ECHO IDAHO

Behavioral Health in Primary Care

Ketamine Therapy

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Project ECHO

Learning Objectives

1. **Mechanisms of Action:**
   - Describe the mechanisms of action, particularly its role as an NMDA receptor antagonist and its impact on other neurotransmitter systems.
2. **Clinical Uses and Indications:**
   - List the approved and off-label therapeutic indications for ketamine, including its use in pain management, treatment-resistant depression, and procedural sedation.
3. **Side Effects, Contraindications, and Safety Considerations:**
   - List the common and rare side effects associated with ketamine use. They will understand its contraindications, potential for misuse or abuse, and be aware of strategies to minimize risks, especially in long-term management.

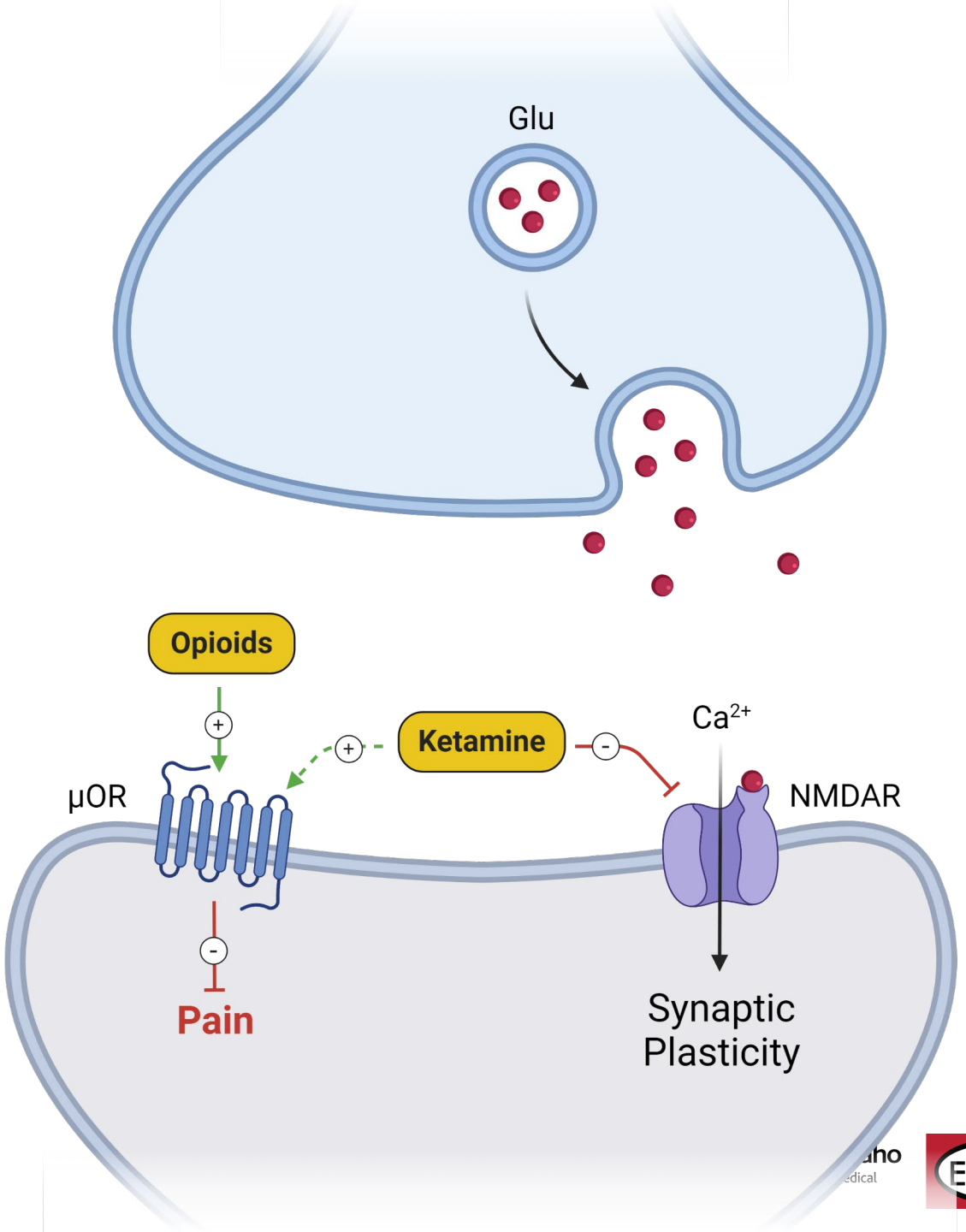
History of ketamine

- **Phencyclidine (PCP)** synthesized in 1956
  - Produced drunkenness in rodents, delirium in dogs, cataleptoid states in pigeons and anesthesia in monkeys
  - Prolonged emergence delirium in humans
- A shorter-acting less potent form was then synthesized by and called "**ketamine**"
- First human anesthetic dose was administered by **Dr. Edward Domino** (picture shown)
- Caused a **dissociative anesthesia**: patients appear awake with preserved airway reflexes and respiratory drive, but are unresponsive to stimuli
  - Term coined by Domino's wife

Lee and Phillip, 2016

Ketamine Mechanism

- MOA: NMDA receptor antagonist
  - Weak agonist at u-opioid receptors
  - Potentiates opioid effects



Summary of clinical uses for ketamine.

Anesthesia	Analgesia and sedation		Psychiatry and neuroscience
Advantageous settings:	*Acute settings*:	*Chronic settings*:	*Emerging use*:
• Hemodynamic instability	• Procedures	• Cancer pain	• Depression
• Pediatric patients	• Burns	• CRPS	• Suicidal ideation
• Uncooperative patients	• ED Agitation/Pain	• Phantom limb pain	• PTSD
• Traumatic brain injury	• Post-operative pain	• Fibromyalgia	*Modeling*:
• Bronchospasm		• Ischemic pain	• Schizophrenia
• Battlefield/Mass casualty		• Migraines	• Consciousness

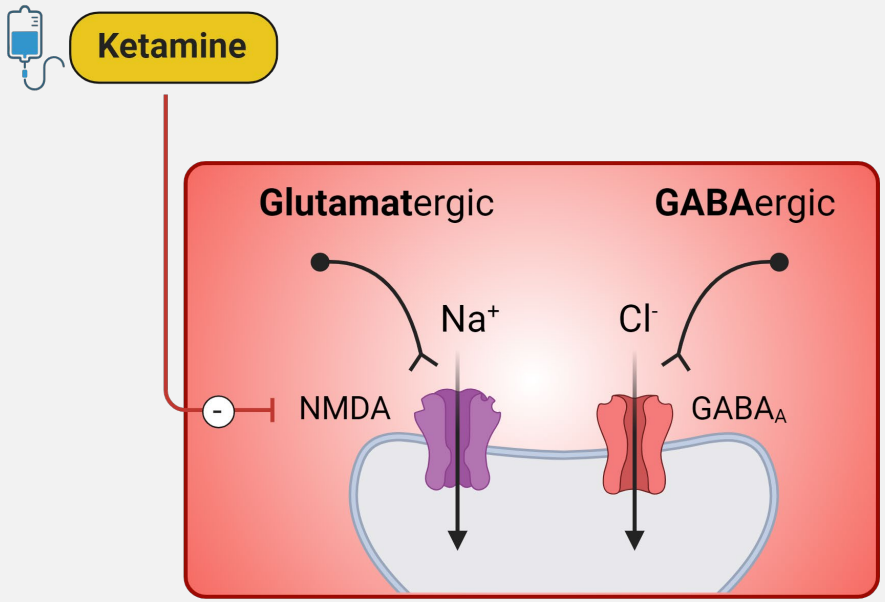
Lee and Phillip, 2016

Ketamine
(NMDA Antagonist)

