Don't Be Blue: Depression Management & Treatment Modalities

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Goals and Objectives Part 1

- Analyze the STAR*D trial's impact on modern Major Depressive Disorder (MDD) and Treatment-Resistant Depression (TRD) treatment approaches
- Evaluate the effectiveness of current augmentation strategies for MDD and TRD
- Discuss emerging therapies and their potential role in treating MDD and TRD

Goals and Objectives Part 2

- Describe novel antidepressant agents: dextromethorphan/bupropion and esketamine
- Discuss the primary literature which led to the FDA approval of dextromethorphan/bupropion and esketamine
- Discuss dextromethorphan/bupropion and esketamine role in therapy for Major Depressive Disorder (MDD)

Abbreviations

- BPRS: Brief Psychiatric Rating Scale
- CADSS: Clinician-Administered Dissociative States Scale
- CGI-I: Clinical Global Impressions Improvement Scale
- CGI-S: Clinical Global Impressions Severity Scale
- C-SSRS: Columbia-Suicide Severity Rating Scale
- CYP: cytochrome P450
- DEA: Drug Enforcement Agency
- DSM-V: Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
- ECG: electrocardiogram
- eGFR: estimated glomerular filtration rate
- FDA: Food & Drug Administration
- GRID-HAMD: Grid Hamilton Rating Scale for Depression
- IDS-C: Inventory of Depressive Symptomatology-Clinician Rating
- MADRS: Montgomery-Åsberg Depression Rating Scale
- MAOI: monoamine oxidase inhibitor
- MDD: major depressive disorder
- MGH: Massachusetts General Hospital
- MOA: mechanism of action
- OCD: obsessive compulsive disorder
- NMDA: N-methyl-D-aspartate
- PO: by mouth
- REMS: Risk Evaluation and Mitigation Strategy
- SJS: Stevens-Johnson Syndrome
- SI: suicidal ideation
- SNRI: serotonin-norepinephrine reuptake inhibitors
- SR: sustained release
- SSRI: selective serotonin reuptake inhibitors
- TEN: toxic epidermal necrolysis
- TRD: treatment-resistant depression

Background

- Major Depressive Disorder (MDD)
  - Diagnosed in patients with a history of at least one major depressive episode and no history of mania or hypomania
- Major depressive episode:
  - Lasts at at least two consecutive weeks
  - Involves 5 or more of the following symptoms:
    - Depressed mood
    - Anhedonia
    - Insomnia or hypersomnia
    - Change in appetite or weight
    - Psychomotor retardation
    - Low energy or fatigue
    - Poor concentration or indecisiveness
    - Thoughts of of worthlessness or guilt
    - Recurrent thoughts about death or suicide

American Psychiatric Association, 2022.

Background

- Treatment Resistant Depression (TRD):
  - A major depressive disorder in which an individual does not respond adequately to at least two antidepressants
- Depression is the number one cause of disability
- The all-cause mortality for those with depression is 1.7 times greater than for the general public
- Approximately 10% of the US adult population has been diagnosed with MDD

American Psychiatric Association, 2022.
Depression fact sheet. World Health Organization. December 2019

Scoring Systems

- Hamilton Rating Scale for Depression (HAMD)
  - Most widely used clinician administered depression assessment scale
  - 17 items, the higher the number the more severe
    - Score 0-7 considered normal
    - Score of 20 or greater is usually required for entry into a clinical trial
  - Limitation of the scale: atypical symptoms of depression (e.g., hypersomnia, hyperphagia) are not assessed
  - Primarily developed for inpatient
- Montgomery-Asburg Depression Rating Scale (MADR)
  - 10 items; each item scored on a scale of 0-6
  - Higher scores indicate more severe depression

Montgomery, S.A. et al. British Journal of Psychiatry. 1979; 134, 382-389
Hamilton M. A rating scale for depression. J Neurol Neurosurg Psychiatry 1960; 23:56–62

STAR*D Trial: Sequenced Treatment Alternatives to Relieve Depression

- Study design
  - Largest, prospective clinical trial of major depressive disorder ever conducted
  - Multicenter, nationwide association of 14 university based regional centers
- Methods
  - All enrolled patients began on a single SSRI: citalopram
  - Followed an algorithm guided acute phase treatment through 5 visits over 12 weeks
  - Algorithm recommended to increase dose if patient that was tolerating oral medication had not achieved remission at any of the critical decision points (weeks 4, 6, 9)
  - Follow-up: 12 months

Rush AJ, et al. *Am J Psychiatry*. 2006;163(11):1905-1917

STAR*D Trial

- Population
  - Inclusion Criteria:
    - Patients with nonpsychotic major depressive disorder identified by clinicians and confirmed based on DSM-IV-TR checklist for which antidepressant treatment is recommended
    - Age 18-75 with a score of ≥14 on the Hamilton Rating Scale for Depression
  - Exclusion:
    - Primary diagnosis of bipolar disorder, obsessive compulsive disorder, eating disorder, history of seizure disorder
  - Total: 4,041 patients
- Setting
  - Both primary and specialty care sites

Rush AJ, et al. *Am J Psychiatry*. 2006;163(11):1905-1917

STAR*D Trial

- Primary outcome: standard definition of remission as measured by the Hamilton Depression Rating Scale (HAM-D)
  - 17 item scale, total score 0-52
- In addition, the 16-item Quick Inventor of Depressive Symptomatology Self-Report (QIDS-SR) was administered at each visit
  - Remission measured as a score ≤ equal to 5
  - QIDS-SR provided more frequent assessment points during the acute phase- may be better reflection of actual remission

Rush AJ, et al. *Am J Psychiatry.* 2006;163(11):1905-1917

STAR*D Trial

- Intervention:
  - Systematic approach to treatment; participants progressed through four different levels
  - Patients with a clinically meaningful response in any of the four levels could enter a 12-month follow-up phase
- Level 1: flexible dose citalopram
  - Average dose: 40mg per day
  - Time to remission: 47 days
- Level 2: 3 augmentation strategies and 4 switch strategies
  - Augmentation:
    - Citalopram + bupropion
    - Citalopram + buspirone
    - Citalopram + CBT

Rush AJ, et al. *Am J Psychiatry.* 2006;163(11):1905-1917

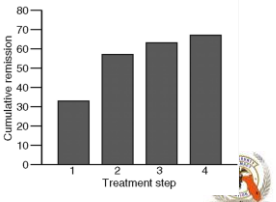
STAR*D Trial

  - Switch strategies:
    - Bupropion
    - Sertraline
    - Venlafaxine
    - Cognitive behavioral therapy (CBT)
- Level 3: 2 augmentation strategies and 2 switch strategies
  - Augmentation:
    - Lithium
    - Thyroid hormone
  - Switch strategies:
    - Nortriptyline
    - Mirtazapine
- Level 4: randomized to treatment with either tranylcypromine or combination venlafaxine XR and mirtazapine

Rush AJ, et al. *Am J Psychiatry.* 2006;163(11):1905-1917

STAR*D Trial Outcomes

- Primary Outcome: Depression remission by QIDS-sR16 Score
  - Step 1: 36.8% (higher remission rate than those in step 2; P<0.001)
  - Step 2: 30.6% (higher remission rate than those in step 3; P<0.001)
  - Step 3: 13.7%
  - Step 4: 13%
- Secondary Outcomes: response measured by clinician and patient self report
  - Step 1: 48.6%
  - Step 2: 28.5%
  - Step 3: 16.8%
  - Step 4: 16.3%



Rush AJ, et al. *Am J Psychiatry*. 2006;163(11):1905-1917

STAR*D Pitfalls

- In 2015, authors of a British Medical Journal article identified protocol violations in the STARD data, specifically the percentage of remission from depression at each of the four stages
  - Reanalyzed STARD raw data according to pre-specified protocol published before the start of the study
  - Previously reported cumulative remission rate: 67%
  - Actual cumulative remission rate: 35%

Pigott HE, et al. *BMJ Open*. 2023;13(7):e063095. Published 2023 Jul 25.

STAR*D Pitfalls

- STAR*D outcomes: remission rates decreased progressively with each step
- Highlights the limitations of conventional antidepressant monotherapy or basic augmentation approaches
- TRD patients often have greater symptom severity, comorbidities, and functional impairments
  - Underscores unmet needs
- There is a growing body of evidence supporting diverse augmentation strategies, such as antipsychotics and psychedelics
  - STAR*D does not specifically evaluate atypical antipsychotic augmentation strategies

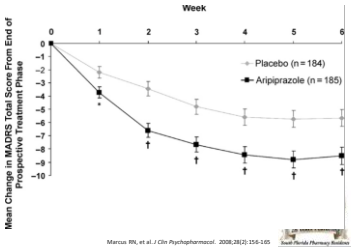
Aripiprazole Adjunctive Therapy

- Aripiprazole
  - Atypical antipsychotic
  - Mechanism of action: agonist at dopamine D2 and D3 and serotonin 5-HT(1A) receptors; antagonist at 5-HT(2A) receptors
  - Initially FDA approved for schizophrenia and bipolar mania; now approved as adjunctive therapy for MDD
- Marcus and colleagues: "The efficacy and safety of aripiprazole as adjunctive therapy in major depressive disorder"
  - Study Design
    - Randomized, double-blind, placebo-controlled study
  - Baseline characteristics
    - Patients: Adults with MDD who had an inadequate response to 1–3 antidepressant trials
      - Mean age: 40
      - Mostly female
    - Medications: SSRIs or SNRIs at stable doses
    - Duration: 6 weeks

Pae CU, et al. *CNS Drugs*. 2011;25(2):109-127
Marcus RN, et al. *J Clin Psychopharmacol*. 2008;28(2):156-165

Aripiprazole Adjunctive Therapy

- Intervention
  - Aripiprazole (2–15 mg/day) as adjunct to antidepressants vs. placebo
- Outcomes
  - Primary: Higher remission rates with aripiprazole (33%) vs. placebo (15%)
  - Secondary: Faster improvement in depressive symptoms
  - Adverse Effects: Akathisia, restlessness



Marcus RN, et al. *J Clin Psychopharmacol*. 2008;28(2):156-165

VAST-D Trial

- Study Design
  - Multicenter, single blind, randomized control trial
- Objective: compare efficacy and adverse effects of 3 alternative MDD treatment strategies
- Participants: 1,522 patients with non-remitted MDD after at least 6 weeks of treatment with an SSRI
- Interventions:
  - Switch group:
    - Discontinuation of SSRI and initiation bupropion sustained release
  - Augmentation group:
    - Aripiprazole
    - Bupropion
- Titration of doses:
  - Bupropion: 150 mg sustained release to 300 mg or 400 mg daily
  - Aripiprazole: 2 mg with titration to 5, 10, or 15 mg daily
  - Until depressive symptoms remitted or adverse effects were intolerable

Mohamed S, et al. *JAMA*. 2017;318(2):132–145

VAST-D Trial

- Primary outcome:
  - Remission defined as defined as a QIDS-C_{16} score of 5 or less at 2 consecutive scheduled follow-up visits during the acute treatment phase
    - range 0-27 with higher scores indicating more severe symptoms
- Secondary outcomes: time to remission, response rates, adverse effects and tolerability
- Results:
  - Remission rates were significantly higher in the aripiprazole augmentation group (28.9%) compared to the switch group (22.3%; RR, 1.30 [95% CI, 1.05-1.60]; *P* = .02)
  - Remission rates were not significantly higher in the aripiprazole augmentation group (28.9%) compared to the bupropion augmentation group (26.9%; RR, 1.08 [95% CI, 0.88-1.31]; *P* = .47)
  - Aripiprazole had a faster time to remission compared to other strategies
  - Adverse effects were more common in the aripiprazole group (akathisia, weight gain)

Mohamed S, et al. *JAMA*. 2017;318(2):132–145

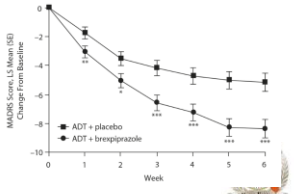
Brexpiprazole Adjunctive Therapy

- Study design:
  - Multicenter, phase 3, randomized, double-blind, placebo-controlled
  - Participants: Adults with a diagnosis of MDD and inadequate response to 1-3 adequate antidepressant trials
    - 379 patients randomized
- Intervention
  - Adjunctive brexpiprazole (N=175): 2 mg/day
  - Adjunctive placebo (N=178)
  - Both groups continued treatment with their antidepressant
  - 8-week antidepressant lead-in followed by 6-week treatment phase

Thase ME, et al. *J Clin Psychiatry*. 2015;76(9):1224–1231

Brexpiprazole Adjunctive Therapy

- Primary outcome: change in MADRS total score from baseline to week 6
- Secondary outcome: response rate defined by ≥ 50% MADRS reduction, remission rate define by MADRS score of ≤ 10, and safety events
- Results:
  - Primary outcome:
    - Brexpiprazole: 8.36 points
    - Placebo: 5.15 points:
    - Mean difference: -3.21 points; p < 0.001



Thase ME, et al. *J Clin Psychiatry*. 2015;76(9):1224–1231

Brexpiprazole Adjunctive Therapy

- Secondary outcomes:
  - Response rate: 26.2% brexpiprazole vs. 15.3% placebo (p = 0.002)
  - Remission rates: 15.4% brexpiprazole vs. 7.4% placebo (p = 0.012)
- Safety outcomes:
  - Common AE: akathisia (7.2% in brexpiprazole vs 0.5% in placebo), headache, weight gain

Thase ME, et al. *J Clin Psychiatry.* 2015;76(9):1224–1231

Quetiapine XR Adjunctive Therapy

- Study Design: multicenter, double-blind, randomized, parallel-group, placebo-controlled Phase II study
  - Duration: 6 weeks
  - Participants: adults with MDD and inadequate response to antidepressant therapy for ≥ 6 weeks
- Intervention: Quetiapine XR (150mg/day or 300mg/day) vs. placebo
  - Ongoing antidepressant treatment was maintained at the same dose
- Primary outcome: change in MADRS score from baseline at week 6
- Secondary outcome:
  - Response rate defined as ≥ 50% reduction in MADRS score
  - Remission rates defined as MADRS score ≤ 8 at week 6

El-Khalili N, et al. *International Journal of Neuropsychopharmacology*, Volume 13, Issue 7, August 2010, Pages 917–932

Quetiapine XR Adjunctive Therapy

- Results:
  - Primary outcome:
    - Mean change in MADRS total score from randomization at week 6 (primary endpoint) was significantly greater with quetiapine XR 300 mg/d than with placebo (−14.70 *vs.* −11.70, $p < 0.01$)
    - Mean total score was also reduced with quetiapine XR 150 mg/day at week 6, but the difference was not statistically significant
  - Secondary outcomes:
    - Response rates
      - Quetiapine XR 150 mg/day: 51.7% (p = 0.329)
      - Quetiapine XR 300 mg/day: 58.9% (p < 0.05)
      - Placebo: 46.2%
    - Remission rates
      - Quetiapine XR 150 mg/day: 35% (p = 0.059)
      - Quetiapine XR 300 mg/day: 42.5% (p < 0.01)
      - Placebo: 24.5%

El-Khalili N, et al. *International Journal of Neuropsychopharmacology*, Volume 13, Issue 7, August 2010, Pages 917–932

Quetiapine XR Adjunctive Therapy

- In the intervention groups, the most common adverse events leading to discontinuation were sedation and somnolence
- Other adverse events:
  - EPS
  - Sexual dysfunction
  - QTC prolongation (1 patient)
  - Suicidality (1 patient)

El-Khalili N, et al. *International Journal of Neuropsychopharmacology*, Volume 13, Issue 7, August 2010, Pages 917–932

Ketamine for TRD

- Originally developed as an anesthetic
- Blocks N-methyl-D-aspartate (NMDA) receptors, a subtype of glutamate receptor in the brain
- In 2000, Berman et al. demonstrated the rapid antidepressant effects of ketamine in a small randomized trial, showing improvement within hours to days after a single infusion
- Subsequent studies have confirmed ketamine's efficacy in TRD

Zarate CA et al., *Nat Rev Drug Discov.* 2007;6(5):426-437
Berman RM, et al. *Biol Psychiatry.* 2000;47(4):351-354

Intravenous Ketamine in Patients With Treatment Resistant Depression

- Study design:
  - Multicenter, randomized, double-blind, placebo-controlled
  - Participants: adults with diagnosed MDD and inadequate response to at least two antidepressants
- Intervention groups:
  - Ketamine 0.5 mg/kg administered twice weekly for 4 weeks
  - Ketamine 0.5 mg/kg administered three times weekly for 4 weeks
  - Placebo administered twice weekly for 4 weeks
  - Administered over 40 minutes

Singh JB, et al. *Am J Psychiatry.* 2016;173(8):816-826.

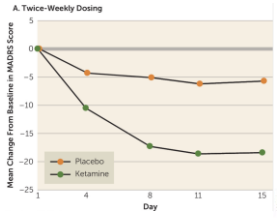
Intravenous Ketamine in Patients With Treatment Resistant Depression

- Primary outcome: change in MADRS score from baseline to day 15
- Secondary outcomes:
  - Response rates defined by ≥ 50 reduction in MADRS
  - Remission rates defined by MADRS score ≤ 10
  - Safety events

Singh JB, et al. *Am J Psychiatry*. 2016;173(8):816-826.

Intravenous Ketamine in Patients With Treatment Resistant Depression

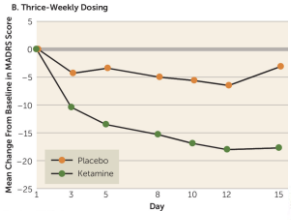
- Primary outcome results:
  - Twice weekly ketamine: mean change in MADRS score at day 15 was −18.4 (SD=12.0)
  - Twice weekly placebo: −5.7 (SD=10.2)



Singh JB, et al. *Am J Psychiatry*. 2016;173(8):816-826.

Intravenous Ketamine in Patients With Treatment Resistant Depression

- Results:
  - Three times weekly ketamine: −17.7 (SD=7.3)
  - Three times weekly placebo: −3.1 (SD=5.7)



Singh JB, et al. *Am J Psychiatry*. 2016;173(8):816-826.

Intravenous Ketamine in Patients With Treatment Resistant Depression

- Secondary outcome results:
  - Response rates at day 15:
    - Twice weekly dosing: ketamine vs. placebo (68.8% vs. 15.4%; p = 0.005)
    - Three times weekly dosing: ketamine vs. placebo (53.8% vs. 6.3%; p = 0.004)
  - Remission rates at day 15:
    - Twice weekly dosing: ketamine vs. placebo (37.5% vs. 7.7%; p = 0.05)
    - Three times weekly dosing: ketamine vs. placebo (76.9% vs. 16%; p = 0.08)
- Safety assessment:
  - Adverse events were higher in both ketamine groups compared with placebo
  - Most common (≥ 20%):
    - Headache
    - Anxiety
    - Dissociation
    - Nausea
    - Dizziness

Singh JB, et al. *Am J Psychiatry*. 2016;173(8):816-826.

Psilocybin: FDA Breakthrough Therapy Approval

- Psilocybin is a tryptamine alkaloid found in some mushrooms, particularly of the *Psilocybe* genus
- Psilocin in the pharmacologically active metabolite of psilocybin
- Psychoactive effects are due to its partial agonist activity at the 5HT2A receptor
  - Additionally binds to 5HT2B, 5HT1D, dopamine D1, 5HT1E, 5HT1A, 5HT5A, 5HT7, 5HT6, D3, 5HT2C, and 5HT1B
- Lower addiction liability and toxic effects compared to ketamine
- Generally not associated with long-term perceptual, cognitive or neurologic dysfunction
- Received FDA breakthrough therapy approval for MDD in 2018

Dodd S, et al. *CNS Spectrums*. 2023;28(4):416-426
Davis AK, et al. *JAMA Psychiatry*. 2021;78(5):481-489
Ray, TS. *PLoS One*. 2010;5(2):e9019

Effects of Psilocybin-Assisted Therapy on Major Depressive Disorder

- Study Design:
  - Single center, randomized, waiting list controlled clinical trial
  - Participants: Adults aged 21 to 75 years with an MDD diagnosis, not currently using antidepressant medications, and without histories of psychotic disorder, serious suicide attempt, or hospitalization
    - 24 patients, mean age of 39.8, mostly female
    - Mean baseline GRID-HAMD: 22.8
- Intervention:
  - Two psilocybin sessions in the context of supportive psychotherapy (approximately 11 hours)
    - Session 1: 20 mg/70 kg
    - Session 2: 30 mg/70 kg
  - Placebo: wait-list group differed for 8 weeks

Davis AK, *et al. JAMA Psychiatry*. 2021;78(5):481-489

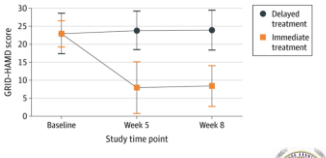
Effects of Psilocybin-Assisted Therapy on Major Depressive Disorder

- Primary outcome: depression severity measured by GRID-HAMD score at 4 weeks post-treatment
- Secondary outcomes:
  - Symptom severity measured by QIDS-SR
  - Response rates defined as ≥50% reduction in GRID-HAMD score
  - Remission rates defined as ≤7 GRID-HAMD score

Davis AK, *et al. JAMA Psychiatry.* 2021;78(5):481-489

Effects of Psilocybin-Assisted Therapy on Major Depressive Disorder

- Results:
  - Primary outcome:
    - Immediate Treatment Group (Weeks 1 and 4)
      - Week 1: 8.0 (SD 7.1)
      - Week 4: 8.5 (SD 5.7)
    - Effect sizes for GRID-HAMD
      - Week 5: Cohen's d = 2.5 (95% CI: 1.4-3.5; P < .001)
      - Week 8: Cohen's d = 2.6 (95% CI: 1.5-3.7; P < .001)
  - Statistically significant reductions compared to delayed treatment group



Davis AK, *et al. JAMA Psychiatry.* 2021;78(5):481-489

Effects of Psilocybin-Assisted Therapy on Major Depressive Disorder

- Secondary outcomes:
  - QIDS-SR depression scores:
    - Baseline vs Day 1 after Session 1:
      - Baseline: 16.7 (SD 3.5)
      - Day 1: 6.3 (SD 4.4)
      - Effect Size: Cohen's d = 2.6 (95% CI: 1.8-3.5; P < .001)
    - Baseline vs Week 4:
      - Week 4: 6.0 (SD 5.7)
      - Effect Size: Cohen's d = 2.3 (95% CI: 1.5-3.0; P < .001)
  - Clinically significant response rates
    - Week 1:
      - 17 participants (71%) achieved ≥50% reduction in GRID-HAMD score.
      - 14 participants (58%) achieved remission (≤7 GRID-HAMD score)
    - Week 4:
      - 17 participants (71%) achieved ≥50% reduction in GRID-HAMD score
      - 13 participants (54%) achieved remission (≤7 GRID-HAMD score)

Davis AK, *et al. JAMA Psychiatry.* 2021;78(5):481-489

"Pharmacological and Pharmacokinetic Profile of CYB003"

- CYB003: deutorated psilocybin
- Safety pharmacology and toxicology studies demonstrated that CYB003 is well-tolerated in the rat (50-200mg/kg)
- Pharmacological profiles of CYB003 and psilocin were compared using serotonin (5-HT) receptor binding and functional assays to evaluate potency, efficacy, and selectivity at serotonin receptors; both compounds were also screened for activity at a panel of over 100 proteins
- Selectivity profile of CYB003 was comparable to that with psilocin
  - (5-HT2A Ki: CYB003 37 nM; psilocin 31 nM)

Palfreyman M, et al. In Vitro and In Vivo Profile of CYB003. Cybin Inc.

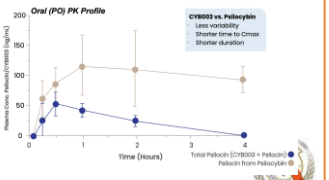
"Pharmacological and Pharmacokinetic Profile of CYB003"

- CYB003 produced a dose-dependent increase in both blood pressure and heart rate
  - Appears to be dose dependent; no effect on QTC interval
- CYB003 induces head twitch responses and hyperactivity in mice similar to psilocin
  - Indicative of in-vivo 5HT2A receptor engagement

Palfreyman M, et al. In Vitro and In Vivo Profile of CYB003. Cybin Inc.

"Pharmacological and Pharmacokinetic Profile of CYB003"

- Pharmacokinetic profile of CYB003 following either intravenous or oral administration is similar to psilocin
- CYB003 exhibits less plasma level variability, shorter time to peak (Cmax), and a shorter duration



Palfreyman M, et al. In Vitro and In Vivo Profile of CYB003. Cybin Inc.

CE Question

- In the study by Khalili and colleagues, what was the most common side effect that lead patients to discontinue Quetiapine XR?

A. EPS
B. Agitation
C. Somnolence
D. Headache
E. None of the above

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CE Question

- What is the most common depression severity scoring tool, that is also used in the STAR*D Trial?

A. Quick Inventor of Depressive Symptomatology Self-Report (QIDS-SR)
B. Montgomery-Asburg Depression Rating Scale (MADR)
C. Hamilton Depression Rating Scale (HAM-D)
D. None of the above

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C. Hamilton Depression Rating Scale (HAM-D)
D. None of the above

Summary

- MDD and TRD affects ~ 10% of adults
- The STAR*D trial highlights the unmet needs for patients with TRD
- Antipsychotics like aripiprazole, brexiprazole, and quetiapine are effective augmentation strategies in patients that have failed an adequate course of antidepressants
- Additionally, emerging therapies like ketamine and psilocybin show promising results for

Dextromethorphan/Bupropion

- Indication: treatment of major depressive disorder (MDD) in adults.
- Mechanism of action (MOA):
  - Dextromethorphan: non-competitive antagonist of the N-methyl D-aspartate (NMDA) receptor (an ionotropic glutamate receptor) and a sigma-1 receptor agonist.
    - Mechanism in the treatment of MDD is unclear
  - Bupropion: unclear in treatment of MDD; Relatively weak inhibitor of neuronal reuptake of norepinephrine and dopamine.
    - Competitively inhibits CYP2D6 which increases plasma levels of dextromethorphan

Auvelity [package insert]. New York, NY: Axsome Therapeutics, Inc; December 2022
Stahl SM. *CNS Spectr.* 2019;24(5):461-466

Dextromethorphan/Bupropion

- Dosing:
  - Initial: 45 mg dextromethorphan/105 mg bupropion 1 tablet by mouth daily in the morning.
    - After 3 days: Increase frequency to twice daily (given at least 8 hours a part).
  - Renal impairment (eGFR 30 – 59 mL/minute/1.73 m^2), concomitant use with strong CYP2D6 inhibitors, known CYP2D6 poor metabolizers: 1 tablet by mouth daily in the morning.

Auvelity [package insert]. New York, NY: Axsome Therapeutics, Inc; December 2022

Dextromethorphan/Bupropion

- Contraindications:
  - Patients with seizure disorders
  - Current or prior diagnosis of bulimia or anorexia nervosa
  - Undergoing abrupt discontinuation of alcohol, benzodiazepines, barbiturates, and antiepileptic drugs.
  - Taking within 14 days of stopping an MAOI due to risk of hypertensive crisis and serotonin syndrome.
  - Concomitant use with MAOI
  - Hypersensitivity to any component of dextromethorphan/bupropion (SJS/TEN risk).
- **Boxed Warning**: suicidal thoughts and behaviors in pediatric and young adult patients taking antidepressants

Auvelity [package insert]. New York, NY: Axsome Therapeutics, Inc; December 2022

ASCEND trial

- Phase 2 efficacy and safety trial of dextromethorphan/bupropion in treatment of MDD.
- Randomized, double-blind, multicenter, parallel-group trial.
  - Four sites in the United States
  - Study period: May 2018 – December 2018
- 97 adult patients with MDD were randomly assigned in a 1:1 ratio to receive dextromethorphan/bupropion 105 mg/45 mg or bupropion SR 105 mg PO once daily for three days, and twice daily thereafter, for a total of 6 weeks.

Tabuteau H, et al. *Am J Psychiatry.* 2022;179(7):490-499

ASCEND trial

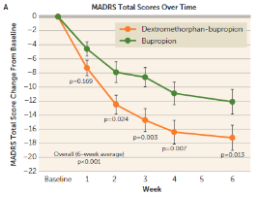
- Primary Outcome: Average change of MADRS score from baseline to week 6 of treatment.
- Secondary Outcomes:
  - Clinical response: reduction ≥ 50% from baseline MADRS score
  - Remission: MADRS score ≤ 10.
- Safety Endpoints: incidence of adverse events

Tabuteau H, et al. *Am J Psychiatry.* 2022;179(7):490-499

ASCEND trial

- Results – Efficacy
  - Primary Outcome:
    - Statistically significant difference in MADRS total score change from baseline in dextromethorphan/bupropion group after 6 weeks
      - Dextromethorphan/Bupropion : -13.7 points
      - Bupropion: -8.8 points
      - Least mean difference: -4.9 points

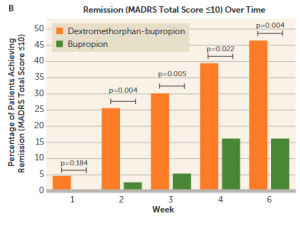
FIGURE 2. MADRS total scores and remission over time in a phase 2 trial of AXS-05 (dextromethorphan-bupropion) for major depressive disorder[a]



Tabuteau H, et al. *Am J Psychiatry.* 2022;179(7):490-499

ASCEND trial

- Results – Efficacy
  - Remission: statistically significant difference favoring dextromethorphan/bupropion group at Weeks 2 and 6
    - Week 2 Least mean difference: 22.9%
    - Week 6 Least mean difference: 30.3%
  - Clinical response: no significant difference among groups



Tabuteau H, et al. *Am J Psychiatry.* 2022;179(7):490-499

ASCEND trial

- Results – Safety
  - Any adverse events
    - Dextromethorphan/Bupropion: 72.9% (N=35)
      - Most common adverse events: **dizziness**, nausea, dry mouth, decreased appetite, and anxiety.
    - Bupropion: 64.6% (N=31)
      - Most common adverse events: nausea, headache, dry mouth, decreased appetite, and constipation.
  - All other safety endpoints were not statistically significant

Tabuteau H, et al. *Am J Psychiatry.* 2022;179(7):490-499

ASCEND trial

- Strengths
  - Found statistically significant reductions compared to bupropion in treatment of MDD after two weeks
  - High internal validity
  - Balanced cohorts based on severity of MDD
- Limitations
  - Exclusion of patients with MDD that had concomitant psychiatric disorders
  - Low external validity due to frequent assessments and strict exclusion criteria
  - Small sample size after assessment for eligibility
  - Cohort was not balanced based on demographics
  - Bupropion dose was not optimized

Tabuteau H, et al. *Am J Psychiatry.* 2022;179(7):490-499

GEMINI trial

- Phase 3 efficacy and safety trial of dextromethorphan/bupropion in treatment of MDD.
- Randomized, double-blind, multi-center, placebo-controlled trial
  - 40 centers in the United States
  - Study period: June 2019 – December 2019
- 327 adult patients, experiencing a major depressive episode of at least 4 weeks, underwent 1:1 randomization to receive dextromethorphan/bupropion or placebo PO once daily for three days, and twice daily thereafter for a total of 6 weeks.

