Ketamine and Esketamine in Suicide Prevention
Breakthrough or Hype?

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November 22, 2024
9th Vilnius Conference on Suicide Intervention Methods

Declaration of Interest

- No financial ties to the industry
- Working in a clinic where Esketamine is used

A Breakthrough? From where?

Do conventional antidepressants (SSRIs/SNRIs) work well?

👍

*"Antidepressants have an **impressive effect size** in the treatment of acute cases of depression"* and *"antidepressants have an **impressive ability to prevent recurrence of depression** … makes them **one of the most effective of all drugs**".*

Nutt et al. (2014) Attacks on antidepressants: signs of deep-seated stigma? Lancet, Vol 1, Issue 2, P102-104

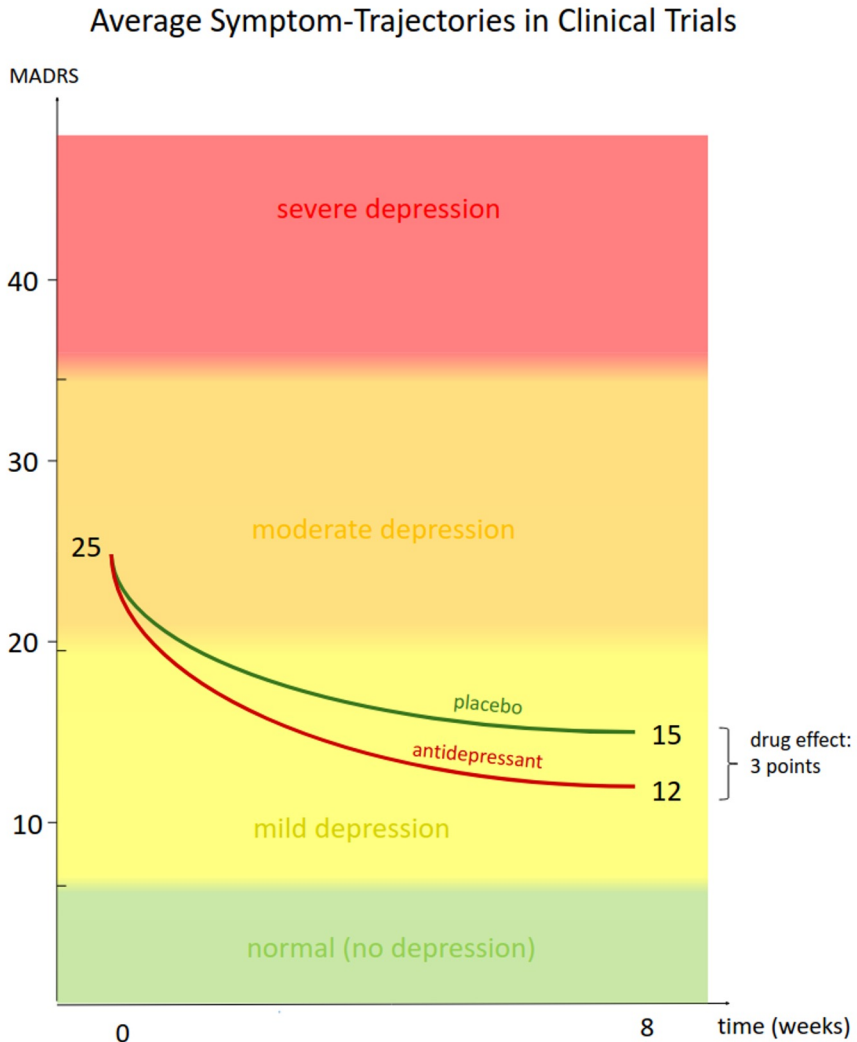
👎

E.g., Kirsch, Moncrieff, Hengartner

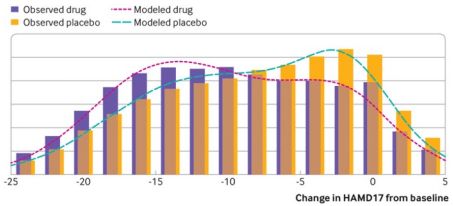
- poor efficacy
- harms (including suicide risk)

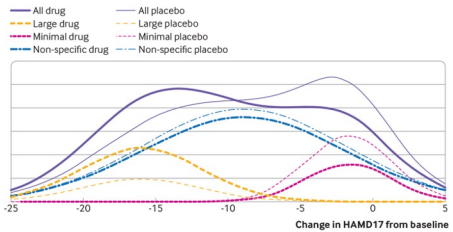
Efficacy of conventional antidepressants

- develops only gradually
  (Hieronymus et al. 2016, Transl Psychiatry)
- only ≈ 3 MADRS points
  (or d = 0.3)
  (Hengartner et al. 2020, PloSONe)
- below threshold of clinical significance:
  ≈ 3-9 MADRS points
  (or d = 0.3 - 0.5)
  (Hengartner & Plöderl, 2021, BMJ Evidence Based Medicine)



Do some people benefit especially well?

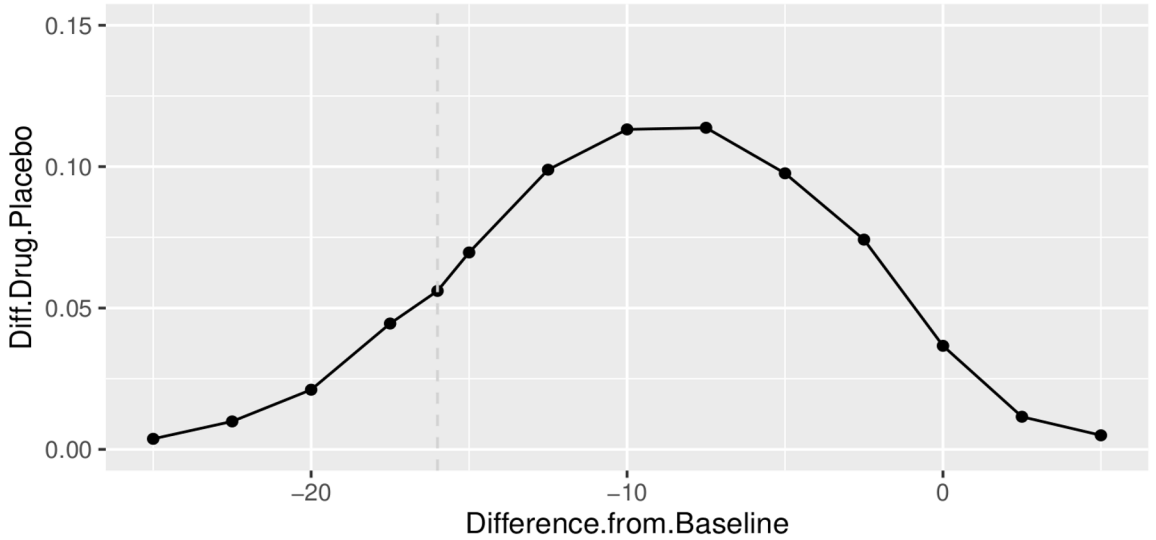




Distribution	Mean change from baseline	SEM	SD	Estimated proportion of overall population			
				Active drug	95% CI	Placebo	95% CI
Large	-16.00	0.22	4.22	24%	20% to 29%	10%	6% to 13%
Minimal	-1.68	0.11	2.99	12%	10% to 14%	21%	19% to 24%
Non-specific	-8.94	0.15	6.96	63%	58% to 69%	69%	65% to 73%

Maximum of 12% greater chance to improve with antidepressants compared to placebo

(for a cut-off of 10 points improvement as criterion for “response”)



Stone, …., & Kirsch, I. (2022). Response to acute monotherapy for major depressive disorder in randomized, placebo controlled trials submitted to the US Food and Drug Administration: individual participant data analysis. *BMJ*, *378*.

https://graz.social/@ploederl/109466156260340519

Antidepressants and Suicide Risk

- **Highest-level evidence:** randomized placebo controlled clinical trials (RCTs)
  - Short-term
    - Suicide attempts
      - Increased risk for younger people < 25 J
      - Decreased risk for older people
    - Suicides: inconclusive evidence
  - Longer-term: Increased risk for suicide attempts (perhaps also suicides)

- **Lower-level evidence:** observational studies
  - Increased risk for suicide attempts (and perhaps suicides), all age-groups
  - especially when correcting for publication bias
  - and in studies without COIs to the industry.

