From Withdrawal to Breakthrough:

Rethinking Alcohol Withdrawal Care and the Rise of Novel Psychoactive Therapies for Mood Disorders

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Disclosures

The planner(s) and speaker(s) have indicated that there are no relevant financial relationships with any ineligible companies to disclose.

Learning Objectives

At the end of this session, learners should be able to:

- Describe the comparative benefits, disadvantages, effectiveness, and safety of phenobarbital and benzodiazepines for the treatment of alcohol withdrawal.
- Discuss potential phenobarbital dosing schemes and strategies for the management of alcohol withdrawal treatment.
- Define key mechanisms of action for ketamine, LSD, and psilocybin relevant to mood and anxiety disorders.
- Compare and contrast these emerging therapies (ketamine, LSD, and psilocybin) to standard therapy guidelines.

Abbreviation Key

ADR - Adverse Drug Reaction
AUD - Alcohol Use Disorder
AW - Alcohol Withdrawal
BDNF - Brain-Derived Neurotrophic Factor
BP - Blood Pressure
BZD - Benzodiazepines
CAD - Coronary Artery Disease
CBT - Cognitive Behavioral Therapy
CI – Confidence Interval
CIWA-AR - Clinical Institute Withdrawal Assessment of Alcohol Scale, revised
DDI - Drug Drug Interaction
DMN - Default Mode Network
ECT - Electroconvulsive Therapy
EtOH - Alcohol
FDA - Food & Drug Administration
GABA: Gamma aminobutyric acid
GAD – Generalized Anxiety Disorder
HAM-A – Hamilton Anxiety Rating Scale
HDRS – Hamilton Depression Rating Scale
HF – Heart Failure
HR – Heart Rate
HTN – Hypertension
IBW – Ideal Body Weight
ICU – Intensive Care Unit
IN – Intranasal
IV – Intravenous
LSD – Lysergic Acid Diethylamide
MADRS – Montgomery–Åsberg Depression Rating Scale
MAOI(s) – Monoamine Oxidase Inhibitor(s)
MDD – Major Depressive Disorder
MOA – Mechanism of Action
mTOR – Mechanistic Target of Rapamycin
MW - Midwest
NMDA – N-Methyl-D-Aspartate
NS – Normal Saline
NT - Neurotransmitter
PHB – Phenobarbital
PO – By Mouth
PRN – As Needed
REMS – Risk Eval & Mitigation Strategy
rTMS – Repetitive Transcranial Magnetic Stimulation
SGA(s) – Second-Generation Antipsychotic(s)
SL – Sublingual
SNRI(s) – Serotonin–Norepinephrine Reuptake Inhibitor
SSRI(s) – Selective Serotonin Reuptake Inhibitor
TRD – Treatment-Resistant Depression
UGT - Uridine Diphosphate-Glucuronosyltransferases
VA – Veterans Affairs

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Alcohol Withdrawal Background

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Diagnostic Criteria

- Cessation or reduction in heavy & prolonged alcohol use

≥ 2 symptoms

- Increased hand tremor, insomnia, nausea, vomiting, transient hallucinations/illusions, anxiety, grand mal seizures

- Symptoms cause clinically significant distress or impairment
- Symptoms are not due to a medical condition

National Institute on Alcohol Abuse and Alcoholism, www.niaaa.nih.gov, 2024.
Bayard, et al., *Am Fam Physician,* 2004.

Symptoms

Severity Category	Associated CIWA-AR Range	Symptom Description
Mild	< 10	Mild/moderate anxiety, sweating & insomnia
Moderate	10-18	Moderate anxiety, sweating, insomnia & mild tremor
Severe	≥ 19	Severe anxiety and moderate/severe tremor
Complicated	≥ 19	Seizure or signs/symptoms of delirium (confusion, hallucinations)

The ASAM Clinical Practice Guideline on Alcohol Withdrawal Management., *J Addict Med,* 2020.

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AUD Pathophysiology

A.

Bayard, et al., *Am Fam Physician,* 2004.
Bharadwaj et al., Industrial Psychiatry Journal, 2013.
Malone et al., Neuropsychopharmacol Rep, 2013.

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AUD Pathophysiology

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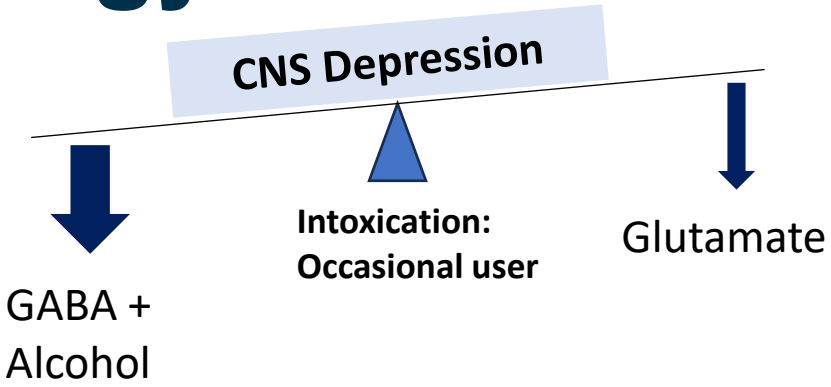

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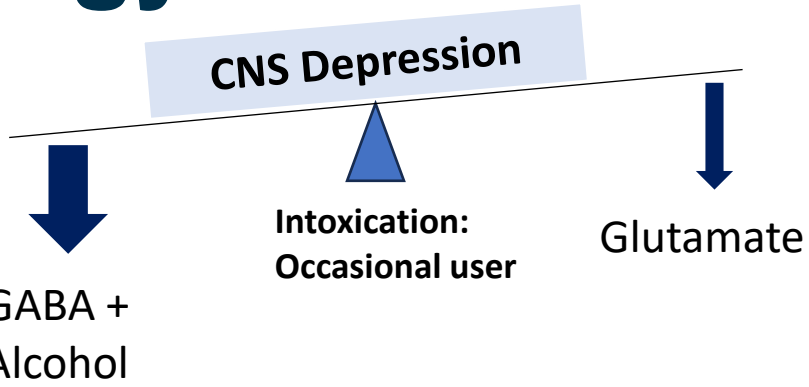

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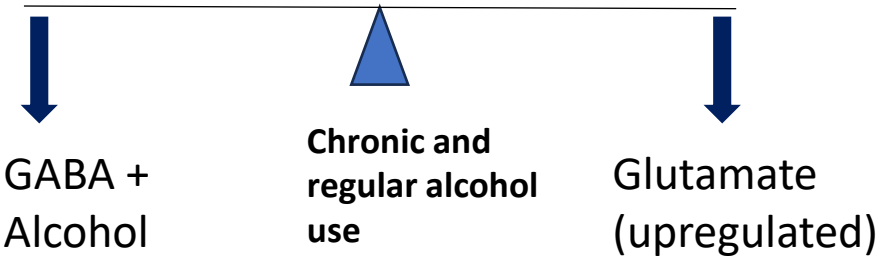

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Bharadwaj et al., Industrial Psychiatry Journal, 2013.
Malone et al., Neuropsychopharmacol Rep, 2013.

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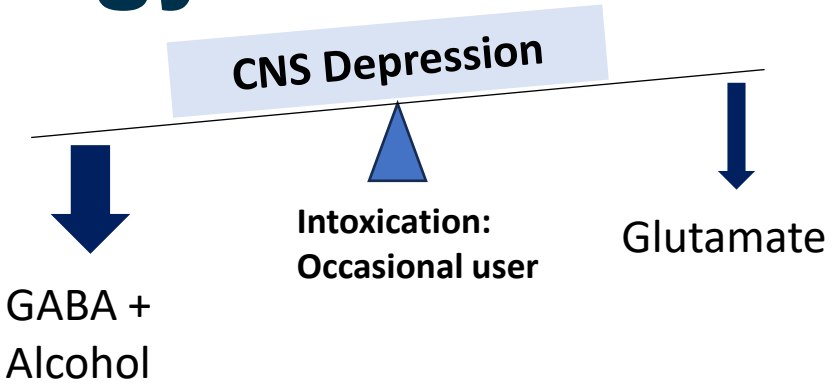

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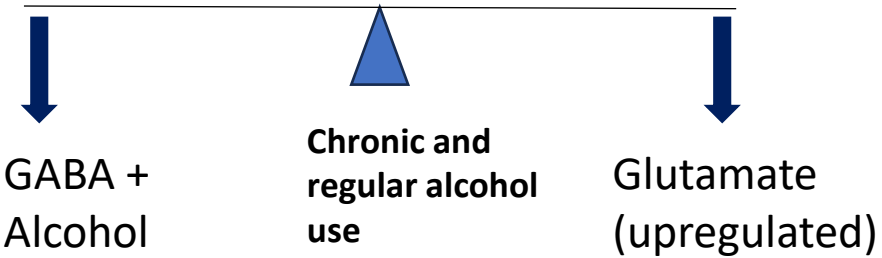

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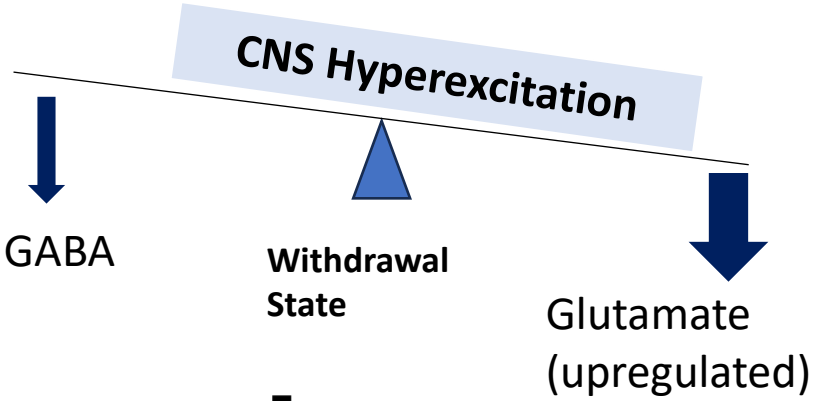

Bayard, et al., *Am Fam Physician,* 2004.
Bharadwaj et al., Industrial Psychiatry Journal, 2013.
Malone et al., Neuropsychopharmacol Rep, 2013.

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Guideline Recommendations

ASAM:

- CIWA-AR < 10: may give pharmacotherapy or supportive care
- CIWA-AR 10-18: BZDs first line
  - Carbamazepine or gabapentin as alternatives
- CIWA-AR ≥ 19: BZDs first line
  - **PHB**, carbamazepine or gabapentin as alternatives

The ASAM Clinical Practice Guideline on Alcohol Withdrawal Management, *J Addict Med,* 2020.
Mayo-Smith MF, *JAMA, 1997.*
Saitz et al., *JAMA*. 1994.