Iosifescu DV, et al. *J Clin Psychiatry.* 2022;83(4):21m14345

GEMINI trial

- Inclusion Criteria
  - Men or women aged 18 to 65 years old with a primary diagnosis of MDD, experiencing a major depressive episode of at least 4 weeks
    - MADRS score ≥ 25
    - CGI-S score scale ≥ 4
- Exclusion Criteria
  - Bipolar disorder
  - Psychotic disorder
  - Panic disorder
  - OCD
  - TRD
  - Alcohol or substance use disorder within past year
  - Clinically significant risk of suicide
  - History of seizure disorder

Iosifescu DV, et al. *J Clin Psychiatry.* 2022;83(4):21m14345

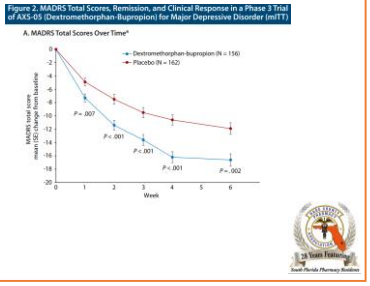
GEMINI trial

- Primary Outcome: MADRS total score change from baseline to week 6
- Key Secondary Outcomes:
  - Remission (MADRS ≤ 10 at week 2 of therapy and every week thereafter until week 6)
  - Clinical response (≥ 50% reduction in MADRS total score at weeks 1 – 4 and week 6)
- Safety Endpoints: incidence of adverse events

Iosifescu DV, et al. *J Clin Psychiatry.* 2022;83(4):21m14345

GEMINI trial

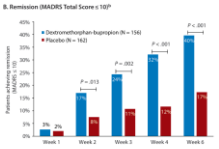
- Results – Efficacy
  - Significantly greater decrease in MADRS total score at 6 weeks in dextromethorphan/bupropion group compared to the placebo group (- 15.9 points vs. - 12.0 points)

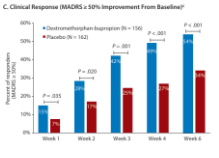


Iosifescu DV, et al. *J Clin Psychiatry.* 2022;83(4):21m14345

GEMINI trial

- Results – Efficacy
  - Secondary Outcomes:
    - Remission and Clinical Response: statistically significant increase favoring dextromethorphan/bupropion compared to placebo
- Safety Endpoints: similar findings of adverse events as ASCEND trial





Iosifescu DV, et al. *J Clin Psychiatry.* 2022;83(4):21m14345

GEMINI trial

- Strengths
  - Bigger sample size compared to ASCEND trial
  - More balanced cohort based on demographics compared to ASCEND trial
  - Balanced cohort based on severity of MDD
  - Reinforced findings of ASCEND trial of improvement in MADRS score and remission in MDD
- Limitations
  - Exclusion of patients with MDD that had concomitant psychiatric disorders
  - Key secondary endpoints were the only outcomes adjusted for multiplicity
  - Same study duration as Phase 2 ASCEND trial (6 weeks)

Iosifescu DV, et al. *J Clin Psychiatry.* 2022;83(4):21m14345

Dextromethorphan/Bupropion: Role in Therapy

- Should be considered in patients with recent diagnoses of MDD without suicidal ideation
- Has not been studied in bipolar disorder, panic disorder, and OCD
- Should be avoided in patients with epilepsy or seizure disorders
- Not an approved pharmacologic treatment option in TRD

Tabuteau H, et al. *Am J Psychiatry.* 2022;179(7):490-499
Iosifescu DV, et al. *J Clin Psychiatry.* 2022;83(4):21m14345

CE Question

- What was a key exclusion criterion for the GEMINI trial which evaluated the efficacy and safety of dextromethorphan/bupropion?

A. Adult patients aged 18-65 years old with primary diagnosis of major depressive disorder
B. Patients with schizoaffective disorder
C. Patients with non-productive cough
D. Patients with treatment-resistant depression

Iosifescu DV, et al. *J Clin Psychiatry.* 2022;83(4):21m14345

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C. Patients with non-productive cough
D. Patients with treatment-resistant depression

Iosifescu DV, et al. *J Clin Psychiatry.* 2022;83(4):21m14345

Esketamine Nasal Spray

- Indication: conjunctive therapy with an oral antidepressant for treatment-resistant depression (TRD) in adults.

- MOA: non-selective, non-competitive antagonist of the NMDA receptor. Mechanism of antidepressant effect is unclear.
  - S-enantiomer of racemic ketamine
  - Pharmacokinetic profile
    - Half-life ($t_{1/2}$): 7 – 12 hours
      - Noresketamine (active metabolite): ~8 hours
    - Time to peak plasma concentrations: 20 – 40 minutes

Spravato [package insert]. Titusville, NJ: Janssen Pharmaceuticals, Inc.; March 2019

Esketamine Nasal Spray

- Dosing:
  - Induction Phase (Weeks 1 to 4):
    - Day 1: 56 mg
    - Subsequent doses: 56 mg or 84 mg (Administered twice per week).
  - Maintenance Phase:
    - Only if there is evidence of therapeutic benefit
    - Weeks 5 to 8: 56 mg or 84 mg (administered once weekly).
    - Week 9 and after: 56 mg or 84 mg (administer every 1-2 weeks; individualized to the least frequent dosing based on remission and response).

Daly EJ, et al. *JAMA Psychiatry*. 2019;76(9):893-903
Spravato [package insert]. Titusville, NJ: Janssen Pharmaceuticals, Inc.; March 2019

Esketamine Nasal Spray

- Contraindications
  - Aneurysmal vascular disease (including thoracic and abdominal aorta, intracranial and peripheral arterial vessels) or arteriovenous malformation.
  - Intracerebral hemorrhage
  - Hypersensitivity to esketamine or ketamine.
- **Boxed Warnings**
  - Sedation, dissociation after administration.
  - Potential for abuse and misuse (Controlled Substance Schedule III). Consider risks/benefits in patients at higher risk of abuse.
  - Spravato REMS
  - Increased risk of suicidal thoughts and behaviors in pediatric and young adult patients taking antidepressants.

Spravato [package insert]. Titusville, NJ: Janssen Pharmaceuticals, Inc.; March 2019

Popova – Esketamine Trial Design

- Phase 3 clinical trial on switching patients with TRD to esketamine and a new antidepressant versus placebo nasal spray and a new antidepressant.
- Double-blind, active-controlled, multicenter study at 39 outpatient referral centers between August 2015 and November 2017.
- 227 patients underwent computer-generated 1:1 randomization to receive double-blind treatment with either esketamine (56 mg or 84 mg) or placebo nasal spray administered twice weekly

Popova V, et al. *Am J Psychiatry*. 2019;176(6):428-438

Popova – Esketamine Outcomes

- Outcomes
  - Primary Outcome: MADRS score change from baseline to day 28
  - Key Secondary Outcomes – Hierarchal testing
    - Percentage of patients with onset of clinical response
  - Safety Endpoints
    - Incidence of adverse events
    - Sedation: Modified Observer's Assessment of Alertness/Sedation scale every 15 minutes from before dosing to 90 minutes after dosing

Popova V, et al. *Am J Psychiatry*. 2019;176(6):428-438

Popova – Esketamine Results

- Mean change in baseline MADRS score after 28 days
  - Statistically significant difference in the change from baseline MADRS score after 28 days favoring esketamine group
    - **Least means difference: -4.4 points**
- Pre-specified treatment difference of 6.5 points in MADRS score between esketamine and placebo groups was not met!

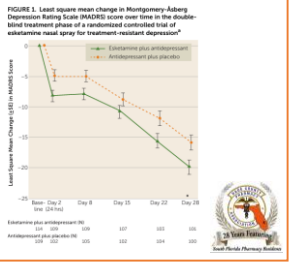


FIGURE 1. Least square mean change in Montgomery-Åsberg Depression Rating Scale (MADRS) score over time in the double-blind treatment phase of a randomized controlled trial of esketamine nasal spray for treatment-resistant depression[a]

Popova V, et al. *Am J Psychiatry*. 2019;176(6):428-438

Popova – Esketamine Results

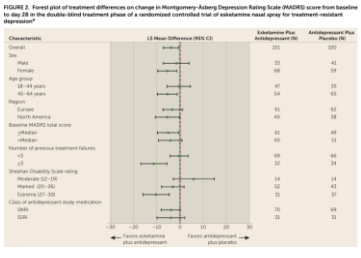


FIGURE 2. Forest plot of treatment differences on change in Montgomery-Åsberg Depression Rating Scale (MADRS) score from baseline to day 28 in the double-blind treatment phase of a randomized controlled trial of esketamine nasal spray for treatment-resistant depression[a]

The esketamine group favored the following patients with TRD:

- Higher severity of functional impairment from depression (based on SDS)
- Patients with at least 3 previous treatment failures
- Female patients
- Patients aged 45 – 64 years old

Popova V, et al. *Am J Psychiatry*. 2019;176(6):428-438

Popova – Esketamine Results

- Hierarchical testing of key secondary endpoints
  - ≥ 50% improvement from baseline in MADRS score by day 2 maintained to day 28: no difference
    - Esketamine group: 9/114 (7.9%)
    - Placebo group: 5/109 (4.6%)
  - Analysis not performed for other two key secondary endpoints due to lack of statistical significance

Popova V, et al. *Am J Psychiatry*. 2019;176(6):428-438

Popova - Esketamine Safety Outcomes

- Sedation: statistically significant difference between groups
  - Esketamine group: 66/115 patients (57.4%)
  - Placebo group: 11/109 patients (10.1%)
  - Not associated with hypoxemia
- Nine patients experienced one or more adverse events leading to discontinuation

TABLE 3. Most frequently reported adverse events in the double-blind treatment phase of a randomized controlled trial of esketamine nasal spray for treatment-resistant depression[a]

	Esketamine Plus Antidepressant (N=114)		Antidepressant Plus Placebo (N=109)	
Adverse Event	N	%	N	%
Dissociation	30	26.1	4	3.7
Nausea	30	26.1	7	6.4
Vertigo	30	26.1	3	2.8
Dysgeusia	28	24.3	13	11.9
Dizziness	24	20.9	5	4.6
Headache	23	20.0	39	37.4
Somnolence	15	13.0	7	6.4
Blurred vision	14	12.2	3	2.8
Paresthesia	13	11.3	1	0.9
Anxiety	12	10.4	5	4.6
Increased blood pressure	11	9.6	1	0.9
Insomnia	11	9.6	5	4.6
Vomiting	11	9.6	2	1.8
Diarrhea	10	8.7	10	9.2
Dry mouth	9	7.8	3	2.8
Feeling drunk	9	7.8	1	0.9
Oral hypoesthesia	9	7.8	1	0.9
Oral paresthesia	9	7.8	1	0.9
Throat irritation	9	7.8	5	4.6
Postural dizziness	8	7.0	1	0.9
Hypoesthesia	8	7.0	1	0.9
Nasal discomfort	8	7.0	2	1.8
Fatigue	5	4.3	6	5.5

[a] The table lists adverse events with an incidence >5% in either treatment group, listed in decreasing order based on incidence within the esketamine plus antidepressant group, and in alphabetical order for events with the same incidence.

Popova V, et al. *Am J Psychiatry*. 2019;176(6):428-438

Popova – Esketamine Trial Overview

- Strengths
  - Balanced cohort based on baseline MADRS score
  - Found significant differences in change of MADRS score after 28 days in esketamine group for patients with:
    - Extreme functional severity
    - At least three previous treatment failures
- Weaknesses
  - Limited demographics based on race; Most patients identified as white
  - Patients enrolled that did not meet DSM-V definition of TRD
  - Prespecified treatment difference for primary endpoint was not achieved despite statistically significant difference favoring esketamine

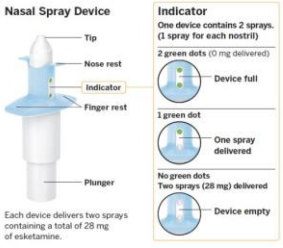
Popova V, et al. *Am J Psychiatry*. 2019;176(6):428-438

Esketamine

- Administration:
  - Intranasal administration only.
  - Must be self-administered under direct supervision of a healthcare provider.

Spravato [package insert]. Titusville, NJ: Janssen Pharmaceuticals, Inc.; March 2019

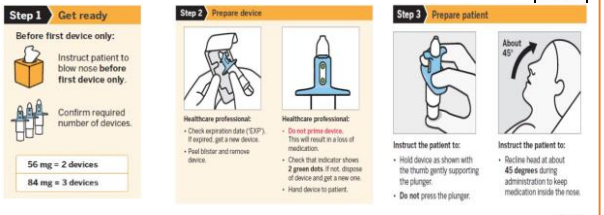
Esketamine



Spravato [package insert]. Titusville, NJ: Janssen Pharmaceuticals, Inc.; March 2019

Esketamine

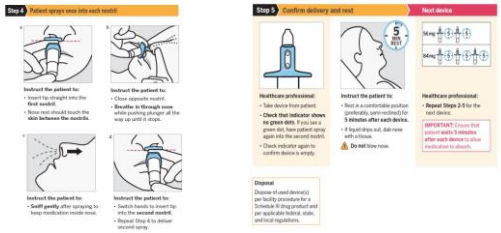
Administration



Spravato [package insert]. Titusville, NJ: Janssen Pharmaceuticals, Inc.; March 2019

Esketamine

Administration



Spravato [package insert]. Titusville, NJ: Janssen Pharmaceuticals, Inc.; March 2019

CE Question

- What should the certified healthcare provider supervising the patient's self-administration of esketamine consider during the administration process?

A. Two red dots on the nasal device indicators indicate that the device is full of medication.
B. The nasal devices cannot be primed as this will result in the loss of medication.
C. The patient should blow their nose after each spray of medication.
D. The patient should be given three consecutive sprays without breaks as esketamine has short stability.

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Spravato REMS

- Esketamine is only available through a restricted distribution program Spravato REMS due to the risks of serious adverse outcomes from sedation, dissociation, and abuse and misuse.
- Intended for use only in a certified healthcare setting
- Intended for patient administration under the direct observation of a healthcare provider.
- Esketamine may never be directly dispensed to a patient for home use

Spravato® REMS. https://www.spravatorems.com/

Spravato REMS

- Important requirements:
  - Healthcare settings must be certified in the program and ensure that esketamine is:
    - Only dispensed to certified healthcare settings
    - Administered by patients under the direct observation of a healthcare provider
    - Monitored by a healthcare provider for at least 2 hours after administration
    - Relevant staff involved in prescribing, dispensing, and administering of esketamine must be trained and documentation of training must always be maintained.
  - Pharmacies must be certified in the REMS and must only dispense esketamine to healthcare settings that are certified in the program.
  - Notify program if transfer of patient treatment from one REMS-certified healthcare setting to another

Spravato® REMS. https://www.spravatorems.com/

Spravato REMS

Registration Type	Requirements and Caveats
Inpatient Healthcare Setting	• Not required to enroll patients in program • Not required to submit Patient Monitoring Forms
Pharmacy	• Required for outpatient dispensing only! • Must verify Outpatient Healthcare Setting is certified prior to dispensing esketamine • A separate Spravato REMS registration is not required if an inpatient pharmacy shares the same physical location and DEA license with registered Inpatient Healthcare Setting

Outpatient Healthcare Setting	• Prescriber must enroll patient into programs by completing Patient Enrollment Form and submitting
	• Before treatment: patient counseling from healthcare provider
	• During treatment:
	  ○ Supervise patient administration of esketamine
	  ○ Monitor each patient for at least 2 hours after administration of esketamine
	  ○ Submit Patient Monitoring form

Patients	• Enroll in Spravato REMS program if receiving treatment from Outpatient Healthcare Setting • Receive counseling, self-administer esketamine under direct observation from healthcare provider, and be monitored for at least 2 hours post-administration

Spravato® REMS. https://www.spravatorems.com/

CE Question

- Which of the following is true regarding the Spravato REMS program?

A. Esketamine may be dispensed directly to the patient for home use by a certified pharmacy
B. Spravato REMS program does not require notification of transfer in patient treatment if transfer of care is from one REMS-certified Healthcare Setting to another certified setting.
C. Relevant staff involved in prescribing, dispensing, and administering of esketamine must be trained and documentation of training must always be maintained.
D. Patients who do not have a history of serious adverse events following administration of esketamine may be discharged immediately after administration of esketamine.

CE Question

- Which of the following is true regarding the Spravato REMS program?

A. Esketamine may be dispensed directly to the patient for home use by a certified pharmacy
B. Spravato REMS program does not require notification of transfer in patient treatment if transfer of care is from one REMS-certified Healthcare Setting to another certified setting.
C. Relevant staff involved in prescribing, dispensing, and administering of esketamine must be trained and documentation of training must always be maintained.
D. Patients who do not have a history of serious adverse events following administration of esketamine may be discharged immediately after administration of esketamine.

Esketamine: Role in Therapy

- Esketamine can be used as a concomitant agent; it has been administered with optimized dosing of the following antidepressants: duloxetine, venlafaxine ER, sertraline, and escitalopram
- In the short-term trial, esketamine demonstrated a treatment benefit in TRD over placebo in patients with at least 3 treatment failures for MDD and higher severity of functional impairment from MDD
- Careful consideration should be taken in patients with substance use disorder due to risk of abuse and adverse effects related to dissociation

Popova V, et al. *Am J Psychiatry*. 2019;176(6):428-438
Daly EJ, et al. *JAMA Psychiatry*. 2019;76(9):893-903

Summary

- Dextromethorphan/bupropion is approved for use in adult patients with major depressive disorder (MDD)
- The use of dextromethorphan/bupropion should be restricted to patients with one or less treatment failure of previous antidepressant for MDD; dextromethorphan/bupropion has not been studied in patients with treatment-resistant depression (TRD)
- Intranasal esketamine is approved for use in adult patients with treatment-resistant depression
- Esketamine is only available through the Spravato REMS program due to high risk of abuse, dissociative, and sedative adverse effects

References

- Tabuteau H, Jones A, Anderson A, Jacobson M, Iosifescu DV. Effect of AXS-05 (Dextromethorphan-Bupropion) in Major Depressive Disorder: A Randomized Double-Blind Controlled Trial. *Tabuteau H, et al. Am J Psychiatry.* 2022;179(7):490-499
- Iosifescu DV, Jones A, O'Gorman C, et al. Efficacy and Safety of AXS-05 (Dextromethorphan-Bupropion) in Patients With Major Depressive Disorder: A Phase 3 Randomized Clinical Trial (GEMINI). *Iosifescu DV, et al. J Clin Psychiatry.* 2022;83(4):21m14345
- Popova V, Daly EJ, Trivedi M, et al. Efficacy and Safety of Flexibly Dosed Esketamine Nasal Spray Combined With a Newly Initiated Oral Antidepressant in Treatment-Resistant Depression: A Randomized Double-Blind Active-Controlled Study. *Am J Psychiatry.* 2019;176(6):428-438
- Daly EJ, Trivedi MH, Janik A, et al. Efficacy of Esketamine Nasal Spray Plus Oral Antidepressant Treatment for Relapse Prevention in Patients With Treatment-Resistant Depression: A Randomized Clinical Trial. *JAMA Psychiatry*. 2019;76(9):893-903
- Stahl SM. Dextromethorphan/Bupropion: A novel oral NMDA (N-methyl-d-aspartate) receptor antagonist with multimodal activity. *CNS Spectr.* 2019;24(5):461-466
- Auvelity [package insert]. New York, NY: Axsome Therapeutics, Inc; December 2022. Accessed September 2024
- Spravato [package insert]. Titusville, NJ: Janssen Pharmaceuticals, Inc.; March 2019. Accessed September 2024
- Spravato® REMS. Accessed December 22, 2024. https://www.spravatorems.com/

References

- American Psychiatric Association, 2022. Depression fact sheet. World Health Organization. December 2019
- Montgomery, S.A. et al. British Journal of Psychiatry. 1979; 134, 382-389
- Hamilton M. A rating scale for depression. J Neurol Neurosurg Psychiatry 1960; 23:56–62
- Rush AJ, Trivedi MH, Wisniewski SR, et al. Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: a STAR*D report. Am J Psychiatry. 2006;163(11):1905-1917. doi:10.1176/ajp.2006.163.11.1905
- Pigott HE, Kim T, Xu C, Kirsch I, Amsterdam J. What are the treatment remission, response and extent of improvement rates after up to four trials of antidepressant therapies in real-world depressed patients? A reanalysis of the STAR*D study's patient-level data with fidelity to the original research protocol. BMJ Open. 2023;13(7):e063095. Published 2023 Jul 25. doi:10.1136/bmjopen-2022-063095
- Pae CU, et al. CNS Drugs. 2011;25(2):109-127
- Berman RM, Marcus RN, Swanink R, et al. The efficacy and safety of aripiprazole as adjunctive therapy in major depressive disorder: a multicenter, randomized, double-blind, placebo-controlled study. J Clin Psychiatry. 2007;68(6):843-853. doi:10.4088/jcp.v68n0604Mohamed S, et al. JAMA. 2017;318(2):132–145
- Thase ME, Youakim JM, Skuban A, et al. Efficacy and safety of adjunctive brexpiprazole 2 mg in major depressive disorder: a phase 3 randomized, placebo-controlled study in patients with inadequate response to antidepressants. J Clin Psychiatry. 2015;76(9):1224 doi:10.4088/JCP.14m09688
- El-Khalili N, et al. International Journal of Neuropsychopharmacology, Volume 13, Issue 7, August 2010, Pages 917–932
- Sanacora G, Zarate CA, Krystal JH, Manji HK. Targeting the glutamatergic system to develop novel, improved therapeutics for mood Nat Rev Drug Discov. 2008;7(5):426-437Berman RM, et al. Biol Psychiatry. 2000;47(4):351-354

References

- Singh JB, Fedgchin M, Daly EJ, et al. A Double-Blind, Randomized, Placebo-Controlled, Dose-Frequency Study of Intravenous Ketamine in Patients With Treatment-Resistant Depression. Am J Psychiatry. 2016;173(8):816-826.
- Dodd S, Norman TR, Eyre HA, et al. Psilocybin in neuropsychiatry: a review of its pharmacology, safety, and efficacy. CNS Spectr. 2023;28(4):416-426. doi:10.1017/S1092852922000888 Spectrums. 2023;28(4):416-426
- Davis AK, Barrett FS, May DG, et al. Effects of Psilocybin-Assisted Therapy on Major Depressive Disorder: A Randomized Clinical Trial [published correction appears in JAMA Psychiatry. 2021 Feb 10:569. doi: 10.1001/jamapsychiatry.2020.4714]. JAMA Psychiatry. 2021;78(5):481-489.
- Palfreyman M, et al. In Vitro and In Vivo Profile of CYB003. Cybin Inc

Don't Be Blue: Depression Management & Treatment Modalities

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Miami, FL
Sunday, January 26th, 2024

Goals and Objectives Part 1

- Analyze the STAR*D trial's impact on modern Major Depressive Disorder (MDD) and Treatment-Resistant Depression (TRD) treatment approaches
- Evaluate the effectiveness of current augmentation strategies for MDD and TRD
- Discuss emerging therapies and their potential role in treating MDD and TRD

Goals and Objectives Part 2

- Describe novel antidepressant agents: dextromethorphan/bupropion and esketamine
- Discuss the primary literature which led to the FDA approval of dextromethorphan/bupropion and esketamine
- Discuss dextromethorphan/bupropion and esketamine role in therapy for Major Depressive Disorder (MDD)

Abbreviations

- BPRS: Brief Psychiatric Rating Scale
- CADSS: Clinician-Administered Dissociative States Scale
- CGI-I: Clinical Global Impressions Improvement Scale
- CGI-S: Clinical Global Impressions Severity Scale
- C-SSRS: Columbia-Suicide Severity Rating Scale
- CYP: cytochrome P450
- DEA: Drug Enforcement Agency
- DSM-V: Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
- ECG: electrocardiogram
- eGFR: estimated glomerular filtration rate
- FDA: Food & Drug Administration
- GRID-HAMD: Grid Hamilton Rating Scale for Depression
- IDS-C: Inventory of Depressive Symptomatology-Clinician Rating
- MADRS: Montgomery-Åsberg Depression Rating Scale
- MAOI: monoamine oxidase inhibitor
- MDD: major depressive disorder
- MGH: Massachusetts General Hospital
- MOA: mechanism of action
- OCD: obsessive compulsive disorder
- NMDA: N-methyl-D-aspartate
- PO: by mouth
- REMS: Risk Evaluation and Mitigation Strategy
- SJS: Stevens-Johnson Syndrome
- SI: suicidal ideation
- SNRI: serotonin-norepinephrine reuptake inhibitors
- SR: sustained release
- SSRI: selective serotonin reuptake inhibitors
- TEN: toxic epidermal necrolysis
- TRD: treatment-resistant depression

Background

- Major Depressive Disorder (MDD)
  - Diagnosed in patients with a history of at least one major depressive episode and no history of mania or hypomania
- Major depressive episode:
  - Lasts at at least two consecutive weeks
  - Involves 5 or more of the following symptoms:
    - Depressed mood
    - Anhedonia
    - Insomnia or hypersomnia
    - Change in appetite or weight
    - Psychomotor retardation
    - Low energy or fatigue
    - Poor concentration or indecisiveness
    - Thoughts of of worthlessness or guilt
    - Recurrent thoughts about death or suicide

American Psychiatric Association, 2022.

Background

- Treatment Resistant Depression (TRD):
  - A major depressive disorder in which an individual does not respond adequately to at least two antidepressants
- Depression is the number one cause of disability
- The all-cause mortality for those with depression is 1.7 times greater than for the general public
- Approximately 10% of the US adult population has been diagnosed with MDD

American Psychiatric Association, 2022.
Depression fact sheet. World Health Organization. December 2019

Scoring Systems

- Hamilton Rating Scale for Depression (HAMD)
  - Most widely used clinician administered depression assessment scale
  - 17 items, the higher the number the more severe
    - Score 0-7 considered normal
    - Score of 20 or greater is usually required for entry into a clinical trial
  - Limitation of the scale: atypical symptoms of depression (e.g., hypersomnia, hyperphagia) are not assessed
  - Primarily developed for inpatient
- Montgomery-Asburg Depression Rating Scale (MADR)
  - 10 items; each item scored on a scale of 0-6
  - Higher scores indicate more severe depression

Montgomery, S.A. et al. British Journal of Psychiatry. 1979; 134, 382-389
Hamilton M. A rating scale for depression. J Neurol Neurosurg Psychiatry 1960; 23:56–62

STAR*D Trial: Sequenced Treatment Alternatives to Relieve Depression

- Study design
  - Largest, prospective clinical trial of major depressive disorder ever conducted
  - Multicenter, nationwide association of 14 university based regional centers
- Methods
  - All enrolled patients began on a single SSRI: citalopram
  - Followed an algorithm guided acute phase treatment through 5 visits over 12 weeks
  - Algorithm recommended to increase dose if patient that was tolerating oral medication had not achieved remission at any of the critical decision points (weeks 4, 6, 9)
  - Follow-up: 12 months

Rush AJ, et al. *Am J Psychiatry*. 2006;163(11):1905-1917

STAR*D Trial

- Population
  - Inclusion Criteria:
    - Patients with nonpsychotic major depressive disorder identified by clinicians and confirmed based on DSM-IV-TR checklist for which antidepressant treatment is recommended
    - Age 18-75 with a score of ≥14 on the Hamilton Rating Scale for Depression
  - Exclusion:
    - Primary diagnosis of bipolar disorder, obsessive compulsive disorder, eating disorder, history of seizure disorder
  - Total: 4,041 patients
- Setting
  - Both primary and specialty care sites

Rush AJ, et al. *Am J Psychiatry*. 2006;163(11):1905-1917

STAR*D Trial

- Primary outcome: standard definition of remission as measured by the Hamilton Depression Rating Scale (HAM-D)
  - 17 item scale, total score 0-52
- In addition, the 16-item Quick Inventor of Depressive Symptomatology Self-Report (QIDS-SR) was administered at each visit
  - Remission measured as a score ≤ equal to 5
  - QIDS-SR provided more frequent assessment points during the acute phase- may be better reflection of actual remission

Rush AJ, et al. *Am J Psychiatry.* 2006;163(11):1905-1917

STAR*D Trial

- Intervention:
  - Systematic approach to treatment; participants progressed through four different levels
  - Patients with a clinically meaningful response in any of the four levels could enter a 12-month follow-up phase
- Level 1: flexible dose citalopram
  - Average dose: 40mg per day
  - Time to remission: 47 days
- Level 2: 3 augmentation strategies and 4 switch strategies
  - Augmentation:
    - Citalopram + bupropion
    - Citalopram + buspirone
    - Citalopram + CBT

Rush AJ, et al. *Am J Psychiatry.* 2006;163(11):1905-1917

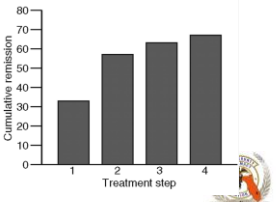
STAR*D Trial

  - Switch strategies:
    - Bupropion
    - Sertraline
    - Venlafaxine
    - Cognitive behavioral therapy (CBT)
- Level 3: 2 augmentation strategies and 2 switch strategies
  - Augmentation:
    - Lithium
    - Thyroid hormone
  - Switch strategies:
    - Nortriptyline
    - Mirtazapine
- Level 4: randomized to treatment with either tranylcypromine or combination venlafaxine XR and mirtazapine

Rush AJ, et al. *Am J Psychiatry.* 2006;163(11):1905-1917

STAR*D Trial Outcomes

- Primary Outcome: Depression remission by QIDS-sR16 Score
  - Step 1: 36.8% (higher remission rate than those in step 2; P<0.001)
  - Step 2: 30.6% (higher remission rate than those in step 3; P<0.001)
  - Step 3: 13.7%
  - Step 4: 13%
- Secondary Outcomes: response measured by clinician and patient self report
  - Step 1: 48.6%
  - Step 2: 28.5%
  - Step 3: 16.8%
  - Step 4: 16.3%



Rush AJ, et al. *Am J Psychiatry*. 2006;163(11):1905-1917

STAR*D Pitfalls

- In 2015, authors of a British Medical Journal article identified protocol violations in the STARD data, specifically the percentage of remission from depression at each of the four stages
  - Reanalyzed STARD raw data according to pre-specified protocol published before the start of the study
  - Previously reported cumulative remission rate: 67%
  - Actual cumulative remission rate: 35%

Pigott HE, et al. *BMJ Open*. 2023;13(7):e063095. Published 2023 Jul 25.

