MASSACHUSETTS GENERAL HOSPITAL
PSYCHIATRY ACADEMY

Ketamine and Esketamine
From Research to Clinical practice

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Associate Professor HMS

Disclosures

Cristina Cusin 2012-2017:

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

Major Depressive Disorder

- MDD is the leading cause of disability and loss of work worldwide, affecting more than 300 million people
- In US lifetime incidence of MDD is approximately 17%
- Estimated cost to the economy: **over $200 billion/yr**
- Associated with suicide, 3rd leading cause of death, more than 44,000/yr in the US alone

- No new antidepressant mechanisms since Prozac…that was **December 1987**, and it was still monoamine-based

Why a talk on ketamine?

- Hundreds of inquiries from patients and colleagues

- Hype in the media
  (spoiler alert - it's **NOT** magic!!)

- Is it just another fad? Or is it real?
- Should my patient get ketamine? When to recommend it?
- Can I start prescribing ketamine in my office right now? Can they get it at the local CVS?
- This patient does not want any med, but wants ketamine, is it ok?
- This patient has been depressed for 50 years, do you think 1-2 infusions would be enough? (see bullet point #2)

Overview

- **What is ketamine?**
- **Does it work?**
  - Ketamine : efficacy and early studies
  - Esketamine studies and FDA approval
- **Is it safe?**
  - Side effects and risks
- **For how long?**
  - Duration of treatment
- **For which patients?**
- **How to get ketamine at MGH**
  - – insurance coverage
- Symptomatic improvement vs functional recovery
- Ketamine clinic and working with very sick patients

Still no updates..

- Comparative effectiveness
- 1 infusion each
- Monitored for 7 days
- Primary outcome 24 hrs
- 96 subjects, Brazil
- Failed 1 AD

- Design published in 2018
- Study is ongoing

Study Protocol Clinical Trial

Medicine

OPEN

Comparative study of esketamine and racemic ketamine in treatment-resistant depression

Protocol for a non-inferiority clinical trial

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Abstract

Introduction: The use of ketamine as an option in the treatment of depressive disorder is growing rapidly, supported by numerous clinical trials attesting its efficacy and safety. Esketamine, the S (+) enantiomer of ketamine, is the most widely used form in the anesthetic environment in some countries, and new studies have shown that it may also be effective in depression and with better tolerability. However, no study so far has directly compared esketamine with racemic ketamine. Here we propose a protocol of a clinical trial to evaluate esketamine as a noninferior medication when compared to ketamine in the treatment of patients with treatment-resistant depression.

Methods/design: This study protocol is for a randomized, controlled, double-blind noninferiority clinical trial. Subjects will be 18 years or older, with major depression characterized as treatment-resistant. Participants will receive a single infusion of either esketamine (0.25 mg/kg) or ketamine (0.5 mg/kg) over 40 minutes. The primary outcome will be the difference in remission rates between the 2 treatment arms at 24 and 72 hours after drug infusion. Secondary outcomes will include other timepoints, measurements of cognition, dissociation, and blood biomarkers.

Discussion: A head-to-head study is the best way to evaluate whether the esketamine is in fact comparable to the racemic ketamine in terms of both efficacy and safety, and, if positive, it would be an initial step to increase the access to that type of treatment worldwide.

Ethics and dissemination: The study was approved by the local Institutional Review Board (University Hospital Professor Edgard Santos—Federal University of Bahia—Number: 46657415.0.0000.0049). Subjects will only participate after voluntarily agreeing and signing the Informed Consent Form. The study findings will be published in peer-reviewed journals and presented at national and international conferences.

Trial registration: This trial has been registered in the Japan Primary Registries Network (JPRN): UMIN000032355, which is affiliated with the World Health Organization.

Still no updates..

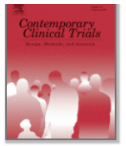
- Comparative effectiveness
- Non-inferiority
- Multi-center
- 6 infusions vs 6 ECT
- Projected sample 400

- Design published in 2019
- Study is ongoing

ELSEVIER

Contemporary Clinical Trials

Volume 77, February 2019, Pages 19-26



ELEctroconvulsive therapy (ECT) vs. Ketamine in patients with Treatment-resistant Depression: The ELEKT-D study protocol

Sanjay J. Mathew [a, b, 1], Samuel T. Wilkinson [c, 1], Murat Altinay [d, e, f], Ali Asghar-Ali [a, b], Lee C. Chang [g], Katherine A. Collins [h], Roman M. Dale [d, e, f], Bo Hu [i], Kamini Krishnan [j], Charles H. Kellner [k], Donald A. Malone [d, e, f], James W. Murrough [h, l], Robert B. Ostroff [c], Gerard Sanacora [c], Mingyuan Shao [i], Amit Anand [d, e, f]

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https://doi.org/10.1016/j.cct.2018.12.009

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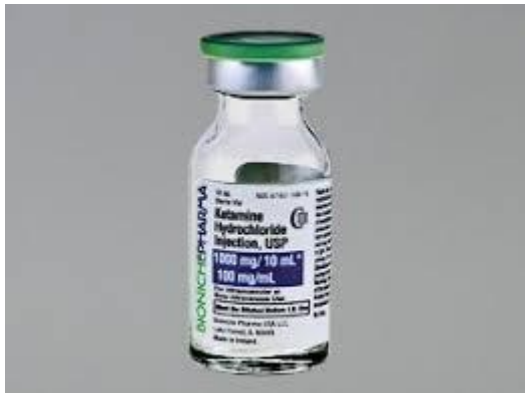
Abstract

Major depressive disorder (MDD) is the most common mental illness and the leading cause of disability worldwide. Electroconvulsive therapy (ECT) is the most effective treatment for MDD and the gold-standard therapy for treatment-resistant depression (TRD), yet it remains underutilized due to factors such as limited availability, stigma, and concerns about cognitive side effects. Ketamine has

What is ketamine?



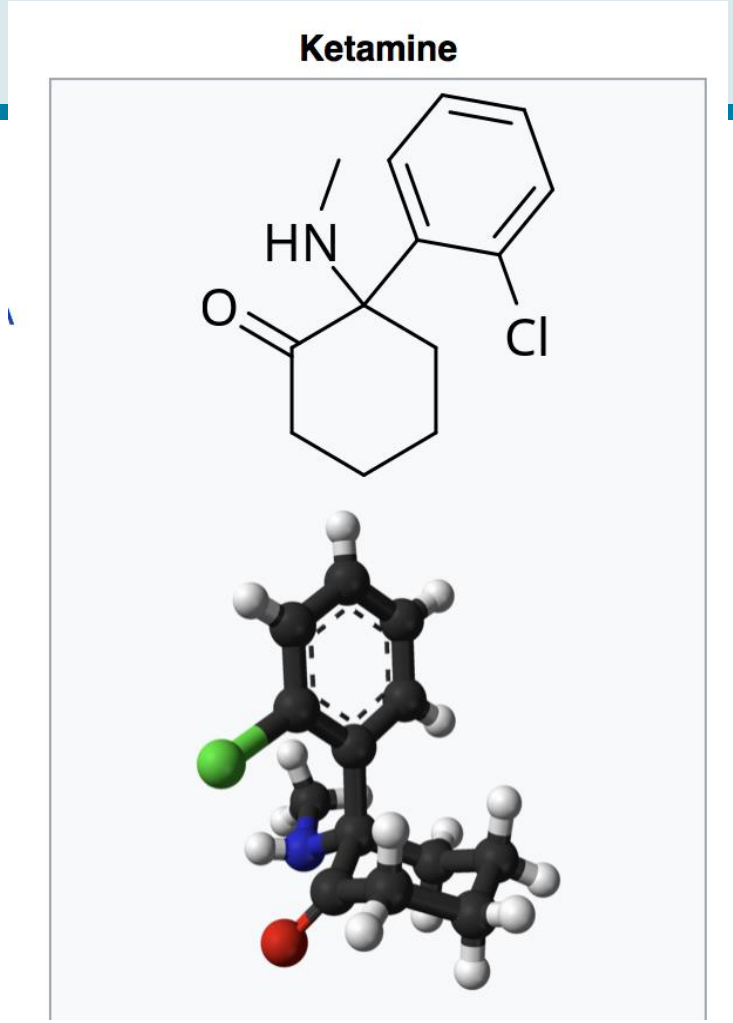
Ketamine facts

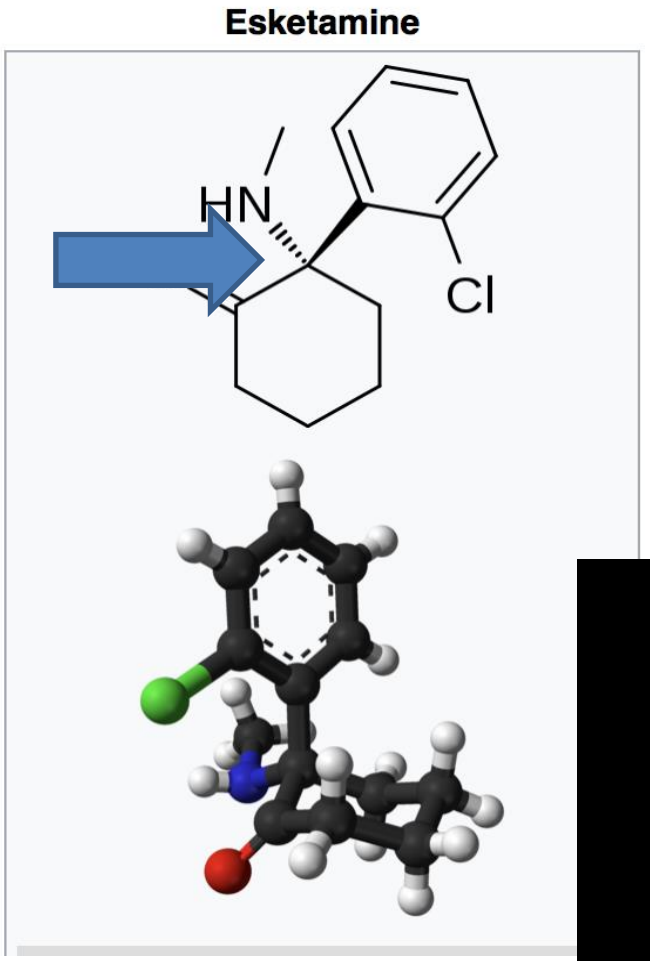
- **Ketamine** is an **old anesthetic and analgesic**, FDA-approved in 1970, widely used in the ED, OR, ECT, pain clinics, battlefield, veterinary medicine

- "Indications: trauma patients with moderate to severe pain and whose vital signs are potentially unstable, excited delirium, rapid sequence airway management, and for the maintenance of sedation."
- Use: pre-anesthesia, procedures, children, does not suppress breathing and allows lower use of opiates for post-surgical pain
- It is also a drug of abuse "party drug" or "special K"

  - **For depression ketamine is still OFF LABEL**

What is S-ketamine?





