Brigham and Women's Hospital
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Depression Update

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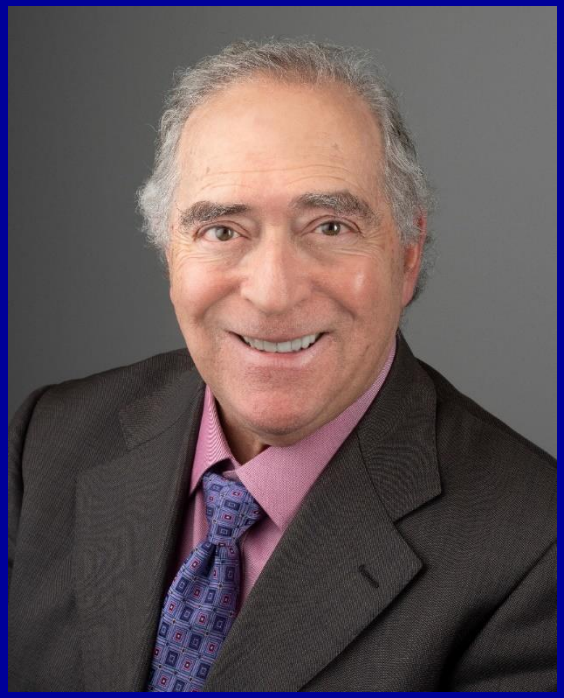

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Disclosures

No Disclosures

Learning Objectives

- Understand the sub-categories of major depressive disorders and their clinical significance
- Review the latest developments in medical treatment of depressive disorders, including the role of rTMS and Ketamine
- Examine approaches to treatment-resistant depression

Prevalence of Mood Disorders

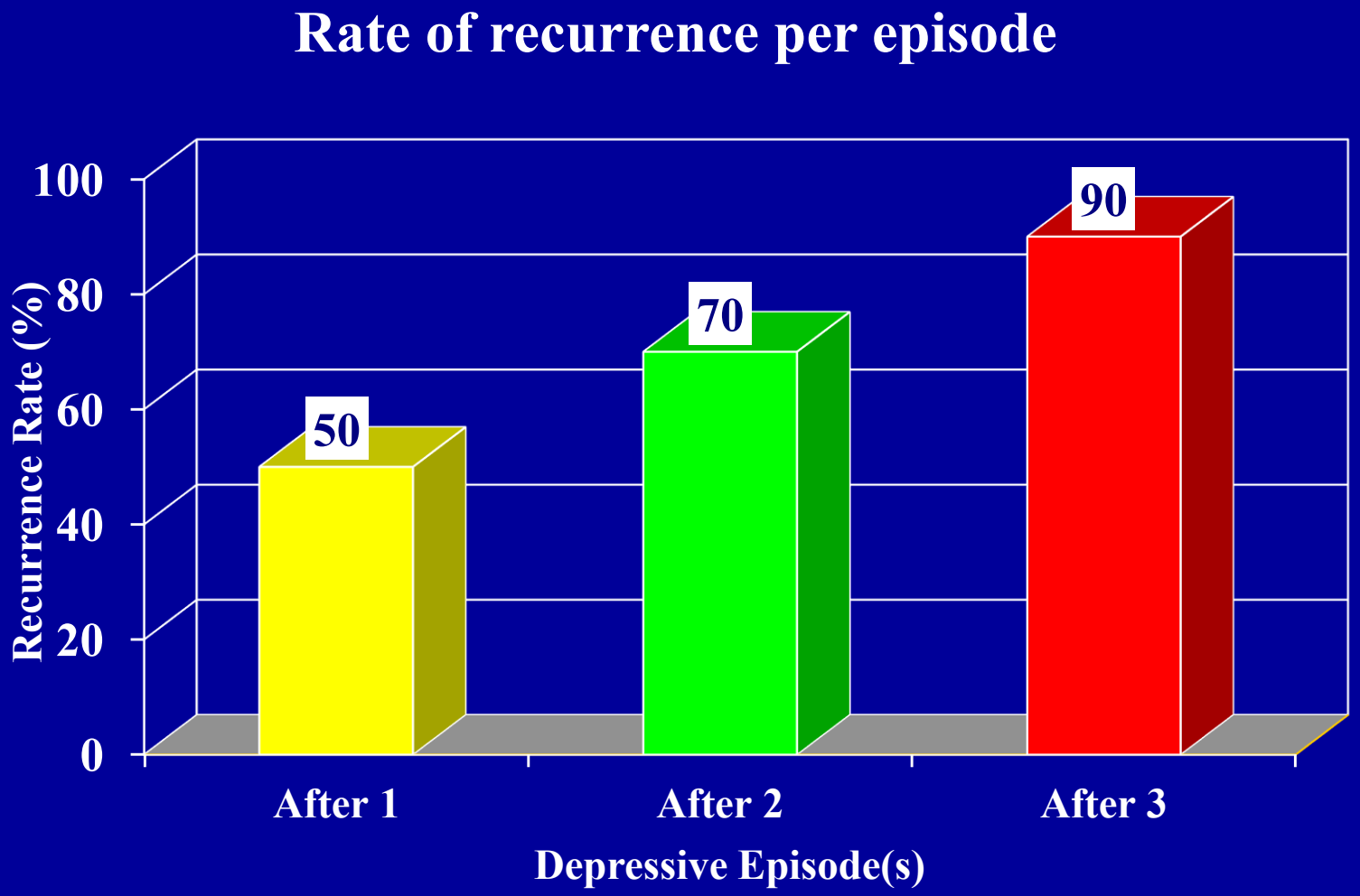
	1 Year (%)	Lifetime (%)
Major Depressive Episode	10.3	17.1
Manic Episode	1.3	1.6
Dysthymia	2.5	6.4
Any Mood Disorder	11.3	19.3