References/discussion: https://www.psychiatrymargins.com/p/antidepressants-and-the-tangle-of

Even Key Opinion Leaders are changing their views…

👍

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👎

Nutt et al. in 2022:

*"Even the best-performing antidepressant drugs show **modest efficacy**, non-negligible side effects, **discontinuation problems and high relapse rates**, highlighting the need for new, improved treatments".*

Increased global integration in the brain after psilocybin therapy for depression. 11 April 2022. Nature Medicine, 28, pages844–851.

https://holeousia.com/2024/02/15/money-talk/

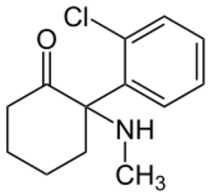
What drug would be like to have in suicide prevention ?

- Rapid and substantial improvement in
  - Suicide risk factors - espicially depression symptoms
  - Suicidality (ideation, behavior)

Ketamine and Esketamine

Ketamine and Esketamine

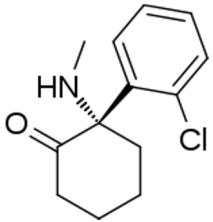
- **Ketamine**: anesthetic, recreational drug



https://www.redbubble.com/de/i/t-shirt/Ketamin-Keta-Urlaub-Droge-Druffie-Geschenkidee-von-LaniStephens/117425955.WFLAH.XYZ

- **Esketamine**: patented enantiomer

  345 Euro per spray,
  2 x weekly, 4 weeks: 8280 Euro



Spießl, 2021, Psychatr Prax 48: 227-230

Ketamine and Esketamine – what you read in journal papers

- "proven **rapid-onset efficacy** in" MDD
  https://psychiatryonline.org/doi/10.1176/appi.ajp.2020.20081251

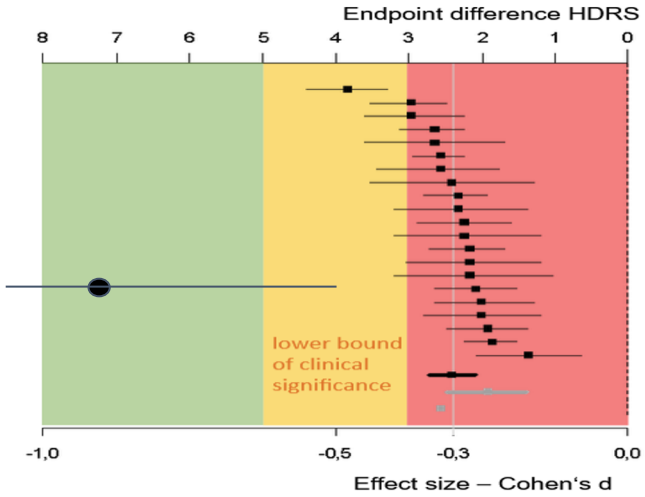
- "… **rapid antidepressant effects** in adults with TRD
  https://www.sciencedirect.com/science/article/pii/S0165032721006182

- "the only FDA-approved antidepressant that **works in hours not weeks**—thus potentially **transforming treatment of suicidal patients**
  https://www.sciencedirect.com/science/article/pii/S0091743521001080

Promising early results for Ketamine - Depression Symptoms

- quick/substantial reduction of depression
- Cochrane review: **d ≈ 0.9 (24h)** compared to d = 0.3 after weeks for ADs
  but: evidence is “very uncertain”, 8 Studies, n = 231

  Dean et al. (2021). Ketamine and other glutamate receptor modulators for depression in adults with unipolar major depressive disorder. *Cochrane Database of Systematic Reviews* 2021

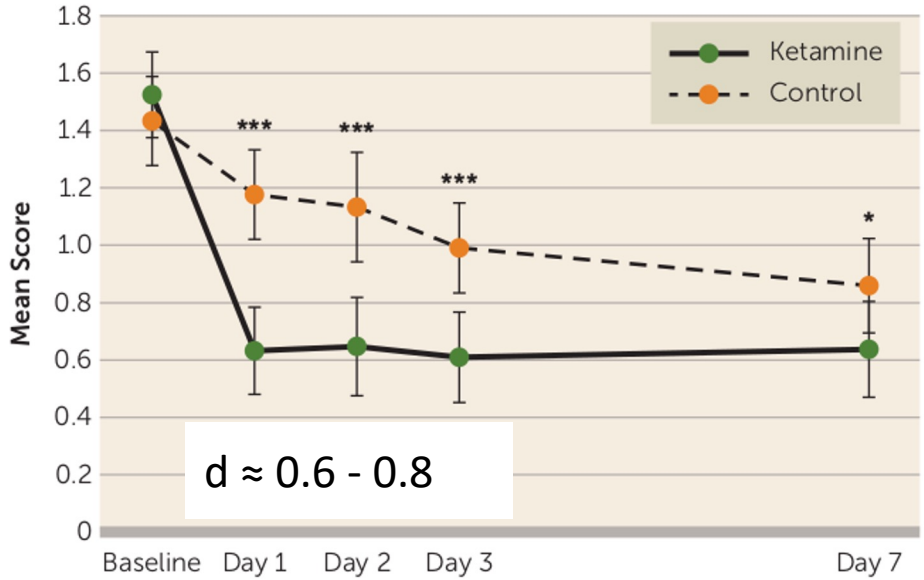


Promising early results for Ketamine - Suicide Ideation

- quick/substantial reduction of suicide ideation

FIGURE 4. Effect of a Single Dose of Ketamine on Suicidal Ideation, as Indicated by Self-Report Measures[a]

A. Self-Reported Suicidal Ideation



Wilkinson et al. The effect of a single dose of intravenous ketamine on suicidal ideation: a systematic review and individual participant data meta-analysis. *American J Psychiatry* 2018

Things speeding up

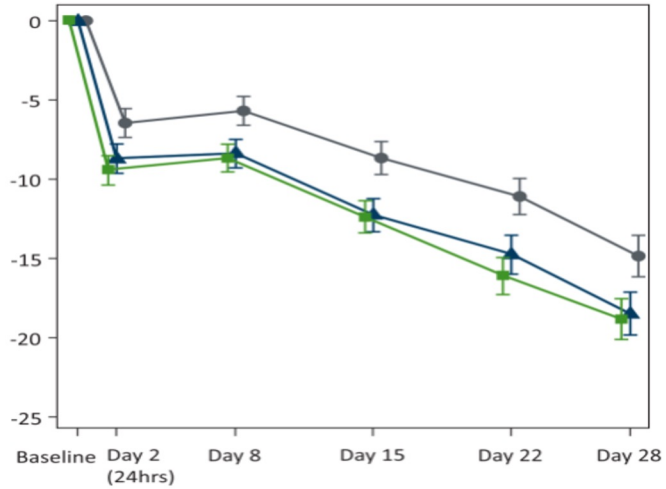
- FDA fast-track approval procedure for esketamine

