MASSACHUSETTS GENERAL HOSPITAL
PSYCHIATRY ACADEMY

Ketamine and Esketamine
From Research to Clinical practice

Cristina Cusin, MD
Depression Clinical and Research Program, MGH
Associate Professor HMS

Disclosures

Cristina Cusin 2012-2017:

- **Speaking/CME/Consulting:** Janssen, Takeda, Boehringer, Lundbeck, Alkermes, Perception
- **Research Grants**: Clexio, Janssen, Shenox, Otsuka
- **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)

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

- Design published in 2018

Study Protocol Clinical Trial

Medicine

OPEN

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

Protocol for a non-inferiority clinical trial

Fernanda S. Correia-Melo, MD[a], Gustavo C. Leal, MD[a,b], Michelle S. Carvalho, MSc[c], Ana Paula Jesus-Nunes, BA, MSc[a], Carolina B.N. Ferreira, MD, MSc[c], Flávia Vieira, BA[a], Guilherme Magnavita, MD[b], Lucas A.S. Vale, MD[d], Rodrigo P. Mello, MD[b], Carolina Nakahira, MD[e], Felipe C. Argolo, MD[c], Tanise Cardoso, BA[f], Cezar D.S. Souza, MD[d], Ana Teresa C. Fontes[b], Marcelo B. Ferreira, MD[d], Lucas Araújo-de-Freitas, MD[a], Marco A. Tuena, MD[e], Mariana V.F. Echegaray, MD[b], Diogo E. Cavalcanti, BA, MSc[b], Ana C. Lucchese, MS[e], Igor D. Bandeira, MD, MSc[b], Manuela Telles, MD[b], Cássio S. Lima, BA, MSc[f], Aline S. Sampaio, MD[a,b], Samantha S. Silva, MD[b], Roberta F. Marback, BA, PhD[b], José A. Del-Porto, MD, PhD[e], José Neander Abreu, BA, PhD[f], Luciana M. Sarin, MD[e], Camilla S. Paixão, MSc[g,h], Lucas P. Carvalho, BS, PhD[g,h], Paulo R.L. Machado, MD, PhD[g], Gustavo Turecki, MD, PhD[i], Acioly L.T. Lacerda, MD, PhD[c,e,j], Lucas C. Quarantini, MD, PhD[a,b,*]

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.

JAMA Network | Open

Original Investigation | Psychiatry

Assessment of Relationship of Ketamine Dose With Magnetic Resonance Spectroscopy of Glx and GABA Responses in Adults With Major Depression
A Randomized Clinical Trial

Matthew S. Milak, MD; Rain Rashid, BS; Zhengchao Dong, PhD; Lawrence S. Kegeles, MD, PhD; Michael F. Grunebaum, MD; R. Todd Ogden, PhD; Xuejing Lin, MA; Stephanie T. Mulhern, BA; Raymond F. Suckow, PhD; Thomas B. Cooper, MA; John G. Keilp, PhD; Xiangling Mao, MS; Dikoma C. Shungu, PhD; J. John Mann, MD

38 subjects

TRD on no meds (?)

Placebo/ketamine

(0.1,0.2,0.3,0.4, 0.5) mg/kg

MRS

VMPFC

Glx and GABA levels

Abstract

IMPORTANCE A single subanesthetic dose of ketamine produces an antidepressant response in patients with major depressive disorder (MDD) within hours, but the mechanism of antidepressant effect is uncertain.

OBJECTIVE To evaluate whether ketamine dose and brain glutamate and glutamine (Glx) and γ-aminobutyric acid (GABA) level responses to ketamine are related to antidepressant benefit and adverse effects.

DESIGN, SETTING, AND PARTICIPANTS This randomized, parallel-group, triple-masked clinical trial included 38 physically healthy, psychotropic medication–free adult outpatients who were in a major depressive episode of MDD but not actively suicidal. The trial was conducted at Columbia University Medical Center. Data were collected from February 2012 to May 2015. Data analysis was conducted from January to March 2020.

INTERVENTION Participants received 1 dose of placebo or ketamine (0.1, 0.2, 0.3, 0.4, or 0.5 mg/kg) intravenously during 40 minutes of a proton magnetic resonance spectroscopy scan that measured ventro-medial prefrontal cortex Glx and GABA levels in 13-minute data frames.

MAIN OUTCOMES AND MEASURES Clinical improvement was measured using a 22-item version of the Hamilton Depression Rating Scale (HDRS-22) 24 hours after ketamine was administered. Ketamine and metabolite blood levels were measured after the scan.

Key Points

Question What is the relationship between the antidepressant effect of ketamine and ketamine dose and bloc level, and is its antidepressant effect mediated by an effect on ventro-medi prefrontal cortical glutamate and glutamine or γ-aminobutyric acid response?

Findings This randomized clinical tria of 38 patients with major depression found a relationship of ketamine dose and blood level with antidepressant response at 24 hours. Ketamine suppression of glutamate and glutami in the ventro-medial prefrontal cortex mediated the relationship of ketamine dose and level with antidepressant effect but was unrelated to psychotomimetic side effects.

Meaning The findings of this study suggest that glutamate and glutamine

RESULTS

The **lower** the Glx response, the better the antidepressant response

Glx and GABA response were not related to adverse effects

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 does ketamine work?**
- **How to get ketamine at MGH**
  - – insurance coverage
- Symptomatic improvement vs functional recovery
- Ketamine clinic and working with very sick patients