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

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

“S” vs “R” vs “SR”

- Esketamine (S) is approximately twice as potent as anesthetic as racemic (SR) ketamine.
- (S) has shorter half-life than (R) or (SR)
- In mice rapid antidepressant effect of R was greater and lasted longer than S
- (S) inhibits dopamine transporters 8x >R
- (S) is generally considered to be more pleasant by patients
- (S) has affinity for the PCP binding site of the NMDA receptor 3 to 4x >(R)
- (S) does not bind significantly to opioid sigma receptors.
- (S) “more dissociative”, (R) “more relaxing”

- **No rigorous comparison studies in depression**

Open label study on R-ketamine IV

Limited research on R-ketamine

Springer Link

Short Communication | Published: 20 February 2020

Intravenous arketamine for treatment-resistant depression: open-label pilot study

Gustavo C. Leal, Igor D. Bandeira, Fernanda S. Correia-Melo, Manuela Telles, Rodrigo P. Mello, Flavia Vieira, Cassio S. Lima, Ana Paula Jesus-Nunes, Lívia N. F. Guerreiro-Costa, Roberta F. Marback, Ana Teresa Caliman-Fontes, Breno L. S. Marques, Marília L. O. Bezerra, Alberto L. Dias-Neto, Samantha S. Silva, Aline S. Sampaio, Gerard Sanacora, Gustavo Turecki, Colleen Loo, Acioly L. T. Lacerda & Lucas C. Quarantini

European Archives of Psychiatry and Clinical Neuroscience (2020) | Cite this article

554 Accesses | **16** Citations | **32** Altmetric | Metrics

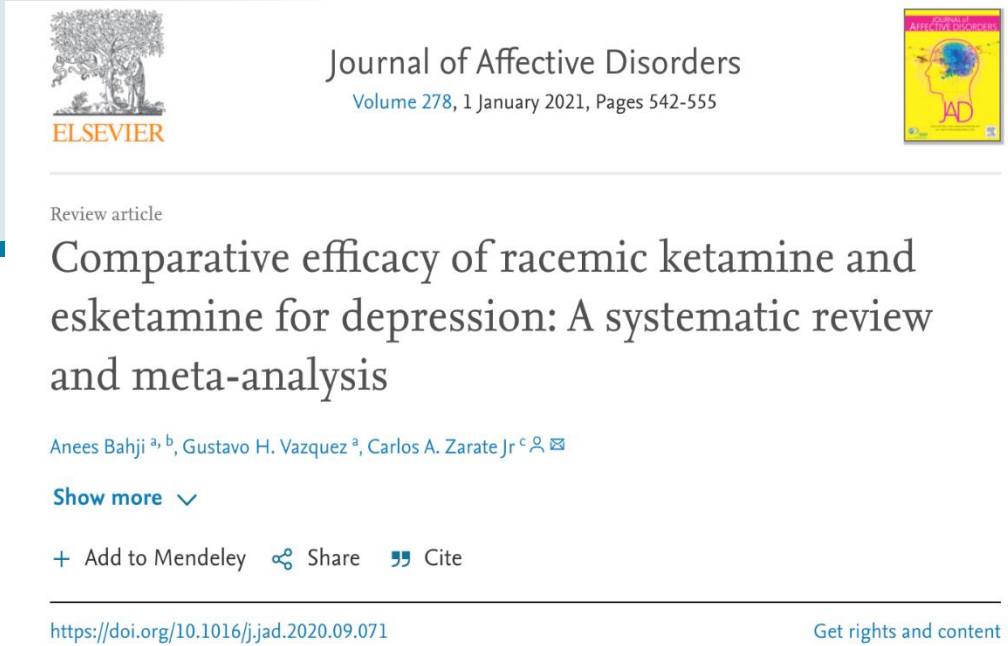
Abstract

We aimed to analyze the efficacy and safety of arketamine, the *R*(−)-enantiomer of ketamine, for treatment-resistant depression (TRD) in humans. Open-label pilot trial, seven subjects with TRD received a single intravenous infusion of arketamine (0.5 mg/kg); primary outcome was change in Montgomery–Åsberg Depression Rating Scale (MADRS) 24 h after. Mean MADRS dropped from 30.7 before infusion to 10.4 after one day, a mean difference of 20.3 points [CI 95% 13.6–27.0; $p < 0.001$]; dissociation was nearly absent. Arketamine might produce fast-onset and sustained antidepressant effects in humans with favorable safety profile, like previously reported with animals; further controlled-trials are needed.

Does ketamine work?

- Anecdotal studies on low-dose ketamine as model of psychosis – mood improves transiently (early 2000s)
- A single low dose of ketamine IV rapidly improved depressive symptoms for up to 3 days (n=7 patients with treatment-resistant depression -TRD) (*Berman, Biol. Psychiatry, 2000*).
- *Zarate et al.2006*: double-blind, placebo-controlled, crossover study: single ketamine infusion had fast and sustained antidepressant effects in 17 patients with TRD (*Arch General Psychiatry*)
- Replicated independently in multiple studies involving patients with MDD and BP depression

Efficacy



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Journal of Affective Disorders

Volume 278, 1 January 2021, Pages 542-555

Review article

Comparative efficacy of racemic ketamine and esketamine for depression: A systematic review and meta-analysis

Anees Bahji [a, b], Gustavo H. Vazquez [a], Carlos A. Zarate Jr [c]

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Jan 2021 – review
24 trials , 1877 participants

Racemic ketamine vs esketamine demonstrated
greater overall response (RR = 3.01 vs. RR = 1.38)
remission rates (RR = 3.70 vs. RR = 1.47
lower dropouts (RR = 0.76 vs. RR = 1.37).

most esketamine-treated patients - more rigorous definition of TRD
one trial of older adults receiving esketamine –negative
Functional unblinding in research

Does S-ketamine work?

- In March 2019 the FDA approved Intranasal Esketamine (Spravato) for treatment-resistant depression, in conjunction with a standard antidepressant
- 2 pivotal Phase-3 trials were positive in adults (18-65)
- Trial in elderly pts >65 was stopped early – not statistically significant
- One randomized blinded discontinuation study also showed that continuing Esketamine decreased the risk for relapse

Overview of Randomized Trials of Esketamine

Key Trials	Treatment Groups*	N	Age, yrs	Duration of Current Episode, yrs	Failures of ≥ 3 ADs, %	MADRS
TRANSFORM-1	Esketamine 56 mg Esketamine 84 mg Placebo	342	47	3.9	40%	37.5
TRANSFORM-2	Esketamine (flexible) Placebo	223	46	2.2	36%	37.0
TRANSFORM-3	Esketamine (flexible) Placebo	137	70	4.1	39%	35.0
SUSTAIN-1	Esketamine (flexible) Placebo	297	48	NR	NR	38.3

*Patients in all arms also received a newly initiated open-label antidepressant, referred to as background antidepressant.

Primary Outcome: Change in MADRS at Week 4

Trial	Intervention	Baseline	Δ from Baseline	Esketamine vs. Placebo	
				Mean Difference*	p-value
TRANSFORM-1	Placebo	37.5	-14.8	—	—
	Esketamine 56 mg	37.4	-19.0	-4.1	0.011
	Esketamine 84 mg	37.8	-18.8	-3.2	0.088
TRANSFORM-2	Placebo	37.3	-17.0	—	—
	Esketamine	37.0	-21.4	-4.0	0.020

*LSMD: least square mean difference, estimated using mixed model for repeated measures

- Meta-analysis of TRANSFORM-1 & -2: greater improvement on MADRS score for esketamine compared to placebo (**mean difference -3.8; 95% CI: -6.3, -1.4)**
- TRANSFORM-3: similar improvement was observed, but not statistically significant (mean difference -3.6; 95% CI: -7.2, 0.07)

Clinical Response & Remission at Week 4

Trial	Intervention	N	Response, %	Remission, %
TRANSFORM-1	Placebo	113	37.2	29.2
	Esketamine 56 mg	115	52.2	34.8
	Esketamine 84 mg	114	45.6	33.3
TRANSFORM-2	Placebo	109	47.7	28.4
	Esketamine	114	61.4	46.5

- Results of meta-analysis
  - **Clinical response**: patients on esketamine more likely to achieve clinical response compared to placebo (**relative risk 1.30; 95% CI: 1.08, 1.56)**
  - **Remission**: similar relative risk, but not statistically significant (**relative risk 1.37; 95% CI: 0.99, 1.91)**

Esketamine: Relapse Outcomes

- **SUSTAIN 1:** 705 patients enrolled
  - 176 achieved stable remission
  - 121 achieved stable response
- **Stable remitters (n=176):**
  - Esketamine reduced risk of relapse by 51% (HR 0.49; 95% CI: 0.29, 0.84)
- **Stable responders (n=121):**
  - Esketamine reduced risk of relapse by 70% (HR 0.30; 95% CI: 0.16, 0.55)

Some balanced views

The American Journal of Psychiatry

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Special Article

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Synthesizing the Evidence for Ketamine and Esketamine in Treatment-Resistant Depression: An International Expert Opinion on the Available Evidence and Implementation

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Published Online: 17 Mar 2021 | https://doi.org/10.1176/appi.ajp.2020.20081251

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Abstract

Replicated international studies have underscored the human and societal costs associated with major depressive disorder. Despite the proven efficacy of monoamine-based antidepressants in major depression, the majority of treated individuals fail to achieve full syndromal and functional recovery with the index and subsequent pharmacological treatments. Ketamine and esketamine represent pharmacologically novel treatment avenues for adults with treatment-resistant depression. In addition to providing hope to affected persons, these agents represent the first non-monoaminergic agents with proven rapid-onset efficacy in major depressive disorder. Nevertheless, concerns remain about the safety and tolerability of ketamine and esketamine in mood disorders. Moreover, there is uncertainty about the appropriate position of these agents in treatment algorithms, their comparative effectiveness, and the appropriate setting, infrastructure, and personnel required for their competent and safe implementation. In this article, an international group of mood disorder experts provides a synthesis of the literature with respect to the efficacy, safety, and tolerability of

And the perennial skeptics…

Small improvement
Esketamine has more side eff than placebo !!
Pts relapse when they stop it

pidemiology and Psychiatric Sciences

ambridge.org/eps

pidemiology for Clinical Psychopharmacology

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Esketamine for treatment resistant depression: a trick of smoke and mirrors?

