Difficult to Treat Depression

A Carlat Guide



Chris Aiken, MD

CARLAT PUBLISHING

DIFFICULT TO TREAT DEPRESSION

FIRST EDITION

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To Kellie Newsome

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Illustrations by Eleanor Aiken

TABLE 2-1. Choosing an Initial Antidepressant Based on Clinical Features

Clinical Scenario	First-Line Recommendations
Fatigue	Bupropion
Comorbid anxiety disorder	Escitalopram, sertraline
Insomnia, weight loss	Mirtazapine
Cognitive problems	Bupropion, vortioxetine
Sexual side effects are a dealbreaker	Bupropion, mirtazapine, or vortioxetine
Weight gain is a dealbreaker	Bupropion or fluoxetine
Chronic pain, fibromyalgia	Duloxetine
Smoking cessation	Bupropion
ADHD + depression	Bupropion
Bulimia	Fluoxetine
Atypical features (hypersomnia, etc.)	Monoamine oxidase inhibitors (MAOIs, often underused, but effective)
Child or adolescent	Fluoxetine

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TABLE 4-1. Patient Health Questionnaire-2 (PHQ-2)

*Over the **last two weeks,** how often have you been bothered by the following problems?*	Not at all	Several days	More than half the days	Nearly every day
Little interest or pleasure in doing things	0	1	2	3
Feeling down, depressed, or hopeless	0	1	2	3

Interpretation

- Score 0–2: Minimal symptoms
- Score 3–6: Clinically significant symptoms

TABLE 4-2. General Symptom Scale

Over the ***past week*** have you had problems with	Not at all	Mild		Moderate		Severe	
Depression, low energy/motivation, or lack of pleasure?	0	1	2	3	4	5	6
Anxiety, nervousness, or excessive worry?	0	1	2	3	4	5	6
Irritable, agitated, angry, quick to argue?	0	1	2	3	4	5	6
Trouble falling or staying asleep?	0	1	2	3	4	5	6
Poor concentration, attention, or distractibility?	0	1	2	3	4	5	6

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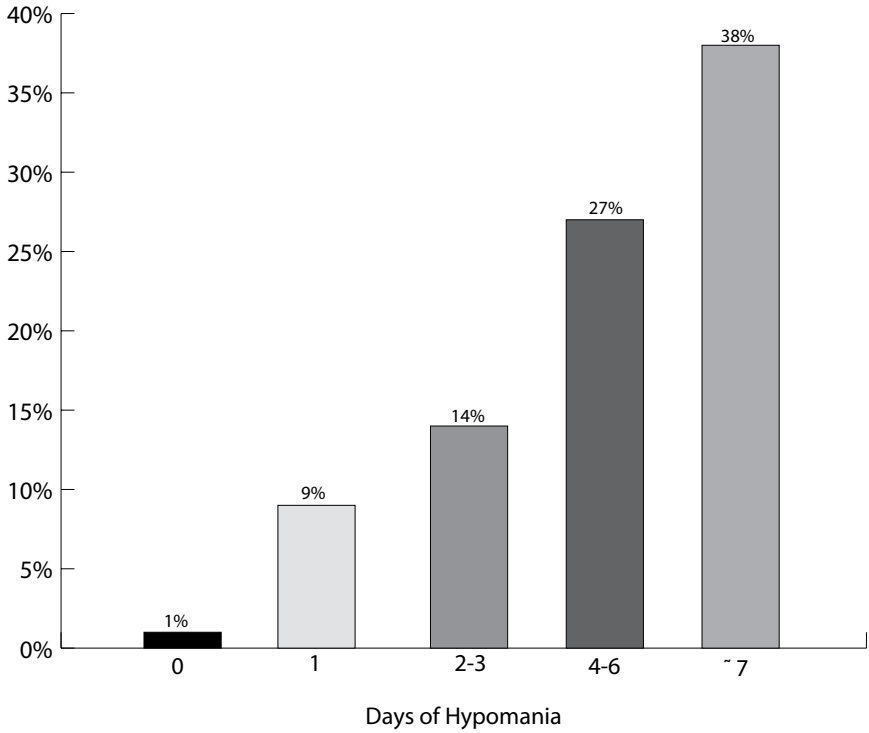


FIGURE 5-2. Risk of antidepressant-induced mania/hypomania rises with duration of past manic/hypomanic symptoms

Bipolar Disorders			Unipolar Depression		
Bipolar 1	Bipolar 2	Cyclo thymia	Brief hypomania	Mixed Features	Pure depression (no hypomania)

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SCREENER 5-1. Rapid Mood Screener II

Consider your whole life as you answer these questions		
Have there been at least six different periods of time (at least two weeks) when you felt deeply depressed?	Yes	No
Did you have problems with depression before the age of 18?	Yes	No
Have you ever had to stop or change your antidepressant because it made you highly irritable or hyper?	Yes	No
Have you ever had a period of time during which you were more talkative than normal with thoughts racing in your head? *If yes, what was the longest it lasted for?*		
No • Yes, 1–3 days • Yes, 4 or more days • Yes, 7 or more days		
Have you ever had a period of time during which you felt any of the following: unusually happy; unusually outgoing; or unusually energetic? *If yes, what was the longest it lasted for?*		
No • Yes, 1–3 days • Yes, 4 or more days • Yes, 7 or more days		
Have you ever had a period of time during which you needed much less sleep than usual? *If yes, what was the longest it lasted for?*		
No • Yes, 1–3 days • Yes, 4 or more days • Yes, 7 or more days		

Scoring: Positive if 4 or more YES's

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SCREENER 5-2. Bipolar Spectrum Diagnostic Scale

Instructions: Please read through the entire passage below before filling in any blanks.

Some individuals notice that their mood and/or energy levels shift drastically from time to time____. These individuals notice that, at times, their mood and/or energy level is very low, and at other times, very high ____. During their "low" phases, these individuals often feel a lack of energy; a need to stay in bed or get extra sleep; and little or no motivation to do things they need to do____. They often put on weight during these periods ____. During their low phases, these individuals often feel "blue," sad all the time, or depressed____. Sometimes, during these low phases, they feel hopeless or even suicidal____. Their ability to function at work or socially is impaired____. Typically, these low phases last for a few weeks, but sometimes they last only a few days____.

Individuals with this type of pattern may experience a period of "normal" mood in between mood swings, during which their mood and energy level feels "right" and their ability to function is not disturbed____. They may then notice a marked shift or "switch" in the way they feel____. Their energy increases above what is normal for them, and they often get many things done they would not ordinarily be able to do____. Sometimes, during these "high" periods, these individuals feel as if they have too much energy or feel "hyper" ____. Some individuals, during these high periods, may feel irritable, "on edge," or aggressive____. Some individuals, during these high periods, take on too many activities at once____. During these high periods, some individuals may spend money in ways that cause them trouble____. They may be more talkative, outgoing, or sexual during these periods____. Sometimes, their behavior during these high periods seems strange or annoying to others____. Sometimes, these individuals get into difficulty with co-workers or the police during these high periods____. Sometimes, they increase their alcohol or nonprescription drug use during these high periods____.

Now that you have read this passage, please check one of the following four boxes (consider your whole life when you answer, including recent times):

- ☐ This story fits me very well, or almost perfectly (6).
- ☐ This story fits me fairly well (4).
- ☐ This story fits me to some degree, but not in most respects (2).
- ☐ This story does not really describe me at all (0).

Now please go back and put a check after each sentence that definitely describes your life.

Scoring

Add one point for each box checked in the paragraph, and 6, 4, 2, or 0 points for the final items. Scores ≥ 13 are suggestive of bipolar disorder.

Source: Ghaemi SN et al, *J Affect Disord.* 2005;84(2–3):273–277.

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TABLE 5-1. Aiken's Structured Interview for Mania and Hypomania

DSM Symptom	Screening Question
Elevated mood	"Have you ever felt more up, driven, and/or* energized than usual, even if it was an uncomfortable, wired, anxious energy?"
Irritability	"Have you ever been angry, irritable, or quick to argue for several days?"
If they endorse *elevated mood* or *irritability*, ask about the associated symptoms below. Look for stretches of time when they were more or less this way, most of the time. Manic symptoms are in rapid flux, so the symptoms may not overlap 100%. They may occur during depression in a mixed state. "When you felt [elevated mood/energy/irritability—use their words] did you also . . ."	
Confidence	" . . . feel more confident, like you can achieve great things? Or more demanding, pushy, sure of yourself?"
Short sleep	" . . . sleep less than usual but still kept going the next day, even if you wished you could get more sleep?"
Talkative	" . . . talk more than usual? Did people think you were loud or difficult to interrupt?"
Racing thoughts	" . . . have racing thoughts, multiple trains of thought, or thoughts that jumped around so quickly that it was hard to keep up with them?"
Distracted	" . . . get easily distracted by little things around you or your own thoughts? Jump quickly from one activity to another?"
Hyperactive	" . . . do a lot more than usual, like taking on more projects or being more socially or sexually active? Feel more driven or restless even if you didn't know what to do with the drive?"
Impulsive	" . . . jump into things without thinking about the consequences? Do things that others thought were extreme, impulsive, or out of character for you?" [List examples "overspending, aggressive driving, sudden travel, breaking the law or breaking things, or doing things that could hurt your job, school, relationships, or your life]"
Duration	"Were you ever more or less this way [summarize the symptoms in their words] for four days in a row? For seven days in a row?"
Consequences	"What was the biggest problem that these symptoms caused? What is the most extreme thing you did?" If they seem hesitant, remind them there is no shame here and suggest extreme examples like prison, bankruptcy, loss of jobs or relationships. **Hypomania** = mild-moderate problems. They were able to overcome the consequences without great difficulty (eg, traffic tickets, arguments, warnings at work, overspending within budget). **Mania** = severe problems. The consequences were potentially or actually irreversible or difficult to overcome. They could have led to arrest or hospitalization (eg, violence; major debt; loss of job, school, or relationships).

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TABLE 5-1. Aiken's Structured Interview for Mania and Hypomania

Scoring

This interview is positive for bipolar disorder if they endorse:

1) Elevated mood and at least 3 out of 7 associated symptoms *or*
2) Irritable mood and at least 4 out of 7 associated symptoms

The type of bipolar depends on the duration and severity:

Short duration hypomania: longest duration less than 4 days and problems were mild-moderate (if the hypomanic symptoms cycle with brief depressions it is cyclothymic disorder).

Hypomania: longest duration at least 4 days and problems were mild-moderate. Diagnosis is bipolar II if they also had a history of full depression.

Mania: longest duration at least 7 days and consequences were severe or psychotic symptoms were involved. Duration can be less than 7 days if the symptoms led to hospitalization. Diagnosis is Bipolar I if any mania, regardless of whether there was depressive episode.