STAR*D Pitfalls

- STAR*D outcomes: remission rates decreased progressively with each step
- Highlights the limitations of conventional antidepressant monotherapy or basic augmentation approaches
- TRD patients often have greater symptom severity, comorbidities, and functional impairments
  - Underscores unmet needs
- There is a growing body of evidence supporting diverse augmentation strategies, such as antipsychotics and psychedelics
  - STAR*D does not specifically evaluate atypical antipsychotic augmentation strategies

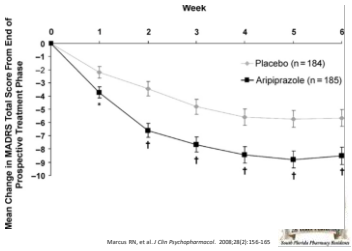
Aripiprazole Adjunctive Therapy

- Aripiprazole
  - Atypical antipsychotic
  - Mechanism of action: agonist at dopamine D2 and D3 and serotonin 5-HT(1A) receptors; antagonist at 5-HT(2A) receptors
  - Initially FDA approved for schizophrenia and bipolar mania; now approved as adjunctive therapy for MDD
- Marcus and colleagues: "The efficacy and safety of aripiprazole as adjunctive therapy in major depressive disorder"
  - Study Design
    - Randomized, double-blind, placebo-controlled study
  - Baseline characteristics
    - Patients: Adults with MDD who had an inadequate response to 1–3 antidepressant trials
      - Mean age: 40
      - Mostly female
    - Medications: SSRIs or SNRIs at stable doses
    - Duration: 6 weeks

Pae CU, et al. *CNS Drugs*. 2011;25(2):109-127
Marcus RN, et al. *J Clin Psychopharmacol*. 2008;28(2):156-165

Aripiprazole Adjunctive Therapy

- Intervention
  - Aripiprazole (2–15 mg/day) as adjunct to antidepressants vs. placebo
- Outcomes
  - Primary: Higher remission rates with aripiprazole (33%) vs. placebo (15%)
  - Secondary: Faster improvement in depressive symptoms
  - Adverse Effects: Akathisia, restlessness



Marcus RN, et al. *J Clin Psychopharmacol*. 2008;28(2):156-165

VAST-D Trial

- Study Design
  - Multicenter, single blind, randomized control trial
- Objective: compare efficacy and adverse effects of 3 alternative MDD treatment strategies
- Participants: 1,522 patients with non-remitted MDD after at least 6 weeks of treatment with an SSRI
- Interventions:
  - Switch group:
    - Discontinuation of SSRI and initiation bupropion sustained release
  - Augmentation group:
    - Aripiprazole
    - Bupropion
- Titration of doses:
  - Bupropion: 150 mg sustained release to 300 mg or 400 mg daily
  - Aripiprazole: 2 mg with titration to 5, 10, or 15 mg daily
  - Until depressive symptoms remitted or adverse effects were intolerable

Mohamed S, et al. *JAMA*. 2017;318(2):132–145

VAST-D Trial

- Primary outcome:
  - Remission defined as defined as a QIDS-C_{16} score of 5 or less at 2 consecutive scheduled follow-up visits during the acute treatment phase
    - range 0-27 with higher scores indicating more severe symptoms
- Secondary outcomes: time to remission, response rates, adverse effects and tolerability
- Results:
  - Remission rates were significantly higher in the aripiprazole augmentation group (28.9%) compared to the switch group (22.3%; RR, 1.30 [95% CI, 1.05-1.60]; *P* = .02)
  - Remission rates were not significantly higher in the aripiprazole augmentation group (28.9%) compared to the bupropion augmentation group (26.9%; RR, 1.08 [95% CI, 0.88-1.31]; *P* = .47)
  - Aripiprazole had a faster time to remission compared to other strategies
  - Adverse effects were more common in the aripiprazole group (akathisia, weight gain)

Mohamed S, et al. *JAMA*. 2017;318(2):132–145

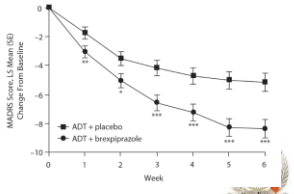
Brexpiprazole Adjunctive Therapy

- Study design:
  - Multicenter, phase 3, randomized, double-blind, placebo-controlled
  - Participants: Adults with a diagnosis of MDD and inadequate response to 1-3 adequate antidepressant trials
    - 379 patients randomized
- Intervention
  - Adjunctive brexpiprazole (N=175): 2 mg/day
  - Adjunctive placebo (N=178)
  - Both groups continued treatment with their antidepressant
  - 8-week antidepressant lead-in followed by 6-week treatment phase

Thase ME, et al. *J Clin Psychiatry*. 2015;76(9):1224–1231

Brexpiprazole Adjunctive Therapy

- Primary outcome: change in MADRS total score from baseline to week 6
- Secondary outcome: response rate defined by ≥ 50% MADRS reduction, remission rate define by MADRS score of ≤ 10, and safety events
- Results:
  - Primary outcome:
    - Brexpiprazole: 8.36 points
    - Placebo: 5.15 points:
    - Mean difference: -3.21 points; p < 0.001



Thase ME, et al. *J Clin Psychiatry*. 2015;76(9):1224–1231

Brexpiprazole Adjunctive Therapy

- Secondary outcomes:
  - Response rate: 26.2% brexpiprazole vs. 15.3% placebo (p = 0.002)
  - Remission rates: 15.4% brexpiprazole vs. 7.4% placebo (p = 0.012)
- Safety outcomes:
  - Common AE: akathisia (7.2% in brexpiprazole vs 0.5% in placebo), headache, weight gain

Thase ME, et al. *J Clin Psychiatry.* 2015;76(9):1224–1231

Quetiapine XR Adjunctive Therapy

- Study Design: multicenter, double-blind, randomized, parallel-group, placebo-controlled Phase II study
  - Duration: 6 weeks
  - Participants: adults with MDD and inadequate response to antidepressant therapy for ≥ 6 weeks
- Intervention: Quetiapine XR (150mg/day or 300mg/day) vs. placebo
  - Ongoing antidepressant treatment was maintained at the same dose
- Primary outcome: change in MADRS score from baseline at week 6
- Secondary outcome:
  - Response rate defined as ≥ 50% reduction in MADRS score
  - Remission rates defined as MADRS score ≤ 8 at week 6

El-Khalili N, et al. *International Journal of Neuropsychopharmacology*, Volume 13, Issue 7, August 2010, Pages 917–932

Quetiapine XR Adjunctive Therapy

- Results:
  - Primary outcome:
    - Mean change in MADRS total score from randomization at week 6 (primary endpoint) was significantly greater with quetiapine XR 300 mg/d than with placebo (−14.70 *vs.* −11.70, $p < 0.01$)
    - Mean total score was also reduced with quetiapine XR 150 mg/day at week 6, but the difference was not statistically significant
  - Secondary outcomes:
    - Response rates
      - Quetiapine XR 150 mg/day: 51.7% (p = 0.329)
      - Quetiapine XR 300 mg/day: 58.9% (p < 0.05)
      - Placebo: 46.2%
    - Remission rates
      - Quetiapine XR 150 mg/day: 35% (p = 0.059)
      - Quetiapine XR 300 mg/day: 42.5% (p < 0.01)
      - Placebo: 24.5%

El-Khalili N, et al. *International Journal of Neuropsychopharmacology*, Volume 13, Issue 7, August 2010, Pages 917–932

Quetiapine XR Adjunctive Therapy

- In the intervention groups, the most common adverse events leading to discontinuation were sedation and somnolence
- Other adverse events:
  - EPS
  - Sexual dysfunction
  - QTC prolongation (1 patient)
  - Suicidality (1 patient)

El-Khalili N, et al. *International Journal of Neuropsychopharmacology*, Volume 13, Issue 7, August 2010, Pages 917–932

Ketamine for TRD

- Originally developed as an anesthetic
- Blocks N-methyl-D-aspartate (NMDA) receptors, a subtype of glutamate receptor in the brain
- In 2000, Berman et al. demonstrated the rapid antidepressant effects of ketamine in a small randomized trial, showing improvement within hours to days after a single infusion
- Subsequent studies have confirmed ketamine's efficacy in TRD

Zarate CA et al., *Nat Rev Drug Discov.* 2007;6(5):426-437
Berman RM, et al. *Biol Psychiatry.* 2000;47(4):351-354

Intravenous Ketamine in Patients With Treatment Resistant Depression

- Study design:
  - Multicenter, randomized, double-blind, placebo-controlled
  - Participants: adults with diagnosed MDD and inadequate response to at least two antidepressants
- Intervention groups:
  - Ketamine 0.5 mg/kg administered twice weekly for 4 weeks
  - Ketamine 0.5 mg/kg administered three times weekly for 4 weeks
  - Placebo administered twice weekly for 4 weeks
  - Administered over 40 minutes

Singh JB, et al. *Am J Psychiatry.* 2016;173(8):816-826.

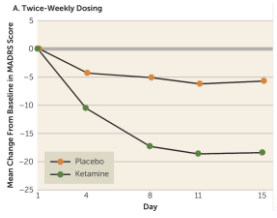
Intravenous Ketamine in Patients With Treatment Resistant Depression

- Primary outcome: change in MADRS score from baseline to day 15
- Secondary outcomes:
  - Response rates defined by ≥ 50 reduction in MADRS
  - Remission rates defined by MADRS score ≤ 10
  - Safety events

Singh JB, et al. *Am J Psychiatry*. 2016;173(8):816-826.

Intravenous Ketamine in Patients With Treatment Resistant Depression

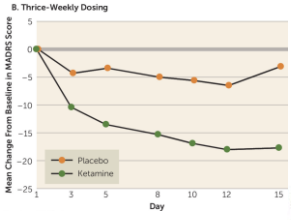
- Primary outcome results:
  - Twice weekly ketamine: mean change in MADRS score at day 15 was −18.4 (SD=12.0)
  - Twice weekly placebo: −5.7 (SD=10.2)



Singh JB, et al. *Am J Psychiatry*. 2016;173(8):816-826.

Intravenous Ketamine in Patients With Treatment Resistant Depression

- Results:
  - Three times weekly ketamine: −17.7 (SD=7.3)
  - Three times weekly placebo: −3.1 (SD=5.7)



Singh JB, et al. *Am J Psychiatry*. 2016;173(8):816-826.

Intravenous Ketamine in Patients With Treatment Resistant Depression

- Secondary outcome results:
  - Response rates at day 15:
    - Twice weekly dosing: ketamine vs. placebo (68.8% vs. 15.4%; p = 0.005)
    - Three times weekly dosing: ketamine vs. placebo (53.8% vs. 6.3%; p = 0.004)
  - Remission rates at day 15:
    - Twice weekly dosing: ketamine vs. placebo (37.5% vs. 7.7%; p = 0.05)
    - Three times weekly dosing: ketamine vs. placebo (76.9% vs. 16%; p = 0.08)
- Safety assessment:
  - Adverse events were higher in both ketamine groups compared with placebo
  - Most common (≥ 20%):
    - Headache
    - Anxiety
    - Dissociation
    - Nausea
    - Dizziness

Singh JB, et al. *Am J Psychiatry*. 2016;173(8):816-826.

Psilocybin: FDA Breakthrough Therapy Approval

- Psilocybin is a tryptamine alkaloid found in some mushrooms, particularly of the *Psilocybe* genus
- Psilocin in the pharmacologically active metabolite of psilocybin
- Psychoactive effects are due to its partial agonist activity at the 5HT2A receptor
  - Additionally binds to 5HT2B, 5HT1D, dopamine D1, 5HT1E, 5HT1A, 5HT5A, 5HT7, 5HT6, D3, 5HT2C, and 5HT1B
- Lower addiction liability and toxic effects compared to ketamine
- Generally not associated with long-term perceptual, cognitive or neurologic dysfunction
- Received FDA breakthrough therapy approval for MDD in 2018

Dodd S, et al. *CNS Spectrums*. 2023;28(4):416-426
Davis AK, et al. *JAMA Psychiatry*. 2021;78(5):481-489
Ray, TS. *PLoS One*. 2010;5(2):e9019

Effects of Psilocybin-Assisted Therapy on Major Depressive Disorder

- Study Design:
  - Single center, randomized, waiting list controlled clinical trial
  - Participants: Adults aged 21 to 75 years with an MDD diagnosis, not currently using antidepressant medications, and without histories of psychotic disorder, serious suicide attempt, or hospitalization
    - 24 patients, mean age of 39.8, mostly female
    - Mean baseline GRID-HAMD: 22.8
- Intervention:
  - Two psilocybin sessions in the context of supportive psychotherapy (approximately 11 hours)
    - Session 1: 20 mg/70 kg
    - Session 2: 30 mg/70 kg
  - Placebo: wait-list group differed for 8 weeks

Davis AK, *et al. JAMA Psychiatry*. 2021;78(5):481-489

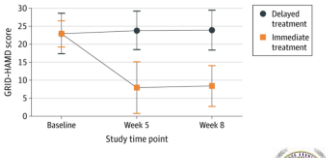
Effects of Psilocybin-Assisted Therapy on Major Depressive Disorder

- Primary outcome: depression severity measured by GRID-HAMD score at 4 weeks post-treatment
- Secondary outcomes:
  - Symptom severity measured by QIDS-SR
  - Response rates defined as ≥50% reduction in GRID-HAMD score
  - Remission rates defined as ≤7 GRID-HAMD score

Davis AK, *et al. JAMA Psychiatry.* 2021;78(5):481-489

Effects of Psilocybin-Assisted Therapy on Major Depressive Disorder

- Results:
  - Primary outcome:
    - Immediate Treatment Group (Weeks 1 and 4)
      - Week 1: 8.0 (SD 7.1)
      - Week 4: 8.5 (SD 5.7)
    - Effect sizes for GRID-HAMD
      - Week 5: Cohen's d = 2.5 (95% CI: 1.4-3.5; P < .001)
      - Week 8: Cohen's d = 2.6 (95% CI: 1.5-3.7; P < .001)
  - Statistically significant reductions compared to delayed treatment group



Davis AK, *et al. JAMA Psychiatry.* 2021;78(5):481-489

Effects of Psilocybin-Assisted Therapy on Major Depressive Disorder

- Secondary outcomes:
  - QIDS-SR depression scores:
    - Baseline vs Day 1 after Session 1:
      - Baseline: 16.7 (SD 3.5)
      - Day 1: 6.3 (SD 4.4)
      - Effect Size: Cohen's d = 2.6 (95% CI: 1.8-3.5; P < .001)
    - Baseline vs Week 4:
      - Week 4: 6.0 (SD 5.7)
      - Effect Size: Cohen's d = 2.3 (95% CI: 1.5-3.0; P < .001)
  - Clinically significant response rates
    - Week 1:
      - 17 participants (71%) achieved ≥50% reduction in GRID-HAMD score.
      - 14 participants (58%) achieved remission (≤7 GRID-HAMD score)
    - Week 4:
      - 17 participants (71%) achieved ≥50% reduction in GRID-HAMD score
      - 13 participants (54%) achieved remission (≤7 GRID-HAMD score)

Davis AK, *et al. JAMA Psychiatry.* 2021;78(5):481-489

"Pharmacological and Pharmacokinetic Profile of CYB003"

- CYB003: deutorated psilocybin
- Safety pharmacology and toxicology studies demonstrated that CYB003 is well-tolerated in the rat (50-200mg/kg)
- Pharmacological profiles of CYB003 and psilocin were compared using serotonin (5-HT) receptor binding and functional assays to evaluate potency, efficacy, and selectivity at serotonin receptors; both compounds were also screened for activity at a panel of over 100 proteins
- Selectivity profile of CYB003 was comparable to that with psilocin
  - (5-HT2A Ki: CYB003 37 nM; psilocin 31 nM)

Palfreyman M, et al. In Vitro and In Vivo Profile of CYB003. Cybin Inc.

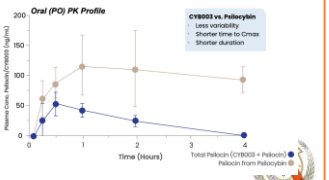
"Pharmacological and Pharmacokinetic Profile of CYB003"

- CYB003 produced a dose-dependent increase in both blood pressure and heart rate
  - Appears to be dose dependent; no effect on QTC interval
- CYB003 induces head twitch responses and hyperactivity in mice similar to psilocin
  - Indicative of in-vivo 5HT2A receptor engagement

Palfreyman M, et al. In Vitro and In Vivo Profile of CYB003. Cybin Inc.

"Pharmacological and Pharmacokinetic Profile of CYB003"

- Pharmacokinetic profile of CYB003 following either intravenous or oral administration is similar to psilocin
- CYB003 exhibits less plasma level variability, shorter time to peak (Cmax), and a shorter duration



Palfreyman M, et al. In Vitro and In Vivo Profile of CYB003. Cybin Inc.

CE Question

- In the study by Khalili and colleagues, what was the most common side effect that lead patients to discontinue Quetiapine XR?

A. EPS
B. Agitation
C. Somnolence
D. Headache
E. None of the above

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E. None of the above

CE Question

- What is the most common depression severity scoring tool, that is also used in the STAR*D Trial?

A. Quick Inventor of Depressive Symptomatology Self-Report (QIDS-SR)
B. Montgomery-Asburg Depression Rating Scale (MADR)
C. Hamilton Depression Rating Scale (HAM-D)
D. None of the above

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A. Quick Inventor of Depressive Symptomatology Self-Report (QIDS-SR)
B. Montgomery-Asburg Depression Rating Scale (MADR)
C. Hamilton Depression Rating Scale (HAM-D)
D. None of the above

Summary

- MDD and TRD affects ~ 10% of adults
- The STAR*D trial highlights the unmet needs for patients with TRD
- Antipsychotics like aripiprazole, brexiprazole, and quetiapine are effective augmentation strategies in patients that have failed an adequate course of antidepressants
- Additionally, emerging therapies like ketamine and psilocybin show promising results for

Dextromethorphan/Bupropion

- Indication: treatment of major depressive disorder (MDD) in adults.
- Mechanism of action (MOA):
  - Dextromethorphan: non-competitive antagonist of the N-methyl D-aspartate (NMDA) receptor (an ionotropic glutamate receptor) and a sigma-1 receptor agonist.
    - Mechanism in the treatment of MDD is unclear
  - Bupropion: unclear in treatment of MDD; Relatively weak inhibitor of neuronal reuptake of norepinephrine and dopamine.
    - Competitively inhibits CYP2D6 which increases plasma levels of dextromethorphan

Auvelity [package insert]. New York, NY: Axsome Therapeutics, Inc; December 2022
Stahl SM. *CNS Spectr.* 2019;24(5):461-466

Dextromethorphan/Bupropion

- Dosing:
  - Initial: 45 mg dextromethorphan/105 mg bupropion 1 tablet by mouth daily in the morning.
    - After 3 days: Increase frequency to twice daily (given at least 8 hours a part).
  - Renal impairment (eGFR 30 – 59 mL/minute/1.73 m^2), concomitant use with strong CYP2D6 inhibitors, known CYP2D6 poor metabolizers: 1 tablet by mouth daily in the morning.

Auvelity [package insert]. New York, NY: Axsome Therapeutics, Inc; December 2022

Dextromethorphan/Bupropion

- Contraindications:
  - Patients with seizure disorders
  - Current or prior diagnosis of bulimia or anorexia nervosa
  - Undergoing abrupt discontinuation of alcohol, benzodiazepines, barbiturates, and antiepileptic drugs.
  - Taking within 14 days of stopping an MAOI due to risk of hypertensive crisis and serotonin syndrome.
  - Concomitant use with MAOI
  - Hypersensitivity to any component of dextromethorphan/bupropion (SJS/TEN risk).
- **Boxed Warning**: suicidal thoughts and behaviors in pediatric and young adult patients taking antidepressants

Auvelity [package insert]. New York, NY: Axsome Therapeutics, Inc; December 2022

ASCEND trial

- Phase 2 efficacy and safety trial of dextromethorphan/bupropion in treatment of MDD.
- Randomized, double-blind, multicenter, parallel-group trial.
  - Four sites in the United States
  - Study period: May 2018 – December 2018
- 97 adult patients with MDD were randomly assigned in a 1:1 ratio to receive dextromethorphan/bupropion 105 mg/45 mg or bupropion SR 105 mg PO once daily for three days, and twice daily thereafter, for a total of 6 weeks.

Tabuteau H, et al. *Am J Psychiatry.* 2022;179(7):490-499

ASCEND trial

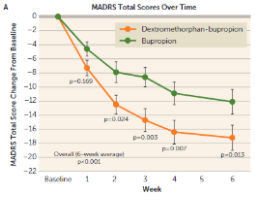
- Primary Outcome: Average change of MADRS score from baseline to week 6 of treatment.
- Secondary Outcomes:
  - Clinical response: reduction ≥ 50% from baseline MADRS score
  - Remission: MADRS score ≤ 10.
- Safety Endpoints: incidence of adverse events

Tabuteau H, et al. *Am J Psychiatry.* 2022;179(7):490-499

ASCEND trial

- Results – Efficacy
  - Primary Outcome:
    - Statistically significant difference in MADRS total score change from baseline in dextromethorphan/bupropion group after 6 weeks
      - Dextromethorphan/Bupropion : -13.7 points
      - Bupropion: -8.8 points
      - Least mean difference: -4.9 points

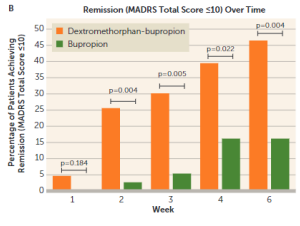
FIGURE 2. MADRS total scores and remission over time in a phase 2 trial of AXS-05 (dextromethorphan-bupropion) for major depressive disorder[a]



Tabuteau H, et al. *Am J Psychiatry.* 2022;179(7):490-499

ASCEND trial

- Results – Efficacy
  - Remission: statistically significant difference favoring dextromethorphan/bupropion group at Weeks 2 and 6
    - Week 2 Least mean difference: 22.9%
    - Week 6 Least mean difference: 30.3%
  - Clinical response: no significant difference among groups



Tabuteau H, et al. *Am J Psychiatry.* 2022;179(7):490-499

ASCEND trial

- Results – Safety
  - Any adverse events
    - Dextromethorphan/Bupropion: 72.9% (N=35)
      - Most common adverse events: **dizziness**, nausea, dry mouth, decreased appetite, and anxiety.
    - Bupropion: 64.6% (N=31)
      - Most common adverse events: nausea, headache, dry mouth, decreased appetite, and constipation.
  - All other safety endpoints were not statistically significant

Tabuteau H, et al. *Am J Psychiatry.* 2022;179(7):490-499

ASCEND trial

- Strengths
  - Found statistically significant reductions compared to bupropion in treatment of MDD after two weeks
  - High internal validity
  - Balanced cohorts based on severity of MDD
- Limitations
  - Exclusion of patients with MDD that had concomitant psychiatric disorders
  - Low external validity due to frequent assessments and strict exclusion criteria
  - Small sample size after assessment for eligibility
  - Cohort was not balanced based on demographics
  - Bupropion dose was not optimized

Tabuteau H, et al. *Am J Psychiatry.* 2022;179(7):490-499

GEMINI trial

- Phase 3 efficacy and safety trial of dextromethorphan/bupropion in treatment of MDD.
- Randomized, double-blind, multi-center, placebo-controlled trial
  - 40 centers in the United States
  - Study period: June 2019 – December 2019
- 327 adult patients, experiencing a major depressive episode of at least 4 weeks, underwent 1:1 randomization to receive dextromethorphan/bupropion or placebo PO once daily for three days, and twice daily thereafter for a total of 6 weeks.

Iosifescu DV, et al. *J Clin Psychiatry.* 2022;83(4):21m14345

GEMINI trial

- Inclusion Criteria
  - Men or women aged 18 to 65 years old with a primary diagnosis of MDD, experiencing a major depressive episode of at least 4 weeks
    - MADRS score ≥ 25
    - CGI-S score scale ≥ 4
- Exclusion Criteria
  - Bipolar disorder
  - Psychotic disorder
  - Panic disorder
  - OCD
  - TRD
  - Alcohol or substance use disorder within past year
  - Clinically significant risk of suicide
  - History of seizure disorder

Iosifescu DV, et al. *J Clin Psychiatry.* 2022;83(4):21m14345

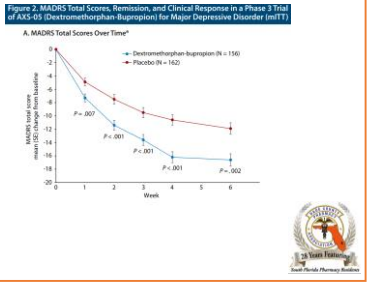
GEMINI trial

- Primary Outcome: MADRS total score change from baseline to week 6
- Key Secondary Outcomes:
  - Remission (MADRS ≤ 10 at week 2 of therapy and every week thereafter until week 6)
  - Clinical response (≥ 50% reduction in MADRS total score at weeks 1 – 4 and week 6)
- Safety Endpoints: incidence of adverse events

Iosifescu DV, et al. *J Clin Psychiatry.* 2022;83(4):21m14345

GEMINI trial

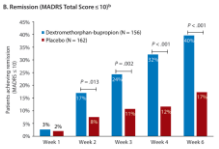
- Results – Efficacy
  - Significantly greater decrease in MADRS total score at 6 weeks in dextromethorphan/bupropion group compared to the placebo group (- 15.9 points vs. - 12.0 points)

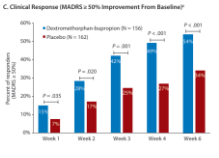


Iosifescu DV, et al. *J Clin Psychiatry.* 2022;83(4):21m14345

GEMINI trial

- Results – Efficacy
  - Secondary Outcomes:
    - Remission and Clinical Response: statistically significant increase favoring dextromethorphan/bupropion compared to placebo
- Safety Endpoints: similar findings of adverse events as ASCEND trial





Iosifescu DV, et al. *J Clin Psychiatry.* 2022;83(4):21m14345

GEMINI trial

- Strengths
  - Bigger sample size compared to ASCEND trial
  - More balanced cohort based on demographics compared to ASCEND trial
  - Balanced cohort based on severity of MDD
  - Reinforced findings of ASCEND trial of improvement in MADRS score and remission in MDD
- Limitations
  - Exclusion of patients with MDD that had concomitant psychiatric disorders
  - Key secondary endpoints were the only outcomes adjusted for multiplicity
  - Same study duration as Phase 2 ASCEND trial (6 weeks)

Iosifescu DV, et al. *J Clin Psychiatry.* 2022;83(4):21m14345

Dextromethorphan/Bupropion: Role in Therapy

- Should be considered in patients with recent diagnoses of MDD without suicidal ideation
- Has not been studied in bipolar disorder, panic disorder, and OCD
- Should be avoided in patients with epilepsy or seizure disorders
- Not an approved pharmacologic treatment option in TRD

Tabuteau H, et al. *Am J Psychiatry.* 2022;179(7):490-499
Iosifescu DV, et al. *J Clin Psychiatry.* 2022;83(4):21m14345

CE Question

- What was a key exclusion criterion for the GEMINI trial which evaluated the efficacy and safety of dextromethorphan/bupropion?

A. Adult patients aged 18-65 years old with primary diagnosis of major depressive disorder
B. Patients with schizoaffective disorder
C. Patients with non-productive cough
D. Patients with treatment-resistant depression

Iosifescu DV, et al. *J Clin Psychiatry.* 2022;83(4):21m14345

CE Question

- What was a key exclusion criterion for the GEMINI trial which evaluated the efficacy and safety of dextromethorphan/bupropion?

A. Adult patients aged 18-65 years old with primary diagnosis of major depressive disorder
B. Patients with schizoaffective disorder
C. Patients with non-productive cough
D. Patients with treatment-resistant depression

Iosifescu DV, et al. *J Clin Psychiatry.* 2022;83(4):21m14345

Esketamine Nasal Spray

- Indication: conjunctive therapy with an oral antidepressant for treatment-resistant depression (TRD) in adults.

- MOA: non-selective, non-competitive antagonist of the NMDA receptor. Mechanism of antidepressant effect is unclear.
  - S-enantiomer of racemic ketamine
  - Pharmacokinetic profile
    - Half-life ($t_{1/2}$): 7 – 12 hours
      - Noresketamine (active metabolite): ~8 hours
    - Time to peak plasma concentrations: 20 – 40 minutes

Spravato [package insert]. Titusville, NJ: Janssen Pharmaceuticals, Inc.; March 2019

Esketamine Nasal Spray

- Dosing:
  - Induction Phase (Weeks 1 to 4):
    - Day 1: 56 mg
    - Subsequent doses: 56 mg or 84 mg (Administered twice per week).
  - Maintenance Phase:
    - Only if there is evidence of therapeutic benefit
    - Weeks 5 to 8: 56 mg or 84 mg (administered once weekly).
    - Week 9 and after: 56 mg or 84 mg (administer every 1-2 weeks; individualized to the least frequent dosing based on remission and response).

Daly EJ, et al. *JAMA Psychiatry*. 2019;76(9):893-903
Spravato [package insert]. Titusville, NJ: Janssen Pharmaceuticals, Inc.; March 2019

Esketamine Nasal Spray

- Contraindications
  - Aneurysmal vascular disease (including thoracic and abdominal aorta, intracranial and peripheral arterial vessels) or arteriovenous malformation.
  - Intracerebral hemorrhage
  - Hypersensitivity to esketamine or ketamine.
- **Boxed Warnings**
  - Sedation, dissociation after administration.
  - Potential for abuse and misuse (Controlled Substance Schedule III). Consider risks/benefits in patients at higher risk of abuse.
  - Spravato REMS
  - Increased risk of suicidal thoughts and behaviors in pediatric and young adult patients taking antidepressants.

