KETAMINE IN PSYCHIATRIC SETTING

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September 28, 2024

DISCLOSURES

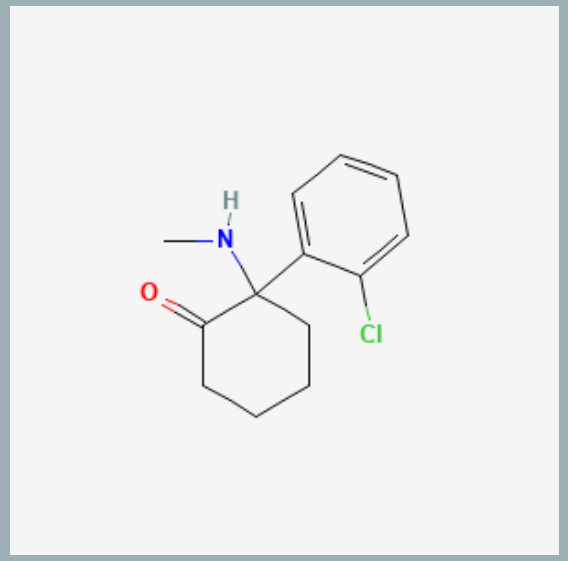
NO FINANCIAL DISCLOSURES

LEARNING OBJECTIVES

- Participants will gain knowledge about development of ketamine
- Participants will have a basic understanding of the proposed mechanisms of action of ketamine
- Participants will understand differences between intravenous and intranasal ketamine
- Participants will have a good understanding of who may be a candidate for ketamine and be able to explain the side effects to patients

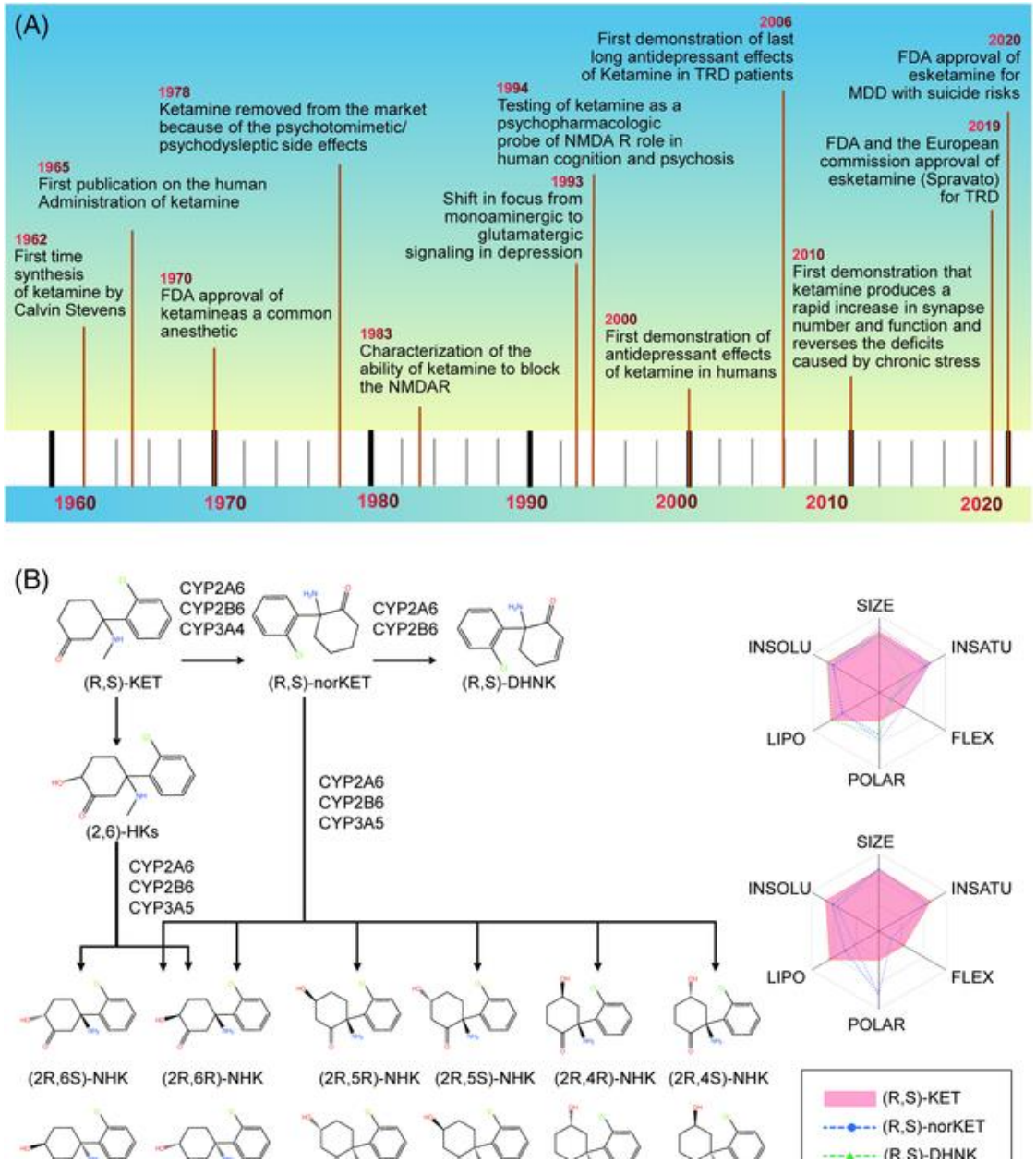
INTRODUCTION

Structure of ketamine



- Anesthetic with dissociative, amnesic, sedative and analgesic properties
- Used in multiple settings – ED, anesthesiology, pain and psychiatric clinics and in veterinary medicine
- Drug of abuse used in club setting
- Classified as Schedule III non-narcotic substance
- Comes in several formulations

HISTORY


(A)
1962
First time synthesis of ketamine by Calvin Stevens
1965
First publication on the human Administration of ketamine
1970
FDA approval of ketamineas a common anesthetic
1978
Ketamine removed from the market because of the psychotomimetic/ psychodysleptic side effects
1983
Characterization of the ability of ketamine to block the NMDAR
1993
Shift in focus from monoaminergic to glutamatergic signaling in depression
1994
Testing of ketamine as a psychopharmacologic probe of NMDA R role in human cognition and psychosis
2000
First demonstration of antidepressant effects of ketamine in humans
2006
First demonstration of last long antidepressant effects of Ketamine in TRD patients
2010
First demonstration that ketamine produces a rapid increase in synapse number and function and reverses the deficits caused by chronic stress
2019
FDA and the European commission approval of esketamine (Spravato) for TRD
2020
FDA approval of esketamine for MDD with suicide risks
1960
1970
1980
1990
2000
2010
2020
(B)
CYP2A6
CYP2B6
CYP3A4
(R,S)-KET
CYP2A6
CYP2B6
(R,S)-norKET
(R,S)-DHNK
(2,6)-HKs
CYP2A6
CYP2B6
CYP3A5
CYP2A6
CYP2B6
CYP3A5
(2R,6S)-NHK
(2R,6R)-NHK
(2R,5R)-NHK
(2R,5S)-NHK
(2R,4R)-NHK
(2R,4S)-NHK
SIZE
INSATU
FLEX
POLAR
LIPO
INSOLU
SIZE
INSATU
FLEX
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LIPO
INSOLU
(R,S)-KET
(R,S)-norKET
(R,S)-DHNK

HISTORY CONTINUED

1950's

investigations for a new anesthetic at Parke-Davis and Co. Labs

- 1956 Dr. Maddox discovers PCP
- 1957 PCP testing on animals
- 1958 PCP human trials