TABLE 5-2. Structured Bipolar Interview: Ambiguous Answers

Ambiguous Answer	Interpretation
"Not in a long time" "Very rarely" "Almost never"	These answers are consistent with bipolar. People with bipolar spend only 4%–15% of their lifespan in manic or hypomanic states.
"Yes, but that's just the way I always am." "Yes, that's how I am when I'm not depressed. I have energy and motivation."	These answers make bipolar less likely, but do not rule it out. Hypomania reflects a change from the person's usual state, but many patients have affective temperaments, meaning their baseline personality is a little hypomanic or irritable.
"Yes, but only when I'm with a lot of friends, having a good time, or when I have a lot to do."	This means "Yes." Avoid downgrading symptoms because they have an understandable explanation. People are more likely to socialize and take on projects when hypomanic. Likewise, when someone has felt depressed for two weeks "but only because I lost my job," we still code it as depression.
"Yes, I do impulsive things [sex, drugs, travel, or retail therapy], but that's because it's the only way I can feel better when depressed"	This means "Yes." As with the above, beware of contextualization. Hedonic behaviors are rare during depression, and their appearance is suggestive of a mixed state.
"Yes, I'm often distracted with racing thoughts. That's my ADHD."	This means "Yes." Comorbidities like ADHD and anxiety are common in bipolar disorder and should not be used to explain away the symptoms.

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SCREENER 5-3. The Bipolarity Index

Directions: Circle the bulleted items that are positive in the patient's history. Score each of the five sections by circling the highest number (0–20) for which there is at least one positive item. The final score is the sum of all five sections.

I. EPISODE CHARACTERISTICS	
Score	**Criteria**
20	• Acute manic episode with prominent euphoria, grandiosity, or expansiveness and no significant medical or other secondary etiology
15	• Acute mixed episode or dysphoric or irritable mania with no significant medical or other secondary etiology
10	• Hypomanic episode with no significant medical or other secondary etiology; or • Cyclothymic with no significant medical or other secondary etiology; or • A manic episode within 12 weeks of starting an antidepressant
5	• A hypomanic episode within 12 weeks of starting an antidepressant • Episodes with characteristic symptoms of hypomania, but symptoms, duration, or intensity are subthreshold for hypomania; or • A single MDE with psychotic or atypical features (atypical is ≥ 2 of the following: hypersomnia, hyperphagia, or leaden paralysis of limbs); or • Any postpartum depression
2	• Recurrent unipolar major depressive disorder (≥ 3 episodes); or • History of any kind of psychotic disorder (ie, presence of delusions, hallucinations, ideas of reference, or magical thinking)
0	• No history of significant mood elevation, recurrent depression, or psychosis
II. AGE OF ONSET (FIRST AFFECTIVE EPISODE OR SYNDROME)	
Score	**Criteria**
20	• 15 to 19 years
15	• Before age 15 or between age 20 and 30
10	• 30 to 45 years
5	• After age 45
0	• No history of affective illness (no episodes, cyclothymia, dysthymia, or unspecified bipolar)
III. COURSE OF ILLNESS & ASSOCIATED FEATURES	
Score	**Criteria**
20	• Recurrent, distinct manic episodes separated by at least 2 months of full recovery

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SCREENER 5-3. The Bipolarity Index

15	• Recurrent, distinct manic episodes with incomplete inter-episode recovery; or • Recurrent, distinct hypomanic episodes with full inter-episode recovery
10	• Any substance use disorder (excluding nicotine/caffeine); or • Psychotic features only during acute mood episodes; or • Incarceration or repeated legal offenses related to manic behavior (eg, shoplifting, reckless driving, or bankruptcy)
5	• Recurrent unipolar major depressive disorder (MDD) with ≥ 3 major depressive episodes; or • Recurrent, distinct hypomanic episodes without full inter-episode recovery; or • Borderline personality disorder; anxiety disorder, including post-traumatic stress disorder (PTSD) and obsessive-compulsive disorder (OCD); eating disorder; or history of ADHD with onset before puberty; or • Engagement in gambling or other risky behaviors with the potential to pose a problem for patient, family, or friends; or • Behavioral evidence of premenstrual exacerbation of mood symptoms
2	• Baseline hyperthymic personality when not manic or depressed; or • Marriage 3 or more times (including remarriage to the same individual); or • In two or more years, has started a new job and changed jobs after less than a year; or • Has more than two advanced degrees
0	• None of the above.
IV. RESPONSE TO TREATMENT	
Score	**Criteria**
20	• Full recovery within 4 weeks of therapeutic treatment with a mood stabilizer
15	• Full recovery within 12 weeks of therapeutic treatment with a mood stabilizer or relapse within 12 weeks of discontinuing treatment; or • Affective switch to mania (pure or mixed) within 12 weeks of starting a new antidepressant or increasing dose
10	• Worsening dysphoria or mixed symptoms during antidepressant treatment subthreshold for mania (exclude worsening that is limited to known antidepressant side effects such as akathisia, anxiety, or sedation); or • Partial response to one or two mood stabilizers within 12 weeks of therapeutic treatment; or • Antidepressant-induced new or worsening rapid-cycling course
5	• Treatment resistance: lack of response to complete trials of three or more antidepressants; or • Affective switch to mania during antidepressant withdrawal
2	• Immediate, near-complete response to antidepressant withdrawal within one week or less
0	• None of the above, or no treatment

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SCREENER 5-3. The Bipolarity Index

V. FAMILY HISTORY	
Score	**Criteria**
20	• At least one first-degree relative with clear bipolar disorder
15	• At least one second-degree relative with clear bipolar disorder; or • At least one first-degree relative with recurrent unipolar MDD and behavioral evidence suggesting bipolar disorder
10	• First-degree relative with recurrent unipolar MDD or schizoaffective disorder; or • Any relative with possible bipolar disorder or recurrent unipolar MDD and behavioral evidence suggesting bipolar disorder
5	• First-degree relative with clear substance use disorder (excluding nicotine/caffeine); or • Any relative with possible bipolar disorder
2	• First-degree relative with possible recurrent unipolar MDD; or • First-degree relative with anxiety disorder (including PTSD and OCD), eating disorder, or ADD/ADHD
0	• None of the above or no family history of psychiatric disorders

Total score (0 –100). Add the highest number in each section. A score ≥ 50 indicates a high probability of bipolar disorder.

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TABLE 7-1. Screening for Psychotic Depression

Delusions	Screening Question
Guilt	Do you feel guilty about anything?
Punishment	Do you feel you are being punished, or that you deserve punishment, like you've done something that can't be forgiven?
Persecution	Do you feel you can't trust people or that they have it in for you? Do you worry that authorities like the police are after you?
Illness	Do you believe you are physically ill? That your symptoms are due to a physical illness?
Nihilism	Does everything seem meaningless? Do you think about death a lot? What are your thoughts about it?
Worthlessness	Do you feel incapable, worthless, or unlovable? That people would be better off without you?
Hallucinations	**Screening Question**
Audio-Visual	Have you heard or seen things that others can't?
Kinesthetic	Have you experienced unusual smells, tastes, or feelings in your body?

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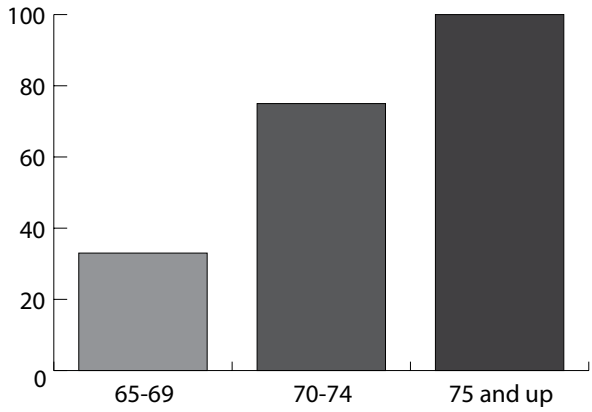


FIGURE 8-1. Age-Related Prevalence of Vascular Depression

Source: Park JH et al, *J Affect Disord* 2015;180:200-206

TABLE 8-1. Signs of Vascular Depression

Feature	Vascular Depression	Nonvascular Depression
Age of onset	Often later in life	Any age
Cognitive deficits	More prominent	Less prominent
Executive dysfunction	Common	Less common
Psychomotor retardation	More severe	Variable
Insight into illness	Often reduced	Usually preserved
Apathy	Prominent	Variable
Guilt/worthlessness	Less pronounced	Often prominent
Response to antidepressants	Reduced	Standard

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TABLE 8-2. Nimodipine Summary

FDA Approval	Hypertension
Off-Label Benefits	Vascular depression Ultra-rapid cycling bipolar disorder Prevention of cerebral vasospasm after subarachnoid hemorrhage
Dosing	Start at 30 mg TID, raise by 15 mg every 10 days to target of 90 mg TID (If patient is taking an antihypertensive, start at 15 mg TID and consult with PCP)
Risks	Hypotension (check blood pressure and pulse during titration) Avoid in pregnancy (Category C)
Side Effects	Nausea, diarrhea
Half-Life	8–9 hours
Interactions	Take on an empty stomach (food decreases absorption by 30%–50%). Metabolized through CYP3A4 and CYP3A5 with minor contributions from CYP2C19.

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TABLE 9-1. Risk Factors for Inflammation

Childhood trauma	Smoking, sedentary lifestyle
Recent significant stress	Recent chemotherapy or radiation
Chronic medical illness	Recent bodily injury or surgery
Obesity (BMI ≥ 30 kg/m^2)	Recent infection
Western diet	Postpartum and perimenopause

References: Ferrucci L and Fabbri E, *Nat Rev Cardiol* 2018;15(9):505–522; Majd M et al, *Front Neuroendocrinol* 2020;56:100800

TABLE 9-2. Treatments for Inflammatory Depression

First-Line Medications	
Celecoxib	This anti-inflammatory pain medication has 17 randomized trials in depression, and a few of them suggest it works preferentially when inflammation is high (200 mg BID).
Bupropion	Inflammation (CRP ≥ 3 mg/L) and obesity (BMI ≥ 30 kg/m2) predict response to bupropion augmentation of SSRIs (150–450 mg XL QAM).
Pramipexole	This medication targets the dopamine tracks that are disrupted by inflammation, and it reduced inflammatory markers and anhedonia in trials of depression (0.5–2.5 mg QHS).
Second-Line Medications	
Nortriptyline	Elevated CRP predicts a better response to nortriptyline than escitalopram in major depression (50–150 mg/day, dose by serum level).
Minocycline	This antibiotic has anti-inflammatory properties. It has a mix of positive and negative results in depression, but trends toward the positive in patients with elevated CRP (100 mg BID).
Complementary and Alternative Therapies	
N-acetylcysteine (NAC)	Elevated CRP predicts response to NAC in anxiety and depression (2,000 mg/day).
L-methylfolate	Inflammation impairs folate metabolism, and elevated inflammation (CRP ≥ 3 mg/L) predicts response to this folate vitamin (15 mg/day).
Omega-3	Elevated CRP predicts response to omega-3, and higher doses may be needed for inflammatory depression (4,000 mg EPA).
Lifestyle	Exercise, yoga, tai chi, the Mediterranean diet, mindfulness, and cognitive behavioral therapy for insomnia have anti-inflammatory and antidepressant effects.