Spravato [package insert]. Titusville, NJ: Janssen Pharmaceuticals, Inc.; March 2019

Popova – Esketamine Trial Design

- Phase 3 clinical trial on switching patients with TRD to esketamine and a new antidepressant versus placebo nasal spray and a new antidepressant.
- Double-blind, active-controlled, multicenter study at 39 outpatient referral centers between August 2015 and November 2017.
- 227 patients underwent computer-generated 1:1 randomization to receive double-blind treatment with either esketamine (56 mg or 84 mg) or placebo nasal spray administered twice weekly

Popova V, et al. *Am J Psychiatry*. 2019;176(6):428-438

Popova – Esketamine Outcomes

- Outcomes
  - Primary Outcome: MADRS score change from baseline to day 28
  - Key Secondary Outcomes – Hierarchal testing
    - Percentage of patients with onset of clinical response
  - Safety Endpoints
    - Incidence of adverse events
    - Sedation: Modified Observer's Assessment of Alertness/Sedation scale every 15 minutes from before dosing to 90 minutes after dosing

Popova V, et al. *Am J Psychiatry*. 2019;176(6):428-438

Popova – Esketamine Results

- Mean change in baseline MADRS score after 28 days
  - Statistically significant difference in the change from baseline MADRS score after 28 days favoring esketamine group
    - **Least means difference: -4.4 points**
- Pre-specified treatment difference of 6.5 points in MADRS score between esketamine and placebo groups was not met!

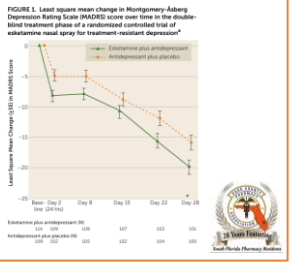


FIGURE 1. Least square mean change in Montgomery-Åsberg Depression Rating Scale (MADRS) score over time in the double-blind treatment phase of a randomized controlled trial of esketamine nasal spray for treatment-resistant depression[a]

Popova V, et al. *Am J Psychiatry*. 2019;176(6):428-438

Popova – Esketamine Results

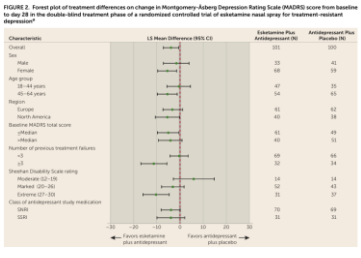


FIGURE 2. Forest plot of treatment differences on change in Montgomery-Åsberg Depression Rating Scale (MADRS) score from baseline to day 28 in the double-blind treatment phase of a randomized controlled trial of esketamine nasal spray for treatment-resistant depression[a]

The esketamine group favored the following patients with TRD:

- Higher severity of functional impairment from depression (based on SDS)
- Patients with at least 3 previous treatment failures
- Female patients
- Patients aged 45 – 64 years old

Popova V, et al. *Am J Psychiatry*. 2019;176(6):428-438

Popova – Esketamine Results

- Hierarchical testing of key secondary endpoints
  - ≥ 50% improvement from baseline in MADRS score by day 2 maintained to day 28: no difference
    - Esketamine group: 9/114 (7.9%)
    - Placebo group: 5/109 (4.6%)
  - Analysis not performed for other two key secondary endpoints due to lack of statistical significance

Popova V, et al. *Am J Psychiatry*. 2019;176(6):428-438

Popova - Esketamine Safety Outcomes

- Sedation: statistically significant difference between groups
  - Esketamine group: 66/115 patients (57.4%)
  - Placebo group: 11/109 patients (10.1%)
  - Not associated with hypoxemia
- Nine patients experienced one or more adverse events leading to discontinuation

TABLE 3. Most frequently reported adverse events in the double-blind treatment phase of a randomized controlled trial of esketamine nasal spray for treatment-resistant depression[a]

	Esketamine Plus Antidepressant (N=114)		Antidepressant Plus Placebo (N=109)	
Adverse Event	N	%	N	%
Dissociation	30	26.1	4	3.7
Nausea	30	26.1	7	6.4
Vertigo	30	26.1	3	2.8
Dysgeusia	28	24.3	13	11.9
Dizziness	24	20.9	5	4.6
Headache	23	20.0	39	37.4
Somnolence	15	13.0	7	6.4
Blurred vision	14	12.2	3	2.8
Paresthesia	13	11.3	1	0.9
Anxiety	12	10.4	5	4.6
Increased blood pressure	11	9.6	1	0.9
Insomnia	11	9.6	5	4.6
Vomiting	11	9.6	2	1.8
Diarrhea	10	8.7	10	9.2
Dry mouth	9	7.8	3	2.8
Feeling drunk	9	7.8	1	0.9
Oral hypoesthesia	9	7.8	1	0.9
Oral paresthesia	9	7.8	1	0.9
Throat irritation	9	7.8	5	4.6
Postural dizziness	8	7.0	1	0.9
Hypoesthesia	8	7.0	1	0.9
Nasal discomfort	8	7.0	2	1.8
Fatigue	5	4.3	6	5.5

[a] The table lists adverse events with an incidence >5% in either treatment group, listed in decreasing order based on incidence within the esketamine plus antidepressant group, and in alphabetical order for events with the same incidence.

Popova V, et al. *Am J Psychiatry*. 2019;176(6):428-438

Popova – Esketamine Trial Overview

- Strengths
  - Balanced cohort based on baseline MADRS score
  - Found significant differences in change of MADRS score after 28 days in esketamine group for patients with:
    - Extreme functional severity
    - At least three previous treatment failures
- Weaknesses
  - Limited demographics based on race; Most patients identified as white
  - Patients enrolled that did not meet DSM-V definition of TRD
  - Prespecified treatment difference for primary endpoint was not achieved despite statistically significant difference favoring esketamine

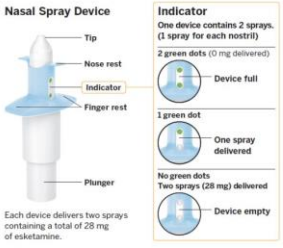
Popova V, et al. *Am J Psychiatry*. 2019;176(6):428-438

Esketamine

- Administration:
  - Intranasal administration only.
  - Must be self-administered under direct supervision of a healthcare provider.

Spravato [package insert]. Titusville, NJ: Janssen Pharmaceuticals, Inc.; March 2019

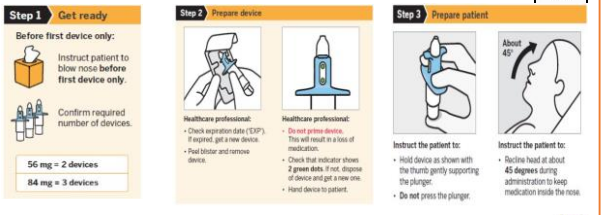
Esketamine



Spravato [package insert]. Titusville, NJ: Janssen Pharmaceuticals, Inc.; March 2019

Esketamine

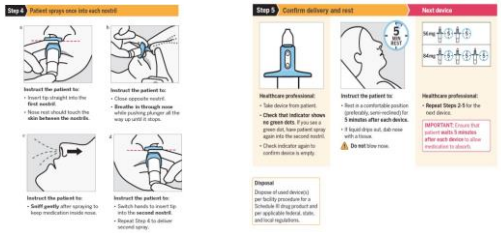
Administration



Spravato [package insert]. Titusville, NJ: Janssen Pharmaceuticals, Inc.; March 2019

Esketamine

Administration



Spravato [package insert]. Titusville, NJ: Janssen Pharmaceuticals, Inc.; March 2019

CE Question

- What should the certified healthcare provider supervising the patient's self-administration of esketamine consider during the administration process?

A. Two red dots on the nasal device indicators indicate that the device is full of medication.
B. The nasal devices cannot be primed as this will result in the loss of medication.
C. The patient should blow their nose after each spray of medication.
D. The patient should be given three consecutive sprays without breaks as esketamine has short stability.

CE Question

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C. The patient should blow their nose after each spray of medication.
D. The patient should be given three consecutive sprays without breaks as esketamine has short stability.

Spravato REMS

- Esketamine is only available through a restricted distribution program Spravato REMS due to the risks of serious adverse outcomes from sedation, dissociation, and abuse and misuse.
- Intended for use only in a certified healthcare setting
- Intended for patient administration under the direct observation of a healthcare provider.
- Esketamine may never be directly dispensed to a patient for home use

Spravato® REMS. https://www.spravatorems.com/

Spravato REMS

- Important requirements:
  - Healthcare settings must be certified in the program and ensure that esketamine is:
    - Only dispensed to certified healthcare settings
    - Administered by patients under the direct observation of a healthcare provider
    - Monitored by a healthcare provider for at least 2 hours after administration
    - Relevant staff involved in prescribing, dispensing, and administering of esketamine must be trained and documentation of training must always be maintained.
  - Pharmacies must be certified in the REMS and must only dispense esketamine to healthcare settings that are certified in the program.
  - Notify program if transfer of patient treatment from one REMS-certified healthcare setting to another

Spravato® REMS. https://www.spravatorems.com/

Spravato REMS

Registration Type	Requirements and Caveats
Inpatient Healthcare Setting	• Not required to enroll patients in program • Not required to submit Patient Monitoring Forms
Pharmacy	• Required for outpatient dispensing only! • Must verify Outpatient Healthcare Setting is certified prior to dispensing esketamine • A separate Spravato REMS registration is not required if an inpatient pharmacy shares the same physical location and DEA license with registered Inpatient Healthcare Setting

Outpatient Healthcare Setting	• Prescriber must enroll patient into programs by completing Patient Enrollment Form and submitting
	• Before treatment: patient counseling from healthcare provider
	• During treatment:
	  ○ Supervise patient administration of esketamine
	  ○ Monitor each patient for at least 2 hours after administration of esketamine
	  ○ Submit Patient Monitoring form

Patients	• Enroll in Spravato REMS program if receiving treatment from Outpatient Healthcare Setting • Receive counseling, self-administer esketamine under direct observation from healthcare provider, and be monitored for at least 2 hours post-administration

Spravato® REMS. https://www.spravatorems.com/

CE Question

- Which of the following is true regarding the Spravato REMS program?

A. Esketamine may be dispensed directly to the patient for home use by a certified pharmacy
B. Spravato REMS program does not require notification of transfer in patient treatment if transfer of care is from one REMS-certified Healthcare Setting to another certified setting.
C. Relevant staff involved in prescribing, dispensing, and administering of esketamine must be trained and documentation of training must always be maintained.
D. Patients who do not have a history of serious adverse events following administration of esketamine may be discharged immediately after administration of esketamine.

CE Question

- Which of the following is true regarding the Spravato REMS program?

A. Esketamine may be dispensed directly to the patient for home use by a certified pharmacy
B. Spravato REMS program does not require notification of transfer in patient treatment if transfer of care is from one REMS-certified Healthcare Setting to another certified setting.
C. Relevant staff involved in prescribing, dispensing, and administering of esketamine must be trained and documentation of training must always be maintained.
D. Patients who do not have a history of serious adverse events following administration of esketamine may be discharged immediately after administration of esketamine.

Esketamine: Role in Therapy

- Esketamine can be used as a concomitant agent; it has been administered with optimized dosing of the following antidepressants: duloxetine, venlafaxine ER, sertraline, and escitalopram
- In the short-term trial, esketamine demonstrated a treatment benefit in TRD over placebo in patients with at least 3 treatment failures for MDD and higher severity of functional impairment from MDD
- Careful consideration should be taken in patients with substance use disorder due to risk of abuse and adverse effects related to dissociation

Popova V, et al. *Am J Psychiatry*. 2019;176(6):428-438
Daly EJ, et al. *JAMA Psychiatry*. 2019;76(9):893-903

Summary

- Dextromethorphan/bupropion is approved for use in adult patients with major depressive disorder (MDD)
- The use of dextromethorphan/bupropion should be restricted to patients with one or less treatment failure of previous antidepressant for MDD; dextromethorphan/bupropion has not been studied in patients with treatment-resistant depression (TRD)
- Intranasal esketamine is approved for use in adult patients with treatment-resistant depression
- Esketamine is only available through the Spravato REMS program due to high risk of abuse, dissociative, and sedative adverse effects

References

- Tabuteau H, Jones A, Anderson A, Jacobson M, Iosifescu DV. Effect of AXS-05 (Dextromethorphan-Bupropion) in Major Depressive Disorder: A Randomized Double-Blind Controlled Trial. *Tabuteau H, et al. Am J Psychiatry.* 2022;179(7):490-499
- Iosifescu DV, Jones A, O'Gorman C, et al. Efficacy and Safety of AXS-05 (Dextromethorphan-Bupropion) in Patients With Major Depressive Disorder: A Phase 3 Randomized Clinical Trial (GEMINI). *Iosifescu DV, et al. J Clin Psychiatry.* 2022;83(4):21m14345
- Popova V, Daly EJ, Trivedi M, et al. Efficacy and Safety of Flexibly Dosed Esketamine Nasal Spray Combined With a Newly Initiated Oral Antidepressant in Treatment-Resistant Depression: A Randomized Double-Blind Active-Controlled Study. *Am J Psychiatry.* 2019;176(6):428-438
- Daly EJ, Trivedi MH, Janik A, et al. Efficacy of Esketamine Nasal Spray Plus Oral Antidepressant Treatment for Relapse Prevention in Patients With Treatment-Resistant Depression: A Randomized Clinical Trial. *JAMA Psychiatry*. 2019;76(9):893-903
- Stahl SM. Dextromethorphan/Bupropion: A novel oral NMDA (N-methyl-d-aspartate) receptor antagonist with multimodal activity. *CNS Spectr.* 2019;24(5):461-466
- Auvelity [package insert]. New York, NY: Axsome Therapeutics, Inc; December 2022. Accessed September 2024
- Spravato [package insert]. Titusville, NJ: Janssen Pharmaceuticals, Inc.; March 2019. Accessed September 2024
- Spravato® REMS. Accessed December 22, 2024. https://www.spravatorems.com/

References

- American Psychiatric Association, 2022. Depression fact sheet. World Health Organization. December 2019
- Montgomery, S.A. et al. British Journal of Psychiatry. 1979; 134, 382-389
- Hamilton M. A rating scale for depression. J Neurol Neurosurg Psychiatry 1960; 23:56–62
- Rush AJ, Trivedi MH, Wisniewski SR, et al. Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: a STAR*D report. Am J Psychiatry. 2006;163(11):1905-1917. doi:10.1176/ajp.2006.163.11.1905
- Pigott HE, Kim T, Xu C, Kirsch I, Amsterdam J. What are the treatment remission, response and extent of improvement rates after up to four trials of antidepressant therapies in real-world depressed patients? A reanalysis of the STAR*D study's patient-level data with fidelity to the original research protocol. BMJ Open. 2023;13(7):e063095. Published 2023 Jul 25. doi:10.1136/bmjopen-2022-063095
- Pae CU, et al. CNS Drugs. 2011;25(2):109-127
- Berman RM, Marcus RN, Swanink R, et al. The efficacy and safety of aripiprazole as adjunctive therapy in major depressive disorder: a multicenter, randomized, double-blind, placebo-controlled study. J Clin Psychiatry. 2007;68(6):843-853. doi:10.4088/jcp.v68n0604Mohamed S, et al. JAMA. 2017;318(2):132–145
- Thase ME, Youakim JM, Skuban A, et al. Efficacy and safety of adjunctive brexpiprazole 2 mg in major depressive disorder: a phase 3 randomized, placebo-controlled study in patients with inadequate response to antidepressants. J Clin Psychiatry. 2015;76(9):1224 doi:10.4088/JCP.14m09688
- El-Khalili N, et al. International Journal of Neuropsychopharmacology, Volume 13, Issue 7, August 2010, Pages 917–932
- Sanacora G, Zarate CA, Krystal JH, Manji HK. Targeting the glutamatergic system to develop novel, improved therapeutics for mood Nat Rev Drug Discov. 2008;7(5):426-437Berman RM, et al. Biol Psychiatry. 2000;47(4):351-354

References

- Singh JB, Fedgchin M, Daly EJ, et al. A Double-Blind, Randomized, Placebo-Controlled, Dose-Frequency Study of Intravenous Ketamine in Patients With Treatment-Resistant Depression. Am J Psychiatry. 2016;173(8):816-826.
- Dodd S, Norman TR, Eyre HA, et al. Psilocybin in neuropsychiatry: a review of its pharmacology, safety, and efficacy. CNS Spectr. 2023;28(4):416-426. doi:10.1017/S1092852922000888 Spectrums. 2023;28(4):416-426
- Davis AK, Barrett FS, May DG, et al. Effects of Psilocybin-Assisted Therapy on Major Depressive Disorder: A Randomized Clinical Trial [published correction appears in JAMA Psychiatry. 2021 Feb 10:569. doi: 10.1001/jamapsychiatry.2020.4714]. JAMA Psychiatry. 2021;78(5):481-489.
- Palfreyman M, et al. In Vitro and In Vivo Profile of CYB003. Cybin Inc

Guideline Updates on Schizophrenia: Current and Emerging Treatments

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January 26th, 2025

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Objectives

1. Elaborate on the current FDA- approved medications for schizophrenia and their mechanisms of action
2. Demonstrate recent advancements in schizophrenia treatments, particularly muscarinic agents
3. Evaluate the efficacy and side effect profiles of emerging therapies in the treatment of schizophrenia

2

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Overview of Schizophrenia

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The Scope of Schizophrenia

➢ Schizophrenia is a chronic psychiatric disorder characterized by:

Positive symptoms
- delusions, hallucinations

Negative symptoms
- blunted affect, anhedonia, social withdrawal, avolition

Cognitive symptoms
- speech abnormalities, cognitive deficit

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The Scope of Schizophrenia

➢ Nearly 20 million people worldwide are diagnosed with schizophrenia
➢ Early adulthood onset
➢ High morbidity and significant impact on quality of life
➢ Economic burden due to healthcare costs, including frequent hospitalizations, and loss of productivity

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The Scope of Schizophrenia

➢ Etiology:

Genetic factors	Neurodevelopmental factors	Environmental triggers
• Rates of ~50% in identical twins	• Early-life/maternal infections, hypoxia, and maternal stress	• Drug use, psychosocial stress, urban living

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Pathophysiology of Schizophrenia

Dopamine Hypothesis:

- Hyperactivity in the mesolimbic pathway -> Positive symptoms (hallucinations, delusions)
- Hypoactivity in the mesocortical pathway -> Negative and cognitive symptoms

Glutamate Hypothesis:

- NMDA receptor hypofunction/misfunction leads to dysregulation of excitatory and inhibitory signaling

Structural Brain Changes:

- Reduced gray matter volume in prefrontal cortex; enlarged ventricles

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Typical Antipsychotics

- ➢ Examples include haloperidol, fluphenazine, chlorpromazine
- ➢ Mechanism of Action:
  - Potent dopamine (D2) receptor blockade
- ➢ Efficacy:
  - ➢ Particularly effective for positive symptoms
- ➢ Side effects:
  - ➢ Extrapyramidal symptoms (EPS): acute dystonia, akathisia, psuedoparkinsonianism
  - ➢ Tardive dyskinesia

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Atypical Antipsychotics

- ➢ Ex: clozapine, risperidone, olanzapine, quetiapine, and aripiprazole
- ➢ Mechanism of Action:
  - Block dopamine D2 receptors, but also modulate serotonin 5-HT2a and 1a
  - Aripiprazole is also a partial agonist at D2 and antagonistic at the 5HT2a receptor
- ➢ Advantages:
  - ➢ Lower risk of EPS and tardive dyskinesia
  - ➢ Alleges to cover positive, negative and cognitive symptoms

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Atypical Antipsychotics (Cont.)

- Side effects:
  - Metabolic syndrome: weight gain, insulin resistance, dyslipidemia
  - Sedation, orthostasis, and hypotension
  - Hyperprolactinemia
- Dualistic mechanism of actions allows for different uses and indications

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Clozapine: A Special Case

- Indication:
  - Typically reserved for treatment-resistant schizophrenia
- Mechanism of Action:
  - Broad receptor activity (Dopamine, 5-HT2a, alpha-adrenergic, muscarinic antagonism)
- Clinical Benefits:
  - Superior efficacy in reducing positive and negative symptoms
  - Efficacious in suicidality
- Unique Black Box Warnings:
  - Seizures, agranulocytosis, orthostasis, myocarditis
    - Unique monitoring

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Additional Indications for Antipsychotics

- Typical antipsychotics:

Typical antipsychotic	Additional Indication(s)
haloperidol	Tourette syndrome
prochlorperazine	Generalized non-psychotic anxiety
trifluoperazine	Generalized non-psychotic anxiety

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Additional Indications for Antipsychotics

Atypical antipsychotic	Additional Indication(s)
aripiprazole	Bipolar disorder monotherapy or adjunct; adjunct for major depression; irritability in autistic children
brexpiprazole	Agitation associated with Alzheimer's
asenapine	Bipolar disorder type 1
olanzapine	Bipolar disorder, adjunct in depression, agitation associated with schizophrenia and mania

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Additional Indications for Antipsychotics

Atypical antipsychotic	Additional Indication(s)
paliperidone	Schizoaffective disorder
quetiapine	Bipolar disorder (acute mania, depression and maintenance)
risperidone	Bipolar disorder (manic/mixed), irritability in autism
ziprasidone	Bipolar disorder (manic/mixed, maintenance), acute agitation in schizophrenia

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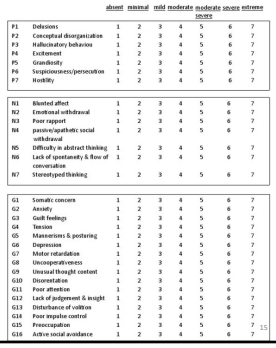
Assessment of Treatment

- PANSS Score- Positive and Negative Syndrome Scale
- Measures symptom severit in patients with schizophre
- Gold standard for evaluatin the effects of psychopharmacological treatments



		absent	minimal	mild	moderate	moderate severe	severe	extreme
P1	Delusions	1	2	3	4	5	6	7
P2	Conceptual disorganization	1	2	3	4	5	6	7
P3	Hallucinatory behaviou	1	2	3	4	5	6	7
P4	Excitement	1	2	3	4	5	6	7
P5	Grandiosity	1	2	3	4	5	6	7
P6	Suspiciousness/persecution	1	2	3	4	5	6	7
P7	Hostility	1	2	3	4	5	6	7
N1	Blunted affect	1	2	3	4	5	6	7
N2	Emotional withdrawal	1	2	3	4	5	6	7
N3	Poor rapport	1	2	3	4	5	6	7
N4	passive/apathetic social withdrawal	1	2	3	4	5	6	7
N5	Difficulty in abstract thinking	1	2	3	4	5	6	7
N6	Lack of spontaneity & flow of conversation	1	2	3	4	5	6	7
N7	Stereotyped thinking	1	2	3	4	5	6	7
G1	Somatic concern	1	2	3	4	5	6	7
G2	Anxiety	1	2	3	4	5	6	7
G3	Guilt feelings	1	2	3	4	5	6	7
G4	Tension	1	2	3	4	5	6	7
G5	Mannerisms & posturing	1	2	3	4	5	6	7
G6	Depression	1	2	3	4	5	6	7
G7	Motor retardation	1	2	3	4	5	6	7
G8	Uncooperativeness	1	2	3	4	5	6	7
G9	Unusual thought content	1	2	3	4	5	6	7
G10	Disorientation	1	2	3	4	5	6	7
G11	Poor attention	1	2	3	4	5	6	7
G12	Lack of judgement & insight	1	2	3	4	5	6	7
G13	Disturbance of volition	1	2	3	4	5	6	7
G14	Poor impulse control	1	2	3	4	5	6	7
G15	Preoccupation	1	2	3	4	5	6	7
G16	Active social avoidance	1	2	3	4	5	6	7

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Novel Schizophrenia Treatments

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Unmet Needs in Schizophrenia

- Persistent negative symptoms remain inadequately treated
- Cognitive deficits are not directly addressed by current therapies
- Prevalent side effect profiles in the form of metabolic syndrome and EPS
- Limited options for individuals with treatment resistance

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Emerging Treatments: Muscarinic Agents

- Novel focus on muscarinic acetylcholine receptors (mAChRs) for symptomatic improvement
- Mechanism of Action:
  - Targets M1 and M4 receptor subtypes to modulate psychotic processes (agonism)
- Advantages:
  - Potential to further address negative and cognitive symptoms
  - Reduction in risk of dopaminergic and serotonergic side effects (EPS, metabolic syndrome, etc.)

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Cobenfy (Xanomeline-Trospium)

- Cobenfy is composed of two ingredients
  - **Xanomeline** is the central muscarinic (M1/M4) agonist utilized for schizophrenia management
  - **Trospium** is utilized to mitigate peripheral side effects via muscarinic antagonism
- Clinical trial results:
  - Significant placebo-subtracted PANSS scores
  - FDA approved September 2024

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EMERGENT-1 Trial

- Phase-2 trial
  - Evaluate safety and tolerability, including side effects
  - Assess efficacy through changes in PANSS (Positive and Negative Syndrome Scale) scores
- LS mean difference in PANSS total score at week 5: -11.6% ($p < 0.001$)
- Significant improvement across all PANSS subscales
- Most common side effects: nausea, vomiting, constipation

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EMERGENT-2 Trial

- Phase-3 trial
  - Evaluate the efficacy in reducing the PANSS total score in inpatients diagnosed with schizophrenia
- Was not associated with adverse events seen with traditional antipsychotics (EPS, metabolic issues, or prolactin elevation)
- Hypertension was higher in treatment group (10% to 1%)
- Most common side effects: nausea, vomiting, constipation
- LS mean difference in PANSS total score: -9.6%

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EMERGENT-3 Trial

- Phase-3 trial
  - Similar endpoints to EMERGENT-2
- Statistically significant 8.4-point greater reduction in PANSS total score compared to placebo by week 5
- Most common side effects: nausea and vomiting
- Most side effects were mild to moderate and subsided within the first few weeks
- Transient increases in blood pressure and heart rate were noted

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Cobenfy Place in Therapy

- Contraindications: Narrow-angle glaucoma, allergies to ingredients, gastric retention, moderate or severe hepatic impairment, urinary retention
- Warning for angioedema, heart rate increase, CNS effects, and anticholinergic side effects
- Cobenfy, and likely other agents, presents a "third" side effect profile to choose from
  - This leads to entire patient populations that cannot use this medication (elderly, etc.)

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Other Emerging Therapies

- Other muscarinic agents:
  - Emraclidine (M4 selective) – Cervel Therapeutics
  - NBI-1117568 (M4 selective) – Neurocrine
    - Possible further drugs that differ in proportions of M1/M4 selectivity (M4 preferring/M1 preferring)
- Trace Amine-Associated Receptor 1 (TAAR1) Agonists
  - Ulotaront – Sumitomo Pharma
- Psychedelics
  - Investigating psilocybin and MDMA for severe, refractory cases

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Conclusion

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Guideline Updates

- Antipsychotics equally efficacious
  - selection based on side effects and tolerability; continue medication if effective
- Treatment-resistant schizophrenia or suicidality: Clozapine
- Long-acting injectable antipsychotics benefit in non-compliance
- Newer agents not currently in already-existing guidelines
  - Consider as third side-effect profile to choose from

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Knowledge Check

1. What side effect is most commonly associated with olanzapine?
   A. Extrapyramidal symptoms
   B. Constipation
   C. Metabolic syndrome
   D. Weight loss

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Knowledge Check

1. What side effect is most commonly associated with olanzapine?
   A. Extrapyramidal symptoms
   B. Constipation
   C. **Metabolic syndrome**
   D. Weight loss

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Knowledge Check

2. What is the mechanism of action for aripiprazole?
   A. D2 receptor blocker
   B. D2 partial agonist + antagonism at 5HT2a receptor
   C. 5HT2a partial agonist + antagonism at D2 receptor
   D. 5HT1a receptor blocker

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Knowledge Check

2. What is the mechanism of action for aripiprazole?
   A. D2 receptor blocker
   B. **D2 partial agonist + antagonism at 5HT2a receptor**
   C. 5HT2a partial agonist + antagonism at D2 receptor
   D. 5HT1a receptor blocker

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Knowledge Check

3. What is the novel mechanism of the xanomeline in the treatment of schizophrenia?

A. Alpha blockage
B. M1 and M4 blockade
C. M1 and M4 agonism
D. Histamine agonism

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Knowledge Check

3. What is the novel mechanism of the xanomeline in the treatment of schizophrenia?

A. Alpha blockage
B. M1 and M4 blockade
C. **M1 and M4 agonism**
D. Histamine agonism

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References

- Stahl SM. *Stahl's essential psychopharmacology*. Published online July 29, 2021. doi:10.1017/9781108975292
- Muench J, Hamer AM. Adverse effects of antipsychotic medications. *Am Fam Physician*. 2010;81(5):617-622.
- Cobenfy [package insert]. Princeton, NJ: Bristol-Myers Squibb Company; 2024. Accessed December 21, 2024
- Bodick NC, Offen WW, Levey AI, et al. Effects of xanomeline, a selective muscarinic receptor agonist, on cognitive function and behavioral symptoms in Alzheimer disease. *Arch Neurol*. 1997;54(4):465-473. doi:10.1001/archneur.1997.00550160091022
- Chan WY, McKinzie DL, Bose S, et al. Allosteric modulation of the muscarinic M4 receptor as an approach to treating schizophrenia. *Proc Natl Acad Sci U S A*. 2008;105(31):10978-10983. doi:10.1073/pnas.0800567105
- Berman JA, Talmage DA, Role LW. Cholinergic circuits and signaling in the pathophysiology of schizophrenia. *Int Rev Neurobiol*. 2007;78:193-223. doi:10.1016/S0074-7742(06)78007-2

33

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References

- Correll CU, Angelov AS, Miller AC, Weiden PJ, Brannan SK. Safety and tolerability of KarXT (xanomeline–trospium) in a phase 2, randomized, double-blind, placebo-controlled study in patients with schizophrenia. Schizophrenia. 2022;8(1). doi:https://doi.org/10.1038/s41537-022-00320-1
- Kaul I, Sawchak S, Correll CU, et al. Efficacy and safety of the muscarinic receptor agonist KarXT (xanomeline–trospium) in schizophrenia (EMERGENT-2) in the USA: results from a randomised, double-blind, placebo-controlled, flexible-dose phase 3 trial. The Lancet. 2023;403(10422). doi:https://doi.org/10.1016/s0140-6736(23)02190-6
- Kaul I, Sawchak S, Walling DP, et al. Efficacy and Safety of Xanomeline-Trospium Chloride in Schizophrenia. JAMA psychiatry. Published online May 1, 2024. doi:https://doi.org/10.1001/jamapsychiatry.2024.0785
- McKenna A, Tice JA, Whittington MD, et al. KarXT for schizophrenia-effectiveness and value: A summary from the Institute for Clinical and Economic Review's New England Comparative Effectiveness Public Advisory Council. J Manag Care Spec Pharm. 2024;30(6):624-628. doi:10.18553/jmcp.2024.30.6.624

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Any Questions?

