroot	Omega-3 augmentation SMD 0.40 in one meta-analysis, but Cochrane found insufficient high-quality evidence; VA/DoD recommends against omega-3 and vitamin D
Insufficient	Probiotics	Augmentation SMD 0.36 in 13 small RCTs; CANMAT: equivocal
Against	Cannabis	No evidence of efficacy; risk of harm; labeled CBD products may contain THC

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PART 6

When the Patient Is Not Better

Recognize It, Look for the Reason, Then Optimize, Switch, or Augment

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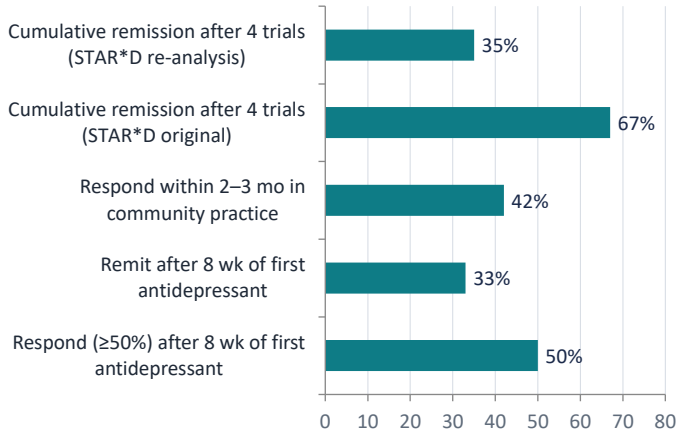
PART 6 · NON-RESPONSE

Lam 2024 (CANMAT) · Simon 2024 (JAMA) · Qaseem 2023 (ACP)

Expect Non-Response

About Half Respond and a Third Remit with a First Antidepressant



What this means

- Up to 70% do not remit after initial SGA treatment
- More than 60% have at least one adverse effect
- Of poor responders, 35–67% eventually improve with an alternative strategy
- Poor response reflects both discontinuation and non-response

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PART 6 · THE 4-WEEK RULE

Coles 2025 (AFP) · Lam 2024 (CANMAT) · Simon 2024 (JAMA)

The 4-Week Rule: Act Early

Lack of ≥20% Improvement by 2–4 Weeks Strongly Predicts Non-Response and Non-Remission at 8–12 Weeks

Week 0	Baseline PHQ-9; start at 1/2 dose; five adherence messages; safety plan
Week 2	Contact: side effects, adherence, increase dose to lower therapeutic range; PHQ-9
Week 4	PHQ-9: ≥20% better → continue <20% better at an adequate dose → increase dose or switch
Week 8	Response (≥50%)? If not, second-line strategy. Reassess the diagnosis if <50% improvement
Week 8–16	Treat to remission (PHQ-9 ≤4); then maintenance phase

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PART 6 · THE 4-WEEK RULE

Coles 2025 (AFP) · Lam 2024 (CANMAT) · Simon 2024 (JAMA)

The 4-Week Rule: Act Early

Nuances

- Increasing the dose of the existing medication is as effective as switching but brings more adverse effects (CANMAT)
  - Switch instead when tolerability is the problem
- "No benefit at all after 4 weeks at a dose in the recommended range should prompt consideration of second-line treatment" (JAMA review)
- Partial response at 4 weeks may justify continuing another 2–4 weeks before changing course

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PART 6 · BEFORE ESCALATING

Lam 2024 (CANMAT) · Simon 2024 (JAMA)

Before Escalating: Why Isn't This Working?