1962

Dr. Calvin Stevens develops ketamine

- Analogue of PCP
- Ketone + amine = Ketamine

1964

first trials in humans

- Volunteer prisoners at Jackson Prison were given ketamine

1965

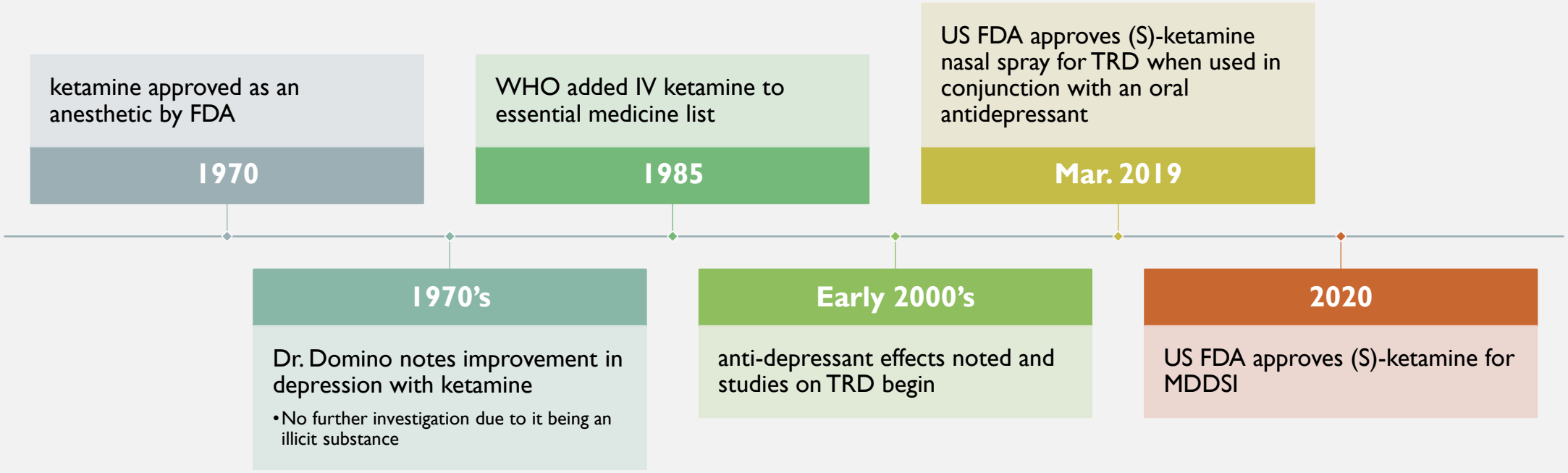
first clinical trial data published

- Disconnected feeling like floating = dissociative anesthetic

PCP LIMITATIONS

- Effective anesthetic and analgesic for procedures without decreased risk of cardiovascular and respiratory depression when compared to many other anesthetics
- Short onset
  - Inhalation: 2-5 mins
  - PO ingestion: 30-60 mins
- Long, variable duration of action
- No longer clinically used due to post-surgical delirium/excitation, "sensory deprivation" and prolonged hallucinations
- Used in studies to precipitate schizophrenia like state to better understand the illness
- Schedule II Drug with high rates of abuse

HISTORY CONTINUED



Is Ketamine a psychedelic?

Psychedelic defined by the Cambridge dictionary is "(of a drug) causing effects on the mind, such as feelings of deep understanding or unusually strong experiences of color, sound, taste and touch."

IS KETAMINE A PSYCHEDELIC ?

Psychedelics

Dissociative agents

Empathogens

Serotonergic (5HT-2A) agonists

- True psychedelics that work on serotonin as primary mechanism

- DMT – dimethyltryptamine
- Psilocybin
- Peyote/Mescaline
- LSD – lysergic acid diethylamide

NMDA antagonists

- Dissociative agents that do not directly target serotonin and work through glutamate signaling and NMDA receptors

- PCP (phencyclidine)
- Ketamine
- DXM (dextromethorphan)

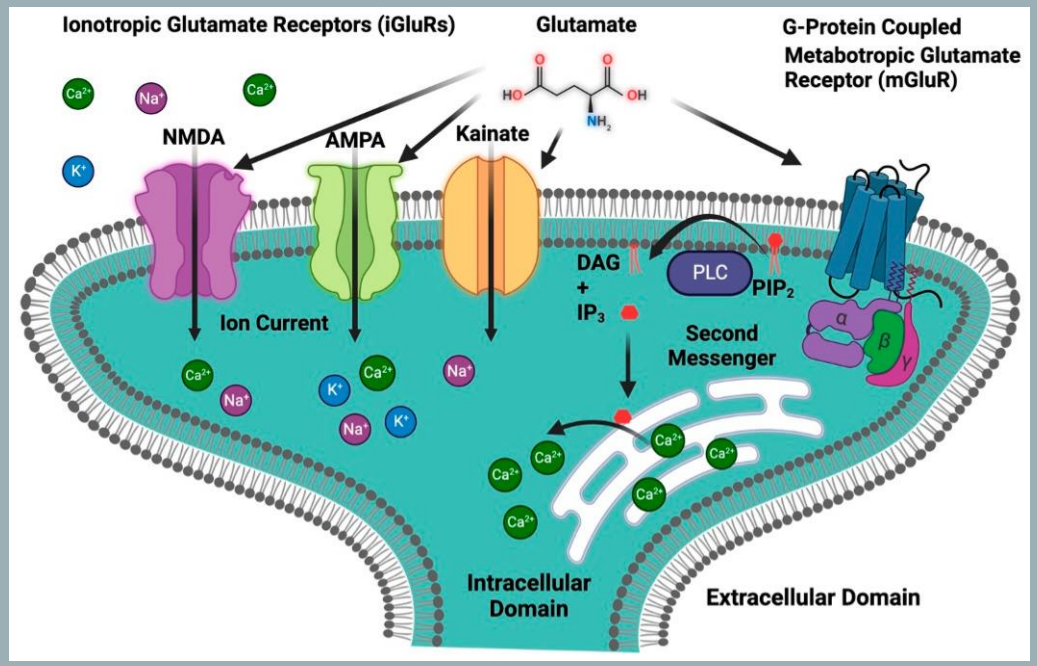
Serotonin and dopamine reuptake inhibitors and releasers

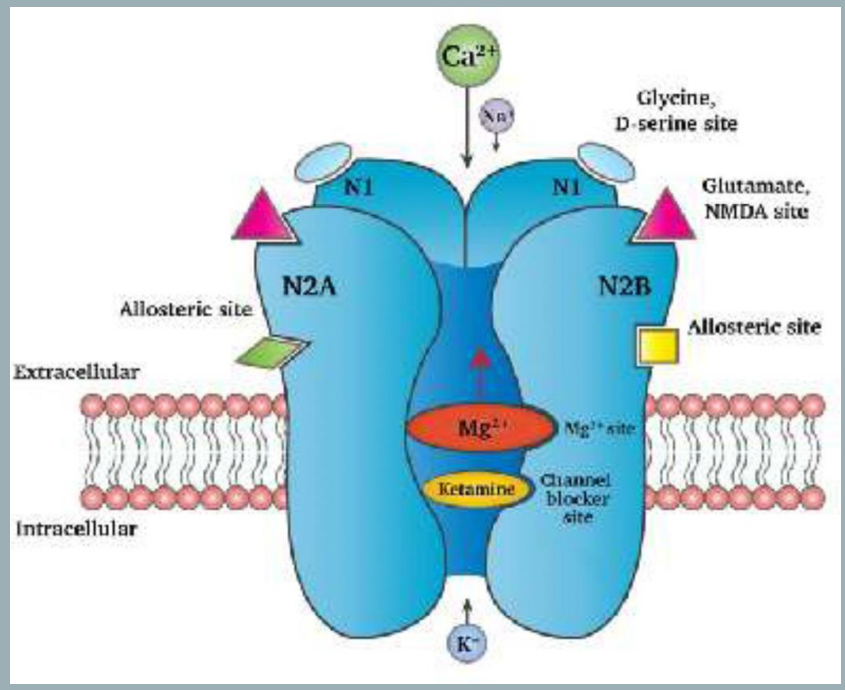
- Empathogens that increase empathy and bonding feelings

