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# Ketamine and Esketamine for Major Depression



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# Disclosures

## Cristina Cusin 2017-2024:

- **Speaking/CME/Consulting:** Perception, Compass, Clexio, Boehringer
- **Research Grants:** Janssen, Livanova, ATAI
- **Equity:** None
- **Royalty/patent:** PCT/US15/56192; 070919.00032 Acylliccucurbit[N]uril type molecular containers to treat intoxication and substance abuse
  - Springer (book on TRD)

# Why a talk on ketamine?



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- Does a talk on ketamine belong to this conference?

It depends...

- Is ketamine a psychedelic drug?
- It does not share mechanisms of action with other psychedelics
- It may share experience, results in psychiatric disorders
- 'gateway drug'? Would psychedelics have REMS?





## \*What does it mean “off label”?

- Ketamine has an indication, or “label”, for the treatment of pain, for rapid induction of anesthesia.
- Its patent expired in the ‘70s
- Any manufacturer can produce ketamine generic
- A company would not invest millions in adding a label for depression if they cannot secure a patent and a revenue

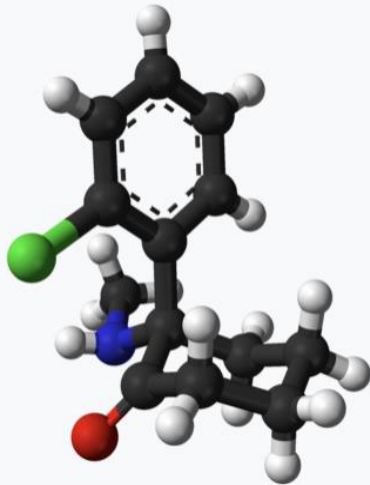
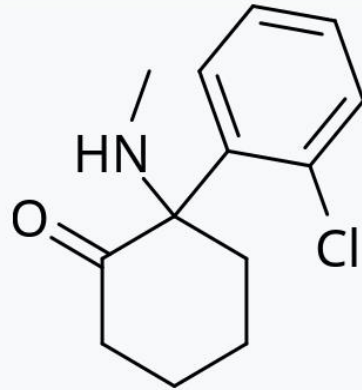
# What is S-ketamine?



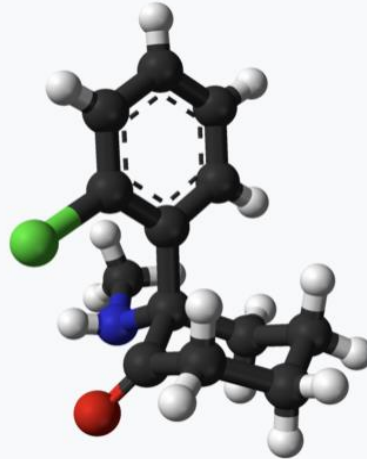
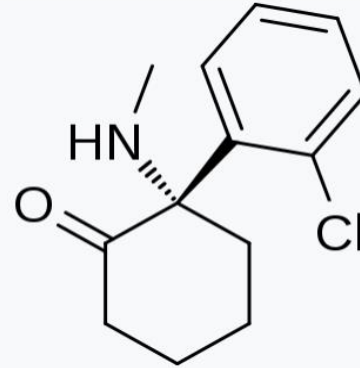
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**Ketamine**



**Esketamine**



50% S-ketamine + 50% R-ketamine= **ketamine**



S- ketamine  
(Spravato® by Janssen)  
FDA approved for TRD

# -CAVEAT-



- **Ketamine** has an indication as **anesthetic and analgesic**, for rapid intubation, in veterinary medicine; approved for induction and maintenance of general anesthesia
- Serendipitous discovery of antidepressant effect in early 2000s – **that was 20 years ago!!!**
- Ketamine is **NOT FDA-approved for the treatment of any psychiatric disorder** = “OFF LABEL”
- **S-ketamine** is FDA-approved :
  - 2019 “in conjunction with an oral antidepressant, for **the treatment of depression in adults** who have tried other antidepressant medicines but have not benefited from them (treatment-resistant)”
  - 2020 “to treat Depressive Symptoms in **adults** with MDD with Acute Suicidal Ideation or Behavior” however in the label “the effectiveness of esketamine in preventing suicide or in reducing suicidal ideation or behavior has not been demonstrated”