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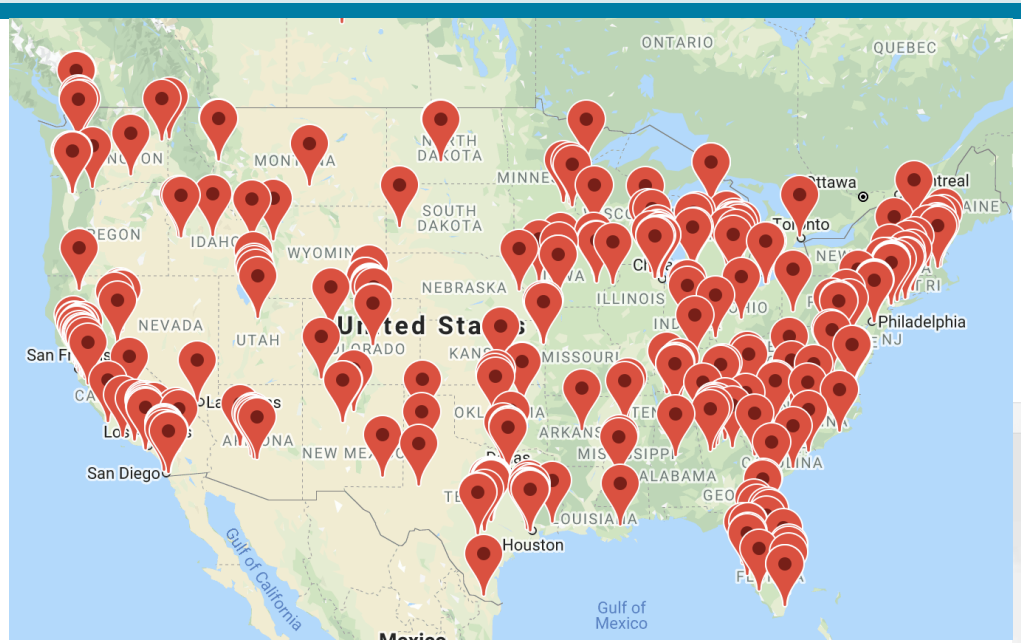
Abstract

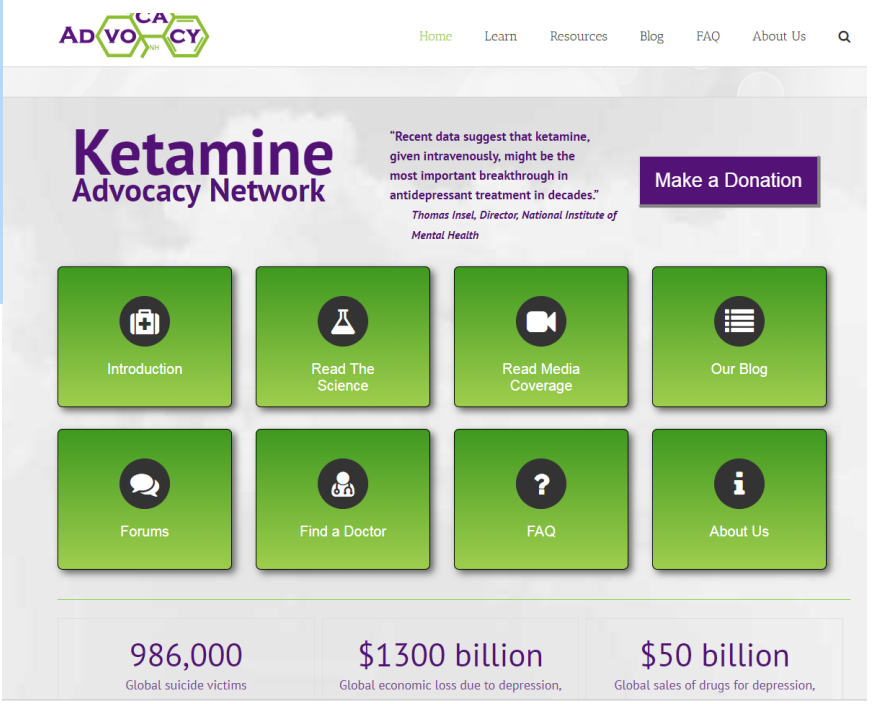
In March 2019, the US Food and Drug Administration (FDA) approved a nasal spray formulation of esketamine for the treatment of resistant depression in adults. Esketamine is the S-enantiomer of ketamine, an FDA-approved anaesthetic, known to cause dissociation and, occasionally, hallucinations. While ketamine has not been approved for depression in the USA or in any other country, it has been used off-label in cases of severe depression. This commentary critically reviewed the evidence on esketamine submitted to the FDA, aiming to draw implications for clinical practice, research and regulatory science.

In March 2019, the US Food and Drug Administration (FDA) approved a nasal spray formulation of esketamine for the treatment of resistant depression in adults. Treatment-resistant depression (TRD) refers to a depressive episode with inadequate response to at least two antidepressant (AD) trials of adequate doses and duration. According to the FDA label, esketamine is indicated in TRD in association with AD treatment. This new drug has been under review by the European Medicine Agency (EMA) for approval and licensing, and received a positive feedback and may be soon available for clinical use also in European countries.

Esketamine is the S-enantiomer of ketamine, an FDA-approved anaesthetic. While ketamine has not been approved for depression in the USA or in any other country, it has been used off-label in cases of severe depression (Daly and Singh, 2018; Popova *et al.*, 2019; Zhang and Hashimoto, 2019). However, ketamine is used for recreational purposes because it produces desired mental and behavioural changes, such as euphoria, and perceptual changes, such as dissociation and, occasionally, hallucinations (Caddy *et al.*, 2015). These effects,

Ketamine providers





Why a ketamine clinic at MGH?

- Tertiary care center, extremely treatment-refractory patients, experts in psychopharmacology who have tried every other option
- Patients have failed multiple interventions including medications, psychotherapies, TMS, ECT
- Frequent in this population is a history of 'tachyphylaxis' or loss of response to antidepressants
- For those patients we do not have clear guidelines
- Patients seeking 'experimental' treatments participated to research trials with ketamine and had benefit

A note about Clinical trials for TRD

- **None** of my patients with TRD ever qualifies for clinical trials
- Patients have messy histories, give complex answers to questionnaires, cannot remember past medication trials, episodes, timeline, have symptoms of fluctuating severity
- Have multiple medical comorbidities
- On medications and cannot stop them without relapsing
- They have failed too many antidepressants (8.3 ± 5.7)
- They are often too hopeless to inquire or too fatigued to attend all the visits

But how to…

How is ketamine administered?

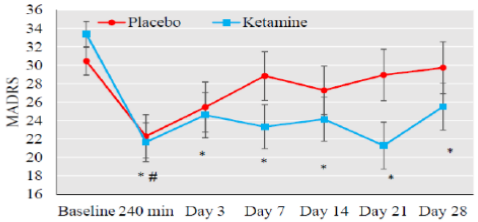
- **LOW** Bioavailability when ketamine is given **orally** (17-25% of IV dose) or sublingually (30-40%)
  - Few small studies in cancer pain
  - Slow onset of action
- **Intranasal administration (IN)** - approx. 50%
- Extensive first-pass hepatic metabolism
- Half-life 3-5 hours
- **Intravenous (IV) has 100% bioavailability**

- **The current options are IV, IN, SL –** under development oral, transdermal

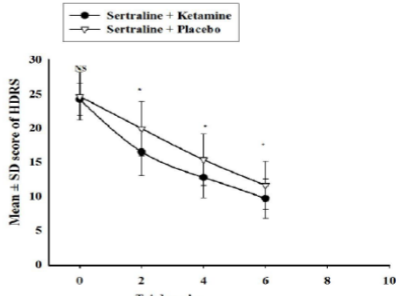
Oral ketamine in MDD?

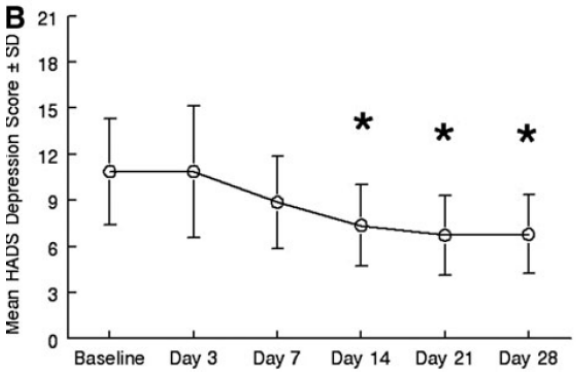
- **Ichilov study, Israel** (Domany et al, 2018)
  - 1 mg/kg oral Ketamine 3 times a week
  - PEP: MADRS at 21 days
  - Largest effect observed at day 21

FIGURE 2: MADRS scores at baseline, 240 min, 3 days, 7 days, 14 days, 21 days, and 28 days, in the Ketamine and placebo groups.



- **Tehran study, Iran** (Arabzadeh et al, 2018)
  - 25 mg oral Ketamine twice a day
  - PEP: HDRS at 2 weeks
  - Largest effect observed at week 2 (diff Placebo-ketamine absolute HDRS=-3.41, p<0.001)
  - At 4 weeks still significant difference between Placebo and Ketamine (-2.61, p=0.001)





- **San Diego Open-label study** (Irwin et al. 2013)
  - Hospice patients
  - Daily 0.5 mg/kg oral ketamine
  - PEP: HADS change at 4 weeks
  - Mean time to response: 14 days
  - Effect sustained over 4 weeks

Oral ketamine - II

- **Not** rapid, **2-6 weeks** - Dosages and frequency of administration were variable (ie, 0.5-7.0 mg/kg 3 times daily to once monthly), with most studies using dosages of 1-2 mg/kg every 1-3 days.

› Ther Adv Psychopharmacol. 2020 May 18;10:2045125320922474.
doi: 10.1177/2045125320922474. eCollection 2020.

Safety and efficacy of extended release ketamine tablets in patients with treatment-resistant depression and anxiety: open label pilot study

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Affiliations – collapse

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Free PMC article

Abstract

Background: Ketamine's defining side effects are dissociation and increased blood pressure/heart rate. An oral formulation with delayed absorption could minimize these effects. We recently reported safety and tolerability data for an extended release ketamine tablet in healthy volunteers.