- MDMA/ecstasy - methylenedioxymethamphetamine

MECHANISM OF ACTION

NMDA receptor antagonist





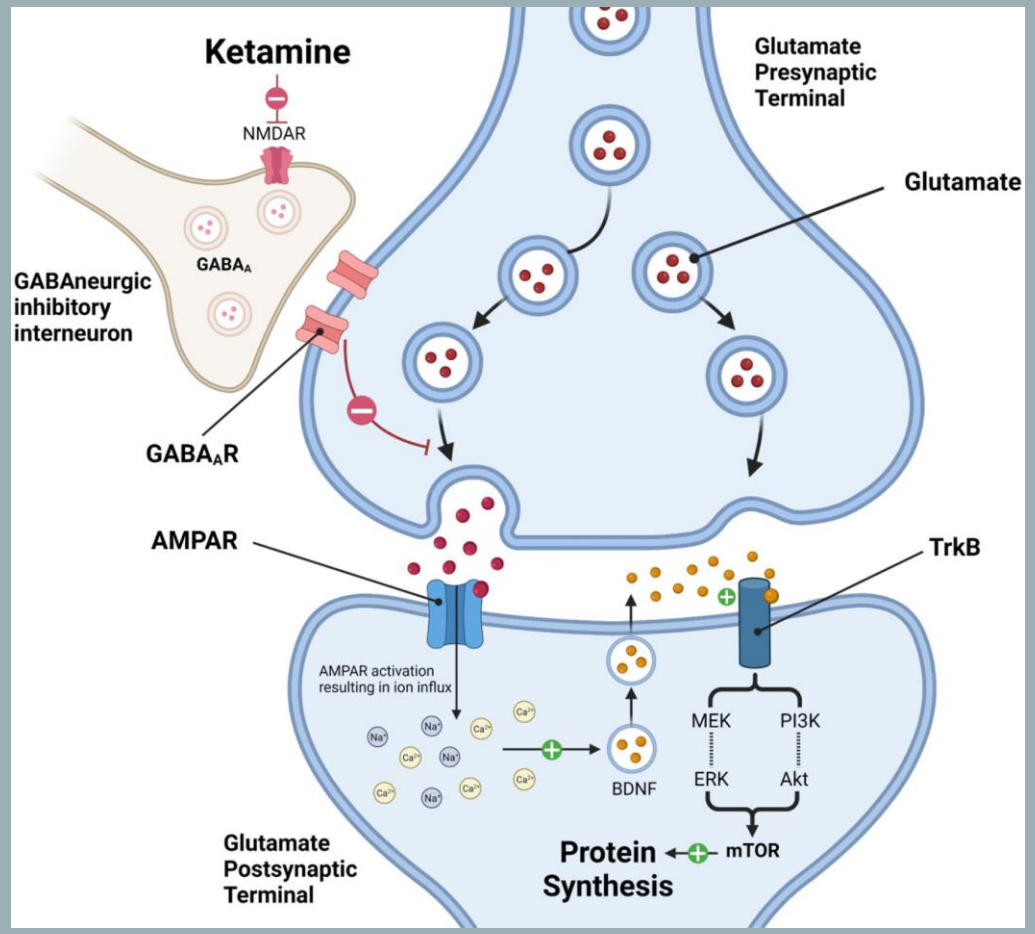
MECHANISM OF ACTION

1) Ketamine blocks presynaptic NMDA receptors on GABA containing neurons

2) GABA receptors are not activated

3) Release of glutamate is not blocked

4) AMPA receptors are able to be activated by glutamate and protein synthesis can occur through cascade