Kessler RC, et al. *Arch Gen Psychiatry*. 1994;51:8.

Subtypes of Depressive Disorders

- Bipolar/Unipolar
  - Rapid Cycling as a sub-variant
- Melancholic/Non-Melancholic
- Psychotic/Non-Psychotic
- Agitated/Retarded
- Responsive/Non-responsive
- Atypical
  - Rejection Sensitive Dysphoria
- Seasonal Affective Disorder

Recurrence is Common



DSM-IV: 1994;341-342.

Detecting Bipolar Disorder

- History of mood elevation
- Family history of bipolar disorder
- Sub-syndromal mood elevation
- Mixed states/racing thoughts
- Antidepressant associated mania
- Response to mood stabilizers
- No biological markers established

Factors Affecting the Choice of Antidepressant

- Side effect profile
- History of previous response
- Family history of response
- Safety in overdose
- Differential effects in subtypes of depression

Selecting Among Antidepressants

- Initial choices – SSRI/SNRI
  - Half-life considerations
  - Activation – sedation
- Secondary options
  - Tricyclic antidepressants
  - Mirtazapine
  - Bupropion
- MAO-inhibitors
  - Phenelzine, Tranylcypromine

Differences between the SSRIs

- Half-life of fluoxetine much greater than paroxetine
- Inhibition of P450 2D6 enzymes much greater with paroxetine and fluoxetine as compared to sertraline or citalopram
- Inhibition of P450 34A
  - Fluvoxamine delays clearance of alprazolam
- Inhibition of P450 1A2, 3A4, 2C9
  - Fluvoxamine delays clearance of warfarin, theophylline,propranolol, clozapine

SSRI Side Effects

- Jitters, fatigue, insomnia, headache
- Sexual dysfunction, erectile dysfunction, anorgasmia
- Weight gain may occur
- Rare risk of GI bleeding possibly due to inhibition of platelet function
- Inappropriate SIADH in the elderly
- Switch to mania, agitation
- Osteoporosis, risk of non-vertebral fracture in elderly (Diem et al, Arch Intern Med, 2007)

Serotonin Syndrome

- GI – cramping, diarrhea, bloating
- Neurological – Tremor, dysarthria
- Cardiovascular –tachycardia, hypertension
- Psychiatric – confusion, mania, restless

