

# Depression Update

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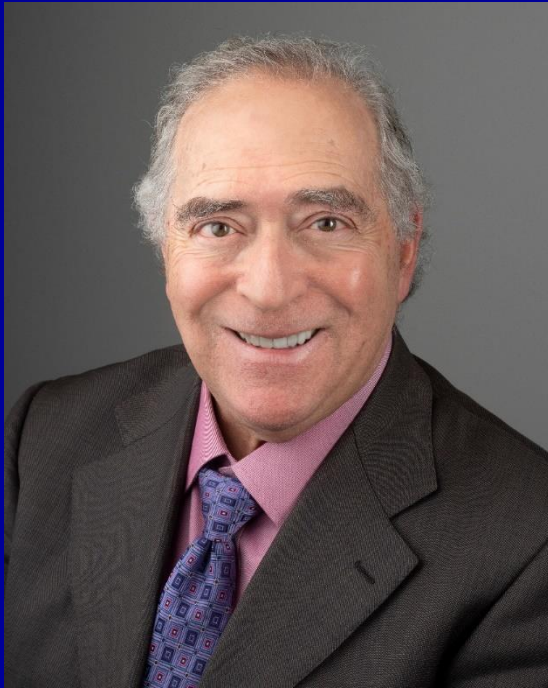
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# Disclosures

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

# Prevalence of Mood Disorders

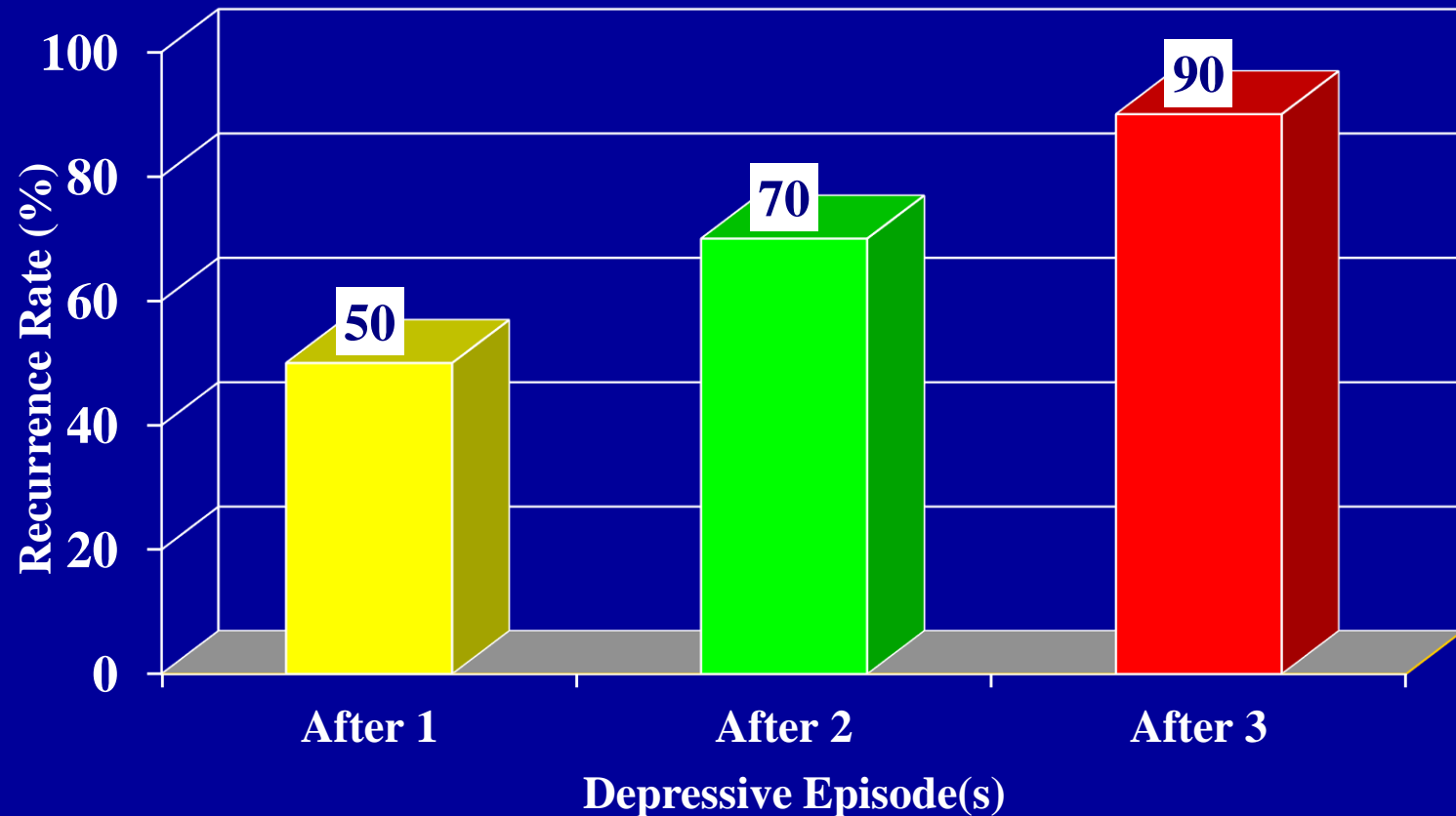
	1 Year (%)	Lifetime (%)
Major Depressive Episode	10.3	17.1
Manic Episode	1.3	1.6
Dysthymia	2.5	6.4
Any Mood Disorder	11.3	19.3