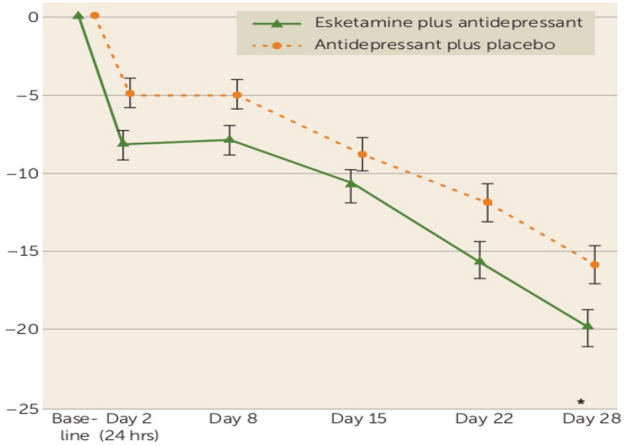
- FDA Approval of esketamine
  - 2019 for “treatment resistant depression”
  - 2020 for “depression with suicide ideation/attempts”
  - EMA followed

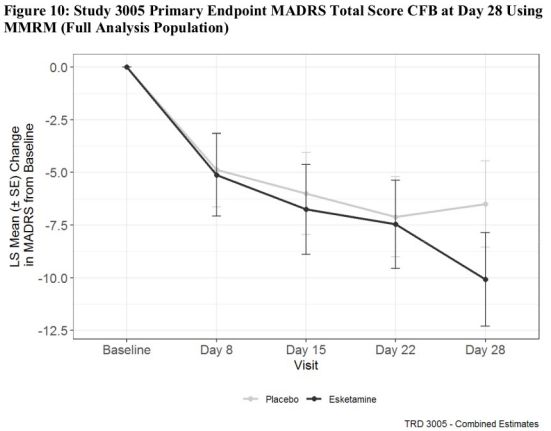
- Immediate critical responses in the scientific community:

Horowitz & Moncrieff (2020) Are we repeating mistakes of the past? A review of the evidence for esketamine. Brit J Psychiatry 216:1–4.
Cristea & Naudet (2019) US Food and Drug Administration approval of esketamine and brexanolone. Lancet Psychiatry 6(12):975-7.
Turner (2019) Esketamine for treatment-resistant depression: seven concerns …. Lancet Psychiatr 6(12):977–9.
Gastaldon et al. (2020) Esketamine for treatment resistant depression: a trick of smoke and mirrors? Epidemiol Psychiatr Sci 29:e79.
Schatzberg AF (2019) A Word to the Wise About Intranasal Esketamine. American Journal of Psychiatry 176(6):422–4

Esketamine Phase 3 Clinical Trials for TRD (TRANSFORM 1-3)







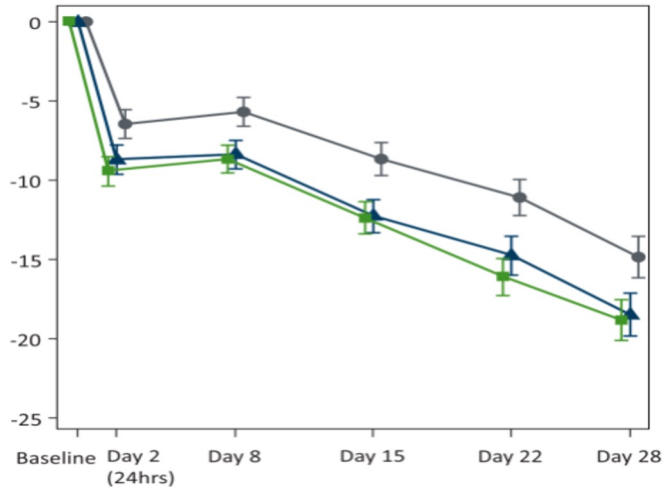
Source: Andrew Potter, PhD, Statistical Reviewer

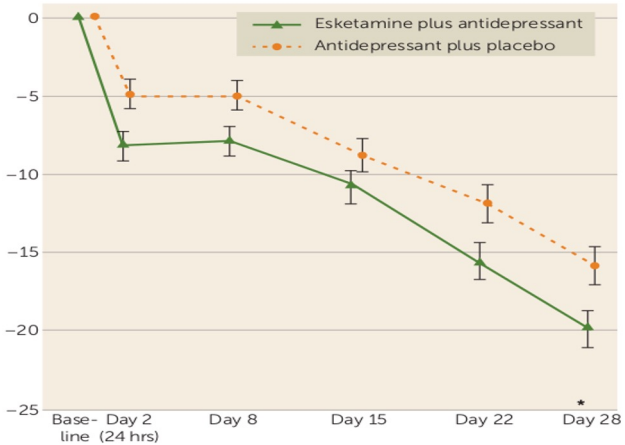
TRANSFORM 1
Fedgchin et al. 2019,
Intern J Neuropsychopharm 22: 616

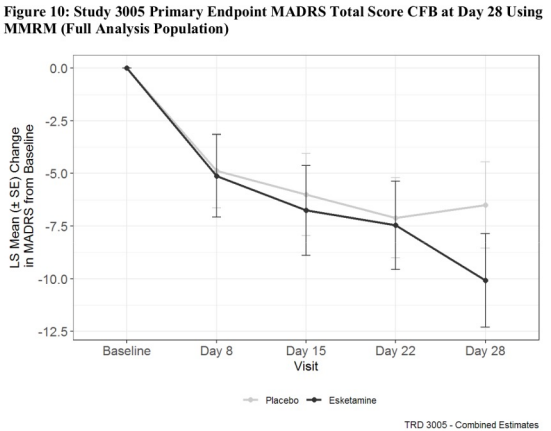
TRANSFORM 2
Popova et al. 2019,
Am J Psychiatry 2019; 176:428

TRANSFORM 3
Ochs-Ross et al. 2020,
Am J of Geriatric Psychiatry 28: 121

Esketamine Phase 3 Clinical Trials for TRD (TRANSFORM 1-3)