MOA: NMDA receptor antagonist
- Weak agonist at mu-opioid receptors
- Potentiates opioid effects

Therapeutics: Dissociative anesthesia, pain
- Esketamine: Treatment-resistant depression

Adverse Effects:
- Emergence phenomenon: Nightmares or delirium while awakening
- Sympathetic stimulation (↑HR, BP, cardiac work)
- Direct negative cardiac inotrope
  - Cause hemodynamic instability in patients with depleted endogeneous catecholamines (e.g. patients in shock)
- Minimal respiratory depressant – but associated with increased respiratory secretions
- Analgesic effect
- Increased cerebral blood flow



Anesthetics

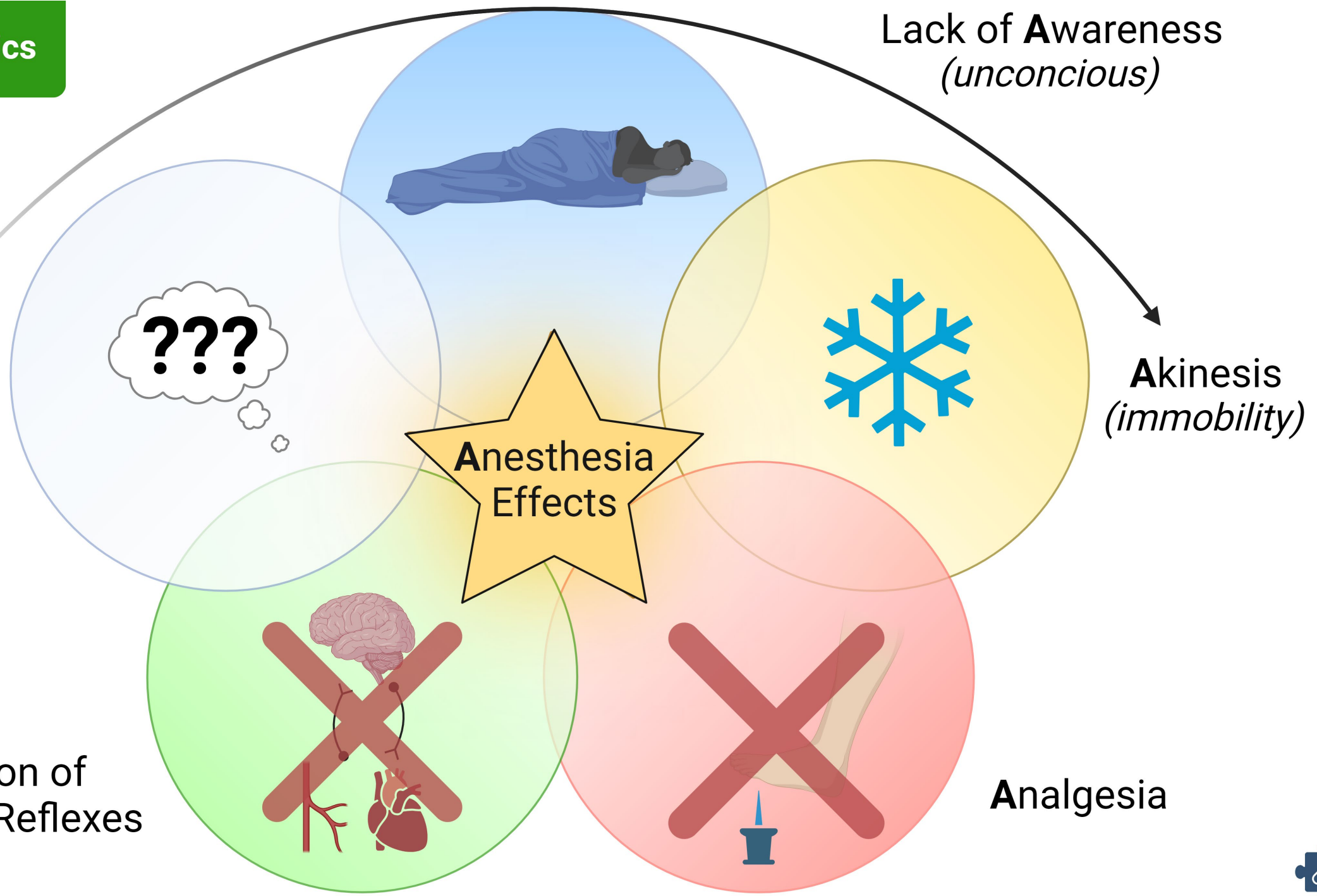
Amnesia

Lack of **A**wareness
(unconcious)

Akinesis
(immobility)

