

Ketamine and Esketamine

From Research to Clinical practice

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Disclosures

Cristina Cusin 2022-2026:

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

Why a talk on ketamine?

I have been told

- Ketamine is 'old news' (compared to psilocybin, MDMA and other psychedelics)

However...

Ketamine is **STILL** the only one actually available for clinical care, while the others for now are mostly available through research trials only

More to come next year?

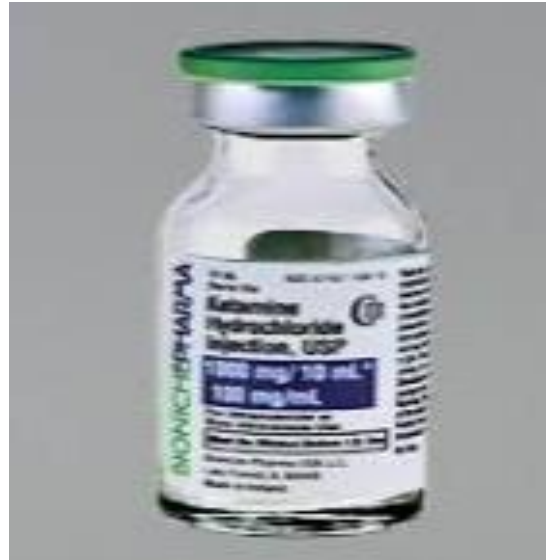
We have a TRD problem

- MDD THE single largest contributor to loss of healthy life years (WHO)
- costs >100mil worldwide
- **US : <30% TRD patients receive adequate treatment**, with the remainder either receiving suboptimal regimens or remaining on ineffective therapies without appropriate adjustment (McIntyre RS, et al. Treatment-Resistant Depression: Definition, Prevalence, Detection, Management, and Investigational Interventions. World Psychiatry. 2023;22(3):394-412.
- MDD individuals **in Canada** diagnosed and receiving adequate treatment: **20%** (Patten et al. Major Depression in Canada: What Has Changed Over the Past 10 Years? Can J Psychiatry 2016)
- European cohort study: despite low remission rates, 60% of patients remained on the same treatment for a year (Heerlein K et al Real-World Evidence From a European Cohort Study. JA. 2021)
- **Adolescent** in US receiving adequate treatment for depression: **34%** (Lee CM, et al. The Need Factors Associated With Adequate Depression Treatment Utilization Among U.S. Adolescents. Psychiatr Serv. 2025)

-CAVEAT-

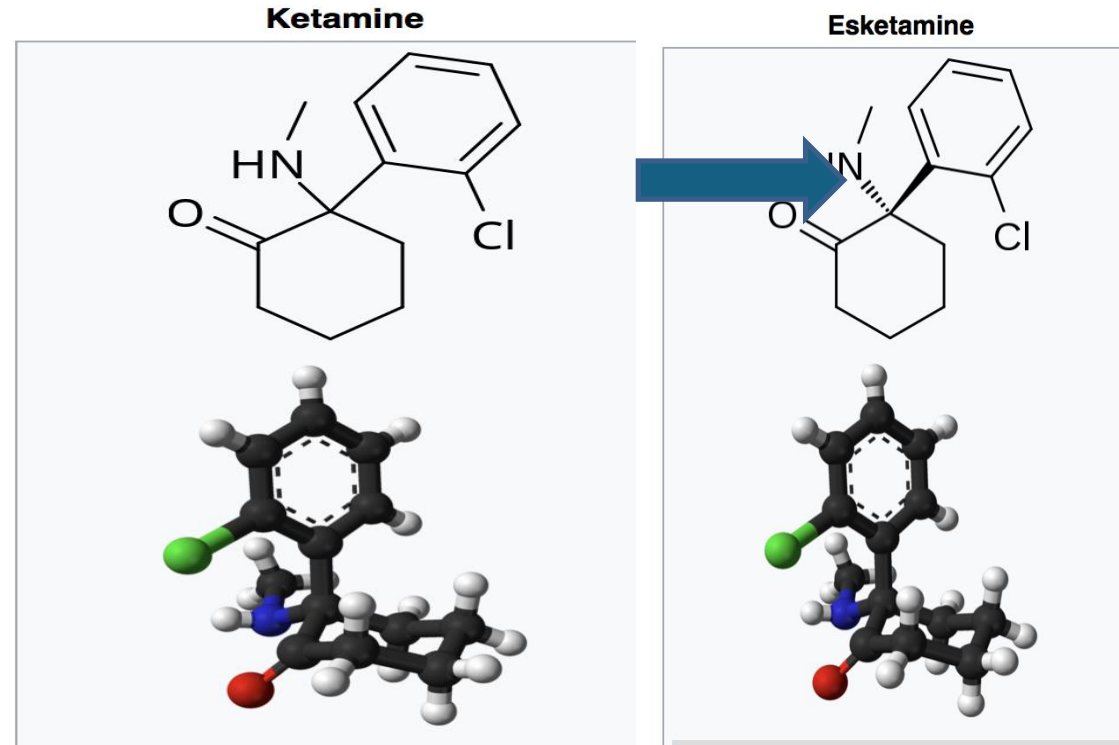
- **Ketamine** has an indication as **anesthetic and analgesic**, for rapid intubation, in veterinary medicine; approved for induction and maintenance of general anesthesia
- Serendipitous discovery of antidepressant effect in early 2000s – **that was 20 years ago!!!**
- Ketamine is **NOT FDA-approved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