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SCREENER 10-1. Trauma and Depression Screener

Event	Happened to Me	Witnessed It	Learned About It	Not Sure	Doesn't Apply
Natural disaster (*examples:* flood, hurricane, earthquake, fire, explosions)					
Accidents and toxicity (*examples:* car accident, explosions, exposure to dangerous chemicals)					
Assault (*examples:* attacked, hit, slapped, kicked, beaten up, shot, stabbed, threatened)					
Sexual assault (rape, attempted rape, made to perform any type of sexual act through force or threat of harm, or any other unwanted or uncomfortable sexual experience)					
Combat or exposure to a war-zone (in the military or as a civilian)					
Captivity (*examples:* kidnapped, abducted, held hostage, prisoner of war)					
Life-threatening illness, injury, or severe suffering					
Sudden, unexpected death of someone close to you					
Any other very stressful event or experience					

As a child . . .	Yes	Not Sure	Doesn't Apply
Did you feel that you didn't have enough to eat, had to wear dirty clothes, or had no one to protect or take care of you?			
Did you live with anyone who was depressed, mentally ill, had a problem with drugs, or attempted suicide?			
Did your parents or adults in your home ever hit, punch, beat, or threaten to harm each other?			
Did you live with anyone who went to jail or prison?			
Did a parent or adult in your home ever swear at you, insult you, or put you down?			
Did a parent or adult in your home ever hit, beat, kick, or physically hurt you in any way?			
Did you feel that no one in your family loved you or thought you were special?			
Were you frequently bullied by other children at school?			

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TABLE 10-1. Prazosin Summary

FDA Approval	Hypertension
Off-Label Benefits	PTSD (nightmares and daytime symptoms) Benign prostatic hyperplasia
Dosing	Start 1 mg QHS, raise by 1–2 mg every 4–7 days based on response. Average 12–16 mg/day; max 25 mg/day for men and 12 mg/day for women. Divide the dose at ≥ 3–5 mg/day (give 25% in morning).
Risks	Syncope (1%, usually occurs in first week) Check blood pressure and pulse and monitor for falls during titration. Consult with PCP if patient is taking other antihypertensives. Avoid in pregnancy (Category C)
Side Effects	Dizziness, headache, fatigue, palpitations, nausea
Half-Life	2–4 hours
Interactions	Additive hypotension with other antihypertensives

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TABLE 11-1. The Neurotic Temperament

I get stressed-out easily
I dislike myself
I worry about things
I have frequent mood swings
I often get angry or irritated
I panic easily
I am often down in the dumps
I am easily bothered by things
I have trouble relaxing
I am easily frustrated
I fear the worst
I am rarely calm under pressure
I feel threatened easily
I am filled with doubts about things

TABLE 11-2. Opposing Symptoms: Melancholic vs Atypical Depression

Feature	Atypical	Melancholic
Mood quality	Tearful, anxious, relatable in a way that is similar to ordinary sadness	Different from ordinary sadness: anhedonic, empty, despondent, tormented by groundless fears
Timing and reactivity	Worse in evening; highly reactive to daily events, especially rejection	Worse in morning; does not react much to daily events
Thoughts	Easily overwhelmed by stress and interpersonal rejection	Inflexible negative thoughts of guilt, nihilism, worthlessness, or foreboding doom, which may reach psychotic level
Appetite	High	Low
Sleep	Oversleeping	Early morning awakening
Motor	Leaden paralysis (arms or legs feel pulled down by lead weights)	Marked psychomotor agitation (eg, pacing) or retardation (eg, slow, unmoving)
Population	More common in outpatients, women (before menopause), and bipolar II	More common in inpatients

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TABLE 11-3. Causes of Anxious Depression

Cause	Features	Pharmacotherapy
Anxiety disorder	The anxiety is accompanied by phobic behavior or, in the case of generalized anxiety, futile attempts to stop the worry.	SSRI or SNRI (dosed at the higher end of the optimal ranges for depression, see table 15.1).
Atypical features	Anxiety is a reaction to rejection or daily stressors	MAOIs or SSRIs
Melancholic features	Anxiety about guilt or a foreboding sense of doom	Tricyclics
Mixed features	Free floating nonspecific anxiety with somatic symptoms	Mood stabilizers and second-generation antipsychotics (SGAs)
Neurotic temperament	Lifelong tendency to experience negative emotions, such as anxiety, self-consciousness, and irritability	SSRIs
Rumination	A repetitive cycle of negative self-talk	Does not point to a specific med, but is a risk factor for recurrence of depression
Distress	Some patients use "anxiety" as a synonym for distress	Does not point to a specific med, but is a risk factor for side effects, treatment dropout, and suicide

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TABLE 11-4. Augmentation Strategies for Depressive Subtypes

Melancholic features	Tricyclics
Atypical features	MAOIs
Anxious depression	Mirtazapine (30–45 mg QHS) Buspirone (45–90 mg/day, divided BID-TID) Quetiapine (150–300 mg QHS)
Mixed features	Aripiprazole (5–10 mg QD) Lumateperone (42 mg QHS) Lurasidone (20–60 mg QD with food) Ziprasidone (40–80 mg BID with food) Bupropion (150–300 mg XL Qam) Trazodone (150–300 mg QHS)
Postpartum depression	Zuranolone (50 mg QHS)
Seasonal depression	Light therapy
Fatigue	Modafinil (100–200 mg Qam) Armodafinil (150–250 mg Qam)
Insomnia	Eszopiclone (3 mg QHS)
Cognitive impairment	Vortioxetine (10–20 mg QD) Bupropion (150–300 mg XL Qam) TMS Probiotics
Suicidality	Lithium (target level: 0.6–0.8 mmol/L)

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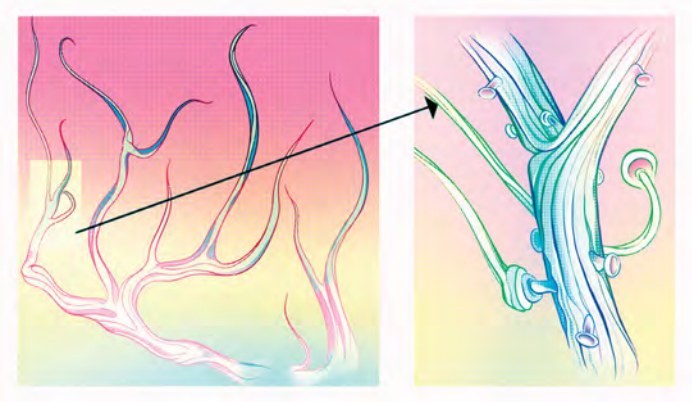


FIGURE 12-1. Stress and depression have caused the neurons in this picture to shrink back, forming fewer dendritic connections.

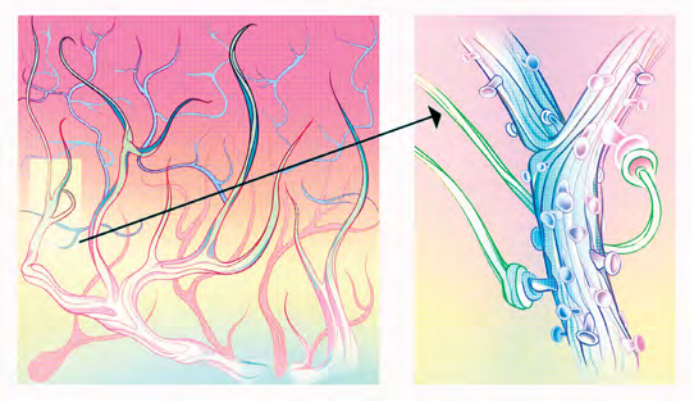
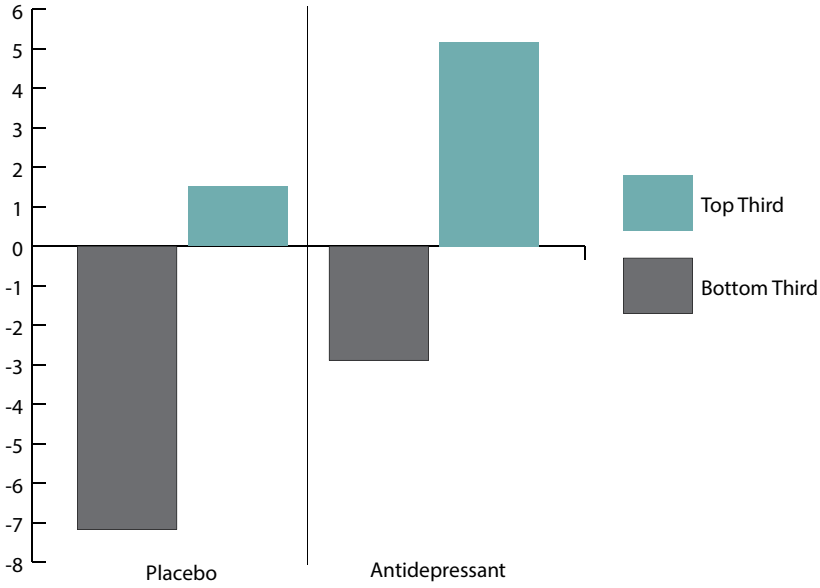


FIGURE 12-2. The neurons have grown and formed more connections after treatment with neuroprotective agents like medication, psychotherapy, exercise, and other lifestyle changes.

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Psychiatrists from the NIMH Collaborative Depression Trial were divided into the top and bottom third based on their subject's outcomes. In the graph, psychiatrists from the top third achieved better responses with placebo than those from the bottom third did with imipramine.

FIGURE 12-3. Antidepressant and Placebo Response Varies by Psychiatrist

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TABLE 14-1. Lifestyle and Depression: A Patient Guide

Movement	Brisk walking 30–45 minutes every other day
People	Too much interaction is stressful, but a minimum amount of supportive contact gives the brain the sparks it needs to make antidepressants work.
Activity	Look for activities that are absorbing or in line with your goals or values. Start by adding a few good minutes of them to each day.
Rhythm	Set your biological clock with morning sunlight and evening darkness. Wake up at regular times, stay out of bed during the day, and schedule a wind-down time before bed.
Sleep	If you have insomnia, there are behavioral steps that improve mood and sleep.
Nature	Walking or just being in nature two hours a week reduces depression and negative cycles of worry.
Food	A Mediterranean-style diet rich in fruits, vegetables, nuts, beans, fish, whole grains, and lean meats has a big effect on depression.
Health	Mental health improves when you take better care of your physical health. This is true for nearly all health problems, from diabetes to dental health, smoking to sleep apnea.