Abrogation of
Autonomic Reflexes

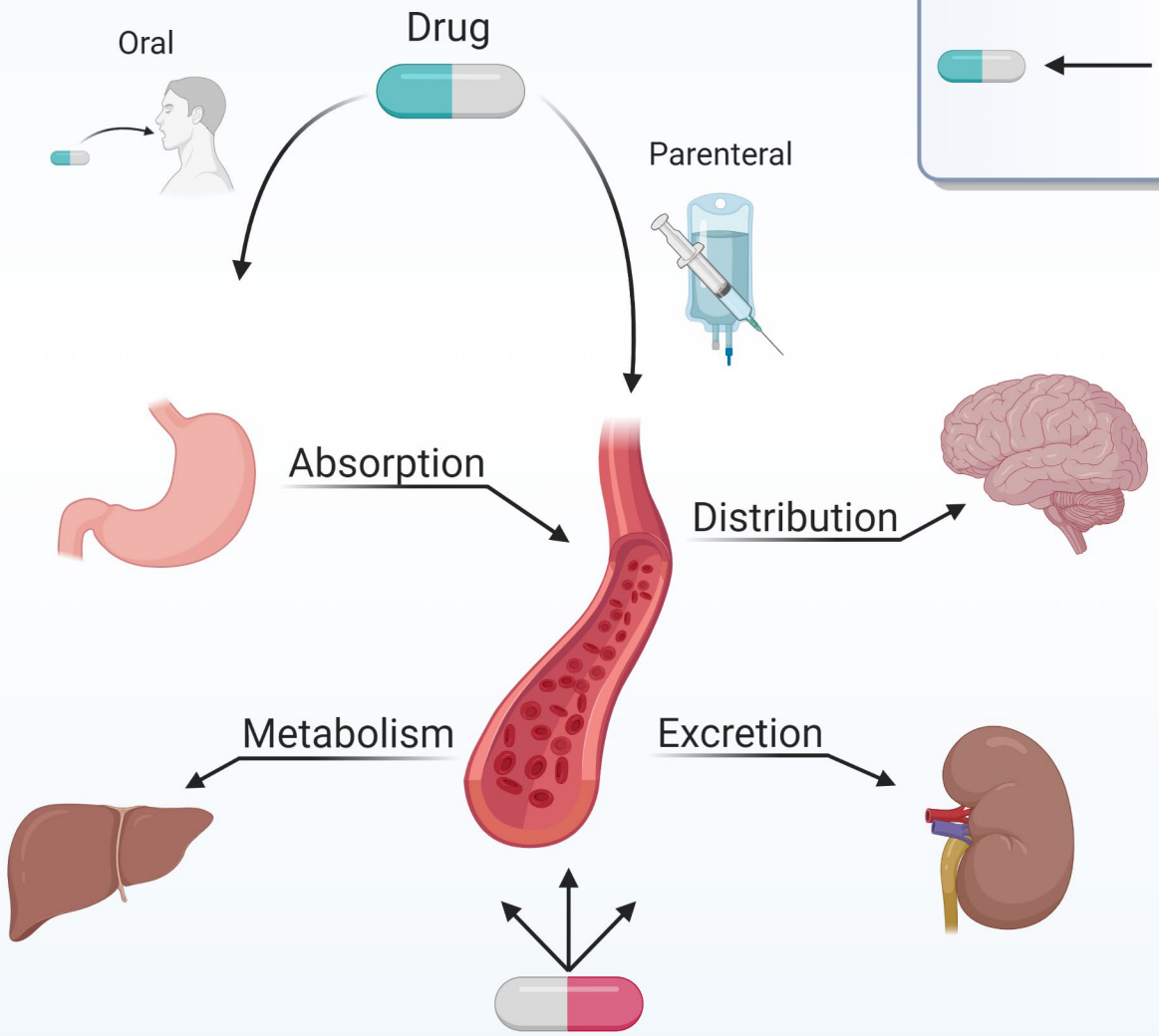
Analgesia

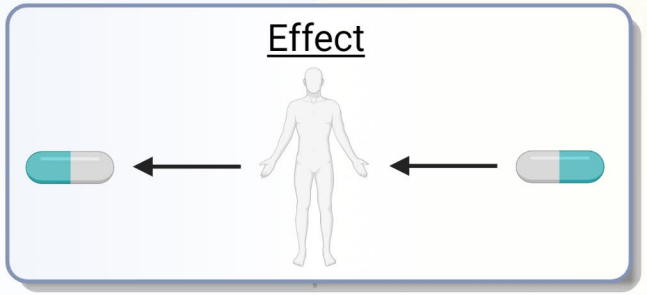


Pharmacology

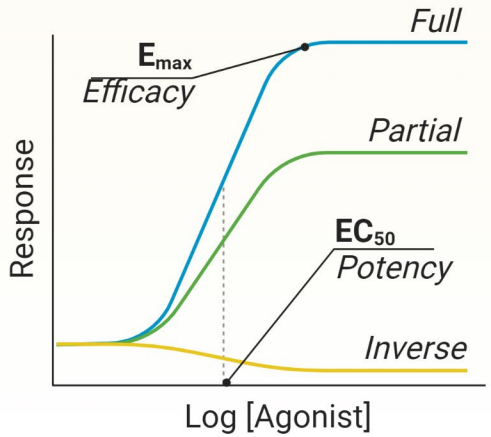
Pharmaco**genomics**

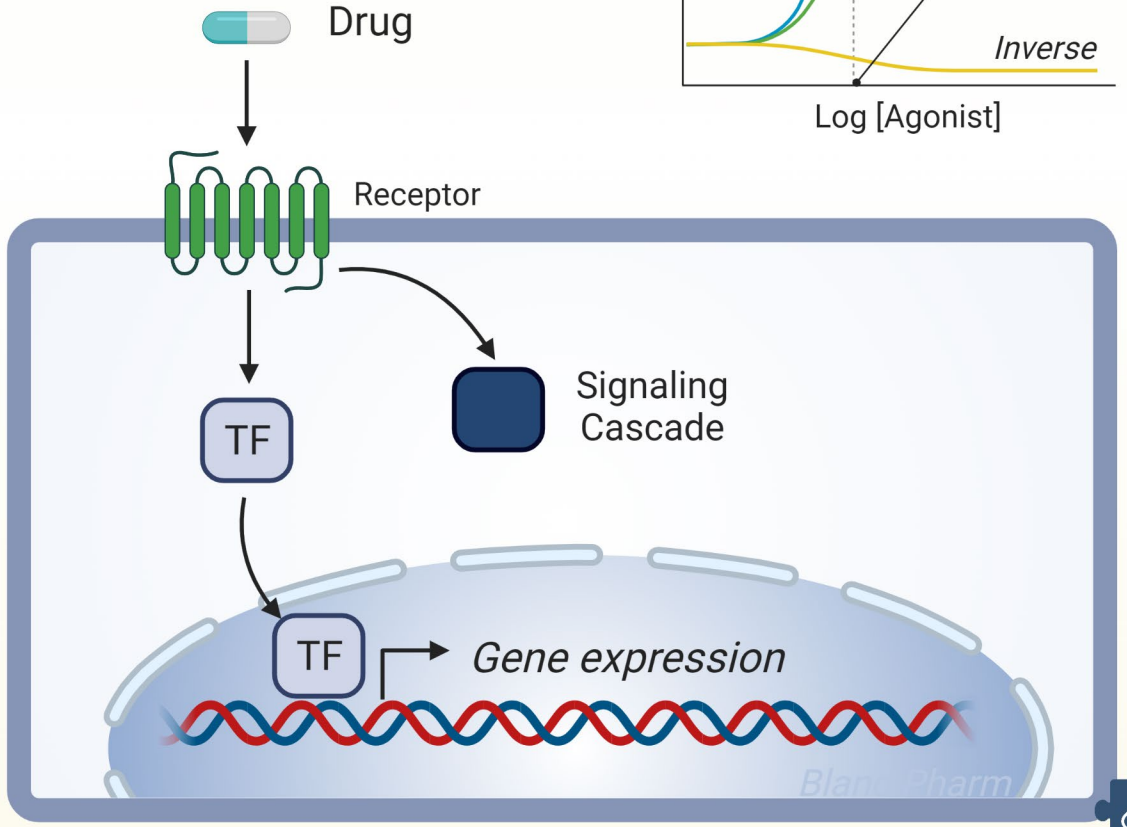
Pharmaco**kinetics**





Pharmaco**dynamics**





ADME

- Distribution
  - Lipophilic so easily crosses the BBB

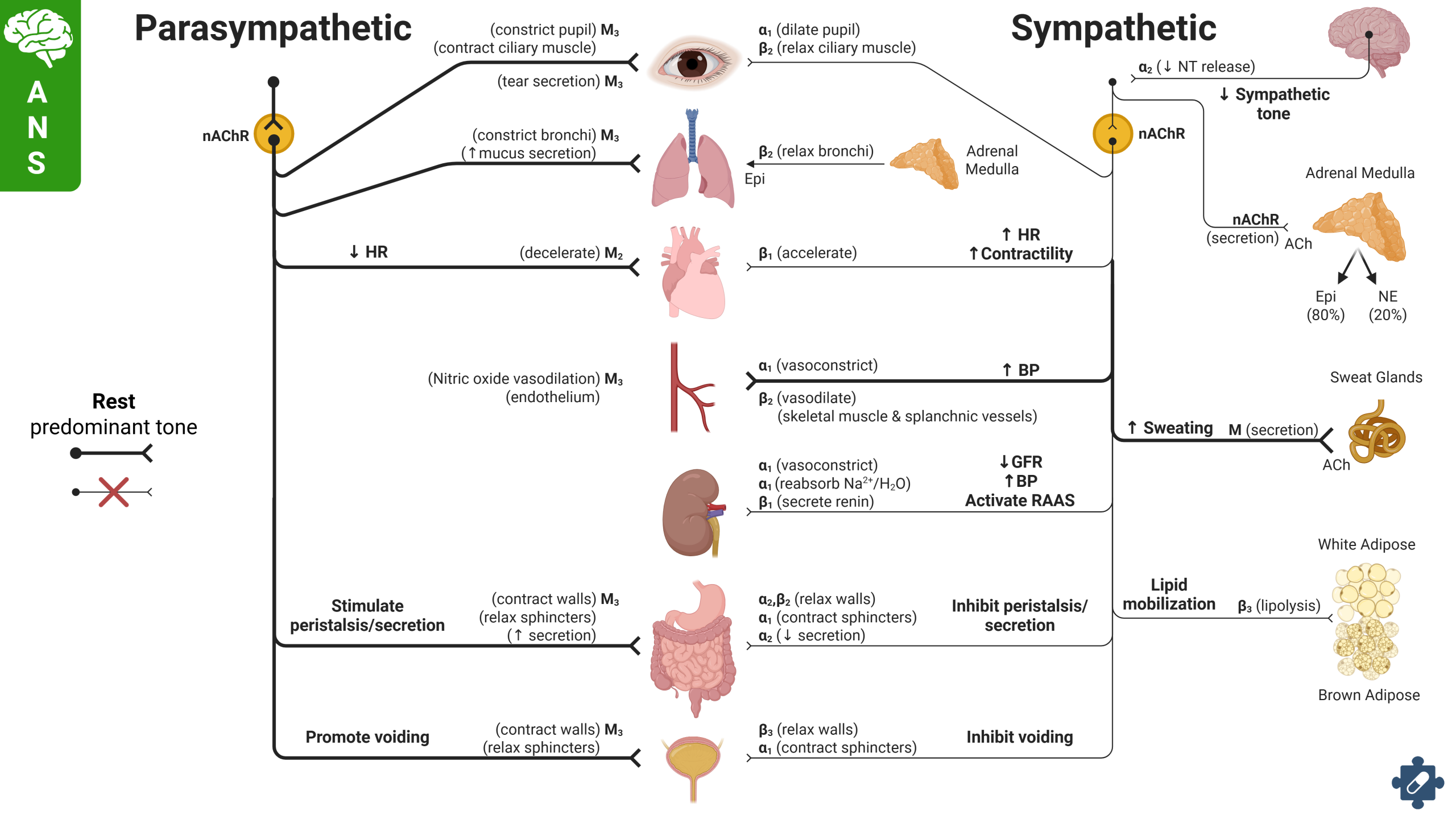
Route	Onset of action	Duration	Recovery
IV	Anesthetic: 30 sec	Anesthetic: 5-10 min	1-2 hr
IM	Anesthetic: 3-4 min Analgesic: 10-15 min	Anesthetic: 12-25 min Analgesic: 15-30 min	3-4 hr