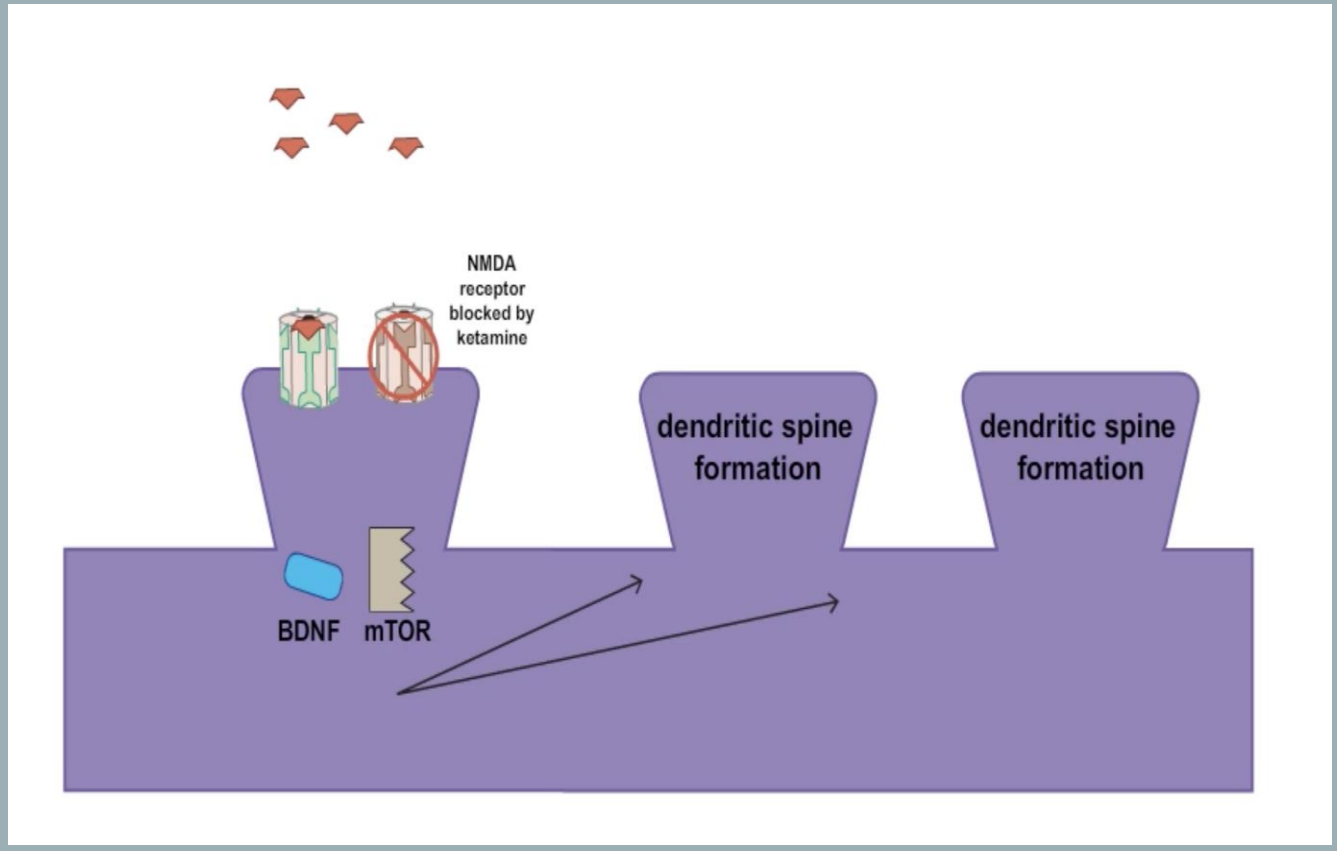
MECHANISM OF ACTION

- NMDA receptor "inactive" by ketamine

and more glutamate to be directed to AMPA

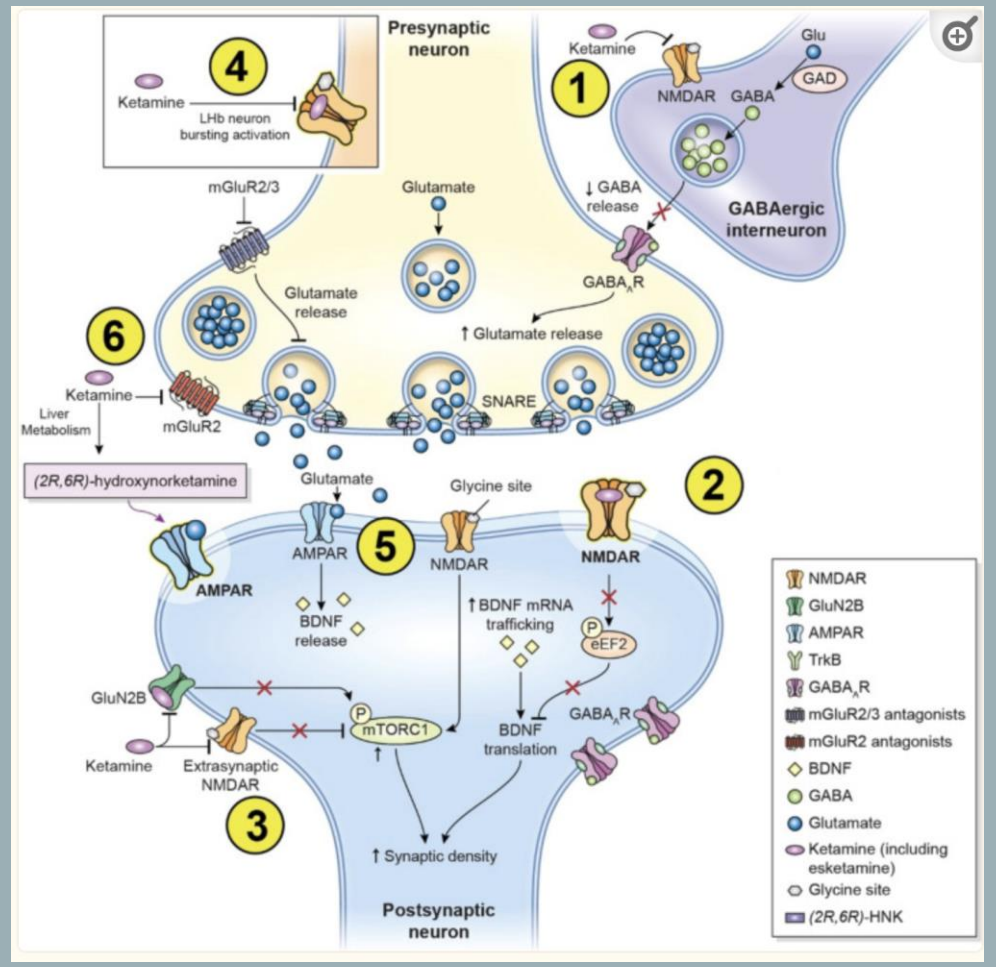
- Ketamine converted to norketamine

- Norketamine direct agonist at AMPA receptor

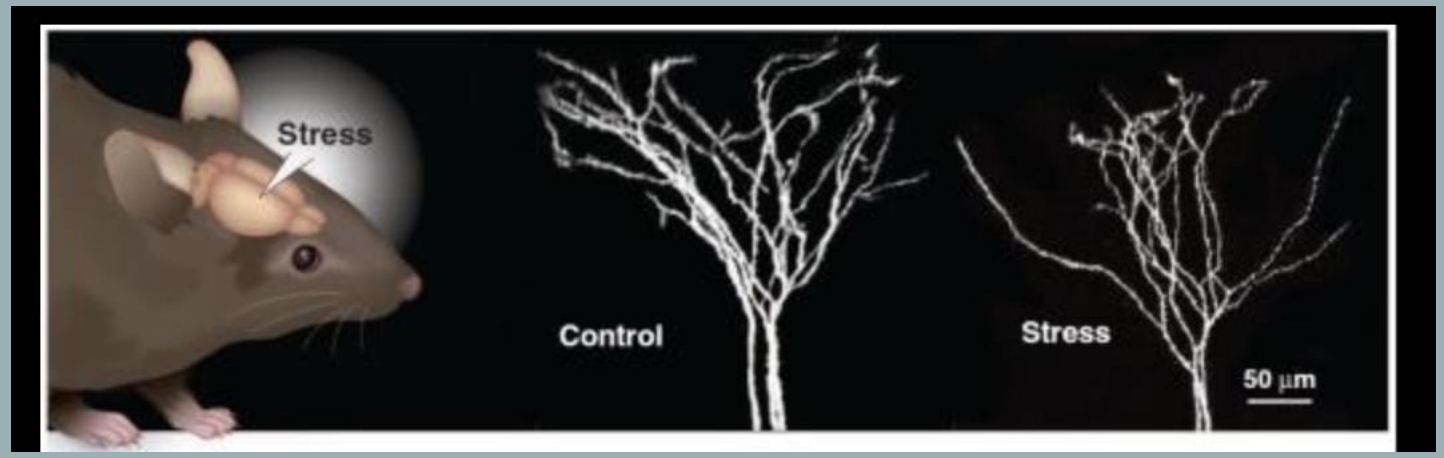


MECHANISM OF ACTION

- Glutamate binding at AMPA receptor
- Cascade of neurotrophic growth factor release
  - BDNF
  - VEGF
  - mTORC1
- Increase in dendritic spine formation formation and synapse proteins leading to rapid improvement in depression