**\*Not approved for BP depression**

# MGH IV Ketamine Clinic (opened in Oct 2018)



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- >10000 infusions
- Self-pay until October 2020, only 2 insurers since then agreed to cover IV ketamine
- MDD/BP depression, multiple comorbidities (62%)
- Generally healthy, or well controlled medical issues, highly educated, current episode duration  $7.1 \pm 10.5$  ys
- Failed >4 antidepressants, 35% failed ECT, 28% failed TMS
- Referred by primary provider, in treatment
  - No moderate/severe SUD current, no hx of psychosis
- Flexible ketamine dose (based on tolerability, efficacy)
- insurance coverage for Esketamine (increasing)

# Ketamine side effects



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- Most of the adverse effects peak within 40 minutes and cease within 40 minutes post-infusion
- **Nausea** (about 35% pre-medicated with ondansetron), vomiting may occur
- perceptual disturbances, dissociative and psychotomimetic effects, **anxiety**, dysphoria ->20-30% require IV/PO lorazepam
- Moderate headache (acetaminophen 2-3%).
- Brief hypertensive episodes (labetalol), ↑male, ↑>55, ↑CV hx
- 1 asthma attack in pt with known asthma and prior allergic reaction to anesthetics – used her own inhaler
- 1 suspected seizure in pt with >30 uneventful infusions





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# Working at MGH

## A reality check



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- TRD= On multiple meds- (mood stabilizers, atypical antipsychotics, benzodiazepines)
- NEVER seen in consult a TRD pt on monotherapy
- Failed 8-15 previous medication trials, 40% had failed ECT, TMS
- Current meds provide a marginal improvement (20-25% at best)
- No way we can safely discontinue most meds
- Patients are extremely ill, high likelihood of worsening, needing hospitalization/ED, missed visits, drop out, etc.
- Also losing insurance, escort, \$\$ strain

# What are our outcomes?



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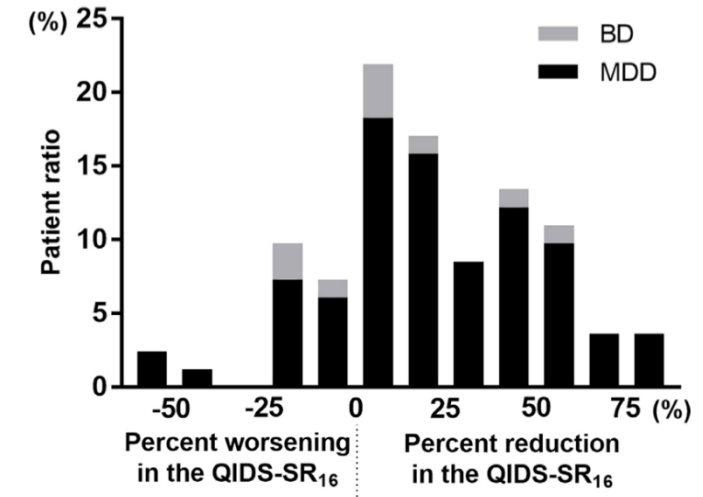
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- 350 individual patients with QIDS score at every visit
- 83% completed 6 infusions
- 78% improved score between infusion 1-6
- drop out –tolerability, insufficient improvement and **costs (self-pay)**
- **15% worsened on QIDS between infusion 1-6 and 7% no change**
- Slightly **less than 20% achieved response** defined as 50% improvement, **and 1/3 improve 35% or more** (on QIDS-16 score)
- 12 % achieve remission
- WHY SO LOW????
- YET approximately 50% decides to continue with maintenance infusions <self-pay
- These patients report marked improvement in concentration, motivation, and social functioning

# Comparable to?



- In (STAR\*D) Level 4 trial, response rates after up to 14 weeks of MAOI and combination treatment (VEN+MIR) were **12.1% and 23.5%**, respectively (McGrath et al., 2006)
- Vagal Nerve Stimulation (VNS), the cumulative response rate of TAU at 3 months was **less than 10%** for those who had on average 7.3 failed treatments for depression (Aaronson et al., 2017)



Oliver et al. J Cin Psych 2022

N=424, IV ketamine at private clinic; 50% response rate and 20% remission rate on PHQ9. Response and remission were 72% and 38%, respectively, after 10 infusions