Source: Andrew Potter, PhD, Statistical Reviewer

4 points difference, d ≈ 0.30

Threshold clinical significance: 3-9 points

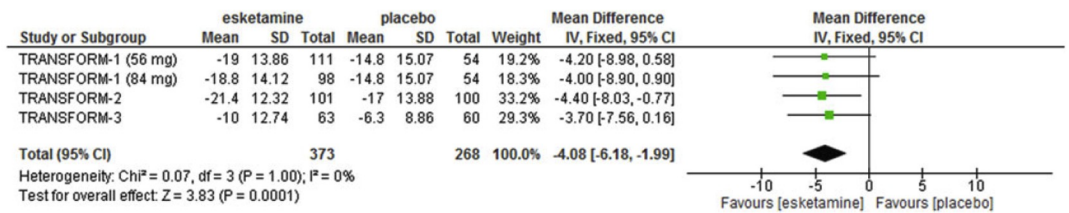
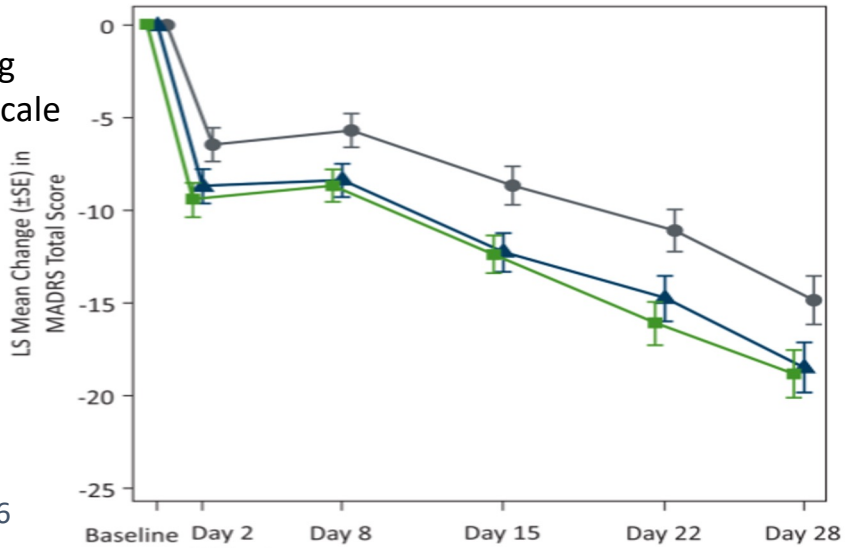


Fig. 1. Mean difference between esketamine and placebo at day 28 (study endpoint) measured with the Montgomery–Asberg Depression Rating Scale (MADRS).

Gastaldon et al. (2020). Esketamine for treatment resistant depression: a trick of smoke and mirrors?*Epidemiology and Psychiatric Sciences*, *29*.

TRD really so treatment resistant?

MADRS:
Montgomery-Asberg
Depression Rating Scale



-15 points placebo (40%)

-19 points esketamine (51%)

difference: ≈ 4 points

TRANSFORM I
Fedgchin et al. 2019,
Intern J Neuropsychopharm 22: 616

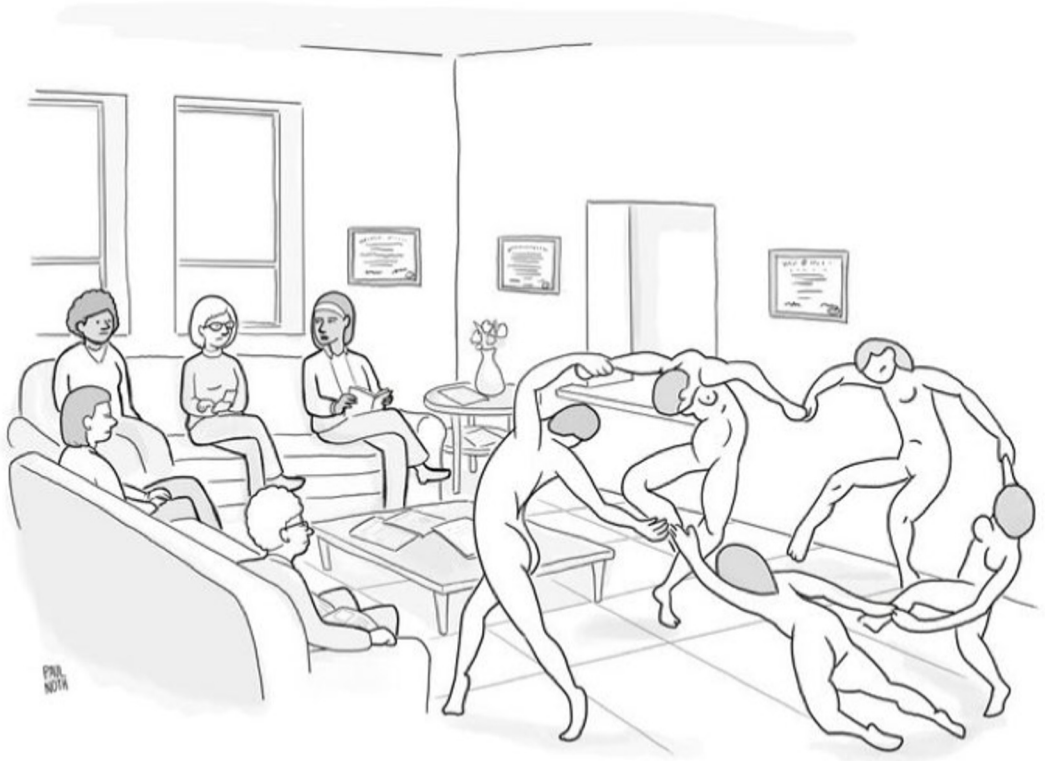
No. of Patients :	Baseline	Day 2 (24hrs)	Day 8	Day 15	Day 22	Day 28
Esketamine 56 mg/Oral Antidepressant	115	105	114	110	107	111
Esketamine 84 mg/Oral Antidepressant	114	104	107	99	96	98
Oral Antidepressant/Placebo	113	101	111	106	105	108
LS mean (SE) treatment difference vs. placebo:						
Esketamine 84 mg		-2.2 (1.29)	-2.7 (1.26)	-3.6 (1.48)	-3.7 (1.65)	-3.6 (1.86)
Esketamine 56 mg		-3.0 (1.29)	-3.0 (1.24)	-3.8 (1.45)	-5.0 (1.61)	-4.0 (1.81)

Rapid and persistent reduction of depression?

- Pre-specified criterion:
  - 50% reduction of depression achieved between 2-8 days
  - Reduction persistent until day 28
- Criterium achieved
  - Esketamine: 11%
  - Placebo: 6%

More problems

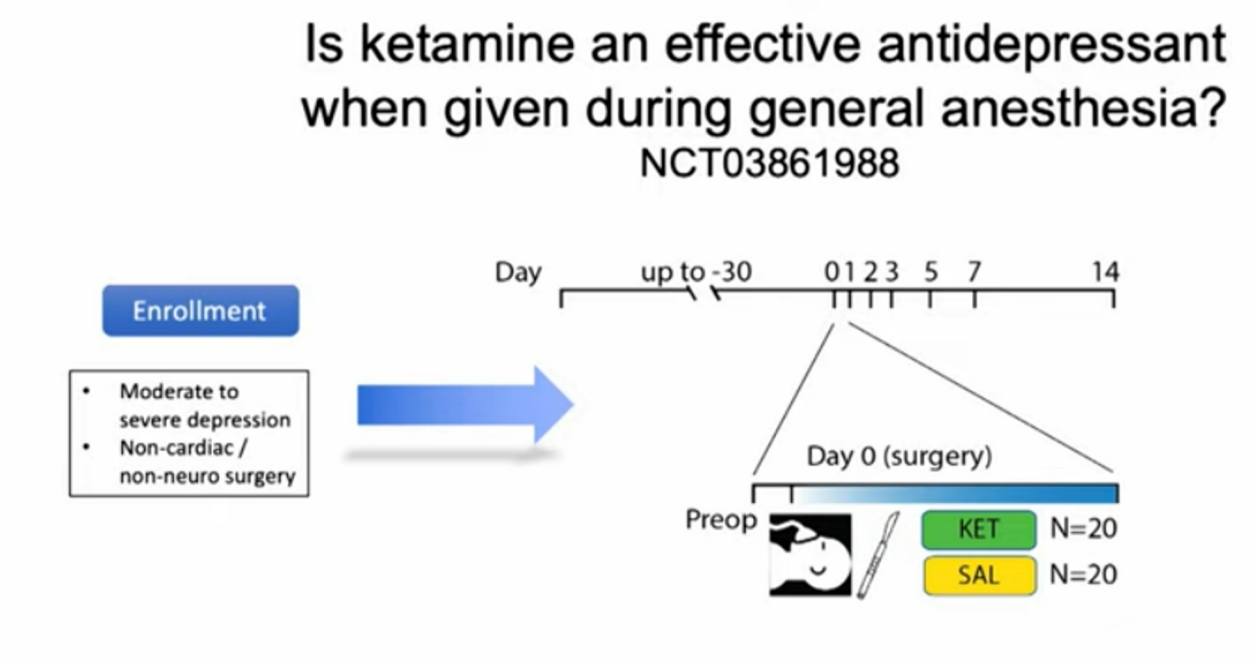
- 7-times more drop-out under esketamine (24 vs. 3%)
- 42% of serious adverse events not reported in publication (de Laportalière et al. 2023)
- **Unblinding** leads to overestimated efficacy