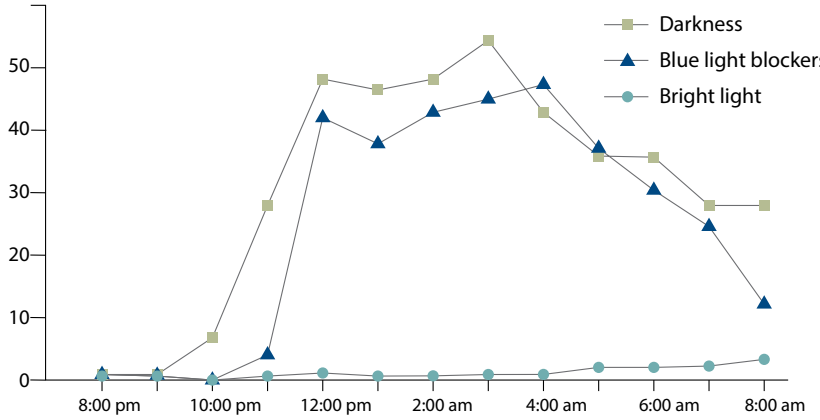


FIGURE 14-1. Evening light suppresses melatonin, but melatonin levels rise when people are in a dark room or wear blue light blocking glasses

Source: Kayumov L et al, *J Clin Endocrinol Metab* 2005;90(5):2755-2261

TABLE 14-2. Mediterranean Diet for Depression

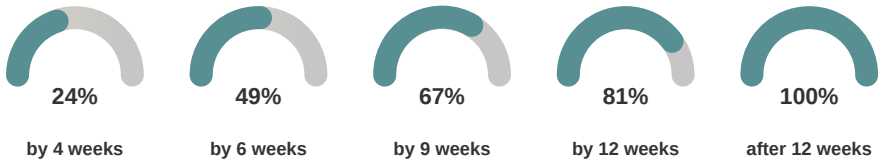
Enjoy in Abundance	Fruit	Fresh or frozen are fine; dried and juiced fruits are a bit sugar heavy
	Vegetables	Aim for a variety of colors; olives and mushrooms count
	Beans	Hummus counts
	Fish	Especially oily fish, like salmon, tuna, sardines, anchovies, and mussels
	Nuts and seeds	Salt-free is best; nut butters with low sugar and minimal processing are great
	Whole grains	Brown rice, oatmeal, quinoa, homemade popcorn, and breads or pasta with "100% whole grain" on the label
	Extra virgin olive oil	The "extra" means more antioxidants, and it's safe to cook with up to 375°F
Appreciate in Moderation	Chicken and lean red meats	One serving/day of either meat; avoid fried chicken, bacon, and processed deli meats
	Eggs	Six eggs/week
	Dairy	One serving/day; avoid processed cheeses like Velveeta and yogurt with artificial flavorings.
Eat Less	Fried & fast foods Processed foods Sodas Sweets Simple carbs Refined flour Bacon & sausage Deli meats Condiments	Limit to three small servings a week of any of these foods (small = 120 calories) Choose packaged foods with low sugar, salt, and fewer processed chemicals; the Open Food Facts App rates packaged foods by scanning the bar codes
Drinks	Black and green tea lowers depression risk (up to 6 cups/day) Coffee limit to 2–3 8 oz cups of regular or 2–4 shots espresso/day Avoid alcohol or limit to 1 drink every other day (prefer red wine)	Aim for drinks low in sugar, salt, and chemical ingredients

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TABLE 14-3. Reasons for Inaction

Reason	Solution
Forgot	Have them set a calendar alert on their smartphone, a sticky note in a prominent place, or involve a supportive person to remind them.
Skill deficit	For social skills (eg, meeting people), consider a more dedicated psychotherapy. For nonsocial skills (eg, how to cook a fish or find a dentist), consider courses, online learning, and practice.
External factors	Here the change would cause problems with other people or conflict with other responsibilities. Solutions include bringing the other person into session or problem solving.
Experiential avoidance	Here the change causes internal sensations that the patient wants to avoid (usually anxiety). Solutions include psychotherapy with a focus on distress tolerance and connecting the changes to the patient's values.

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Chance of response to a second antidepressant trial rises over 12 weeks

FIGURE 15-1. Chance of Response to a Second Antidepressant Trial

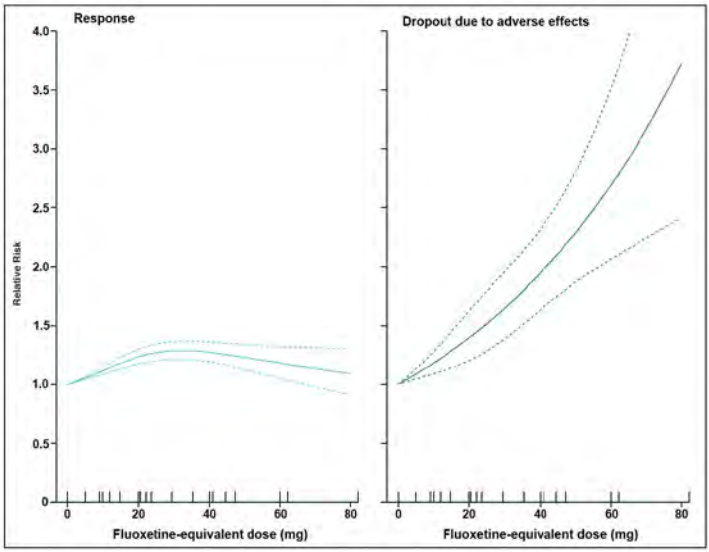


FIGURE 15-2. Response and Side Effects by SSRI Dose

[Dose-response curves for response and side effects to SSRIs in depression, based on 99 fixed-dose groups. Source: Furukawa TA et al. *Lancet Psychiatry* 2019;6(7):601–609.]

TABLE 15-1. Optimal Dose Ranges for Second-Generation Antidepressants

Antidepressant	Optimal Dose (mg/d)*	FDA Max in Depression
Citalopram	20–40	60
Escitalopram	10–20	20
Fluoxetine	20–40	80
Fluvoxamine	100–150	n/a
Paroxetine	20–30	50
Sertraline	50–100	200
Duloxetine	40–60	120
Desvenlafaxine	50–200	400
Venlafaxine	75–150	225
Bupropion	150–300	450
Mirtazapine	15–30	45
Nefazodone*	300–600	600
Trazodone*	150–300	600
Vilazodone	10–20	20
Vortioxetine	20–40	40

*Optimal doses are derived from dose-response curves from fixed-dose studies; that data is not available for nefazodone and trazodone (Furukawa TA et al, 2019; Hamza T et al, 2024)

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TABLE 16-1. MAOI Antidepressants

Name	Dosing	Common Adverse Effects
Tranylcypromine (Parnate)	Start 10 mg once or twice daily, titrate every 5–7 days to 30–60 mg/day, divided BID	Sexual dysfunction, orthostatic hypotension, insomnia, agitation, peripheral edema
Isocarboxazid (Marplan)	Start 10 mg QD, titrate every 5–7 days to 30–60 mg/day, divided BID	Sexual dysfunction, orthostatic hypotension, weight gain, insomnia, sedation, peripheral edema, vitamin B6 deficiency
Phenelzine (Nardil)	Start 15 mg once or twice daily, titrate every 5–7 days to 45 mg-90 mg/day	Sexual dysfunction, weight gain, orthostatic hypotension, insomnia, sedation, peripheral edema, vitamin B6 deficiency
Selegiline transdermal (Emsam)	Start 6 mg QD transdermal, raise if incomplete response to 9–12 mg QD	Insomnia, topical reactions at patch site, false-positive on drug screen for methamphetamine

TABLE 16-2. Medications that Can Cause Serotonin Syndrome with MAOIs

Serotonergic Psychotropics	Serotonergic antidepressants (SSRIs, SNRIs, other MAOIs, vortioxetine, vilazodone, clomipramine, imipramine, and possibly trazodone and nefazodone); viloxazine, dextromethorphan (Auvelity), ketamine, esketamine, lumateperone, ziprasidone, and possibly buspirone, gepirone, and lithium
Stimulants	Amphetamine, methylphenidate, phentermine, and local anesthetics that contain sympathomimetics
Serotonergic Opioids	Fentanyl, methadone, meperidine, oxycodone, propoxyphene, tramadol
Other	Fenfluramine, linezolid, methylene blue, moclobemide
Over-the-Counter	L-tryptophan, SAMe, St. John's wort, and decongestants containing phenylephrine, pseudoephedrine, dextromethorphan, brompheniramine, or chlorpheniramine
Drugs of Misuse	Cocaine, amphetamines, LSD, MDMA, Ecstasy, bath salts

*These meds can also cause serotonin syndrome with SSRIs and SNRIs, but the risk with these combinations is much lower

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TABLE 16-3. A Modernized MAOI Diet

Avoid Completely	• Highly aged cheeses and aged beef (eg, charcuterie boards) • Sourdough bread that is homemade or from a bakery (commercially produced is OK) • Fermented soybean products (found in Asian foods like tempeh, miso, pickled tofu, and bean paste) • Raw meat or fish that has not been refrigerated properly or is past the use by date • Homemade beer or wine
OK in Small Portions (less than a typical serving size)	• Specialty soy sauce • Dried, aged sausage and salami • Sauerkraut • Beer that is micro-brewed, on tap, or requires refrigeration (limit to 1 standard drink)
OK in Normal Portions (but don't overindulge)	• Cheeses that are not highly aged • Chocolate • Caffeinated beverages • Wine from a commercial producer (no more than 2 glasses) • Beer that is shelf-stable or pasteurized (no more than 2 pints) • Fresh beef or fish • Fava beans • Bananas and avocados that aren't overly ripe • Soy sauce or fish sauce from grocery store brands • Worcestershire sauce • Kimchi • Commercially produced sourdough bread • Fermented yeast products (Marmite and Vegemite)
No Restrictions (barely any tyramine here)	• Milk, yogurt, cream • Nonaged, soft cheese (mozzarella, American, ricotta, cottage cheese, cream cheese) • Dry, cured meats (prosciutto, pepperoni) • Smoked or pickled fish • Fresh chicken, duck, pork, and sausage • Stock cubes, powder, or bullion • Nonfermented soybean products