# Comparisons With Real-World Data



Author	Sample Size	Settings	Treatment	TRD	Measure	Response	Remission	% any SI baseline	SI Post
MGH	166 MDD	Medical Center	5 IV	>4 failed trials	QIDS	15%	11.4%	74%	61%
Nikayin 2022	129 (IV) MDD and BP	Medical Center		Not reported	QIDS	38.%	30%		
McIntyre 2020	213 MDD and Bipolar	Real world Canada	4 IV	≥2 failed trials	QIDS	27%	13%	87%	.58 change (sig)
Chisamore 2022	75 (38 TAY vs 37 GA) MDD+BD	Community Clinic Canada	4 IV			TAY 34%; GA 40%	TAY 9%; GA 8%	Tay 38%; GA 54%	not reported
Pfeiffer 2024	215	VA	6 weeks	Mean 2 trials	PHQ-9	26%	15%		
McInnes 2022	537	Community clinics out of pocket	4-8 IV	No	PHQ-9	54%	29%	73%	42% no longer SI at post
Oliver 2022	424 (MDD; SI; Anxiety)	Community clinics/Out of pocket	6 IV	80% failed ≥2 trials	PHQ-9	50%	20%	50%	50 of initial



# Informed consent: what are my chances of responding to ketamine?

- From literature 65-70%
- In extremely treatment refractory patients, at our site lower
- On average 40-50%
- Post ECT failure still 45-50%
- Patients expect usually a 100% of “success”\*
- Informed consent is a long process
- **NEED TO ABSOLUTELY HAVE A PLAN B ready** from the evaluation visit, especially for patients with extremely treatment refractory MDD and SI
- They don’t take a NO very well...

\*how to define success?



# Few comments...

- Response rate to IV ketamine in our clinic appears significantly lower compared to rates published from RCT
- For 50% of patients the 'apparent' low level of improvement is sufficient to justify continuing ketamine treatment, despite side effects and costs
- High level of treatment resistance of our population
- High level of comorbidities
- Ketamine is one component of complex intervention – therapy, medication adjustments, CBT, rehab, MI for SUD etc
- Common fluctuations with life events, medical illness (COVID)
- In cases of long-term, severe chronic illness stopping the ketamine is almost invariably associated with relapse



# How long is the treatment?



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- No rigorous long-term data beside registry on Esketamine, case series from MGH (5 ys), Yale and Emory
- Similar to other chronic medical conditions
- Young patients with intermittent disease and long intervals between episodes may have a relatively short course (?) and pause, until they relapse
- Patients who have been chronically ill for >5 ys (most of the patients in the clinic) **do relapse** when they stop ketamine, usually within months
- If nothing else works, we continue





# Informed consent: long-term side effects?



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- At present unknown
- Data from Esketamine trials, presented to FDA reassuring in short and medium-term (5 years)
- Concerns for neurotoxicity and addiction over long term? Olney's lesions?
- Fear of some yet unknown long-term possible side effect
- Anecdotal tolerance for high dose IN



# Suicidal Ideation



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- > 30% of individuals with MDD reported SI
- At MGH ketamine clinic is >70%
- no medications specifically evaluated for use in this population in the acute setting
- The trials of esketamine in patients with major depressive disorder with active suicidal ideation or behavior are the first large-scale trials in patients considered at imminent risk of suicide
  - esketamine has been approved for use in patients with depression at risk of suicide and for psychiatric emergency in the US and Europe



# Clinical efficacy VS EFFECTIVENESS

## HOW DO WE KNOW IF IT “WORKS”?

(and what “works” MEAN?)

- Easier for esketamine, published RCTs, FDA approval
  - Meta-analyses of RCTs on ketamine
  - Systematic reviews of real-world effectiveness of ketamine
  - Comparison with traditional antidepressant treatments including ECT.
- 
- What would convince a clinical committee?
  - What is the right endpoint?

ORIGINAL ARTICLE

## Real-world effectiveness of repeated ketamine infusions for treatment-resistant bipolar depression

Farhan Fancy, Nelson B. Rodrigues, Joshua D. Di Vincenzo, Edmond H. Chau, Rickinder Sethi, Muhammad I. Husain, Hartej Gill, Aniq Tabassum, Andrea Mckenzie, Lee Phan ... [See all authors](#) ▾

First published: 14 December 2022 | <https://doi.org/10.1111/bdi.13284> | Citations: 5

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### Abstract

#### Background

Clinical trials have demonstrated rapid antidepressant effects with intravenous (IV) ketamine for major depressive disorder, with relatively less research specifically for bipolar depression. Herein, we describe the real-world effectiveness of repeated ketamine infusions for treatment-resistant bipolar depression.