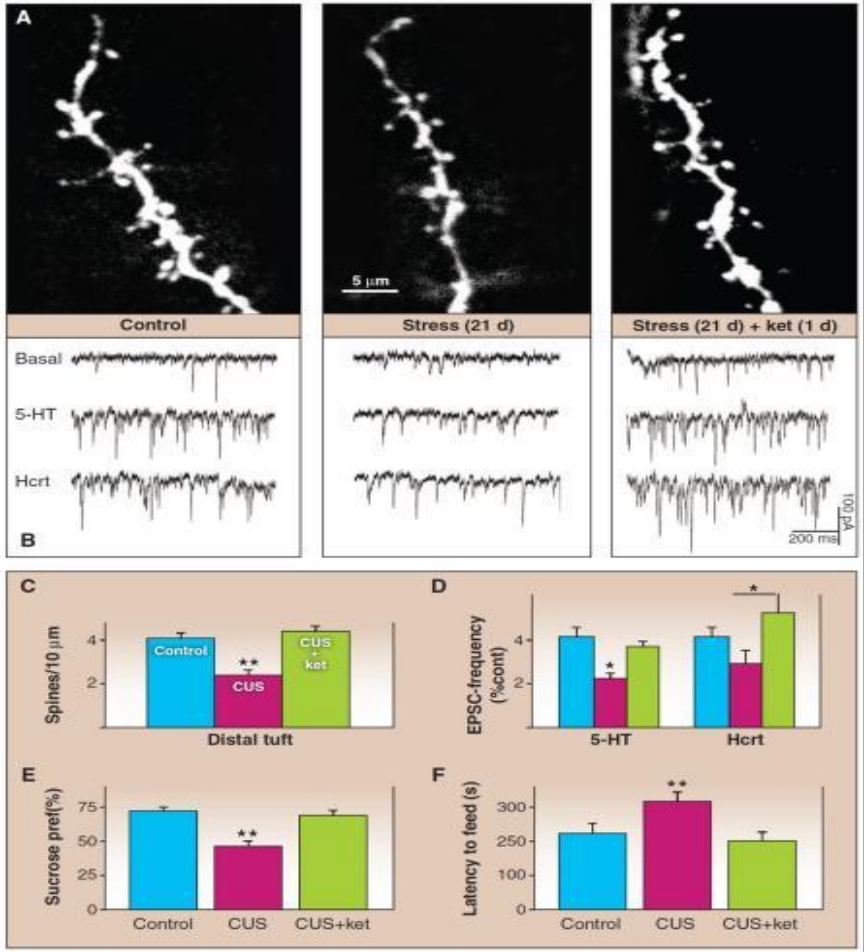


MECHANISM OF ACTION



Stressed mouse models have loss of dendritic spines and synapses

MECHANISM OF ACTION



- Single dose of ketamine in mouse models who underwent 21 days of chronic stress appeared to have rapid regrowth of spines and synapses in 24 hrs.
- Thought that this regrowth is what contributes to the rapid improvement of depressive symptoms when ketamine is given

PHARMACOKINETICS

Bioavailability

- IV 100%
- IM 93%
- PO 16-29%
- Intranasal 45-50%
- Intrarectal 25-30%

Time to reach peak plasma concentration

- IV approximately 1 minute
- IM 5 to 30 minutes
- PO 20-30 minutes
- Intranasal 20-30 minutes

PHARMACOKINETICS

- Metabolism
  - CYP3A4, CYP2B6 and CYP2C9
  - 80% metabolized into norketamine
- Distribution
  - Lipid soluble and rapidly crosses blood brain barrier
  - 10-30% bound to plasma proteins
- Half-life
  - 1-3 hrs
- Elimination
  - Excreted through bile and urine

FIRST KETAMINE STUDY FOR MDD

Antidepressant effects of ketamine in depressed patients

- In 2000 first double-blind, placebo-controlled, crossover human study with ketamine for treatment of depression
- N = 7
- IV Ketamine 0.5mg/kg vs. saline solution
- One week later crossover for second infusion
- Significant improvements in depressive symptoms after 72 hrs. of ketamine infusion but no significant improvements with saline based on mean changes in HAMD rating scale scores

BRIEF REPORTS | VOLUME 47, ISSUE 4, P351-354, FEBRUARY 15, 2000 Download Full Issue

Antidepressant effects of ketamine in depressed patients

Robert M Berman • Angela Cappiello • Amit Anand • ... George R Heninger • Dennis S Charney • John H Krystal • Show all authors

DOI: https://doi.org/10.1016/S0006-3223(99)00230-9

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Abstract
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Abstract

Background: A growing body of preclinical research suggests that brain glutamate systems may be involved in the pathophysiology of major depression and the mechanism of action of antidepressants. This is the first placebo-controlled, double-blinded trial to assess the treatment effects of a single dose of an *N*-methyl-D-aspartate (NMDA) receptor antagonist in patients with depression.

Methods: Seven subjects with major depression completed 2 test days that involved intravenous treatment with ketamine hydrochloride (.5 mg/kg) or saline solutions under randomized, double-blind conditions.

Results: Subjects with depression evidenced significant improvement in depressive symptoms within 72 hours after ketamine but not placebo infusion (i.e., mean 25-item Hamilton Depression Rating Scale scores decreased by 14 ± SD 10 points vs. 0 ± 12 points, respectively during active and sham treatment).

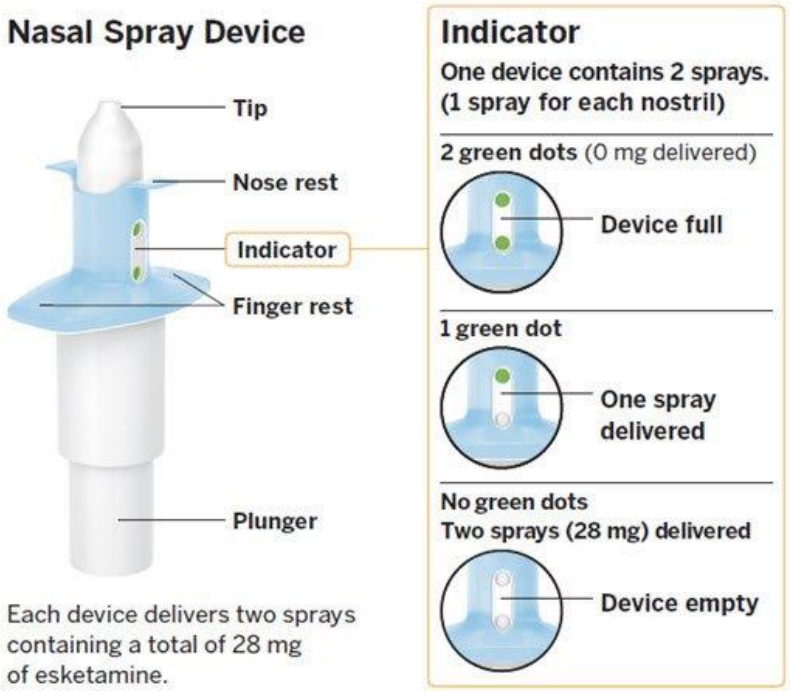
Conclusions: These results suggest a potential role for NMDA receptor-modulating drugs in the treatment of depression.

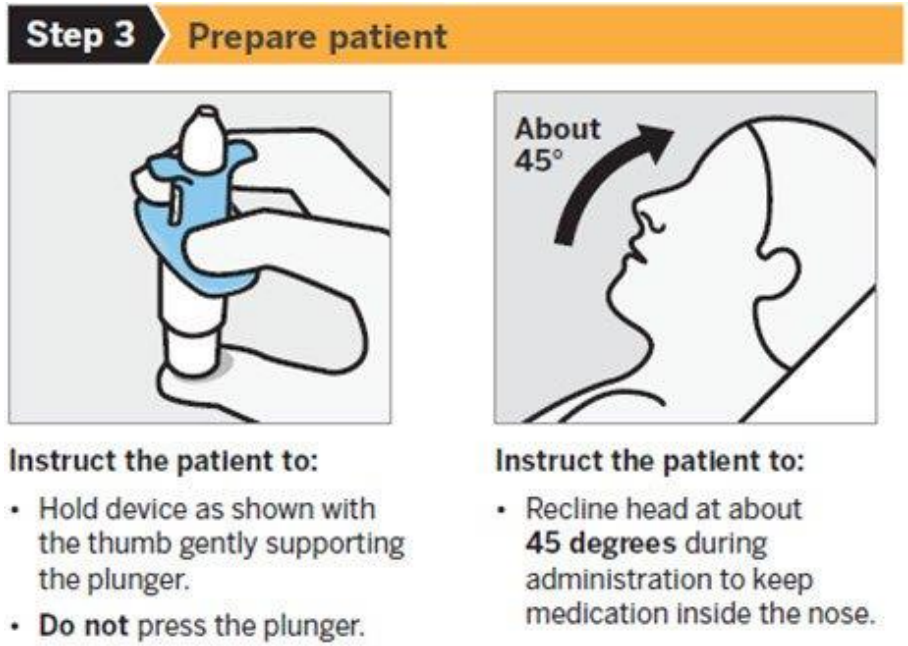
WHAT TO EXPECT WITH ESKETAMINE TREATMENT