"So I'm guessing we're in the placebo group."

Quelle: Paul Noth, https://twitter.com/PaulNoth/status/1624455657637175296?s=20

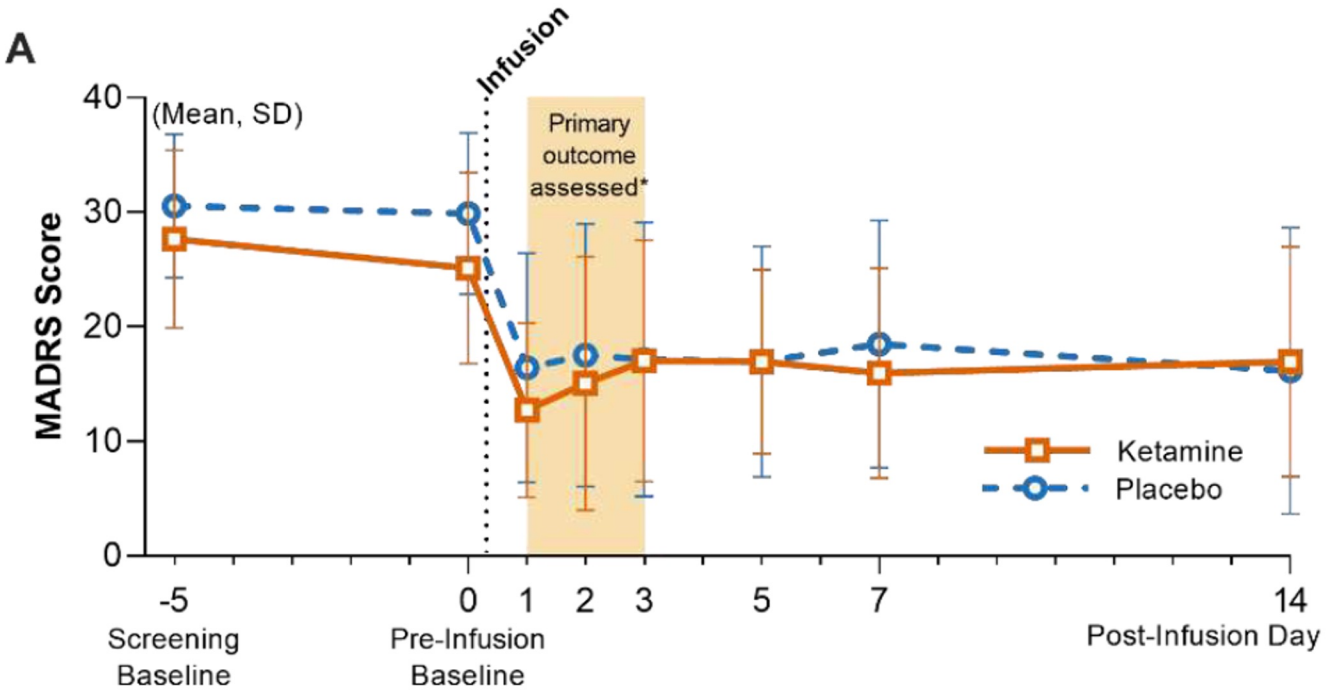
“Perfect blinding” - Ketamine/Placebo during Surgical Anesthesia



https://twitter.com/TheBorisLab/status/1578567415729750016?s=20&t=TkHmmdAbqN3VhLVrRxnCsw
https://www.youtube.com/watch?v=CHduyIe4jsU

Lii, Theresa R., et al. "Randomized trial of ketamine masked by surgical anesthesia in patients with depression." *Nature mental health* 1.11 (2023): 876-886.

“Perfect blinding” - Ketamine/Placebo during Surgical Anesthesia



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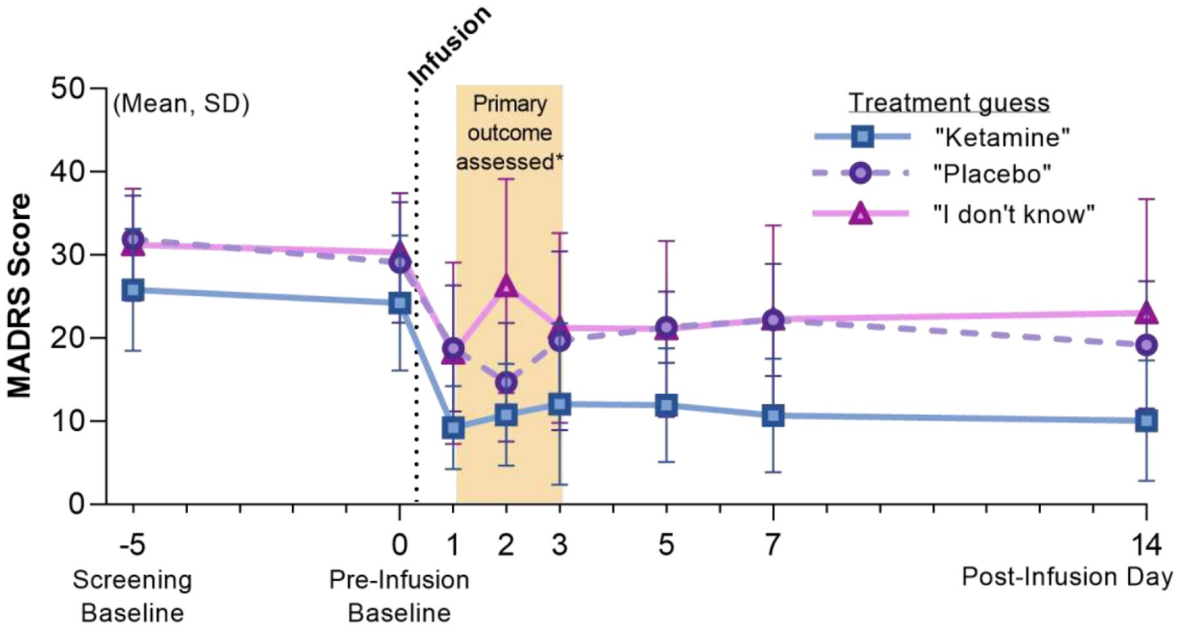
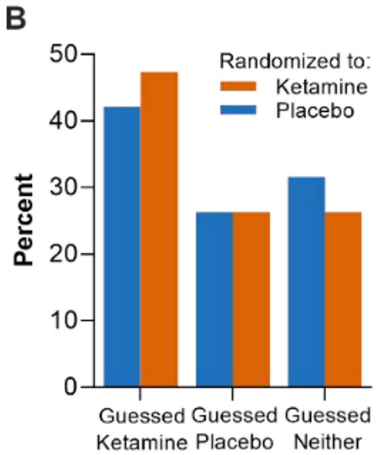
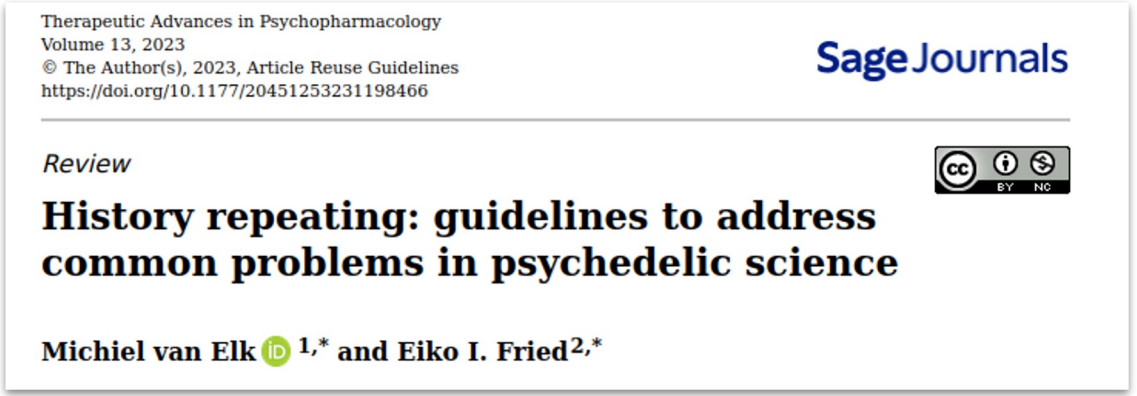




