

Ketamine 101

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Ketamine basics

- General Anesthetic and an NMDA receptor antagonist
- Schedule III controlled substance due to abuse potential
- Used for anesthesia, depression, and surgical pain
- Ketamine is the only psychedelic or psychedelic-adjacent drug on the World Health Organization Essential Medicines List
- Global market projected to grow from \$750 million to \$3.42 billion by 2034.

History of Ketamine

Phencyclidine (PCP) first synthesized

Developed as a potential anesthetic. Effective, but caused prolonged psychosis-like reactions

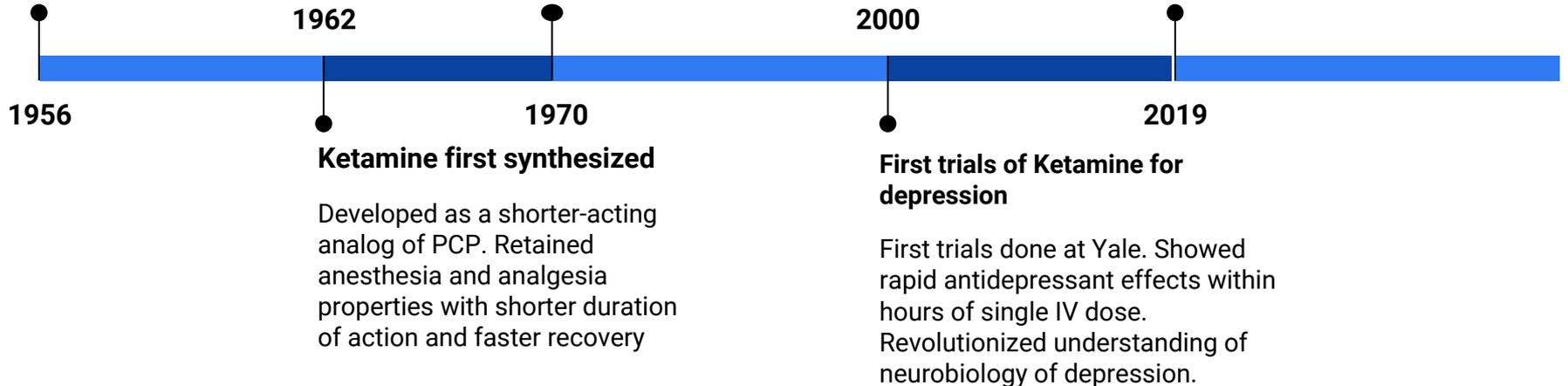
FDA approval for anesthesia

Approved for procedural sedation, especially effective in trauma due to cardio and pulmonary stability.

Widely used during Vietnam War for battlefield anesthesia - fast, safe, no ventilator required.

FDA approves Esketamine (Spravato)

S-enantiomer of ketamine approved as a nasal spray for TRD and suicidal ideation. First new depression mechanism in 30+ years.



Current Standing: 2020s

- Ketamine is recognized as the prototype rapid-acting antidepressant.
- Support by APA consensus statements, and 100s of studies including meta-analyses for Treatment Resistant Depression (TRD) and suicidality.
- Response/Remission Rates for TRD: 60-80%/10-60% (pending maintenance treatment)
- Used across psychiatry, pain medicine, and emergency care.
- 8/2025 FDA approves new medication KetaRX for surgical pain management

Mechanistic Understanding

- A noncompetitive NMDA receptor antagonist, causing a glutamate surge
- Increases BDNF release and synaptogenesis via AMPA receptor agonism.
- Restores connectivity in the prefrontal-limbic network, associated with emotional regulation
- Effects occur within hours to days, unlike most antidepressants.

Formulations

1. Injectable

- a. IV or IM generic ketamine or Ketalar®
- b. Used for Anesthesia induction/maintenance, procedural sedation, depression, pain, status epilepticus
- c. Gold Standard, most control

2. Intranasal

- a. Esketamine (Spravato®)
- b. S+ Enantiomer only
- c. FDA approved for TRD and MDD with SI
- d. Under REMS program

3. Oral / Sublingual / Lozenge

4. Others

- a. Rectal (sometimes used in pediatrics)
- b. Transdermal (experimental, poor/inconsistent absorption)

Formulations cont.

- IV ketamine remains the most evidence-based and controlled method for TRD.
- Intranasal esketamine (Spravato®) is FDA-approved under REMS.
- Compounded intranasal and oral formulations are off-label but commonly used for maintenance.
- Typical antidepressant effects last 3–7 days; maintenance dosing varies 1–4 weeks.
- All administrations should include cardiovascular and dissociation monitoring when appropriate.