Source: https://psychotropical.info/wp-content/uploads/2018/02/3_MAOI_Diet_Abbreviated_2016_3.1–1.pdf

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TABLE 17-1. Tricyclic Antidepressants: Comprehensive Guide

Medication	Unique Features	Dosing	Therapeutic Serum Range (ng/mL)
Secondary Amines			
Desipramine	Strongest norepinephrine effects, lowest anticholinergic burden, low risk of sedation	Start 25–50 mg QD, target 75–300 mg QD	150–300
Nortriptyline	Lowest risk of orthostasis and weight gain, along with lithium, a good combo to maintain recovery after ECT	Start 25–50 mg QD, target 50–150 mg QD	50–150*
Protriptyline	Least sedating and may be activating	Start 5–10 mg QD, target 15–60 mg QD	70–170
Tertiary Amines			
Amitriptyline	Highest anticholinergic burden, high sedation	Start 25–50 mg QHS, target 150–300 mg QHS	100–250*
Clomipramine	Best for OCD, most serotonergic	Start 25 mg QD, target 150–250 mg QD	70–200 (for clomipramine) 150–300 (for norclomipramine)
Doxepin	Most sedating, approved for insomnia in low doses	Start 25–75 mg QHS, target 150–300 mg QHS (for insomnia, 3–6 mg QHS or use generic liquid 10 mg/ml, 0.3–0.5 ml QHS)	120–250
Imipramine	Best studied for panic disorder and anxious depression	Start 25–50 mg QD, target 150–300 mg QD	150–300*

*Therapeutic ranges with amitriptyline, imipramine, and nortriptyline are well-established

Sources: Goldberg JF and Stahl SM. Practical Pharmacology, 2021; Kaplan & Sadock's Comprehensive Textbook of Psychiatry, 2017.

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TABLE 17-2. The Human Cost of Anticholinergic Drugs

Anticholinergic Effect	Why it Matters
Dry mouth	Tooth decay, gum inflammation and ulceration, halitosis; poor dental hygiene is a risk factor for depression and dementia
Constipation	Bowel obstruction with potentially fatal paralytic ileus and sepsis
Urinary retention	Urinary tract infections, renal or bladder damage
Dilated pupils	Acute narrow-angle glaucoma, traffic accidents, falls
Impaired papillary accommodation	Inability to read fine print
Increased heart rate	Increased risk of cardiac arrest
Decreased sweating	Hyperthermia
Decreased bronchial secretions	Mucous plugging of small airways, which worsens respiratory illnesses like asthma and bronchitis
Cognitive impairment	Poor memory and concentration; delirium; increased risk of dementia

TABLE 17-3. Managing Tricyclic Side Effects

Side Effect	Management Approach
Constipation	Combination of docusate 100 mg with sennosides 8.6 mg BID (eg, Peri-Colace). Polyethylene glycol (start 17 g daily, titrate based on response). Bethanechol 10–25 mg TID for severe cases.
Dry mouth	Xylitol gum (eg, Spry) TID[1] Biotene products Pilocarpine 4% drop solution (dilute by mixing 1 part med with 3 parts water. Swish solution in mouth for 1 min q8hr prn dry mouth, do not swallow)
Orthostasis	Elastic abdominal binders or support stockings Oral fludrocortisone 0.1–0.2 mg QD or midrodine 0.5 mg TID
Urinary retention	Bethanechol 25 mg TID
Sexual dysfunction	May improve with dose reduction or switching to a different tricyclic; secondary amines are less likely to cause anorgasmia but more likely to cause erectile dysfunction

[1]Xylitol is a natural sugar substitute that protects the teeth from cavity-causing bacteria. Although xylitol gum is often recommended for dry mouth, recent studies have linked xylitol-sweetened beverages to cardiovascular risks.

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TABLE 19-1. Lithium Levels

Level	Children and Adults	Geriatrics (≥65)	Treats
Low	0.1–0.5	0.1–0.3	Unclear; low levels may augment other mood stabilizers, and might prevent dementia, suicide, and the progression of bipolar disorder
Medium	0.6–0.8	0.4–0.7	Depression (as monotherapy in bipolar depression, or as antidepressant augmentation in unipolar); this is also a good maintenance level to prevent episodes of mania or depression
High	0.8–1.2	0.6–0.9	Active mania
Toxic	>1.2	Varies	Only causes harm

TABLE 19-2. Lithium Summary

FDA Approval	Bipolar disorder (age 7 and up)
Off-Label Benefits	Antidepressant augmentation, recurrent depression Prevention of suicide, psychiatric hospitalizations, and depression after ECT Medical benefits include prevention of cancer, osteoporosis, viral infections, and possibly dementia and stroke
Dosing	Start 150–300 mg QHS, raise every 5–7 days to target of 600–900 mg QHS then dose by serum level Target level 0.6–0.8 mEq/L Aim 20%–30% lower in older adults
Labs	Check every 3–6 months: TSH, creatinine (eGFR), calcium (more often if older age or drug interactions present) Optional: WBC (benign neutrophil elevation) In vulnerable patients: ECG
Risks	Renal impairment (worse if level > 0.8), hypothyroidism (15%), hyperparathyroidism, nephrogenic diabetes insipidus, psoriasis, cardiac arrhythmias, toxicity
Signs of Toxicity	Ataxia, slurred speech, coarse tremor, hyperreflexia, myoclonus, somnolence (typically at levels > 1.2)
Side Effects	Common: Nausea, tremor, thirst, diarrhea. Rare: acne, hair changes, muscle weakness, sexual dysfunction
Half-Life	18–36 hours
Interactions	See Table 19.4

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TABLE 19-3. Treatments for Lithium Side Effects

Treatment	Benefits	Potential Psych Benefits	Dose
Propranolol	Tremor	Anxiety	80–240 mg/day
Vitamin B6	Tremor	Depression	500–1,000 mg/day*
Nimodipine	Tremor	Vascular depression, bipolar disorder	240–480 mg/day, divided TID
Gabapentin	Tremor	Social anxiety, alcohol/ cannabis use disorders	600–1,200 mg/day divided BID-TID
Ondansetron	Nausea	OCD, binge drinking, bulimia	4 mg q 12 hr prn
Ginger	Nausea	None	1,000–2,000 mg q12 hr prn
Promethazine	Nausea	None	25 mg q12 hour prn
Metoclopramide	Nausea	None	5–20 mg q4–6 hour prn
Amiloride	Nephrogenic diabetes insipidus	None	5 md/day
Aspirin	Sexual dysfunction in men	None	240 mg/day
Minocycline	Acne	Depression	100–200 md/day
Probiotics	Acne	Depression, anxiety	1 capsule/day
Omega-3	Acne, psoriasis	Depression	2,000–3,600 mg/ day of EPA + DHA
Inositol	Psoriasis	Depression, bulimia	12,000–18,000 mg/ day
N-acetylcysteine (NAC)	Renal protection	Depression	1,200–2,000 mg/ day divided BID

*Vitamin B6 carries a risk of neuropathy that may be avoided by using active form, pyridoxal 5'-phosphate, 200–500 mg, instead of pyridoxine 500–1,000 mg

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TABLE 19-4. Factors that Alter Lithium Levels

Raises lithium	Lowers lithium
Drug Interactions: Antihypertensives, diuretics, NSAIDs, and more (see Table 19-5)	Drug Interactions: Acetazolamide, xanthines (aminophylline, theophylline), mannitol
Dehydration	Caffeine
Aging	Active mania*
Renal slowing	Pregnancy
Low sodium diet	Going off a low sodium diet

*Lithium levels fall during active mania, possibly due to increased urination in the manic state.

TABLE 19-5. Medications that Raise Lithium

Class	Examples
Thiazides and loop diuretics	The "—ides": bumetanide, chlorothiazide, furosemide, hydrochlorothiazide (potassium-sparing diuretics like amiloride and spironolactone are OK)
ACE-inhibitors	The "—prils": benazepril, captopril, enalapril, lisinopril
Angiotensin II antagonists	The "—sartans": azilsartan, losartan, valsartan
NSAIDs and COX-2 inhibitors	Over-the-counter: Ibuprofen, naproxen (aspirin is OK) Prescription: Celecoxib, diclofenac, indomethacin, meloxicam (sulindac is usually OK)
Antibiotics	Metronidazole, tetracycline

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TABLE 20-1. Second-Generation Antipsychotics for Antidepressant Augmentation*

Medication	Dose Range (mg/day)*	Optimal Dose (mg/day)*	Pros	Cons
FDA Approved				
Aripiprazole	5–15	5	Supported by the most studies, including studies of 2–4 antidepressant failures	Akathisia; long-term weight gain
Brexpiprazole	2–3	2	Effective for comorbid post-traumatic stress disorder (PTSD) with sertraline; favorable tolerability	Small effect size
Cariprazine	1.5–3	1.5	Favorable tolerability	Small effect size
Lumateperone	42	42	Favorable tolerability within its class (FDA approval pending)	Sedation
Olanzapine-fluoxetine combination	6/25-12/50 olanzapine/ fluoxetine	9/45	FDA-approved for treatment-resistant depression (≥ 2 failed trials); effective for depression with mixed features (with fluoxetine)	High rate of metabolic problems; only studied with fluoxetine
Quetiapine	150–300	300	Unique benefits in anxiety and sleep; only antipsychotic with good evidence as monotherapy in major depression; low rates of akathisia	High risk of sedation, orthostasis, and metabolic problems
Off-Label				
Lurasidone	20–60 (with a full meal)	36	Effective for depression with mixed features (as monotherapy)	Only tested in depression with mixed features
Risperidone	0.5–3	1.5	Ranks high in efficacy, along with aripiprazole	High risk of prolactinemia and EPS
Ziprasidone	40–160 (with a full meal, divided BID)	98	Low metabolic risks; treats depression as augmentation and mixed features as monotherapy.	Only two positive trials

*The SGAs omitted from this chart are best avoided in major depression because they are either untested (asenapine, clozapine, iloperidone, and xanomeline-trospium) or failed (pimavanserin).

*Dose ranges are based on clinical trials or FDA approval. Optimal dose derived from dose-response curves (where available) or average levels in clinical trials.