*Not approved for BP depression



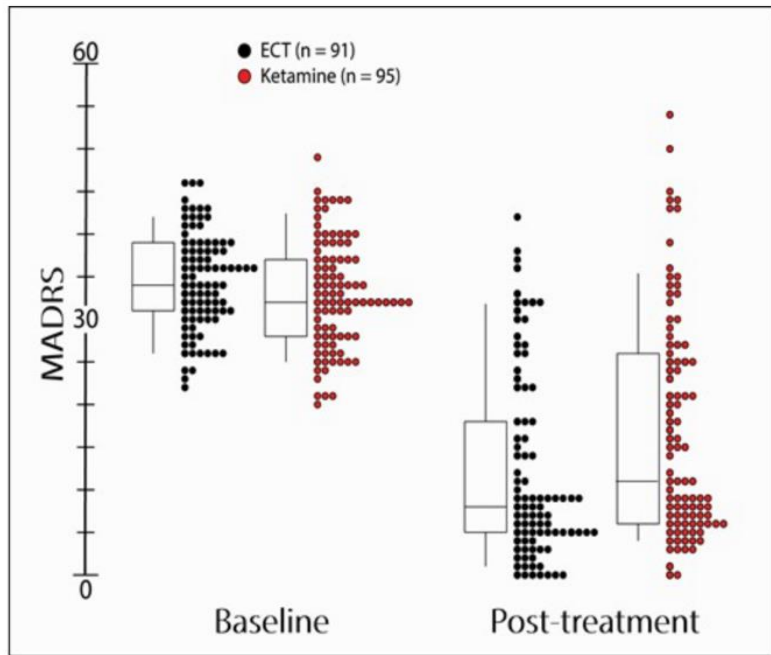
50% S-ketamine + 50% R-ketamine= **ketamine**

Ketamine /Esketamine



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

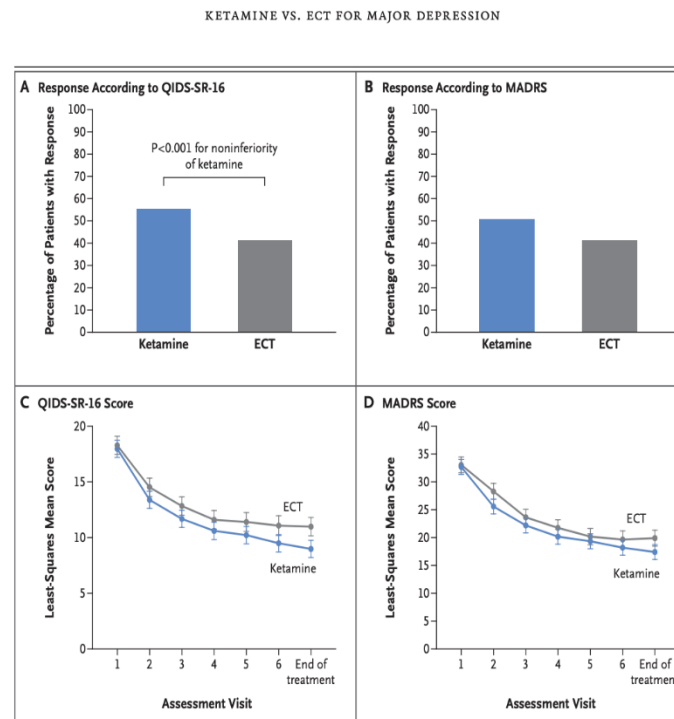




Ketamine vs ECT RCT (Ekstrand et al. 2022)
 95 ket/91 ECT, Fixed ketamine, variable ECT
 param,
Remiss 45% K vs 61% ECT ($P < 0.034$)

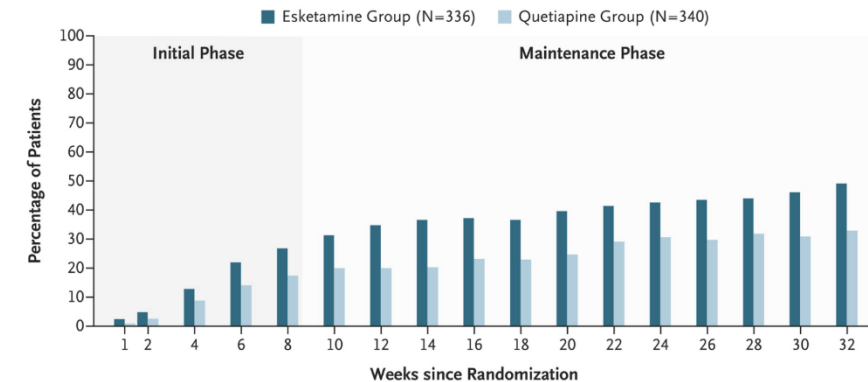
ESKETAMINE VS QUETIAPINE (ESCAPE-TRD 2023)

336 Esket/340 quet (150-300mg) as ADD-ON
 SSRI/SNRI
 60% failed 2 prior AD tx
Remiss wk8 27.1% K vs 17.6%Q



Ketamine vs ECT RCT (Anand et al., 2023)
 200 ket/203 ECT
Resp 55.4% K vs 41.2% ECT (difference,
 14.2% 95% CI, 3.9 to 24.2; $P < 0.001$)

Remission According to Treatment Phase



Current TRD guidelines

Where does ketamine sit?