- Medications that may contribute:
  - Isoniazid, Linezolid
  - Tramadol, Dextromorphan, St. John's Wort

SSRI Withdrawal

- CNS Symptoms
  - Sleep disturbance, vivid dreams
  - Anxiety, restlessness
  - Headache
- Parasympathetic Symptoms
  - Sweating, sialorrhea
  - Nausea, vomiting, cramps, diarrhea

Citalopram

- Highly selective SSRI; Minimal NE/Dopamine activity
- Dosage range 10 – 40 mg; QT prolongation FDA warning
- Metabolized by liver; No active metabolites
- SSRI side effects generally well tolerated
- Rare side-effects – hyponatremia, SIADH
- No in-patient depression studies conducted

Venlafaxine

- SNRI – serotonin effects at lower dosages;
- Norepinephrine effects at higher dosages
- Dosage range – 75 mg – 300 mg
- Monitor BP at higher dosage range
- FDA approved for generalized anxiety and major depression.
- Probable greater antidepressant efficacy at higher dosage
- Extended release formulation available

Wellbutrin (Bupropion)

- Dopaminergic/Noradrenergic agonist
- Stimulating antidepressant -75 -375 mg qd
  - Sustained and Extended-Release options
- No sexual dysfunction
- Contraindicated in patients with seizures
- Effective in ADHD
- Avoid concurrent use of stimulants
- Insomnia may be a side-effect
- Limited anti-anxiety properties; may cause anxiety

Duloxetine (Cymbalta)

- SNRI Dosage range 20-30 mg bid; 60-90 mg in refractory patients
- Avoid use in patients with renal or hepatic impairment
- May increase anti-arrythmic blood levels
- May be useful in pain syndromes
- Side –effects – dry mouth, nausea, constipation, dizziness, fatigue
- Avoid in pregnancy

Mirtazapine

- Alternative to SSRI/SNRI
- Less sexual dysfunction
- Sedation and weight gain side-effects
- Anti-anxiety properties
- Dosage range 15-60 mg qd
- Excellent for sleepless, underweight patients, including elderly
- NE and 5HT1 agonist

Standard MAOIs are Particularly Effective for:

- Atypical Depression
- Resistant Depression
- Elderly Depressives (maintenance effects)
- Social Phobia
- Neuroticism
- Interpersonal Hypersensitivity
- Phobic Avoidance

Heterogeneity of Treatment Resistant Depression

- Bipolar Depression and Latent Bipolar
- Axis II Co-morbidity
- Substance Abuse
- Anxiety Disorders
- Trauma, Abuse and Psychosocial Crisis
- Occult Medical Disorders
- Undiagnosed Sleep Apnea
- Schizoaffective, Schizophrenia Spectrum

Adapted from Fagiolini and Kupfer, Biol Psychiatry 2003;53:640-648

Treatment of Bipolar Depression

- Lithium 300 – 600 mg/qd
- Lamotrigine (Lamictal) 200-400 mg/qd
- Lurasidone (Latuda) 20-60 mg/qd
- Cariprazine (Vraylar) 1.5 mg/qd
- Lumateperone (Caplyta) 42 mg/qd
- Olanzapine+ Fluoxetine 6 mg/25 mg qd
- Quetiapine (Seroquel) 300 mg/qd
- SSRI or Bupropion in low dose as adjunct

Augmentation Strategies for TRD

- Lithium – best established. Blood levels -0.4-0.6 meq/l effective. Monitor renal/thyroid function
- T3 (liothyronine) – 25-50 mcg.
- SSRI/SNRI + Bupropion (targets fatigue)
- SSRI/SNRI + Mirtazapine (targets insomnia)
- Buspirone (*Buspar)* 15-30 mg qd is effective in anxious depression
- Pramipexole (*Mirapex) 0.25-2.5 mg qd (targets energy/anhedonia)*

Adjunctive Neuroleptics augment Antidepressant Response

- Aripiprazole - 2-15 mg/qd. Efficacy well established.
- Lumateperone - 42 mg /qd. Less metabolic effects.
- Cariprazine - 1.5- 3.0 mg/qd
- Brexpiprazole – 1.0 – 3.0 mg/qd. Less akathisia than Aripriprazole.
- Quetiapine XR – 150-300 mg/qd. Metabolic risk
- Olanzapine/Fluoxetine combination – 12/50 mg is the fixed dosage; dosage flexibility is possible
- Risperidone - 0.5-3 mg/qd. Reduces obsessions/ruminations.