Please email me at:
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Guideline Updates on Bipolar Disorder: Current and Emerging Treatments

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January 26th, 2025

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Objectives

1. Assess the clinical implications of novel treatment strategies in the management of bipolar disorder
2. Identify the mood stabilizers and atypical antipsychotics used in the treatment of bipolar disorder

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Outline

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Patient Case

BD is a 22-year-old, white female who presents to your clinic with feelings of low mood, anhedonia, and constant tiredness for the past month

- Reports her **symptoms to be severe** and interfering with her work and social activities
- Denies suicidal or homicidal ideation
- Denies audio or visual hallucinations
- **No relevant past psychiatric history**
- All relevant **lab work within normal limits**

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Patient Case (cont.)

BD is open to starting medication today to help manage her symptoms

Which of the following would you recommend?

A. Lithium 300 mg two times daily
B. Effexor XR (venlafaxine HCl ER) 37.5 mg daily
C. Abilify (aripiprazole) 5 mg daily
D. Seroquel XR (quetiapine ER) 50 mg daily at bedtime

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Patient Case (cont.)

BD is open to starting medication today to help manage her symptoms

Which of the following would you recommend?

A. Lithium 300 mg two times daily
B. **Effexor XR (venlafaxine HCl ER) 37.5 mg daily**
C. Abilify (aripiprazole) 5 mg daily
D. Seroquel XR (quetiapine ER) 50 mg daily at bedtime

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Patient Case (cont.)

Two months after starting escitalopram 5 mg daily, BD is seen for a follow-up visit and presents with the following:

- Increased energy
- Flight of ideas
- Grandiosity
- Lack of sleep (~3 hours/night for the last week)
- Increase in risky spending

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Bipolar Disorder Background

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Definitions

Mania	• Severe social or occupational impairment • May require hospitalization • Last at least 7 days • Can have psychotic features • Can have high libido • Lack of sleep
Hypomania	• No significant social or occupational impairment • No hospitalization • Lasts no more than 4 days • No psychotic features • Can have high libido • Lack of sleep
Mixed episode	• Meeting requirements of both manic and major depressive episodes each day for at least 1 week
Rapid cycling	• Greater than 4 mood episodes within 12 months
Bipolar I	• Requires at least one manic or mixed episode
Bipolar II	• Requires at least 1 hypomanic episode and at least 1 depressive episode of at least 4 months
Cyclothymia	• 2 or more years of switching between hypomania and major depressive episodes that do not meet requirements for diagnosis of bipolar disorder or MDD

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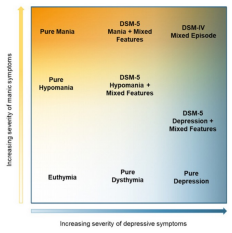
Spectrum of Symptoms[1]



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Epidemiology

- From 2019 data, ~40 million people globally were living with bipolar disorder[2]
- Distribution is about equal among different sexes, races, ethnicities, and urban vs rural environments[3]
- Mean age of onset is in the early twenties[3]
- People with bipolar disorder live 10 years less than the general population, on average[4]
  - Driven by substance use, suicide, and comorbid conditions

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Risk Factors

Unknown cause, but believed to be due to genetic and environmental factors[3]

- Genetic predisposition
- Likely heritable as prevalence is high among those with 1st degree relative with bipolar disorder
- Childhood maltreatment
- Comorbid substance use

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Novel Test in the Pipeline for Bipolar Depression

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Current Issues in Diagnosis

- A first presentation of bipolar depression is clinically indistinguishable from unipolar depression
- Estimates of patients transitioning to bipolar depression within three years of a major depressive disorder diagnosis range from 20-30%[5]
- Some research has found that ~60% of patients with bipolar disorder were initially misdiagnosed as a major depressive disorder[6]
- Screening tools such as the Mood Disorder Questionnaire have a sensitivity of ~80% and specificity of ~70%[7]

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Blood Test Under Investigation[6]

- Uses a machine learning model/artificial intelligence to analyze data from blood of the post-transcriptional modifications made at specific ribonucleic acid (RNA) sites
- Aims to distinguish between bipolar depression and major depressive disorder
- First published study in 2022
- External validation study in April 2024

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Background of Test[6]

- RNA can be altered by epitranscriptomic mechanisms such as RNA editing
- One example of RNA editing is adenosine-to-inosine conversion by deamination
- These editing events can alter the effect of the gene
  - Altering permeability of ion channels
  - Impacting response to neurotransmitters
- Certain genes may be edited differently between major depressive disorder and bipolar depression

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External Validation Study Results[6]

- Biomarkers selected: *GAB2,* IFNAR1*, LYN, MDM2,* PRKCB*,* IL17RA*, PTPRC,* ZNF267
- Data from external replication cohort (n=143)
  - Sensitivity = 86.4%
  - Specificity = 80.8%
- Testing was found to be statistically significant ($p<0.05$)

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Current Pharmacologic Treatments for Bipolar Disorder

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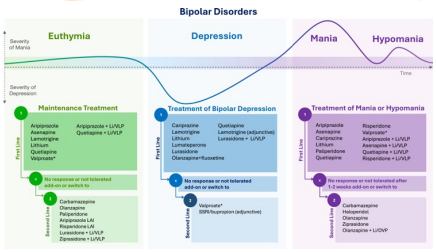
Current Treatments[8]



Generally, treatment consists of an antipsychotic, a mood stabilizer, or a combination of the two

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Lithium

- Labelled indications for mania and maintenance treatment, but can be used in all phases
- Like clozapine, lithium has shown a decrease in suicidal behaviors
- Side effects:
  - Tremor (fine hand tremor is normal, but coarse tremor may indicate toxicity)
  - Polydipsia and polyuria
  - Hypothyroid
  - Nausea/vomiting
- May interact with thiazide diuretics, leading to an increase in lithium concentration
- Therapeutic range: 0.8-1.2 mEq/L (acute mania) or 0.6-1 mEq/L (maintenance)

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Anti-seizure medications

- Valproate
  - Labelled for use in acute mania, but may be used in all phases
  - Therapeutic range: 50-125 mcg/mL
  - Serious adverse effects: Hepatotoxic (avoid in liver injury/cirrhosis), CNS depression, may cause hyperammonemia (encephalopathy), pancreatitis, hypersensitivity reaction (SJS, DRESS)
- Carbamazepine
  - Labelled for the acute treatment phases, but may be used in all phases
  - Therapeutic range: 4-12 mcg/mL
  - CYP3A4 auto-inducer
  - Adverse effects: nausea/vomiting, dizziness, drowsiness, ataxia, hepatotoxicity, hyponatremia, and blood dyscrasias

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Anti-seizure medications (cont.)

- Lamotrigine
  - Labelled for use in maintenance, may be used off-label for bipolar depression, but is not indicated for mania
  - Serious adverse effects: hypersensitivity reaction (SJS, DRESS), blood dyscrasias
  - Dosing is dependent on if the patient is taking an interacting medication
    - Inhibitor (e.g. valproate): blue dose pack (titrates to 100mg/day)
    - No interacting medication: orange dose pack (titrates to 200mg/day)
    - Inducer (e.g. carbamazepine): green dose pack (titrates to 400mg/day)

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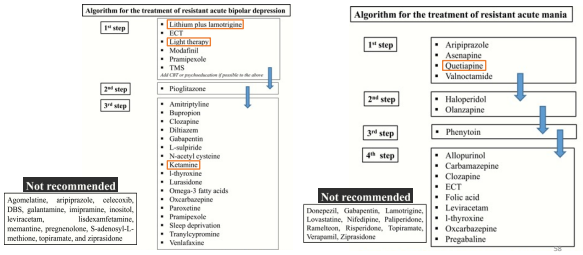
CINP: International College of Neuropsychopharmacology
ECT: electroconvulsive therapy
TMS: transcranial magnetic stimulation

CINP Guidelines on Treatment Resistant Bipolar Disorders[9]



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Emerging Therapies

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Emerging Medications

- BHV-7000[10]
  - Selective activator of Kv7.2/3 potassium channels in the axonal initial segment which can help reduce neuronal firing and thereby reduce hyperexcitable states
  - Main role being examined is in epilepsy but may have a role in the treatment of mania
- JNJ-55308942[11]
  - Antagonist of the ATP-gated P2X7 ion channel widely expressed on microglia
  - Activation of P2X7 leads to the release of proinflammatory cytokines (IL-1β and IL-18) which lead to neuroinflammation and could be linked to the pathogenesis of depression
  - May be beneficial in neurodegenerative disorders as well as depressive states
- GH001[12]
  - Serotonergic agonist, psychedelic drug delivered by inhalation
  - Small-scale trials in treatment resistant depression, postpartum depression and bipolar disorder type II

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Knowledge Check

1. Which of the following is the most appropriate drug regimen for a patient with bipolar disorder type I in acute mania with suicidal ideation?
   A. Lamotrigine
   B. Quetiapine + aripiprazole
   C. Cariprazine
   D. Quetiapine + lithium

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Knowledge Check

1. Which of the following is the most appropriate drug regimen for a patient with bipolar disorder type I in acute mania with suicidal ideation?
   A. Lamotrigine
   B. Quetiapine + aripiprazole
   C. Cariprazine
   D. **Quetiapine + lithium**

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References

1. GBD 2019 Mental Disorders Collaborators. Global, regional, and national burden of 12 mental disorders in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. Lancet Psychiatry. 2022;9:137–50. doi:10.1016/S2215-0366(21)00395-3.
2. Rowland TA, Marwaha S. Epidemiology and risk factors for bipolar disorder. Ther Adv Psychopharmacol. 2018;8(9):251-269. Published 2018 Apr 24. doi:10.1177/2045125318769235
3. Kwun Nam Chan J, Ho Yi Yong C, Sau Man Wong C, et al. Life expectancy and years of potential life lost in bipolar disorder: systematic review and meta-analysis. Br J Psychiatry. 2022;221(3):567–76. doi:10.1192/bjp.2022.19.
4. Yatham LN, Chakrabarty T, Bond DJ, et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) recommendations for the management of patients with bipolar disorder with mixed presentations. Bipolar Disord. 2021;23(8):747–788. doi:10.1111/bdi.13131
5. McIntyre RS, Berk M, Brietzke E, et al. Bipolar disorders. Lancet. 2020 Dec 05;396(10265):1841-1856
6. Salvetat, N., Checa-Robles, F.J., Patel, V. et al. A game changer for bipolar disorder diagnosis using RNA editing-based biomarkers. Transl Psychiatry 12, 182 (2022). https://doi.org/10.1038/s41398-022-01938-6
7. Wang YY, Xu DD, Liu R, et al. Comparison of the screening ability between the 32-item Hypomania Checklist (HCL-32) and the Mood Disorder Questionnaire (MDQ) for bipolar disorder: A meta-analysis and systematic review. Psychiatry Res. 2019 Mar;272:461-466.
8. Oliva V, Fico G, DePriscoM, Gonda X, Rosa A, et al. Bipolar disorders: an update on critical aspects. The Lancet Regional Health - Europe. 48. 2024. doi:101135. 10.1016/j.lanepe.2024.101135.
9. Fountoulakis KN, Yatham LN, Grunze H, et al. The CINP Guidelines on the Definition and Evidence-Based Interventions for Treatment-Resistant Bipolar Disorder. Int J Neuropsychopharmacol. 2020;23(4):230-256. doi:10.1093/ijnp/pyz064
10. Lerner J, Awcare R, Sevinsky H, et al. BHV-7000, A Novel, Selective Kv7.2/7.3 Potassium Channel Activator, Demonstrates Dose-Dependent Pharmacodynamic Effects on EEG Parameters in Healthy Adults. Neurotherapeutics. 2024. DOI: 10.1016/j.neurot.2024.e00402
11. Bhattacharya A, Lord B, Grigoleit JS, et al. Neuropsychopharmacology of JNJ-55308942: evaluation of a clinical candidate targeting P2X7 ion channels in animal models of neuroinflammation and anhedonia. Neuropsychopharmacology. 2018;43(13):2586-2596. doi:10.1038/s41386-018-0141-6
12. Reckweg JT, van Leeuwen CJ, Henquet C, et al. A phase 1/2 trial to assess safety and efficacy of a vaporized 5-methoxy-N,N-dimethyltryptamine formulation (GH001) in patients with treatment-resistant depression. Front Psychiatry. 2023;14:1130414. Published 2023 Jun 20. doi:10.3389/fpsyt.2023.1130414

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Any Questions?

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One Day at a Time: Chronic Disease & Mental Health

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January 26, 2025

Objectives

- **Educate** the audience on the interconnectedness of chronic disease and mental health, emphasizing that managing one often requires addressing the other.
- **Inform** the audience about common mental health challenges associated with chronic diseases.
- **Provide** practical strategies for coping with both chronic disease and mental health conditions.
- **Promote** the importance of seeking professional help and support.

What is a Chronic Disease?

"A chronic disease is a condition that lasts at least one year and requires ongoing medical attention or limits activities of daily living or both. Examples of chronic diseases include autoimmune diseases, diabetes, cancer, epilepsy, heart disease, HIV/AIDS, hypothyroidism, multiple sclerosis, and pain."

Risk Factors for Chronic Disease

Smoking

- Cigarette smoking causes more than 480,000 deaths each year in the United States
- Over 16 million Americans are living with a disease caused by smoking
- Causes cancer, heart disease, stroke, lung diseases, diabetes, and chronic obstructive pulmonary disease (COPD), which includes emphysema and chronic bronchitis

CDC

Risk Factors for Chronic Disease

Poor nutrition and physical inactivity

- Significant risk factors for obesity and other chronic diseases, such as
  - Type 2 diabetes
  - Heart disease
  - Stroke
  - Cancer
  - Depression

CDC

Risk Factors for Chronic Disease

Excessive alcohol use

Excessive alcohol use leads to serious problems

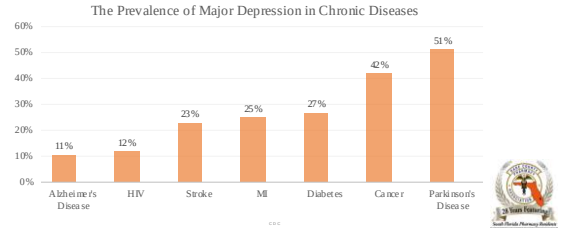
- Alcohol use disorder
- Problems with learning memory
- Mental health

Chronic health conditions

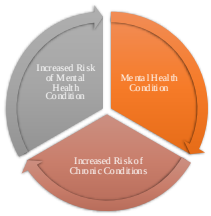
- High blood pressure
- Heart disease
- Stroke
- Liver disease
- Cancer

CDC

Impact on Mental Health



The Cycle of Mental & Physical Health



Focus of Presentation

- Parkinson's Disease (PD)
- Cancer
- Diabetes Mellitus (DM)

What is Depression?

A mood disorder in which a person experiences overwhelming feelings of hopelessness and sadness to the point that these feelings begin to interfere with the ability to function.

Signs include a loss of interest in usual activities, decreased attention to hygiene, and increased fatigue.

According to the Centers for Disease Control and Prevention (CDC), about 80% of older adults who are depressed have at least one chronic health condition.

CDC

What is Anxiety?

A feeling of worry, nervousness, or unease, typically about an imminent event or something with an uncertain outcome.

Includes agoraphobia, anxiety disorder due to a medical condition, generalized anxiety disorder, panic disorder, and social anxiety disorder.

Signs include excessive fear and worry, uncontrollable or unwanted thoughts, sudden waves of terror, nightmares and ritualistic behaviors.

CDC

Parkinson's Disease (PD)

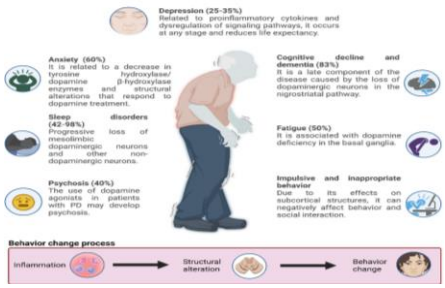
Parkinson's Disease

- Age-related degenerative brain condition
- Affects at least 1% of people over age 60 worldwide
- Motor related symptoms
- Non-motor related symptoms

Prevalence of Mental Health Conditions

- 51% of Parkinson's patients also have depression.
- 40% of patients with Parkinson's will experience some form of anxiety.
- Parkinson's causes changes in areas of the brain that produce the chemicals responsible for regulating mood and motivation.

Behavioral disorders of Parkinson's disease



Depression

Recognizing depressive symptoms in PD can be challenging.

- Depression (negative mood) vs. Apathy (neutral mood)

Antidepressants with the most evidence for treating depression in PD

- Citalopram, sertraline, paroxetine, fluoxetine, venlafaxine, amitriptyline, nortriptyline, and desipramine.

Randomized double-blind, placebo-controlled multicenter trial (ADAGIO study)

- Rasagiline in combination with antidepressant therapy was well tolerated and associated with reducing worsening of depression in patients with Parkinson's disease.

Selective Serotonin Reuptake Inhibitors

SSRI	Dose Range (mg/day)	Side Effects	Warnings
Fluoxetine (Prozac)	10-60mg/day	**Common:** GI side effects, sexual dysfunction, insomnia **Rare/serious:** induction of mania, activation of suicidal ideation	**Caution** with other serotonergic agents due to risk of serotonin syndrome Monoamine oxidase type B inhibitors (MAOBIs): rasagiline, selegiline
Citalopram (Celexa)	10-40mg/day (10-20mg/day in poor CYP2C19 metabolizers and patients >60 y.o.)		
Sertraline (Zoloft)	25-200mg/day		
Paroxetine (Paxil)	10-50mg/day		

Anxiety

Most common:

- Women
- Disease onset at an early age
- Advanced disease

Anxiety may occur before the onset of the motor signs of PD

- Low levels of GABA

Common fears and worries of PD may trigger anxiety

Pharmacologic treatment options

- SSRIs
- Benzodiazepines

Common Benzodiazepines

Benzodiazepine	Dose Range (mg/day)	Side Effects	Warnings
Diazepam (Valium)	4-40mg/day	**Common:** drowsiness, fatigue, dizziness, ataxia **Significant:** withdrawal syndrome, anterograde amnesia	Hazardous sleep-related activities such as sleep-driving, increased risk of suicidal thoughts/behavior
Lorazepam (Ativan)	0.5-6mg/day		
Clonazepam (Klonopin)	0.5-4mg/day		
Alprazolam (Xanax)	0.5-6mg/day		

Psychosis: Hallucinations/Delusions

Between 20-40% of people with PD report the experience of hallucinations or delusions.

PD medications can lead to symptoms of psychosis

- Carbidopa-levodopa (Sinemet) and dopamine agonists
- Amantadine and anticholinergics (Artane and Cogentin)

Risk Factors for Psychosis

- Dementia or impaired memory
- Depression
- Sleep disorders
- Impaired vision
- Older age
- Advanced or late-stage PD
- Use of PD medications

Treating Psychosis

Clinical evaluation of symptoms considering prior history, disease stage and available support systems.

Treatment, when needed, generally begins with adjustment of PD medications and referral to counseling.

If further intervention is needed, antipsychotic therapy may be initiated

- Pimavanserin (Nuplazid) FDA approved in 2016 for PD psychosis.
- Clozapine (Clozaril) effective in improving hallucinations and delusions in PD.
- Quetiapine (Seroquel) has fewer side effects, but limited evidence for efficacy in PD.
- Avoid olanzapine (Zyprexa) due to risk of worsening PD symptoms.

Sleep Disorders

- Sleep-related symptoms are reported by more than 75% of people with PD
- Excessive daytime sleepiness is seen in about 30 to 50% of people with PD
- PD medications can disrupt sleep or cause daytime sedation

PD Medication	Effect on Sleep
Dopamine Agonists	Daytime sleepiness, vivid dreams
Levodopa	Insomnia, daytime sleepiness
Selegiline	Stimulant properties (worsen insomnia)
Amantadine	Insomnia
Antidepressants	Worsen insomnia

Most Common Sleep Issues

- Difficulty falling and staying asleep
- Excessive daytime sleepiness
- REM Sleep Behavioral Disorder, RBD
  - Talking, yelling out, physically acting out while asleep
- Vivid dreaming
- Leg movements, jerking, cramping (restless leg syndrome)
- Difficulty turning over in bed
- Waking up to go to the bathroom

Tips for Better Sleep

- Keep a regular sleep schedule
- Create a bedtime routine
- Spend time outdoors and exercise daily; avoid exercise after 8:00pm
- Avoid napping after 3:00pm
- Sleep in a cool dark place
- Avoid reading, watching TV, or using electronic devices in bed
- Avoid liquids three hours before bedtime to reduce frequent nighttime urination
- Take medications for urinary frequency

Treatment of Sleep Disorders in PD

Sleep Disorder	Pharmacologic Treatment
Excessive Daytime Sleepiness	Stimulants like caffeine, modafinil (Provigil) and methylphenidate (Ritalin)
REM Sleep Behavioral Disorder	Melatonin doses up to 12mg; clonazepam (Klonopin) 0.5mg to 1mg
Insomnia	Sedatives such as zolpidem (Ambien)

Knowledge Check

Which of the following medications is commonly used to treat depression in individuals with Parkinson's disease?

A. Levodopa
B. Selegiline
C. Amantadine
D. Sertraline

Knowledge Check

Which of the following medications is commonly used to treat depression in individuals with Parkinson's disease?

A.Levodopa
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C.Amantadine
D.Sertraline

Cancer

Depression and Cancer

One in four people who have, or had, cancer experiences depression.

Increased Risk for Depression:

- Advanced cancer
- Certain types of cancer (such as pancreatic or head and neck cancers)
- Diagnosis at a young age (teens and young adults)
- Living alone or being socially isolated
- Having young children
- Difficulty caring for yourself
- Uncontrolled pain
- History of substance use disorder, abuse, or trauma

Psychotherapy for Depression

- Cognitive Behavioral Therapy (CBT)
- Acceptance and Commitment Therapy (ACT)
- Interpersonal Therapy (IPT)
- Eye Movement Desensitization and Reprocessing (EMDR)

Pharmacotherapy for Depression

Selective Serotonin Reuptake Inhibitors (SSRIs)

- Most common: fluoxetine (Prozac), paroxetine (Paxil), sertraline (Zoloft), and escitalopram (Lexapro)
- Common side effects: sexual problems (low libido, erectile dysfunction), weight gain, GI problems (heartburn, nausea, diarrhea, or constipation), insomnia, headaches, and dizziness.

- Serotonin Norepinephrine Reuptake Inhibitors (SNRIs)
- Tricyclic Antidepressants (TCAs)
- Monoamine Oxidase Inhibitors (MAOIs)

Anxiety and Cancer

Cancer-related phobias - intense fears related to cancer:

- Cancer treatment and possible side effects
- Not knowing what to expect (or knowing too much about what to expect)
- Effects on family, relationships, job, or responsibilities
- Fear of worsening or recurrence
- Mortality

If left untreated, anxiety can lead to many other problems:

- Weakened immune system, digestive problems, worse treatment side effects, slower physical recovery, poorer quality of life, decreased survival

What Increases Risk of Anxiety?

- Living alone
- Younger age at diagnosis
- Advanced disease
- History of mental health treatment
- Other health conditions
- Social isolation

Psychotherapy for Anxiety

- Cognitive Behavioral Therapy (CBT)
- Acceptance and Commitment Therapy (ACT)
- Interpersonal Therapy (IPT)
- Eye Movement Desensitization and Reprocessing (EMDR)

Pharmacotherapy for Anxiety

Drug Class	Drugs Approved for Anxiety
SSRIs	fluoxetine (Prozac), sertraline (Zoloft), escitalopram (Lexapro), paroxetine (Paxil),
SNRIs	duloxetine (Cymbalta), venlafaxine (Effexor)
Other	buspirone (Buspar), benzodiazepines

Tips for Coping with Depression/Anxiety

- Reflect
- Take one moment at a time
- Stay informed and ask questions
- Have a reliable support system
- Find someone you can talk to
- Take deep, slow breaths
- Use a journal
- Try yoga, massage, imagery, writing, music, or pet therapy
- Get help with the stressors in life

Knowledge Check

Which of the following antidepressants classes is generally considered safer to use in patients with cancer due to a lower risk of drug-drug interactions with common cancer treatments?

A. Monoamine oxidase inhibitors (MAOIs)
B. Tricyclic antidepressants (TCAs)
C. Selective serotonin reuptake inhibitors (SSRIs)
D. Noradrenergic and specific serotonergic antidepressants (NaSSAs)

Knowledge Check

Which of the following antidepressant classes is generally considered safer to use in patients with cancer due to a lower risk of drug-drug interactions with common cancer treatments?

A. Monoamine oxidase inhibitors (MAOIs)
B. Tricyclic antidepressants (TCAs)
C. Selective serotonin reuptake inhibitors (SSRIs)
D. Noradrenergic and specific serotonergic antidepressants (NaSSAs)

Diabetes Mellitus (DM)

Depression and Diabetes

- Roughly 37 million Americans have diabetes
- 2 to 3 times more likely to develop depression than people without diabetes
- Only 25%–50% of diabetics with depression are diagnosed and treated
- Patients with diabetes who have depressive symptoms have a 46% increased risk for all-cause mortality than diabetics who are not depressed
- A disparity exists in the medical care field where the emotional dimension of a patient is often overlooked

Depression and Diabetes

Diabetes patients dealing with depression show

- Poorer glycemic control
- Decreased physical activity
- Higher obesity
- Diabetes end-organ complications and impaired function

Getting treatment for depression can be challenging

Destigmatize depression

Managing Diabetes and Depression

- Diabetes self-management programs
- Psychotherapy
- Medications and lifestyle changes
- Collaborative Care

Antidepressant Effects on Blood Glucose

Effect	Medications
Antidepressants that can **increase** blood glucose	sertraline (Zoloft) paroxetine (Paxil) duloxetine (Cymbalta) mirtazapine (Remeron) fluvoxamine (Luvox)
Antidepressants that can **decrease** blood glucose	fluoxetine (Prozac) escitalopram (Lexapro) citalopram (Celexa)

Anxiety and Diabetes

- Patients with DM are 20% more likely than those without DM to have anxiety.
- Managing a long-term condition like DM is a major source of anxiety for some.
- Patients with DM may have concerns related to regularly counting carbohydrates, measuring insulin levels, and thinking about long-term health.

Causes of Anxiety in Diabetes

- Monitoring glucose levels, weight, and diet
- Short-term health complications, such as hypoglycemia, as well as long-term effects such as heart disease, kidney disease, and stroke
- Management of DM pharmacotherapy, especially when insulin is involved

Diabetes and Mental Health. CDC

Anxiety-Diabetes Comorbidity Hypotheses

- Anxiety as a risk factor for the development of diabetes
- Diabetes as a risk factor for the development of anxiety
- Anxiety and diabetes are indirectly related via mutual factors

Sinha Q., M. alla Ireland H. Treating Patients With Co-morbid Anxiety and Diabetes Mellitus. Physician and Cases. 2014;5:1-5.

Anxiety vs. Hypoglycemia

- Anxiety can feel like low blood sugar and vice versa.
- Anxiety can cause panic attacks, which are sudden, intense episodes of fear that aren't related to any apparent threat or danger.
- Hypoglycemia is a dangerous condition in which a person's blood sugar can become too low.

Symptoms of Panic Attack	Symptoms of Hypoglycemia
Rapid HR, shaking, sweating	Rapid HR, shaking, sweating
Chest pain, SOB, hyperventilating	Blurry vision, dizziness, trouble concentrating
Difficulty swallowing/breathing	Sudden mood changes/nervousness
Stomach pain, nausea	Unexplained fatigue
Tingling or numbness	Pale skin, skin tingling
Feeling that death is imminent	HA, LOC, seizure, coma

staff.cdc.gov

Nonpharmacologic Therapy for Anxiety

- Relaxation exercises, like meditation or yoga
- Calling or texting a friend who understands (not someone who is causing you stress)
- Scheduling "you" time
- Lifestyle changes: exercise, diet, avoiding alcohol and other recreational drugs, limiting caffeine, sleep
- Cognitive Behavioral Therapy (CBT)
- Exposure Therapy

Pharmacologic Therapy

- Antidepressants
- Anti-anxiety medications such as buspirone
- Benzodiazepine for relief of panic attacks

Knowledge Check

Which of the following antidepressants may cause hyperglycemia?

- a) Citalopram
- b) Escitalopram
- c) Sertraline
- d) All of the above

Knowledge Check

Which of the following antidepressant may cause hyperglycemia?

- a) Citalopram
- b) Escitalopram
- **c) Sertraline**
- d) All of the above

Concluding Thought

While there is a growing recognition of the connection between mental and physical health, effectively treating chronic illness requires a stronger integration of mental health, primary care, and specialty care services.