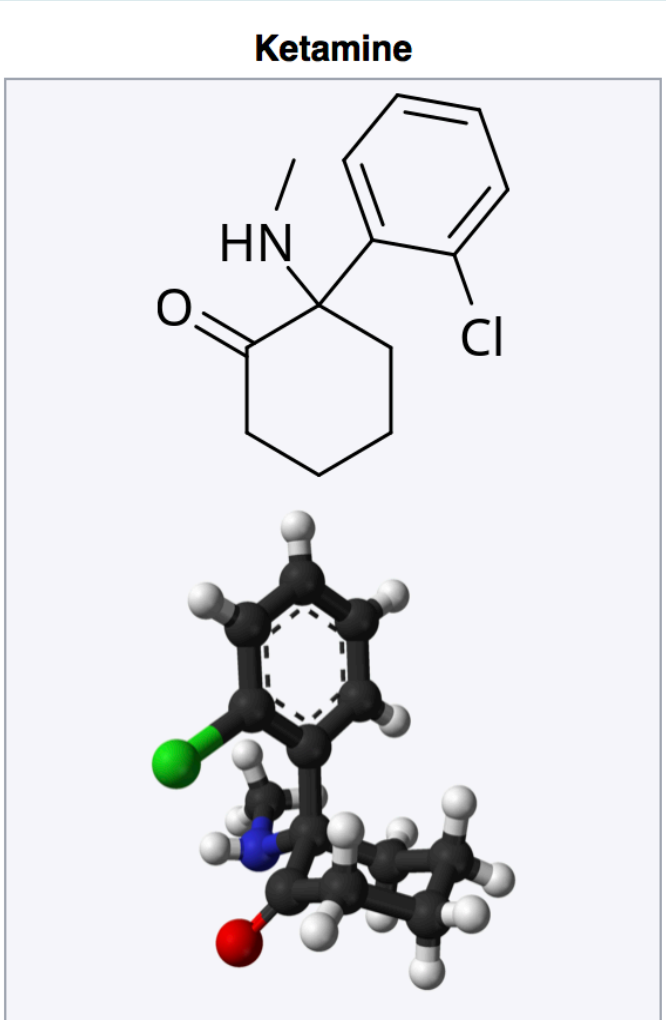
Ketamine facts

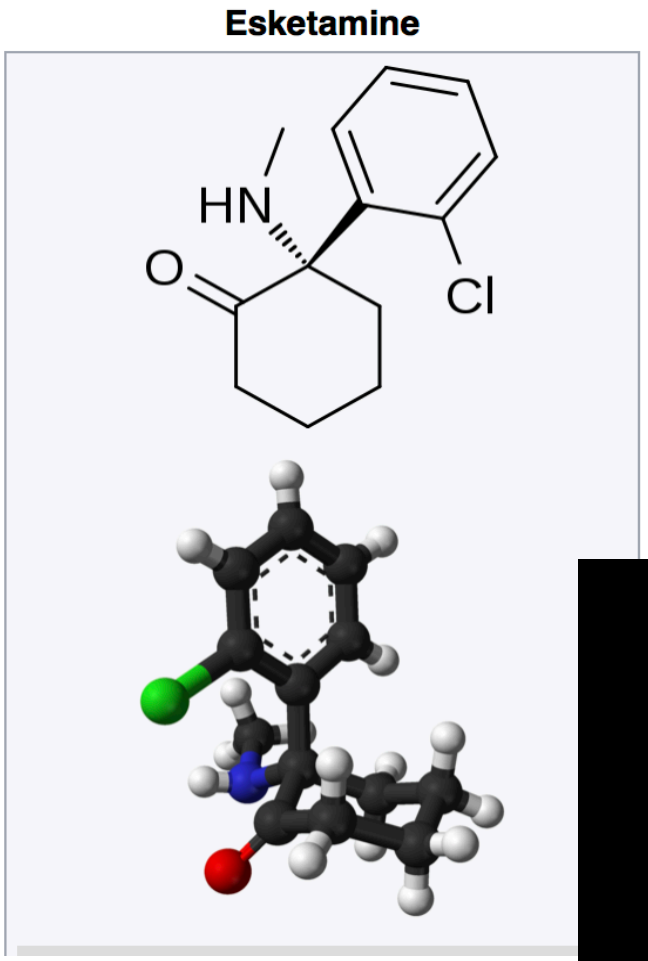
- **Ketamine** is an **old anesthetic and analgesic**, FDA-approved in 1970, widely used in the ED, OR, ECT, pain clinics, battlefield, veterinary medicine

- 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

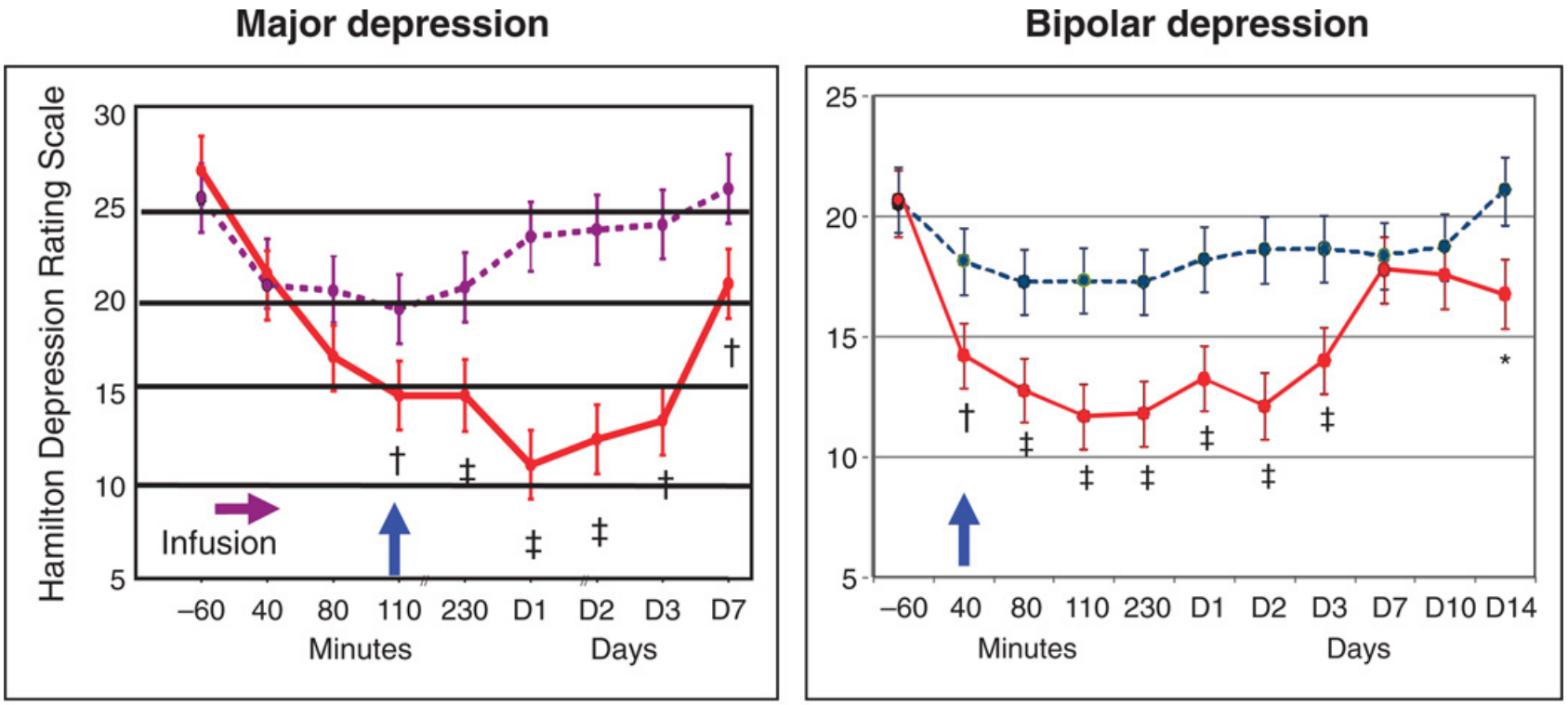
Abstract

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

Ketamine vs. Placebo in Unipolar and Bipolar Depression



‡$P < 0.001$; †$P < 0.01$; and *$P < 0.05$.

