DEPRESSIVE DISORDERS

Major Depressive Disorder

MDD

DSM-5-TR 296.2X-296.3X | ICD-10-CM F32.X, F33.X

Discrete episodes of pervasive low mood or anhedonia with neurovegetative and cognitive change, driving disability and suicide risk.

LIFETIME PREVALENCE	TYPICAL ONSET	SEX RATIO	COURSE
~21% (US adults)	Mid-20s; any age	~2:1 female:male	Recurrent; ~50% relapse

CLINICAL PICTURE

- Patients describe anhedonia more reliably than sadness; ask about loss of interest in previously reinforcing activities over the past two weeks.
- Neurovegetative signs dominate the presentation: early morning awakening, appetite and weight shift, psychomotor slowing, and profound diurnal fatigue.
- Cognitive complaints of poor concentration and indecisiveness are frequently misattributed to ADHD, early dementia, or simple occupational burnout.
- Guilt is excessive and self-referential rather than proportionate, ranging from ruminative self-blame to mood-congruent psychotic delusions.
- Older adults and men often present somatically with pain, irritability, or substance use rather than reporting a sad mood at all.
- Suicidal ideation ranges from passive wishes to be dead to active planning; ask directly at every visit and document intent, plan, and means.

DIAGNOSTIC CRITERIA AT A GLANCE

- Requires five or more symptoms within the same two-week window, with at least one being depressed mood or loss of interest and pleasure.
- The symptom pool spans mood, interest, weight or appetite, sleep, psychomotor activity, energy, worthlessness or guilt, concentration, and death thoughts.
- Symptoms must occur nearly every day, cause significant distress or functional impairment, and not be better explained by another condition.
- The episode cannot be attributable to a substance, medication, or medical illness, and any history of mania or hypomania reclassifies the case as bipolar.
- Specifiers code severity, psychotic features, anxious distress, mixed features, melancholic, atypical, catatonic, peripartum, and seasonal patterns.

NEUROBIOLOGY & PHYSIOLOGY

- Reduced serotonergic, noradrenergic, and dopaminergic signaling remains the pharmacologic target, though monoamine depletion alone does not induce depression.
- Hyperactive subgenual anterior cingulate and amygdala with hypoactive dorsolateral prefrontal cortex produce negative bias and weak top-down control.
- HPA axis dysregulation yields elevated cortisol, blunted dexamethasone suppression, and hippocampal volume loss proportional to untreated episode burden.
- Elevated IL-6, TNF-alpha, and CRP link inflammation to sickness behavior, and interferon therapy reliably induces depressive syndromes in treated patients.
- Heritability is roughly 35 to 40 percent, polygenic and heavily overlapping with anxiety, with gene-by-environment interaction around early adversity.
- Reduced BDNF and impaired hippocampal neuroplasticity normalize with antidepressant response, supporting the neurotrophic model of recovery.

PSYCHOLOGICAL MECHANISMS

- Beck's cognitive triad of negative views of self, world, and future is maintained by latent schemas and automatic thoughts activated under stress.
- Rumination, the stable response style described by Nolen-Hoeksema, prolongs episodes and predicts recurrence more strongly than raw symptom count.
- Behavioral models frame depression as loss of response-contingent positive reinforcement, with avoidance narrowing the reinforcement pool even further.
- Learned helplessness and a pessimistic attributional style that is internal, stable, and global predict hopelessness, the strongest cognitive suicide risk factor.
- Insecure attachment and early maltreatment sensitize stress reactivity and shape the interpersonal role disputes targeted by interpersonal therapy.

DIFFERENTIAL & COMORBIDITY

- Screen every depressed patient for prior mania or hypomania; antidepressant monotherapy in bipolar depression risks switching and cycle acceleration.
- Rule out hypothyroidism, anemia, vitamin B12 deficiency, obstructive sleep apnea, and medication effects before attributing symptoms to a mood disorder.
- Distinguish from persistent depressive disorder by episodicity, from adjustment disorder by threshold and severity, and from grief by pervasive self-loathing.
- Anxiety disorders co-occur in roughly 60 percent of cases; substance use, PTSD, chronic pain, and personality pathology worsen course and treatment response.
- Lifetime suicide risk is substantially elevated and peaks with hopelessness, insomnia, agitation, prior attempts, and the first weeks of treatment.

Treatment EVIDENCE-BASED MANAGEMENT

PHARMACOLOGIC

- SSRIs are first line: **sertraline 50-200 mg/day**, **escitalopram 10-20 mg/day**, or fluoxetine 20-60 mg/day, with GI upset and sexual dysfunction most limiting.
- SNRIs such as **venlafaxine XR 75-225 mg/day** or duloxetine 60-120 mg/day help comorbid pain; monitor blood pressure at the higher dose range.
- **Bupropion XL 150-450 mg/day** avoids sexual side effects and sedation but lowers seizure threshold and is avoided in active eating disorders.
- Allow 4 to 6 weeks at an adequate dose before declaring failure; continue treatment 6 to 12 months past remission and longer after recurrent episodes.
- For treatment resistance, augment with **aripiprazole 2-15 mg/day**, lithium, or T3, or use **esketamine** nasal spray under REMS monitoring.

PSYCHOTHERAPY

- **CBT** delivered over 12 to 20 weekly sessions matches medication for mild to moderate episodes and roughly halves relapse risk after discontinuation.
- **Behavioral activation** is equally effective, simpler to train and disseminate, and works well with low-functioning or cognitively fatigued patients.
- **Interpersonal therapy** targets role transitions, disputes, and grief across 12 to 16 sessions with particularly strong peripartum evidence.
- Combined pharmacotherapy plus psychotherapy outperforms either alone in severe, chronic, or highly recurrent presentations.
- **MBCT** delivered in 8 group sessions reduces relapse for patients carrying three or more prior depressive episodes.

ADJUNCT & SUPPORTIVE

- **ECT** remains most effective for psychotic, catatonic, or acutely suicidal depression, with response near 70 to 80 percent and transient memory effects.
- **rTMS** to the left dorsolateral prefrontal cortex is a reasonable outpatient option after one or more adequate medication trials have failed.
- Track outcome with the **PHQ-9** at every visit; a 50 percent score reduction defines response and a score under 5 defines remission.
- Aerobic exercise three times weekly, sleep regularization, and reduction of alcohol intake produce measurable adjunctive effect sizes.
- Escalate to intensive outpatient, partial hospitalization, or inpatient care based on suicide risk, functional collapse, and capacity for self-care.

CLINICAL PEARLS

- Always screen for past hypomania before starting an antidepressant.
- Hopelessness and insomnia predict suicide better than reported sadness.
- Anhedonia, not sadness, is the symptom patients report most reliably.

References

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NOTE

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