Line of treatment	Adjunctive agent	Target dose*
First-line	Aripiprazole	2–10 mg
	Brexpiprazole	0.5–2 mg
Second-line	Bupropion	150–450 mg
	Intranasal esketamine	56–84 mg intranasally
	IV racemic ketamine	0.5–1.0 mg/kg IV
	Olanzapine	2.5–10 mg
	Quetiapine-XR	150–300 mg
	Risperidone	1–3 mg
	Lithium	600–1200 mg (therapeutic serum level: 0.5–0.8 mmol/L)
	Cariprazine	1.5–3 mg
	Mirtazapine/Mianserin	30–60 mg/30–90 mg
	Modafinil	100–400 mg
	Triiodothyronine	25–50 mcg
Third-line	Other antidepressants, including TCA	Varies with the medication
	Stimulants	Varies with the medication
	Lamotrigine	100–300 mg
	Non-IV racemic ketamine	Varies with the medication
	Pramipexole	1–2 mg twice daily
	Ziprasidone	20–80 mg twice daily
Investigational	Psychedelic-assisted psychotherapy	Moderate to high doses accompanied by psychotherapy
Not recommended	Cannabis (insufficient evidence for efficacy; risk of harms)	n/a

Lam RW, Kennedy SH, Adams C, et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) 2023 Update on Clinical Guidelines for Management of Major Depressive Disorder in Adults. Can J Psychiatry 2024

Clinical trials vs real world

- Patients resistant to 2 antidepressants
- Patients generally healthy from medical point of view
- Patients on no other meds, or discontinued - benzo, stimulants, atypicals antipsychotics, opiates, etc
- 6 weeks in duration
- Patients have failed 8-12 antidepressants
- We have to google rare medical conditions
- Patient's list of medications is two pages long and we cannot stop any - interactions unknown
- Pt almost never leave the clinic if they respond

MGH Ketamine Clinic (opened in 2018)

- >15,000 infusions
- Self-pay until October 2020, only 2 insurers since then agreed to cover IV ketamine
- MDD/BP depression, multiple comorbidities (OCD, PTSD, GAD)
- highly educated, current episode 7.1 ± 10.5 ys
- Failed >4 antidepressants (4-15), 35% failed ECT, 28% failed TMS
- No mod/severe SUD current, no psychosis
- Flexible ketamine dose (based on tolerability, efficacy)
- One year: esketamine visits, currently 35 a day

Overview: the HOW

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

Informed consent

- It is a long process
- Cognitive symptoms of depression
- Unrealistic expectations
- Logistics and barriers (30% of pts inquiring do not have an escort, or transportation)->share ride now allowed for esketamine
- Insurance and comparison Ketamine vs esketamine
- Risk factors - cardiovascular



RISK ASSESSMENT

The WHO

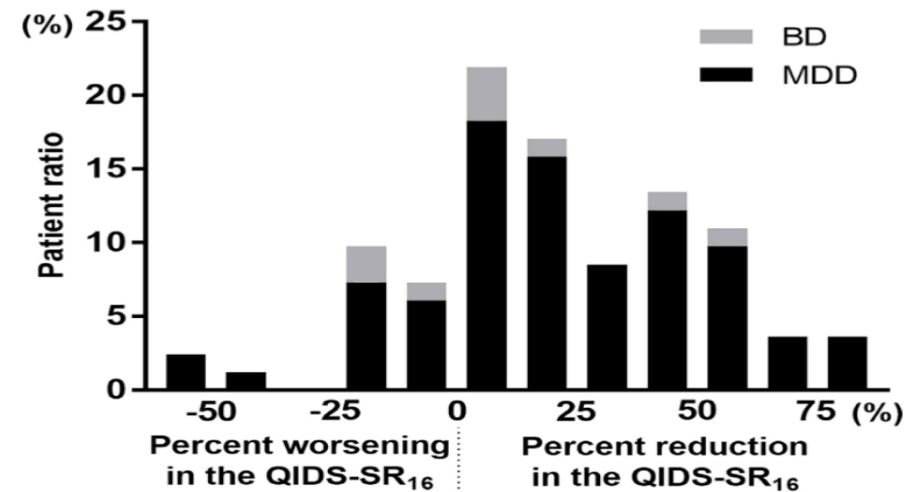
- Primary indication: MDD or BP depression
- Almost any psychiatric comorbidity
- NO primary pain conditions
- No moderate /severe SUD, AUD (>3 months)
- No history of psychosis
- No aneurysms, recent MI, uncontrolled HTN or intracranial processes, unstable serious medical conditions, severe urinary conditions? Glaucoma?

What are our outcomes?

- Ketamine in severe TRD is NOT THAT FAST (in elderly patients and extremely TRD it may take 10-12 treatments)
- Small percentage achieved response defined as 50% improvement, and 1/3 improve 35% or more
- Patients report marked improvement in concentration, motivation, and social functioning
- Marked improvement in SI

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)



Few comments...

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



PLANNING

Still a good thing to do first.

 **Massachusetts General Hospital**
Founding Member, Mass General Brigham
Psychiatry Academy

Ketamine 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 ->30-40% required IV/PO lorazepam
- K-hole at random times
- Moderate headache (acetaminophen 2-3%)
- Some patients have **insomnia** the night after K
- **hypertensive** episodes (labetalol), more common at higher doses, in males >50

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

Ketamine is effective for SI

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. Kelp, Ph.D., Vivek K. Molra, M.D., Michelle S. Parris, B.A., Julia E. Marver, B.A., Ainsley K. Burke, Ph.D., Matthew S. Hlask, M.D., H. 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>

 Sections  View Options

 Tools  Share

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 $\geq 50\%$ 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.