Smith-Apeldoorn *et al. BMC Psychiatry* (2019) 19:375
https://doi.org/10.1186/s12888-019-2359-1

BMC Psychiatry

STUDY PROTOCOL Open Access

Oral esketamine for treatment-resistant depression: rationale and design of a randomized controlled trial

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Abstract

Background: There is an urgent need to develop additional treatment strategies for patients with treatment-resistant depression (TRD). The rapid but short-lived antidepressant effects of intravenous (IV) ketamine as a racemic mixture have been shown repeatedly in this population, but there is still a paucity of data on the efficacy and safety of (a) different routes of administration, and (b) ketamine's enantiomers esketamine and arketamine. Given practical advantages of oral over IV administration and pharmacodynamic arguments for better antidepressant efficacy of esketamine over arketamine, we designed a study to investigate repeated administration of oral esketamine in patients with TRD.

Methods: This study features a triple-blind randomized placebo-controlled trial (RCT) comparing daily oral esketamine versus placebo as add-on to regular antidepressant medications for a period of 6 weeks, succeeded by a follow-up of 4 weeks. The methods support examination of the efficacy, safety, tolerability, mechanisms of action, and economic impact of oral esketamine in patients with TRD.

Discussion: This is the first RCT investigating repeated oral esketamine administration in patients with TRD. If shown to be effective and tolerated, oral esketamine administration poses important advantages over IV administration.

Trial registration: Dutch Trial Register, NTR6161. Registered 21 October 2016.

Keywords: Esketamine, Oral administration, Clinical trial, Treatment-resistant depression

But… is it safe?

Acute side effects

- 205 intravenous (IV) ketamine infusions (0.5 mg/kg) in 97 participants with DSM-IV-MDD from 3 clinical trials
- 4 of 205 infusions (1.95%) were discontinued due to AEs. The overall attrition rate was 3.1%.
- In the first 4 hours after the infusion, **the most common general AEs were drowsiness, dizziness, poor coordination, blurred vision, and feeling strange or unreal**. **Increase in BP, not clinically significant**.
- No cases of persistent psychotomimetic effects, adverse medical effects, or increased substance use in a subgroup of patients with available long-term follow-up information.

Wan et al. J Clin Psychiatry. 2015 Mar;76(3):247-52

Esketamine side effects

- Controlled data on long-term efficacy and safety of intranasal esketamine in 297 patients with TRD, followed for up to 92 weeks (Daly et al., 2019).
- Transient dysgeusia, vertigo, dissociation, somnolence, and dizziness (Daly et al., 2019)
- No report of persistent cognitive disturbances or urinary problems.
- In another 56-week open-label maintenance
  - 9.5% of the patients with TRD initially considered responders, discontinued the drug due to adverse events such as anxiety, depression, blood pressure increased, dizziness, suicidal ideation, and dissociation

Driving the day after

-26 volunteers

-Driving simulator

-Esketamine (84 mg) vs placebo vs oral mirtazapine (30 mg) significantly impaired

-on road driving performance

No significant difference in **driving** performance was observed at 8 hrs

Springer PSYCHOPHARMACOLOGY
springer.com

Psychopharmacology (Berl). 2017; 234(21): 3175–3183. PMCID: PMC5660834
Published online 2017 Jul 28. doi: 10.1007/s00213-017-4706-6 PMID: 28755104

The effects of intranasal esketamine (84 mg) and oral mirtazapine (30 mg) on on-road driving performance: a double-blind, placebo-controlled study

Aurora J. A. E. van de Loo,[1,2] Adriana C. Bervoets,[1] Loes Mooren,[1] Noor H. Bouwmeester,[1] Johan Garssen,[1,3] Rob Zuiker,[4] Guido van Amerongen,[4] Joop van Gerven,[4] Jaskaran Singh,[5] Peter Van der Ark,[6] Maggie Fedgchin,[5] Randall Morrison,[5] Ewa Wajs,[6] and Joris C. Verster[1,2,7]

Abstract

Go to:

Rationale

The purpose of this study is to evaluate the single dose effect of intranasal esketamine (84 mg) compared to placebo on on-road driving performance. Mirtazapine (oral, 30 mg) was used as a positive control, as this antidepressant drug is known to negatively affect driving performance.

Methods

Twenty-six healthy volunteers aged 21 to 60 years were enrolled in this study. In the evening, 8 h after treatment administration, participants conducted the standardized 100-km on-road driving test. Primary outcome measure was the standard deviation of lateral position (SDLP), i.e., the weaving of the car. Mean lateral position, mean speed, and standard deviation of speed were secondary outcome measures. For SDLP, non-inferiority analyses were conducted, using +2.4 cm (relative to placebo) as a predefined non-inferiority margin for clinical relevant impairment.

Side effects in the clinic

- >1200 intravenous (IV) ketamine infusions **at the MGH ketamine clinic** since October 2018
- 4 infusions were discontinued due to AEs.
- 1 instance of BP increase requiring labetalol 5mg (elderly pt with poorly controlled BP)
- Approximately 3% of patients dropped out after one infusion, disliking the experience
- Nausea is common (35%) – treated with ondansetron
- During the infusion: dizziness, sedation, dissociation
- 1 day Post infusion: headache, nausea, insomnia, fatigue
- No cases of persistent side effects beyond day 1, no urinary problems, no new onset of psychotic sx, 1 case severe dissociation in patients with PTSD (improved over time)

Informed consent: what are the side effects?

- Most of the adverse effects peak within 40 minutes and cease within 40 minutes post-infusion
- **Nausea** (about 35% pre-medicated with ondansetron)
- perceptual disturbances, dissociative and psychotomimetic effects, **anxiety**, dysphoria ->10-15% required IV/PO lorazepam
- Moderate headache (acetaminophen 4-5%).
- Brief hypertensive episodes (labetalol N=1), very rare
- 1 asthma attack in pt with known asthma and prior allergic reaction to anesthetics – used her own inhaler

Who are the right patients? (IV)

- AT MGH: Must be referred by treating psychiatrist
- Any of the following
  - Severe MDD, with significant functional consequences
  - ECT is being considered, has failed, or lead to intolerable side effects
  - Suicide risk in MDD or BP
  - Significant mood or suicide-related symptoms in setting of other Axis I psychiatric disorders
  - Symptoms known to be responsive to antidepressants in other psychiatric conditions; symptoms that severely interfere with life or confer suicide risk
  - Maintenance of antidepressant response in patients who had good therapeutic response from an acute course of ketamine treatment
  - No major acute medical issues **

Who are the right patients? (IV Ketamine)

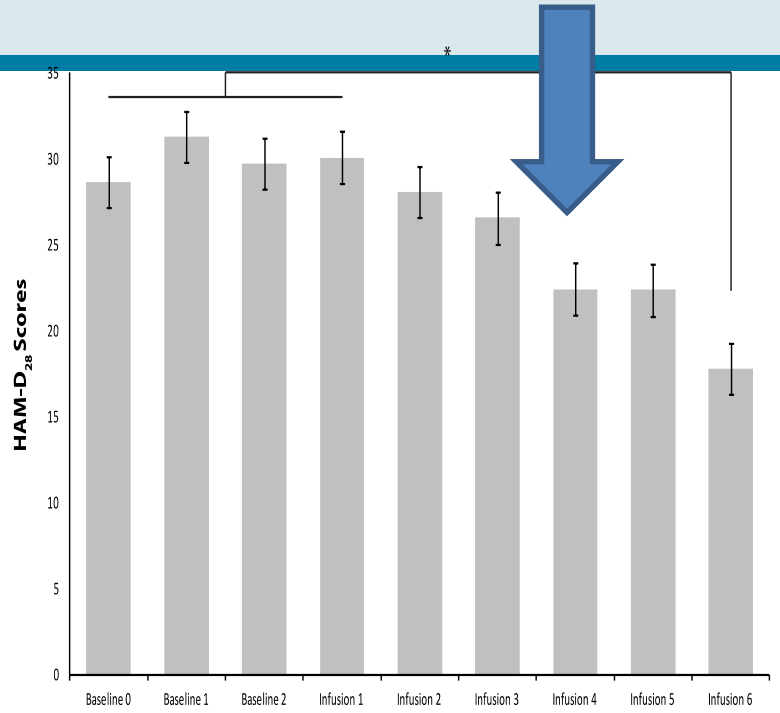
Exclusions:

- substance use disorders (sobriety for how long? *),
- Psychosis
- Unstable medical illness (?).
- Psychiatrist not involved, patients self-referred
- No escort available for transportation – MGH mandates an escort, no exceptions (no matter how low the dose)
- Patient not providing access to medical records, Urine tox screen, release to talk to psychiatrist
- Not failed enough*? Ethical dilemma of when it is "enough" and need for guidelines
  - Balancing acute need for relief (i.e. suicidal, about to drop out of college) vs rigid rule about # past treatments
  - Pts who refuse standard ADs?
- What about patients with advanced cancer and depression?
- What about MCI and depression?
- What about mixed state/rapid cycling?

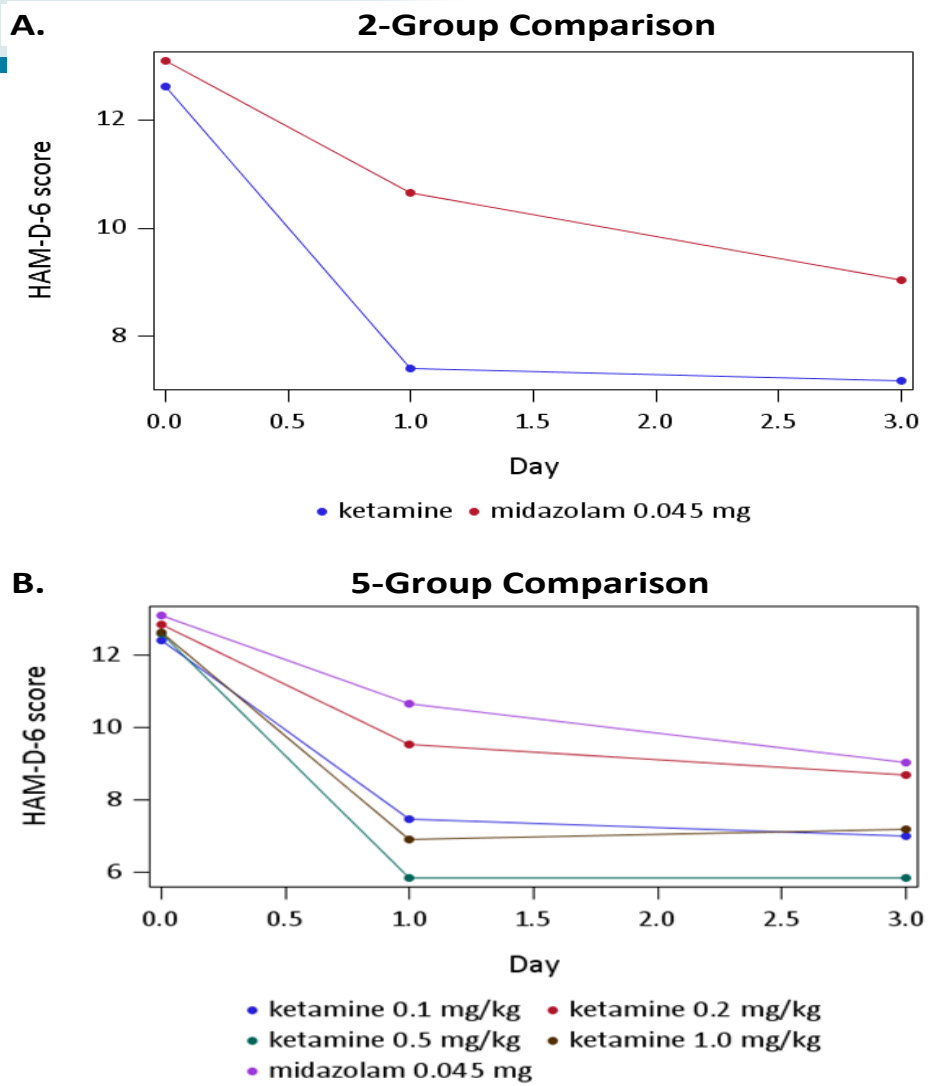
Who are the right patients? (Esketamine, IN)