Benzodiazepines

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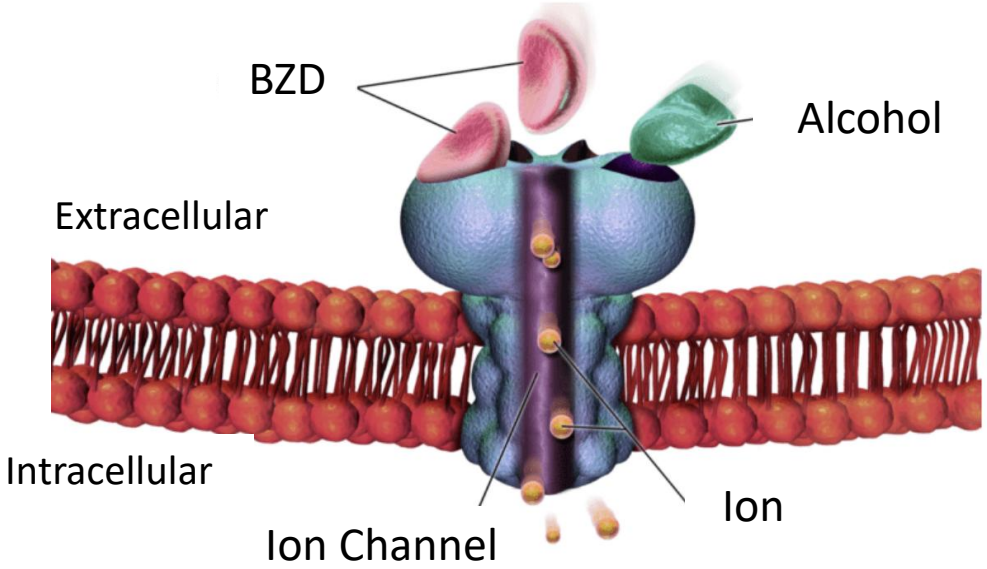
Mechanism of Action



Mechanism of Action, Benzodiazepine Information Coalition, 2021.

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Guideline Recommendations

- No particular benzodiazepine is effective over the other
- Long acting are preferred
- Signs/symptoms of liver disease, use benzodiazepine with less hepatic metabolization

The ASAM Clinical Practice Guideline on Alcohol Withdrawal Management, *J Addict Med,* 2020.

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Comparing Benzodiazepines

Medication	Onset (min)	Half Life (hrs)	Metabolism
Lorazepam	15-30	10-20	Glucuronidation
Diazepam	0-15	20-100	Hepatic
Chlordiazepoxide	15-30	5-100	Hepatic
Midazolam	0-15	1-4	Hepatic

Staff, The Alliance for Benzodiazepine Best Practices, 2020.

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Dosing Recommendations

- Preferred: symptom triggered dosing with continuous monitoring
- Other options:
  - Front loading for **severe** withdrawal (diazepam and chlordiazepoxide)
  - Fixed dose regimen with gradual taper for short acting

The ASAM Clinical Practice Guideline on Alcohol Withdrawal Management, *J Addict Med,* 2020.

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MW Advocate Order Set

MED IP ALCOHOL WITHDRAWAL – CIWA - AR
CIWA-AR ≥ 8: Benzodiazepines - PO, IV, or IM doses *IV route is preferred in rapidly changing or elevated CIWA-AR scores*
Escalating PO/IV lorazepam **OR**
Non-escalating PO/IV/IM lorazepam

ICU Refractory Alcohol Withdrawal Orders
CIWA < 15: Lorazepam 2mg & 4mg PO/IV every hour PRN
CIWA ≥ 15: Lorazepam 4 mg IV every 15 minutes PRN
CIWA ≥ 15: Lorazepam standard infusion and bolus

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Key Considerations

Advantages

- Historical data support
- Clinician comfortability
- Variety of agents available based on necessity
  - Lorazepam: use for suspected liver disease, old age, or pregnancy
  - Diazepam: long acting
- Lack of DDIs

Disadvantages

- ADR: sedation, shallow breathing
- Long term: dependence, cross tolerance
- Lack of therapeutic monitoring + non-linear kinetics/dose stacking
- IV drug shortage

Sachdeva et al., J Clin Diagn Res, 2015.
Bounds et al., StatPearls Publishing, 2026.
Whitledge et al., J, Med Toxico,. 2023.

Assessment Question #1

DR is a 52-year-old male with a past medical history of hypertension, liver disease, type 2 diabetes, and chronic alcohol abuse. He presents after abruptly discontinuing alcohol consumption and has a CIWA-Ar score of 14. What is the preferred pharmacologic treatment for DR?

A. Alprazolam
B. Lorazepam
C. Gabapentin
D. Diazepam

Phenobarbital

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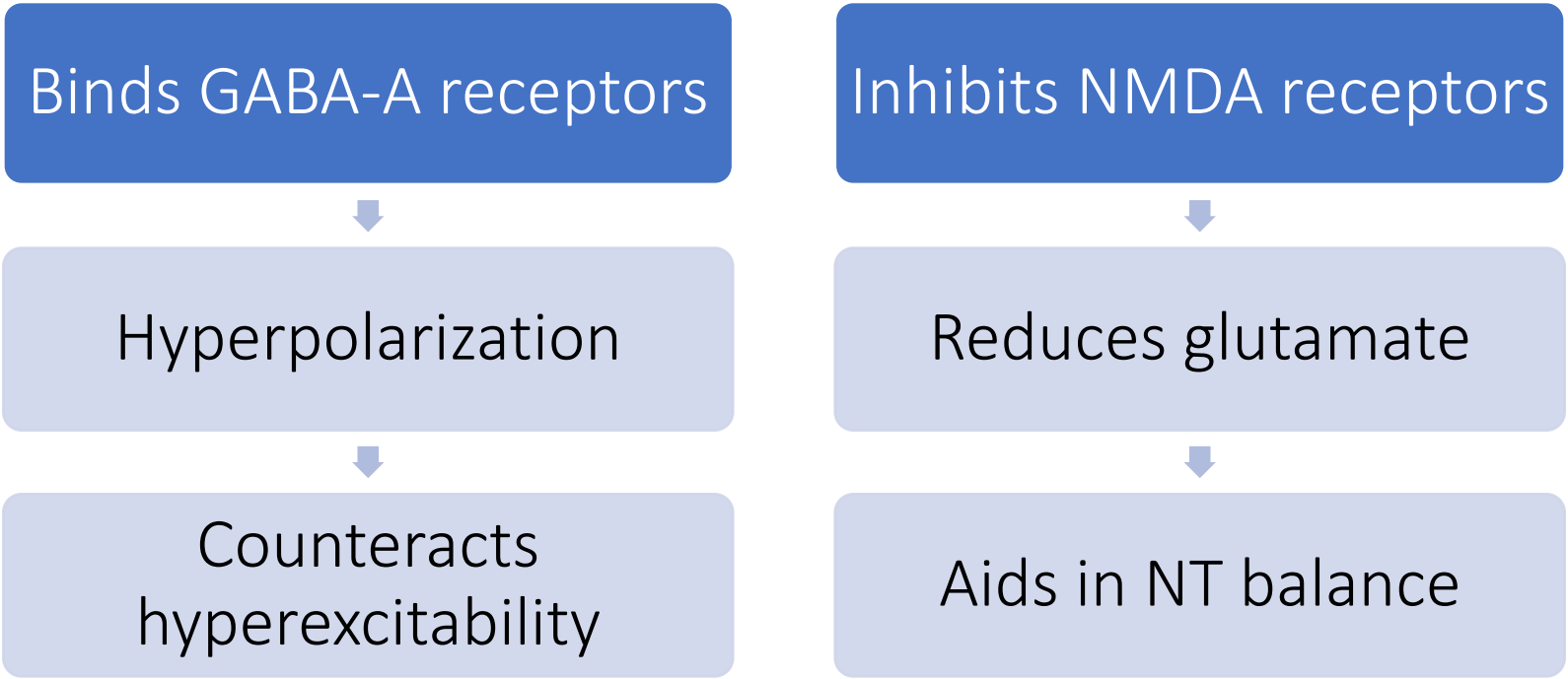
Mechanism of Action



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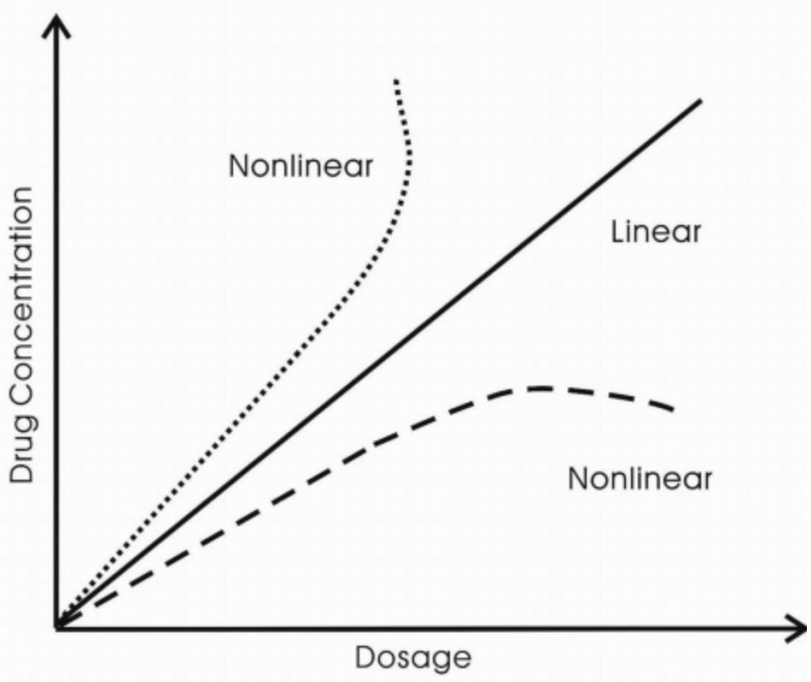
Phenobarbital, Tulane.edu, 2024.

Pharmacokinetics

- Linear kinetics
  - Volume of distribution: ~0.65 kg/L
  - Estimated therapeutic window: 10-30 ug/mL
  - Half life: 80-120 hrs
- Narrow therapeutic window
  - Therapeutic Epilepsy: 15-40 ug/mL
  - Toxicity
    - Mild: > ~50 ug/mL
    - Severe: >~65 ug/mL
    - Life threatening: > ~100 ug/mL



UFO Themes, Basicmedical Key, 2016.
Nelson et al., J Clin Pharmachol, 1982

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Guideline Recommendation

- Inpatient settings when used by experienced clinician
- Monotherapy indicated if contradiction to BZD or at risk of severe AW
- Adjunct to BZD if at risk of severe AW

The ASAM Clinical Practice Guideline on Alcohol Withdrawal Management, *J Addict Med,* 2020.