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TABLE 20-2. Treatments for Antipsychotic Side Effects

Treatment	Dose	Benefits	Risks
METABOLIC			
Liraglutide (Saxenda) (subcutaneous injection)	Start: 0.6 mg QD (as subcutaneous injection). Target: 3 mg, after increasing by 0.6 mg weekly	Weight loss	Nausea, gastroparesis, biliary disease, pancreatitis
Melatonin	3–5 mg QHS	Weight loss, insomnia	
Metformin	Start: 500 mg QD with food Target: 2,000 mg daily, divided BID or as XR QD	Weight loss, insulin sensitivity, triglycerides, and prolactinemia	B12 deficiency, hypoglycemia, lactic acidosis; nausea improved by taking with food or using XR.
Naltrexone	50 mg QD with food	Weight loss	Nausea; rare liver toxicity; prevents opioids from working.
Probiotics	1 capsule QD (take with a prebiotic, see Chapter 40: Probiotics)	Weight loss, insulin sensitivity	Risks in immunocompromised
Samidorphan (Lybalvi)	Dosed as combo with olanzapine	Weight loss	Prevents opioids from working
Semaglutide (Wegovy) (subcutaneous injection)	Start: 0.25 mg qWeek. Increase every 4 weeks to target of 2.4 mg qWeek	Weight loss	Nausea, gastroparesis, biliary disease, pancreatitis
Tirzepatide (Zepbound) (subcutaneous injection)	Start: 2.5 mg qWeek. Increase by 2.5 mg to target of 5–15 mg qWeek	Weight loss	Nausea, gastroparesis, biliary disease, pancreatitis
Topiramate	Start: 25 mg QHS Increase by 25 mg/week to target of 50–200 mg QHS (or divide BID)	Weight loss	Cognitive, renal stones
AKATHISIA			
Benzodiazepines	Varies (eg, lorazepam 1–3 mg/day divided BID or TID)	Akathisia	Sedation, cognition, dependence
Propranolol	Start 20–40 q8hr mg PRN. Switch to ER once daily dose is established (80–240)	Akathisia	Hypotension, bradycardia, Raynaud's phenomenon
Vitamin B6	150–300 mg BID as pyridoxal 5'-phosphate*	Akathisia, tremor, prolactinemia	Neuropathy (dose-dependent)
TARDIVE DYSKINESIA			
Amantadine	Start 100 mg Qam. Increase to 200–300 mg divided BID after 1 week (give in morning and afternoon)	Weight loss, tardive dyskinesia	Rare hallucinations; caution in congestive heart failure

*Vitamin B6 carries a risk of neuropathy that may be avoided by using active form, pyridoxal 5'-phosphate

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TABLE 20-2. Treatments for Antipsychotic Side Effects

Treatment	Dose	Benefits	Risks
Deutetrabenazine	Start 6 mg BID, increase by 3 mg BID every week to 24 mg BID (take with food)	Tardive dyskinesia	QTc prolongation (reduced with XR form)
Valbenazine	Start 40 mg QD, raise to 80 mg QD after a week	Tardive dyskinesia	QTc prolongation
Ginkgo (EGb-761, Tebonin form)	80 mg TID	Tardive dyskinesia, extrapyramidal side effects, cognition	
Hyperprolactinemia			
Bromocriptine	2.5 mg QHS	Prolactinemia	Hallucinations
Metformin	Start: 500 mg QD with food Target: 2,000 mg daily, divided BID or as XR QD	Weight loss, insulin sensitivity, triglycerides, and prolactinemia	B12 deficiency, hypoglycemia, lactic acidosis
Vitamin B6	150–300 mg BID as pyridoxal 5'-phosphate	Akathisia, tremor, prolactinemia, extrapyramidal side effects	Neuropathy

*Vitamin B6 carries a risk of neuropathy that may be avoided by using active form, pyridoxal 5'-phosphate

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TABLE 20-3. FDA Warnings with Antipsychotics

Risk	Details	Increased or Decreased in . . .
Tardive dyskinesia	Involuntary writhing movements that develop with long-term use, most often in the tongue, face, fingers, and toes	• ↑ Elderly, women, mood disorders • ↑ Patients with akathisia or extrapyramidal side effects
Metabolic syndrome	Obesity, type II diabetes, dyslipidemia	• ↑ Adolescents, women, non-whites • ↑ Clozapine, olanzapine, and quetiapine • ↓ Lumateperone, ziprasidone
Hyperprolactinemia	Serum prolactin ≥ 15–20 ng/ml raises risk of breast cancer, osteopenia, and visual loss; presents as breast engorgement, milk production, sexual dysfunction, and menstrual irregularities	• ↑ Risperidone • ↓ Aripiprazole, quetiapine
Orthostatic hypotension	Syncope and falls Drop in systolic by ≥ 20 mmHg or diastolic by ≥ 10 mmHg within 3 minutes of standing	• ↑ Elderly, heart disease, dehydration, pregnancy, alcohol use • ↓ Dividing dose BID or using XR
Arrhythmias	Increased risk of potentially fatal torsade's de point with QTc prolongation	• ↑ Elderly, women • ↑ Heart disease* or electrolyte disturbance (low K or Mg) • ↑ Multiple meds that prolong QTc (check at crediblemeds.org)
Anticholinergic effects	These slowly wear down health and quality of life (see Table 17.2)	• ↑ Elderly • ↑ Multiple anticholinergics (check at acbcalc.com) • ↑ Olanzapine • ↓ Brexpiprazole, lumateperone, and lurasidone
Hyperthermia	Impaired thermoregulatory control	• ↑ Elderly
Neuroleptic Malignant Syndrome	Rare, life-threatening syndrome involving fever, muscle rigidity, tremor, confusion, irregular blood pressure and pulse	
Mortality in dementia	Increased risk of death from stroke in older patients with dementia	

*Cardiac problems that raise the risk of torsade's de point include low left ventricular ejection fraction, left ventricular hypertrophy, ischemia, and slow heart rate

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TABLE 21-1. Pramipexole Summary

FDA Approval	Parkinson's disease Restless leg syndrome
Off-Label Benefits	Major depression, bipolar depression
Dosing	Start 0.25 mg QHS, raise by 0.25 mg every 5–7 days to target of 1–3 mg QHS
Risks	Hypotension, edema Hedonic dysregulation (1-3%), hallucinations (0.4%), sleep attacks
Side Effects	Nausea, fatigue
Half-Life	8–12 hours
Interactions	Pramipexole has few interactions because it is excreted unchanged in the urine; cimetidine raises levels by 50% (inhibits renal secretion)

TABLE 22-1. Triiodothyronine Summary

Off-Label Benefits	Depression (unipolar and bipolar)
Dosing	Start T3 (triiodothyronine, Cytomel) 25 mcg QD ×1 week then 50 mcg QD × 1 week; if no response at 50 mcg, raise by 25 mcg/week to max of 150 mcg QD
Duration	Continue for at least six months after recovery (many patients need longer to prevent depression)
Risks	Decreased bone mineral density, cardiac arrhythmias
Side Effects	Anxiety, tachycardia, hot sweats, headache, tremor, restlessness
Half-Life	22–24 hours
Interactions	Bile acid sequestrants and ion exchange resins reduce absorption (take 4 hours apart) Enzyme inducers (phenobarbital, phenytoin, carbamazepine, and rifampin) lower T3 levels
Monitoring	Check thyroid panel at baseline and every 3–12 months Lower dose if resting pulse > 100 bpm or symptoms of hyperthyroidism appear (see Side Effects)

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TABLE 23-1. Celecoxib Summary

FDA Approval	Arthritis (osteoarthritis, rheumatoid arthritis, ankylosing spondylitis), acute pain, primary dysmenorrhea
Off-Label Benefits	Major depression, bipolar depression
Dosing	200 mg BID
Risks	Gastric ulcer, thrombosis (heart attacks, stroke), hypertension, heart failure, hepatotoxicity (1%), renal toxicity, asthma, hepatitis, and anemia (0.2%) Avoid if allergies to sulfa or aspirin (can cause Stevens-Johnson Syndrome, anaphylaxis, and asthma); avoid in pregnancy.
Side Effects	GI distress
Half-Life	11 hours
Interactions	Metabolized through CYP2C9. Inhibits CYP2D6 and raises lithium levels by 20–100%.
Monitoring	CBC, LFT, creatinine annually

TABLE 24-1. Amantadine Summary

FDA Approval	Dyskinesia in Parkinson's disease (as Gocovri XR), influenza A (as Symmetrel, instant release)
Off-Label Benefits	Depression, OCD, irritability (due to autism or traumatic brain injury), ADHD, post-COVID fatigue, tardive dyskinesia, weight loss, sexual dysfunction
Dosing	Start 100 mg Qam × 1 week then 100 mg BID (max 400 mg/day)
Risks	Edema, orthostasis, anticholinergic effects, skin pigmentation (livedo reticularis) Hallucinations, confusion, ataxia, hedonic dysregulation (impulsive gambling)
Side Effects	Insomnia, dizziness, nausea, dry mouth
Half-Life	10–25 hours
Interactions	Renally cleared (drugs that impair renal clearance may raise levels)

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TABLE 25-1. D-Cycloserine Summary

FDA Approval	Multi-drug-resistant tuberculosis
Off-Label Benefits	Depression Augmentation of TMS and exposure therapy
Dosing	Depression: 500 mg BID Augment TMS: 100 mg 1–2 hours before TMS for first 2 weeks of therapy Augment exposure therapy: 50–100 mg 1–2 hours before exposure session
Risks	In high doses: seizures (4%), psychosis, mania
Side Effects	Dizziness, headache, visual changes, tinnitus, tremor, confusion, drowsiness, slurred speech
Half-Life	10 hours
Interactions	Renally cleared (drugs that impair renal clearance may raise levels)

TABLE 26-1. Minocycline Summary

FDA Approval	Bacterial infections. Acne vulgaris and rosacea (as topical and oral XR preparations).
Off-Label Benefits	Depression, negative symptoms of schizophrenia, rheumatoid arthritis
Dose	100 mg BID
Risks	Hepatotoxicity, fungal infection, altered microbiome Avoid if pregnant or allergic to any tetracycline
Side Effects	Diarrhea, headache, dizziness, photosensitivity
Half-Life	11–23 hours
Interactions	May accentuate effects of anticoagulants. Absorption decreased by antacids containing aluminum, calcium, magnesium, or iron.