Ketamine is effective for SI -II

Randomized Controlled Trial > [BMJ. 2022 Feb 2;376:e067194. doi: 10.1136/bmj-2021-067194.](#)

Ketamine for the acute treatment of severe suicidal ideation: double blind, randomised placebo controlled trial

Mocrane Abbar¹, Christophe Demattei², Wissam El-Hage³, Pierre-Michel Llorca⁴, Ludovic Samalin⁴, Pierre Demaricourt⁵, Raphael Gaillard⁵, Philippe Courtet^{6 7}, Guillaume Vaiva^{8 9}, Philip Gorwood⁵, Pascale Fabbro², Fabrice Jollant^{10 5 11 12 13}

Affiliations [+ expand](#)

PMID: 35110300 PMCID: [PMC8808464](#) DOI: [10.1136/bmj-2021-067194](#)

[Free PMC article](#)

Abstract

Objective: To confirm the rapid onset anti-suicidal benefits of ketamine in the short term and at six weeks, overall and according to diagnostic group.

Design: Prospective, double blind, superiority, randomised placebo controlled trial.

Setting: Seven French teaching hospitals between 13 April 2015 and 12 March 2019.

Eligibility criteria for participants: Aged 18 or older with current suicidal ideation, admitted to hospital voluntarily. Exclusion criteria included a history of schizophrenia or other psychotic disorders, substance dependence, and contraindications for ketamine.

Participants: 156 participants were recruited and randomised to placebo (n=83) or ketamine (n=73), stratified by centre and diagnosis: bipolar, depressive, or other disorders.

156 with SI

2 infusions k vs placebo at T0 and D1
63.0% in the ketamine arm vs 31.6%
reached remission of SI (OR 3.7 (1.9 -
7.3), P<0.001).

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., Hussein 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)

Clinical Trial > *Int J Neuropsychopharmacol*. 2021 Jan 20;24(1):22-31.

doi: 10.1093/ijnp/pyaa068.

Esketamine Nasal Spray for Rapid Reduction of Depressive Symptoms in Patients With Major Depressive Disorder Who Have Active Suicide Ideation With Intent: Results of a Phase 3, Double-Blind, Randomized Study (ASPIRE II)

Dawn F Ionescu¹, Dong-Jing Fu², Xin Qiu³, Rosanne Lane⁴, Pilar Lim⁴, Siegfried Kasper⁵, David Hough², Wayne C Drevets¹, Hussein Manji², Carla M Canuso²

Affiliations + expand

PMID: 32861217 PMCID: [PMC7816667](#) DOI: [10.1093/ijnp/pyaa068](#)

[Free PMC article](#)

Abstract

Background: Patients with major depressive disorder (MDD) having active suicidal ideation with intent require immediate treatment.

Methods: This double-blind study (ASPIRE II) randomized adults (aged 18–64 years) with MDD having active suicidal ideation with intent to esketamine 84 mg or placebo nasal spray twice weekly for 4 weeks, given with comprehensive standard of care (hospitalization ≥5 days and newly initiated or optimized oral antidepressant[s]). Change from baseline to 24 hours post-first dose in

Esketamine has been approved for use in patients with depression at risk of suicide and for psychiatric emergency in the US.

Esketamine monotherapy?

- phase 4, double-blind, placebo-controlled RCT at 51 outpatient centers, N= 378
- 1:1:2 ratio to fixed-dose intranasal esketamine (56 mg or 84 mg) or matching intranasal placebo, twice weekly for 4 weeks.
- At day 28, the least-square (LS) mean difference (SE) between esketamine and placebo was -5.1 (1.42) (95% CI, -7.91 to -2.33) for the 56-mg dose and -6.8 (1.38) (95% CI, -9.48 to -4.07) for the 84-mg dose

Janik A, et al. Esketamine Monotherapy in Adults With Treatment-Resistant Depression: A Randomized Clinical Trial. JAMA Psychiatry. 2025 Sep 1;82(9):877-887..

Ketamine IV for inpatients?

- The KARMA-Dep 2, double-blind, RCT midazolam-controlled, pragmatic trial conducted at an academic center in Ireland
- 8 TW intravenous infusions of ketamine (0.5 mg/kg) or midazolam (0.045 mg/kg) as an adjunct to usual-care, UP or BP
- end-of-treatment MADRS scores did not significantly differ between the ketamine and midazolam groups (adjusted mean difference, -3.16 points, 95% CI, -8.54 to 2.22; $P = .25$; Cohen d , -0.29)
- Note: (n = 3517) prescreened -Potentially eligible patients (n = 371) were invited- (n = 74) enrolled,

Jelovac A, et al. Serial Ketamine Infusions as Adjunctive Therapy to Inpatient Care for Depression: The KARMA-Dep 2 Randomized Clinical Trial. JAMA Psychiatry. 2025 Dec 1;82(12):1216-1224.