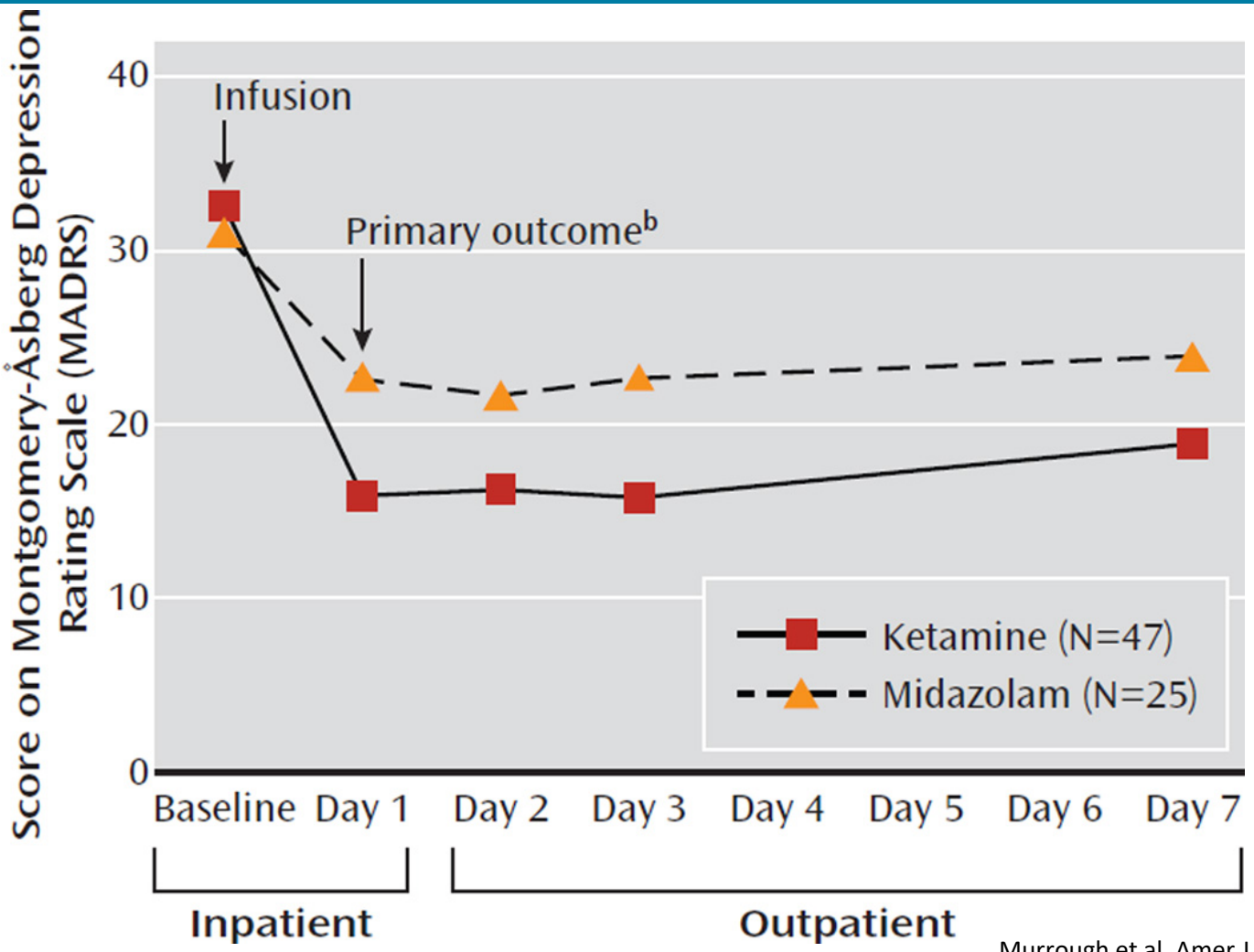
Dotted Line = Placebo

Solid Line = Ketamine

Zarate et al. Arch. Gen. Psychiatry, 2006.
Diazgranados et al. Arch. Gen. Psychiatry, 2010.

Courtesy Dr Ionescu

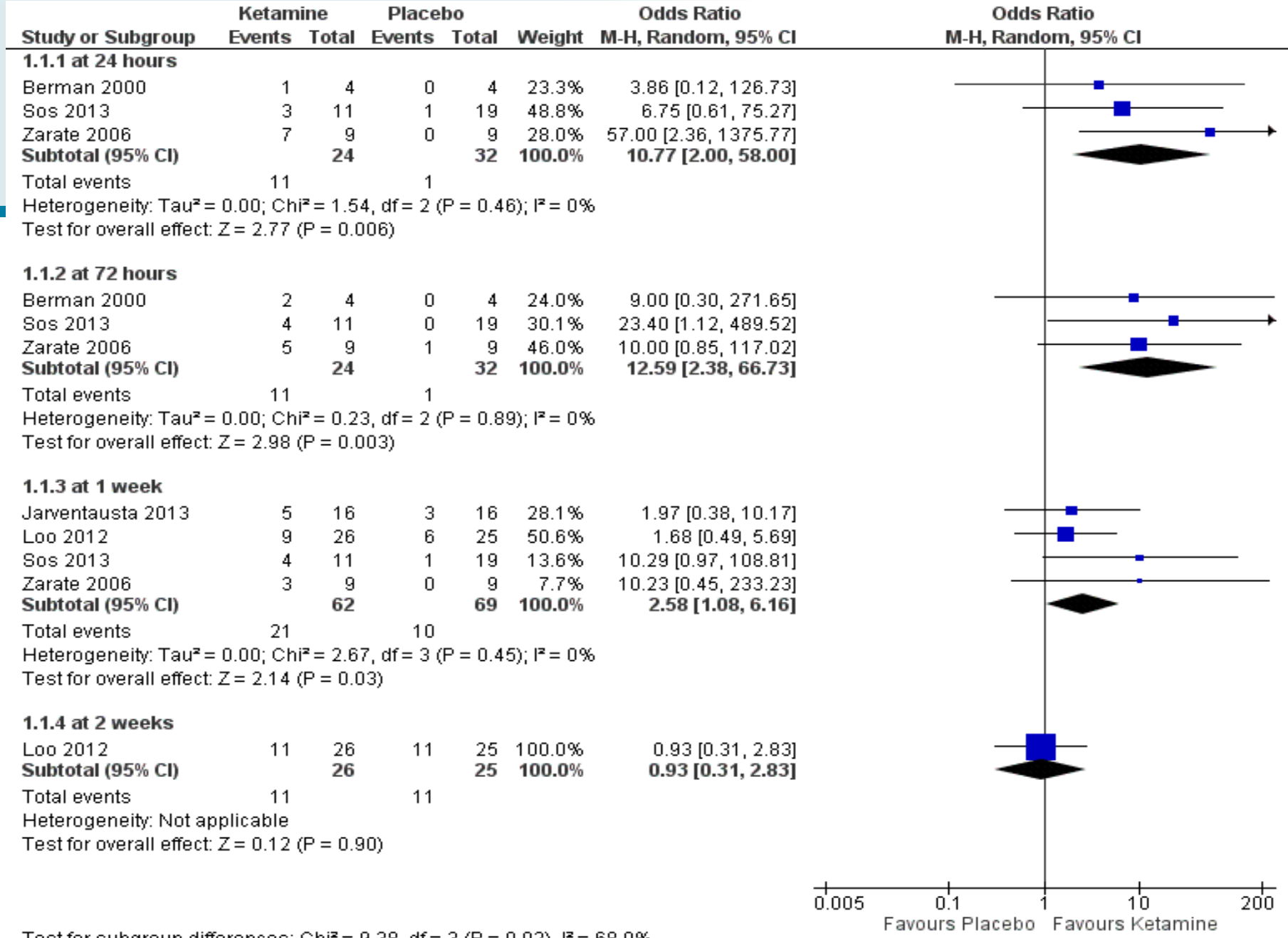
Ketamine vs. Midazolam in TRD



p≤0.02;

Murrough et al, Amer J Psych. 2013

Courtesy Dr Ionescu



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Cochrane review 2015

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)

How is ketamine administered?