Nasal	Analgesic: 10 min Sedation (children 2-6 yo): 5-8 min	Analgesic: 60 min	(children 2-6 yo): 30-45 min

Up-to-date

Ketamine Adverse Effects

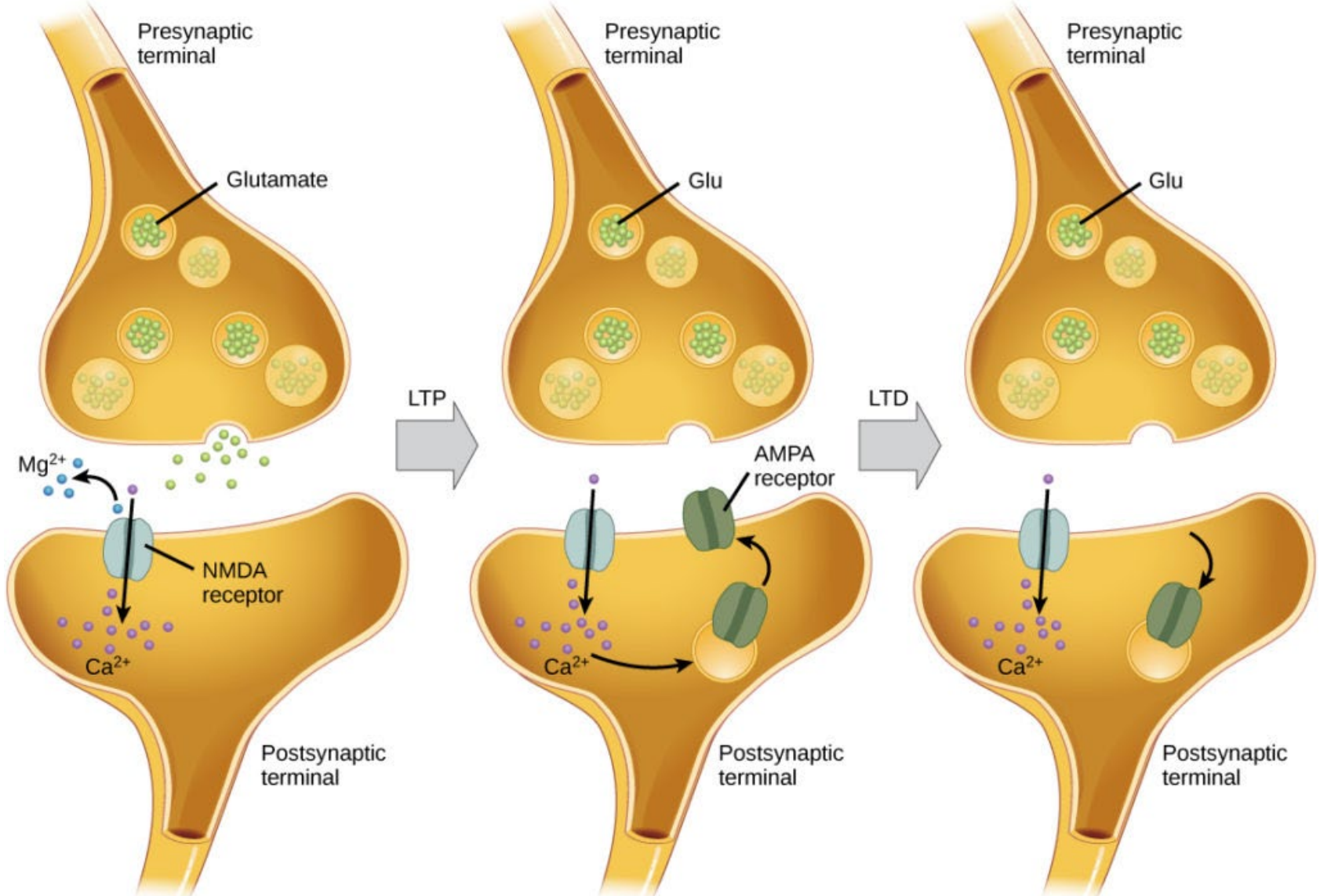
- Dissociative anesthesia
- Amnesia
- Sympathomimetic effects:
  - Increase in HR and BP
  - Bronchodilation
- Respiratory depression at high doses when administered too quickly
- Emergence phenomenon:
  - Hallucinations, flashbacks, unusual thoughts, extreme fear, excitement, and irrational behavior
  - Can be reduced by decreasing the dose or co-admin with benzodiazepine (midazolam)
  - Treat with low-dose, short-acting barbiturate or benzodiazepine (diazepam)