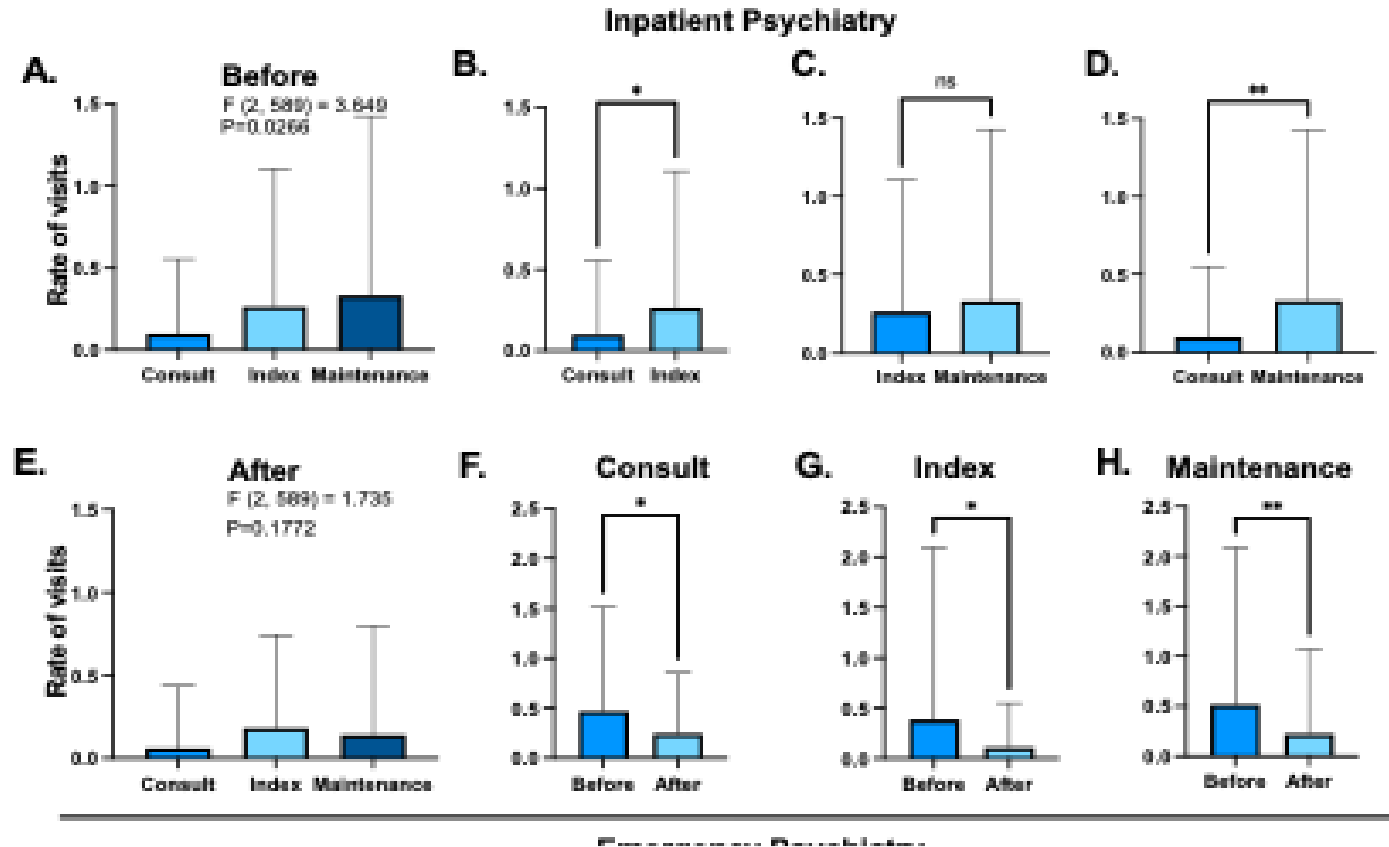
More lessons from clinical practice

- offer to try ketamine ONLY if can provide maintenance to the responders
- If it works, it keeps working for a long time (maybe not in 100% of cases)
- When it does NOT WORK patients can get much worse

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

- From literature 65-70%
- In extremely treatment refractory patients, at our site is lower
- On average 40-50%
- Post ECT failure still 45-50%
- We do NOT know who is going to respond

Prevention of readmission?





PLAN B
Because you failed Plan A

How long is the treatment?

- No rigorous long-term data beside registry on Esketamine, case series from MGH (5-6 ys), Yale and Emory
- Similar to other chronic medical conditions
- Young patients with intermittent disease and long intervals between episodes may have a relatively short course (?) and pause, until they relapse
- Patients who have been chronically ill for >5 ys (most of the patients in the clinic) **do relapse** when they stop ketamine, usually within 1-2 months
- If nothing else worked, we continue

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
- NEW RESEARCH STUDY MRI and neuropsych testing in patients in long-term maintenance

Ketamine use disorder?

- **There is a risk, more for psychological addiction than physical**
- low dependence potential, compared to both nicotine and alcohol; much lower compared to cocaine, meth, opiates
- Withdrawal? Anxiety, depression, cravings
- **Anecdotal cases of tolerance**
- **90% of our patients mildly dislike/really dislike the experience**
- Actual rate of developing addiction symptoms unknown

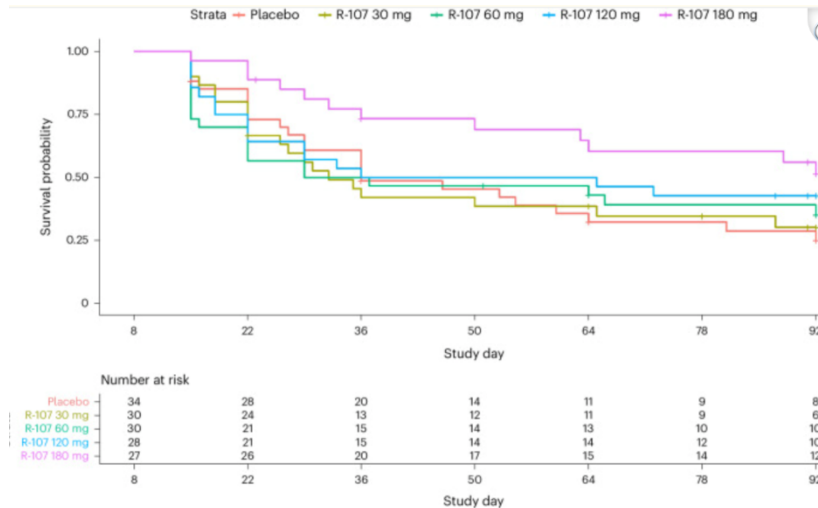
Ketamine subcutaneous?