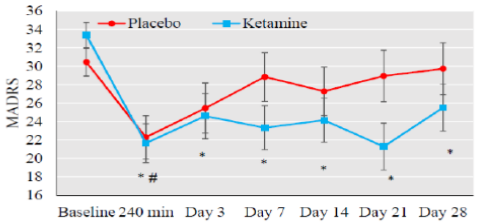
- LOW Bioavailability when ketamine is given **orally** (17-25% of IV dose) or sublingually (30-40%)
  - Few small studies in cancer pain
  - Slow onset of action
- I**ntranasal administration (IN)** is approx. 50%
- Extensive first-pass hepatic metabolism
- Half-life 3-5 hours
- **Intravenous (IV) has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

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

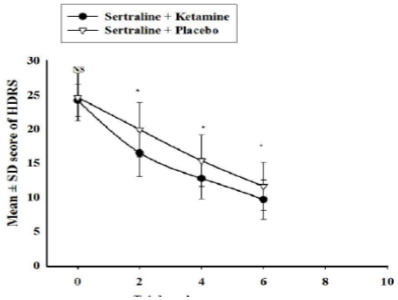
Oral ketamine?

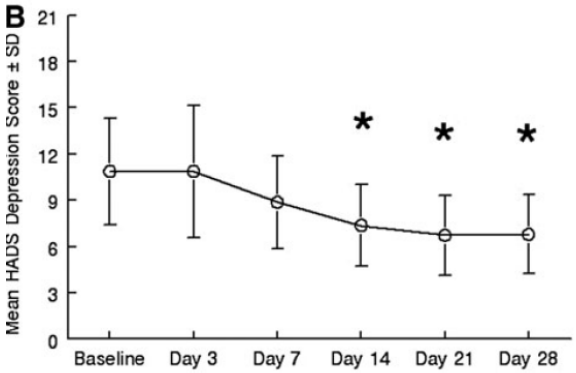
- **Ichilov study, Israel** (Domany et al, 2018)
  - 1 mg/kg oral Ketamine 3 times a week
  - PEP: MADRS at 21 days
  - Largest effect observed at day 21

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

Paul Glue [1], Natalie J Medlicott [2], Shona Neehoff [3], Peter Surman [4], Fred Lam [5], Noelyn Hung [5], Cheung-Tak Hung [5]

Affiliations – collapse

Affiliations

1 Hazel Buckland Chair of Psychological Medicine, School of Medical Sciences, University of Otago, PO Box 913, Dunedin, 9054, New Zealand.
2 School of Pharmacy, University of Otago, Dunedin, New Zealand.
3 Psychological Medicine, University of Otago, Dunedin, New Zealand.
4 Douglas Pharmaceuticals Ltd, Auckland, New Zealand.
5 Zenith Technology Ltd, Dunedin, New Zealand.

PMID: 32523677 PMCID: PMC7235665 DOI: 10.1177/2045125320922474
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

Sanne Y. Smith-Apeldoorn[1*], Jolien K. E. Veraart[1,2], Jeanine Kamphuis[1], Antoinette D. I. van Asselt[3], Daan J. Touw[4], Marije aan het Rot[5] and Robert A. Schoevers[1]

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

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 who were 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) or placebo

oral mirtazapine (30 mg)

significantly impaired

on road driving performance

Springer PSYCHOPHARMACOLOGY
springer.com

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

PMCID: PMC5660834
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]

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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

- >750 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)

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:

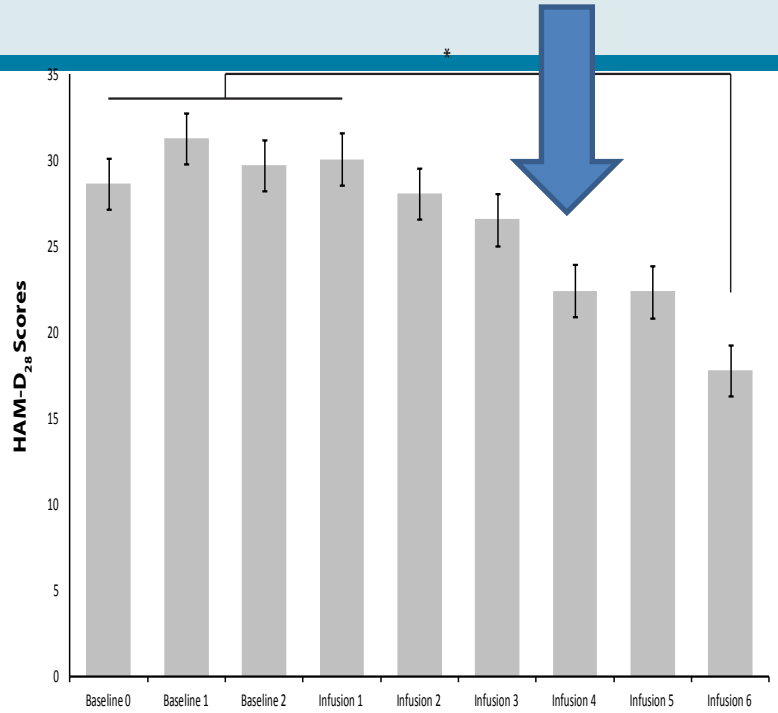
- substance use disorders (sobriety for how long? *),
- Psychosis
- Unstable medical illness (?).
- Psychiatrist not involved, patients self-referred
- No escort available for transportation – MGH mandates an escort, no exceptions (no matter how low the dose)
- Patient not providing access to medical 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

- What about patients with advanced cancer and depression?
- What about MCI and depression?
- What about mixed state/rapid cycling?