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Risk Factors for Complicated Withdrawal

- History of withdrawal delirium or seizure
- Numerous withdrawal episodes
- 65 years or older
- Long duration of heavy and regular alcohol consumption
- Dependence on GABAergic agents

The ASAM Clinical Practice Guideline on Alcohol Withdrawal Management, *J Addict Med,* 2020.

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Phenobarbital for Acute Alcohol Withdrawal: A Prospective Randomized Double-Blind Placebo-Controlled Study

Rosenson et al., *J Emerg Med,* 2013.

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Efficacy Study Summary

Trial Design	Randomized, double blinded & placebo-controlled
Intervention	• Control group (N =51): 100 mL NS • PHB group (N= 51): IV PHB 10 mg/kg in 100 ml bag
Primary Outcome	• Initial level of admission (ICU): ○ PHB: 8%; placebo: 25% (difference: 17%; [95% CI 4 - 32%])

Secondary Results	• Continuous lorazepam infusion
	  ○ PHB: 4%; placebo: 31% (difference: 27%; [95% CI 14 - 41%])
	• Intubation
	  ○ PHB: 2%; placebo: 2% (difference: 0%; [95% CI –0.05 - 0.05%])

Limitations	• Small study size • Utilization of unvalidated clinical assessment tool • Estimated patient weight
Conclusion	• Introduces PHB as an effective adjunctive agent for AW • PHB may decrease ICU admission when given an early loading dose

Rosenson et al., *J Emerg Med,* 2013

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Evaluation of phenobarbital based approach in treating patient with alcohol withdrawal syndrome: A systematic review and meta analysis

Pourmand et al., *Am J Emerg Med*., 2023.

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Efficacy Study Summary

Trial Design	Meta Analysis
Intervention	• 12 studies – BZD (N = 765); PHB (N = 1169)

Primary Outcome	• Rate of intubation
	  ○ Relative Risk: 0.7 (95% CI 0.36 - 1.38, P-value = 0.3)
	  ○ I^2 = 62%

Limitations	• High heterogeneity • Various independent variables (PHB monotherapy vs adjunct, type of BZD used, dosing, definition of severe AW, populations used)
Conclusion	• Reinforces PHB as effective option • Additional studies needed to identify which populations may benefit more

Pourmand et al., *Am J Emerg Med*., 2023.

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Front-Loaded Versus Low-Intermittent Phenobarbital Dosing for Benzodiazepine-Resistant Severe Alcohol Withdrawal Syndrome

Shah et al., Med Toxicol, 2022

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Dosing Study Summary

Trial Design	Retrospective
Intervention	• Low intermittent (N = 41): 260 mg IV push x 1 followed by 130 mg IV push every 15 mins PRN • Front load (N = 46): 10 mg/kg
Primary Outcome	• Incidence mechanical ventilation ○ Low: 63%; Front: 28% (OR 4.4, 95% CI 1.8 - 11%, P-value = 0.001)

Secondary Results	• ICU length of stay
	  ○ Low: 115 hours; Front: 156 hours (P-value = 0.07)
	• PHB cumulative dose
	  ○ Low: 1200 mg; Front: 1170 mg (P-value = 0.29)
	• Lorazepam cumulative administrations post PHB dose
	  ○ Low: 228 mg; Front: 86 mg (P-value = <0.01)

Limitations	• Small study size • Varying time periods
Conclusion	• Large front loaded PHB given early in course may be preferred

Shah et al., Med Toxicol, 2022

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MW Advocate Order Set

ICU Refractory Alcohol Withdrawal Orders
CIWA ≥ 15 & unresolved after 12 mg lorazepam injections: Phenobarbital loading dose: 10 mg/kg once PRN

Key Considerations

Advantages

- GABA agonism and glutamate antagonism
- Predictable kinetics
- Self tapering effects

Disadvantages

- Toxic ADRs: nystagmus, hypotension, loss of consciousness, slurred speech, respiratory failure
- Dosing controversial
- Additive effects with BZD
- Avoid use in liver failure
- DDI's
  - CYP 450 & UGT inducer

Ghattas et al., Pharmacotherapy: The Journal of Human Pharmacology and Drug therapy, 2026

Assessment Question #2

JK presents to the emergency room with anxiety and auditory hallucinations after abruptly ceasing alcohol intake. He is a 34-year-old male (IBW: 65 kg) with a PMH significant for alcohol abuse and numerous withdrawal episodes resulting in seizures. Which of the following options are reasonable dosing regimens to start the patient on? (Select all that apply)

A. Lorazepam 4 mg every 15 mins PRN
B. Phenobarbital 65 mg once
C. Phenobarbital 40 mg/kg once
D. Phenobarbital 10 mg/kg once

Summary

BZDs remain a cornerstone of AW therapy

Literature shows PHB has potential as an adequate alternative/adjunctive therapy for AW

- Additional literature is needed to identify standard dosing and further demonstrate efficacy

History and Evolution of Psychoactive Therapies

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History and Evolution

Antiquity - Early Modern

Early psychedelic use in ritual, healing, and spiritual ceremonies across cultures

Wasson RG. *Life*. 1957
Hofmann A. *LSD:* My *Problem Child*. 1980
Nichols DE. *Pharmacol Rev*. 2016.

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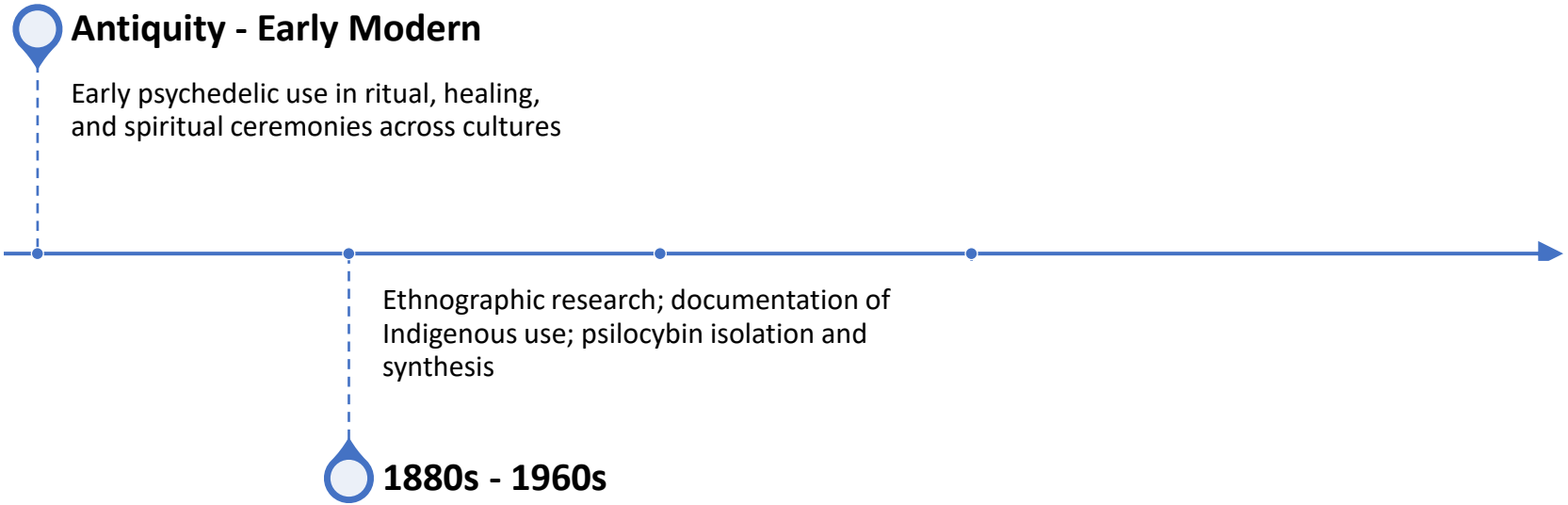
History and Evolution



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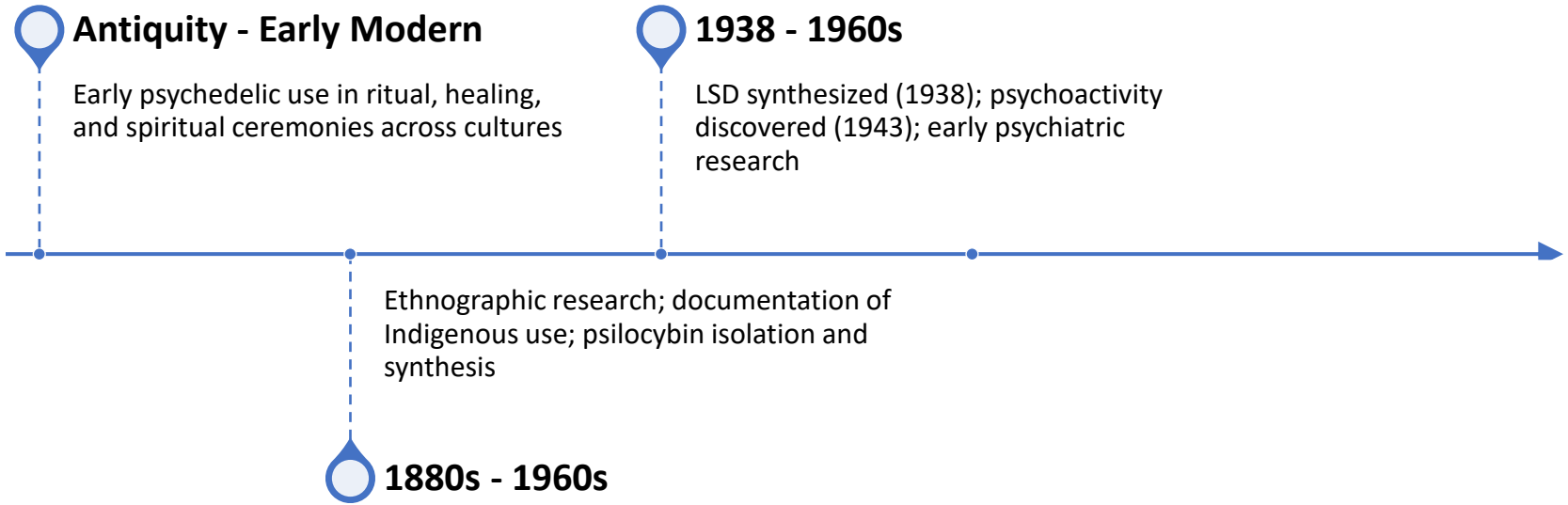
Hofmann A. *LSD: My Problem Child*. 1980
Nichols DE. *Pharmacol Rev*. 2016.