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TABLE 27-1. Rapid-Acting Medications for Depression

Rapid-Acting Medications for Depression
• **Alprazolam:** A benzodiazepine with short-term benefits in depression • **Eszopiclone:** A sleep medication that accelerates antidepressant response • **Auvelity:** A pill that pairs bupropion with dextromethorphan, a rapid-acting glutamatergic • **Ketamine/Esketamine:** A glutamatergic, dissociative anesthetic with acute antidepressant effects • **Pindolol:** A beta-blocker that speeds selective serotonin reuptake inhibitor (SSRI) response • **Thyroid:** A hormone that can speed up antidepressant response and augment when antidepressants fail • **Zuranolone:** A neuroactive steroid for postpartum depression • **Psychedelics:** Emerging treatments whose powerful psychological effects can be harnessed in psychotherapy

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TABLE 28-1. Alprazolam Summary

FDA Approval	Panic disorder Generalized anxiety disorder (GAD)
Off-Label Benefits	Acute depression
Dosing	0.5–3 mg XR QD for 4–6 weeks followed by a 2-week taper
Risks	Overdose when used with opioids Tolerance, withdrawal, misuse liability Falls, motor vehicle accidents Worsening of respiratory disorders
Side Effects	Drowsiness, cognitive dysfunction
Half-Life	6–27 hours
Interactions	Strong CYP3A4 inhibitors double levels (eg, grapefruit juice, fluvoxamine) while inducers lower them (eg, modafinil, carbamazepine)

TABLE 29-1. Eszopiclone Summary

FDA Approval	Primary insomnia
Off-Label Benefits	Acute depression or generalized anxiety disorder
Dosing	1–3 mg QHS for 4–8 weeks, followed by 1–2 week taper
Risks	Sleep behavior disorders Falls Low risk of tolerance, withdrawal, misuse
Side Effects	Drowsiness, metallic taste, headache, dizziness
Half-Life	6 hours
Interactions	Strong CYP3A4 inhibitors double levels (eg, grapefruit juice, fluvoxamine) while inducers lower them (eg, modafinil, carbamazepine)

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TABLE 30-1. Auvelity Summary

FDA Approval	Major depressive disorder Dextromethorphan (DM) is approved as a cough suppressant and (with quinidine, as Nuedexta) in pseudobulbar affect.
Off-Label Benefits	DM has evidence in bipolar depression and agitation in dementia.
Dosing	Start 45 mg/105 mg daily for 3 days, then 45 mg/105 mg BID Alternative: Titrate components separately with DM in evening
Risks	Bupropion: Seizures DM: Dissociation, psychosis, DM misuse
Side Effects	Drowsiness, nausea, dizziness, headache, dry mouth
Half-Life	2–4 hours (DM); 21 hours (bupropion)
Interactions	DM can cause serotonin syndrome with serotonergics and monoamine oxidase inhibitors (MAOIs); levels are raised and half-life extended by CYP2D6 inhibitors (a desirable interaction). Bupropion inhibits CYP2D6.

TABLE 31-1. Ketamine Summary

FDA Approval	IN esketamine: Treatment-resistant depression, depression with acute suicidality IV ketamine: anesthetic (not approved in psychiatry)
Off-Label Benefits	Bipolar depression, post-traumatic stress disorder (PTSD)
Dosing	IN esketamine: 56–84 mg twice weekly for 4 weeks, then taper off or continue as weekly for 4 weeks, then every 1–2 weeks IV ketamine: 0.5 mg/kg over 40 minutes, typically twice weekly for 2–3 weeks
Risks	Hypertension, dissociation, psychosis, mania Bladder dysfunction with long-term use Possible increased suicide risk during withdrawal
Side Effects	Sedation, nausea, transient cognitive impairment, dizziness, bitter taste
Half-Life	2–4 hours
Interactions	Metabolized by CYP2B6 and CYP3A4 with minor contributions from CYP2C9 and CYP2C19 Naltrexone and benzodiazepines may interfere with response Additive hypertensive effects with stimulants

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TABLE 32-1. Pindolol Summary

FDA Approval	Hypertension
Off-Label Benefits	Accelerating SSRI response Potential benefits in panic disorder and obsessive-compulsive disorder (OCD)
Dosing	5 mg TID Duration: 4–6 weeks followed by 2–4 week taper
Risks	Contraindicated in asthma, heart failure, severe bradycardia, heart block, cardiogenic shock
Side Effects	Insomnia, vivid dreams, fatigue, dizziness, peripheral edema
Half-Life	8 hours
Interactions	Metabolized through glucuronidation and hydroxylation. Hypotension with other beta-blockers. May reduce effectiveness of beta-agonist inhalers.
Monitoring	Blood pressure and heart rate at baseline and during dose changes

TABLE 33-1. Zuranolone Summary

FDA Approval	Postpartum depression
Dosing	30–50 mg QHS for 2 weeks Take with a high-fat meal
Risks	Driving impairment, risk of misuse Do not use while breastfeeding
Side Effects	Sedation, diarrhea
Half-Life	16–23 hours
Interactions	Strong CYP3A4 inhibitors double levels (eg, grapefruit juice, fluvoxamine) while inducers lower them (eg, modafinil, carbamazepine)

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TABLE 34-1. Psilocybin Summary

FDA Approval	None
Off-Label Benefits	Existential despair in terminal illness Major depression Potential benefits in substance use disorders, obsessive-compulsive disorder (OCD), and cluster headaches
Dosing	25 mg single oral dose, with a second dose possible 3-4 weeks later
Risks	Psychosis, mania, and risk of boundary violations in therapy
Side Effects	Headache, nausea, anxiety, dizziness
Half-Life	2-4 hours
Interactions	Psilocybin is a pro-drug that is activated by conversion into psilocin (by the enzyme alkaline phosphatase) Serotonergic medications (risk of serotonin syndrome) Lithium and tramadol (increased seizure risk)

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TABLE 35-1. Summary of Natural Therapy Evidence

Therapy	Effect Size	Evidence Quality	Works as Monotherapy?	Works as Augmentation?
Light therapy	Medium to large	Strong	Yes	Yes
L-methylfolate	Small to medium	Moderate to strong	Possibly (as Enlyte)	Yes
Omega-3 fatty acids	Small to medium	Moderate	Mixed data	Yes
Probiotics	Small to medium	Preliminary but promising	Limited data	Yes
Vitamin D	Small to medium	Mixed results	Only in deficiency	Only in deficiency

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TABLE 36-1. Light Therapy Summary

FDA Approval	None
Off-Label Benefits	Seasonal and nonseasonal depression In winter: bulimia, low libido in men In any season: bipolar depression, PTSD, insomnia, shift-work disorder
Dose	30-120 min in morning (5:00 am-8:00 am)
Risks	Mania Photosensitivity; ocular risks in patients with glaucoma, cataracts, retinal detachment, or retinopathy
Side Effects	Headache, eye strain, insomnia (if used too late)
Interactions	Caution with meds that cause photosensitivity (lamotrigine, tricyclics, antipsychotics)
Recommended Products	Carex Daylight Sky or Elite with LED bulbs (see chrisaikenmd.com/lighttherapy)
Cost	$100-$220 for box



FIGURE 36-1. Positioning the Lightbox

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TABLE 37-1. Predictors of L-Methylfolate Response

MTHFR variation (homozygous or C677T)
Obesity (BMI ≥ 30 kg/m^2)
Inflammation (hs-CRP ≥ 3 mg/L)
Pregnancy and lactation
Eating disorders
Renal failure and GI disease
Poor nutrition
Alcohol use disorders
Smoking
Concomitant medications (eg, lamotrigine, valproate, carbamazepine, phenytoin, fluoxetine, oral contraceptives, methotrexate, metformin, sulfasalazine, warfarin, and triamterene)

TABLE 37-2. L-Methylfolate Summary

FDA Approval	Cleared as a dietary supplement for depression
Off-Label Benefits	Bipolar depression, autism, negative symptoms of schizophrenia
Dosing	15 mg QD
Risks	None
Side Effects	None
Interactions	None
Recommended Products	Prescription form or over-the-counter as MethylPro or Opti-Folate; also available as a part of a proprietary multivitamin (Enlyte, EnBrace HR)
Cost	$8-$30/month

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TABLE 38-1. Vitamin D Summary

FDA Approval	Vitamin D deficiency, corticosteroid-induced osteoporosis (with calcium), refractory rickets, familial hypophosphatemia, hypoparathyroidism (with calcium)
Off-Label Benefits	Depression in vitamin D deficiency
Dosing	Loading dose based on deficiency level, then 800-2,000 IU daily maintenance
Risks	High levels (> 60 ng/mL) may cause hypercalcemia and kidney stones
Side Effects	Minimal at standard doses
Interactions	May increase absorption of calcium and aluminum (relevant for patients on antacids)
Recommended Products	Vitamin D3 preferred over D2; available prescription or over-the-counter
Cost	$3-$10/month

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TABLE 39-1. Omega–3 Fatty Acids Summary

FDA Approval	Elevated triglycerides
Off-Label Benefits	Major depression, bipolar depression, borderline personality disorder, ADHD, autism, negative symptoms of schizophrenia, irritability Psoriasis, acne, fatty liver
Dosing	1,000-4,000 mg QD of EPA + DHA Higher doses for inflammation and psoriasis Use a product with an EPA:DHA ratio ≥ 2:1
Risks	Anticoagulant effects (stop 1 week prior to surgery, restart after surgery); avoid in CHF and atrial fibrillation
Side Effects	Reflux, fishy taste, diarrhea
Interactions	None
Cost	Prescription Vascepa is $30/mth. OTC versions are $5-20/mth.

TABLE 39-2. Recommended Omega–3 Products

Product	EPA/DHA in a capsule	Monthly cost for starting dose (1,000 mg/day)
High concentration (starting dose = 1 capsule)		
Carlson Elite EPA Gems	1,000/16.5 mg	$15
GNC Triple Strength Enteric Coated	734/266 mg	$8
Nature Made 1400	683/252 mg	$9
Nordic Naturals ProOmega (Liquid)	1,950/975 mg	$22
Nutrigold Triple Strength	725/275 mg	$11
Omegavia Ultra Concentrated Enteric Coated	780/260 mg	$15
Spring Valley Max Care 2000 (Walmart)	645/310 mg	$4
Vascepa (Rx only)	960/40 mg	$30
Viva Naturals Triple Strength	750/142.5 mg	(monthly cost) $9
Low concentration (starting dose = 2 capsules)		
OmegaVia EPA 500	500/21.2 mg	$15
Vitacost Super EPA (Vitacost.com)	600/150 mg	$16

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TABLE 40-1. Probiotics Summary

FDA Approval	None
Off-Label Uses	Major depression, bipolar disorder, anxiety, autism, cognition, dementia, negative symptoms of schizophrenia Constipation, irritable bowel syndrome, inflammatory bowel disease, dyslipidemia, weight loss, antibiotic-associated diarrhea, *C. difficile* infection
Dosing	2-10 billion CFUs
Risks	Avoid in immunocompromised
Side Effects	Gas
Interactions	None
Recommended Products	Lifted Naturals Mood Boosting Trunature Advanced Digestive
Cost	$10-$15/month

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TABLE 41-1. Neuromodulation and Interventional Psychiatry: What to Expect

Treatment	Frequency	Activity Limitations	Maintenance Schedule (optional)
ECT	1-hour sessions 3 days a week for 3-4 weeks	Cannot drive on day of session, unable to work during treatment	Monthly
TMS	3-45 min sessions* 5 days a week for 6 weeks	None	1-8 per month
fMRI-guided SNT (SAINT) TMS	10 hours a day for 5 days (with a 10-min treatment every hour)	None beyond time commitment	As needed if symptoms arise (typically 1 day per month)
Ketamine (IV) and Esketamine (IN)	30-45 min sessions Twice weekly for 4 weeks, followed by 4 weekly treatments	Wait 2-3 hours before driving	1-2 per month