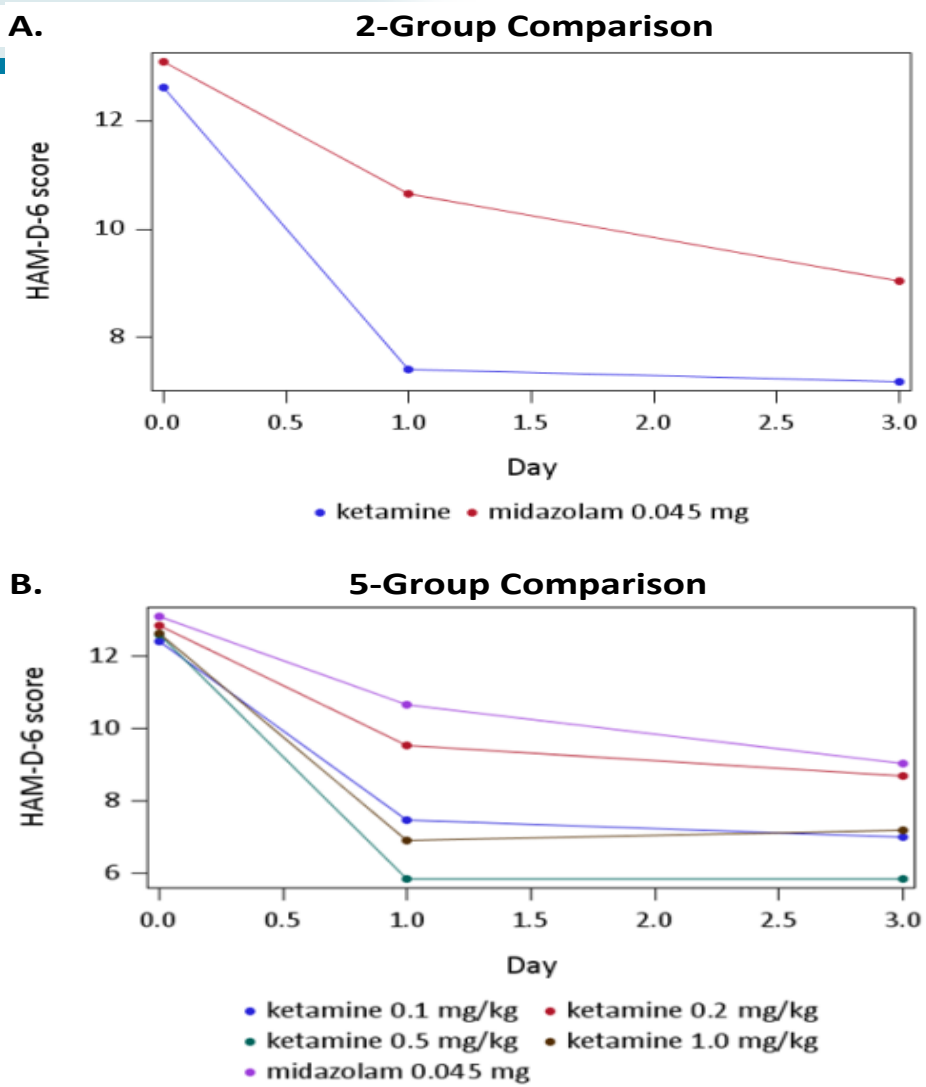
Who are the right patients? (Esketamine, IN)

- Must be referred by treating psychiatrist
- MDD, failed at least 2 antidepressants
- 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)

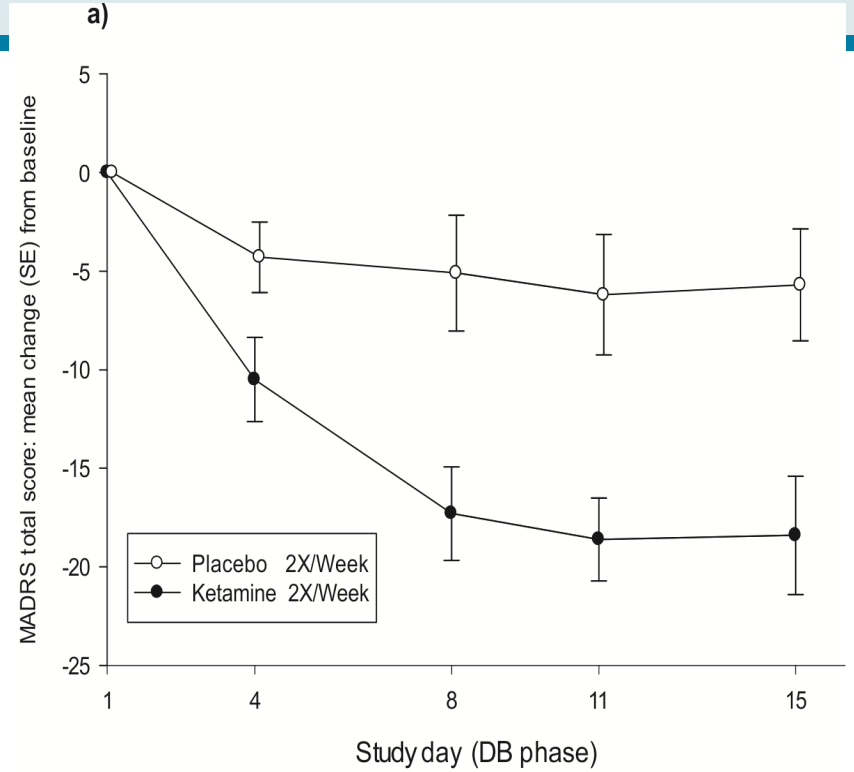


Escalating dose (0.5mg/kg ->0.75mg/kg)
if no response after 3 infusions (defined as 30% improvement HAMD)
(Cusin et al. 2017)



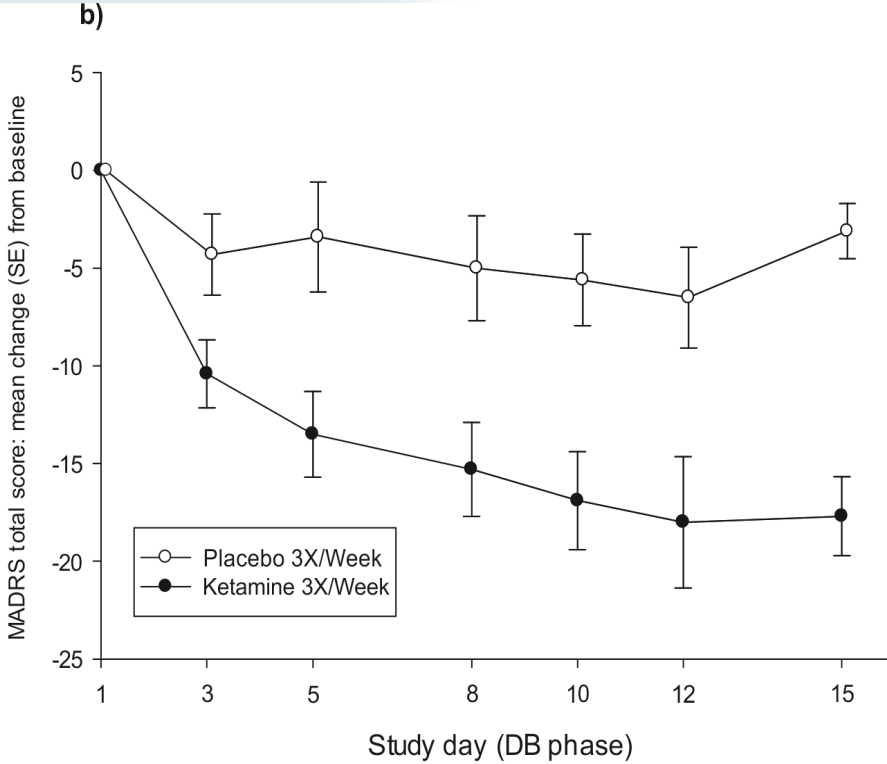
(Fava et al, Mol Psych 2018)