Re-Evaluate the Diagnosis, Comorbidities, Adherence, and Adequacy of Treatment

Clinical factors

- Incorrect diagnosis — especially unrecognized bipolar disorder (≥7% of primary care patients on antidepressants); psychotic features
- Psychiatric comorbidity: anxiety disorders, PTSD, ADHD, substance use, personality disorders
- Medical comorbidity: anemia, obesity, thyroid disease, undiagnosed sleep apnea
- Acute or chronic stressors; abuse; caregiving or work demands

Treatment factors

- Inadequate dose
- Inadequate duration (4–6 weeks at a therapeutic dose)
- Side effects masquerading as symptoms (e.g., fatigue)
- Poor adherence — 28% stop in the first month; ask directly and without judgment
- Pharmacogenetic variability (rapid or slow metabolism)
- Comorbidities change over time

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PART 6 · SECOND-LINE STRATEGIES

Lam 2024 (CANMAT) · Simon 2024 (JAMA) · Qaseem 2023 (ACP)

Second-Line Strategies: Optimize, Switch, or Add

Meta-Analyses Find Roughly Equal Success Rates; Choose Based on What Happened with the First Treatment

Poor response to initial antidepressant	Reassess diagnosis, comorbidity, adherence; optimize dose
Add psychotherapy	First-line therapies have efficacy and few side effects; ACP: switch to or augment with CBT
Switch antidepressant	Preferred when NO response or troublesome side effects; within-class vs between-class makes no difference; pick another first-line drug
Add an adjunctive medication	Preferred when PARTIAL response and the first drug is well tolerated; avoids discontinuation; potential for more side effects, cost
Neuromodulation	rTMS after ≥2 adequate trials; ECT for severe, psychotic, catatonic, or life-threatening illness; ketamine/esketamine after several trials

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PART 6 · SECOND-LINE STRATEGIES

Lam 2024 (CANMAT) · Simon 2024 (JAMA) · Qaseem 2023 (ACP)

Second-Line Strategies: Optimize, Switch, or Add

What the evidence says

- JAMA: changing medication, adding a second antidepressant, or augmenting with a non-antidepressant have approximately equal likelihood of success; one-third to one-half respond to the second step
- CANMAT: switching is not clearly superior to continuing; adjunctive strategies show superior outcomes with similar tolerability in head-to-head RCTs
- Stopped for side effects → Choose psychotherapy or a drug unlikely to cause the same effect
- **Second-line failure → psychiatry consultation**

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PART 6 · SWITCHING

Lam 2024 (CANMAT) · Simon 2024 (JAMA) · Malhi 2026 (Lancet)

How to Switch an Antidepressant

Choosing the second agent

- Switching within class vs to a different class:
  - No difference in outcome in several studies
  - Choose based on side-effect profile, mechanism, and comparative efficacy
  - If switching for inefficacy → a different mechanism is a reasonable preference
- Select a first-line antidepressant with evidence for superior efficacy and favorable tolerability (bupropion, escitalopram, mirtazapine, sertraline, venlafaxine-XR, vortioxetine)
- TCAs and MAOIs remain useful after first- and second-line failures
  - Nortriptyline is the best-tolerated TCA
  - Online tools give titration schedules

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PART 6 · ADJUNCTIVE MEDICATIONS

Lam 2024 (CANMAT) · Simon 2024 (JAMA) · Coles 2025 (AFP)

Adjunctive Medications for Difficult-to-Treat Depression

Low-Dose Atypical Antipsychotics Have the Most Consistent Evidence

Line (CANMAT)	Agent	Target dose	Common adverse effects / notes
First	Aripiprazole	2–10 mg	Akathisia, agitation, insomnia, weight gain, hyperglycemia, dyslipidemia
	Brexpiprazole	0.5–2 mg	As above; less akathisia
Second	Bupropion; mirtazapine	150–450 mg; 30–60 mg	Antidepressant combinations; ACP names both plus buspirone (15 mg daily → 15 mg TID)
	Quetiapine-XR; olanzapine; risperidone; cariprazine	150–300; 2.5–10; 1–3; 1.5–3 mg	Somnolence, weight gain, metabolic effects; monitor weight, glucose, lipids every 6 months

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PART 6 · ADJUNCTIVE MEDICATIONS

Lam 2024 (CANMAT) · Simon 2024 (JAMA) · Coles 2025 (AFP)