- Must be referred by treating psychiatrist
- MDD, failed at least 4* antidepressants
  - At least 2 classes
  - At least one augmentation
- On antidepressant
- No psychosis
- No moderate to severe SUD
- No acute medical issues, uncontrolled hypertension
- Able to comply with REMS rules

What is the right dose? (IV)

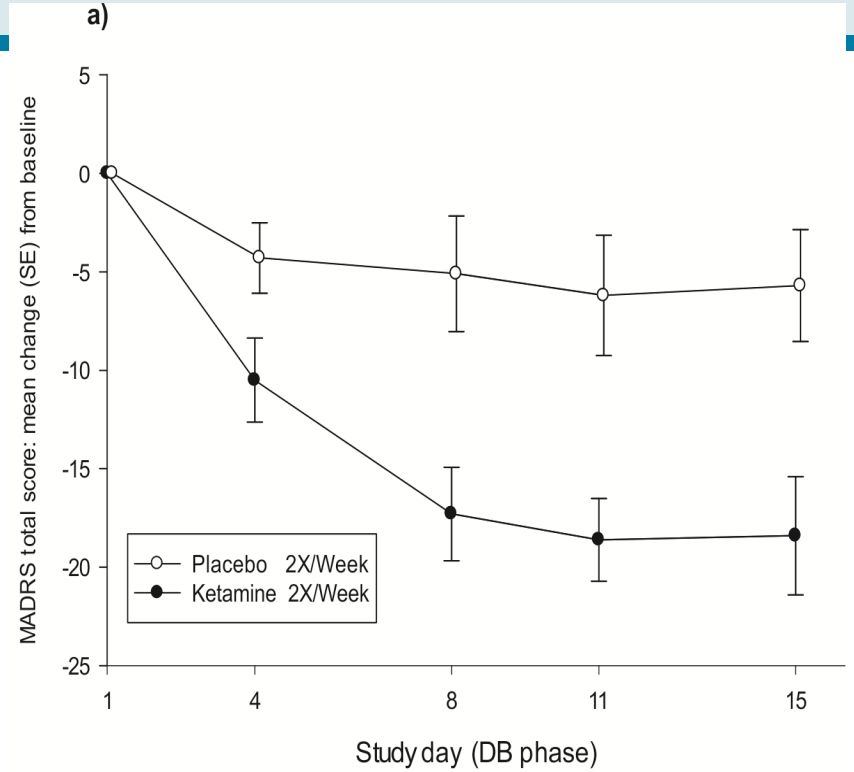


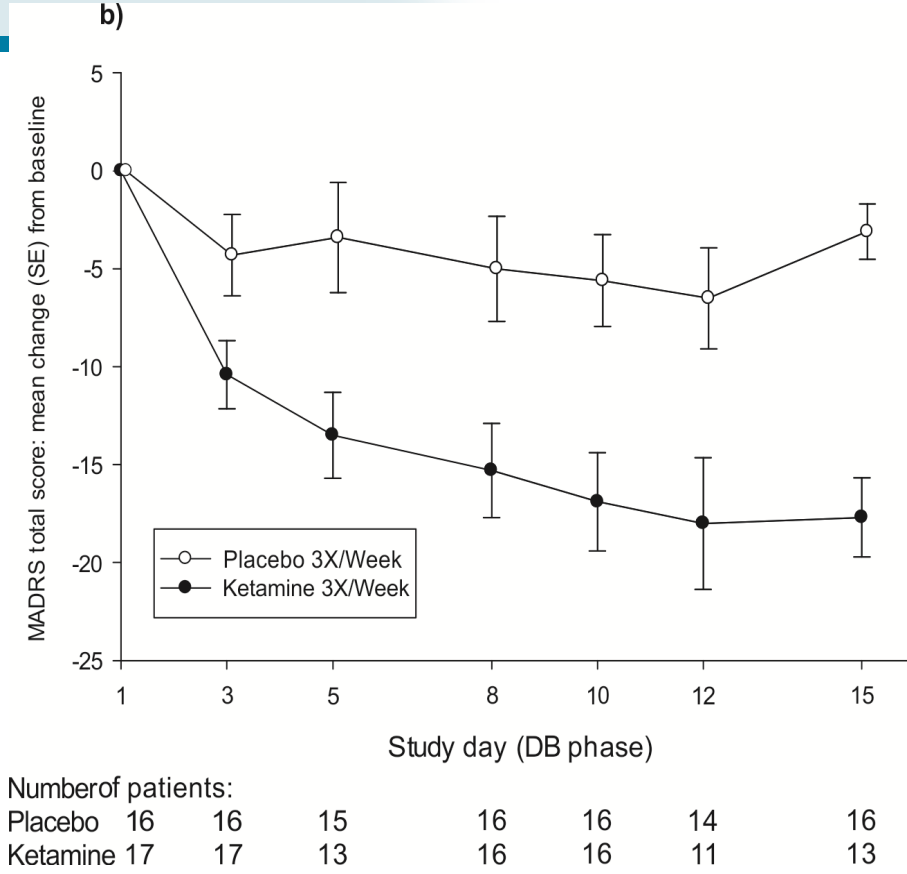
Escalating dose (0.5mg/kg ->0.75mg/kg)
if no response after 3 infusions (defined as 30% improvement HAMD)
(Cusin et al. 2017)



(Fava et al, Mol Psych 2018)

What is the right frequency? (IV)





Intravenous Ketamine in Adult Patients with Treatment-Resistant Depression: A Dose-Frequency Study. (Singh et al. Am J Psych 2016)

2 x/week equally efficacious as 3x/week

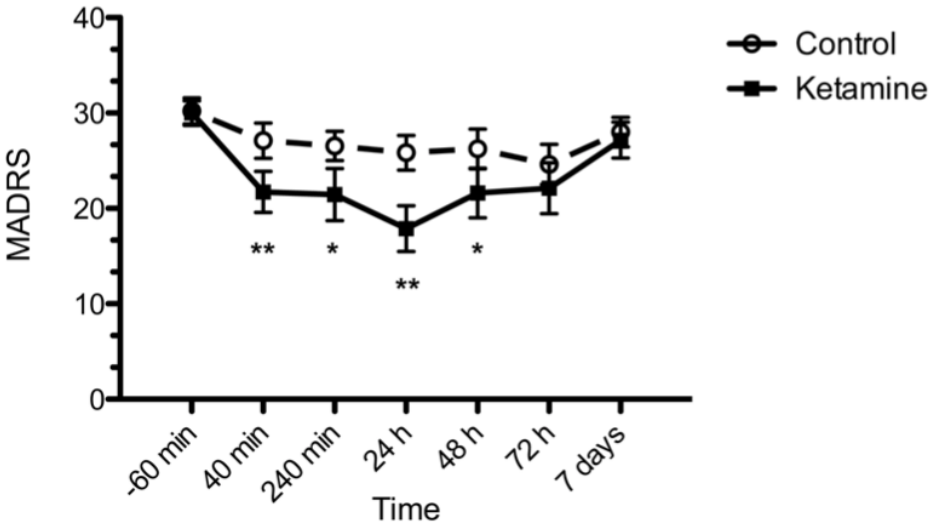
What is the right frequency? (IN)

Published in final edited form as:
Biol Psychiatry. 2014 December 15; 76(12): 970–976. doi:10.1016/j.biopsych.2014.03.026.

A Randomized Controlled Trial of Intranasal Ketamine in Major Depressive Disorder

Kyle A.B. Lapidus[1,2], **Cara F. Levitch**[1], **Andrew M. Perez**[3], **Jess W. Brallier**[3], **Michael K. Parides**[4], **Laili Soleimani**[1,5], **Adriana Feder**[1], **Dan V. Iosifescu**[1,2,6], **Dennis S. Charney**[1,2,7,*], and **James W. Murrough**[1,2,6,*]

[1]Mood and Anxiety Disorders Program, Department of Psychiatry, Icahn School of Medicine at Mount Sinai, New York, New York



50 pts, IN ketamine 50mg vs placebo
Randomized double blind crossover
1 dose IN ketamine vs saline

Significant improvement at 24 hours [p<0.001; est. mean MADRS score difference of 7.6 ± 3.7 (95% CI: 3.9 – 11.3)].
8/18 patients (44%) met response criteria with ketamine, compared to 1 /18 (6%) placebo (p=0.033).

What is the right frequency for Esketamine? (IN)

- Twice a week for 4 weeks - 56 or 84 mg ->weekly /every othr
- Treatment algorhythm:

decrease in treatment frequency on depressive symptom improvement (MADRS ≤ 12) and increase in treatment frequency on depressive symptom worsening (MADRS > 12).

Among 580 responders treated with weekly esketamine for the first 4 weeks in the optimization/maintenance phase 26% continued to improve, 50% maintained clinical benefit, and 24% worsened.

->recommendation was **to individualize frequency**

How long is the treatment?

- No rigorous long-term data beside registry on Esketamine, case series from MGH, 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 (?)
- Patients who have been chronically ill for >5 ys (the majority of patients in the clinic) **do relapse** when they stop ketamine

Ketamine is effective for SI

The American Journal of Psychiatry

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Articles

Full Access

Ketamine for Rapid Reduction of Suicidal Thoughts in Major Depression: A Midazolam-Controlled Randomized Clinical Trial

Michael F. Grunebaum, M.D., Hanga C. Galfalvy, Ph.D., Tse-Hwei Choo, M.P.H., John G. Keilp, Ph.D., Vivek K. Moitra, M.D., Michelle S. Parris, B.A., Julia E. Marver, B.A., Ainsley K. Burke, Ph.D., Matthew S. Milak, M.D., M. Elizabeth Sublette, M.D., Ph.D., Maria A. Oquendo, M.D., Ph.D., J. John Mann, M.D.