- Assess if patient is a good candidate
- Discussion of risks vs. benefits and alternatives
- Restrictions
  - No eating > 2hrs. Prior
  - No nasal sprays >1 hr. prior
  - No liquid intake > 30 min. prior
- Meet with psychiatrist prior to each treatment
  - PHQ-9
  - HAM-D
  - MADRS

WHAT TO EXPECT WITH ESKETAMINE TREATMENT

- Therapeutic environment in group setting
  - Noise cancelling headphones, ear plugs, trash can, emesis bags, tissues, blankets, etc.
- Vitals taken prior to first dose
  - BP less than 150/110

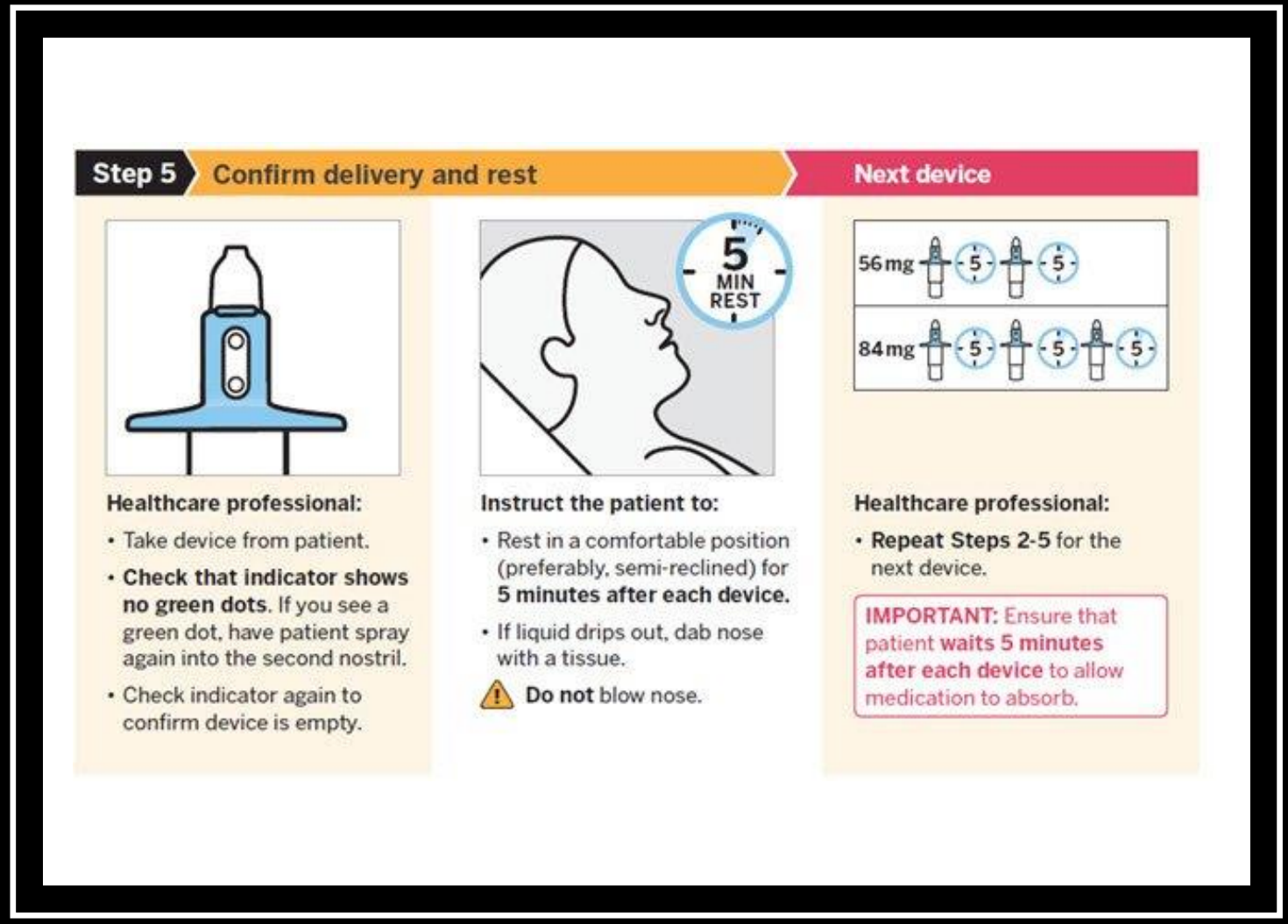




WHAT TO EXPECT WITH ESKETAMINE TREATMENT

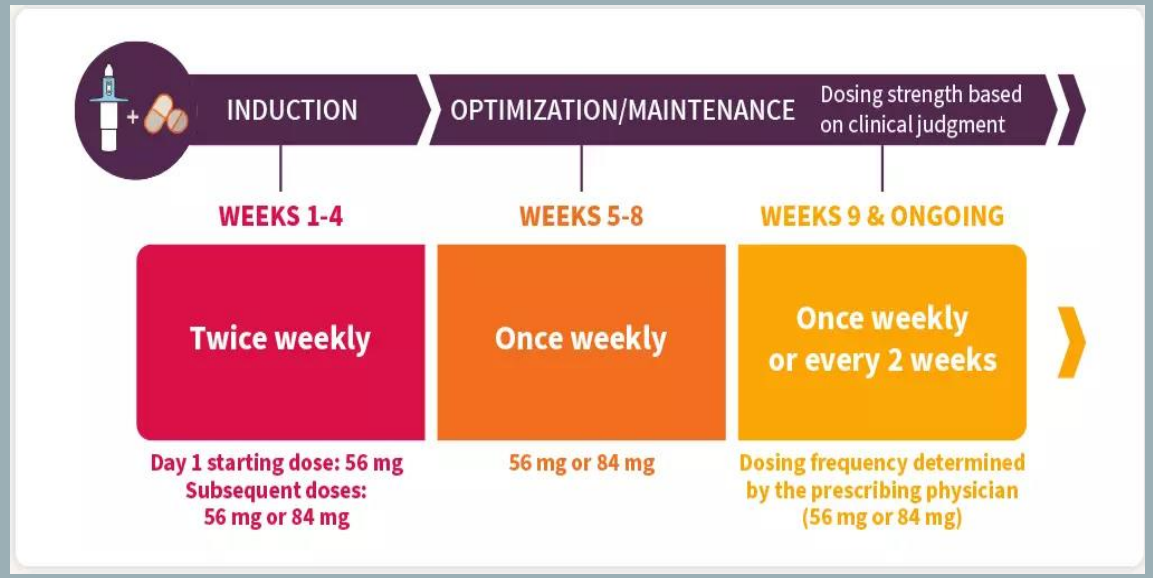
WHAT TO EXPECT WITH ESKETAMINE TREATMENT

- Wait 5 minutes between each dose
  - 56mg = 2 devices
  - 84mg = 3 devices
- Vitals taken 40 minutes after 1st dose administered
  - BP I<180/115
  - Monitor for side effects

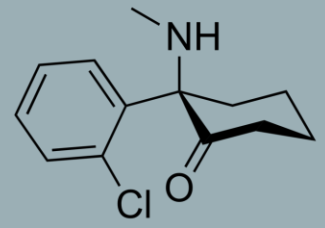


WHAT TO EXPECT WITH ESKETAMINE TREATMENT

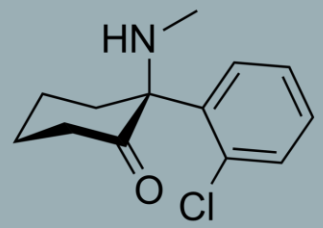
- Assess 120 minutes after 1st dose given
  - Safety concerns (SI, HI)
  - Side effects
  - BP <160/100
- Titrate up to 84mg as tolerated
- Follow tapering schedule
- Assess with scales and for side effects prior to each treatment