TRD – Neuromodulatory Approaches

- Transcranial Magnetic Stimulation (rTMS)
  - Used to augment antidepressant medication
  - Variable dosage schedules vary intensity of treatments. No cognitive side-effects.
- Intranasal Esketamine (Spravato)
  - Adjunctive treatment with antidepressant medication
  - FDA approved, medically supervised
  - IV ketamine not FDA approved, increased risk for psychosis, dissociation.
- Electroconvulsive Therapy (ECT)
  - Gold Standard for severe, suicidal and/or psychotic depression. Transient cognitive side-effects.

Transcranial Magnetic Stimulation

- TMS is the application of electromagnetic impulses to stimulate cortical neurons. rTMS alters neuronal excitability that last beyond the period of stimulation.

- The magnetic field penetrates only a few centimeters beneath the skull surface, but neuroimaging studies show that rTMS-induced effects propagate to deeper brain regions.

- Initial FDA approval in 2008 for MDD; now approved for adolescence and old age.
- Different techniques include standard, accelerated, and theta burst rTMS.

Transcranial Magnetic Stimulation

- Influences downstream network dynamics via connections of the prefrontal cortex to other brain regions implicated in emotion,motivation and cognition.
- Modulates regional and network connectivity and synaptic properties.
- Left dorsolateral prefrontal cortex is the target for stimulation.
- Innovations in technique include Theta Burst Stimulation and Accelerated rTMS.

- Chen et al. Am J Psychiatry 2025;182: 525-541

Transcranial Magnetic Stimulation

- TMS mostly studied in Treatment Resistant Depression
- Different stimulation protocols encompass brain targets, targeting methods, and stimulation frequencies.
- Accelerated rTMS is a treatment course in which more than one stimulation session is delivered each day, typically for five days.
- Standard rTMS involves one treatment session per day, five days per week for 3 - 6 weeks, 20-40 minutes per session.
- Theta Burst Stimulation involves bursts of high-frequency stimulation (50 Hz); 3-10 minutes per session 4-10 sessions per day, for 5 -10 days.
- Accelerated, Theta Burst and standard rTMS are found to be equally effective in many studies.

Transcranial Magnetic Stimulation for Major Depression

- Left prefrontal rTMS, sham controlled 3 weeks of daily weekday treatment
- 195 antidepressant drug free patients with unipolar, non-psychotic depression
- Moderately treatment resistant
- Primary efficacy analysis, 14.1 % remitters with active rTMS and 5.1 % with sham
- “Statistically significant and clinically meaningful antidepressant effect”
  - George et al. Arch Gen Psych 2010;167:281-288

rTMS and Relapse Prevention

- Review of literature indicates potential benefit of maintenance treatment for relapse prevention
- Repeat course of rTMS also beneficial during relapse.
- Effective in unipolar and bipolar depression
- rTMS maintenance protocol may involve weekly reduction from 4 sessions to 1 session over one month;then alternate weekly treatment.
- Antidepressant treatment as usual
  - Rachid et al. Psychiatry Research 2017
  - Benadhira et al Psychiatry Research 2017

Accelerated iTBS Protocol

- 5 days long
- 10 sessions per day; 50 minutes between each session
- 50 minutes interval shown to be optimal
- 90,000 pulses as this is the pulse dosage for a 6 week course of rTMS. FDA approved 18,000 pulses each day.
- Results equivalent to 6-week course rTMS
- Separation from sham at one week persisting for 5 weeks.
  - Cole et al AJP 2021