# 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

Rate of recurrence per episode



# 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

# 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 (Dien 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-arrhythmic 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 5HT<sub>1</sub> agonist

# Dextromethorphan/Bupropion for Depression

- Dextromethorphan 45 mg/ Bupropion 105 mg
- Dextromethorphan is an NMDA receptor antagonist and sigma-1 receptor agonist; it also inhibits serotonin and norepinephrine reuptake.
- Bupropion increases serum concentration of dextromethorphan by inhibiting CYP2D6
- Bupropion inhibits norepinephrine and dopamine reuptake
- Intranasal esketamine is also an NMDA receptor antagonist
- Esketamine and the S-enantiomer of the IV anesthetic Ketamine are also NMDA receptor antagonists

# Dextromethorphan/Bupropion for Depression

- Double blind phase 3 study, 80 patients with MDD randomized to 6 weeks of treatment with dextromethorphan 45 mg/bupropion 105 mg once daily, and then twice daily beginning day 3 compared to bupropion alone
- Mean change in MADRS depression rating scale over 1 to 6 weeks was significantly greater with the combination as compared to bupropion alone.
- The difference was observed at week 1 and statistically significant by week 2
- The remission rate at week 6 was significantly higher with the combination (46.5 % versus 16.2%)

# **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

# Augmentation Medication Strategies for TRD

- Lithium – best established (7/9 controlled studies)  
Lower blood levels -0.4-0.6 meq/l effective
- T3 – 25-50 mcg. Efficacy established with TCAs
- Novel neuroleptics – Aripiprazole (Abilify), 5-10 mg (FDA approved)
- Olanzapine-Fluoxetine combination in bipolar depression

# Cariprazine (Vraylar)

- Approved for treatment of manic or mixed episodes and schizophrenia
- New indication for Bipolar Depression
- 1.5 and 3 mg. dosage showed improvement in bipolar depression over six weeks compared to placebo
- Discontinuation in 6.7% v. 4.8 in placebo – nausea, akathisia, restlessness.
- Partial Agonist dopamine and serotonergic mediated effects.
  - Earley AJP 2019 176:439-448 June 2019



# Lumateperone (Caplyta)

- Second generation antipsychotic approved in 2021 for Bipolar I and Bipolar II depression. Six week placebo controlled trial showed improvement in MADRS as early as one week.
- Dosage 42 mg per day with food.
- In patients with hepatic disease, the dosage is 21 mg per day.
- Valproic acid increases blood levels of lumateperone.
- Common side-effects include sedation/somnolence and dry mouth. Weight gain and EPS not common.