ENANTIOMERS



(*R*)-(+)



(*S*)-(–)

- Racemic mixture of (R,S)-ketamine is used IV for off-label treatment of numerous psychiatric conditions
  - OCD, PTSD, TRD, bipolar
- (S)-ketamine enantiomer utilized for intranasal Spravato
- (R)-ketamine enantiomer is being studied as a possible agent

STUDY ESTABLISHING (S)-KETAMINE IS NOT INFERIOR TO (R,S)-KETAMINE

- *Efficacy and safety of adjunctive therapy using esketamine or racemic ketamine for adult treatment-resistant depression: A randomized, double-blind, non-inferiority study*
- N=63
- 29 received infusion of 0.5mg/kg of (R,S)-ketamine
- 34 received infusion of 0.25mg/kg of (S)-ketamine
- MADRS given at 24 hrs post-infusion
  - (R,S) scores improved from 33 to 16.2
  - (S) scores improved from 33 to 17.5
- Lasting antidepressant effects at day 7 were more potent for (R,S)-ketamine than (S)-ketamine but not statistically significant

PCN-101 (R)-KETAMINE

- Perception Neuroscience Phase 2a double-blind, randomized, placebo-controlled study
- Placebo infusion, 30mg IV (R)-ketamine, 60mg IV (R)-ketamine
- Change in MADRS scores 24 hrs after treatment were not statically significant when compared to placebo
- Good tolerability

	Ketamine	Spravato
Bioavailability	100%	45-50%
Administration	I.V.	Intranasal, self-administered
Dosage	0.5mg/kg Variable	Three dosing options: 28, 56, 84mg
Coverage	Not covered by insurance	May be covered by insurance
Conditions treated	Off-label treatement of MDD, anxiety, SI, PTSD, OCD, pain, etc.	TRD MDD with SI

EFFICACY OF INTRANAVENOUS VS. INTRANASAL KETAMINE

2022: *Does route of administration affect antidepressant efficacy of ketamine? A meta-analysis of double-blind randomized controlled trials comparing intravenous and intranasal administration*

- 11 studies (4 intranasal and 7 IV)
  - 586 received esketamine and 479 received placebo
  - 145 received ketamine and 130 received placebo
- Differences in efficacy assessed using z-test of the mean log odds ratios
  - Response rate in IV trials at 24 hrs.
    - 42% ketamine and 4.6% placebo
    - OR=9.4, 95% CI 3.9-22.8
  - Response rate in IN trials at 24 hrs.
    - 25% esketamine and 16.5% placebo
    - OR=3.3, 95% CI 1.2-9.0
  - Difference in OR was not statistically significant p=0.13

COST OF I.V. KETAMINE VS. INTRANASAL

2022: *Cost-effectiveness of esketamine nasal spray compared to intravenous ketamine for patients with treatment-resistant depression in the US utilizing clinical trial efficacy and real-world effectiveness estimates*

- Cost of ketamine infusion can vary from $295 to $1000 for per infusion
  - Paid out of pocket by patient
- Cost of intranasal ketamine varies from $590 to $858 per treatment
  - Insurance may cover a certain percentage
  - Copay assistance programs
- Cost data obtained from clinical trials and private psychiatric clinic that offers both forms of treatment
- Cost of esketamine was $176,320 higher than cost of ketamine
- Esketamine more cost effective for patients but more expensive for healthcare system
- IV Ketamine more cost effective for healthcare system

FDA warns patients and health care providers about potential risks associated with compounded ketamine products, including oral formulations, for the treatment of psychiatric disorders

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October 10, 2023

What Patients and Health Care Providers Should Know

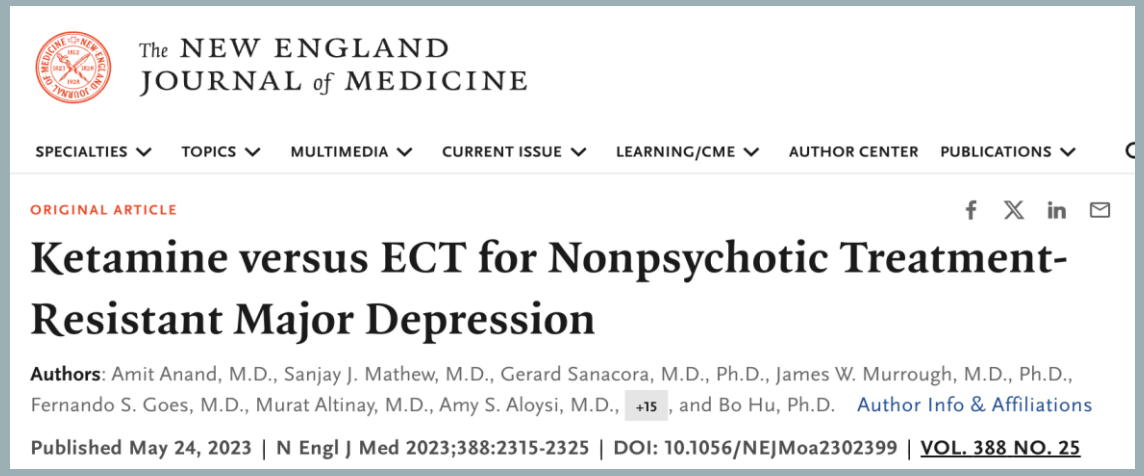
Conten
10/10/2

Positives

- Accessibility
- Comfortable environment
- Well tolerated
- Affordability
- Less reported side effects

Negatives

- Abuse potential
- Requires a peer accompanying
- Longer to take effect
- Safety
- Not FDA regulated



The NEW ENGLAND JOURNAL of MEDICINE

SPECIALTIES TOPICS MULTIMEDIA CURRENT ISSUE LEARNING/CME AUTHOR CENTER PUBLICATIONS

ORIGINAL ARTICLE

Ketamine versus ECT for Nonpsychotic Treatment-Resistant Major Depression

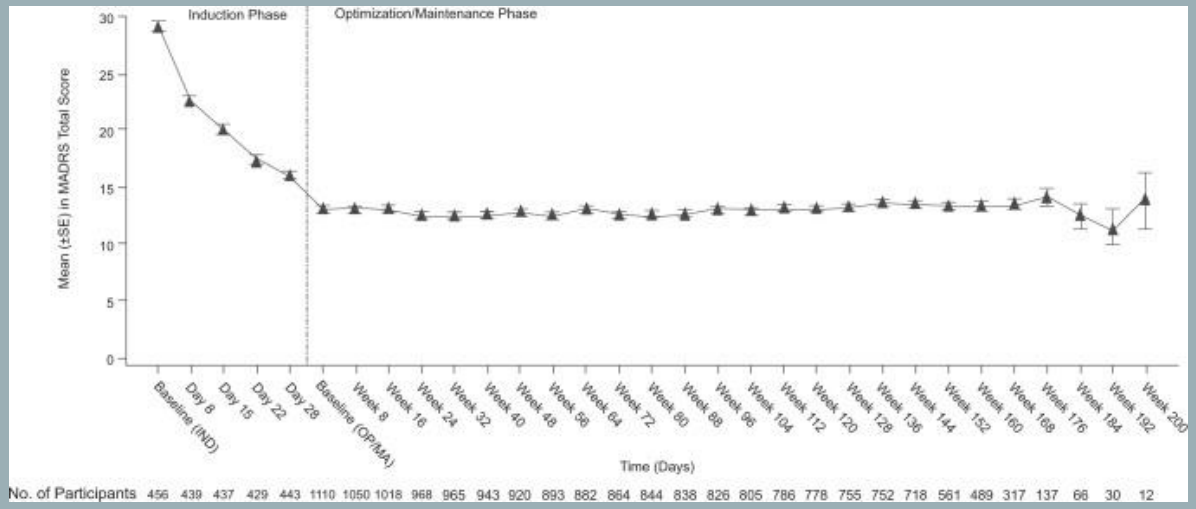
Authors: Amit Anand, M.D., Sanjay J. Mathew, M.D., Gerard Sanacora, M.D., Ph.D., James W. Murrough, M.D., Ph.D., Fernando S. Goes, M.D., Murat Altinay, M.D., Amy S. Aloysi, M.D., +15, and Bo Hu, Ph.D. Author Info & Affiliations