Accelerated rTMS

- 51 patients randomized to sham treatment, accelerated and conventional rTMS
- Accelerated 15 sessions/3 days; conventional 15 sessions/ 3 weeks
- Improvement in depressive symptoms at 3 weeks post-treatment for both active treatment groups; no difference in efficacy or side-effects.
    - Kim et al. Clin Psychopharm and neuroscience, 2021;19 (1):73-83

Transcranial Magnetic Stimulation

- Patients completing 20 or more treatments: 65% response rate and 32% remission rate.
- 1/3 of patients experience some symptom relapse within one year after treatment. Response rate is high (86%) after re-introduction of TMS.
- Responders to initial course likely to respond to repeat treatment course.
- Established optimal treatment technique and course for each patient is key.
    - Sackeim et al. J Affect Disord 2020;227:65-74
    - Senova et al. Brain Stimul 2019;12:119-128

Accelerated Theta Burst TMS (iTMS) for TRD

- 100 participants; 45 active or sham treatments with iTMS over 15 weekdays
- 3 iTBS sessions per day, 30 mins apart, targeting LDLPFC
- Primary outcome change in HRDS -17 at week 5
- Mean change in HRSD-17 at endpoint was 5.57 in the sham group and 9.68 in the active group – $P < .001$.
- Antidepressant medication treatment was stable six weeks before and during treatment
    - Ramos et al. JAMA Psychiatry 2025:82(5):442-450

Intranasal Esketamine for TRD

- 28- 84 mg intranasal each nostril with antidepressant medication as usual
- Twice weekly self-administered for first week; once weekly for first month, then q o wk for one month; flexible dosing thereafter
- Treatment through approved centers; REMS monitoring
- Side-effects; Sedation, dissociation, elevated BP, Suicidal ideation, Urinary symptoms; no driving for 24 hours

The Medical Letter April 8,2019

Intranasal Esketamine and newly initiated antidepressant in TRD

- 56 or 84 mg twice weekly intranasal for 4 weeks in combination with new SSRI or SNRI treatment
- MADRS scores demonstrate mildly positive results at 1 days and 28 days
- TRD patients with no psychiatric comorbidities or substance abuse, no acute suicide risk.
  - Popova et al. AJP 2019 176:428-438

Studies of intranasal ketamine in treatment resistant depression

- Review of four phase three studies suggests efficacy of intranasal ketamine infusion with co-administered oral antidepressant. Three times as likely to induce remission than be discontinued due to side-effects.
- Another study of intranasal ketamine in elderly patients with TRD did not establish significant results; but positive trends seen in those 65-74 and with onset depression before 55 years.
  - Citrone et al. Journal Affective Disorders 27 (2020) 228-238. Ochs-Ross Am J Geriatric Pych 28:2 (2020)
  - 121-141

Esketamine and Ketamine for Treatment Resistant Depression

- Rapid-onset within 1-2 days of efficacy in TRD
- Evidence established for intranasal esketamine and intravenous ketamine.
- Intranasal ketamine efficacy, safety and tolerability established for up to 1 year in adults; not clearly established for intravenous ketamine.
- Safety concerns include dissociation, psychotomimetic, neurocognitive, genitourinary and hemodynamic.
- Esketamine approved for MDD with suicidal ideation; not proven to reduce suicide completion.
- REMS monitoring required; medical setting also required.
  - Am J Psychiatry 2021: 178: 383-399

Esketamine adjunctive therapy in MDD

- Esketamine nasal spray superior to placebo in reduction of MADRAS Depression Rating Scale. From baseline to Day 28; P= 0.001. On Day 2 in patients with SI; P=0.0008

- Long-term relapse rate was significantly lower in the esketamine nasal spray group than the placebo/quetiapine group.