Adjunctive Medications for Difficult-to-Treat Depression

Line (CANMAT)	Agent	Target dose	Common adverse effects / notes
Second (cont.)	Lithium; triiodothyronine; modafinil	600–1200 mg (level 0.5–0.8); 25–50 mcg; 100–400 mg	Lithium: tremor, nausea, diarrhea; check level, renal, thyroid, calcium; T3: tremor, anxiety
	Intranasal esketamine; IV racemic ketamine	56–84 mg; 0.5 mg/kg	After ≥2 adequate trials; monitored settings; misuse potential; long-term data limited
Third	TCAs, stimulants, lamotrigine, pramipexole, ziprasidone, non-IV ketamine	—	Limited evidence and/or safety concerns
Not recommended	Cannabis	—	Insufficient efficacy; risk of harm. Psychedelic-assisted therapy: investigational only

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PART 6 · REFERRAL

Lam 2024 (CANMAT) · McQuaid 2022 (VA/DoD) · Simon 2024 (JAMA)

Treatment-Resistant Depression

Treatment	When
rTMS	Partial or no response to ≥2 adequate pharmacologic trials (VA/DoD weak for)
ECT	Strong recommendation: severe MDD with catatonia, psychosis, severe suicidality, prior good response, need for rapid definitive response; very severe or life-threatening MDE (CANMAT)
Esketamine / IV ketamine	Adjunct after ≥2 (VA/DoD: several) adequate trials; rapid effect on symptoms and suicidal thoughts; limited durability, cost, dependence risk
Others	Vagus nerve stimulation (weak against); Psilocybin and cannabis (strong against)

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PART 7

After Remission

Maintenance, Recurrence Prevention, and How to Stop an Antidepressant

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PART 7 · MAINTENANCE

Lam 2024 (CANMAT) · McQuaid 2022 (VA/DoD) · Simon 2024 (JAMA) · Coles 2025 (AFP)

Maintenance Treatment: How Long?

Maintenance Pharmacotherapy Halves Recurrence; Psychotherapy Protects at Least as Well and May Last Longer

6–12 months

Minimum continuation after remission for ALL patients (CANMAT Level 1; VA/DoD strong: ≥6 months at therapeutic dose)

≥2 years

For patients with risk factors for recurrence; often indefinitely

50%

reduction in recurrence with maintenance medication vs placebo

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PART 7 · MAINTENANCE

Lam 2024 (CANMAT) · McQuaid 2022 (VA/DoD) · Simon 2024 (JAMA) · Coles 2025 (AFP)

Maintenance Treatment: How Long? (Cont.)

Risk factors for recurrence (continue ≥2 years)

- Persistent residual symptoms (anhedonia, sleep, cognition)
- History of adverse childhood experiences
- Greater severity; chronic episodes; greater number of previous episodes (VA/DoD: ≥2 prior episodes)
- Medical or psychiatric comorbidity; poor social support; persistent stressors
- Need for second-line treatment during the acute phase

Maintaining remission

- Keep the lowest effective dose
- Monitor symptoms and side effects with MBC (less often than in the acute phase)
- Sequential psychotherapy (CBT, MBCT, IPT) after response to medication prevents recurrence — even if the drug is later stopped
- Recurrent or severe illness: continue medication during psychotherapy
- Lifestyle, peer support, and early-warning-sign plans

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PART 7 · STOPPING

Lam 2024 (CANMAT) · Malhi 2026 (Lancet) · Simon 2024 (JAMA)

Stopping an Antidepressant

Up to Half of Patients Have Discontinuation Symptoms; Taper Gradually and Know Which Drugs Are Riskiest

FINISH: discontinuation symptoms

- **Flu-like symptoms · Insomnia · Nausea · Imbalance · Sensory disturbances · Hyperarousal**
- Onset within days (peak 36–96 h), usually resolves within 2 weeks (up to 6)
- Improves rapidly if the dose is restored
- Tapering paroxetine or venlafaxine over ≤14 days: symptoms in ≥50%.