- Phase 3, double-blind, RCT, active-controlled in Australia and New Zealand.
- twice-weekly subcutaneous racemic ketamine or midazolam for 4 weeks (flexible-dose ketamine 0.5-0.9 mg/kg or midazolam 0.025-0.045 mg/kg, with response-guided dosing). The primary outcome was remission (MADRS score ≤ 10) at the end of week 4.
- **Results:** ITT: 68 in cohort 1 (fixed-dose), 106 in cohort 2 (flexible-dose).
- Ketamine was more efficacious than midazolam in cohort 2 (remission rate 19.6% v. 2.0%; OR = 12.1, 95% CI 2.1-69.2, $P = 0.005$), but not different in cohort 1 (remission rate 6.3% v. 8.8%; OR = 1.3, 95% CI 0.2-8.2, $P = 0.76$).
- Ketamine was well tolerated. Acute adverse effects (psychotomimetic, blood pressure increases) resolved within 2 h.

Loo et al Br J Psychiatry 2023 Dec;223(6):533-541.

Extended-release ketamine tablets?

- Phase 2 multicenter RCT in TRD - open-label R-107 120 mg per day for 5 days and were assessed on day 8 (enrichment phase).
- On day 8, responders (MADRS scores ≤ 12 and reduction $\geq 50\%$) were randomized on a 1:1:1:1:1 basis to receive double-blind doses of 30, 60, 120 or 180 mg, or placebo, twice weekly for a further 12 weeks.
- Nonresponders on day 8 exited the study.
- each active treatment compared with placebo at 13 weeks, starting with the 180 mg dose, using a fixed sequence step-down closed test procedure.



100 participants had discontinued -94 for lack of efficacy

180 mg TW statistically significant improvement MADRS vs placebo, group-treatment diff. of 6.1.

Glue P, et al; BEDROC study investigators. Extended-release ketamine tablets for treatment-resistant depression: a randomized placebo-controlled phase 2 trial. Nat Med. 2024 Jul;30(7):2004-2009. doi: 10.1038/s41591-024-03063-x

Oral esketamine

- **Oral esketamine in patients with treatment-resistant depression: a double-blind, randomized, placebo-controlled trial with open-label extension**
- 1) a six-week fixed low-dose treatment phase during which 111 participants received oral esketamine 30 mg or placebo three times a day; 2) a four-week wash-out phase; and 3) an optional six-week open-label individually titrated treatment phase
- Fixed low-dose oral esketamine when compared to placebo had no benefit on the HDRS₁₇ total score ($p = 0.626$)

Smith-Apeldoorn SY, et al . Oral esketamine in patients with treatment-resistant depression: a double-blind, randomized, placebo-controlled trial with open-label extension. Mol Psychiatry. 2024 Sep;29(9):2657-2665

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

Predictors of response?

- Transitional age adults?
- Borderline PD?
- Age?
- Anxiety?
- PTSD?
- Chronic pain?
- multiple Axis I psychiatric disorders do not affect the efficacy of IV ketamine on MDD (n=151) (PTSD, OCD, GAD, ADD)

Recent predictors – Ket vs ECT

- greater improvement in depression was observed with IV ketamine among outpatients with nonpsychotic TRD who had moderately severe or severe depression,

Jha MK, et al. Ketamine vs Electroconvulsive Therapy for Treatment-Resistant Depression: A Secondary Analysis of a Randomized Clinical Trial.
JAMA Netw Open. 2024 Jun 3;7(6):e2417786.

Ketamine imaging studies

- Putative brain-based markers of treatment response?
- limbic (subgenual ACC, hippocampus, cingulum bundle-hippocampal portion; anhedonia/suicidal ideation),
- salience (dorsal ACC, insula, cingulum bundle-cingulate gyrus portion; thought rumination/suicidal ideation)
- fronto-parietal (dorsolateral prefrontal cortex, superior longitudinal fasciculus; anhedonia/suicidal ideation)
- default-mode (posterior cingulate cortex; thought rumination),
- subcortical (striatum; anhedonia/thought rumination)

Biomarkers?

Which patients more or less respond?

-Imaging

subgen

cortex

-Blood-based

level

inflammation, IL-6, and TNF- α

BD

Meshkat S, et al. Biomarkers of ketamine's antidepressant effect: An umbrella review, JAD. 323,2023, 598-606,

Canadian data in Bipolar disorder

Observational Study > Bipolar Disord. 2023 Mar;25(2):99-109. doi: 10.1111/bdi.13284.

Epub 2022 Dec 26.

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

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Rickinder Sethi ^{1 4}, Muhammad I Husain ^{4 5}, Hartej Gill ^{1 2}, Aniq Tabassum ¹,
Andrea McKenzie ¹, Lee Phan ¹, Roger S McIntyre ^{1 2 3 4 6 7}, Joshua D Rosenblat ^{1 2 3 4 6}

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PMID: 36516343 DOI: [10.1111/bdi.13284](https://doi.org/10.1111/bdi.13284)

Abstract

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

Methods: This study was conducted in a community clinic in Mississauga, Ontario (Canadian Rapid Treatment Centre of Excellence; Braxia Health). In this observational study ([NCT04209296](https://clinicaltrials.gov/ct2/show/study/NCT04209296)), patients with treatment-resistant bipolar I/II depression (n = 66) received four sub-anesthetic doses of IV ketamine (0.5-0.75 mg/kg) over a two-week period. Symptoms of depression, suicidality, anxiety, and functioning were assessed with validated self-report measures.