Published Online: 5 Dec 2017 https://doi.org/10.1176/appi.ajp.2017.17060647

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Abstract

Objective:

Pharmacotherapy to rapidly relieve suicidal ideation in depression may reduce suicide risk. Rapid reduction in suicidal thoughts after ketamine treatment has mostly been studied in patients with low levels of suicidal ideation. The authors tested the acute effect of adjunctive subanesthetic intravenous ketamine on clinically significant suicidal ideation in patients with major depressive disorder.

Method:

In a randomized clinical trial, adults (N=80) with current major depressive disorder and a score ≥4 on the Scale for Suicidal Ideation (SSI), of whom 54% (N=43) were taking antidepressant medication, were randomly assigned to receive ketamine or midazolam infusion. The primary outcome measure was SSI score 24 hours after infusion (at day 1).

Results:

The reduction in SSI score at day 1 was 4.96 points greater for the ketamine group compared with the midazolam group (95% CI=2.33, 7.59; Cohen's d=0.75). The proportion of responders (defined as having a reduction ≥50% in SSI score) at day 1 was 55% for the ketamine group and 30% for the midazolam group (odds ratio=2.85, 95% CI=1.14, 7.15; number needed to treat=4.0). Improvement in the Profile of Mood States depression subscale was greater at day 1 for the ketamine group compared with the midazolam group (estimate=7.65, 95% CI=1.36, 13.94), and this effect mediated 33.6% of ketamine's effect on SSI score. Side effects were short-lived, and clinical improvement was maintained for up to 6 weeks with additional optimized standard pharmacotherapy in an uncontrolled follow-up.

Esketamine is effective for SI

Efficacy and Safety of Intranasal Esketamine for the Rapid Reduction of Symptoms of Depression and Suicidality in Patients at Imminent Risk for Suicide: Results of a Double-Blind, Randomized, Placebo-Controlled Study

Carla M. Canuso, M.D., Jaskaran B. Singh, M.D., Maggie Fedgchin, Pharm.D., Larry Alphs, M.D., Ph.D., Rosanne Lane, M.A.S., Pilar Lim, Ph.D., Christine Pinter, M.S., David Hough, M.D., Gerard Sanacora, M.D., Ph.D., Husseini Manji, M.D., Wayne C. Drevets, M.D.

Objective: The authors compared the efficacy of standard-of-care treatment plus intranasal esketamine or placebo for rapid reduction of symptoms of major depression, including suicidality, among individuals at imminent suicide risk.

Method: In a double-blind, multicenter, proof-of-concept study, 68 participants were randomly assigned to receive esketamine (84 mg) or placebo twice weekly for 4 weeks, in addition to comprehensive standard-of-care treatment. The primary efficacy endpoint was change in score from baseline to 4 hours after initial dose on the Montgomery-Åsberg Depression Rating Scale (MADRS). Clinician global judgment of suicide risk (from the Suicide Ideation and Behavior Assessment Tool) was also assessed. Secondary endpoints included these measures at 24 hours and double-blind endpoint at day 25.

Results: A significantly greater improvement in MADRS score was observed in the esketamine group compared with the placebo group at 4 hours (least-square mean difference=−5.3, SE=2.10; effect size=0.61) and at ~24 hours (least-square mean difference=−7.2, SE=2.85; effect size=0.65), but not at day 25 (least-square mean difference=−4.5, SE=3.14; effect size=0.35). Significantly greater improvement was also observed in the esketamine group on the MADRS suicidal thoughts item score at 4 hours (effect size=0.67), but not at 24 hours (effect size=0.35) or at day 25 (effect size=0.29). Between-group reductions in clinician global judgment of suicide risk scores were not statistically different at any time point. The most common adverse events among participants in the esketamine group were nausea, dizziness, dissociation, unpleasant taste, and headache.

Conclusions: These preliminary findings indicate that intranasal esketamine compared with placebo, given in addition to comprehensive standard-of-care treatment, may result in significantly rapid improvement in depressive symptoms, including some measures of suicidal ideation, among depressed patients at imminent risk for suicide.

AJP in Advance (doi: 10.1176/appi.ajp.2018.17060720)

From: **Efficacy of Intravenous Ketamine for Treatment of Chronic Posttraumatic Stress Disorder: A Randomized Clinical Trial**

JAMA Psychiatry. 2014;71(6):681-688. doi:10.1001/jamapsy

Ketamine and PTSD

41 pts

0.5 mg/kg

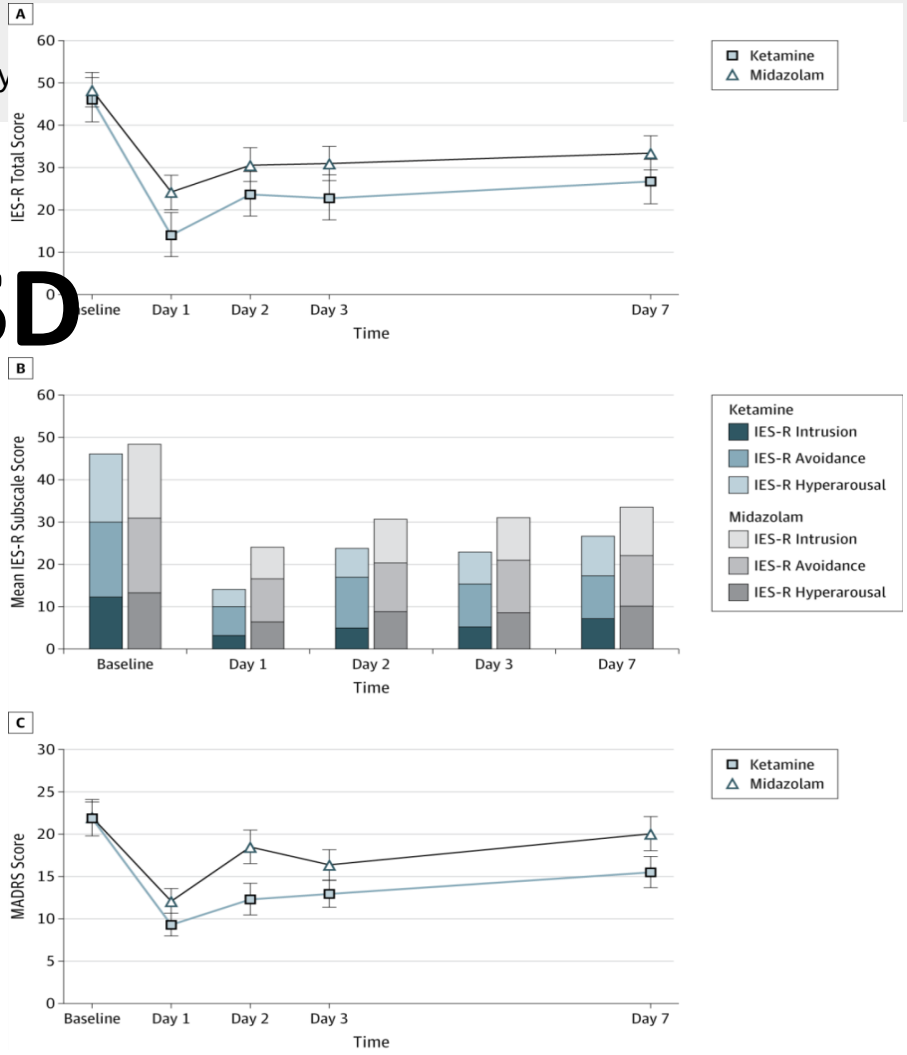


Figure Legend:

Changes in Posttraumatic Stress Disorder and Depressive Symptom Levels During the First PeriodChange in the Impact of Event Scale–Revised (IES-R) total score, the IES-R mean subscale scores, and the Montgomery-Asberg Depression Rating Scale (MADRS) score over 1 week for the first period (n = 41). Error bars represent standard errors. For this study, the IES-R was modified to inquire about symptoms over the previous 24 hours (instead of the previous 7 days).

A Randomized Controlled Trial of Repeated Ketamine Administration for Chronic Posttraumatic Stress Disorder

Adriana Feder, M.D., Sara Costi, M.D., Sarah B. Rutter, M.A., Abigail B. Collins, B.S., Usha Govindarajulu, Ph.D., Manish K. Jha, M.D., Sarah R. Horn, M.A., Marin Kautz, M.A., Morgan Corniquel, M.A., Katherine A. Collins, Ph.D., M.S.W., Laura Bevilacqua, M.D., Ph.D., Andrew M. Glasgow, M.D., Jess Brallier, M.D., Robert H. Pietrzak, Ph.D., M.P.H., James W. Murrough, M.D., Ph.D., Dennis S. Charney, M.D.

Objective: Posttraumatic stress disorder (PTSD) is a chronic and disabling disorder, for which available pharmacotherapies have limited efficacy. The authors' previous proof-of-concept randomized controlled trial of single-dose intravenous ketamine infusion in individuals with PTSD showed significant and rapid PTSD symptom reduction 24 hours postinfusion. The present study is the first randomized controlled trial to test the efficacy and safety of repeated intravenous ketamine infusions for the treatment of chronic PTSD.

Methods: Individuals with chronic PTSD (N=30) were randomly assigned (1:1) to receive six infusions of ketamine (0.5 mg/kg) or midazolam (0.045 mg/kg) (psychoactive placebo control) over 2 consecutive weeks. Clinician-rated and self-report assessments were administered 24 hours after the first infusion and at weekly visits. The primary outcome measure was change in PTSD symptom severity, as assessed with the Clinician-Administered PTSD Scale for DSM-5 (CAPS-5), from baseline to 2 weeks (after completion of all infusions). Secondary outcome measures included the Impact of Event Scale–Revised, the Montgomery-Åsberg Depression Rating Scale (MADRS), and side effect measures.

Results: The ketamine group showed a significantly greater improvement in CAPS-5 and MADRS total scores than the midazolam group from baseline to week 2. At week 2, the mean CAPS-5 total score was 11.88 points (SE=3.96) lower in the ketamine group than in the midazolam group (d=1.13, 95% CI=0.36, 1.91). Sixty-seven percent of participants in the ketamine group were treatment responders, compared with 20% in the midazolam group. Among ketamine responders, the median time to loss of response was 27.5 days following the 2-week course of infusions. Ketamine infusions were well tolerated overall, without serious adverse events.