Lii, Theresa R., et al. "Randomized trial of ketamine masked by surgical anesthesia in patients with depression." *Nature mental health* 1.11 (2023): 876-886.

Biases and Methodological Challenges in Psychedelic Science

- Unblinding
- Expectancy Effects
- COI’s
- Short-term
- Adverse events



Therapeutic Advances in Psychopharmacology
Volume 13, 2023

https://doi.org/10.1177/20451253231198466

Sage Journals

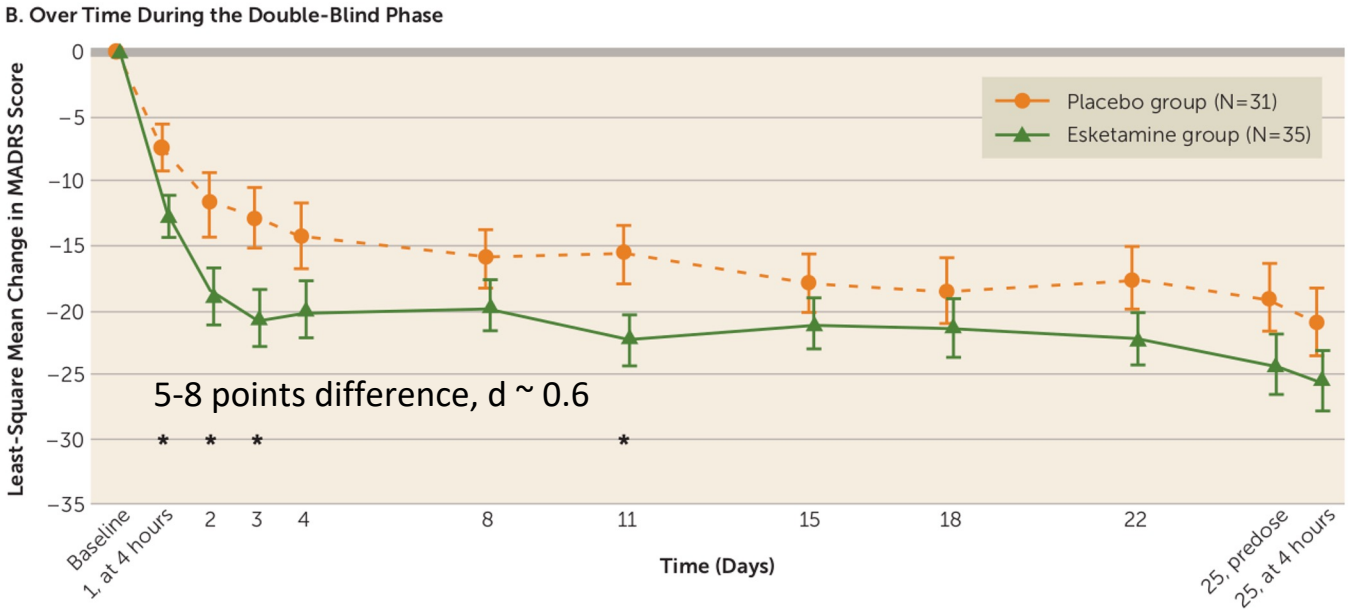
Review

History repeating: guidelines to address common problems in psychedelic science

Michiel van Elk [1,*] and Eiko I. Fried [2,*]

Ketamine and Esketamine for suicidal depression

Esketamine reduces depression in suicidal depressed patients. A promising pre-approval small trial



[a] Baseline is the predose, day 1 value. Last observation carried forward data were analyzed by analysis of covariance. Error bars indicate standard error.
*p<0.05.

Canuso et al. (2018). 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. American Journal of Psychiatry, 175: 620–630.

Two phase-3 trials for suicidal depression (ASPIRE I+II)