#### Methods

This study was conducted in a community clinic in Mississauga, Ontario (Canadian Rapid Treatment Centre of Excellence; Braxia Health). In this observational study (NCT04209296), patients with treatment-resistant bipolar I/II depression ( $n = 66$ ) received four sub-anesthetic doses of IV ketamine (0.5–0.75 mg/kg) over a two-week period.



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Case series, retrospective  
relatively high N

## Clinical Effectiveness of Intravenous Racemic Ketamine Infusions in a Large Community Sample of Patients With Treatment-Resistant Depression, Suicidal Ideation, and Generalized Anxiety Symptoms: A Retrospective Chart Review

Patrick A. Oliver, MD<sup>a</sup>; Andrew D. Snyder, MD<sup>b,c</sup>; Richard Feinn, PhD<sup>d</sup>; Stanislav Malov, MD<sup>b</sup>; Gray McDiarmid, BSc<sup>b</sup>; and Albert J. Arias, MD, MS<sup>b,c,\*</sup>

**Published:** September 12, 2022

 Focus on Suicide


### ABSTRACT

**Introduction:** Few studies have been published to date exploring the effectiveness of ketamine for treatment-resistant depression (TRD) in large clinical samples. We report on the clinical outcomes of a large cohort treated with ketamine as part of clinical practice.

**Methods:** Deidentified electro  
infusion clinic for 424 patients with TRD seen from November 9, 2017, to May 4, 2021. Ketamine infusions were administered at a starting dose of 0.5 mg/kg/40 minutes for 6 infusions within 21

# Real-world effectiveness of ketamine in treatment-resistant depression: A systematic review & meta-analysis

Yazen Alnefeesi<sup>a</sup>, David Chen-Li<sup>a</sup>, Ella Krane<sup>a</sup>, Muhammad Youshay Jawad<sup>a</sup>, Nelson B. Rodrigues<sup>a</sup>, Felicia Ceban<sup>a d</sup>, Joshua D. Di Vincenzo<sup>a</sup>, Shakila Meshkat<sup>a</sup>, Roger C.M. Ho<sup>e f</sup>, Hartej Gill<sup>a</sup>, Kayla M. Teopiz<sup>a</sup>, Bing Cao<sup>a g</sup>, Yena Lee<sup>a</sup>, Roger S. McIntyre<sup>a b c d</sup>, Joshua D. Rosenblatt<sup>a b</sup>  

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<https://doi.org/10.1016/j.jpsychires.2022.04.037> 

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## Abstract

**Ketamine** is a promising therapeutic option in treatment-resistant depression (TRD). The acute efficacy of ketamine in TRD has been demonstrated in

n = 2665 patients

mean antidepressant effect

the effect varies considerably among patients

- more treatment-resistant cases remit less

often ( $p < 0.01$ ), but no difference in response




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> [EClinicalMedicine](#). 2023 Aug 3;62:102127. doi: 10.1016/j.eclinm.2023.102127.  
eCollection 2023 Aug.

## Ketamine for the treatment of major depression: a systematic review and meta-analysis

Stevan Nikolin<sup>1 2</sup>, Anthony Rodgers<sup>3</sup>, Andreas Schwaab<sup>4</sup>, Anees Bahji<sup>5 6</sup>, Carlos Zarate Jr<sup>7</sup>, Gustavo Vazquez<sup>7</sup>, Colleen Loo<sup>1 2 3</sup>

Affiliations 

PMID: 37593223 PMID: PMC10430179 DOI: 10.1016/j.eclinm.2023.102127

[Free PMC article](#)

## Abstract

**Background:** Intranasal esketamine has received regulatory approvals for the treatment of depression. Recently a large trial of repeated dose racemic ketamine also demonstrated efficacy in severe depression. However, uncertainties remain regarding comparative efficacy, dosage, and the time course of response.