History and Evolution



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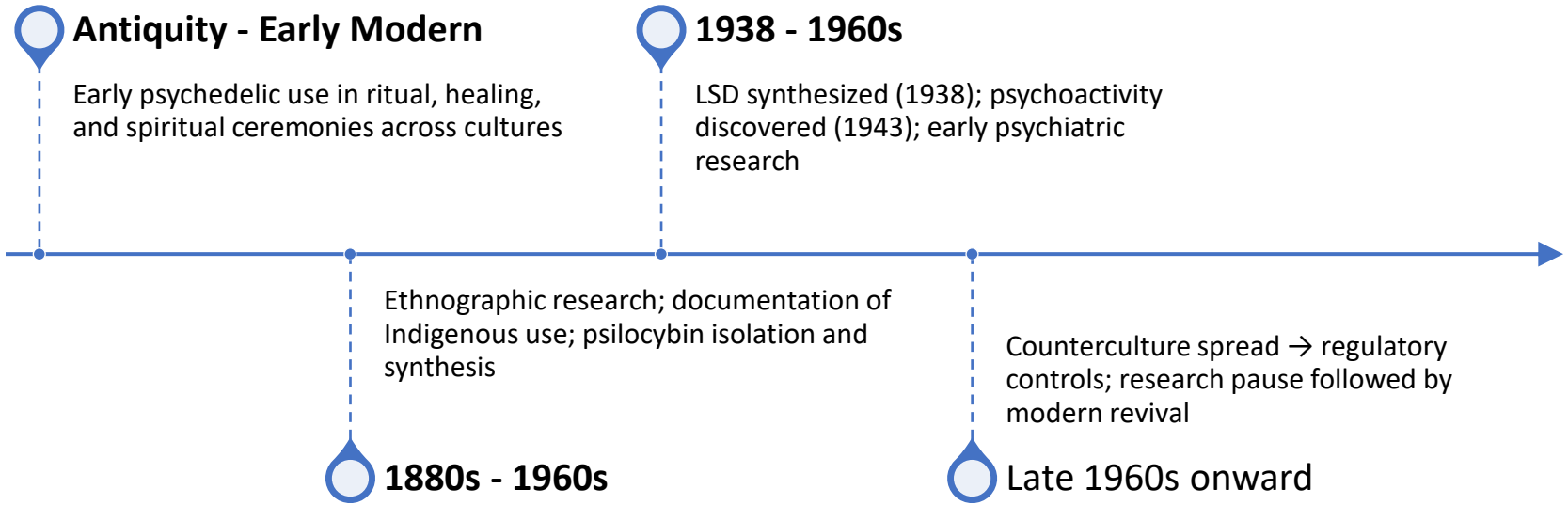
History and Evolution



Wasson RG. *Life*. 1957
Hofmann A. *LSD: My Problem Child*. 1980
Nichols DE. *Pharmacol Rev*. 2016.

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Why renewed interest?

- Rapid onset vs SSRIs/SNRIs
- Neuroplasticity mechanisms
  - Definition: brain's ability to change its structure and function in response to experience, learning, or injury
- Existing operational models

Berman RM et al. *Arch Gen Psychiatry*. 2000
Duman RS, Aghajanian GK. *Neuropsychopharmacology*. 2012
Ly C et al. *Cell Rep*. 2018.

Major Disease States

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Understanding Disease States and Standard Therapies

Disease State	First-Line Therapy	Second-Line / Augmentation
MDD	• SSRIs / SNRIs (i.e. fluoxetine, sertraline, duloxetine, venlafaxine etc.) • Psychotherapy	• Bupropion, mirtazapine • SGA augmentation (i.e. quetiapine) • TCAs / MAOIs (later-line) (amitriptyline, selegiline, etc.)
TRD	• Ensure ≥2 adequate antidepressant trials • Optimize dose/adherence	• Switch or augment (SGAs, lithium, bupropion) • Neuromodulation (ECT, rTMS)
GAD	• SSRIs / SNRIs (i.e. fluoxetine, sertraline, duloxetine, venlafaxine etc.) • CBT	• Buspirone • Gabapentin/Pregabalin • Hydroxyzine • Short-term BZDs (i.e lorazepam, clonazepam, etc.)

Daly EJ et al. *Am J Psychiatry*. 2019
Robison R et al. *JAMA*. 2025.

Ketamine

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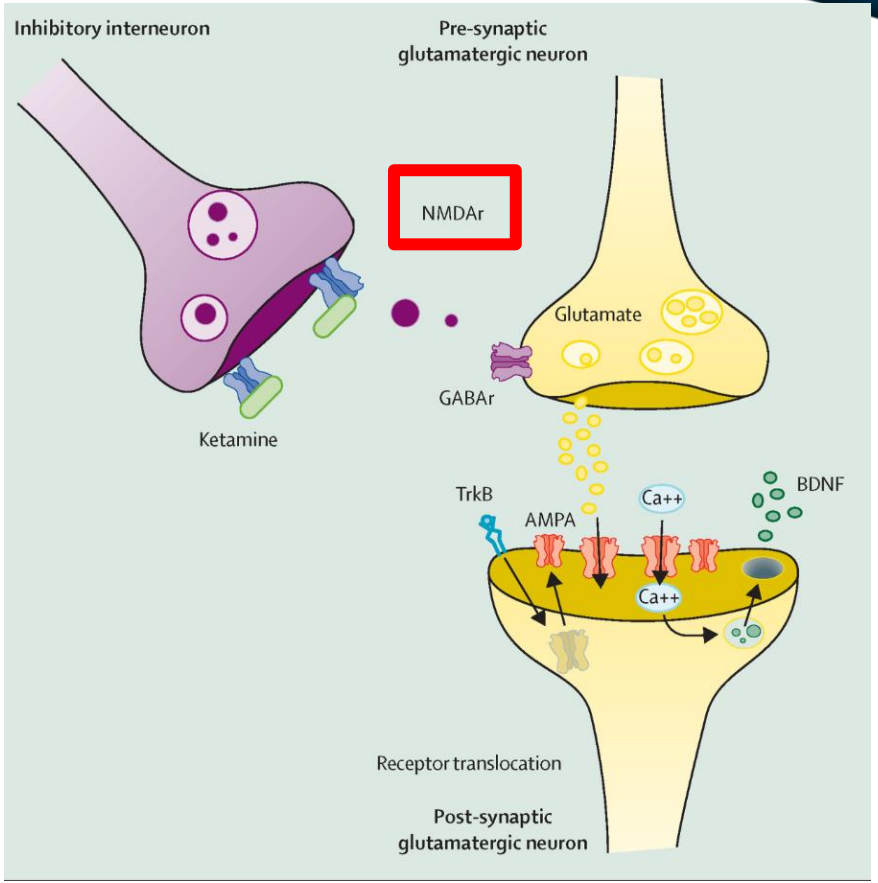
Ketamine enters psychiatry (1990s–present)

- Approved by the US Food and Drug Administration in 1970 for anesthetic use
  - Initially used as a battlefield anesthetic in Vietnam War
- 1990s–2000s: NMDA receptor framing → rapid-acting antidepressant trials in TRD; clinical interest accelerates.
- 2019–2024: Esketamine (IN) gains FDA approvals for TRD and for MDD with acute suicidal ideation/behavior

Berman RM et al. *Arch Gen Psychiatry*. 2000
Mion G. *Eur J Anaesthesiol*. 2017
Vekhova KA et al. Clin Pharmacol Ther. 2025.

Ketamine Mechanism of Action



Marwaha et al., The Lancet, 2022.

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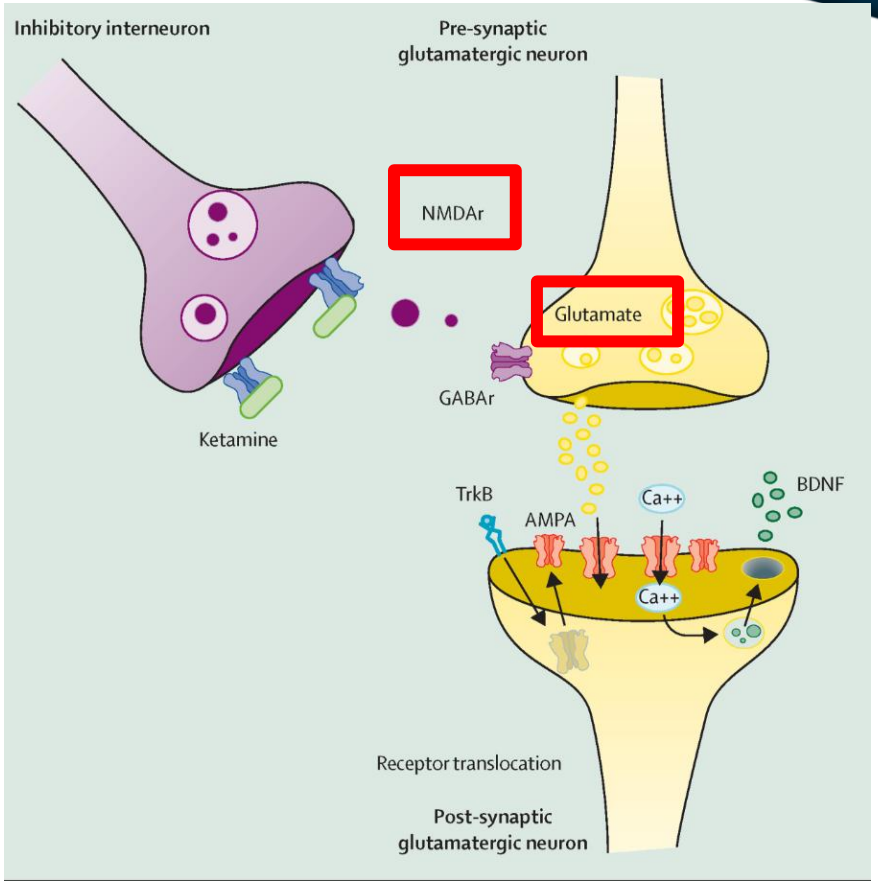
Ketamine Mechanism of Action



Marwaha et al., The Lancet, 2022.