*3 min for intermittent theta-burst stimulation (iTBS), 20 min for Deep TMS (H coil, Brainsway), 45 min for traditional TMS (figure-8 coil)

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TABLE 44-1. Treatment of Menopausal Symptoms

SSRIs	For mood and vasomotor symptoms Paroxetine (7.5–15 mg QHS), escitalopram (10–20 mg QHS), citalopram (10–20 mg QHS)
SNRIs	For mood and vasomotor symptoms Desvenlafaxine (50–150 mg QHS), venlafaxine XR (37.5–150 mg QHS)
Gabapentin	For insomnia and vasomotor symptoms (300-2,400 mg at night)

TABLE 44-2. Contraindications to HRT

History of estrogen-sensitive cancer (eg, breast, ovarian, or uterine)
Unexplained vaginal bleeding
History of deep venous thrombosis (DVT), pulmonary embolism, blood clotting disorder, or stroke
Conditions that increase the risk of stroke (uncontrolled hypertension or elevated triglycerides)

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TABLE 44-3. Estrogen in Psychiatry (OCP and HRT)

OCP vs HRT	Both oral contraceptive pills (OCPs) and hormone replacement therapy (HRT) contain estrogen along with progestin or a synthetic progestin (eg levonorgestrel, desogestrel, drospirenone). HRT contains lower doses that supplement a woman's hormones, while OCP has higher doses that shut down the natural hormones.
HRT for depression	Menopausal depression studies used 17β-estradiol (Estraderm) transdermal 0.05 mg/day with additional medroxyprogesterone acetate 10 mg/day for 1 week of every month
Types of OCP	Monophasic formulations deliver 3 weeks of estrogen/progestin at a constant level followed by 1 week of placebo. Triphasic formulations deliver varying hormones levels throughout the 4-week cycle that more closely mimic the natural cycle. Progestin-only pills are used by women who cannot take estrogen (eg due to cardiovascular or cancer risks or side effects like nausea, breast tenderness, fluid retention, and rash).
OCP most likely to disrupt mood	Progestin formulations, followed by levonorgestrel formulations
OCP least likely to disrupt mood	Desogestrel formulations (eg Yasmin, Yaz)
Risk factors for mood disruption on OCP	Adolescents and women in the postpartum period. Women with a history of perinatal depression or dysmenorrhea.
Estrogen-induced drug interactions	Estrogen-containing OCPs lower lamotrigine by 30%-50%. HRT lowers lamotrigine to a lesser extent. Milder interactions with OCPs include lower levels of benzodiazepines metabolized through glucuronidation (lorazepam, oxazepam, temazepam), higher levels of other benzodiazepines (alprazolam, chlordiazepoxide, diazepam, flurazepam, triazolam), and higher levels of some tricyclic antidepressants.
Drugs that lower OCP and HRT levels	Carbamazepine (very potent), oxcarbazepine, topiramate, the modafinils, and St John's Wort (through CYP-3A4 inhibition). Transdermal and implant formulations partially bypass this hepatic interaction but are still affected by it. If prescribing these meds, recommend barrier methods and/or higher estrogen doses.

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TABLE 44-4. Risks of Testosterone Supplementation

Atrial fibrillation
Acute kidney injury
Thrombosis (eg, pulmonary embolism)
Benign prostatic hyperplasia (BPH)
Low sperm count
Worsening of sleep apnea
Hyperlipidemia
Elevated liver function tests
Acne
Aggression

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TABLE 45-1. Withdrawal Symptoms by Medication Class

Medication	Withdrawal Symptoms
Antipsychotics	**Psychiatric:** Insomnia, anxiety, psychosis **Physical:** Tremor, headache, dizziness, nausea, tachycardia, akathisia, dyskinesias
Benzodiazepines	**Psychiatric:** Anxiety, insomnia, nightmares, irritability, sensory changes, dissociation, paranoia **Physical:** Tremor, tinnitus, headache, dizziness, muscle spasms, GI distress, palpitations, seizures
Bupropion	**Psychiatric:** Anxiety, insomnia, irritability **Physical:** Fatigue, headache, myalgias, restlessness
Buspirone and gepirone	None known
Mirtazapine	**Psychiatric:** Depression, anxiety, insomnia **Physical:** Itch, appetite loss
Modafinils	**Psychiatric:** Depression, anxiety, hypersomnia, brain fog **Physical:** fatigue, headaches, sweats, chills
SSRIs and SNRIs	**Psychiatric:** Dysphoria, anxiety, mania, insomnia, irritability, brain zaps, sensory changes, dissociation **Physical:** Tremor, sweats, myalgias, restlessness, headache, chills, GI distress, tinnitus
Stimulants	**Psychiatric:** Depression, irritability, anxiety, insomnia, nightmares, hypersomnia, brain fog, agitation **Physical:** Crashing fatigue, dystonic movements, increased appetite

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A Hyperbolic Taper for SSRIs

1. Lower to the Minimum Effective Dose

Reduce the dose to the minimum suggested in Table 46.1 if not already there (eg, citalopram 20 mg). At this stage, the dose can be reduced linearly (eg, by 5–10 mg) because the main risk is depressive relapse, not serotonin withdrawal. Lowering every two to four weeks is reasonable for most patients, but longer intervals may be needed for those with a history of withdrawal problems or a long duration of treatment.

2. Assess Baseline Symptoms

Check if the patient is having any symptoms that correspond to SSRI withdrawal symptoms at baseline.

3. Lower For One Month and Reassess

Now move to the first tapering dose in the table (eg, citalopram 10 mg). Monitor for withdrawal symptoms throughout the taper and adjust the rate of taper based on withdrawal symptoms.

4. Start the Long-Tail Taper

The doses for each step of the final taper are listed in Table 46.1 (eg, citalopram 5 mg, then 3.4 mg). How quickly you go down at each step depends on how sensitive the patient is to withdrawal. Your assessment of their symptoms at baseline and one month later will give you a sense of that. At a minimum, allow two weeks between each step; four weeks is a rough average. Patients who experience withdrawal effects benefit from making smaller reductions at each step rather than spacing out the time in between dose reductions.

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TABLE 46-1. Tapering Doses and Liquid Conversions for Common SSRIs

Medication	Minimum Daily Dose*	Tapering Doses (mg/day)	Liquid Conversion (mL/day)
Citalopram	20 mg	10 mg→ 5→ 3.4→ 2.3→ 1.5→ 0.8→ 0.4→ stop	2 mg/mL: 5 mL→ 2.5→ 1.7→ 1.2→ 0.8→ 0.4→ 0.2→ stop
Escitalopram	10 mg	5 mg→ 2.7→ 1.7→ 1.2→ 0.7→ 0.4→ 0.2→ stop	1 mg/mL: 5 mL→ 2.7→ 1.7→ 1.2→ 0.7→ 0.4→ 0.2→ stop
Fluoxetine	20 mg	8.5 mg→ 4.5→ 2.7→ 1.7→ 1.0→ 0.6→ 0.3→ stop	4 mg/mL: 2.1 mL → 1.1→ 0.7→ 0.4→ 0.3→ 0.2→ 0.1→ stop
Fluvoxamine	50 mg	25 mg→ 15→ 10→ 8→ 5→ 2→ 1→ stop	No liquid (use 25 mg tabs or compounding pharmacy)
Paroxetine	20 mg	11.4 mg→ 7.4→ 5.0→ 3.4→ 2.2→ 1.3→ 0.6→ stop	2 mg/mL: 5.7 mL → 3.7→ 2.5→ 1.7→ 1.1→ 0.7→ 0.3→ stop
Sertraline	50 mg	25 mg→ 14→ 9.1→ 5.9→ 3.8→ 2.2→ 0.9→ stop	20 mg/mL: 1.3 mL → 0.7→ 0.5→ 0.3→ 0.2→ 0.1→ 0.05→ stop

*The minimum daily represents the dose that typically achieves 80% occupancy at the serotonin receptor. It roughly corresponds with the minimum effective dose for depression.

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Treatment Menus

TO ENHANCE COLLABORATION, present your patient with a menu of reasonable options. Keep it brief, 3–4 treatment steps that are likely to work. Aim for variety. Instead of presenting three antipsychotics, choose one treatment that is tolerable, one that is very effective, and one from the natural or lifestyle side. In the lists below, I've divided the treatments in this book into approximate categories to get you started.

Favorable Tolerability

- Celecoxib
- Eszopiclone
- Light Therapy
- L-methylfolate
- Omega-3 fatty acids
- Pramipexole
- Probiotics
- Psychotherapy
- Thyroid
- Transcranial magnetic stimulation (TMS)

Large Effect Size

- Electroconvulsive therapy (ECT)
- Ketamines
- Light therapy
- Pramipexole
- SNT (Saint TMS)
- TMS

For High Levels of Treatment Resistance

- ECT
- High-dose monoamine oxidase inhibitors (MAOIs)

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- Pramipexole
- SNT (Saint TMS)

For Prevention in Recurrent Depression

- Exercise
- Lithium
- Natural therapies for deficiency states in chapters 35–40 (possibly)
- Pramipexole
- Psychotherapy

For Anxious Depression

- Benzodiazepine augmentation
- Buspirone augmentation
- Eszopiclone augmentation
- Ketamines
- MAOI switch
- Mirtazapine augmentation
- Probiotics
- Quetiapine
- TMS
- Zuranolone (for postpartum)

For Unipolar Depression with Mixed Features

- Antidepressant taper (though bupropion and trazodone may help)
- Lamotrigine
- Lithium
- Second generation antipsychotics (especially lurasidone and lumateperone)

When the bipolar-unipolar diagnosis is unclear

- Amantadine (possibly)
- ECT
- Ketamines
- Lamotrigine (possibly)

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- Light therapy
- Lithium
- Omega-3 fatty acids
- Pramipexole
- Psychotherapy
- Second generation antipsychotics
- Thyroid
- TMS

For Psychotic Depression

- Antipsychotic augmentation (high dose)
- ECT
- Lithium

For Vascular Depression

- ECT
- Nimodipine
- TMS

For Inflammatory Depression

- Bupropion
- Celecoxib
- L-methylfolate
- Minocycline
- N-acetylcysteine (2,000 mg/day)
- Omega-3 fatty acids (high dose: 4,000 mg/day)
- Pramipexole
- Probiotics
- Psychotherapy

For Depression with Trauma

- Psychotherapy
- Prazosin (Minipress) augmentation

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