**Methods:** In this systematic review and meta-analysis, we searched Embase, Medline, Pubmed, PsycINFO, and CENTRAL up to April 13, 2023, for randomised controlled trials (RCTs) investigating ketamine for depression. Two investigators independently assessed study eligibility and risk of bias and extracted the data on depression severity scores, response and remission rates, and all-cause dropouts. Multivariable mixed-effects meta-regressions incorporated drug formulation (racemic (Rac) or esketamine (Esket)) and dose (Low or High) as covariates. Treatment effects were assessed: immediately following the first dose, during further repeated dosing, and follow-up after the final dose of a treatment course. This study is registered with PROSPERO (CRD42021221157).

**Findings:** The systematic review identified 687 articles, of which 49 RCTs were eligible for analysis, comprising 3299 participants. Standardised mean differences (95% confidence intervals)

49 RCTs, N=3299

Effect size for response  
and remission  
numerically greater for K

Higher doses more  
effective

# Ketamine vs ECT RCT (Ekstrand et al. 2022)

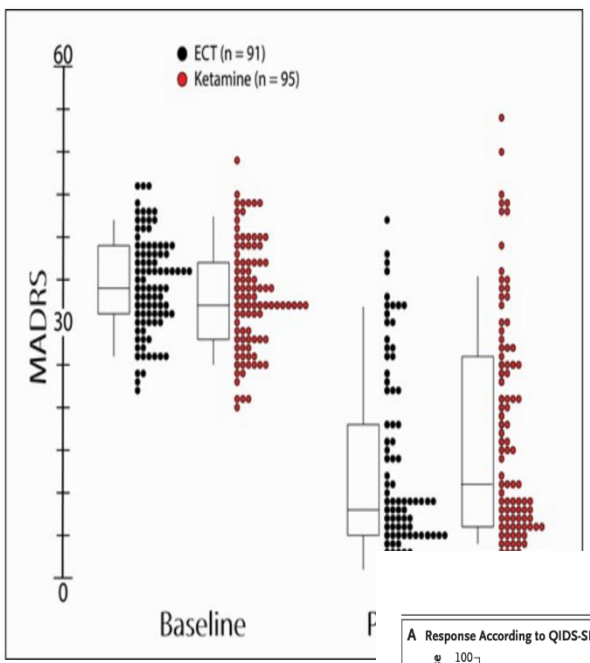
95 ket/91 ECT, Fixed ketamine, variable ECT param.  
Remiss 45% K vs 61% ECT ( P<0.034)



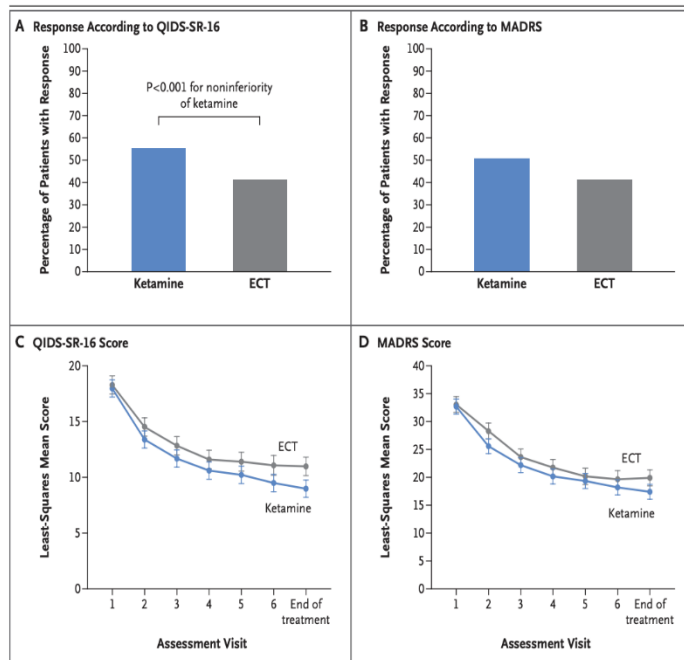
# KETAMINE VS ECT RCT (ANAND, 2023)

200 ket/203 ECT

Resp 55.4% K vs 41.2% ECT (difference, 14.2% 95% CI, 3.9 to 24.2; P<0.001)