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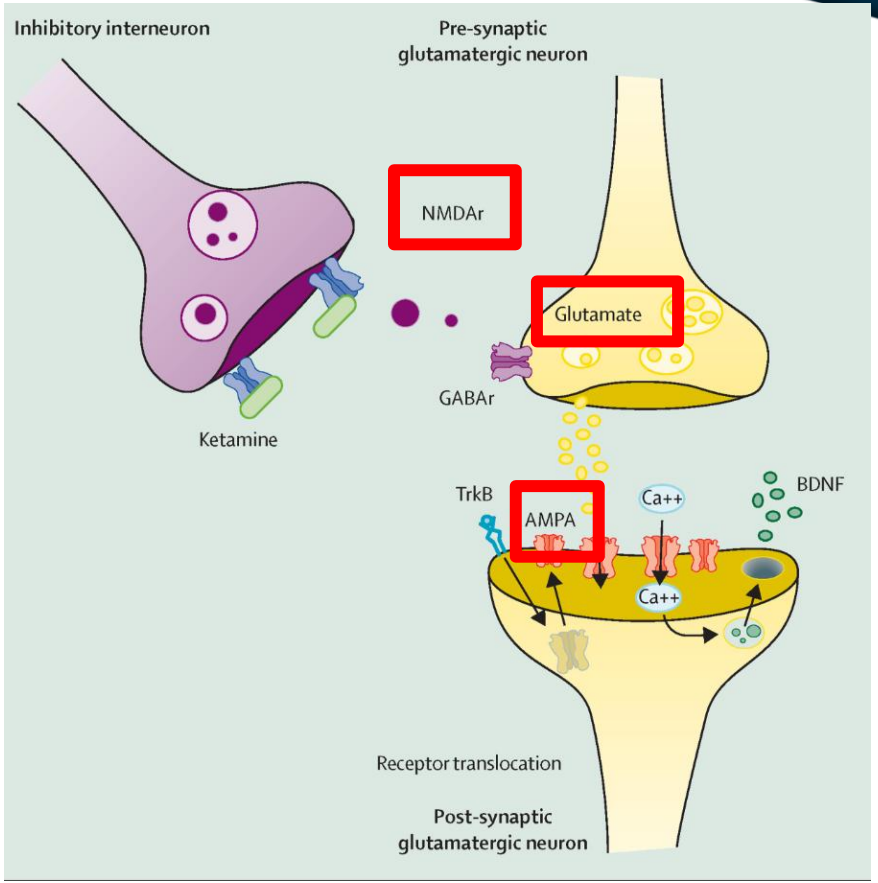
Ketamine Mechanism of Action



Marwaha et al., The Lancet, 2022.

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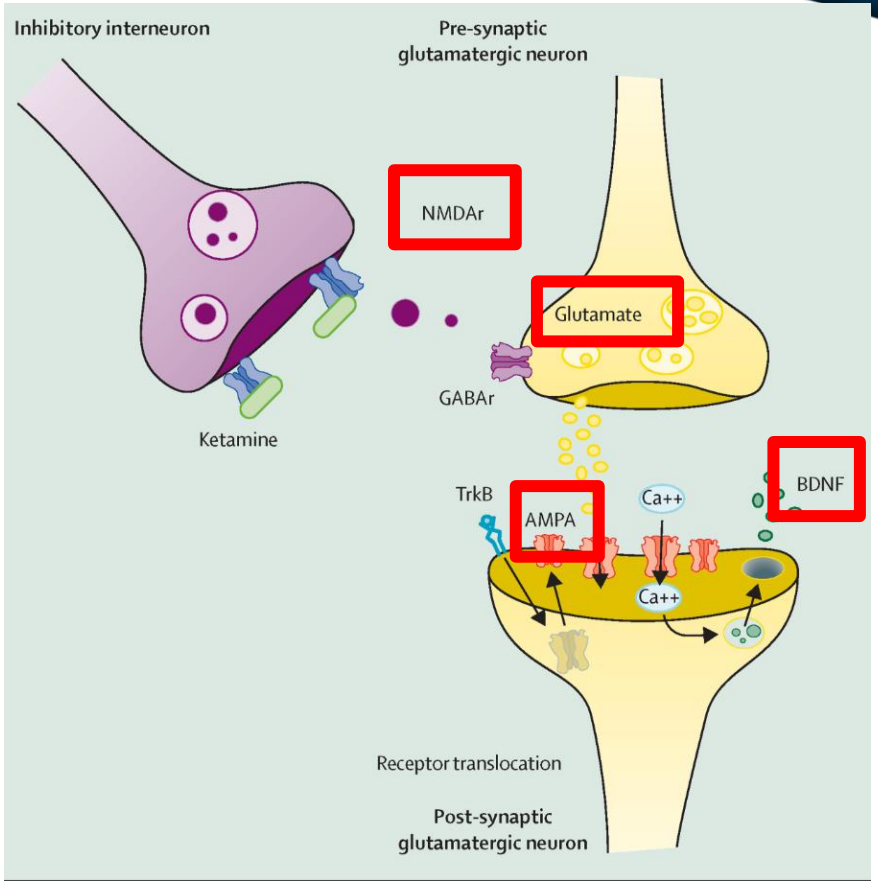
Ketamine Mechanism of Action



Marwaha et al., The Lancet, 2022.

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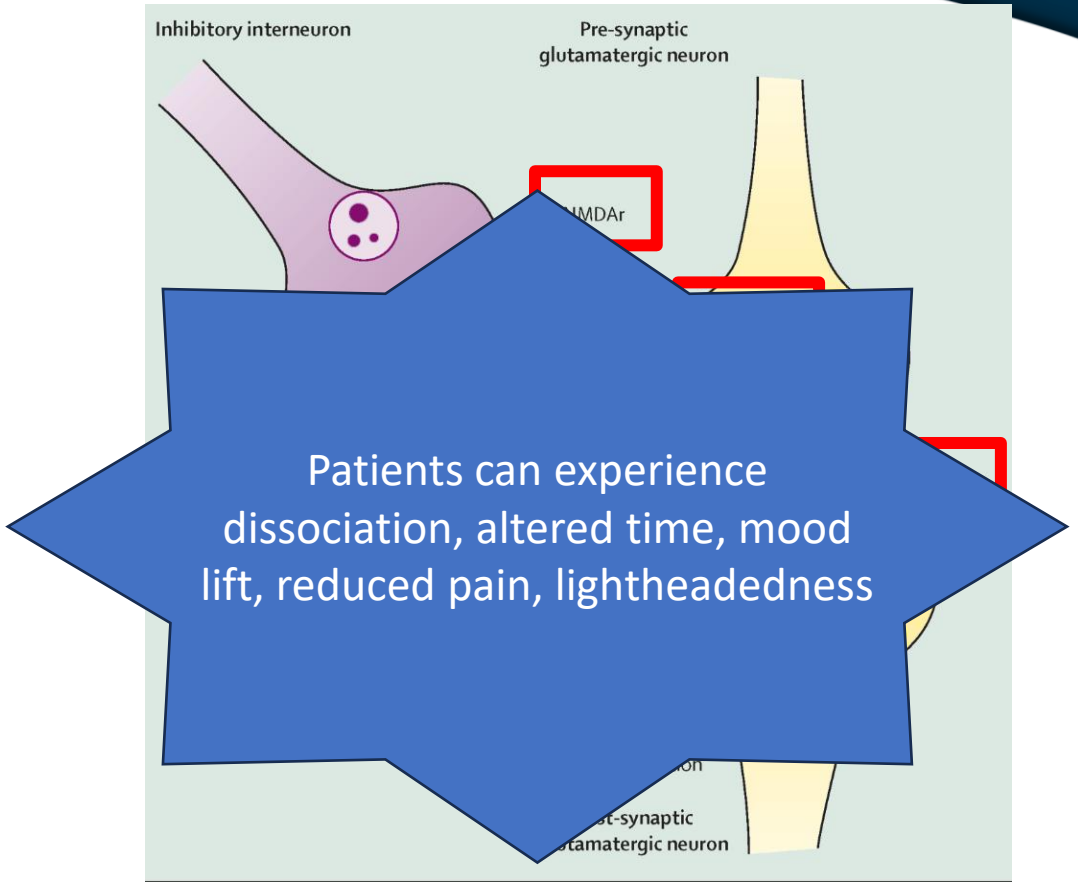
Ketamine Mechanism of Action



Marwaha et al., The Lancet, 2022.

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Ketamine vs Esketamine — Comparison

Feature	**Ketamine**	**Esketamine**
Composition	Racemic mixture (R-ketamine + S-ketamine)	Pure **S-ketamine (esketamine)**
NMDA receptor affinity	Moderate	**~3–4× higher affinity** for NMDA than R-ketamine
Primary antidepressant mechanism	NMDA antagonism → glutamate burst → AMPA → BDNF/mTOR	Same core pathway, but **more NMDA-focused**

Berman RM et al. *Arch Gen Psychiatry*. 2000
Duman RS, Aghajanian GK. *Neuropsychopharmacology*. 2012
FDA SPRAVATO Prescribing Information, 2024.

Ketamine — Indications, Dosing, Safety

Domain	Key Points
Uses & Forms	**IV ketamine**: off-label TRD/severe depression; acute & chronic pain; procedural sedation; status asthmaticus; peri-op adjunct **Oral/SL**: non-FDA-approved (telehealth / at-home programs)
Typical Dosing	**Psych (IV):** ~0.5 mg/kg over ~40 min (0.2–0.5 mg/kg) **Analgesia:** 0.1–0.3 mg/kg IV **Sedation:** 1–2 mg/kg IV
Monitoring & Safety	BP, HR, mental status; airway reflexes (dose-dependent) Dissociation, emergence reactions, N/V
Contraindications / DDIs / Notes	Uncontrolled HTN; severe CAD/HF; severe hepatic disease; active psychosis (relative) **DDIs:** benzodiazepines (↓ antidepressant effect), CNS depressants (↑ sedation), stimulants (↑ BP) No REMS; wide dose range

Berman RM et al. *Arch Gen Psychiatry*. 2000
Duman RS, Aghajanian GK. *Neuropsychopharmacology*. 2012

Esketamine — Indications, Dosing, Safety

Domain	Key Points
Indication & Form	**Intranasal only** TRD; MDD w/ acute suicidal ideation **FDA-approved with REMS**
Typical Dosing	**IN:** 56–84 mg Twice weekly → weekly → q2–4 weeks (maintenance)
Monitoring & Safety	**Observed ≥2 hrs**; BP pre/post Dissociation, sedation No driving until next day
Contraindications / DDIs / Notes	Aneurysmal vascular disease; prior intracerebral hemorrhage; uncontrolled HTN; pregnancy/breastfeeding **DDIs:** CNS depressants, stimulants, CYP3A4 modifiers; benzodiazepines (↓ efficacy) Clinic-administered only; no at-home use

Berman RM et al. *Arch Gen Psychiatry*. 2000
Duman RS, Aghajanian GK. *Neuropsychopharmacology*. 2012
FDA SPRAVATO Prescribing Information, 2024.

Berman et al., 2000

Trial Design	Prospective, single-center, randomized, double-blind, placebo-controlled crossover study (N = 7)
Intervention	Single IV ketamine 0.5 mg/kg over 40 minutes vs placebo
Primary Outcome	Change in depressive symptoms measured by HDRS (Hamilton Depression Rating Scale) within 72 hours
Results	• HDRS score reduction: Mean HDRS-25 decreased by 14 ± 10 points with ketamine vs 0 ± 12 points with placebo within 72 hours ($p < 0.05$) • Onset of effect: Statistically significant antidepressant response observed by ~240 minutes post-infusion (time-by-treatment interaction, $p < 0.05$) • Peak response: Greatest symptom reduction at 24 hours post-infusion, with maximum mean HDRS improvement relative to baseline ($p < 0.05$ vs placebo) • Durability: Antidepressant effects persisted through 72 hours post-dose, with sustained separation from placebo ($p < 0.05$) • Adverse effects: 100% experienced transient dissociative/perceptual symptoms during infusion; symptoms resolved within 2–3 hours post-infusion; no serious adverse events reported
Conclusion	Single-dose IV ketamine produced rapid antidepressant effects, providing first proof-of-concept for NMDA antagonism as a novel mechanism in depression

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Berman RM et al. *Arch Gen Psychiatry*. 2000.