Ketamine StatPearls, NIH


ANS
Parasympathetic
Sympathetic
nAChR
(constrict pupil) M3
(contract ciliary muscle)
(tear secretion) M3
α1 (dilate pupil)
β2 (relax ciliary muscle)
α2 (↓ NT release)
↓ Sympathetic tone
nAChR
(constrict bronchi) M3
(↑mucus secretion)
β2 (relax bronchi)
Epi
Adrenal Medulla
Adrenal Medulla
nAChR
(secretion)
ACh
Epi (80%)
NE (20%)
↓ HR
(decelerate) M2
β1 (accelerate)
↑ HR
↑Contractility
(Nitric oxide vasodilation) M3
(endothelium)
α1 (vasoconstrict)
↑ BP
β2 (vasodilate)
(skeletal muscle & splanchnic vessels)
Sweat Glands
↑ Sweating
M (secretion)
ACh
α1 (vasoconstrict)
α1 (reabsorb Na2+/H2O)
β1 (secrete renin)
↓GFR
↑BP
Activate RAAS
White Adipose
Lipid mobilization
β3 (lipolysis)
Brown Adipose
Stimulate peristalsis/secretion
(contract walls) M3
(relax sphincters)
(↑ secretion)
α2,β2 (relax walls)
α1 (contract sphincters)
α2 (↓ secretion)
Inhibit peristalsis/ secretion
Promote voiding
(contract walls) M3
(relax sphincters)
β3 (relax walls)
α1 (contract sphincters)
Inhibit voiding
Rest
predominant tone

NMDA receptors in synaptic plasticity

- N-methyl-D-aspartate receptors (NMDARs) traditionally act as coincidence detectors that trigger plasticity in other receptors
- Dynamically regulated themselves through activity-dependent long-term potentiation (LTP) and long-term depression (LTD).
- This serves as a powerful mechanism for fine-tuning information encoding, dendritic integration, and the regulation of neuronal bursting activity throughout the brain.
- **In short: NMDAR signaling regulates brain wiring/signaling**



The NMDA receptor is activated by glutamate binding, but only after depolarization removes inhibitory Mg^{2+}. Once the Mg^{2+} is removed, Ca^{2+} can enter the cell.

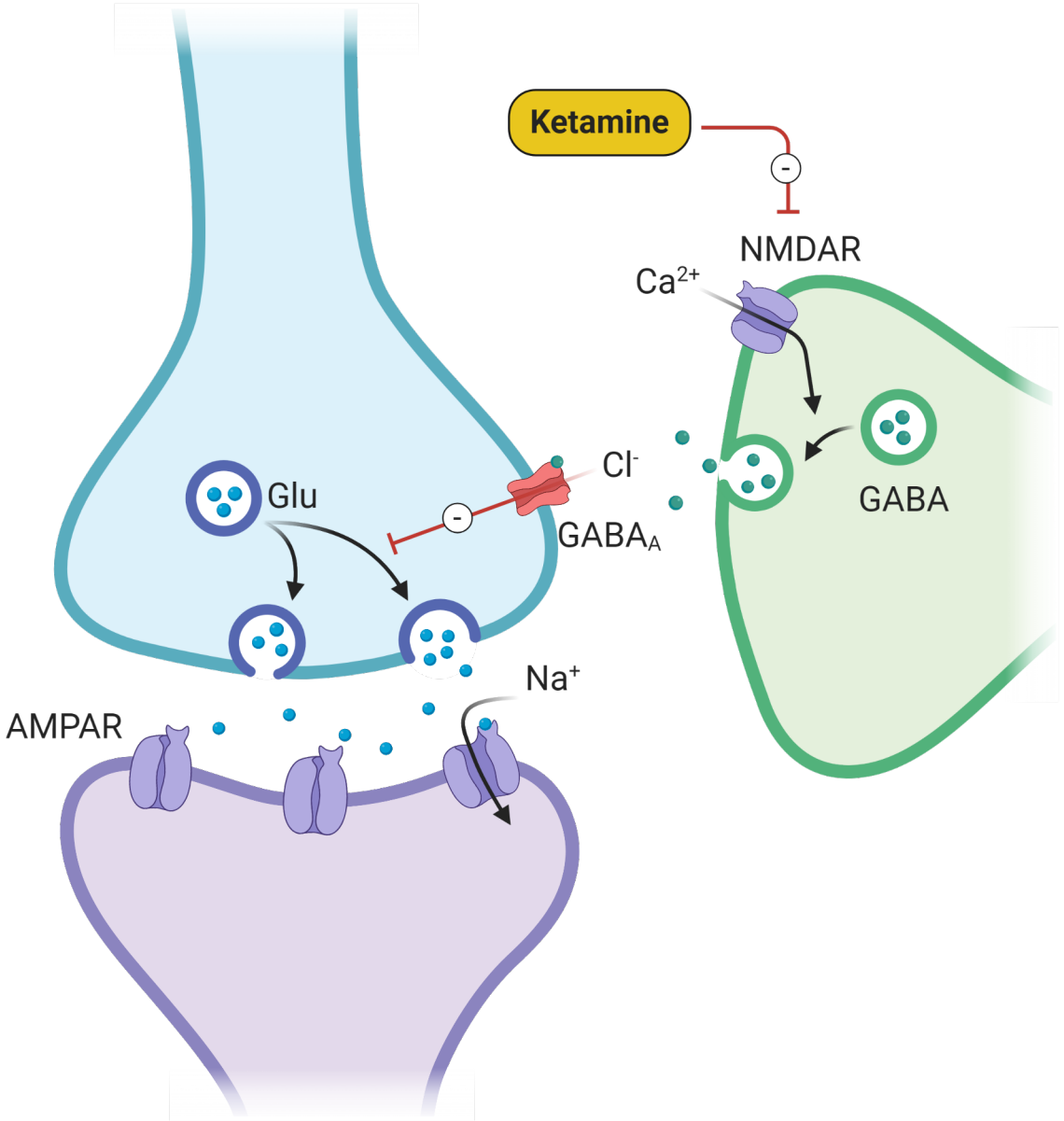
Some AMPA receptors are present in the membrane initially. In response to an increase in intracellular $Ca2^{+}$, more are inserted.

Low-frequency stimulation results in a different Ca^{2+} -signaling cascade. AMPA receptor is removed from the membrane, and as a result, the nerve cell becomes less responsive to glutamate.