What is the right frequency? (IV)



Number of patients:

Placebo	16	15	13	13	13
Ketamine	18	17	15	16	16



Numberof patients:

Placebo	16	16	15	16	16	14	16
Ketamine	17	17	13	16	16	11	13

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

2x/week equally efficacious as 3x/week

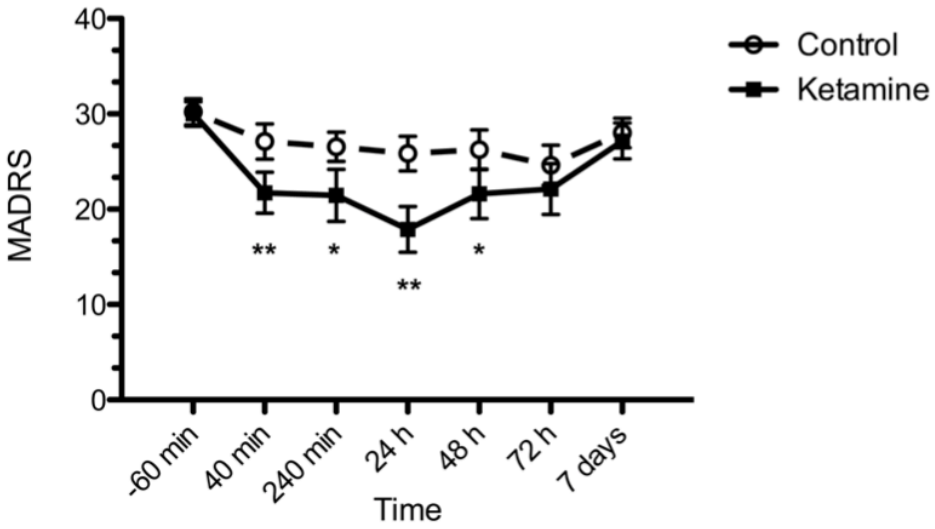
What is the right frequency? (IN)

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
- 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

Current Issue | Archive | About | Residents' Journal | AJP In Advance | Podcast | CME | Authors & Reviewers

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)

Ketamine and PTSD

Efficacy of Intravenous Ketamine for Treatment of Chronic Posttraumatic Stress DisorderA Randomized Clinical Trial

Feder et al JAMA Psych 2014

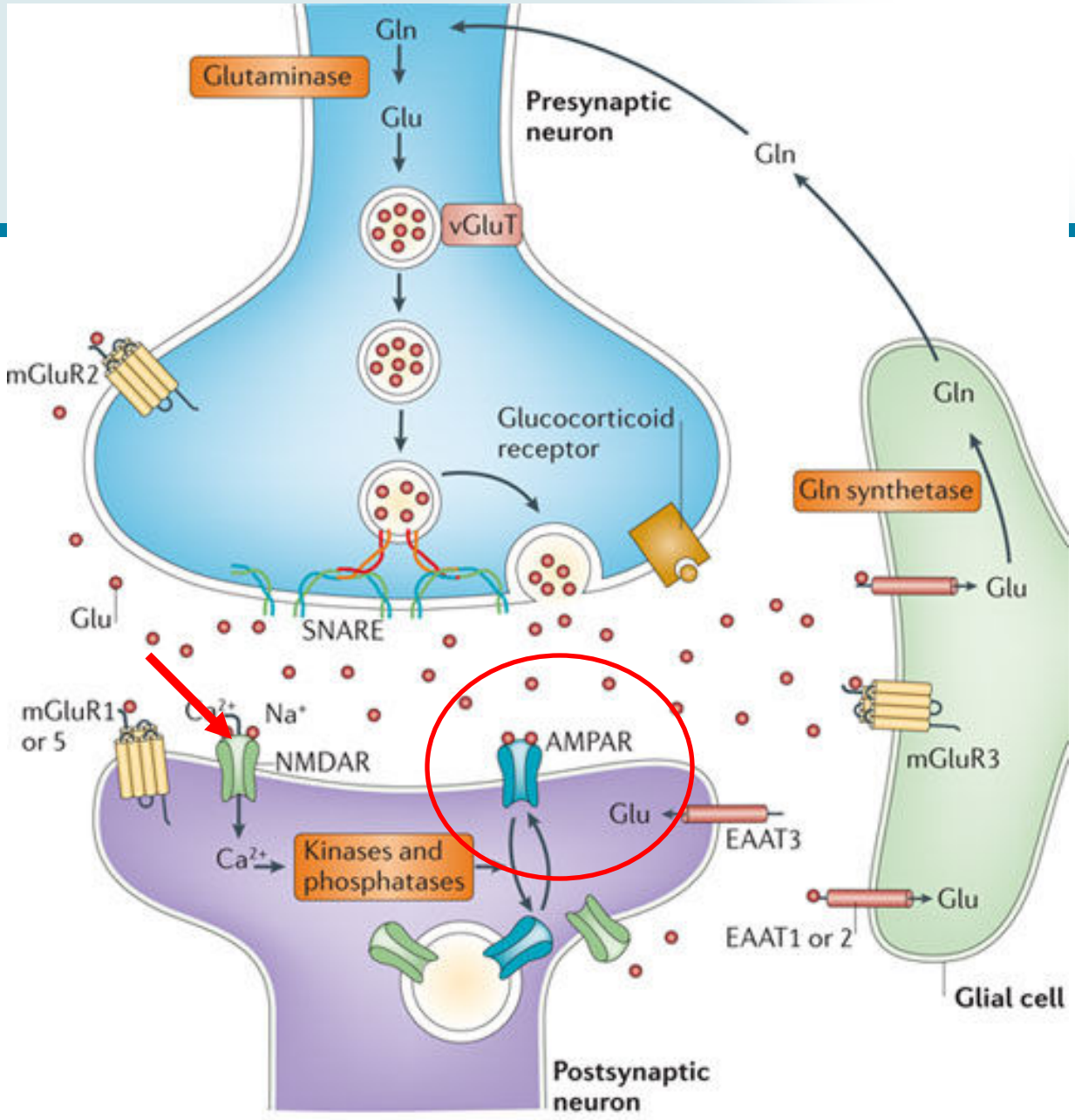
- Proof-of-concept, randomized, double-blind, crossover trial comparing ketamine with an active placebo control, midazolam
- 41 patients randomized

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

How does ketamine work?