TRANSFORM Trials

Trial Design	Phase 3, multicenter, randomized, double-blind, active-controlled trials in adults with treatment-resistant depression: TRANSFORM-1: N = 346, TRANSFORM-2: N = 223, TRANSFORM-3 (older adults ≥65 years): N = 138
Intervention	• Intranasal esketamine 56–84 mg administered twice weekly for 4 weeks • Used in combination with a newly initiated oral antidepressant • Comparator: oral antidepressant plus placebo nasal spray
Primary Outcome	Change in depressive symptoms measured by MADRS (Montgomery–Åsberg Depression Rating Scale) score from baseline to Day 28
Results	• TRANSFORM-1 (N = 346): Mean between-group difference approximately −3.2 points, not statistically significant ($p \approx 0.08–0.09$) • TRANSFORM-2 (N = 223): Least-squares mean MADRS reduction at Day 28 favored esketamine by approximately −4.0 points vs control ($p \approx 0.02$) • TRANSFORM-3 (N = 138; ≥65 yr): Mean difference approximately −3.5 points, narrowly missed statistical significance ($p \approx 0.06$) • Onset: Separation from control observed within 24–48 hours after first dose (early time-point comparisons $p < 0.05$) • AEs: Dissociation ~25–30%, dizziness ~20–25%, nausea ~20%; transient blood pressure increases (mean systolic rise ~8–19 mmHg, resolving same day); treatment discontinuation <10%
Conclusion	• Adjunctive intranasal esketamine produced rapid and clinically meaningful antidepressant effects in treatment-resistant depression. • Despite heterogeneity across individual trials, the overall evidence supported FDA approval of esketamine for TRD, establishing the first approved rapid-acting antidepressant under a REMS program.

Daly EJ et al. *Am J Psychiatry*. 2019
Popova V et al. *Am J Psychiatry*. 2019
Ochs-Ross R et al. *Am J Geriatr Psychiatry*. 2020.

KARMA-Dep 2

Trial Design	Prospective, multicenter, randomized, double-blind, psychoactive-controlled, parallel-group trial conducted in hospitalized adults with major depressive episodes (final analysis N = 62)
Intervention	• Repeated IV ketamine 0.5 mg/kg administered twice weekly • Up to 8 infusions over 4 weeks, in addition to usual inpatient psychiatric care • Comparator: IV midazolam 0.045 mg/kg (active control to maintain blinding)
Primary Outcome	Change in depressive symptoms measured by MADRS (Montgomery–Åsberg Depression Rating Scale) score from baseline to 24 hours after the final infusion
Results	• MADRS difference: Least-squares mean difference −3.16 points vs midazolam (95% CI −8.54 to 2.22; p = 0.25) • Response/remission: No statistically significant between-group differences in response (≥50% MADRS reduction) or remission (MADRS ≤10) (all p > 0.05) • Onset/durability: No significant separation between ketamine and midazolam at any assessed time point during treatment or follow-up (all comparisons p > 0.05) • AEs: Acute dissociative symptoms occurred frequently with ketamine during infusions; functional unblinding was common; despite psychoactive effects, no antidepressant efficacy advantage was observed versus active control • Safety/tolerability: No new safety signals identified; adverse effects were transient and infusion-related; discontinuation rates were not significantly different between groups
Conclusion	• Repeated IV ketamine infusions did not provide additional antidepressant benefit beyond an active psychoactive control when used as an adjunct to inpatient standard care. • KARMA-Dep 2 challenges assumptions about the effectiveness of serial inpatient ketamine therapy and underscores the importance of rigorous controls and real-world clinical settings when evaluating rapid-acting antidepressants.

Jelovac A et al. *JAMA Psychiatry*. 2025.

ADVOCATE HEALTH

Key Takeaways Ketamine

- Rapid efficacy: Produces antidepressant effects within hours, confirmed across multiple trials.
- Magnitude & durability: Benefits are clinically meaningful but transient, lasting days–weeks without maintenance.

Berman RM et al. *Arch Gen Psychiatry*. 2000
Jelovac A et al. *JAMA Psychiatry*. 2025
FDA SPRAVATO Prescribing Information, 2024.

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Assessment Question #3

Which mechanism best explains the rapid antidepressant effects of ketamine in treatment-resistant depression?

A. Inhibition of serotonin reuptake leading to gradual synaptic remodeling

B. NMDA receptor antagonism resulting in a glutamate surge and downstream AMPA activation

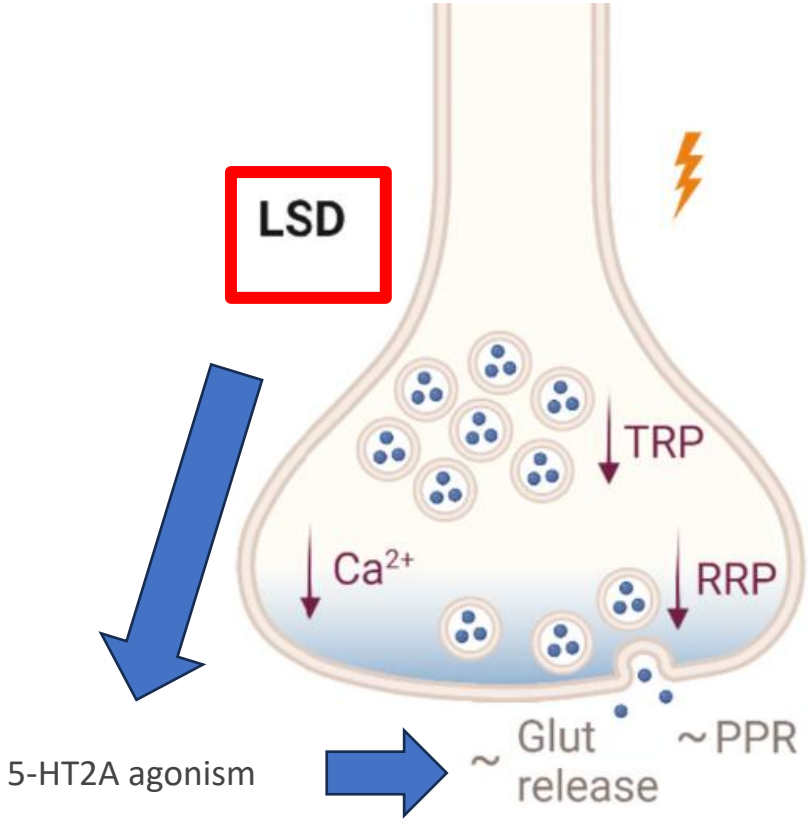
C. Direct stimulation of dopamine D2 receptors in limbic pathways

D. GABA-A receptor potentiation producing anxiolytic effects

Lysergic Acid Diethylamide (LSD)

ADVOCATE HEALTH

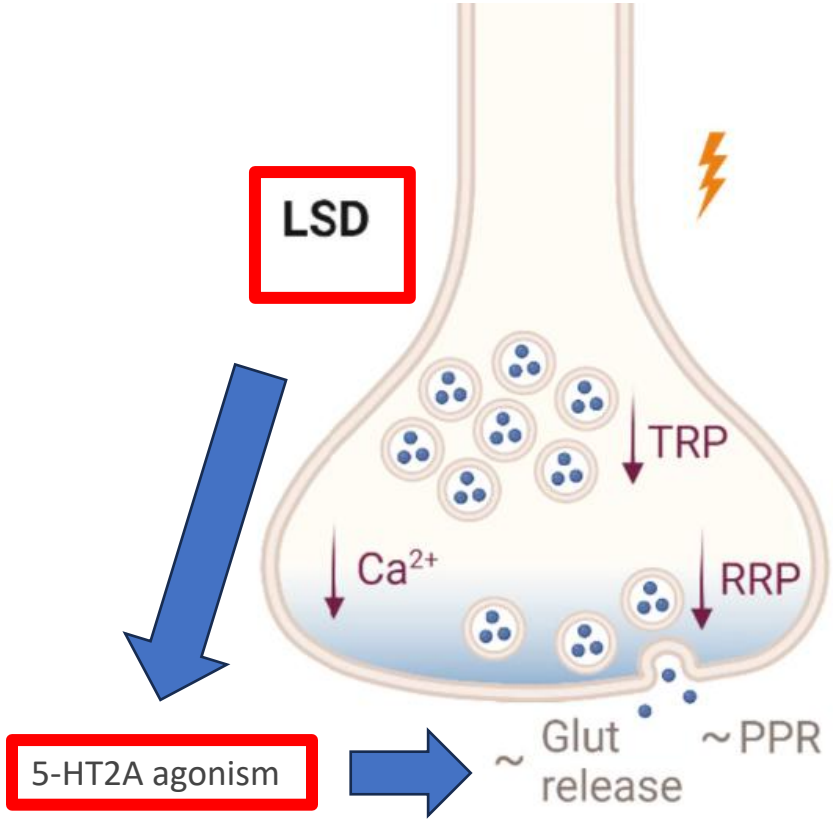
LSD — Mechanism of Action



Petrušková et al., *Journal of Neurochemistry*, 2025.