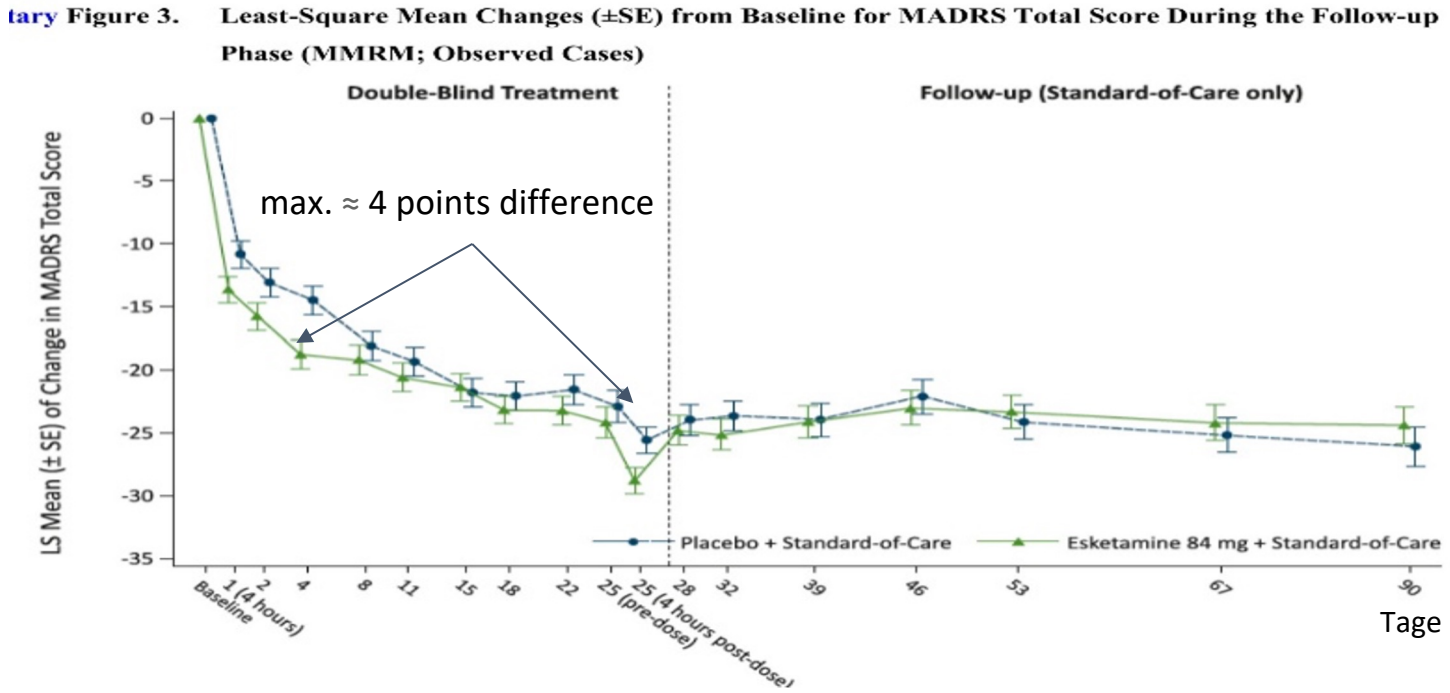
- N = 456
- **85% judged as moderate to extremely suicidal**
- Randomization: esketamine or placebo
- In addition to “standard of care”: psychiatric hospital + regular AD
- Outcome: MADRS and suicide risk (CGI-SS-R) after 24 hours

- Results for depression: 4 points on the MADRS ($p < 0.05$)
    - Lower bound of clinical significance: 3-9 points

Fu, D. J., Ionescu et al. (2020). Esketamine Nasal Spray for Rapid Reduction of Major Depressive Disorder Symptoms in Patients Who Have Active Suicidal Ideation With Intent: Double-Blind, Randomized Study (ASPIRE I). *The Journal of Clinical Psychiatry*, *81*(3).

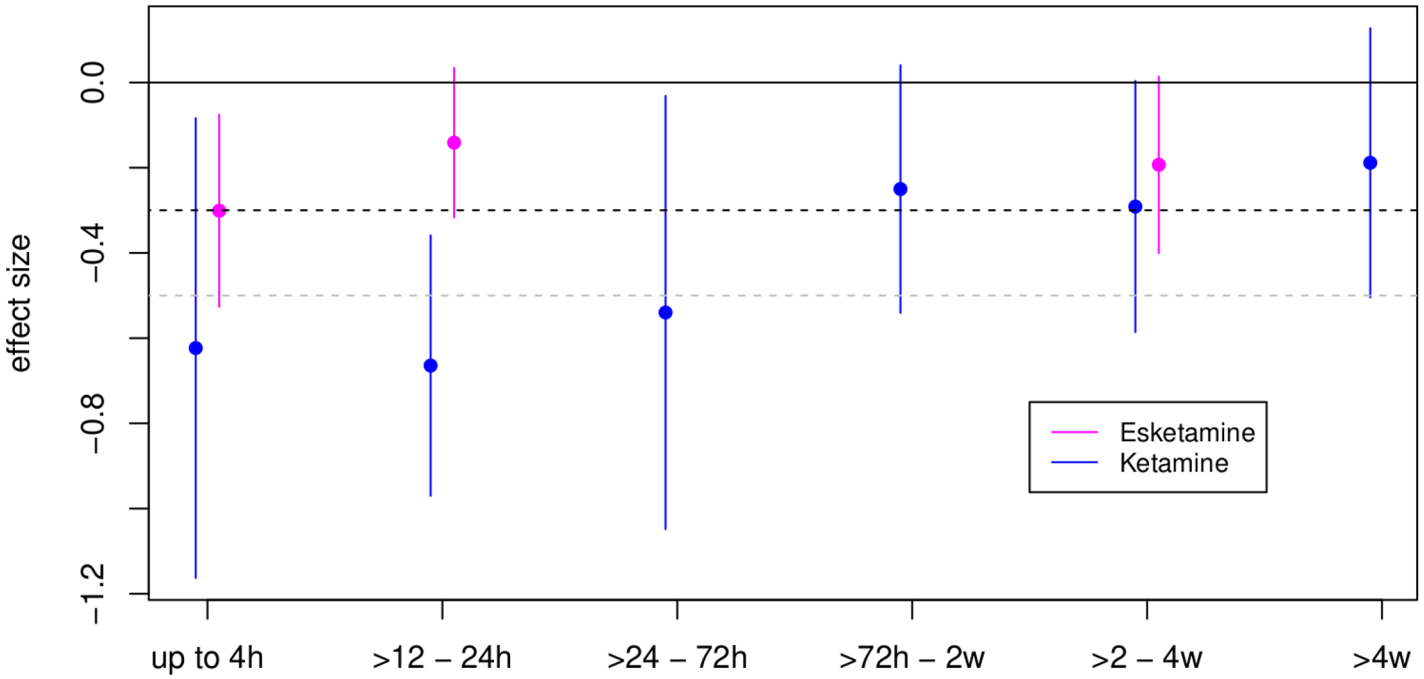
Ionescu DF, Fu D-J, Qiu X et al. (2020) Esketamine Nasal Spray for Rapid Reduction of Depressive Symptoms in Patients with Major Depressive Disorder Who Have Active Suicide Ideation with Intent: Results of a Phase 3, Double-Blind, Randomized Study

Course of depression symptoms (ASPIRE II)



Fu, D. J., Ionescu et al. (2020). Esketamine Nasal Spray for Rapid Reduction of Major Depressive Disorder Symptoms in Patients Who Have Active Suicidal Ideation With Intent: Double-Blind, Randomized Study (ASPIRE I). *The Journal of Clinical Psychiatry*, *81*(3).