References

- Second-generation and other antipsychotic medications: Pharmacology, administration, and side effects. Lexi-Drugs. Lexicomp. Wolters Kluwer Health, Inc. Riverwoods, IL. Available at: http://online.lexi.com.
- Burcu M, Zito JM, Safer DJ, et al. Association of Antidepressant Medications With Incident Type 2 Diabetes Among Medicaid-Insured Youths. JAMA Pediatr. 2017;171(12):1200–1207. doi:10.1001/jamapediatrics.2017.2896
- Barnard K, Peveler RC, Holt RIG. Antidepressant medication as a risk factor for type 2 diabetes and impaired glucose regulation. Diabetes Care. 2013;36(10):3337-3345. doi:10.2337/dc13-0560
- Benzodiazepines: Pharmacology, administration, and side effects. Lexi-Drugs. Lexicomp. Wolters Kluwer Health, Inc. Riverwoods, IL. Available at: http://online.lexi.com.
- Castillo-Rangel C, Marin G, Hernández-Contreras KA, Vichi-Ramírez MM, Zarate-Calderon C, Torres-Pineda O, Diaz-Chiguer DL, De la Mora González D, Gómez Apo E, Teco-Cortes JA, et al. Neuroinflammation in Parkinson's Disease: From Gene to Clinic: A Systematic Review. International Journal of Molecular Sciences. 2023; 24(6):5792. https://doi.org/10.3390/ijms24065792
- Cleveland Clinic. (2024, August 18). Parkinson's Disease: What It Is, Causes, Symptoms & Treatment. Retrieved from my.clevelandclinic.org
- Depression in Adults with a Chronic Physical Health Problem. The NICE Guideline on Treatment and Management. The British Psychological Society and The Royal College of Psychiatrists. 2020;09. https://www.nice.org.uk/guidance/cg91/evidence/full-guideline-pdf-[illegible]
- Fernandez G. 2021; 12. The Intersection of Mental Health and Chronic Disease. John Hopkins Public Health Journal. https://publichealth.jhu.edu/2021/the-intersection-of-mental-health-and-chronic-disease
- Frenklach A. Management of Depression in Parkinson's Disease. American Journal of Psychiatry Residents' Journal. 2016;11(4)8-11. doi:10.1176/appi.ajp-rj.2016.110405
- Lehr J. The Mental Health Aspects of Parkinson's: How Its More Than a Movement Disease. NCOA. 2022; 06
- Managing Cancer Care. American Cancer Society. Last Revised 2024;07. https://www.cancer.org/cancer/managing-cancer/side-effects/emotional-mood-changes/depression.html
- Meng H, Lu J, Zhang X. Metabolic influences of commonly used antidepressants on blood glucose homeostasis. Indian J Pharm Sci. 2019;81(2):188-199. doi:10.36468/pharmaceutical-sciences.498
- Miidera H, Enomoto M, Kitamura S, et al. Association between the use of antidepressants and the risk of type 2 diabetes: a large, population-based cohort study in japan. Diabetes Care. 2020;43(4):885-893. doi:10.2337/dc19-1175
- National Institute of Mental Health. Understanding the Link Between Chronic Disease and Depression. Retrieved 12/19/2024: https://www.nimh.nih.gov/health/publications/chronic-illness-mental-health
- Parkinson's Foundation. Understanding Parkinson's Non-movement Symptoms. 2024. https://www.parkinson.org/understanding-parkinsons/non-movement-symptoms/sleep-disorders
- Roopan S, Larsen ER. Use of antidepressants in patients with depression and comorbid diabetes mellitus: a systematic review. Acta Neuropsychiatr. 2017;29:127-139.
- Sidra Q, Muhammad H. Treating Patients With Comorbid Anxiety and Diabetes Mellitus. Psychiatric Times. 2019; 06. https://www.psychiatrictimes.com/view/treating-patients-comorbid-anxiety-and-diab
- Selective serotonin reuptake inhibitors: Pharmacology, administration, and side effects. Lexi-Drugs. Lexicomp. Wolters Kluwer Health, Inc. Riverwoods, IL. Available at: http://online.lexi.com.

Thank You!

Questions?

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January 26, 2025

The Skin You're In: Skin Cancer Updates

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January 26th, 2025

29 Years Featuring
South Florida Pharmacy Residents

1

Objectives

- Provide an overview of the epidemiology of skin cancer
- Discuss the clinical relevance of prevention strategies
- Review the common types of skin cancer
- Evaluate novel, breakthrough therapies

2

Abbreviations

- Basal cell carcinoma (BCC)
- Squamous cell carcinoma (SCC)
- Cutaneous squamous cell carcinoma (CSCC)
- Ultraviolet (UV)
- Radiation therapy (RT)
- Metastatic basal cell carcinoma (mBCC)
- Locally advanced basal cell carcinoma (laBCC)
- Objective response rate (ORR)
- Duration of response (DoR)
- Sun protection factor (SPF)
- Disease control rate (DCR)
- Immuno-Oncology (IO)
- Progression free survival (PFS)

3

Epidemiology

- Skin cancer is the most common form of cancer in the United States[1]
  - Increasing incidence rates worldwide
- Predominantly affects white populations[1]
- Attributed to increasing exposure to UV radiation[1]

4

Prevention Strategies

- Sun safety – avoid sun with UV index of 3 or higher, wear protective clothing/wide brim hat, wear sunglasses that block both UVA and UVB rays[1]
- Use a broad-spectrum sunscreen with a SPF 15 or higher[1]
- Avoid indoor tanning (bed, booth, sunbed, sunlamp)[1]
- Yearly skin check with dermatologist/self-checks[1]

5

Common types of skin cancer

- Keratinocyte (nonmelanoma) skin cancer
  - Basal Cell Carcinoma
  - Squamous Cell Carcinoma
- Melanoma

6

What is the most common type of skin cancer?

A. Squamous cell carcinoma

B. Basal cell carcinoma

C. Melanoma

D. Other

7

What is the most common type of skin cancer?

A. Squamous cell carcinoma

B. Basal cell carcinoma

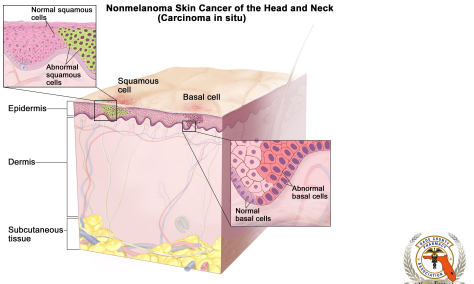
C. Melanoma

D. Other

8

Nonmelanoma Skin Cancer

9



Nonmelanoma Skin Cancer of the Head and Neck (Carcinoma in situ). 2019. National Cancer Institute. Jan, 2025.

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Basal Cell Carcinoma

- Originates in the deepest layer of the epidermis
- Most common type of skin cancer
  - ~2 million new cases annually[2]
- Intensive ultraviolet exposure in childhood and adolescence[2]
- Relatively low mortality[2]

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Basal Cell Carcinoma

- Risk is increased by both ultraviolet A- and B-radiation, and ionizing radiation[3]
- Those that develop on head and neck are more likely to recur[3]
- No relationship between age and recurrence rate[3]

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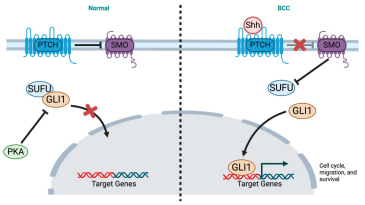
BCC- Histologic Subtypes

Non-aggressive "Low-risk"[3]	Aggressive "High-risk"[3]
Nodular	Micronodular
Superficial	Basosquamous
Keratotic	Infiltrative
Infundibulocystic	Sclerosing/morpheaform
Fibroepithelioma of Pinkus	Basal cell carcinoma with squamous differentiation

13

BCC- Pathogenesis



Therapeutic Advances in Advanced Basal Cell Carcinoma. 2024. Cancers. MDPI. Jan, 2025.

14

New Treatment

15

Cemiplimab-rwlc (Libtayo)

- Approved for advanced BCC in neoadjuvant setting
- For patients who failed hedgehog pathway inhibitor (HHI) therapy or for whom a HHI is not appropriate[5]

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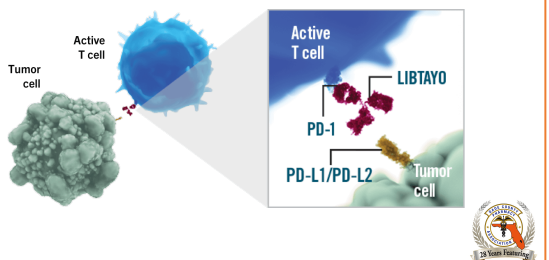

LIBTAYO. Regeneron Pharmaceuticals, Inc. 2024.

17

Study Design

- Open-label, multi-center, non-randomized, phase II trial in patients with advanced BCC who had progressed on HHI therapy, had not had an objective response after 9 months on HHI therapy, or were intolerant of prior HHI therapy[5]

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Intervention

- mBCC (n=54) and laBCC (n=84)
- All patients received cemiplimab-rwlc 350mg every 3 weeks until disease progression, unacceptable toxicity, or completion of planned treatment[5]

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Results

- Primary outcome: confirmed ORR and DOR
  - laBCC arm: ORR=29% (95% CI: 19, 40); median DOR not reached (range: 2.1 to 21.4+ months); 79% of responders maintained their response for 6 months[5]
  - mBCC arm: ORR=21% (95% CI: 8, 41); median DOR not reached (range: 9 to 23.0+ months); all responders maintained their response for 6 months[5]

20

Squamous Cell Carcinoma

- Originates in the cells of the outer layer of the epidermis
- Second most common form of skin cancer[6]
- Associated with chronic, cumulative ultraviolet exposure over various decades[2]

21

Squamous Cell Carcinoma

- Affects men > women[6]
- Incidence increases with increasing age[6]
- Presence of actinic keratoses is strong predictor of SCC[6]

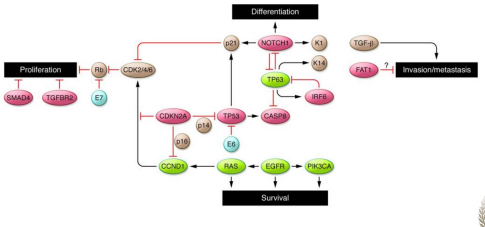
22

SCC- Histologic Features

Histologic Subtypes[7]
Acantholytic (adenoid)
Adenosquamous (mucin-producing)
Metaplastic (carcinosarcomatous)
Desmoplasia

23

SCC- Pathogenesis



The molecular pathogenesis of head and neck squamous cell carcinoma. 2012. Journal of Clinical Investigation. Jan, 2025.

24

New Treatment

25

Cosibelimab-ipdl (Unloxcyt)

- Newly approved for advanced CSCC
  - Adult patients with mCSCC or laCSCC who are not candidates for curative surgery or curative radiation[8]

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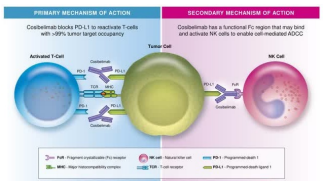


Checkpoint Therapeutics: Another Buying Opportunity Following Cosibelimab's Impressive Topline Results. 2022.

27

Study Design

- Multicenter, multicohort, open-label, phase I trial in patients with mCSCC or laCSCC in patients unsuitable for surgery or radiation therapy[8]

28

Intervention

- mCSCC (n=78) and laCSCC (n=31)
- Cosibelimab administered as fixed dose of 800mg every 2 weeks or 1200mg every 3 weeks until confirmed and worsening progression or clinical deterioration[8]

29

Results

- Primary outcome: ORR and DOR
  - laCSCC arm: ORR= 48% (95% CI: 30, 67); median DOR 17.7 months (range 3.7+, 17.7)[8]
  - mCSCC arm: ORR= 47% (95% CI: 36, 59); median DOR not reached (range: 1.4+, 34.1+)[8]

30

T/F: Skin cancer can only occur on areas of the body that have received sun exposure.

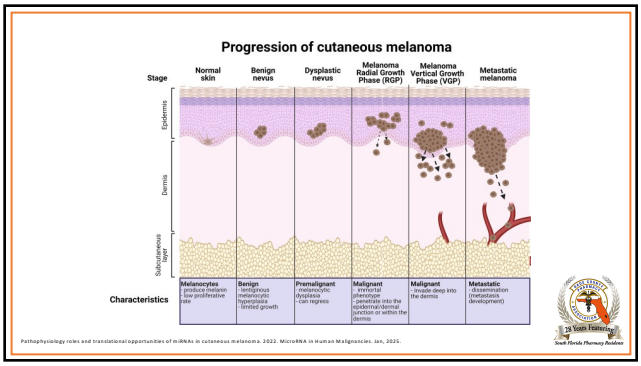
31

T/F: Skin cancer can only occur on areas of the body that have received sun exposure.

32

Melanoma

33



34

Melanoma

- Most dangerous form of skin cancer[9]
- Originates from melanocytes in the basal layer of the epidermis[9]
- Most common in white men with an average age of 65[9]
- Mortality has decreased by 30% in the past decade[9]

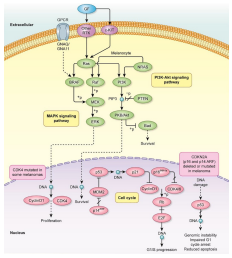
35

Types of Melanoma

- Cutaneous vs uveal melanoma
- Share the same embryonic origin and cellular function[10]
- Different tumor transformation processes[10]

36

Melanoma- Pathogenesis



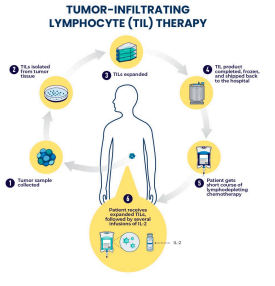
Molecular biology in conjunctival melanoma and the relationship to mucosal melanoma. 2020. Acta Ophthalmologica. Jan, 2025.

37

Lifileucel (Amtagvi)

- Approved for the treatment of adult patients with unresectable or metastatic melanoma previously treated with and progressed on a PD-1 antibody, and if BRAF V600 positive, a BRAF inhibitor with or without a MEK inhibitor[11]

38



First Cancer TIL Therapy Gets FDA Approval for Advanced Melanoma. 2024. National Cancer Institute. Jan, 2025.

39

Study Design

- Multicenter, multicohort, open-label, single-arm, phase II trial in patients with unresectable or metastatic melanoma defined as stage IIIC or stage IV by the American Joint Committee on Cancer[11]

40

Intervention

- Lifileucel administered following lymphodepleting regimen (60mg/kg cyclophosphamide daily + mesna x 2 days) and 25mg/m2 fludarabine daily x 5 days[11]

41

Results

- In patients who received the recommended dose (n=73):
  - ORR= 31.5% (95% CI, 21.1%-43.4%)[11]
    - Complete response rate= 4.1%
    - Partial response rate= 27.4%
  - Median DOR not reached (NR; 95% CI, 4.1 months-NR)[11]
    - Median time to initial response was 1.5 months

42

IBI363

- First-in-class PD-1/IL2α Bispecific Antibody Fusion Protein
- Granted FDA fast track designation for the treatment of patients with unresectable locally advanced or metastatic melanoma that has progressed after 1 or more prior lines of systemic therapy (including a PD-1/PD-L1 inhibitor)[12]

43

How does it work?

- Simultaneously blocks the PD-1 checkpoint on T cells and selectively activates the IL-2 pathway (primarily the IL-2Rα receptor)[12]
  - Restoring exhausted T cells

44

Study Design

- Patients with advanced melanoma who failed or are intolerant to standard therapy were enrolled to receive IBI363 intravenously at different dose levels ranging from 100-2000 mcg/kg QW/Q2W/Q3W[12]
  - Primary objective: safety
  - Secondary objective: efficacy (ORR, DCR, DoR, PFS)

45

Intervention

- Phase 1a/1b trial[12]
  - Among the patients with melanoma that were previously treated with immunotherapy who received 1mg/kg IBI363 and underwent 1 or more tumor evaluations after baseline (n=37)

46

Results

- Phase 1a/1b trial[12]
  - Safety:
  - Efficacy: 11 achieved objective responses (1 complete and 10 partial)
    - **ORR=** 29.7%
    - **DCR=** 73.0%

47

Intervention

- Phase 1 Trial[13]
  - N=347 patients with advanced solid tumors – received IBI363 monotherapy at a range of 0.2 mcg/kg – 3mg/kg once every 3 weeks

48

Results

- Phase 1 Trial – Melanoma Cohort (N=67)[13]
  - Safety:
    - TEAEs occurred in 63 (94.0%); Grade 3 or more TEAEs occurred in 16 (23.9%); No TEAEs lead to death
  - Efficacy:
    - N=67 (Prior treatment lines (2 or more): 59.7%; Prior IO: 89.6%)
    - **Overall ORR**= 28.1% (95% CI: 17.0-41.5%); **Prior IO ORR**= 21.2% (95% CI: 11.1-34.7)
    - **Overall DCR**= 71.9% (95% CI: 58.5-83.0); **Prior IO DCR**= 67.3% (95% CI: 52.9-93.2)

49

Conclusion

- Overall, in patients with advanced melanoma IBI363 has shown appropriate efficacy in different solid tumor subtypes and in patients with prior IO[13]
- Safety profiles were acceptable/manageable[13]

50

Thank you! Questions?

51

References

1. Anthony J. Alberg et al., American Society of Clinical Oncology Policy Statement on Skin Cancer Prevention. *JCO Oncol Pract* **16**, 690–696(2020). DOI: 10.1200/JOP.19.00585

2. Leiter U, Eigentler T, Garbe C. Epidemiology of skin cancer. *Adv Exp Med Biol*. 2014;810:120-140. doi:10.1007/978-1-4939-0437-2_7

3. Schmults, C. D., et al., (2023). Basal cell skin cancer, version 2.2024, NCCN clinical practice guidelines in oncology. *Journal of the National Comprehensive Cancer Network*, *21*(11), 1181–1203. https://doi.org/10.6004/jnccn.2023.0056

4. Alkassis, S., Shatta, M., & Wong, D. J. (2024a). Therapeutic advances in advanced basal cell carcinoma. *Cancers*, *16*(17), 3075. https://doi.org/10.3390/cancers16173075

5. Davis CM, Lewis KD. Brief overview: cemiplimab for the treatment of advanced basal cell carcinoma: PD-1 strikes again. *Ther Adv Med Oncol*. 2022;14:17588359211066147. Published 2022 Jan 19. doi:10.1177/17588359211066147

6. Green AC, Olsen CM. Cutaneous squamous cell carcinoma: an epidemiological review. *Br J Dermatol*. 2017;177(2):373-381. doi:10.1111/bjd.15324

7. Fania L, Didona D, Di Pietro FR, et al. Cutaneous Squamous Cell Carcinoma: From Pathophysiology to Novel Therapeutic Approaches. *Biomedicines*. 2021;9(2):171. Published 2021 Feb 9. doi:10.3390/biomedicines9020171

8. FDA approves cosibelimab-ipdl for metastatic or locally advanced cutaneous squamous cell carcinoma. FDA. December 13, 2024. Accessed December 13, 2024. https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-cosibelimab-ipdl-metastatic-or-locally-advanced-cutaneous-squamous-cell-carcinoma

9. Sagirala K, Barsouk A, Aluru JS, Rawla P, Barsouk A. Epidemiology of Melanoma. *Med Sci (Basel)*. 2021;9(4):63. Published 2021 Oct 20. doi:10.3390/medsci9040063

10. Van der Kooij MK, Speetjens FM, van der Burg SH, Kapiteijn E. Uveal Versus Cutaneous Melanoma; Same Origin, Very Distinct Tumor Types. *Cancers (Basel)*. 2019;11(6):845. Published 2019 Jun 19. doi:10.3390/cancers11060845

11. Julve M, Lythgoe MP, Larkin J, Furness AJS. Lifileucel: the first cellular therapy approved for solid tumours. *Trends Cancer*. 2024;10(8):675-677. doi:10.1016/j.trecan.2024.04.003

12. Biologics, I. (2024, June 2). *Innovent presents phase 1 clinical data of first-in-class PD-L1/4-2a bispecific antibody fusion protein IBI362 in melanoma, colorectal cancer and other solid tumors at the 2024 ASCO annual meeting*. Innov Presents Phase 1 Clinical Data of First-in-class PD-L1/4-2a Bispecific Antibody Fusion Protein IBI362 in Melanoma, Colorectal Cancer and other Solid Tumors at the 2024 ASCO Annual Meeting. https://www.prnewswire.com/news-releases/innovent-presents-phase-1-clinical-data-of-first-in-class-pd-l1-2-bispecific-antibody-fusion-protein-ibi362-in-melanoma-colorectal-cancer-and-other-solid-tumors-at-the-2024-asco-annual-meeting-302161127.html

13. Yu Chen et al., First-in-class PD-L1/4-2 bispecific antibody fusion protein IBI362 in patients with advanced melanoma: Safety and efficacy results from a phase I study, *JCO* 42, 9562-9562(2024). DOI: 10.1200/JCO.2024.42.16_suppl.9

52

Updates In Oncology

Jose Valdes Ledesma, Pharm.D; Jude Pierre, Pharm.D
Baptist Hospital of Miami
Miami, Florida
January 25th, 2025

1

1

Objectives

- Identify new FDA approved cancer therapies
- Provide clinical pearls about these new therapies
- Review the evidence supporting such approvals
- Evaluate place in therapy
- Define Tumor infiltrating lymphocyte (TIL) therapy
- Analyze potential place in therapy for TIL therapy

2

2

Breast Cancer

3

3

Pembrolizumab plus chemotherapy in stage II to III triple-negative breast cancer

Mechanism of Action	Dose	Adverse Effects	Pearls
• Highly selective anti-PD-1 humanized monoclonal antibody • Inhibits programmed cell death-1 (PD-1) activity by binding to the PD-1 receptor on T-cells to block PD-1 ligands (PD-L1 and PD-L2) from binding	• 200 mg once every 3 weeks for 4 cycles for neoadjuvant therapy	• Cardiovascular toxicity • Dermatologic toxicity • Endocrine toxicity • GI toxicity • Hematologic toxicity • Hepatotoxicity • Nephrotoxicity • Neurologic toxicity • Opthalmic toxicity • Pulmonary toxicity	• Infuse over 30 minutes through a 0.2 to 5 micron sterile, nonpyrogenic, low-protein binding inline or add-on filter • Do not infuse other medications through the same infusion line • Interrupt or slow the infusion for grade 1 or 2 infusion-related reactions; permanently discontinue for grade 3 or 4 infusion-related reactions

4

KEYNOTE-522

Trial	Published	Interventions	Comparisons
• Overall Survival with Pembrolizumab in Early-Stage Triple-Negative Breast Cancer • Randomized patients with previously untreated stage II or III triple-negative breast cancer (n=1174)	• September 15, 2024	• Neoadjuvant therapy with four cycles of pembrolizumab or placebo every 3 weeks + paclitaxel and carboplatin • Followed by four cycles of pembrolizumab or: o Placebo plus doxorubicin–cyclophosphamide o Or epirubicin–cyclophosphamide o Definitive surgery: Adjuvant pembrolizumab or placebo every 3 weeks for up to nine cycles	• 784 patients were assigned to the pembrolizumab-chemotherapy group and 390 to the placebo-chemotherapy group

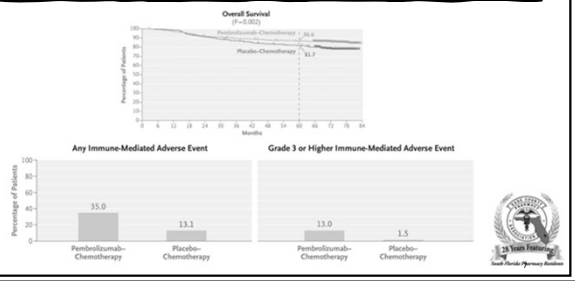
5

KEYNOTE-522 Continued

Primary Endpoint	Secondary Endpoint	Results
• Pathological Complete Response (CR) and Event-Free Survival	• Overall Survival (OS)	• **Median follow-up:** 75.1 months • **OS at 60 months:** 86.6% in the pembrolizumab–chemotherapy group, vs. 81.7% in the placebo–chemotherapy group • Adverse events were consistent with the established safety profiles of pembrolizumab and chemotherapy

6

Overall Survival with Pembrolizumab in Early-Stage Triple-Negative Breast Cancer (KEYNOTE-522) Cont.



7

Knowledge Check: What is the mechanism of action of pembrolizumab?

A. Proteosome Inhibitor
B. IL-2 antagonist
C. PD-1 inhibitor
D. Tyrosine Kinase inhibitor

8

Knowledge Check: What is the mechanism of action of pembrolizumab?

A. Proteosome Inhibitor
B. IL-2 antagonist
C. PD-1 inhibitor
D. Tyrosine Kinase inhibitor

9

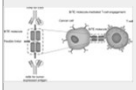
Small Cell Lung Cancer

10

10

Tarlatamab

Mechanism of Action	Dose	Adverse Effects	Pearls
• Bispecific T-cell engager (BiTE) therapy that directs T cells to cancer cells expressing delta-like ligand 3 (DLL3), independent of major histocompatibility complex (MHC) class I	• Step up dosing schedule cycle 1: • **Day 1:** 1mg • **Day 8:** 10mg • **Day 15:** 10mg • Cycle 2 and beyond: • **Day 1** and **15:** 10mg	• Black Box Warning: Cytokine Release Syndrome (CRS) and Immune Effector cell-associated neurotoxicity syndrome (iCANS) • Electrolyte disturbances • Hematologic & Oncologic toxicity • Increased liver enzymes and serum bilirubin • Hypersensitivity • Infection • Musculoskeletal pain	• Step up dosing is recommended to reduce the risk of serious adverse events • Reconstituted and diluted tarlatamab can be stored at room temperature for up to 8 hours or in the refrigerator for up to 7 days • Neurologic adverse events usually occurs within the first 30 days of treatment



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DeLLphi-301

Trial	Published	Interventions
• Tarlatamab for Patients with Previously Treated Small-Cell Lung Cancer • N=222	• October 20, 2023	• **Part 1:** 88 patients received tarlatamab 10 mg, and 88 patients received tarlatamab 100mg • **Part 2:** 12 patients enrolled to receive 10mg dose • **Part 3:** Reduced duration of inpatient monitoring; 34 patients were enrolled • **Median follow-up:** 10.6 months in the 10-mg group and 10.3 months in the 100-mg group

12

12

DeLLphi-301 Continued

Primary Endpoint	Secondary Endpoint	Results
• Confirmed objective response (complete or partial response)	• Duration of objective response, disease control, duration of disease control, progression-free survival, overall survival, adverse events during the treatment period, serum concentration of tarlatamab, and formation of anti-tarlatamab antibody	• **Objective response:** 40% in the 10-mg group and 32% in the 100-mg group • **Median progression-free survival:** 4.9 months in the 10-mg group and 3.9 months in the 100-mg group • **Progression-free survival at 6 months and 9 months:** 40% and 28% in the 10-mg group and 34% and 27% in the 100-mg group • **Overall survival at 6 months and 9 months:** 73% and 68% in the 10-mg group and 71% and 66% in the 100-mg group • **Patients alive at the last follow-up visit:** 57% (57 of 100 patients) in the 10-mg group and 51% (45 of 88 patients) in the 100-mg group, with overall survival data yet to mature

13

13

Knowledge Check: True or False? Treating Small Cell Lung Cancer with Tarlatamab requires step dosing

A. True
B. False

14

14

Knowledge Check: True or False? Treating Small Cell Lung Cancer with Tarlatamab requires step dosing

A. True
B. False

15

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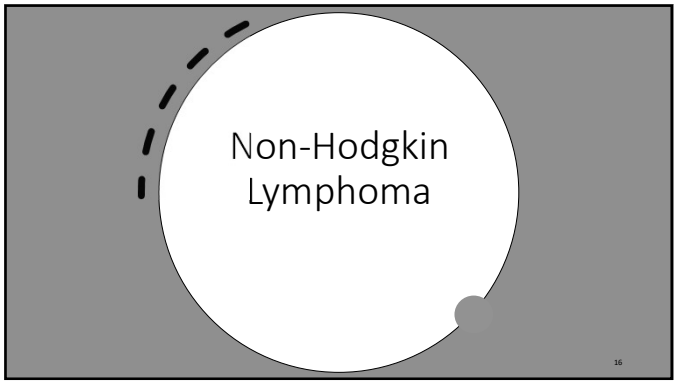


16

Approval of BOVen Regimen for Follicular Lymphoma

- FDA approval: March 7,2024
- Therapy includes zanubrutinib, obinutuzumab, and venetoclax
- Zanubrutinib is the first Brunson Tyrosine Kinase Inhibitor (BTKI) approved for treatment of follicular lymphoma

17

17

BOVen Regimen Medication Profile

	Zanubrutinib	Obinutuzumab	Venetoclax
Mechanism	•**Highly** selective and irreversible Bruton tyrosine kinase (BTK) inhibitor •Forms a covalent bond with a cysteine residue in the BTK active site to inhibit BTK activity	•Binds to CD20 •Activates complement/antibody dependent cytotoxicity, and cellular phagocytosis	•Inhibits BCL-2 to exert its cytotoxic activity in tumor cells
Adverse Effects	Cardiovascular Effects (Hypertension, Edema), **Hemorrhage** (Grades 3-4: 3-4%), Elevated liver enzymes, musculoskeletal pain, Increased serum creatine, Infection, Fever	Infusion-related reaction, Infection, Electrolyte disturbances, Elevated liver enzymes, Increased serum creatinine, Fever	Edema, Electrolyte disturbances, Skin rash, musculoskeletal pain, Increased liver enzymes

18

18

BOVen Regimen Medication Profile Cont.

	Zanubrutinib	Obinutuzumab	Venetoclax
Pearls	•**Highly** selective and irreversible Bruton tyrosine kinase (BTK) inhibitor •Forms a covalent bond with a cysteine residue in the BTK active site to inhibit BTK activity	•Binds to CD20 •Activates complement/antibody dependent cytotoxicity, and cellular phagocytosis	•Inhibits BCL-2 to exert its cytotoxic activity in tumor cells
Other indications	• Chronic lymphocytic leukemia or small lymphocytic lymphoma • Relapsed/refractory follicular lymphoma • Relapsed/refractory Mantle cell lymphoma • Relapsed/refractory marginal zone lymphoma • Waldenström macroglobulinemia	• Previously untreated chronic lymphocytic leukemia • Relapsed/refractory Diffuse large B cell lymphoma • Previously untreated follicular lymphoma • Relapsed/refractory follicular lymphoma	• Newly diagnosed Acute myeloid leukemia • Chronic lymphocytic leukemia/small lymphocytic lymphoma • Relapsed/refractory Mantle cell lymphoma • Relapsed/refractory multiple myeloma

19

19

What are Receptor Tyrosine Kinases (RTK)?