ADVOCATE HEALTH

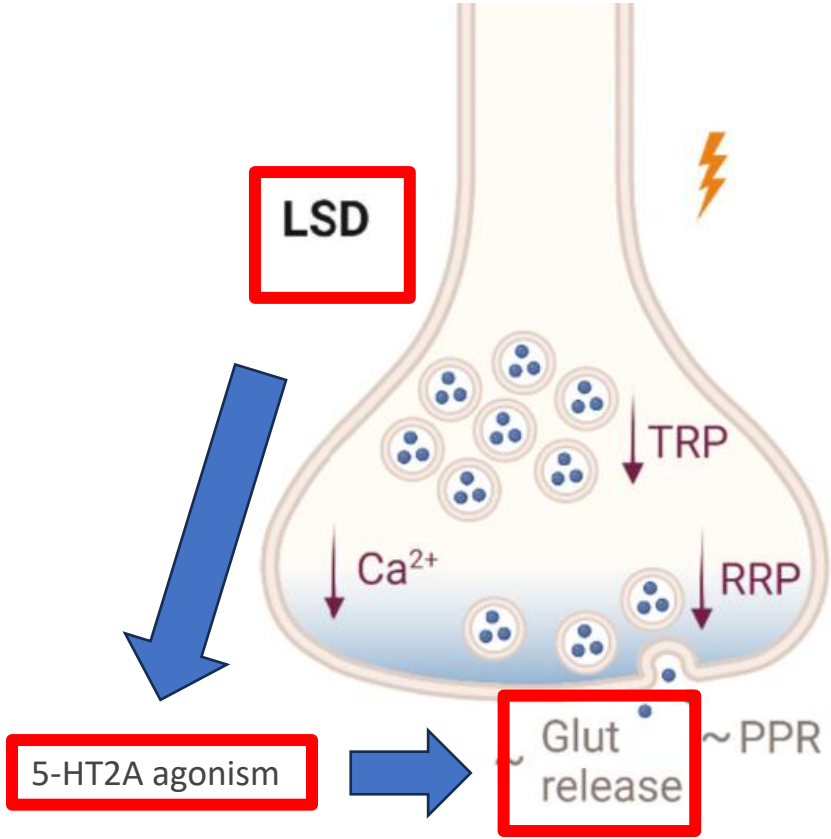
LSD — Mechanism of Action



Petrušková et al., *Journal of Neurochemistry*, 2025.

ADVOCATE HEALTH

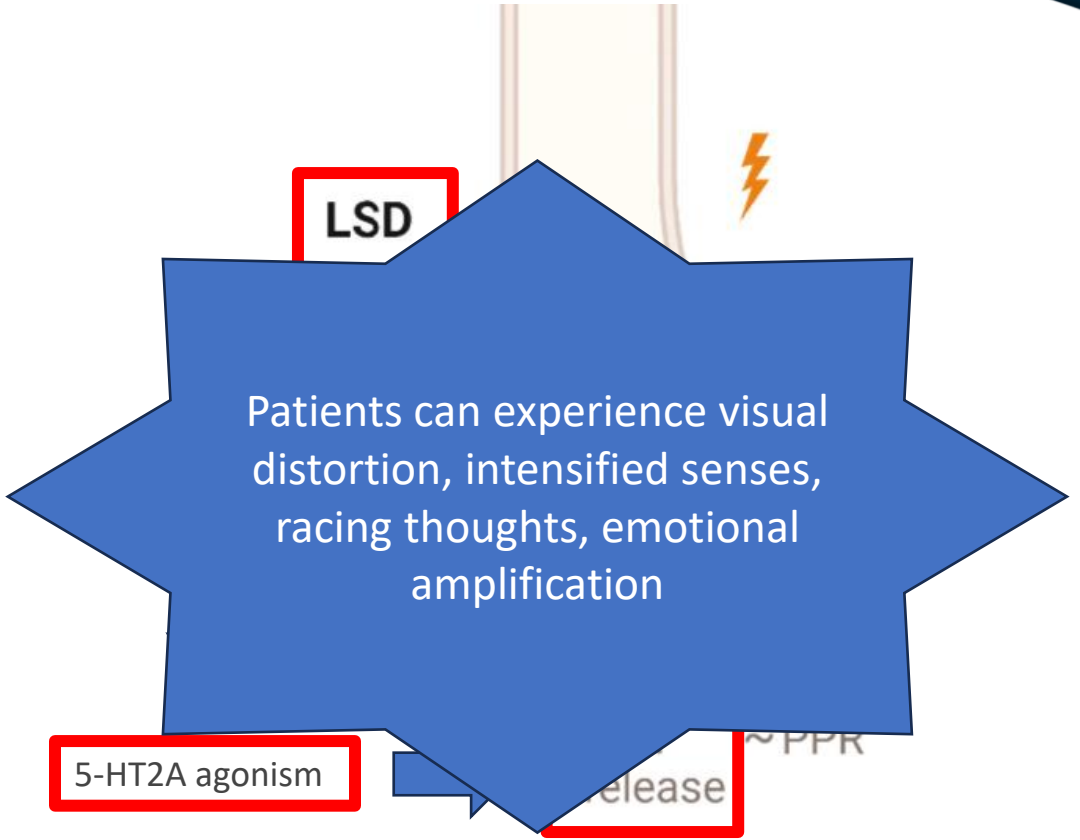
LSD — Mechanism of Action



Petrušková et al., *Journal of Neurochemistry*, 2025.

ADVOCATE HEALTH

LSD — Mechanism of Action



Petrušková et al., *Journal of Neurochemistry*, 2025.

ADVOCATE HEALTH

LSD — Indications, Dosing, Safety

Domain	LSD
Psychiatric Use	Investigational only (research/historical): mood disorders, anxiety in serious illness, substance use disorders
Indications / Forms	**No FDA approval; Schedule I** Research settings only; oral (solution/capsule/blotter-equivalent)
Typical Dosing	No approved dosing; trials use **single or limited oral doses** under strict protocols
Monitoring / Safety	Prolonged effects (8–12 h), anxiety/panic, ↑BP/HR; avoid in psychosis/bipolar; requires controlled setting & continuous monitoring

Passie T et al. *CNS Neurosci Ther*. 2008
Nichols DE. *Pharmacol Rev*. 2016

Robison et al., 2025

Trial Design	**Phase 2b, multicenter, prospective, randomized, double-blind, placebo-controlled, dose-response study conducted at 22 outpatient psychiatric sites in the United States (N = 198 adults with moderate-to-severe generalized anxiety disorder; HAM-A ≥20)**
Intervention	Single oral dose of LSD (lysergide D-tartrate; freebase equivalent) administered as monotherapy at one of four doses: 25 µg, 50 µg, 100 µg, or 200 µg, compared with placebo; no concomitant psychotherapy provided
Primary Outcome	Dose–response relationship for change from baseline in Hamilton Anxiety Rating Scale (HAM-A) score at Week 4, assessed using multiple comparison procedure–modeling (MCP-Mod); minimal clinically important difference defined as 2.5 points
Results	• N = 198 randomized (194 analyzed) • Week 4 HAM-A: −21.3 with MM120 100 µg vs −13.7 with placebo (Δ −7.6; $p < 0.0004$) • Response (≥50% ↓ HAM-A): 65%; Remission (HAM-A ≤7): 48% (both sustained to Week 12) • Safety: Mild–moderate, transient dosing-day AEs; no serious AEs
Conclusion	• A single oral dose of LSD produced rapid, clinically meaningful, and sustained reductions in anxiety symptoms in adults with moderate-to-severe GAD. • The results support 100 µg LSD as the optimal dose and provide strong justification for ongoing Phase 3 trials, positioning LSD as a potential fast-acting, long-duration pharmacologic treatment for GAD • Phase 3 trials underway; if replicated, LSD may become first-in-class single-dose anxiolytic

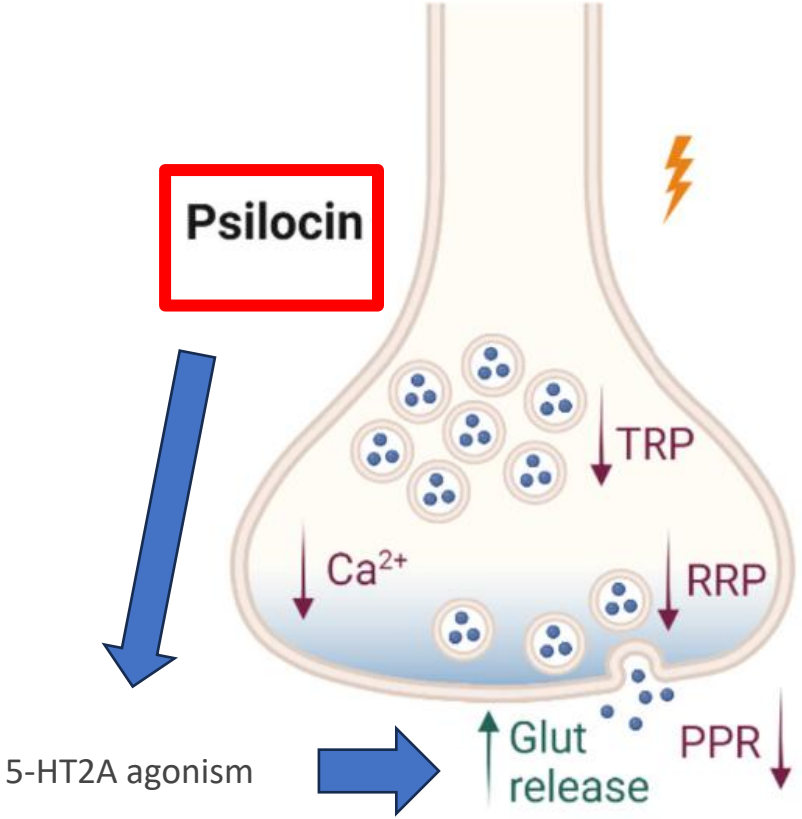
Robison R et al. *JAMA*. 2025.

ADVOCATE HEALTH

Psilocybin

ADVOCATE HEALTH

Psilocybin — Mechanism of Action



Petrušková et al., *Journal of Neurochemistry*, 2025.