Published May 24, 2023 | N Engl J Med 2023;388:2315-2325 | DOI: 10.1056/NEJMoa2302399 | VOL. 388 NO. 25

- Open label, randomized trial
- N=403 with 38 withdrawing from study
- 195 patients received ketamine 0.5mg/kg infused over 40 minutes 2x weekly
- 170 patients received ECT 3x's weekly
- Primary outcome was treatment response on QIDS
- Ketamine group 55.4% had a response
- ECT group 41.2% had a response
- Established noninferiority of ketamine to ECT
  - ($p<0.001$) 95% CI 3.9 to 24.2

Long-term safety and maintenance of response with esketamine nasal spray in participants with treatment resistant depression: interim results of Sustain-3 study

- Phase 3, open-label, long-term study for responders
- Participants entered in both the induction phase (twice weekly dosing) or directly into optimization and/or maintenance phase (individualized dosing schedule) and were continued on daily antidepressant
- 1148 participants
- Mean duration of treatment was 31.5 months with longest being 56 months
- MADRS total score decreased during induction phase and continued through optimization/maintenance phase
- Safety profile remained similar



APPROPRIATE CANDIDATES

- FDA approval
  - Treatment resistant depression in adults who are also on an oral antidepressant
    - Inadequate response to 2 or more antidepressants trials of adequate duration and dose
  - Major depressive disorder with acute suicidal ideation or behavior
- Insurance coverage
  - Different insurance companies vary in criteria
- Logistics
  - Ability to come twice weekly to treatment location
  - Ability to have a driver home from treatments

EXCLUSION CRITERIA

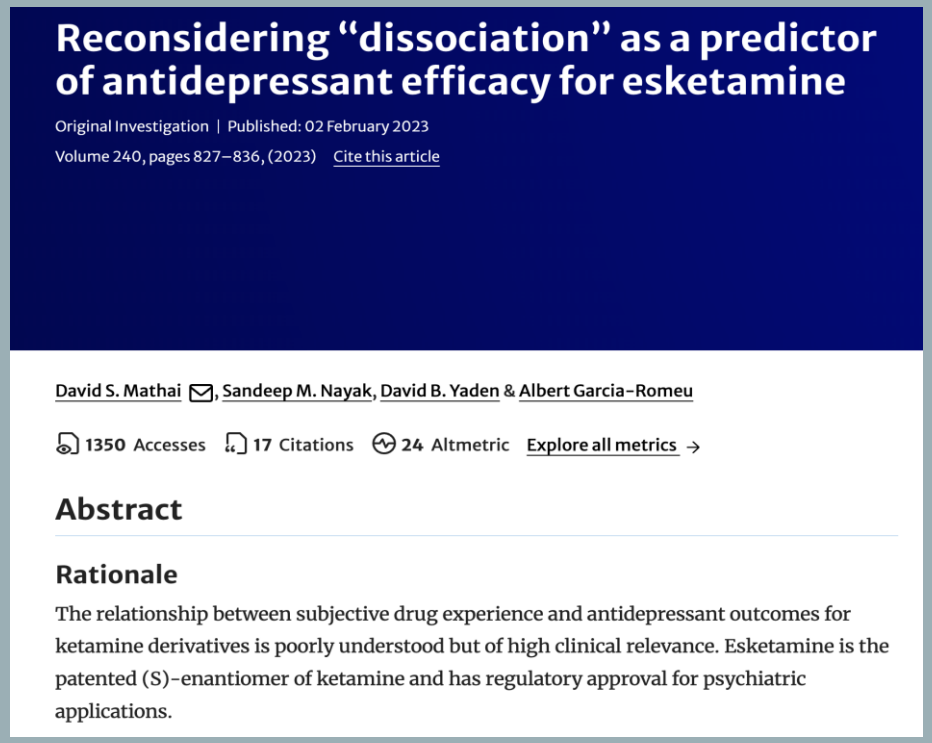
- Aneurysmal vascular disease
  - Thoracic or abdominal aorta aneurysm
  - Intracranial or peripheral arterial vessel disease
- Arteriovenous malformation
- History of intracerebral hemorrhage
- Hypersensitivity/allergy to esketamine or ketamine

SIDE EFFECT PROFILE

- Equal to or > 20% - Vertigo, nausea, dizziness, headache, sedation, dissociation
- 15-19% - dysgeusia, hypoesthesia
- 10-15% - increase in blood pressure, lethargy, anxiety
- 5-10% - diarrhea, dry mouth, vomiting, feeling drunk, insomnia, nasal irritation, throat irritation
- Less than 5% - tachycardia, constipation, feeling abnormal, dysarthria, mental impairment, tremor, euphoric mood, pollakiuria, oropharyngeal pain, hyperhidrosis

MANAGEMENT OF SIDE EFFECTS

- Most side effects are short-term, improve with subsequent treatments and dose dependent
- Appropriate screening of patients
- Educating patients beforehand
- Provide supportive environment with decreased stimulation
- Nausea and/or vomiting
  - Zofran, Compazine, scopolamine patch
- Elevated blood pressure
  - Clonidine, propranolol
- Anxiety
  - Re-assurance
  - Benzodiazepine



Reconsidering "dissociation" as a predictor of antidepressant efficacy for esketamine

Original Investigation | Published: 02 February 2023
Volume 240, pages 827–836, (2023) Cite this article

David S. Mathai, Sandeep M. Nayak, David B. Yaden & Albert Garcia-Romeu

Abstract

Rationale

The relationship between subjective drug experience and antidepressant outcomes for ketamine derivatives is poorly understood but of high clinical relevance. Esketamine is the patented (S)-enantiomer of ketamine and has regulatory approval for psychiatric applications.

Is the side effect of dissociation therapeutic and necessary?

- Post hoc analysis using 4 week induction phase data from TRANSFORM-1 and TRANSFORM-2 data using CADSS and MADRS
  - Linear mixed model did not demonstrate clinical significance for association between dissociation and antidepressant benefits
- Proposed that dissociating may be therapeutic for PTSD
- More studies need to be conducted

INTERACTIONS

- Sympathomimetic medications can cause increased blood pressure
  - Stimulants
  - MAO inhibitors
- CNS depressants can increase sedation, cardiorespiratory depression and can be fatal
  - Opioids
  - Benzodiazepines
  - Alcohol
- Theophylline or aminophylline could decrease seizure threshold
- Lamotrigine
  - Could decrease effects of ketamine
- Naltrexone

FUTURE OF KETAMINE

- Further investigation of (R)-ketamine
- Further understanding of mechanism of ketamine
- Ketamine use in anxiety, OCD, PTSD, addiction and autism
- Ways to sustain antidepressant effects of ketamine
- Decrease abuse potential

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