Conclusions: This randomized controlled trial provides the first evidence of efficacy of repeated ketamine infusions in reducing symptom severity in individuals with chronic PTSD. Further studies are warranted to understand ketamine's full potential as a treatment for chronic PTSD.

Am J Psychiatry 2021; 178:193–202; doi: 10.1176/appi.ajp.2020.20050596

Posttraumatic stress disorder (PTSD) is a chronic and disabling psychiatric disorder, with a lifetime prevalence in the United States of approximately 6% (1). Rates vary by trauma

inhibitors (SSRIs) sertraline and paroxetine—are approved by the U.S. Food and Drug Administration (FDA) for PTSD treatment, and only four medications have shown at least

Ketamine and PTSD

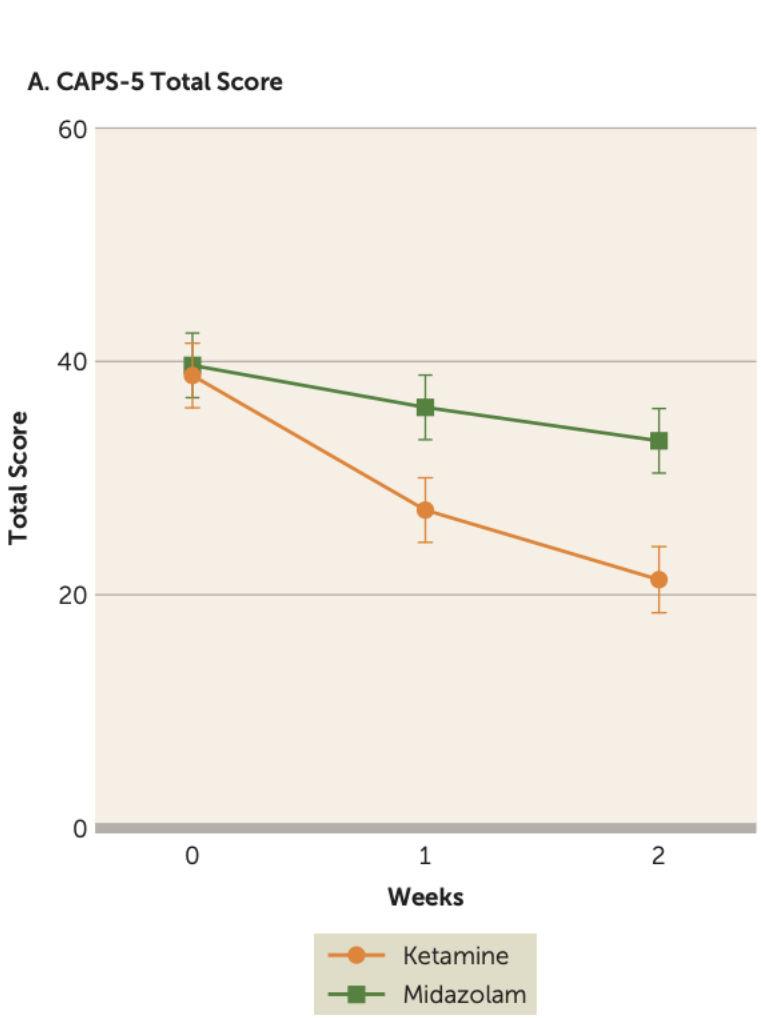
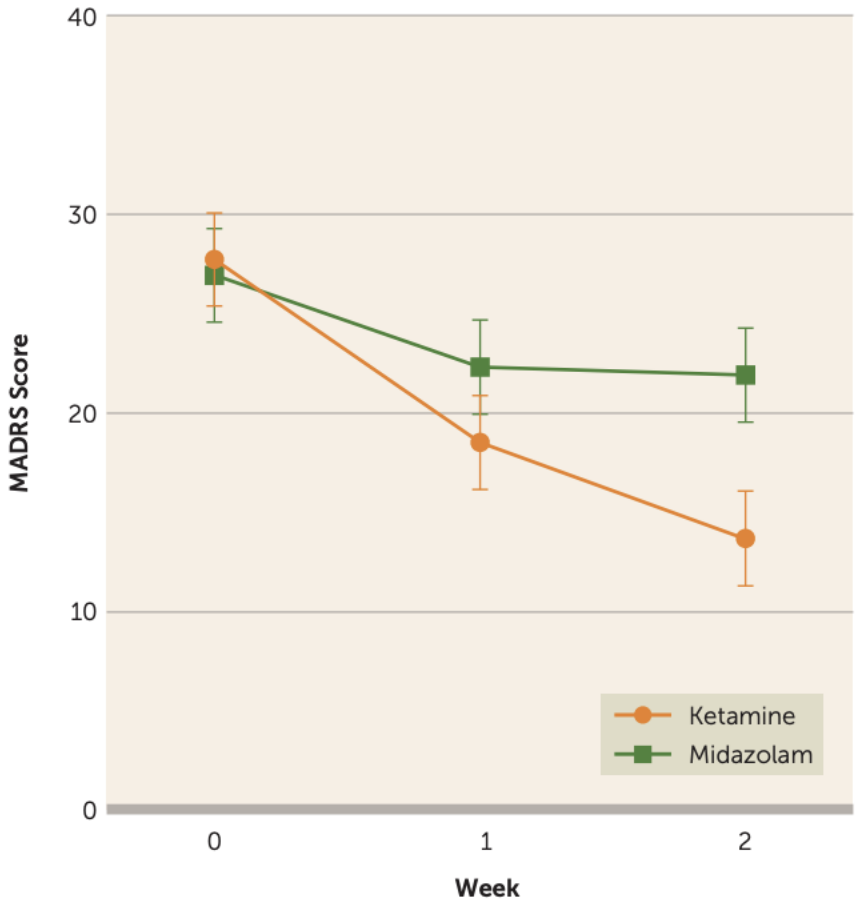


FIGURE 3. Effect of treatment with ketamine compared with midazolam on depressive symptom severity in patients with chronic PTSD[a]



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

- From literature 65-70%
- In extremely treatment refractory patients, at our site lower (Yale - of course - has better numbers..)
- On average 50%
- Post ECT failure still 45-50%
- 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…

Data from our clinic

- 85 patients who were ketamine naïve, QIDS-SR_{16} total score
- 70 % completed the induction series of 6 ketamine infusions,
  - 27 % discontinued and 3% were still in the induction phase
  - Reasons for early discontinuation: insufficient improvement (n=11), side-effects (n=3) including dissociative symptoms, agitation, and migraine, transition to intranasal ketamine treatment (n=3) and lost to follow-up (n=3).

- 18.3% were responders by infusion 6 and 35.4% improved by 35% or more
- BUT 50% of patients transitioned to maintenance treatment –self pay
- age, sex, employment, MDD vs BP, psychiatric comorbidity, history of suicide attempt, hospitalizations, number of failed lifetime antidepressant trials, history of failed lifetime ECT trials, and the QIDS-SR16 total score at baseline **were not associated with outcome**

Sakurai et al, J Affect Disord, 2020

Data from our clinic -II

- Among the 67 patients who had a suicidal ideation score >0
  - 18% achieved complete absence of suicidal ideation by infusion 6, and 37.3% decreased the score by at least 1 level
  - One patient committed suicide approximately 10 days after the fourth treatment of the induction phase possibly in the context of severe life stressors, even though his score of SI had decreased from 2 to 1
  - One pt attempted suicide after complete lack of improvement after infusion #6

55% Female, 70% college or above

average duration of current episode of 6.7±11.1 years

average of 7.4±3.7 previous antidepressant trials

Comorbidites GAD 37%, PTSD 7 %, OCD 7%, ADD 20%, others 25%

33% failed ECT, 28% failed TMS

CGI-S, mean ± SD	5.2±0.7
QIDS-SR16, mean ± SD	17.0±5.1

IV Ketamine Clinic opened in 2018

- Self-pay (until October 2020), 2 insurers since then
- MDD/BP depression, multiple comorbidities
- Generally healthy, well controlled medical issues
- Failed >4 antidepressants
- Referred by primary provider, in treatment
  - No SUD current, no psychosis
- Flexible ketamine dose (based on tolerability, efficacy)

Demographic and Clinical (n=120)

Highly educated
33% employed
High % comorbidities

Age in years, mean ± SD (range)	45.2±18.4
Female, n (%)	65 (54.2%)
Race/Ethnicity, n (%)	
Caucasian	111 (92.5%)
Asian	2 (1.7%)
Others	7 (5.8%)
Education completed, n (%)	
Grade 6-12 or graduated high school	10 (8.3%)
Some college	27 (22.5%)
Graduated 4-year college	46 (38.3%)
Graduate/professional degree	35 (29.2%)
Unknown	2 (1.7%)
Current marital status, n (%)	
Single, never married	61 (50.8%)
Married, civil union, cohabitating	47 (39.2%)
Separated, divorced, widowed	12 (10.0%)
Current employment status, n (%)	
Full-time	40 (33.3%)
Part-time	7 (5.8%)
Not employed	50 (41.7%)
Student	23 (19.2%)
Primary diagnosis, n (%)	
MDD	105 (87.5%)
BD, depressed	15 (12.5%)
Current concomitant psychiatric disorder, n (%)	75 (62.5%)
GAD	43 (35.8%)
PTSD	20 (16.7%)
OCD	10 (8.3%)
ADHD	22 (18.3%)
Others	28 (23.3%)

Demographic and Clinical. -II

Antidepressant combination	52 (43.3%)
Antipsychotic drug	53 (44.2%)
Mood stabilizer	48 (40.0%)
Multiple episodes, n (%)	79 (65.8%)
Duration of current episode, years, mean ± SD	7.1±10.5
History of suicide attempt, n (%)	33 (27.5%)
Lifetime mean number of failed antidepressant trials, mean ± SD	7.8±3.8
Treatment history with ECT, n (%)	42 (35.0%)
Treatment history with TMS, n (%)	32 (26.7%)
QIDS-SR_{16}, mean ± SD	17.4±4.9

What are our Outcomes?