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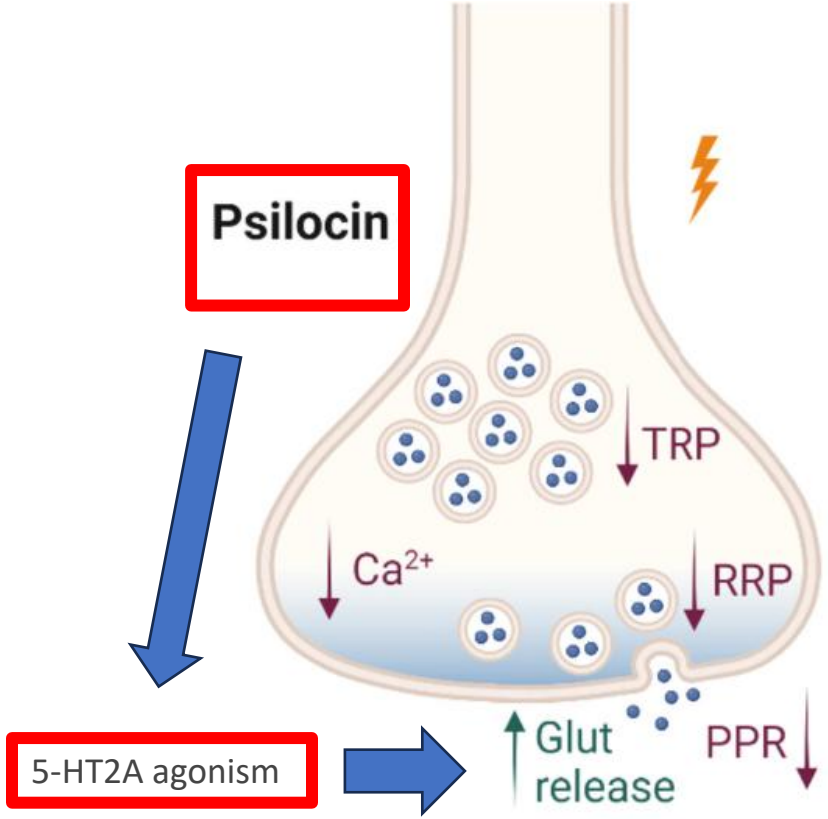
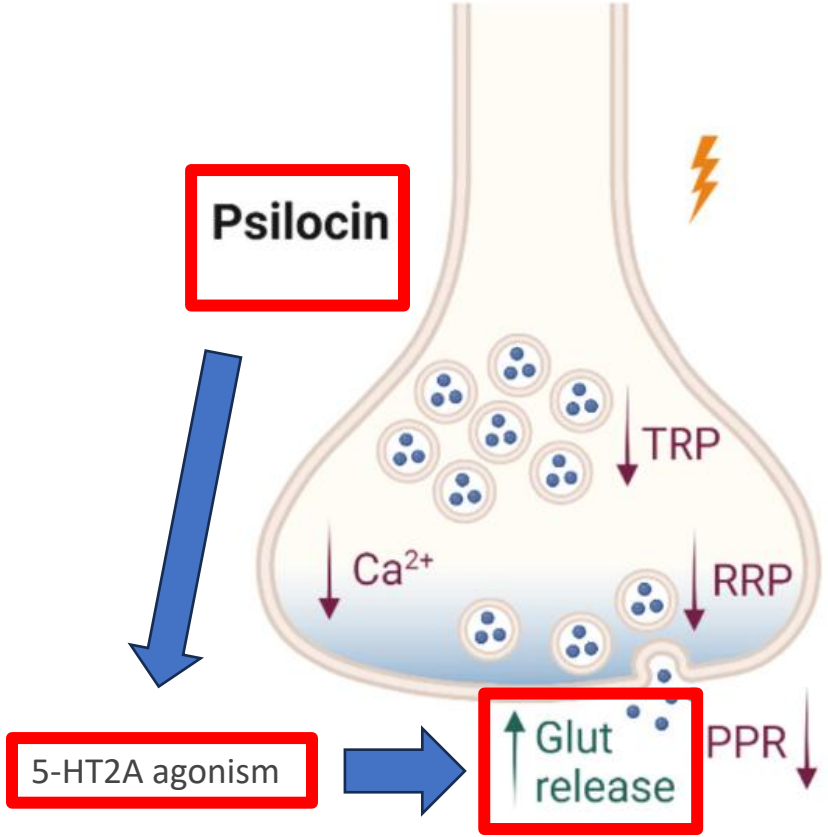
Psilocybin — Mechanism of Action



Petrušková et al., *Journal of Neurochemistry*, 2025.

ADVOCATE HEALTH

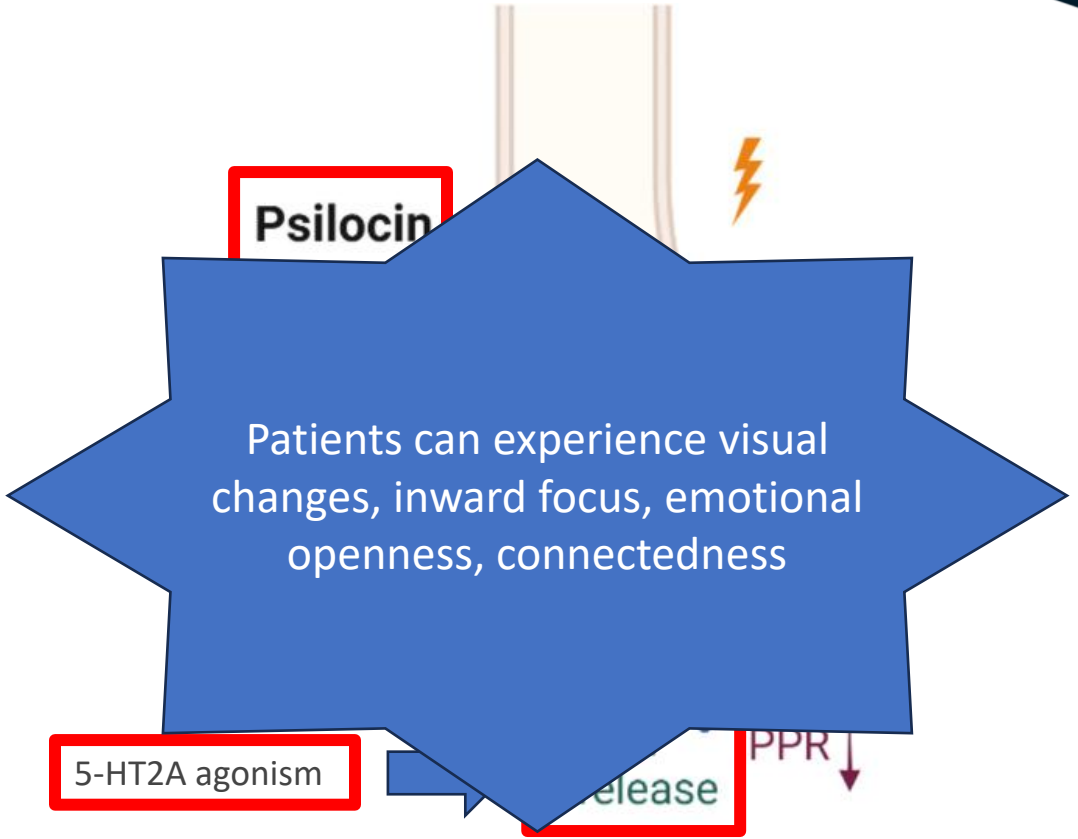
Psilocybin — Mechanism of Action



Petrušková et al., *Journal of Neurochemistry*, 2025.

ADVOCATE HEALTH

Psilocybin — Mechanism of Action



Petrušková et al., *Journal of Neurochemistry*, 2025.

ADVOCATE HEALTH

Psilocybin — Indications, Dosing, Safety

Domain	Psilocybin
Psychiatric Use	Investigational: MDD/TRD, cancer-related distress/end of life care, anxiety, substance use disorders
Indications / Forms	No FDA approval; Schedule I federally (US) (decriminalized in Colorado and Oregon) Research settings only; oral (capsules or synthesized psilocybin derived from mushrooms)
Typical Dosing	No approved dosing; 1–2 supervised oral doses within psychotherapy protocols
Monitoring / Safety	4–6 h effects; anxiety, nausea, ↑BP/HR, perceptual changes Avoid psychosis/bipolar I; controlled setting required

Griffiths RR et al. *Psychopharmacology (Berl)*. 2006
Nichols DE. *Pharmacol Rev*. 2016.
World Population Review, 2026

Griffiths et al., 2006

Trial Design	Randomized, double-blind, active-placebo-controlled, within-subject crossover study at Johns Hopkins (N = 36 healthy, hallucinogen-naïve adults with regular spiritual practice)
Intervention	Single oral psilocybin 30 mg/70 kg vs methylphenidate 40 mg/70 kg (active placebo) in monitored 8-hour sessions; no psychotherapy
Primary Outcome	Mystical-type experience and persisting personal meaning assessed immediately and at 2-month follow-up
Results	• Psilocybin produced significantly greater mystical-type experience and personal meaning than active placebo ($p < 0.001$) • ~61% met criteria for a complete mystical experience, with sustained positive mood and behavior changes at 2 months ($p < 0.05–0.001$) • Transient anxiety was more common; no serious adverse events
Conclusion	A single supervised dose of psilocybin reliably induced profound, meaningful experiences with lasting positive psychological effects, establishing a modern scientific foundation for later therapeutic psilocybin trials.

Griffiths RR et al. *Psychopharmacology (Berl)*. 2006.

COMP360 Psilocybin Trial

Trial Design	Randomized, double-blind, dose-controlled Phase 2b multicenter trial (N = 233 adults with treatment-resistant depression)
Intervention	Single supervised oral dose of COMP360 psilocybin (25 mg, 10 mg, or 1 mg control) with standardized psychological support
Primary Outcome	Change in MADRS depression score from baseline to Week 3
Results	• 25 mg dose significantly reduced MADRS vs 1 mg control (−6.6 points; $p < 0.001$) • ~37% response and ~29% remission at Week 3; ~20% sustained response at Week 12 • Adverse events mostly mild–moderate (headache, nausea, transient anxiety); no serious drug-related AEs
Conclusion	A single 25 mg dose of COMP360 psilocybin produced rapid, clinically meaningful antidepressant effects in treatment-resistant depression, supporting psilocybin-assisted therapy and enabling Phase 3 trials

Young M et al. *Psych Congress*. 2022.

ADVOCATE HEALTH

Key Takeaways LSD & Psilocybin

- LSD: Single-dose therapy with rapid, durable anxiolysis.
- Psilocybin: Supervised dosing plus integration yields sustained antidepressant benefit.

Robison R et al. *JAMA*. 2025
Young M et al. *Psych Congress*. 2022
Griffiths RR et al. *Psychopharmacology (Berl)*. 2006.

Assessment Question #4

Which statement best describes how LSD differs from standard guideline-directed pharmacotherapy for GAD?

A. LSD requires daily chronic dosing similar to SSRIs

B. LSD is FDA-approved as first-line therapy for GAD

C. LSD has demonstrated durable anxiolytic effects after a single supervised dose in clinical trials

D. LSD is preferred over CBT for initial GAD management

Compare & Contrast

Domain	Ketamine / Esketamine	LSD / Psilocybin	SSRIs / SNRIs
Onset	Hours	1–2 days	Weeks
Durability	Days–weeks (without maintenance)	Weeks–months	Requires daily chronic dosing
Setting	Esketamine: REMS clinic (observed dosing)	Supervised dosing sessions	Self-administered
Regulatory Status	FDA-approved (TRD; MDD with acute suicidality as adjunct)	Investigational	FDA-approved standard of care

Daly EJ et al. *Am J Psychiatry*. 2019
Robison R et al. *JAMA*. 2025
Young M et al. *Psych Congress*. 2022.

Summary of Where Psychedelics Fit

Disease State	Where Psychedelics Fit
MDD	• **Esketamine (IN):** On-label adjunct for MDD with acute suicidal ideation/behavior (REMS) • **IV ketamine:** Off-label in severe or refractory cases within protocols
TRD	• **Esketamine (IN):** On-label for TRD (REMS) • **IV ketamine:** Off-label option in structured programs (e.g., VA)
GAD	• **LSD:** Investigational; single-dose anxiolytic with durable benefit • *Not yet standard of care*

Daly EJ et al. *Am J Psychiatry*. 2019
FDA SPRAVATO Prescribing Information, 2024
Robison R et al. *JAMA*. 2025.

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