KETAMINE VS. ECT FOR MAJOR DEPRESSION

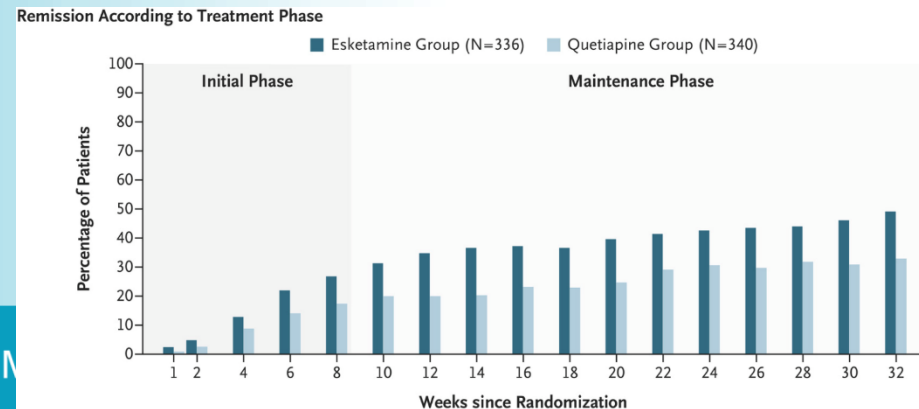


# ESKETAMINE VS QUETIAPINE (ESCAPE-TRD 2023)

336 Esket/340 quet (150-300mg) as ADD-ON SSRI/SNRI

60% failed 2 prior AD tx

Remiss wk8 27.1% K vs 17.6%Q





# Ketamine in children and adolescents



- RCT showing similar results to adults in MDD

Randomized Controlled Trial > Am J Psychiatry. 2021 Apr 1;178(4):352-362.

doi: 10.1176/appi.ajp.2020.20010018. Epub 2021 Mar 3.

## Efficacy of Intravenous Ketamine in Adolescent Treatment-Resistant Depression: A Randomized Midazolam-Controlled Trial

Jennifer B Dwyer<sup>1</sup>, Angeli Landeros-Weisenberger<sup>1</sup>, Jessica A Johnson<sup>1</sup>, Amalia Londono Tobon<sup>1</sup>, José M Flores<sup>1</sup>, Madeeha Nasir<sup>1</sup>, Kevin Couloures<sup>1</sup>, Gerard Sanacora<sup>1</sup>, Michael H Bloch<sup>1</sup>

Affiliations + expand

PMID: 33653121 DOI: 10.1176/appi.ajp.2020.20010018

### Abstract

**Objective:** Adolescent depression is prevalent and is associated with significant morbidity and mortality. Although intravenous ketamine has shown efficacy in adult treatment-resistant depression, its efficacy in pediatric populations is unknown. The authors conducted an active-placebo-controlled study of ketamine's safety and efficacy in adolescents.

**Methods:** In this proof-of-concept randomized, double-blind, single-dose crossover clinical trial 17 adolescents (ages 13-17) with a diagnosis of major depressive disorder received a single intravenous infusion of either ketamine (0.5 mg/kg over 40 minutes) or midazolam (0.045 mg/kg over 40 minutes), and the alternate compound 2 weeks later. All participants had previously tried at least one antidepressant medication and met the severity criterion of a score >40 on the Child Behavior Depression Rating Scale-Revised. The primary outcome measure was score on the Montgomery Åsberg Depression Rating Scale (MADRS) 24 hours after treatment.

**Results:** A single ketamine infusion significantly reduced depressive symptoms 24 hours after



# What do you do then...

- If you have a treatment that seems to work?
- Relatively safe, well tolerated, available in the hospital
- many patients who did really well and then relapse –REALLY BAD
- Depression is mostly a chronic illness and should be managed as such, the short-term antidepressant studies are flawed