20

20

ROSEWOOD Trial

Trial	Published	Interventions
• Phase II Randomized Study of Zanubrutinib Plus Obinutuzumab Monotherapy in Patients with Relapsed or Refractory Follicular Lymphoma • N=217 • Median follow up: 20.2 months	• July 28, 2023	• Zanubrutinib 160 mg twice daily PO, continuously until progressive disease (PD) or unacceptable toxicity • **In both arms:** Obinutuzumab 1,000mg on days 1, 8, and 15 of cycle 1, then on day 1 of cycles 2-6, then once every 8 weeks up to a total of 20 infusions (2-year maintenance)

21

21

ROSEWOOD Trial Continued

Primary Endpoint	Secondary Endpoint	Results
• Overall Response Rate (ORR)	• Duration of Response (DOR), Progression-free survival (PFS), overall survival, and safety	• ORR: 69% (ZO) versus 46% (O) • Complete response rate: 39% (ZO) versus 19% (O) • 18-month DOR rate was 69% (ZO) versus 42% (O) • Median PFS: 28.0 months (ZO) versus 10.4 months (O) • The most common adverse events with ZO were thrombocytopenia, neutropenia, diarrhea, and fatigue; incidences of atrial fibrillation and major hemorrhage were 3% and 1%

22

BOVen Regimen and Venetoclax Ramp Up Studies

Trial	Published	Interventions
• Zanubrutinib, obinutuzumab, and venetoclax with minimal residual disease-driven discontinuation in previously untreated patients with chronic lymphocytic leukemia or small lymphocytic lymphoma: a multicenter, single-arm, phase 2 trial • N=39	• December 1, 2021	• **Zanubrutinib:** 160 mg PO BID on D1 • **Obinutuzumab:** 1000 mg on D1, D8, D15 of C1; D1 of C2-8 • **Venetoclax:** Ramp up initiated C3D1 (target 400 mg QD) ▪ 5 week ramp up to 400 mg daily. ▪ Venetoclax discontinued after 8–24 cycles when prespecified undetectable MRD criteria were met

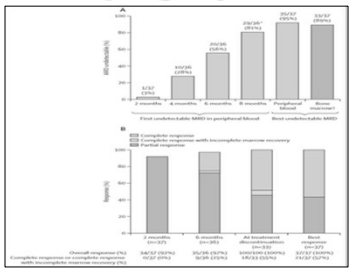
23

BOVen Regimen and Venetoclax Ramp Up Studies Continued

Primary Outcome	Secondary Outcome	Results
• Undetectable MRD in both the peripheral blood and bone marrow	• Safety and tolerability	• **Median follow-up:** 25.8 months • 89% of 37 patients had undetectable MRD in both blood and bone marrow, meeting the prespecified undetectable MRD criteria • Stopped therapy after a median of ten cycles • After median surveillance after treatment of 15.8 months, 94% of 33 patients had undetectable MRD • **Most common adverse events:** ▪ **Thrombocytopenia:** Grade 1-2: 51%, Grade 3: 8%, ▪ **Fatigue:** Grade 1-2: 51%, Grade 3: 3% ▪ **Neutropenia:** Grade 1-2: 33%, Grade 3: 5%, Grade 4: 13% ▪ **Bruising:** Grade 1-2: 51% ▪ One death occurred in a patient with intracranial hemorrhage on C1D1 after initiating intravenous heparin for pulmonary emboli

24

BOVen Regimen and Venetoclax Ramp Up Studies Continued



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BOVen Regimen and Venetoclax Ramp Up Studies Continued

Trial	Published	Interventions
• A Multicenter Phase 2 Trial of Zanubrutinib, Obinutuzumab, and Venetoclax (BOVen) in Patients with Treatment-Naïve, *TP53*-Mutant Mantle Cell Lymphoma • N=25	• November 2, 2023	• BOVen is administered in 28-day cycles: ▪ Zanubrutinib 160 mg PO BID starting D1 ▪ Obin 1000 mg IV D1 or split D1-2, 8, 15 of C1, D1 of C2-8 ▪ Ven ramp up initiated C3D1 (target 400 mg QD) • The 5-week ramp up schedule is designed to gradually reduce tumor burden and the risk of Tumor Lysis Syndrome (TLS) ▪ Week 1: 20mg once daily ▪ Week 2: 50mg once daily ▪ Week 3: 100mg once daily ▪ Week 4: 200mg once daily ▪ Week 5: 400mg once daily, and 400mg daily thereafter

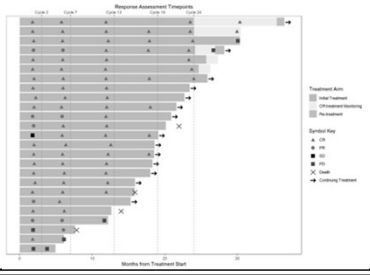
26

BOVen Regimen and Venetoclax Ramp Up Studies Continued

Primary Outcome	Results
• 2-year PFS	• 1-year PFS and overall survival (OS) were 84% and 96% • The 16-month PFS and OS were 75% and 87% respectively

27

Preliminary Results



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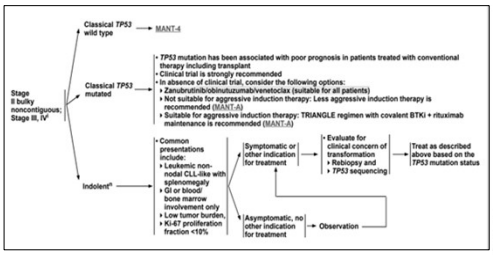
NCCN Guidelines Algorithm



29

Knowledge Check: What is the rationale behind Venetoclax ramp up dosing for use in MCL?

A. Reduce the risk of TLS
B. Improve patient medication adherence
C. Improve medication tolerance
D. Optimize medication efficacy

30

Knowledge Check: What is the rationale behind Venetoclax ramp up dosing for use in MCL?

A. Reduce the risk of TLS
B. Improve patient medication adherence
C. Improve medication tolerance
D. Optimize medication efficacy

31

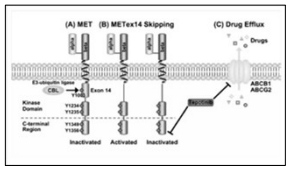
Non-Small Cell Lung Cancer (NSCLC)

32

32

Tepotinib (Tepmetko)

- **FDA Approved:** February 15, 2024
- **MOA**
  - Receptor tyrosine kinase inhibitor that selectively targets mesenchymal-epithelial transition (MET)
  - Inhibits dependent hepatocyte growth factor, independent MET phosphorylation, and MET-dependent downstream signaling pathways
- **Dose**
  - **Non–small cell lung cancer, metastatic, with *MET* exon 14 skipping mutation:** 450 mg PO daily; continue until disease progression or unacceptable toxicity



33

Tepotinib (Tepmetko)

- **Adverse Effects**
  - Hepatotoxicity
  - Pulmonary Toxicity
  - Peripheral Edema
  - Musculoskeletal Pain
  - Hematologic & Oncologic toxicities
- **Pearls**
  - Substrate of CYP3A4 (Minor)
  - MET gene testing required
  - Hepatitis B virus testing is recommended before initiation
  - No hepatic or renal dose adjustments

34

Vision Trial

Trial	Published	Interventions
• Tepotinib in Non–Small-Cell Lung Cancer with *MET* Exon 14 Skipping Mutations • Open label, phase 2 study • N=152	• May 28, 2020	• Tepotinib 500mg PO daily in patients with advanced or metastatic NSCLC with a confirmed *MET* exon 14 skipping mutation • Groups separated between liquid biopsy group and tissue biopsy group

35

Vision Trial Continued

Primary Endpoint	Secondary Endpoint	Results

• Overall Response (OR)	• Investigator-assessed objective response, duration of response, progression-free survival (PFS), Overall survival (OS)	• **Overall Response Rate:** 46%
		  ○ All responses were partial, with no complete responses
		  ○ **Liquid biopsy group:** 48%
		  ○ **Tissue biopsy group:** 50%
		• **Investigator-assessed objective response: Similar to ORR**
		• **Median duration of response:** 11.1 months
		  ○ **Liquid Biopsy group:** 8.5 months
		  ○ **Tissue Biopsy group:** 11.0 months
		• **PFS:** 8.5 months
		• **Median duration of OS:** 17.1 months
		• Serious adverse events were reported in 15% of patients
		• Treatment-related adverse events led to a dose reduction in 33% of patients; 11% of these led to permanent discontinuation
		• Peripheral edema was the most common adverse event (16% led to dose reduction, 18% led to dose interruption, 5% led to permanent discontinuation

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Tepotinib in Non–Small-Cell Lung Cancer with *MET* Exon 14 Skipping Mutations (VISION Trial)

Adverse Events	Safety Population (N=152)		
	All Grades	Grade 1 or 2	Grade 3
		number of patients (percent)	
Any adverse event†	135 (89)	93 (61)	38 (25)
Peripheral edema	96 (63)	85 (56)	11 (7)
Nausea	39 (26)	38 (25)	1 (1)
Diarrhea	33 (22)	32 (21)	1 (1)
Blood creatinine increased	27 (18)	26 (17)	1 (1)

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Knowledge Check: What is the most common adverse event associated with Tepotinib?

A.Cardiac arrhythmias
B.Skin and Soft Tissue Infections
C.Peripheral Edema
D.Hypersensitivity Reactions

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Knowledge Check: What is the most common adverse event associated with Tepotinib?

A.Cardiac arrhythmias
B.Skin and Soft Tissue Infections
C.Peripheral Edema
D.Hypersensitivity Reactions

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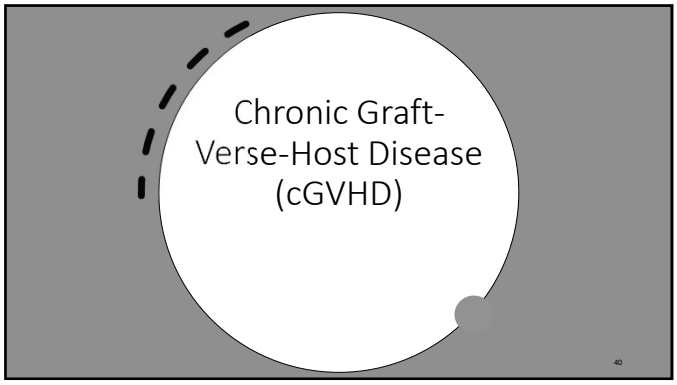

40

Axatilimab-csfr (Niktimvo)

- **FDA Approved: August 14, 2024**
- **MOA**
  - Blocks colony stimulating factor-1 receptors (CSF-1R) expressed on monocytes and macrophages
  - Reduces the levels of these circulating proinflammatory and profibrotic monocytes and monocyte-derived macrophages
  - Inhibits the activity of pathogenic macrophages in tissues
- **Dose**
  - Patients weighing ≥40 kg: **IV:** 0.3 mg/kg (maximum dose: 35 mg) once every 2 weeks until disease progression or unacceptable toxicity

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Axatilimab-csfr (Niktimvo)

- **Adverse Effects**
  - Decreased serum phosphate, increased serum calcium
  - Hematologic & oncologic disturbances (Decrease in Hemoglobin, Hemorrhage)
  - Elevated liver enzymes
  - Hypersensitivity
  - Infection
  - Neuromuscular & skeletal pain
  - Fever
- **Pearls**
  - No renal or hepatic dosing adjustments
  - Grade 4 adverse effects warrant permanent discontinuation of axatilimab-csf
  - Grade 1-3 adverse effects warrant temporary discontinuation until symptoms resolve or are reduced to grade 2

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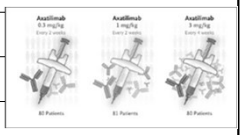
Phase II Agave-201 Trial

Published September 18, 2024

Phase 2, multinational, pivotal, randomized study



Evaluated axatilimab at three different doses in patients with recurrent or refractory cGVHD (n=241)

Patients were administered 0.3mg/kg every 2 weeks, 1mg/kg every 2 weeks, or at a dose of 3mg/kg every 4 weeks

Primary Endpoint: Overall Response (OR) in the first six cycles (Would be met if the lower bound of the 95% CI exceeded 30%)

Secondary Endpoints: Patient reported decrease in cGVHD symptom burden

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Phase II Agave-201 Trial Results

	Overall Response (95% CI)	5 point reduction in modified Lee Symptom Scale	Adverse Events leading to discontinuation
0.3mg dose group	74%	60%	6%
1mg dose group	67%	69%	22%
3mg dose group	50%	41%	18%

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Knowledge Check: Which dose group of axatilimab-csfr (Niktimvo) showed the most benefit regarding its efficacious and safety profile?

A. 0.3mg dose group
B. 1mg dose group
C. 3mg dose group
D. Efficacy and safety was similar across all groups

45

Knowledge Check: Which dose group of axatilimab-csfr (Niktimvo) showed the most benefit regarding its efficacious and safety profile?

A.0.3mg dose group
B.1mg dose group
C.3mg dose group
D.Efficacy and safety was similar across all groups

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Imaging Agents

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Pafolacianine (Cytalux)

- **FDA Approved:**
  - February 29, 2021 for Ovarian Cancer Surgery
  - December 15, 2022 for Lung Cancer Surgery
- **MOA**
  - Binds to folate receptor (FR)-expressing cells with ~1 nM affinity, internalizes via receptor-mediated endocytosis, and accumulates intracellularly
  - Fluorescent drug that targets FR, which is overexpressed in ovarian cancer. The mechanism of pafolacianine detection of lung lesions is not well understood
- **Dose**
  - **Ovarian Cancer:** 0.025 mg/kg as a single dose, administered 1 to 9 hours prior to surgery
  - **Lung Cancer:** 0.025 mg/kg administered over 60 minutes using a dedicated infusion line, 1 hour to 24 hours prior to surgery.

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Pafolacianine (Cytalux)

- **Adverse Effects**
  - Infusion Related Reactions
  - Drug-Drug Interaction with Folate Containing Products
- **Pearls**
  - Avoid folate, folic acid, or folate-containing supplements within 48 hours before administration of pafolacianine
  - No renal/hepatic dose adjustments
  - Antipyretic and antihistamines is recommended as pre-medications according to drug package insert

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Elucidate Trial

Trial	Published	Interventions
• Investigated the Safety and Efficacy of OTL38 Injection for Intraoperative Imaging of Folate Receptor Positive Lung Nodules • Phase 3, Randomized, Single Dose, Open-Label Study • N=112	• March 3, 2023	• Pafolacianine dosed at 0.025mg/kg between 1-24 hours before initiation of fluorescence imaging

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Elucidate Trial Continued

Primary Endpoint	Secondary Endpoint
• Clinically significant events (CSE), identification of cancerous synchronous lesions, localization of primary nodule, and positive resection margins	• Sensitivity for cancerous primary nodules and synchronous lesions, and false positive rates for cancerous primary nodules and synchronous lesions

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Elucidate Trial Continued

Results

- **53%:** ≥1 CSE of evaluated participants compared with a prespecified limit of 10% (P<0.0001)
- **38%:** A close resection margin (margin ≤ 10mm from the resected primary nodule) was identified
- **19%:** Intraoperative molecular imaging located the primary nodule that the surgeon could not locate with white light and palpation
- **8%:** Surgeons found one or more occult malignant lesions that were not previously identified
- **73%:** Intraoperative molecular imaging-discovered synchronous malignant lesions were outside the planned resection field

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Elucidate Trial Continued

Results

- **29%:** Surgeons reported changing the scope of their procedure who received pafolacianine (22 increase, 7 decrease)
- Most common (>2%) mild/moderate drug-related adverse events included nausea (8.9%), vomiting (3.6%), and intermittent hypertension (2.7%)
- Severe intermittent hypertension occurred in 1 (0.9%) patients
- **32.1%:** Subjects with at least one drug-related mild/moderate treatment emergent adverse events (TEAE)
- **2.7%:** Subjects with at least one drug-related severe treatment emergent adverse events (TEAE)
- The total number of subjects with mild/moderate drug related TEAEs was 55
- The total number of subjects with severe drug related TEAEs was 5

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Knowledge Check: What indication(s) are Cytalux FDA approved for?

A. Pancreatic Cancer Surgery
B. Colon Cancer Surgery
C. Breast Cancer Surgery
D. Ovarian and Lung Cancer Surgery

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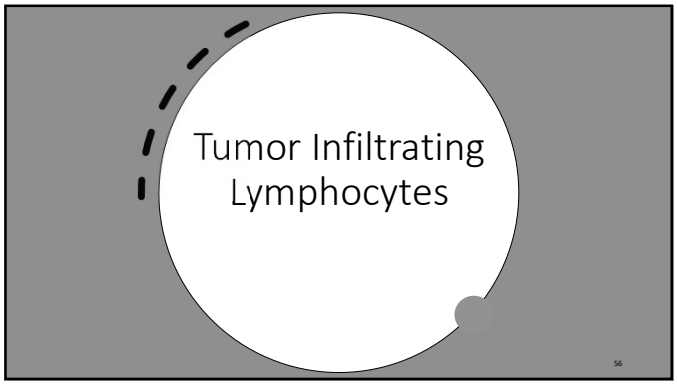

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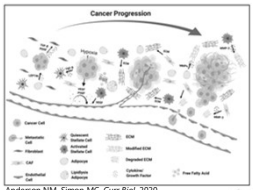
Tumor microenvironment (TME)

- TME is the ecosystem surrounding a tumor, consisting of various cells, molecules, and blood vessels
- Components
  - Cancer Cells
  - Stromal Cells
  - Immune Cells
  - Blood Vessels
  - Extracellular Matrix

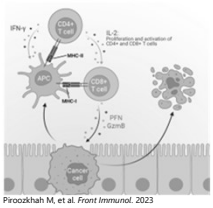


Anderson NM, Simon MC. *Curr Biol*. 2020

57

What are TILs?

- Tumor-Infiltrating Lymphocytes (TILs) are a type of white blood cell that migrates from the bloodstream into a tumor
- TILs recognize and bind to specific antigens on the surface of cancer cells
- Upon binding, TILs become activated and initiate an immune response



Piroozkhah M, et al. *Front Immunol.* 2023

58

TIL Therapy Gets FDA Approval for Advanced Melanoma

Historic FDA Approval:	• The FDA has approved lifileucel (Amtagvi), marking the first cancer treatment using tumor-infiltrating lymphocytes (TILs).
Announcement Date:	• The approval was announced on February 16.
First of Its Kind:	• Lifileucel is the first cellular therapy approved for a solid tumor, specifically for skin cancer melanoma.
Accelerated Approval:	• The FDA's accelerated approval allows the use of lifileucel for advanced melanoma patients whose cancer has progressed after other immunotherapy or targeted treatments.

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Amtagvi (Lifileucel)

Tumor-derived autologous TIL therapy manufactured using resected tumor tissue from the patient, and then expanded ex-vivo

Following lymphodepleting therapy, re-infusion, and in vivo T-cell expansion with high-dose aldesleukin (IL-2)

TILs migrate to tumor sites, target tumor-associated antigens, and facilitate immune-mediated tumor cell lysis and overall tumor regression

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Clinical Pearls

- Administer filgrastim or a biosimilar product to patients beginning Day 1 after lifileucel and continuing daily until the ANC is >1,000 per mm^3 for 3 consecutive days
- Premedicate with acetaminophen and diphenhydramine 30 to 60 minutes prior to lifileucel infusion
- Avoid the use of systemic corticosteroids (may interfere with lifileucel activity)

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Clinical Evidence (C-144-01 Study)

Design	Inclusion Criteria	Intervention	Results

• Prospective
• Phase 2
• Multicohort
• Multicenter study
 	
• Primary endpoint
  • Overall Response Rate
	• Age ≥18 years
	• Unresectable or metastatic melanoma
	• Progressed following ≥1 prior systemic
	• ECOG PS: 0-1
	• Estimated life expectancy of ≥3 months
	• ≥1 resectable lesion providing resected tumor tissue ≥1.5 cm in diameter and ≥1 remaining measurable target lesion
		• **Fludarabine + cyclophosphamide**
		• **Lifileucel** 1×10^9–150×10^9 viable cells
		• **Aldesleukin** 600,000 units/kg every 8 to 12 hours for up to 6 doses
			• Objective Response Rate:
			  • 63.6% CI: 24.1%-39.4%)
			  • 8 complete responses
			  • 40 partial responses
			• Duration of response
			  • Not reached at a median study follow-up of 27.6 month
			  • 41.7% of the responses maintained for ≥18 months
			• Median overall survival
			  • 13.9 months
			• Progression-free survival
			  • 4.1 months

Chesney J, et al. *J Immunother Cancer*. 2022

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Clinical Evidence (IOV-COM-202 Study)

Design	Inclusion Criteria	Intervention	Results

• Prospective
• Phase 2
• Multicohort
• Multicenter study
 	
• Primary endpoint
  • Overall Response Rate
	• Age ≥18 years
	• Unresectable or metastatic melanoma
	• ECOG PS: 0-1
	• Estimated life expectancy ≥6 months
	• **ICI-naïve unresectable or metastatic melanoma**
	• ≥1 resectable lesion providing resected tumor tissue ≥1.5 cm in diameter and ≥1 remaining measurable target lesion
		• **Fludarabine + cyclophosphamide**
		• **Lifileucel** 1×10^9–150×10^9 viable cells
		• **Aldesleukin** 600,000 units/kg every 8 to 12 hours for up to 6 doses
		• **Pembrolizumab** until disease progression or unacceptable toxicity
			• Overall Response Rate:
			  • 63.6%
			  • 5 complete responses
			  • 9 partial responses
			• Duration of response
			  • Not reached at a median study follow-up of 17.2 months
			  • 36.4% of the responses maintained for ≥12 months

Thomas SS, et al. *JCO*. 2024

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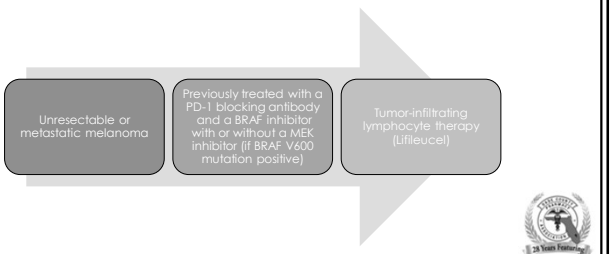
Place in Therapy



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Knowledge check

What is the primary goal of TIL therapy in cancer treatment?

A. To reduce the size of tumors by using radiation

B. To increase the number of cancer-fighting cells by extracting and multiplying lymphocytes from the patient's tumor

C. To replace damaged cells with healthy stem cells

D. To use chemotherapy to kill cancer cells directly

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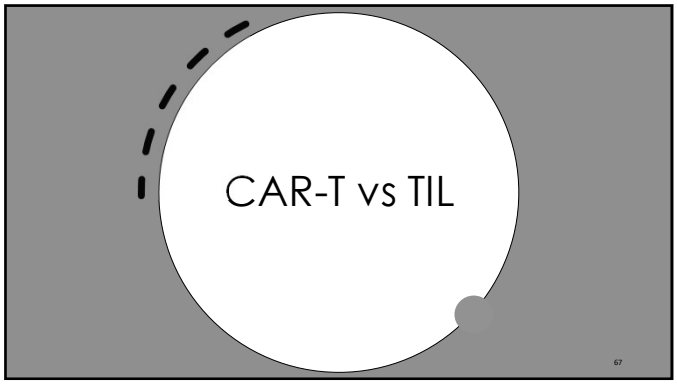

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CAR-T vs TIL

	CAR-T Cell Therapy	TIL Therapy
Definition	• Genetically modified T cells with chimeric antigen receptors (CARs)	• Naturally occurring immune cells extracted from the tumor
Process	• T cells collected from blood • Genetically engineered to express CARs • Expanded and infused back into the patient	• TILs extracted from tumor • Expanded in the lab • Infused back into the patient
Target	• Specific antigens on cancer cells (BCMA,CD19)	• Multiple antigens on cancer cells

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CAR-T vs TIL

	CAR-T Cell Therapy	TIL Therapy
Application	• Primarily blood cancers (leukemia, lymphoma)	• Solid tumors (melanoma)
Advantages	• Highly specific targeting • Potential for long-term remission	• Naturally tailored to patient's tumor • Broad range of tumor antigens
Challenges	• Severe side effects (CRS, neurotoxicity) • Limited effectiveness against solid tumors	• Requires surgical extraction of tumor tissue • Intensive manufacturing process

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Knowledge check

Which of the following statements is true about CAR-T cell therapy and TIL therapy?

A. CAR-T cell therapy is primarily used for solid tumors, while TIL therapy is used for blood cancers

B. TIL therapy involves genetically modifying T cells to express chimeric antigen receptors (CARs)

C. CAR-T cell therapy targets specific antigens on cancer cells, whereas TIL therapy can recognize multiple antigens

D. Both CAR-T cell therapy and TIL therapy require the extraction of tumor tissue for treatment

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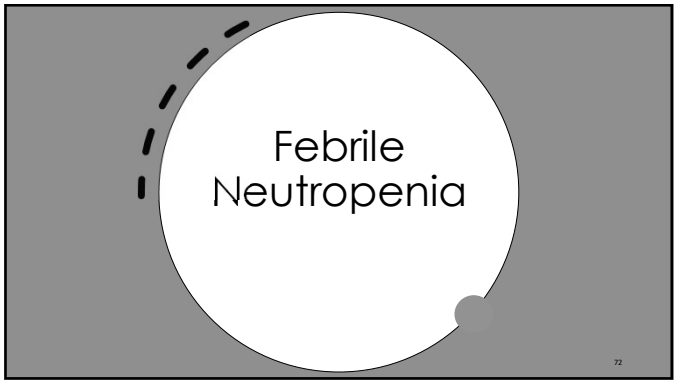

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What is Febrile Neutropenia?

ANC < 500 cells/mm^3 or < 1,000 cells/mm^3 with a predicted decrease to < 500 cells/mm^3 within 48 hours

Nadir typically occurs 7–14 days after completing myelosuppressive chemotherapy

Oral Temperature ≥38.3°C (101°F) x1

Oral Temperature ≥38.0°C (100.4°F) sustained ≥ 1 hour

National Comprehensive Cancer Network. NCCN Guidelines: Cancer-Related Infections. Version 1.2025. Accessed January 13, 2025.

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Risk Factors

Advanced Age	Chemotherapy type and intensity	Previous chemotherapy or radiation
Nutrition status	Poor performance status	Comorbidities

National Comprehensive Cancer Network. NCCN Guidelines: Cancer-Related Infections. Version 1.2025. Accessed January 13, 2025.

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Common Pathogens

Gram negative bacteria	Gram positive bacteria
• E. coli • P. aeuruginosa • Klebsiella • Enterobacter spp.	• S. aureus • S. epidermidis • S. haemolyticus • S. hominis • Viridans group Strep • Enterococci spp

National Comprehensive Cancer Network. NCCN Guidelines: Cancer-Related Infections. Version 1.2025. Accessed January 13, 2025.

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INITIAL RISK ASSESSMENT

- Low risk:
  - Outpatient status at time of development of fever
  - No associated acute comorbid illness, independently indicating inpatient treatment or close observation
  - Anticipated short duration of severe neutropenia (≤100 cells/mcL for <7 days)
  - Good performance status (ECOG 0–1)
  - No hepatic insufficiency
  - No renal insufficiency
  - MASCC Risk-Index Score of ≥21 or CISNE score of <3

National Comprehensive Cancer Network. NCCN Guidelines: Cancer-Related Infections. Version 1.2025. Accessed January 13, 2025. 76

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INITIAL RISK ASSESSMENT

- High risk:
  - MASCC Risk-Index Score of <21 or CISNE score of ≥3
  - Inpatient status at time of development of fever
  - Significant medical comorbidity or clinically unstable Allogeneic HCT
  - Anticipated prolonged severe neutropenia: ≤100 cells/mcL and ≥7 days
  - Hepatic insufficiency (5 times upper limit of normal [ULN] for aminotransferases)
  - Renal insufficiency (creatinine clearance [CrCl] of <30 mL/min)
  - Uncontrolled/progressive cancer
  - Pneumonia or other complex infections at clinical presentation
  - Use of certain immune and/or targeted treatments (INF-A)
  - Mucositis grade 3–4

National Comprehensive Cancer Network. NCCN Guidelines: Cancer-Related Infections. Version 1.2025. Accessed January 13, 2025. 77

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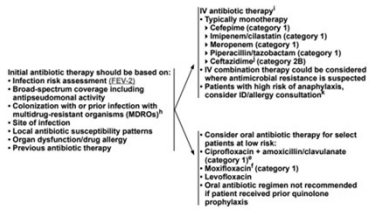
Empiric Treatment



National Comprehensive Cancer Network. NCCN Guidelines: Cancer-Related Infections. Version 1.2025. Accessed January 13, 2025. 78

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Duration of Therapy

Duration of Therapy Guidance	IDSA	NCCN
Bacterial pneumonia	5-14 days	5-14 days
Bacteremia	7-10 days after first (-) blood cultures >14 days for S.aureus	Gram positive: 7-14 days Gram negative: 10-14 days S.aureus: 4 weeks after first (-) blood cultures and normal ECHO
Skin Infection	5-14 days	5-14 days
Bacterial sinusitis	7-14 days	7-14 days
Intraabdominal Infections	7-14 days	7-14 days
Central Line-associated Blood Stream Infection	5-14 days if uncomplicated or up to 8 weeks if complicated (endocarditis, osteomyelitis etc.)	5-14 days if uncomplicated or up to 8 weeks if complicated (endocarditis, osteomyelitis etc.)

National Comprehensive Cancer Network. NCCN Guidelines: Cancer-Related Infections. Version 1.2025. Accessed January 13, 2025.

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Prophylaxis

Low infection risk

- None

Intermediate infection risk

- Antibacterial: Consider fluoroquinolones during neutropenia
- Antiviral: During neutropenia and longer depending on risk
- Antifungal: During neutropenia and for anticipated mucositis

High infection risk

- Antibacterial: Consider fluoroquinolones during neutropenia
- Antiviral: During neutropenia and longer depending on risk
- Antifungal: During neutropenia and for anticipated mucositis

National Comprehensive Cancer Network. NCCN Guidelines: Cancer-Related Infections. Version 1.2025. Accessed January 13, 2025.

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Ryzneuta

Ryzneuta (Efbemalenograstim alfa) is a granulocyte colony-stimulating factor (G-CSF)

Used to lower the risk of infection in patients with neutropenia caused by cancer chemotherapy

Indicated for adult patients with non-myeloid malignancies undergoing myelosuppressive chemotherapy

Ryzneuta. Package Insert. Drugs.com. https://www.drugs.com/pro/ryzneuta.html

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How does it work?