Chemical Structure

Ketamine is a **racemic mixture (R- and S-ketamine)**, but individual enantiomers are studied and used differently:

- **Racemic ketamine** (most IV, oral, nasal compounding): 50% R-, 50% S-
- **Esketamine (S-ketamine)**: More potent NMDA antagonist, shorter duration, on-label nasal spray
- **Arketamine (R-ketamine)**: Investigational; may have longer-lasting antidepressant effects and fewer side effects

IV infusion for depression

- Start at 0.5mg/kg infusion, 20 drip rate
 - Can increase or decrease dose, up to 1mg/kg based on response
- Onset 5-10 minutes, Peak ~ 40 minutes
- 6 infusions done over 2-3 weeks, gives longer lasting results
- Under nurse supervision
 - Monitor BP and HR pre-, mid-, and post-treatment
 - Monitor for psychological response, provide support
- Measure depressive and anxiety symptoms pre and post infusion
- Dissociative effects typically resolve within minutes post infusion, but pt remains sedated
- Transportation required to a from clinic, pt advised to avoid major decision making/work

Side effects

- **Common (10-75%, in descending order):** Dissociation / depersonalization, Dizziness / lightheadedness, Nausea / vomiting, Increased blood pressure, Perceptual disturbances (visual/auditory), Sedation / drowsiness, Headache
- **Rare (5-10%):** Anxiety or agitation, Fatigue / malaise after session, Blurred vision / diplopia, Nystagmus, Transient tachycardia, Urinary urgency / frequency
- **Extremely rare (<1%):** Emergence reactions (severe dysphoria, panic), Allergic reaction, Liver enzyme elevation, Prolonged hypertension or arrhythmia
- Most side effects are transient and resolve within 1–2 hours post-dose.
- Reassurance and supportive measures are first-line interventions.
- Pre-medicate: ondansetron for nausea, propranolol for HTN
- Severe or prolonged symptoms are rare and warrant further evaluation.



Predictors of Sustained Benefit

- Positive Predictors:
 - Early robust response (after 1-2 infusions)
 - Combined psychotherapy or behavioral activation
 - Ongoing antidepressant or mood stabilizer use
 - Active lifestyle, strong social support
- Negative Predictors:
 - Chronic dysthymia or personality pathology
 - Ongoing benzodiazepine or opioid use (blunts response)
 - Severe anhedonia or psychotic features

Ongoing Research & Future Applications

1. Indications beyond depression

- PTSD - several promising studies as a rapid-acting intervention ²
- Substance use disorders - early studies show ketamine may help interrupt relapses by “resetting” reward circuitry ³
- Neurology/movement disorders - some early promise for improving levodopa-induced dyskinesia in Parkinson’s disease ⁴
- Epilepsy / status epilepticus - used for refractory and super-refractory status epilepticus with good response ⁵

2. Novel ketamine-metabolite drugs

- (2R,6R)-hydroxynorketamine (RR-HNK)
- Does not cause sedation or dissociation - less risk of abuse
- Hopeful oral or less intensive formulation with rapid effects

3. Extending duration of effect

- Studies done at Vanderbilt suggest enhancing intracellular signalling (ERK pathway) following ketamine, effects might last up to 2 months from a single dosage ¹

Ongoing Research & Future Applications

4. Integration with psychotherapy / combined protocols

- a. Researchers are exploring how ketamines “window of plasticity” (when synapses are more changeable) can be leveraged by adding psychotherapy after ketamine to extend benefit and improve durability. ⁶

5. Alternative administration/delivery approaches

- a. While IV is the standard, there is growing work/research into oral, sublingual, intranasal, troche, etc. to increase accessibility and reduce barriers
- b. Lower-dose protocols, at-home maintenance under supervision, and formulations with side effects are next steps, which can allow for broader scalability beyond specialized clinics.

Questions?

Resources

1 - Z. Zack Ma *et al.*

,Enhanced ERK activity extends ketamine's antidepressant effects by augmenting synaptic plasticity.*Science***388**,646-655(2025).DOI:10.1126/science.abb6748

2- Janssen-Aguilar R, Meshkat S, Al-Shamali HF, Perivolaris A, Swainson J, Zhang Y, Greenshaw A, Burbach L, Winkler O, Phillips JL, Enns MW, Sareen J, Nicholson A, Vermetten E, Jetly R, Lanius R, Bhat V. Interventional Psychiatry and Emerging Treatments for Posttraumatic Stress Disorder (PTSD): A Systematic Review. *Psychiatry Clin Psychopharmacol.* 2025 Aug 11;35(Suppl 1):S57-S89. doi: 10.5152/pcp.2025.241027. PMID: 40879152; PMCID: PMC12410247.

3 - Derakhshanian S, Zhou M, Rath A, Barlow R, Bertrand S, DeGraw C, Lee C, Hasoon J, Kaye AD. Role of Ketamine in the Treatment of Psychiatric Disorders. *Health Psychol Res.* 2021 Jun 22;9(1):25091. doi: 10.52965/001c.25091. PMID: 35106397; PMCID: PMC8801551.

4 - Abhilasha Vishwanath, Mitchell J Bartlett, Torsten Falk, Stephen L Cowen, Decoupling of motor cortex to movement in Parkinson's dyskinesia rescued by sub-anaesthetic ketamine, *Brain*, Volume 148, Issue 6, June 2025, Pages 2135–2150, <https://doi.org/10.1093/brain/awae386>

5- Alkhachroum A, Der-Nigoghossian CA, Matthews E, et al. Ketamine to treat super-refractory status epilepticus <https://www.neurology.org/doi/10.1212/WNL.000000000010611>. *Neurology* 2020; 95(16):e2286–e2294.

6 - Price, R. B., Spotts, C., Panny, B., Griffo, A., Degutis, M., Cruz, N., Bell, E., Do-Nguyen, K., Wallace, M. L., Mathew, S. J., & Howland, R. H. (2022). A novel, brief, fully automated intervention to extend the antidepressant effect of a single ketamine infusion: A randomized clinical trial. *The American Journal of Psychiatry*, 179(2), 959–968. <https://doi.org/10.1176/appi.ajp.20220216>