Results: Statistically and clinically significant antidepressant effects were observed in the overall sample, as measured by the Quick Inventory for Depression Symptomatology-Self Report-16 (QIDS-SR₁₆) with further reductions in depressive symptoms observed after each subsequent infusion (n = 66; mean QIDS-SR₁₆ reduction of 6.08+/-1.39; p < 0.0001). Significant reductions of

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

Ketamine in BP disorder

- ketamine more efficacious than placebo at 24 for response rate (OR 11.61, 95% confidence interval (CI) 1.25 to 107.74; $P = 0.03$; participants = 33; studies = 2; low-certainty evidence).(*Cochrane Database Syst Rev* 2021 Oct 8;10(10):CD011611.)
- **It is an antidepressant that has risk of hypo/manic switch (case reports)**
- We request that all patients are on mood stabilizer

Ketamine and PTSD?

Study	Design	Subjects	Sample		R	Protocol		Primary outcomes
			Treatment	Control		Treatment	Control	
Abdallah <i>et al.</i> ⁸⁷	Double-blind, placebo-controlled, 3-arm RCT	mPTSD	n = 53 n = 51	n = 54	IV	Ketamine 0.2 or 0.5 mg/kg over 40 min × 8 twice weekly	Placebo (saline) over 40 min × 8 twice weekly	No dose-related improvement of ketamine on PTSD symptoms; reduced comorbid depression using standard dose only
Dadabayev <i>et al.</i> ⁸⁵	Double-blind, active placebo-controlled, 4-arm RCT	mPTSD	n = 11 n = 10	n = 10	IV	Ketamine 0.5 mg/kg over 40 min × 1	Ketorolac 15 mg over 40 min × 1	Improved PTSD and CP symptoms, though comparable: ketamine = ketorolac
Feder <i>et al.</i> ⁸²	Double-blind, active placebo-controlled, crossover RCT	cPTSD	n = 22 n = 19	n = 19	IV	Ketamine 0.5 mg/kg over 40 min × 1	Midazolam 0.045 mg/kg over 40 min × 1	Improved PTSD severity: ketamine >midazolam;

Ketamine and OCD?

- 6/14 of research studies studied ketamine as a treatment for mostly refractory OCD
- 80% of the ketamine studies resulted in a significant decrease in Y-BOCS
- Additional case reports and imaging studies

Ketamine for treatment of SUD?

- Ketamine: better outcomes when used along with behavioral and motivational therapy in few clinical trials; small N, variable methods and outcomes
- Cocaine
 - Dakwar N=5, ket + mindfulness based therapy
- Alcohol
 - Dakwar et al, AMJPsych 2020, N=40, 1 infusion vs placebo. reduced the likelihood of heavy drinking days in 21 days
 - Grabski et al, AMJPsych 2022, N=96, 4 arms, 3 infusions, greater number of days abstinent, no difference in relapse at 6 mo
- Opiates
- Meth – ongoing NIDA trials

Intranasal ketamine in MDE and AUD

- **RCT of the Acute Antisuiicidal and Antidepressant Effects of Intranasal (R,S)-Ketamine in Severe Unipolar and Bipolar Depression With and Without Comorbid Alcohol Use Disorder**
- fixed-dose (50 mg) IN (R,S)-ketamine (or saline comparator) in unmedicated inpatients
- No significant group $\times$ time effect was noted for SI ($F = 1.1$, $P = .36$).
- Within the ketamine group, a significant correlation was observed between improvement in depressive symptoms and SI for patients without comorbid AUD ($r = 0.927$, $P = .023$) that was absent in patients with AUD ($r = 0.39$, $P = .44$).

Jones GH, et al..

J Clin Psychiatry. 2024 Apr 24;85(2):23m14974

ketamine plus naltrexone for MDD comorbid with AUD?

- 3-arm, RCTN= 65 adults with current MDD and AUD, with MADRS $\geq$ 20 and heavy drinking at least 4 times in the month prior
- (IV) ketamine (0.5 mg/kg) once a week for 4 weeks (a total of 4 infusions) plus intramuscular (IM) naltrexone (380 mg), (2) IV ketamine plus IM saline, or (3) IV midazolam (0.045 mg/kg) plus IM saline.
- No group differences were observed in MADRS changes during treatment (primary outcome), although antidepressant effects persisted longer in ketamine groups compared to midazolam.
- There were no significant group differences in alcohol-related outcomes.

Ketamine in pregnancy and postpartum

- **No data on safety during pregnancy**
- **Small study on ketamine IM, 4 women** low and rapidly declining levels of ketamine and metabolites in breast milk during the 12-hour post-dosing period
- studies using ketamine during C-section to prevent postpartum Iran (N=134), China (N=375)

Ketamine in children and adolescents

- RCT - similar results to adults with MDD

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

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

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

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PMID: 33653121 DOI: [10.1176/appi.ajp.2020.20010018](https://doi.org/10.1176/appi.ajp.2020.20010018)

Abstract

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

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

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

Adolescents MDD +SI

Intravenous Esketamine -54 adolescents (aged 13-18 years)

-receive 3 infusions of esketamine (0.25 mg/kg) or midazolam (0.02mg/kg) over 5 days, with routine inpatient care and treatment

C-SSRS Ideation and Intensity scores from baseline to day 6 significantly greater in the esketamine (Ideation, -2.6 [SD = 2.0] vs -1.7 [SD = 2.2], $p = .007$; Intensity, -10.6 [SD = 8.4] vs -5.0 [SD = 7.4], $p = .002$),

changes in MADRS scores baseline to day 6 significantly greater in the esketamine group than in the midazolam group (-15.3 [SD = 11.2] vs -8.8 [SD = 9.4], $p = .004$).