Long-acting recombinant human granulocyte growth factor conjugated with a recombinant human IgG2-Fc fragment allowing for an extended half-life

Binds to granulocyte colony-stimulating factor receptors on hematopoietic cells, triggering signaling pathways to stimulate cell differentiation, proliferation, commitment, and end cell functional activation

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Clinical Evidence (GC-627-04)

Patient Population	122 patients with breast cancer
Chemotherapy Regimen	Doxorubicin 60 mg/m² Docetaxel 75 mg/m² Administered every 21 days for up to four cycl es
Intervention	Efbemalenograstim alfa on cycle 1, day 2 of chemotherapy
Control Group	Placebo
Primary Outcome	**Duration of Severe (Grade 4) Neutropenia** Efbemalenograstim alfa: 1.4 days Placebo: 4.3 days
Secondary Outcome	**Incidence of Febrile Neutropenia** Efbemalenograstim alfa: 4.8% Placebo: 26%
Conclusion	Efbemalenograstim alfa significantly reduced t he duration of severe neutropenia and the inci dence of febrile neutropenia compared to placebo

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Clinical Evidence (GC-627-05)

Patient Population	393 patients with breast cancer
Chemotherapy Regimen	Docetaxel 75 mg/m² Cyclophosphamide 600 mg/m² Administered every 21 days for up to four cycl es
Intervention	Efbemalenograstim alfa
Control Group	Pegfilgrastim
Primary Outcome	Mean Number of Days of Severe Neutropenia i n Cycle 1 **Efbemalenograstim alfa: 0.2 days** **Pegfilgrastim: 0.2 days**
Conclusion	Efbemalenograstim alfa and pegfilgrastim resu lted in the same mean number of days of seve re neutropenia in cycle 1

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Dosage and administration

SUBQ: 20 mg once per chemotherapy cycle

Administer ≥24 hours after cytotoxic chemotherapy

Do not administer within the period from 14 days before to <24 hours after administration of cytotoxic chemotherapy

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Adverse effects

Common Side Effects
- Nausea
- Anemia
- Thrombocytopenia

Serious Side Effects
- Spleen rupture
- Acute Respiratory Distress Syndrome (ARDS)
- Severe allergic reactions
- Sickle cell crises

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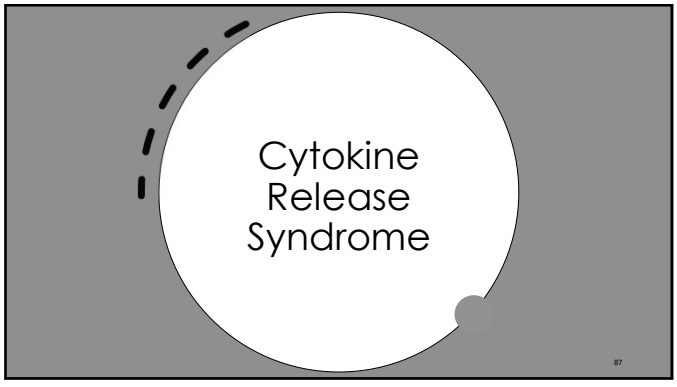

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Cytokine Release Syndrome (CRS)

- **Immune Response:**
  - Overactivation of the immune system leading to excessive cytokine release
- **Symptoms:**
  - Fever
  - Hypotension
  - Organ dysfunction

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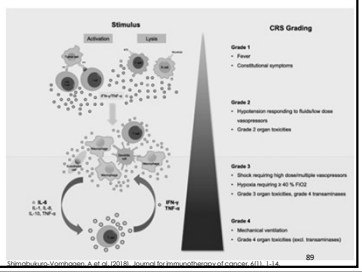
Pathophysiology

- Rapid release of cytokines due to immune therapy activating T cells
  - T cells release IFN-g
  - IFN-g activates macrophages
    - IL-6
    - TNF-alpha
    - IL-10
  - Cardiovascular, renal, neurological, and respiratory toxicity



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Shimabukuro-Vornhagen, A et al. (2018). Journal for immunotherapy of cancer, 6(1), 1-14.

89

Manifestations

Common symptoms	Severe symptoms
• Fever • Fatigue • Nausea and Vomiting • Body Aches • Headache • Rash • Diarrhea	• Low Blood Pressure • Shortness of Breath • Confusion • Organ Dysfunction

Immune system disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Cytokine release syndrome	Fever with or without constitutional symptoms	Hypotension responding to fluids; hypoxia responding to <40% O2	Hypotension managed with one pressor; hypoxia requiring ≥ 40% O2	Life-threatening consequences; urgent intervention indicated	Death

Definition: A disorder characterized by fever, tachypnea, headache, tachycardia, hypotension, rash, and/or hypoxia caused by the release of cytokines.
Navigational Note: Also consider reporting other organ dysfunctions including neurological toxicities such as: Psychiatric disorders: Hallucinations or Confusion; Nervous system disorders: Seizure, Dysphasia, Tremor, or Headache

Shimabukuro-Vornhagen, A et al. (2018). Journal for immunotherapy of cancer, 6(1), 1-14.

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Management

- Refer to drug specific package insert for management
- Tocilizumab:
  - IV tocilizumab 8 mg/kg over 1 hour (not to exceed 800 mg/dose)
  - Repeat in 8 hours if no improvement; no more than 3 doses in 24 hours, with a maximum of 4 doses total
- Dexamethasone:
  - IV dexamethasone 10 mg every 12–24 hours
- Anakinra:
  - IV: 2 mg/kg/hr as CI for up to 72 hrs or 2-10 mg/kg/day in 2-4 doses
  - SQ: 2-10 mg/kg/day in 2-4 doses

Actemra & Heart Attack - The Michael Brady Lynch Firm. The Michael Brady Lynch Firm. Published March 2021. Accessed January 13, 2025. https://mblynchfirm.com/pharmaceutical-litigation/actemra/actemra-heart-attack

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Immune Effector Cell-Associated Neurotoxicity Syndrome

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Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS)

- ICANS results from an inflammatory response triggered by immunotherapy, leading to increased cytokine levels and subsequent neurotoxicity
- Symptoms:
  - Aphasia
  - Impaired cognition
  - Seizures
  - Cerebral edema

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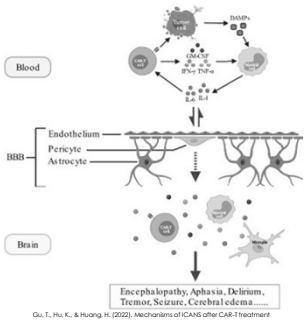
Pathophysiology

- Not fully understood
- Similar to CRS as cytokines are released once T cells are activated
  - Cytokines diffuse through the BBB
  - Activate microglial cells



Gu, T., Hu, K., & Huang, H. (2022). Mechanisms of ICANS after CAR-T treatment

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Manifestations

Mild to Moderate symptoms	Severe symptoms
• Headache • Confusion • Difficulty Speaking • Tremors • Agitation • Lethargy • Hallucinations • Memory Loss	• Seizures • Brain Swelling • Coma

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Diagnosis

ICANS	ICE score[7]	7–9	3–6	0–2	0
	Depressed consciousness not attributable to other cause	Awakens spontaneously	Awakens to voice	Awakens only to tactile stimulus	Arousable with vigorous tactile stimuli, unarousable, stupor, or coma
	Seizures	NA	NA	Any seizure with rapid clinical resolution or with intervention on EEG tracings	Prolonged (>5 min), non-resolving or life-threatening seizures
	Motor findings	NA	NA	NA	Significant focal motor weakness (eg, hemiparesis or paraparesis)
	Elevated ICP/ cerebral edema[1]	NA	NA	Focal edema on brain imaging	Diffuse edema on imaging, or decerebrate/decorticate posturing, CN VI palsy, or Cushing's triad

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Management

- Refer to drug specific package insert for management
- Steroids:
  - IV dexamethasone 10 mg every 6 hours or IV methylprednisolone 1 mg/kg every 12 hours
- Anakinra:
  - 100 mg IV every 6 hours

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Final Thoughts

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Role of Pharmacists

Medication Management:

- Personalizing chemotherapy and supportive-care medications
- Selecting, preparing, dosing, and dispensing drugs

Symptom Management:

- Monitoring disease-related symptoms,
- Managing drug levels
- Assessing drug interactions
- Managing adverse effects

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The future…

- **Immunotherapy:**
  - CAR-T Cell Therapy: Continued development of CAR-T cell therapies, including off-the-shelf and in vivo CAR-T generation, to improve efficacy and accessibility
  - CAR-NK Cell Therapy: Exploring CAR-NK cell therapies, which may offer fewer side effects and broader applicability
- **Precision Medicine:**
  - Personalized Cancer Vaccines: Development of vaccines tailored to individual patients' tumor profiles
  - Genomic Profiling: Using genetic information to guide treatment decisions and develop targeted therapies
- **Artificial Intelligence (AI):**
  - AI Diagnostics: Leveraging AI for early cancer detection and diagnosis through advanced imaging and molecular profiling
  - Predictive Analytics: Using AI to predict treatment responses and optimize therapy plans

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The future…

- **Tumor Infiltrating Lymphocyte (TIL) Therapy:**
  - Expanding Applications: Researching the use of TIL therapy for various solid tumors beyond melanoma
  - Improving Techniques: Enhancing the extraction, expansion, and reinfusion processes to increase success rates
- **Liquid Biopsies:**
  - Non-Invasive Testing: Developing liquid biopsies to detect cancer and monitor treatment response through blood samples
- **CRISPR and Gene Editing:**
  - Targeted Gene Therapy: Using CRISPR technology to edit genes and potentially cure certain types of cancer

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References

- Ahn M, Byoung Chul Cho, Felip E, et al. Tarlatamab for Patients with Previously Treated Small-Cell Lung Cancer. *The New England Journal of Medicine*. 2023;389(22). doi:https://doi.org/10.1056/nejmoa2307980
- Piroozkhah M, Gholinezhad Y, Piroozkhah M, Shams E, Nazemalhosseini-Mojarad E. The molecular mechanism of actions and clinical utilities of tumor infiltrating lymphocytes in gastrointestinal cancers: a comprehensive review and future prospects toward personalized medicine. Front Immunol. 2023;14:1298891. Published 2023 Nov 24. doi:10.3389/fimmu.2023.1298891
- Anderson NM, Simon MC. The tumor microenvironment. Curr Biol. 2020;30(16):R921-R925. doi:10.1016/j.cub.2020.06.081
- Chesney J, Lewis KD, Kluger H, et al. Efficacy and safety of lifileucel, a one-time autologous tumor-infiltrating lymphocyte (TIL) cell therapy, in patients with advanced melanoma after progression on immune checkpoint inhibitors and targeted therapies: pooled analysis of consecutive cohorts of the C-144-01 study. J Immunother Cancer. 2022;10(12):e005755. doi:10.1136/jitc-2022-005755
- Kumar A, Soumerai J, Abramson JS, et al. A Multicenter Phase 2 Trial of Zanubrutinib, Obinutuzumab, and Venetoclax (BOVen) in Patients with Treatment-Naïve, *TP53*-Mutant Mantle Cell Lymphoma. *Blood*. 2023;142(Supplement 1):738-738. doi:https://doi.org/10.1182/blood-2023-180069
- Paik PK, Felip E, Veillon R, et al. Tepotinib in Non–Small-Cell Lung Cancer with MET Exon 14 Skipping Mutations. *New England Journal of Medicine*. 2020;383(10):931-943. doi:https://doi.org/10.1056/nejmoa2004407
- Pier Luigi Zinzani, Mayer J, Flowers CR, et al. ROSEWOOD: A Phase II Randomized Study of Zanubrutinib Plus Obinutuzumab Versus Obinutuzumab Monotherapy in Patients With Relapsed or Refractory Follicular Lymphoma. *Journal of Clinical Oncology*. 2023;41(33):5107-5117. doi:https://doi.org/10.1200/jco.23.00775
- Sajeve Samuel Thomas et al., Efficacy and safety of lifileucel, an autologous tumor-infiltrating lymphocyte cell therapy, and pembrolizumab in patients with immune checkpoint inhibitor-naive unresectable or metastatic melanoma: Updated results from IOV-COM-202 cohort 1A.. JCO 42, 9505-9505(2024).DOI:10.1200/JCO.2024.42.16_suppl.9505
- Sarkaria IS, Martin LW, Rice DC, et al. Pafolacianine for intraoperative molecular imaging of cancer in the lung: The ELUCIDATE trial. *Journal of Thoracic and Cardiovascular Surgery*. 2023;166(6):e468-e478. doi:https://doi.org/10.1016/j.jtcvs.2023.02.025
- Schmid P, Cortes J, Dent R, et al. Overall Survival with Pembrolizumab in Early-Stage Triple-Negative Breast Cancer. *New England Journal of Medicine*. Published online September 15, 2024. doi:https://doi.org/10.1056/nejmoa2409932
- Soumerai JD, Mato AR, Dogan A, et al. Zanubrutinib, obinutuzumab, and venetoclax with minimal residual disease-driven discontinuation in previously untreated patients with chronic lymphocytic leukaemia or small lymphocytic lymphoma: a multicentre, single-arm, phase 2 trial. *The Lancet Haematology*. 2021;8(12):e879-e890. doi:https://doi.org/10.1016/s2352-3026(21)00307-0
- Wolff D, Cutler C, Lee SJ, et al. Axatilimab in Recurrent or Refractory Chronic Graft-versus-Host Disease. *New England Journal of Medicine*. 2024;391(11):1002-1014. doi:https://doi.org/10.1056/nejmoa2401537
- National Comprehensive Cancer Network. Prevention and Treatment of Cancer-Related Infections. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines). Version 1.2025. Accessed January 13, 2025.
- Shimabukuro-Vornhagen A, Gödel P, Subklewe M, et al. Cytokine release syndrome. J Immunother Cancer. 2018;6(1):56. Published 2018 Jun 15. doi:10.1186/s40425-018-0343-9
- Gu T, Hu K, Si X, Hu Y, Huang H. Mechanisms of immune effector cell-associated neurotoxicity syndrome after CAR-T treatment. *WIREs Mech Dis*. 2022;14(6):e1576. doi:10.1002/wsbm.1576
- Evive Biotechnology Singapore Pte. Ltd. Ryzneuta (efbemalenograstim alfa-vuxw) injection, for subcutaneous use. Prescribing Information. Updated March 25, 2024. Accessed January 13, 2025.

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Early Cancer Detection Strategies and Cancer Prevention Vaccines

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January 26th, 2025

29 Years Featuring
South Florida Pharmacy Residents

1

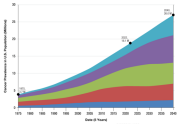
Objectives

- **Review Key Cancer Statistics**
- Examine cancer incidence, mortality rates, and high-risk groups
- **Discuss Standardized Cancer Screenings**
- Review mammograms, skin cancer screenings, colonoscopies, and other essential screenings
- **Explore Early Detection with the Galleri Test**
- Learn about the Galleri test and its role in multi-cancer early detection
- **Understand Vaccine-Preventable Cancers**
- Discuss HPV and Hepatitis B vaccines, including MOA, vaccine schedule and prevention

2

Cancer Statistics

Cancer Prevalence and Projections in U.S. Population from 1975–2040



Over 2 million new cancer cases are expected in the U.S in 2024

1 in 2 people will be diagnosed with cancer in their lifetime, and 1 in 5 will die

Cancer has been a top cause of death in the US for over 75 years
- with 140 deaths every hour

About 840,000 cases of cancer in 2024
- 42% of new diagnoses are avoidable through lifestyle and environmental changes

Mortality rates are declining, but cancer rates are still high

In 2021, men had a 12.7% higher cancer incidence and a 36.7% higher cancer death rate than women

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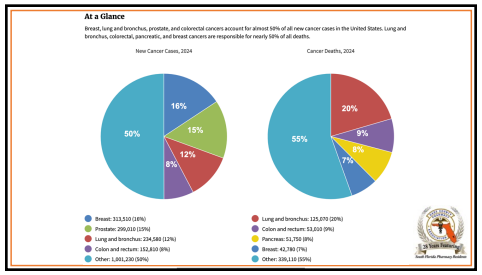

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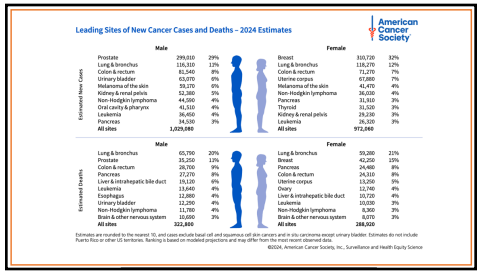

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Test-Your-Knowledge

What is the leading risk factor for cancer?

A. Poor diet
B. Age
C. Obesity
D. Smoking

6

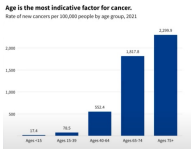
Test-Your-Knowledge

What is the leading risk factor for cancer?

A. Poor diet
B. Age
C. Obesity
D. Smoking

7

Cancer Risk Factors



Age is the biggest cancer risk factor

- with adults over 50 are 13 times more likely to develop cancer than those under 50.

Other factors that increase cancer risk include

- •Diabetes
- •Obesity (BMI ≥ 30)
- •Low muscle mass and lack of exercise
- •Smoking (current or past)
- •Excessive alcohol consumption
- •Chronic inflammation
- •Oxidative stress

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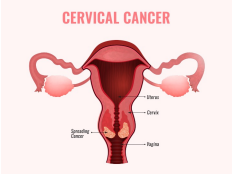
Cancer Screening – Cervical

U.S Preventive Service Task Force recommends cervical screening:

- •Start at age 21 and continue until 65 (if prior screenings are normal and no high risk for cervical cancer)
- •Every 3-5 years if results are normal and screening used (Cytology vs Human Papillomavirus testing)



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Test-Your-Knowledge

What is the recommended frequency of cervical cancer screening (Pap smear with HPV test) for individuals aged 21–65, with normal results?

A. Every year
B. Every 3-5 years
C. Every 10 years
D. Every 5-7 years

10

Test-Your-Knowledge

What is the recommended frequency of cervical cancer screening (Pap smear with HPV test) for individuals aged 21–65, with normal results?

A. Every year
B. Every 3-5 years
C. Every 10 years
D. Every 5-7 years

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Cancer Screening – Prostate

National Comprehensive Cancer Network (NCCN) Prostate screening: Digital Rectal Exam and/or PSA

- Start at age 45-75 for average-risk men
- Age 45 for high-risk men.
  - African Americans, men with a first-degree relative diagnosed before 65
- Age 40 for those with multiple high-risk family members
- Screen every 1-2 years, based on results

U.S Preventive Service Task Force (Digital Rectal Exam and/or PSA)

- Men aged 55-69 should discuss screening with their clinician
- Risk of early testing:
  - false positives, overdiagnosis, overtreatment, treatment complications (incontinence, erectile dysfunction)

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Cancer Screening - Colorectal

Colorectal screening
Colonoscopy: start at age 45-75, with frequency based on results (1, 3, 5, or 10 years)
For ages 76-85, screening depends on personal choice and doctor recommendations

High-risk individuals
- Start screening earlier (8-10 years after diagnosis or at age 35), including those with
  - Strong family history of colorectal cancer
  - Personal history of colorectal cancer, polyps, or inflammatory bowel disease (IBD)
  - Known hereditary colorectal cancer syndromes (e.g., FAP, Lynch syndrome)
  - Past radiation treatment to the abdomen or pelvic area

*FAP: Familial adenomatous polyps

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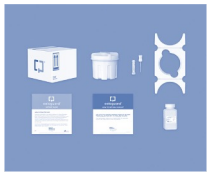
Cologuard

- **Cologuard** (at-home stool test) can be an option, though not the standard of care
  - detects abnormal DNA and blood in stool samples, which can indicate precancerous polyps or colon cancer
- **How effective is Cologuard in detecting colorectal cancer?**
  - Has a 69% sensitivity for detecting high-grade dysplasia
  - But it misses 31% of cases compared to colonoscopy, which only misses 1%



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Cancer Screening - Skin

U.S Preventive Service Task Force Recommends

- Counseling young adults, children, and parents about minimizing exposure to ultraviolet radiation for persons age 6 months to 24 years
- Skin screening with dermatologist as recommended by primary care provider

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Signs to Look for:

- New Growths
- Non-Healing Sores
- Changes in Moles
- Know the ABCDE's of Melanoma

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Cancer Screening - Lung

U.S Preventive Service Task Force Recommends

- **Lung screening:** low dose Computer Tomography (CT)
- Screening of current or former heavy smokers at ages 50 80.

Screening recommendations:

- **High risk** – 50 years of age and over with a 20 pack-year or more history of smoking cigarettes
  - Lung cancer screening is recommended
- **Low risk** – Under 50 years of age or less than a 20 pack-ye history of smoking cigarettes
  - Lung cancer screening is not recommended

Number of packs per day
x years of smoking
= Pack-years

Example:
1.5 packs a day x 30 years =
45 pack-years

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Cancer Screening - Breast

Mammogram NCCN Recommendations

- Ages 40-55: Annual screening
- Age 55+: Screen every 1-2 years
- Start screening 5 years earlier than the age of the earliest diagnosis, or at age 30
  - If family history of breast cancer or are high risk
- **High-risk women** should get annual MRI and mammograms starting at age 30
  - Those with a 20-25% lifetime risk, due to factors like
    - BRCA1/BRCA2 mutations
    - Family history
    - Prior chest radiation (e.g., Hodgkin lymphoma)
- **Self-breast exams can help identify changes or lumps but are not diagnostic**

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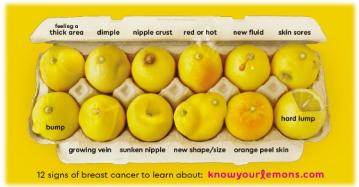
Cancer Screening - Breast



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Laboratory Tests for Cancer Screening

- Complete blood count (CBC)
- Comprehensive metabolic panel (CMP)
- hs-CRP (C-Reactive Protein)
- Prostate specific antigen (PSA)
- Tumor marker tests (ex. CA-125)
- Genetic testing like BRCA
- Galectin-3 is involved in fibrosis as well as cancer progression and metastasis
- Galleri Test

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Galleri Test

The **Galleri test** is a Multi-cancer early detection blood test that screens for over 50 types of cancer, including some of the deadliest, before symptoms appear. I
- It can detect cancers that currently have no recommended screening tests

• Only 5 cancers screening available
- Breast, prostate, cervical, colorectal, and lung have routine screening tests

• Galleri looks for cell-free DNA in your blood to determine if it originates from cancer or healthy cells and identifies the organ of origin

• Adults over 50 or those at high risk of developing cancer may benefit from this test

• Not covered by all health insurance

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Galleri Screening Test

99.5% Specificity
- It has a low false positive rate of 0.5%.
- Helps minimize unnecessary diagnostic procedures

43.1% Positive Predictive Value
- Positive Predictive Value - The proportion of people with Cancer Signal Detected results diagnosed with cancer

98.5% Negative Predictive Value
- The negative predictive value (NPV) for is 98.5%, provides confidence that a no cancer signal detected result is likely a true negative

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Introduction to Cancer Prevention Vaccines

23

Human Papillomavirus (HPV)

- **HPV is the most common Sexual transmitted infection globally.**
- In the U.S., nearly **80 million** people are infected with HPV.
  - **14 million new cases annually**
- A group of more than 200 related viruses
  - with some types causing cancer (e.g., HPV 16, 18)
- Transmitted through skin-to-skin contact, including sexual activity

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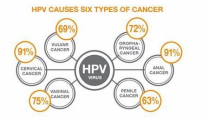
Human Papillomavirus (HPV)

- **How It Replicates**
  - HPV infects basal cells of the skin or mucosal surfaces, using host cell machinery to replicate its DNA
- **High-risk types (HPV 16, 18)**
  - Can cause genetic changes in cells, leading to abnormal growth and cancer



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HPV Vaccine – Mechanism of Action

- The HPV vaccine introduces virus-like particles (VLPs) that mimic the structure of the virus but do not contain live virus
- Stimulates the immune system to create antibodies that recognize and neutralize HPV, preventing future infection and related cancers

GARDASIL 9

- **Key Types Covered by the Vaccine:**
  - HPV types 6, 11 (low-risk, cause warts)
  - HPV types 16, 18 (high-risk, cause cancers)

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HPV Vaccination Schedule

- **Recommended Age**
- Start at **age 11-12** (can begin as early as age 9)
  - Can be given up to age **26** (and up to age **45** for some high-risk individuals)

- **Dosing Schedule:**

2 doses
- For those starting before age 15
- First dose followed by a second dose 6-12 months later

3 doses
- For those starting at age 15 or older
- 0, 1-2 months, and 6 months

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Test-Your-Knowledge

What is the routine age range for adolescents and adults to receive the HPV vaccination?

A. 10–15 years
B. 16–21 years
C. 9–26 years
D. 30–45 years

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Test-Your-Knowledge

What is the routine age range for adolescents and adults to receive the HPV vaccination?

A. 10–15 years
B. 16–21 years
C. 9–26 years
D. 30–45 years

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Hepatitis B virus (HBV)

- Hepatitis B is a **DNA virus** that affects the liver
- Spread through blood, sexual contact, and from mother to child during childbirth
- **Incidence: Estimated 296 million people** worldwide live with chronic HBV infection. In the U.S., **2.4 million** people are chronically infected with HBV

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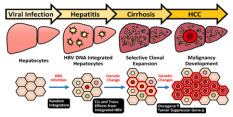
Hepatitis B virus (HBV)



- **How It Replicates:** uses its own DNA polymerase to replicate and produce viral proteins in liver cells (hepatocytes)
- Over time, Chronic infection can lead to cirrhosis, liver failure, and liver cancer (hepatocellular carcinoma)

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Center of Disease Control and Prevention HBV Recommendations

- The CDC recommends hepatitis B vaccination for
- All adults age 19-59
- Adults 60 years or older with risk factors
- Adults 60 or older without known risk factors

CDC
CENTERS FOR DISEASE CONTROL AND PREVENTION

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HBV Vaccine – Mechanism of Action

- The vaccine Contains the **hepatitis B surface antigen (HBsAg)**, which is a protein found on the virus's surface
- The immune system recognizes HBsAg as foreign and produces antibodies, preventing infection by neutralizing the virus
- Prevents both chronic HBV infection and its complications, including liver cancer

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HBV Vaccination Schedule

- This recommendation applies to adults who have not received a complete hepatitis B vaccine series in their lifetime
- **Recommended Age**
- Infants First dose at birth, followed by doses at 1-2 months and 6-18 months
- **Adults**: 3-dose series (0, 1, and 6 months) for those at risk of HBV infection
- **At-Risk Groups**
  - Healthcare workers
  - People with multiple sexual partners
  - People with chronic liver disease

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HBV Vaccination Schedule

Vaccine Type	Formulation	Dosing Schedule	Target Population	Notable Features
Recombinant (Engerix-B, Recombivax HB)	Monovalent (Hepatitis B only)	3 IM doses (0, 1, 6 months). **For special population** a 4th dose may be given.	Newborns, infants, and high-risk adults	Standard and widely used; safe and effective

- Special population
  - Adults on hemodialysis: A series of 4 doses (2 mL each) as a single 2-mL dose or as two 1-mL doses on a 0, 1, 2, 6-month schedule.

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HBV Vaccination Schedule

Vaccine Type	Formulation	Dosing Schedule	Target Population	Notable Features
Combination (Pediarix, Twinrix)	Combination with other vaccines (DTaP, IPV, Hep A)	Pediarix: 3 IM doses (2, 4, 6 months) Twinrix: 3 IM doses (0, 1, 6 months)	Pediarix: Infants Twinrix: Adults (>19 years of age) and travelers	Dual protection, especially for travelers

- Twinrix (Rapid dosing - travelers)
  - Accelerated regimen: IM: 1 mL/dose administered on day 0, day 7, and days 21 to 30, followed by a booster dose at 12 months for a total of 4 doses.

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HBV Vaccination Schedule

Vaccine Type	Formulation	Dosing Schedule	Target Population	Notable Features
Heplisav-B	**Adjuvanted** recombinant vaccine	2 IM doses (0, 1 month)	Adults 18+	Faster completion with 2 doses, adjuvanted for stronger immune response

- An adjuvant is an ingredient used in some vaccines that helps create a stronger immune response in people receiving the vaccine.

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HBV Vaccine Adjuvants

Vaccine Type	Adjuvant	Mechanism of Action
Recombinant (Engerix-B, Recombivax HB), Pediarix, and Twinrix	Aluminum	• Small amounts of aluminum are added to some vaccines to help the body build stronger immunity • Many hypotheses exist as to the mode of action of these adjuvants, such as depot formation, antigen (Ag) targeting, and the induction of inflammation
Heplisav-B	Cytosine phosphoguanine (CpG)	• CpG is a synthetic form of DNA that mimics bacterial and viral genetic material • When CpG 1018is included in a vaccine, it increases the body's immune response

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Test-Your-Knowledge

At what age should the first dose of the Hepatitis B vaccine be administered ?

A. At birth
B. At 2 months
C. At 6 months
D. At 1 year

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Test-Your-Knowledge

- **At what age should the first dose of the Hepatitis B vaccine be administered ?**

A. At birth
B. At 2 months
C. At 6 months
D. At 1 year

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Conclusion

- **Cancer Screening**
  - Regular screening is essential for early detection
  - It should be individualized based on age, risk factors, and preferences
- **Galleri Test**
  - A multi-cancer early detection test
  - Can identify cancers before symptoms appear
- Discuss with healthcare provider
- **Preventative Vaccines**:
  - **HPV Vaccine**: Prevents certain types of HPV that cause cervical, anal, and oropharyngeal cancer
  - **Hepatitis B Vaccine**: Reduces the risk of liver cancer by preventing Hepatitis B infection

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Conclusion

NCCN National Comprehensive Cancer Network®

U.S. Preventive Services TASK FORCE | Prevention TaskForce

- For further questions, always consult your healthcare provider
- Refer to trusted resources like the NCCN and U.S. Preventive Services Task Force.

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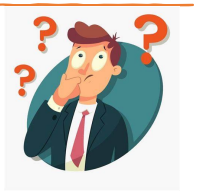

43

References

- American Cancer Society. *Cancer Facts & Figures 2024*. American Cancer Society, 2024, www.cancer.org/research/cancer-facts-statistics.html.
- Centers for Disease Control and Prevention (CDC). "Human Papillomavirus (HPV) Vaccination." *CDC*, 27 Sept. 2023, www.cdc.gov/hpv/vaccine.html.
- Centers for Disease Control and Prevention (CDC). "Hepatitis B Vaccination." *CDC*, 8 Oct. 2023, www.cdc.gov/hepatitis/hbv/vaccination.htm.
- Centers for Disease Control and Prevention (CDC). "Cancer Screening Recommendations." *CDC*, 15 Nov. 2023, www.cdc.gov/cancer/screening.htm.
- National Cancer Institute. "Cancer Statistics." *National Cancer Institute*, 2024, www.cancer.gov/about-cancer/understanding/statistics.
- U.S. Department of Health and Human Services. "Hepatitis B Vaccination for Adults." *Health.gov*, 6 Sept. 2023, www.health.gov/our-work/nutrition-physical-activity/health-promotion/hepatitis-b-vaccination.
- World Health Organization (WHO). "Hepatitis B." *WHO*, 15 Oct. 2023, www.who.int/news-room/fact-sheets/detail/hepatitis-b.
- World Health Organization (WHO). "HPV Vaccine to Prevent Cancer." *WHO*, 24 Aug. 2023, www.who.int/news-room/fact-sheets/detail/human-papillomavirus-(hpv)-vaccination.

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