- Esketamine in conjunction with antidepressant controls short and long-term depressive symptoms in MDD and TRD
    - Wang et al.Clin Pharm and Therapeutic, 117/6 June 2025

Esketamine Long Term Safety and Efficacy

- Mean Exposure to esketamine was 42.9 months in a total of 1148 patients.
- Intranasal esketamine dosing was flexible and individualized to depression severity during maintenance (weekly, every other week, or every 4 weeks)
- Dizziness,headache,nausea and dissociation ranged from 25 -36 %; 6.4% discontinued due to adverse event.
- 49.6% of patients were in remission at week 112.
    - Zaki et al. Int J Neuropsychopharmacol. 2025 June 6;28 (6)

Esketamine Monotherapy in TRD

- 378 patients,two weeks antidepressant free, randomized 1:1:2 to dosage of 56 mg or 84 mg esketamine or matching placebo.
- At Day 28,for both the 56 mg and 84 mg dosage, administered twice weekly for 4 weeks, the reduction in MADRS score was significant at P=.001.
- At Day 2, 24 hours after the first dosage the reduction in MADRS score was P=.004 for the 56 mg, and P=.006 for the 84 mg group.

- Janik et al. JAMA Psychiatry. 2025;82(9):877-887

Electroconvulsive Therapy

- Key indications – Psychotic Depression, Suicidal Press, Food Refusal, Treatment Refractory Depression, Parkinson's Disease, Refractory Manic Excitement.

- Medical Concerns – 4 deaths/100,000 treatments. Cardiac risks- recent myocardial infarction, unstable angina, hypertension, atrial fibrillation, post-cerebrovascular accident, intracranial aneurysm or space-occupying lesions or other causes of increased intracranial pressure.

- Post ECT maintenance – High rate of relapse particularly with psychotic depression; Post ECT medications - nortriptylene and lithium, MAO-I, Maintenance ECT.

Psilocybin for Depression –Phase III Studies Underway

- A review of 8 studies indicates:
- Psychotherapy is important for optimal result
- Reduction in depressive symptoms occurs within 1 day to 1 week after 1 to 2 doses of Psilocybin
- Moderate to High Dose 10 mg to 30 mg/70 kg were more effective than 1 mg/70 kg dosage.
- Adverse effects mitigated by a controlled supportive environment.
- After each dosage, integration psychotherapy sessions occurred.
- Psilocybin was as effective as escitalopram in one study
  - Dawood Hristova et al Behav Sciences 2023, Vol 13, Issue 4, Article 297.

Summary – Key Points

- Assess the Depressive Spectrum – Appreciate the longitudinal history and co-morbidity
- Watch for latent bipolarity
- Careful follow-up to assess early side-effect experience –particularly in young adults and adolescents
- Watch for latent psychosis in the elderly
- Medical monitoring is important for all treatments

Question 1

- Which of the following is not an appropriate treatment for bipolar depression?

A. Lurasidone
B. Lithium Carbonate
C. Buproprion as a stand alone medication
D. Low dose anti-depressant covered by a mood stabilizer anti-manic medication.
E. Quetiapine in a dosage of 300 mg per day

Answer - Question 1 - C

- Answer C – Antidepressants can trigger mania if prescribed without a concomitant mood stabilizing medication.
- Lurasidone, Lithium and Quetiapine all have antidepressant properties in bipolar depression.
- It is reasonable to consider low dose antidepressants with mood stabilizer coverage in bipolar depression.

Question 2

- What is the most rapid and effective treatment for psychotic depression with command hallucinations in the elderly?
- A. Antidepressant medication
- B. Antipsychotic medication
- C. Electroconvulsive therapy
- D. Antidepressant combined with antipsychotic medication

Answer – Question 2 - C

- ECT is the most rapid and effective treatment for psychotic depression.
- Combination of antidepressant and antipsychotic medication may be effective in treating psychotic depression but may take days to weeks to be effective.
- Antipsychotic medication or antidepressant medication alone is not consistently effective in treating psychotic depression.

Question 3

- Which of the following parameters must be monitored during esketamine treatment?
- A – Blood pressure increases
- B – Dizziness
- C - Dissociation
- D - Nausea
- E - All of the above.

Answer Question 3

- All of the Above
- Patients must be monitored under direct supervision for two hours.
- Elevations in blood pressure may occur
- Patients should not eat or drink liquids for two hours prior to treatment due to nausea and vomiting risk.
- Intranasal corticosteroids and decongestants should not be used within one hour of treatment.
- No driving or hazardous activity until the day following treatment.

References

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