Risk by drug (CANMAT)

- **High:**
  - Paroxetine, venlafaxine (Lancet adds desvenlafaxine, TCAs; MAOIs very high)
- **Moderate:**
  - Citalopram, escitalopram, sertraline, fluvoxamine, desvenlafaxine, duloxetine, levomilnacipran, vilazodone, TCAs, MAOIs
- **Low:**
  - Fluoxetine, bupropion, mirtazapine, vortioxetine

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PART 7 · STOPPING

Lam 2024 (CANMAT) · Malhi 2026 (Lancet) · Simon 2024 (JAMA)

Stopping an Antidepressant (Cont.)

How to taper

- Fluoxetine needs no taper
- If on AD for <4 weeks (e.g., stopping for side effects): taper over 2 weeks
- Otherwise, taper over 1-2 months (maybe longer)
  - Reduce gradually over weeks to months, with more time between reductions near the end
- Severe symptoms of discontinuation
  - Return to prior dose and taper more slowly
  - Or switch to fluoxetine and taper that
- Add CBT or MBCT before or during the taper
- Hyperbolic tapering: insufficient evidence
- Discuss relapse warning signs and schedule follow-up a few months later

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PART 7 · SPECIAL POPULATIONS

McQuaid 2022 (VA/DoD) · Lam 2024 (CANMAT) · Simon 2024 (JAMA) · Malhi 2026 (Lancet)

Special Populations at a Glance

Where the General Rules Bend

Older adults

- Psychotherapy first for mild–moderate MDD (VA/DoD weak)
- Avoid anticholinergic agents
- Watch for hyponatremia, bleeding, falls, QTc; check electrolytes
- New-onset late-life depression: consider neuroimaging
- Suicide risk falls with antidepressants after 65

Pregnancy and postpartum

- Screen during pregnancy and postpartum (USPSTF B)
- Evidence-based psychotherapy first-line for mild–moderate MDD (VA/DoD strong)
- Continue effective medication when relapse risk is high; weigh risk to mother and fetus
- Zuranolone and ~~brexanolone~~ are options for postpartum depression

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PART 7 · SPECIAL POPULATIONS

McQuaid 2022 (VA/DoD) · Lam 2024 (CANMAT) · Simon 2024 (JAMA) · Malhi 2026 (Lancet)

Special Populations at a Glance (Cont.)

Adolescents and young adults

- Fluoxetine or escitalopram preferred
- Higher risk of activation and treatment-emergent suicidality
- Moderate-to-high intensity aerobic exercise has good evidence
- Screen for cannabis use; adolescent use raises depression risk

Chronic medical illness

- Depression is 2–3× more prevalent; treatments retain medium effects
- Prefer low-interaction agents
- Duloxetine/SNRIs for pain
- Avoid TCAs in cardiac disease
- Collaborative care is especially effective here
- Depression amplifies pain and fatigue; treating both improves each

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SUMMARY · BOTTOM LINE

Bottom Line for Primary Care

Ten Things the Guidelines Agree On

1. Screen with the PHQ-2/PHQ-9, but only where a positive screen can lead to assessment and treatment
2. Diagnosis is clinical; look for comorbid conditions
3. Assess suicide risk; the month around starting or stopping is the riskiest
4. Match treatment to severity: therapy or exercise for mild, therapy or medication for moderate, both for moderately severe and severe
5. Antidepressants are equally effective and differ mainly in tolerability; escitalopram and sertraline are sound defaults; use side-effect profiles to your advantage

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SUMMARY · BOTTOM LINE

Bottom Line for Primary Care (Cont.)

6. Start low, reach the range in 1-2 weeks, contact at 2 weeks, measure at 4: less than 20% improvement means change something.
7. Non-response is common; adding therapy, switching, and augmenting work about equally — augment when partially responding, switch when not or intolerant.
8. Collaborative and measurement-based care are the interventions with the best evidence for improving real-world outcomes.
9. Continue 6–12 months after remission, 2 years or more with risk factors; sequential psychotherapy protects against recurrence.
10. Taper slowly, with psychological support, and differentiate discontinuation from relapse

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