- Conventional wisdom suggests that ketamine's effects are mediated through the **glutamatergic N-methyl-D aspartate receptor (NMDAR)**.
- noncompetitive antagonist, binds within the ion channel and blocks Ca influx
- Several other NMDAR antagonists have been shown to have antidepressant-like properties in rodents
- NR2B selective drug, **CP-101 606**, and **AZD6765** (lanicemine), progressed in antidepressant clinical trials to Phase 2b
- **memantine**, also NMDAR antagonist, shares many pharmacodynamic features with ketamine but it has not been consistently shown to have antidepressant effects

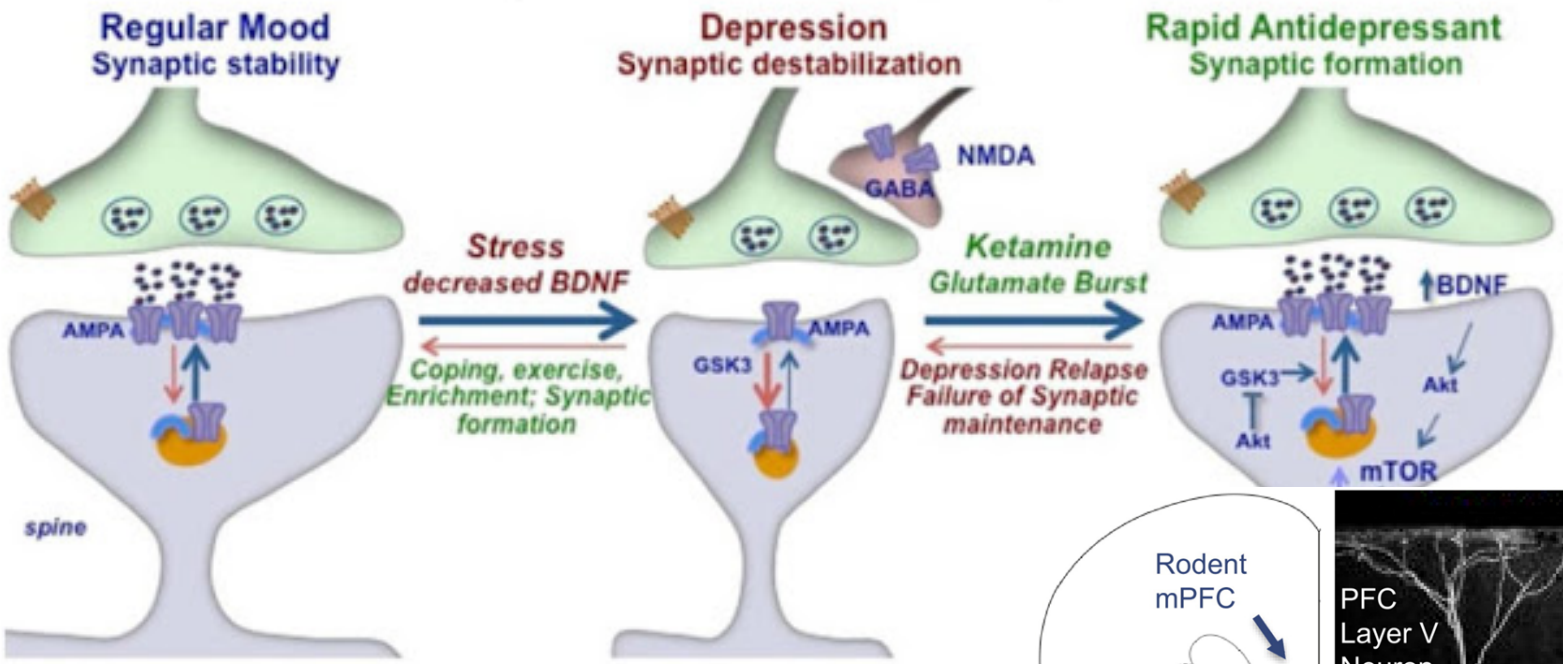


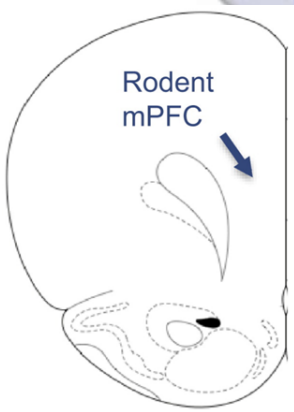
Nature Reviews | Neuroscience

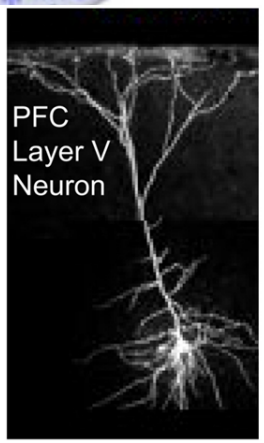
How does ketamine work? - II

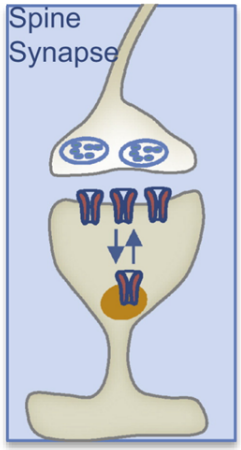
- The antidepressant effect **peaks at 24 hrs**, after the drug has cleared from the body
- Downstream effects from NMDA action are critical in generating and sustaining the response
- Enhancement of spine-remodeling and synaptoplasticity are necessary in the antidepressant effects in rodents
- Activation of the mammalian target of rapamycin complex1 (mTORC1) signaling pathway, synaptic protein synthesis
- Rapid eEF2- and BDNF-dependent potentiation mediated through increased surface expression of AMPA receptors

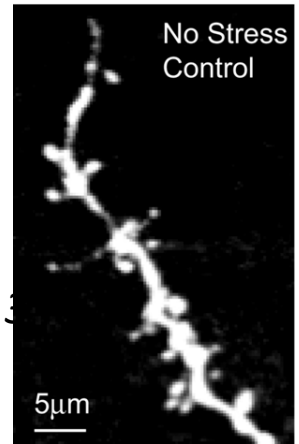
Ketamine Mechanism of Action

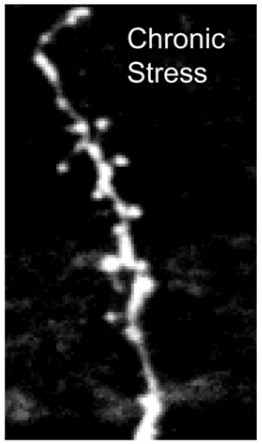


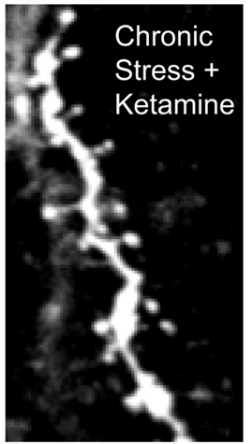












Dwyer and Duman, Biological Psychiatry, 201

How does ketamine work? - III

- Other putative mechanisms: necessary a transient increase in glutamate transmission through the postsynaptic a-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors (AMPAR)
- the co-administration of AMPAR antagonists can block the antidepressant effect of ketamine in animal models