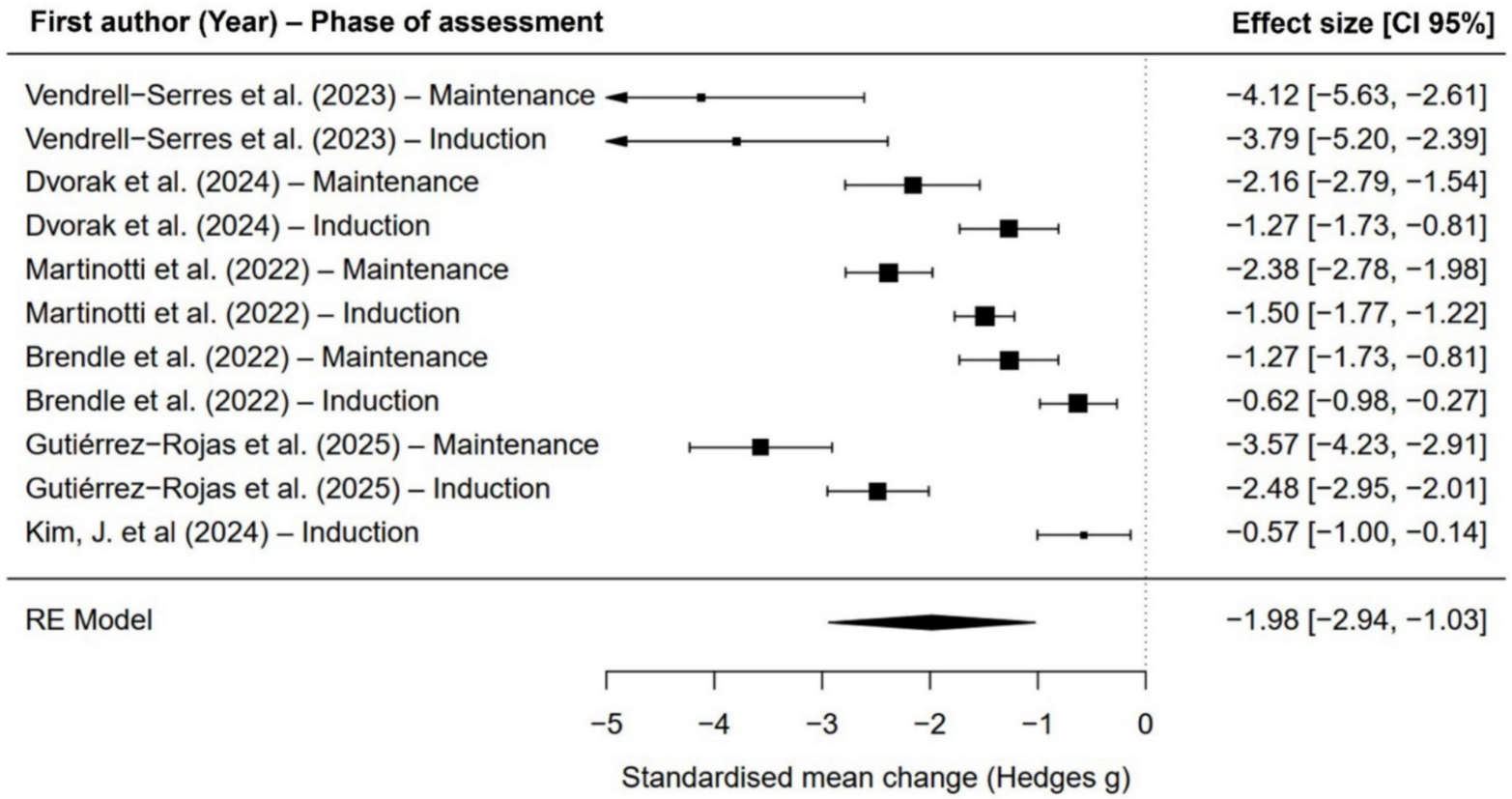
Esketamine

On-label:

- Anti-depressive for treatment-resistant depression (TRD)
  - Non-responsive to ≥ 2 pharmacologic agents
- In combination with other oral antidepressants
- Monotherapy (FDA approved 2025)



Changes in depressive symptoms (meta-analysis)



- Real-world effectiveness of esketamine (nasal) in treatment resistant depression
- Negative values = greater symptom reduction
- Suggests treatment resistant patients may benefit from esketamine

Lapa et al, 2026

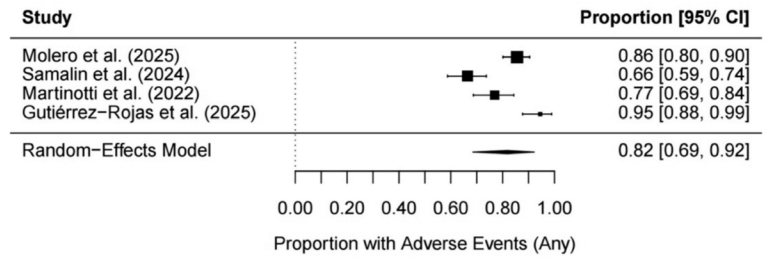
University of Idaho School of Health and Medical Professions

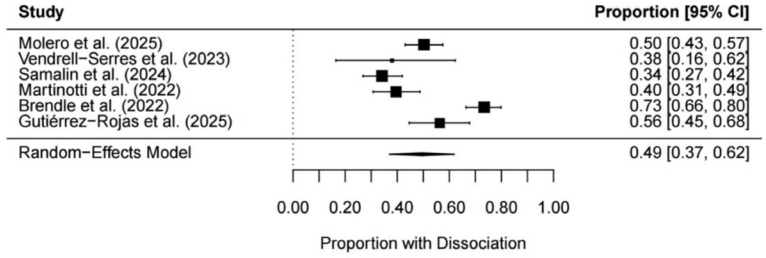
Project ECHO

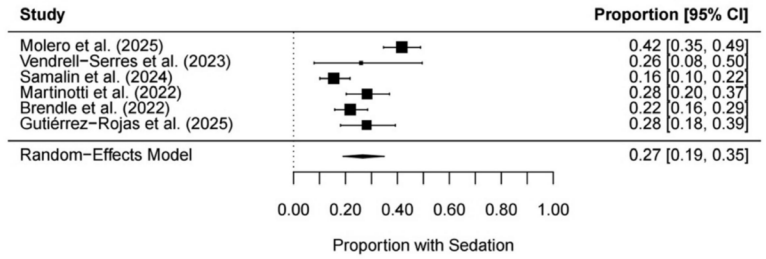
Esketamine US Boxed Warning

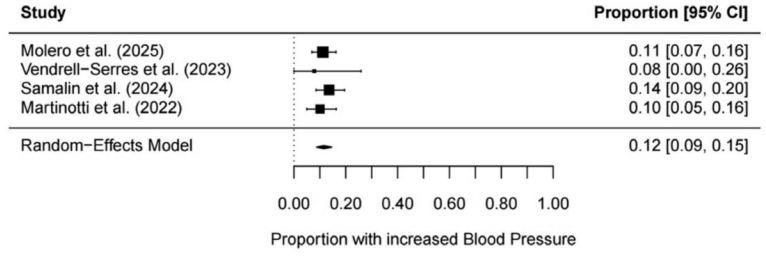
- **Sedation**
- **Dissociation**
- **Respiratory depression**
  - Patients must be monitored for at least **2 hours** at each treatment session, followed by an assessment to determine when the patient is considered clinically stable and ready to leave the health care setting.
- **Abuse & misuse**
- **Suicidal thoughts & behaviors**
  - Pediatric and young adult patients