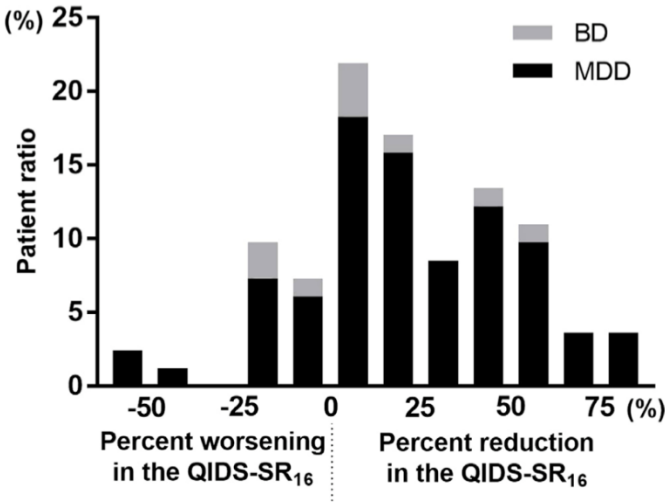
- Over 70% of patients complete the initial series of 6
- 30% drop out –tolerability, insufficient improvement and costs
- Mean final dose of ketamine was 0.60-75mg/kg

- Slightly less than 20% achieved response defined as 50%improvement, **and 1/3 improve 35% or more** (on QIDS-16 score)
- YET approximately 50% decides to continue with maintenance infusions – self-pay
- 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)



Canadian data

- Adults (N = 213; age = 45) with MDD or BP
- minimum of Stage 2 antidepressant resistance
- 0.5-0.75 mg/kg
- response rate (QIDS-SR16 ≥ 50%) **was 27%**
- remission (QIDS-SR16 total score ≤5) was 13%
- anxiolytic effects, improved overall psychosocial function and reduced suicidal ideation

J Affect Disord 2020 Sep 1;274:903-910.

Predictors of response?

	F	P value
Age	6.68	0.01*
Sex	2.06	0.16
Marriage	2.78	0.07
Employment	0.95	0.42
Primary diagnosis	0.07	0.79
Psychiatric comorbidity	0.29	0.59
Recurrence	1.90	0.17
Duration of current episode	0.67	0.41
Prior suicide attempt	1.49	0.23
History of neuromodulation	5.12	0.03 *
Number of failed antidepressant trials	0.18	0.68
Prior tachyphylaxis	0.04	0.84
QIDS-SR_{16} at baseline	0.82	0.37

Few comments…

- For 50% of patients the apparently low level of improvement is sufficient to justify continuing ketamine treatment, despite side effects during the infusion and costs of the treatment
- Response rate to IV ketamine in our clinic appears significantly lower compared to rates published in RCT
- High level of treatment resistance of our population
- Complex medication regimen
- QIDS-16 assessment at the time of the visit does not capture change in functional outcome
- Common fluctuations with life events, medical illness
- In cases of long-term, severe chronic illness stopping the ketamine is almost invariably associated with relapse

Informed consent: do I need to change my meds?

- BP disorder: must be on mood stabilizers *
- Early on tried to taper BDZ, gabaergic drugs

J Clin Psychiatry. 2017 Mar;78(3):e308-e309. doi: 10.4088/JCP.16l11277.

The Antidepressant Effect of Repeat Dose Intravenous Ketamine Is Delayed by Concurrent Benzodiazepine Use.

Aust N Z J Psychiatry. 2015 Dec;49(12):1227. doi: 10.1177/0004867415590631. Epub 2015 Jun 9.

Benzodiazepines may reduce the effectiveness of ketamine in the treatment of depression.

Ford N[1], Ludbrook G[2], Galletly C[3].

-Rifampicine, Itraconazole, Ticlopidine, Macrolides, Grapefruit juice

*Lamotrigine?

16 HV, pretreatment with lamotrigine (300 mg) attenuated acute effects of IV ketamine at 5' (Anand et al. Arch Gen Psych 2000)

- naltrexone?

Other meds and ketamine

Pharmacodynamic interactions between ketamine and psychiatric medications used in the treatment of depression: a systematic review. Veraart et al, 2021

- 24 studies included.
- Lithium, valproic acid: no significant interactions
- Lamotrigine: 2/5 studies indicated attenuated effects
- Benzodiazepines: reduce the duration of antidepressant effect.
- MAO-I: no relevant changes in vital signs
- Haloperidol 1/3 studies indicated an interaction
- Risperidone 4 imaging studies, attenuating effect on ketamine-induced brain perfusion changes.
- Clozapine: blunted ketamine-induced positive symptoms in patients with schizophrenia, but not in healthy subjects.
- Olanzapine no effect on ketamine's acute psychotomimetic effects.

Informed consent: what happens after 6 infusions?

- How to sustain the effect of ketamine?
- Continue the AD –relapse when the AD is stopped
- More ketamine infusions? $$
- Lithium? Possibly in BP, no clear signal in MDD
- riluzole not effective

Cumulative and sustained benefit

Am J Psychiatry. 2019 May 1;176(5):401-409. doi: 10.1176/appi.ajp.2018.18070834. Epub 2019 Mar 29.

Single, Repeated, and Maintenance Ketamine Infusions for Treatment-Resistant Depression: A Randomized Controlled Trial.

Phillips JL[1], Norris S[1], Talbot J[1], Birmingham M[1], Hatchard T[1], Ortiz A[1], Owoeye O[1], Batten LA[1], Blier P[1].

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Abstract

OBJECTIVE: Subanesthetic ketamine doses have been shown to have rapid yet transient antidepressant effects in patients with treatment-resistant depression, which may be prolonged by repeated administration. The purpose of this study was to evaluate the antidepressant effects of a single ketamine infusion, a series of repeated ketamine infusions, and prolongation of response with maintenance infusions.

METHODS: Forty-one participants with treatment-resistant depression completed a single-site randomized double-blind crossover comparison of single infusions of ketamine and midazolam (an active placebo control). After relapse of depressive symptoms, participants received a course of six open-label ketamine infusions administered thrice weekly over 2 weeks. Responders, classified as those participants who had a ≥50% decrease in their scores on the Montgomery-Åsberg Depression Rating Scale (MADRS), received four additional infusions administered once weekly (maintenance phase).

RESULTS: Compared with midazolam, a single ketamine infusion elicited a significantly greater reduction in depressive symptoms at the primary efficacy endpoint (24 hours postinfusion). Linear mixed models revealed cumulative antidepressant effects with repeated infusions and doubling of the antidepressant response rate. Fifty-nine percent of participants met response criteria after repeated infusions, with a median of three infusions required before achieving response. Participants had no further change in MADRS scores during weekly maintenance infusions.

CONCLUSIONS: Repeated ketamine infusions have cumulative and sustained antidepressant effects. Reductions in depressive symptoms were maintained among responders through once-weekly infusions. These findings provide novel data on efficacious administration strategies for ketamine in patients with treatment-resistant depression. Future studies should further expand on optimizing administration to better translate the use of ketamine into clinical settings.

Informed consent: long-term side effects?

- 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

How to get ketamine at MGH

- Rapidly evolving situation
- **BCBS of MA and Allways agreed to cover infusions**
- **IV ketamine SELF PAY** is 530$ per infusion, recommended x6 in 3 weeks, followed by monthly maintenance infusions

Esketamine at MGH?

- **S-ketamine** or Spravato is FDA-approved for TRD
- Drug cost: 600-900$ per dose
- **CAN BE ADMINISTERED AT THE OFFICE ONLY**
- Twice a week for 4 weeks, then weekly afterwards
- **2 hours** mandatory observation period EACH VISIT
- REMS (Risk Evaluation and Mitigation Strategy):
  - Healthcare setting certified
  - Providers certified
  - Dispensing Pharmacy certified
  - Patient enrolled in a registry – monitoring forms
  - Vital signs and AEs monitoring

Esketamine in the ED?

- Janssen is pursuing the indication for MDD with SI with intent
- Two identical, **double-blind, randomized, placebo-controlled, phase 3 studies** evaluated the efficacy of Esketamine nasal spray plus Standard of Care compared with placebo nasal spray + SOC in reducing depression symptoms in **patients with MDD and active suicidal ideation with intent** (N approx. 450)
- Unclear effect on suicidal BEHAVIOR

IN Ketamine in the ED?

ARCHIVES OF SUICIDE RESEARCH
https://doi.org/10.1080/13811118.2021.1878078

Single, Fixed-Dose Intranasal Ketamine for Alleviation of Acute Suicidal Ideation. An Emergency Department, Trans-Diagnostic Approach: A Randomized, Double-Blind, Placebo-Controlled, Proof-of-Concept Trial

Yoav Domany and Cheryl B. McCullumsmith

ABSTRACT

Background: Suicidal patients often present to the emergency department, where specific anti-suicidal treatment is lacking. Ketamine, a Glutamate modulator and a rapidly acting antidepressant with anti-suicidal properties, might offer relief.

Aims: Evaluation of single, fixed-dosed intranasal ketamine for acute suicidal ideation in the emergency department.

Methods: Between August 2016 and April 2018, 30 eligible suicidal subjects, scheduled for psychiatric hospitalization, independently of their psychiatric diagnosis, were randomized to intranasal ketamine 40 mg or saline placebo. Safety and efficacy evaluations were scheduled for 30, 60, 120 and 240 min post administration and on days 1, 2, 3, 4, 5, 7, 21 and 28. Primary outcome was suicidal ideation.

Results: Fifteen subjects were randomized for each study group. All were analyzed for primary and secondary outcomes. Four hours post administration, the mean difference in suicidal symptoms between the groups, measured by the Montgomery-Åsberg Depression Rating Scale (MADRS) item of suicidal thoughts (MADRS-SI), was 1.267 (95% confident interval 0.1–2.43, $p < 0.05$) favoring treatment. Remission from suicidal ideation was evident in 80% for the ketamine group compared with 33% for the controls ($p < 0.05$). The mean difference in depressive symptoms, measured by MADRS, at the same time was 9.75 (95% confident interval 0.72–18.79, $p < 0.05$) favoring ketamine. Treatment was safe and well-tolerated. Conclusions: Single, fixed-dose, intranasal ketamine alleviated suicidal ideation and improved depressive symptoms four hours post administration. We present here an innovative paradigm for emergency department management of suicidal individuals. Future larger-scale studies are warranted. ClinicalTrials.gov Identifier: NCT02183272

KEYWORDS
Ketamine; intra-nasal; suicidal ideation; emergency department

Access issues at MGH

- 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, 9 new patients every 3-4 weeks - no waitlist

- Extremely complex patients, multiple psychiatric comorbidities, mood fluctuations, relapses

Any ketamine in the ED? In the unit?

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?

Symptomatic improvement vs Functional Recovery

- 40-50% of patients **felt better with ketamine for the first time in years**
- Short duration of effect (treatment resistance -> 1/duration of effect, often only 1-2 days)
- Then can become again severely depressed and suicidal
- In chronically ill patients symptom improvement does not translate in functional recovery!
- Need good CBT team

Future thoughts

- Access to the clinic from ED or inpatient unit for pts with elevate suicidal risk? Induction -> maintenance
- Integration with psychosocial interventions, CBT specifically developed for patients on ketamine, IOP, PE +ketamine for PTSD
- rehabilitation center (especially vocational)
- **NEW : MGH center for Neuroscience of Psychedelics**

questions?