How does ketamine work? - IV

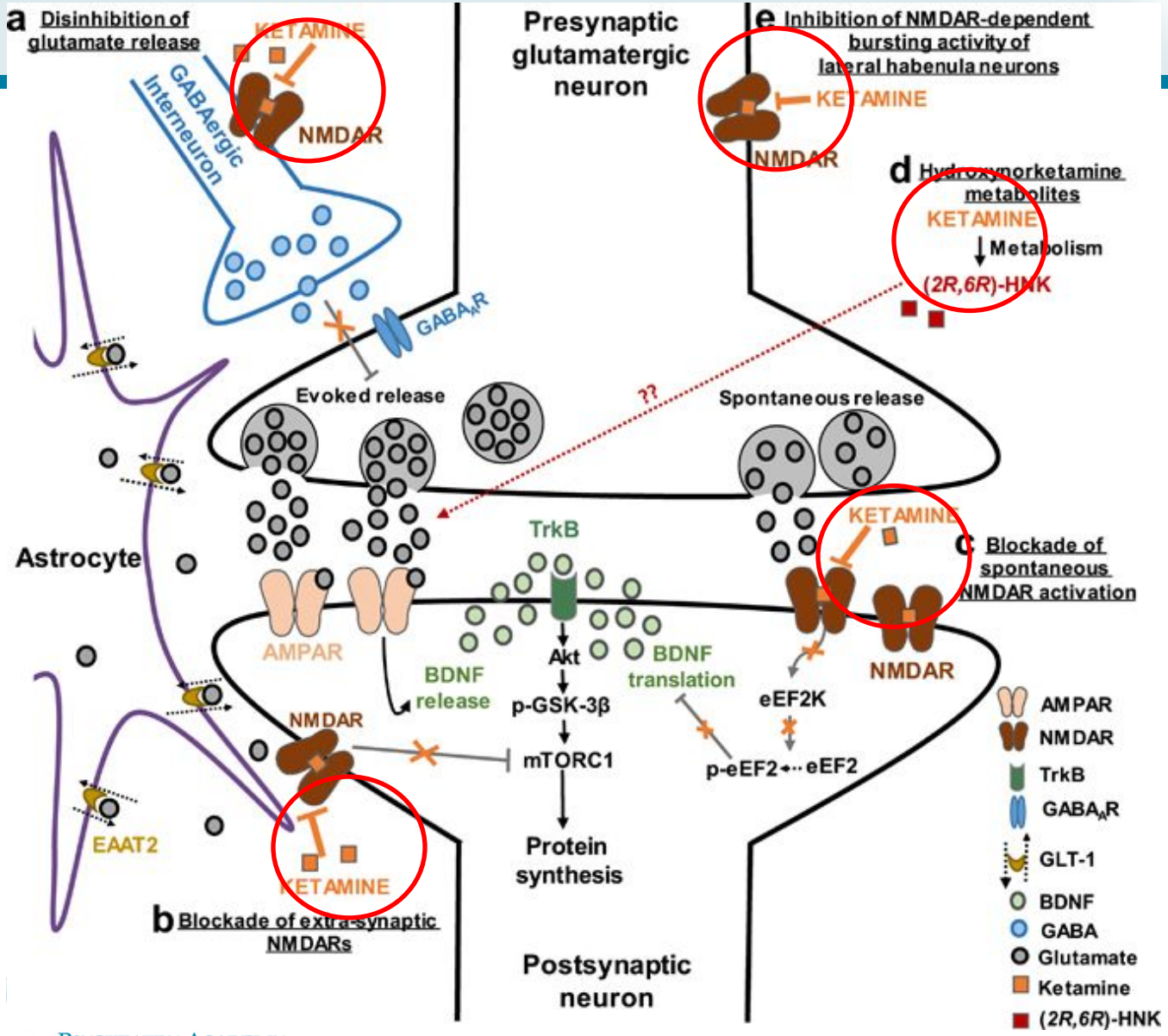
- A ketamine metabolite enantiomer (2***R***,6***R***)-hydroxynorketamine (HNK) has rapid and sustained antidepressant effects without the side-effects associated with ketamine, and no abuse potential (Zanos et al. Nature 2016) - in rodents
- no comparison of AD efficacy between S and R, or 2R,6R-HNK

How does ketamine work? - V

(More hype)

- Is ketamine acting though opioid system?
- Small pilot study on 12 patients, pretreatment with naltrexone partially blocked the effect of ketamine
- Published x2 in high impact journals
- Lot of publicity in the media, fear of ketamine being and opiate-like drug, highly addictive, leading to tolerance and dependence

No, really...How does it work?



a) NMDA block on GABA inhibitory neurons
b) Dishinibition excitatory neurons
c) And d)direct effect on postsynaptic NMDA receptors
e) Inhibition burst on habenula

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**

Data from our clinic

- Among the 67 patients who had a suicidal ideation score >0
  - 17.9% 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

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.

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

Informed consent: do I need to change my meds?

- Pts with 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?

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].

Author information

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 just agreed to cover infusions**
- **IV ketamine is SELF PAY ONLY** 530$ per infusion, recommended x6 in 3 weeks, followed by monthly maintenance infusions
- **IN ketamine is SELF PAY**– 2-3 supervised administrations (400$), then home administrations, with regular follow up visits at the office

IN ketamine clinic

- Since July 2015 approximately 90 pts evaluated, 50+treated, 35+ on maintenance
- Intranasal, (docs ACLS certified)
- Patient has few supervised administrations at the clinic and continues at home, comes for check-ins every 2-3 months
- Cumbersome, frequent contact to adjust dose and frequency
- Mild side effects
- High rate of drop-out for lack of acute benefit
- 1 SA, 1 complete suicide (after >2 ys, 7th SA)
- Patients are really involved in research, in their own monitoring ("stakeholders"), in identifying augmentations and interactions with concomitant drugs, in becoming advocates for us

S-ketamine at MGH? Almost there..

- **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

Drug Regimens

Drug	Dosage	Schedule	Route
Esketamine	56 mg (33% of patients) 84 mg (67% of patients)	Induction (weeks 1-4): Twice weekly Maintenance (weeks 5-8): Once weekly Maintenance (after week 8): Once weekly to every other week	Intranasal, administered in the physician's office
Ketamine	0.5 – 1.0 mg/kg	Twice weekly for two weeks, reduced to every other week or once monthly thereafter	Intravenous, administered in a ketamine clinic

Access issues at MGH

- Patients have been asking to try ketamine since 2012, about 5-10 calls per week
- 1.9 Years of waiting list for the current IN ketamine clinic, seeing 1-2 pts per month
- Lower potency and duration of IN administration, need to monitor home administrations, frequent contacts
- High drop out rate
- 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

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**