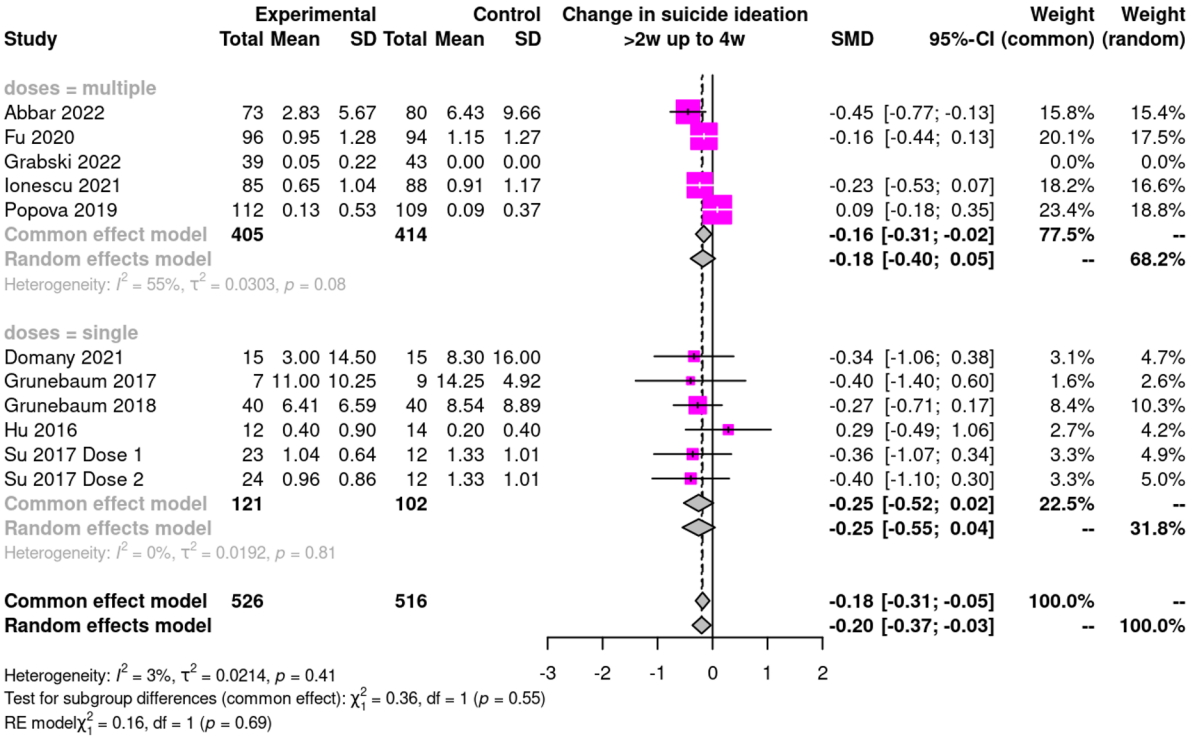
Efficacy suicide ideation over time - Studies on Suicidal Patients



Lower bound for clinical significance

Results from upcoming systematic Review

Effect for Suicide Ideation - single vs. repeated dosing



Suicide attempts in Ketamine/Esketamine trials

	(Es)Ketamine n = 955	**Control** n = 789
Double blind phase	5 (0.5%)	5 (0.6%)
Follow-up phase	18 (1.9%)	15 (1.9%)

Suicidal behavior in Esketamine ASPIRE I + II

	Esketamine n = 228	**Placebo** n = 225
Double blind phase	4	4
Follow-up phase	8 7 suicide attempts 1 suicide	3
Total	**12**	**7**

Barnards Test: p = 0.27

https://www.spravatohcp.com/
Retrieved September 28, 2020

Reports of adverse events to the FDA

- Possibility to reports adverse events by clinicians to the FDA
- Esketamine: signal for increased risk for suicide ideation and suicides
- Methodological problems:
  - Confounding by indication: esketamine for those with high suicide risk
  - Reluctance towards esketamine (or any new drug)
  - However, only reporting when causal effect is likely?

Gastaldon et al. (2020) Post-Marketing Safety Concerns with Esketamine: A Disproportionality Analysis of Spontaneous Reports Submitted to the FDA Adverse Event Reporting System. Psychoth Psychosomat.

Adverse events in case series

- First 4 patients treated with esketamine in the Toulouse University Hospital
- TRD (4-5 failed tx attempts with AD)
- 84mg weekly in first 4 weeks, followed by 84mg every 2 weeks
- Serious adverse events:
  - Increase blood pressure requiring initiation of hypertensive drug
  - Suicide attempt (jump from 3rd floor) 1h after esketamine
- Discontinuation
  - Only one patient discontinued after 9 months, without tapering, relapse with suicide ideation, again on esketamine
  - One pt could not tolerate spacing the dose from 2 to 3 weeks
  - All 4 patients still on esketamine

de Laportalière et al. (2022). How to deprescribe esketamine in resistant depression? A point of view after first clinical uses. *Epidemiology and psychiatric sciences*, *31*.

Adverse events (ASPIRE I+II combined)

	Placebo + SOC n = 225		Esketamine + SOC (n = 227)		
	n	%	n	%	**RR**
Dizziness	31	13.8	87	38.3	**2.8**
Dissociation	13	5.8	77	33.9	**5.8**
Nausea	31	13.8	61	26.9	**1.9**
Somnolence	23	10.2	47	20.7	**2.0**
Headache	46	20.4	46	20.3	**1.0**
Dysgeusia	29	12.9	45	19.8	**1.5**
Blurred vision	11	4.9	27	11.9	**2.4**
Blood pressure increase	9	4	26	11.5	**2.9**
Paresthesia	7	3.1	26	11.5	**3.7**
Vomiting	12	5.3	26	11.5	**2.2**
Anxiety	17	7.6	23	10.1	**1.3**
Sedation	5	2.2	23	10.1	**4.6**

Some professional organizations do not recommend esketamine:

- UK: National Institute for Health and Care Excellence (NICE)
  "Taking this uncertainty into account, the cost-effectiveness estimates for esketamine are much higher than what NICE considers a cost-effective use of NHS resources. So, it cannot be recommended."
  https://nice.org.uk/consultations/1053/1/recommendations

  Appeal by Janssen and the Royal College of Psychiatrists (!) - ongoing process

- Danish council of medicine

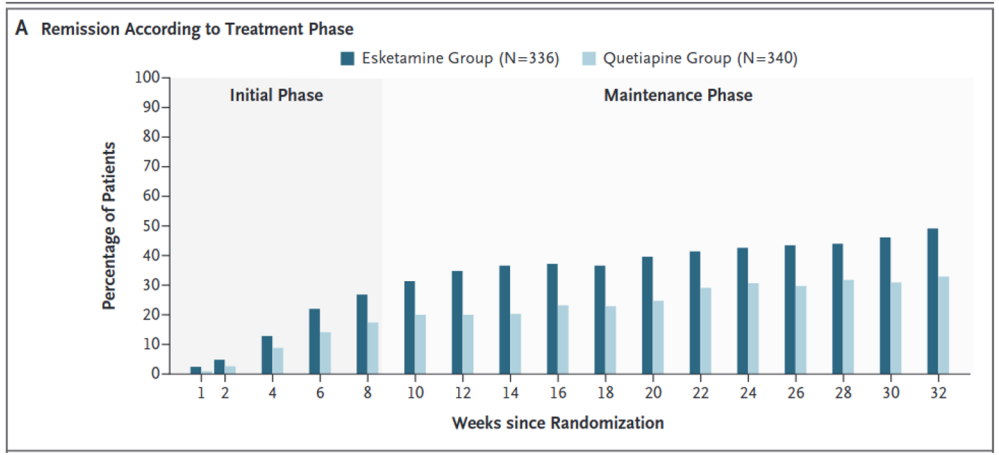
- Unabhängiges Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (IQWiG): “Zusatznutzen nicht belegt” [*additional benefit not proven*]
  https://www.iqwig.de/download/a21-24_esketamin_nutzenbewertung-35a-sgb-v_v1-0.pdf

ESCAPE Trial might change recommendations, but…

- Esketamine vs. Quetiapine
- Open Label
- Remission free: 22 vs. 14%

- Study discontinuation counted as non-remission: problem when participants leave study because they do not receive esketamine (open label, no blinding)
- More contact in Esketamine arm
- Only ~ 2 MADRS points difference

The NEW ENGLAND JOURNAL of MEDICINE



Summary

- Ketamine: substantial effect on suicide ideation
  - short term only (in first 5 days)
  - uncertainty remains
- Esketamine has no/minimal effect on suicide idation
  - no uncertainty
- Inconclusive evidence for suicidal behavior
  - Some signals of harm, but no strong evidence
- Repeated dosing?
- Biases in favor of EsKetamine
- Hype or breakthrough?