The rates of antisuicidal and antidepressant responses at 4 weeks were 69.2% and 61.5% after esketamine, and 52.5% and 52.5% after midazolam

Zhou Y, et al ,Effect of Repeated Intravenous Esketamine on Adolescents
With Major Depressive Disorder and Suicidal Ideation: A Randomized Active-
Placebo-Controlled Trial. J Am Acad Child Adolesc Psychiatry. 2024 May;63(5):507-518.

Why no psychosis?

- Ketamine may induce transient psychotic sx, no persistent psychosis in HV (N>2000)
- Reports of delusional sx in chronic k/MDMA abusers
- Few studies indicate alteration in prefrontal dopaminergic system
- History of psychosis is usually exclusionary for TRD studies
- Published 41 cases TRD w/Psych with ketamine – considered safe, very low level of evidence

How to calculate risk?

- Young age
- M
- Strong FHx of psychosis
- Few med trials

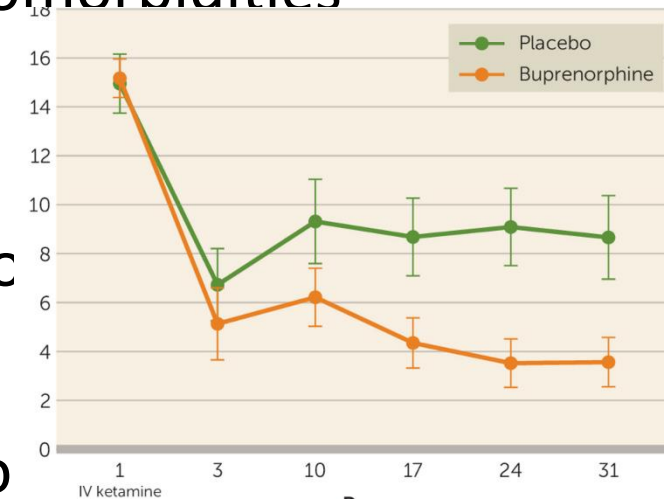
		CONSEQUENCES					
		1	2	3	4	5	
LIKELIHOOD	1	1	2	3	4	5	Low Risk
	2	2	4	6	8	10	
	3	3	6	9	12	15	Medium Risk
	4	4	8	12	16	20	
	5	5	10	15	20	25	High Risk

Why no SUD?

- Concomitant use of cannabis and alcohol blocks at least partially (if not totally) the antidepressant effect of ketamine
- We have allowed patients on stable low suboxone with no complications
- Difficult logistics to ensure sobriety
- Bar too high?

Recent controversies

- **Low-Dose Buprenorphine Following Ketamine Treatment for Suicidal Ideation in Major Depressive Disorder: A Randomized, Double-Blind, Placebo-Controlled Trial**
- 1:1 ratio to receive either sublingual buprenorphine (0.6 to 0.8 mg/day) or placebo for 4 weeks, beginning 48 hours after a single open-label intravenous ketamine infusion (0.5 mg/kg over 40 minutes)
- N=50 - 45 completed at least 1 week of up. No SUD, no comorbidities
- Both groups showed significant reductions in SSI total scores,
- greater improvement in the buprenorphine group (mean change, -11.6, SD=5.8; N=23) than the placebo group (mean change, -6.3, SD=7; N=22) (Glass delta=0.76, 95% CI=0.11, 1.39).
- Depression scores did not differ significantly between groups



Coverage?

- 2 insurers cover Ketamine for MDE (MDD/BP)
- Adults (>18 only)

Despite data in support of efficacy in other conditions or age range, IV ketamine is available only out of pocket

More insurers, including Medicare, cover Esketamine – for MDD ONLY, no BP

Practical considerations

- 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 80 slots per week – 95% IV ketamine, 8 new patients every 3-4 weeks
- Esketamine clinic 36 slots/day x5 days
- Extremely complex patients, multiple psychiatric comorbidities, mood fluctuations, relapses – **personalized care vs helping as many patients as we can**
- Current set up of the clinic: 12 attendings, 18 nurses, 15 Med assistants, 3 admins

Practical considerations -II

Esketamine or ketamine **in the ED?**

The logistic becomes even more complicated..

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



WELCOME TO THE ER

You'd better hope you brought a book.

KAP?

- Ketamine-enhanced psychotherapy has been tried for chronic neuropathic pain, opioid tapering, MDD, GAD, OCD, PTSD, ADHD(!), and SUD
- Some studies did not report the type of psychotherapy- CBT, mindfulness-based interventions, motivational enhancement therapy (MET), exposure, existentially oriented therapy and functional analytic psychotherapy (FAP)
- sessions, ranging from as few as 4 to as many as 60

3 ketamine paradigms

- Medical/psychopharm: focuses on the biological effects of ketamine
 - dissociative/psychedelic are problematic side effects
- Psychotherapeutic: synchronous, ketamine as facilitator of therapy, lower doses
- Psychedelic: inducing a temporary altered state of consciousness

RCT using ketamine followed by CBT

- Wilkinson et al, 2021
- 6 IV ketamine (0.5mg/kg), 42 patients
- 66.7% achieved response
- 28 ketamine responders were randomized into either a CBT or TAU for an additional 14 weeks.
- TAU (n=14) attended a visit with the study physician every 1–2 weeks, focusing on medication management and management of adverse events.
- CBT (n=14) received CBT twice weekly for 2 weeks, then once weekly for the remaining 12 weeks.
- They found a significant difference in MADRS scores from baseline to week 17 (fourteen weeks after the last ketamine infusion), finding greater sustained improvements in the CBT group.

Practical considerations - again

- Concurrent psychotherapy? Limited time, privacy, no reimbursement
 - Added value to the treatments?
 - Not for everybody
- Asynchronous psychotherapy?
- CBT? Difficult access anyway



Future thoughts

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



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My family



Questions?