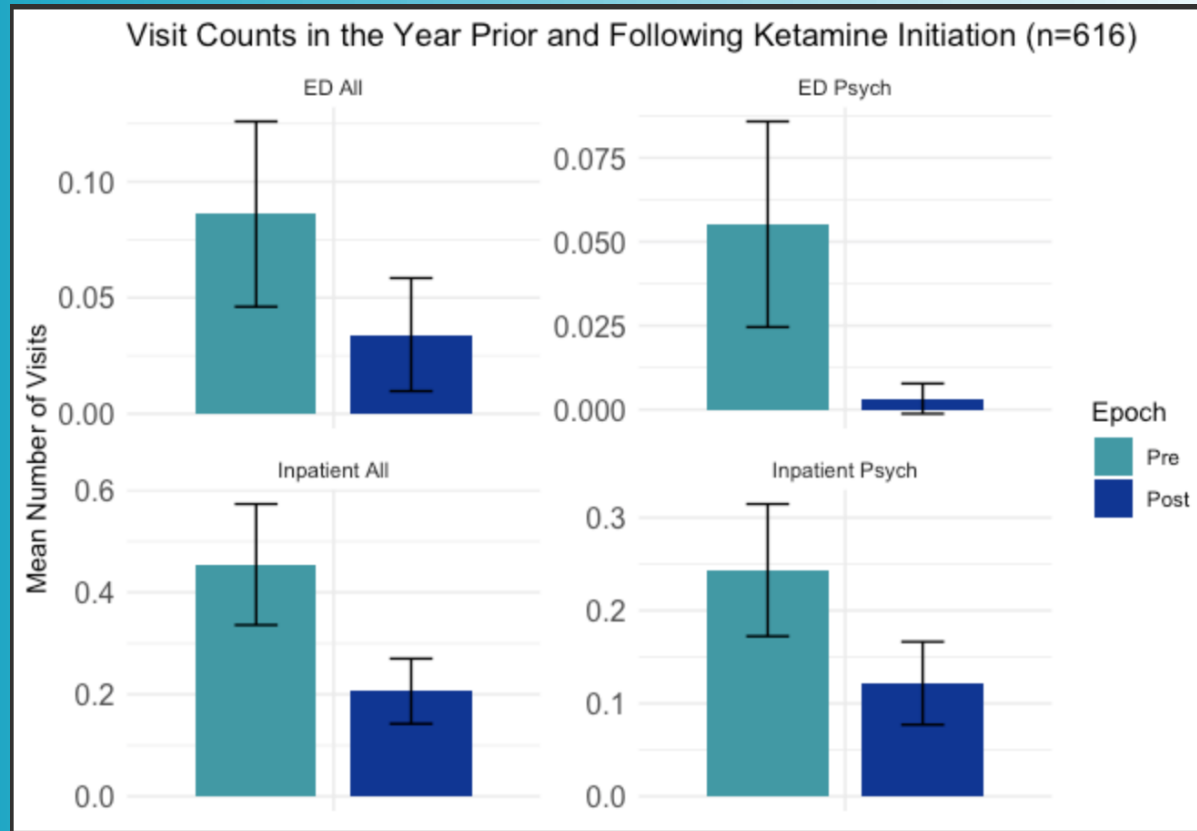




# Lessons learned from clinical practice

- Once you offer to try ketamine you need to be able to provide maintenance to the responders
- If it works, it keeps working for a long time
- When it does NOT work patients can get much worse, hopelessness on top of depression is a bad combo
- The burocracy is always worse than you think

# Ketamine and prevention of hospitalization and ED visits



-2 suicide attempts  
-1 completed suicide (1 week after tx 4), no warning signs  
-1 completed months after dropping out from study (tx2) and moving out of state

N=616, Unpublished data

# Practical considerations



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- Patients have been asking to try ketamine since 2012, about 5-10 calls per week
- The patients who remain in the clinic >3 months are likely to require long-term care for **an indefinite period of time**
- IV clinic allows multiple patients to be treated at the same time, 6-8 new patients every 3-4 weeks
- Waitlist currently >170
- Extremely complex patients, multiple psychiatric comorbidities, mood fluctuations, relapses



# Practical considerations – I

- Concurrent psychotherapy? Limited time, limited privacy, no reimbursement
  - Added value to the treatments?
  - Not for everybody
- Asynchronous psychotherapy? CBT? Difficult access
- Evidence based for other therapies?



# Practical considerations -II

## Esketamine or ketamine **in the ED?**

The logistic becomes even more complicated..

- Who approves a patient? Ketamine clinic staff available 24/7?
- Who pays for ketamine/esketamine? Getting pre-auth- BCBS can take 2 weeks. If insurance denies it?
- How to ensure there is slot in the ketamine clinic to continue tx? First opening is 2 months from now
- Who is responsible for the patient's safety between ED discharge and first clinic opening?
- Finding a team for patients not connected with care?



# Current study

AFSP funded an effectiveness study

100 inpatients, with MDD +SI/SA

Up to #8 IV ketamine and maintenance with esketamine, as add on to TAU

Outcome: prevention of readmission and suicide re-attempt at 6 months

Compared to matched 3:1 historical controls from our network of hospitals