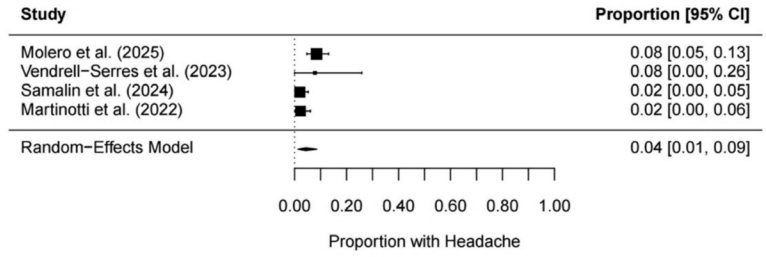
Up-to-Date; Lapa et al, 2026





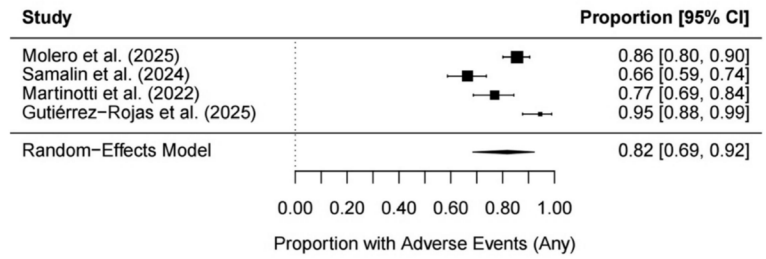


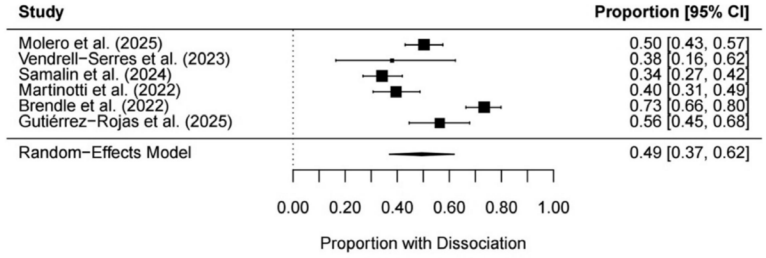


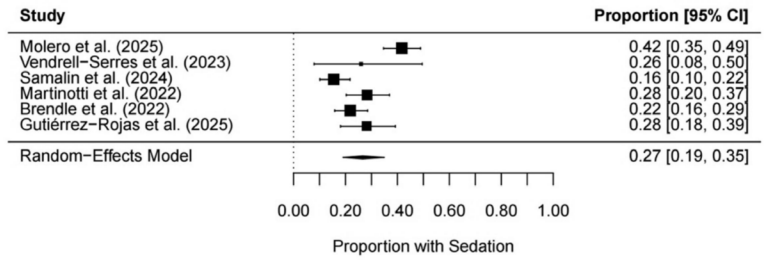


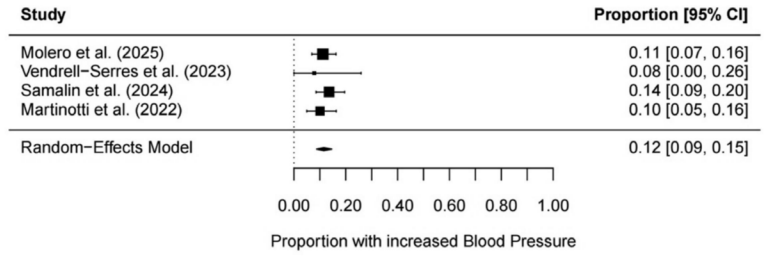
Esketamine Adverse Effects

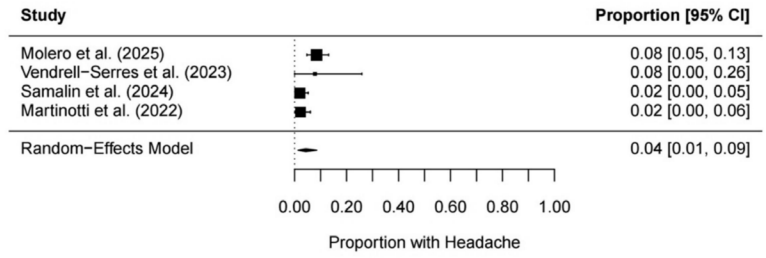
- **Nausea/vomiting**
- **Dissociative reaction/dizziness/headache**
- **Increases in systolic and/or diastolic BP**
  - C/I in patients with aneurysmal vascular disease, arteriovenous malformation, history of intracerebral hemorrhage









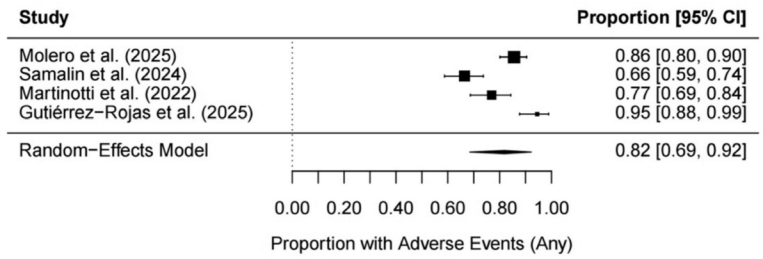


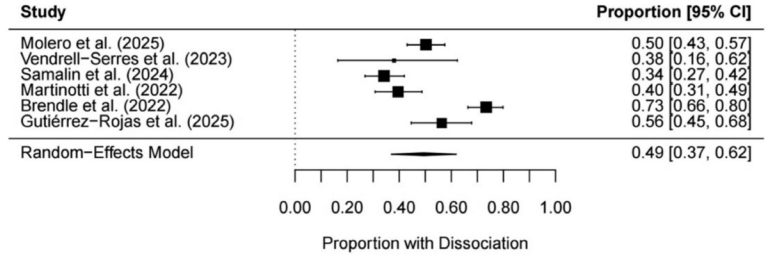
Up-to-Date; Lapa et al, 2026

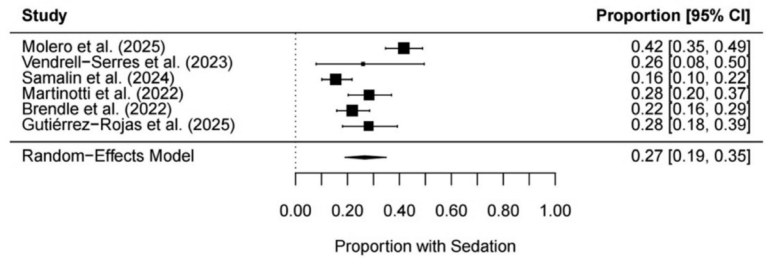
Esketamine Adverse Effects

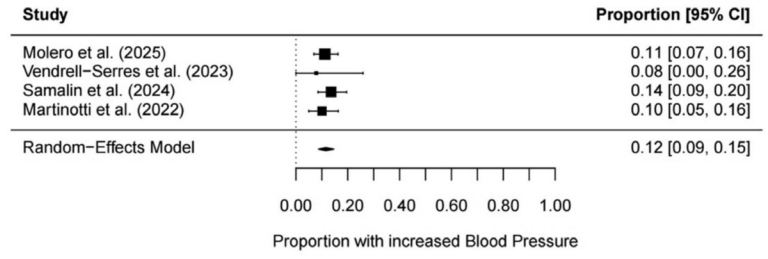
- **Pregnancy**
  - Crosses the placenta and passes through breastmilk
  - Medications that inhibit NMDA receptors and/or GABA receptors may affect brain development (animal studies)
  - Untreated and undertreated mental health conditions are associated with adverse pregnancy outcomes.
- Management should be made as part of a shared decision-making process
- Manufacturer recommends not becoming pregnant during esketamine therapy.