# Electroconvulsive Therapy

- After full course of 8-12 treatments, three times per week, treatment is not stopped abruptly ( relapse rate 84% if no medication).
- Nortriptylene and lithium best studied post-ECT meds, significantly reduce relapse rate
- Maintenance ECT commonly employed in tapering manner with medications to support remission. F/U ECT treatments weekly for 1-2 months may be considered.
  - Espinoza and Keller NEJM 2022;386:667-72

# 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 from 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

# Stanford Neuromodulation Therapy

- Ten sessions of active or sham iTBS delivered daily, 18,000 pulses per day on 5 consecutive days
- Stimulation at 90% of resting motor threshold, adjusted for depth of the individual fMRI target
- Depth- corrected intensities were used since the strength of the induced electrical field decreases with increasing distance from the rTMS coil

# Stanford Neuromodulation Therapy

- Resting state fMRI used to individually target the left anterolateral prefrontal cortex most functionally anticorrelated with the subgenual anterior cingulate cortex .
- The primary outcome was score on the MADRS depression rating scale.
- 29 patients with treatment resistant depression: active treatment (N=14); sham treatment (N=15)
- Mean percent reduction in MADRAS score from baseline 4 weeks after treatment was 52.5% in the active treatment group and 11.1% in the sham treatment group.

# Ketamine -Consensus Statement -2021

- Rapid-onset action 1-2 days for intranasal and IV infusion in TRD
- Efficacy in TRD best established for intranasal and intravenous ketamine; insufficient evidence for oral, subcutaneous or intramuscular ketamine
- Intranasal ketamine safety, efficacy, and tolerability for up to one year
- Evidence for long-term efficacy safety and tolerability of intravenous ketamine in TRD is insufficient

# Ketamine Consensus Statement 2021

- Safety concerns with respect to ketamine and esketamine include psychiatric (dissociation, psychotomimetic), neurocognitive, genitourinary, and hemodynamic
- Esketamine is FDA approved for major depressive disorder with suicidal ideation or behavior but not proven to reduce completed suicide
- Esketamine and ketamine should be administered in settings with multidisciplinary personnel including those with expertise in assessment of mood disorders.
  - McIntyre et al Am J Psychiatry 2021; 178:383-399



# Intranasal Esketamine for TRD

- 28 mg intranasal each nostril for total of 56 mg.
- Twice weekly self-administered for first month; then once weekly for four weeks, then flexible dosing thereafter q 1-2 weeks
- Treatment through approved centers;REMS monitoring
- Side-effects; Sedation, dissociation, elevated BP, Suicidal ideation, Urinary symptoms; no driving for 24 hours

## 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
- 56 mg is the dosage for TRD; 84 mg is the dosage for MDD and suicidal ideation
- MADRS scores demonstrate mildly positive results at 1 day and 28 days
- TRD patients with no psychiatric comorbidities or substance abuse, no acute suicide risk were in the initially studied TRD protocol.
  - Popova et al. AJP 2019 176:428-438

The New York Times

# ***A Fraught New Frontier in Telehealth: Ketamine***

With loosened rules around remote prescriptions, a psychedelic-like drug has become a popular treatment for mental health conditions. But a boom in at-home use has outpaced evidence of safety.

# Summary – Key Points

- Assess the Depressive Spectrum – Appreciate the longitudinal history and comorbidity
- 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
- Ketamine should be administered in well-equipped hospital settings.

## Question 1

- Which of the following is not an appropriate treatment for bipolar depression?
  - A. Lurasidone
  - B. Lithium Carbonate
  - C. Bupropion 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.



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