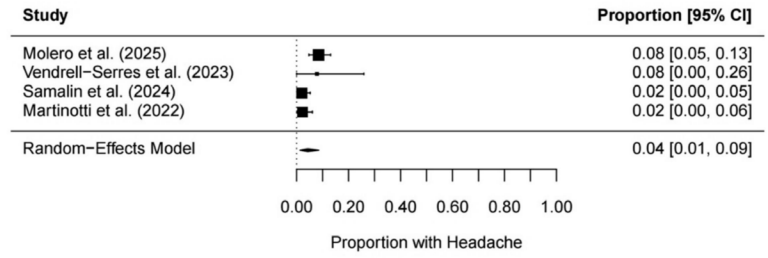
Up-to-Date; Lapa et al, 2026











Esketamine Adult Dosing

- Treatment resistant depression (intranasal)
  - Monotherapy or used with other antidepressants
  - **Induction:** 56 or 84 mg twice weekly. Re-evaluate for efficacy after 4 weeks
  - **Maintenance:**
    - Week 5: Using current dosing, decrease frequency to once weekly.
    - Week 9 and onward: Continue once weekly or decrease to every 2 weeks
- Major depressive disorder (unipolar), with suicidality (intranasal)
  - Use in conjunction with other antidepressant
  - Induction: 84 mg twice weekly; may reduce to 56 mg based on tolerability
  - Maintenance: Use beyond 4 weeks has not been evaluated

Up-to-Date

Key Points

1. **Historical context:** Discovery and initial use.
2. **Mechanism of action:** NMDA receptor antagonist and uOR agonist
3. **Clinical Uses and Indications:**
    1. Procedural sedation
    2. Pain management
    3. Treatment-resistant depression
4. **Side Effects, Contraindications, and Safety Considerations:**
    1. Dissociative anesthesia
    2. Amnesia
    3. Sympathomimetic effects:
    4. Respiratory depression at high doses when administered to quickly
    5. Emergence phenomenon

Case Studies

Case 1 - Presentation

The patient was a 52-year-old married Caucasian man with a 30-year history of generalized anxiety disorder, panic disorder, and depression. At his consultation for esketamine, he reported persistent fatigue, poor sleep, anhedonia, and a lack of interest in any activities, including household chores. Additionally, he experienced vivid nightmares related to his childhood emotional abuse. He also reported significant emotional distress stemming from constant worry about his life and future. He denied any suicidal ideation.

Abbas et al, 2025

Case 1 - Presentation

Before this consultation, his treatment regimen included **vilazodone** 40 mg, **bupropion** extended-release 300 mg, **mirtazapine** 15 mg, and L-**methylfolate** 15 mg, with no apparent symptomatic relief. He was also administered **gabapentin** 800 mg three times daily and **lamotrigine** 100 mg once daily; however, these were discontinued to facilitate **ECT** treatment. He underwent 10 ECT sessions over three weeks without improvement in depressive symptoms. He has also previously completed 56 sessions of repetitive **TMS**, which likewise produced no symptom improvement.

Abbas et al, 2025

Case 1 - Presentation

Previous pharmacological trials included **sertraline** 100 mg, **fluoxetine** 40 mg, **paroxetine** 40 mg, **escitalopram** 20 mg, extended-release **venlafaxine** 300 mg, **duloxetine** 60 mg, **brexpiprazole** 2 mg, and **aripiprazole** 10 mg; however, the patient exhibited no response to any of these psychotropic medications. He also underwent **acupuncture** and **neuro-linguistic programming** and reported a history of multiple inpatient psychiatric admissions.

Abbas et al, 2025

Case 1 – Esketamine trial

The patient exhibited minimal improvement over the first three esketamine treatments but reported **double vision** and **feeling "drunk"** during the first 5-7 minutes of administration. His **blood pressure also spiked**, with systolic and diastolic pressures increasing by 20 mmHg and 10 mmHg, respectively. He experienced noticeable improvement in the first two to three days after each treatment, but this effect diminished significantly before the next weekly session. After completing 17 treatments, he decided to discontinue further treatment due to side effects and lack of sustained improvement.

Abbas et al, 2025

Case 2 – Presentation

The patient was a 37-year-old Caucasian woman with a history of depression, anxiety, mitochondrial myopathy, scoliosis, and back pain owing to herniated discs. She was referred by her psychiatrist for evaluation and treatment of her TRD. Over the past two weeks, she reported feeling hopeless and helpless, crying multiple times a day. Although she denied current suicidal ideation, she expressed that if it were not for her children, she would probably want to die. She stated, "I would stay in my house 24 hours a day if I could," and also endorsed confusion, increased word-finding difficulty, and decreased energy.

Abbas et al, 2025

Case 2 – Presentation

Her symptoms had acutely worsened four years prior to presentation after the loss of her full-term baby, a trauma that caused significant guilt. At the time of presentation, she was administered extended-release **bupropion** 300 mg daily, **vortioxetine** 10 mg daily, **fluoxetine** 80 mg daily, **clomipramine** 75 mg daily, and **clonazepam** 2 mg twice daily, with no symptom relief.

Abbas et al, 2025

Case 2 – Presentation

She also described feeling as though she were "walking through quicksand" due to her lack of energy and psychomotor retardation. To address this, she was prescribed mixed **amphetamine salts** 30 mg twice daily and an additional 30 mg of extended-release mixed amphetamine salts twice daily. Finally, she was administered **zolpidem** 10 mg nightly to assist with sleep, which she reported was effective. She also failed a full course of **ECT**.

Abbas et al, 2025

Case 2 – Esketamine trial

The patient gradually responded to esketamine over the first eight treatments, reporting **increased concentration and energy**, and she was able to **complete household chores**. She became more involved in caring for her children and experienced **improvement in her interpersonal relationships**. By the completion of 12 treatments, she observed significant improvement overall with **no major side effects** reported. She opted to continue with maintenance esketamine treatment at a dose of 56 mg once weekly.

Abbas et al, 2025

Discussion

- Patient 1 had experience depressive symptoms since childhood, and had an extensive history of failed treatments. He also experience adverse effects (double vision, dizziness).
- Patient 2 also had a history of failed treatments, but her symptoms had worsened over the previous 4 years and were milder than Patient 1. She also reported no serious adverse effects

Conclusion: Esketamine has potential to treat TRD, but is not a miracle drug and carries significant adverse effects.

- NNT: 11

Abbas et al, 2025; Calder et al, 2024

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