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Ketamine and Esketamine: The Amazing, The Good, The Bad, and The Ugly

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Disclosures

- ***Research/Grants:*** National Institutes of Health (NIH)
- ***Consultant:*** ACADIA Pharmaceuticals Inc.; Bracket (Clintara); EMA Wellness; Gerson Lehrman Group, Inc. (GLG); Intra-Cellular Therapies, Inc.; Janssen Research & Development LLC; Magstim, Inc.; Navitor Pharmaceuticals, Inc.; Sunovion Pharmaceuticals Inc.; Taisho Pharmaceutical Inc.; Takeda Pharmaceuticals North America, Inc.; TC MSO, Inc.; Xhale, Inc.
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- ***Advisory Board:*** American Foundation for Suicide Prevention (AFSP); Anxiety Disorders Association of America (ADAA); Bracket (Clintara); Brain & Behavior Research Foundation (BBRF); Laureate Institute for Brain Research, Inc.; Skyland Trail; Xhale, Inc.
- ***Board of Directors:*** American Foundation for Suicide Prevention (AFSP); Anxiety Disorders Association of America (ADAA); GratitudeAmerica, Inc.; Xhale, Inc.
- ***Income Sources or Equity of $10,000 or More:*** American Psychiatric Publishing; Bracket (Clintara); CME Outfitters, LLC; EMA Wellness; Intra-Cellular Therapies, Inc.; Magstim, Inc.; Xhale, Inc.
- ***Patents:*** Method and devices for transdermal delivery of lithium (US 6,375,990B1); Method of assessing antidepressant drug therapy via transport inhibition of monoamine neurotransmitters by ex vivo assay (US 7,148,027B2); Compounds, Compositions, Methods of Synthesis, and Methods of Treatment (CRF Receptor Binding Ligand) (US 8,511,996B2)

Learning Objective 1

Evaluate the latest evidence regarding the efficacy and side effects of ketamine and esketamine in patients with TRD

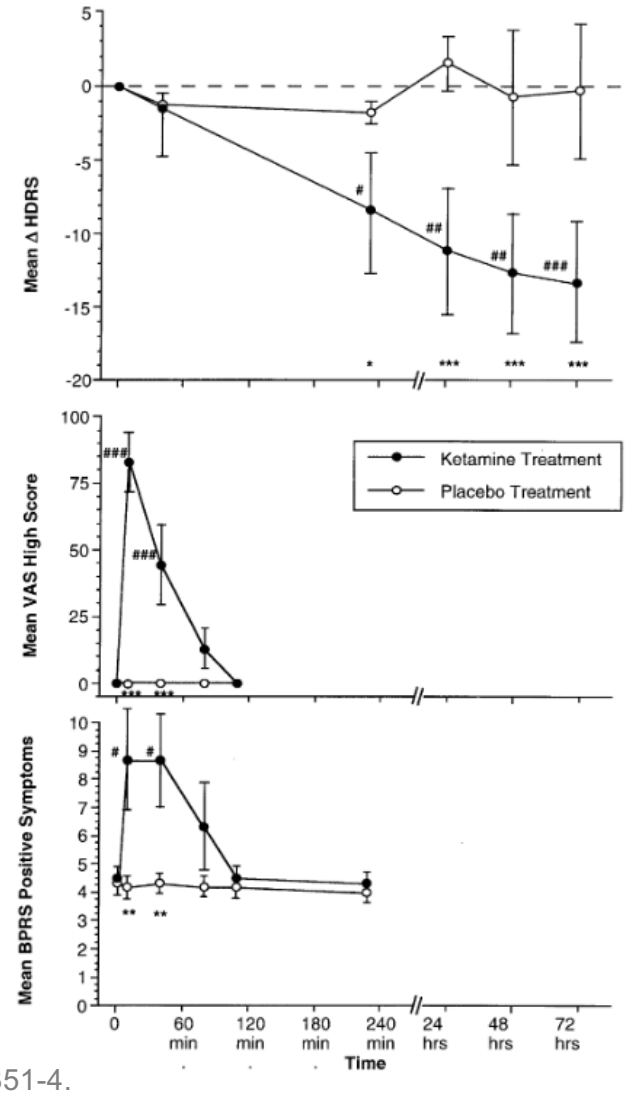
The Amazing

BRIEF REPORTS

Antidepressant Effects of Ketamine in Depressed Patients

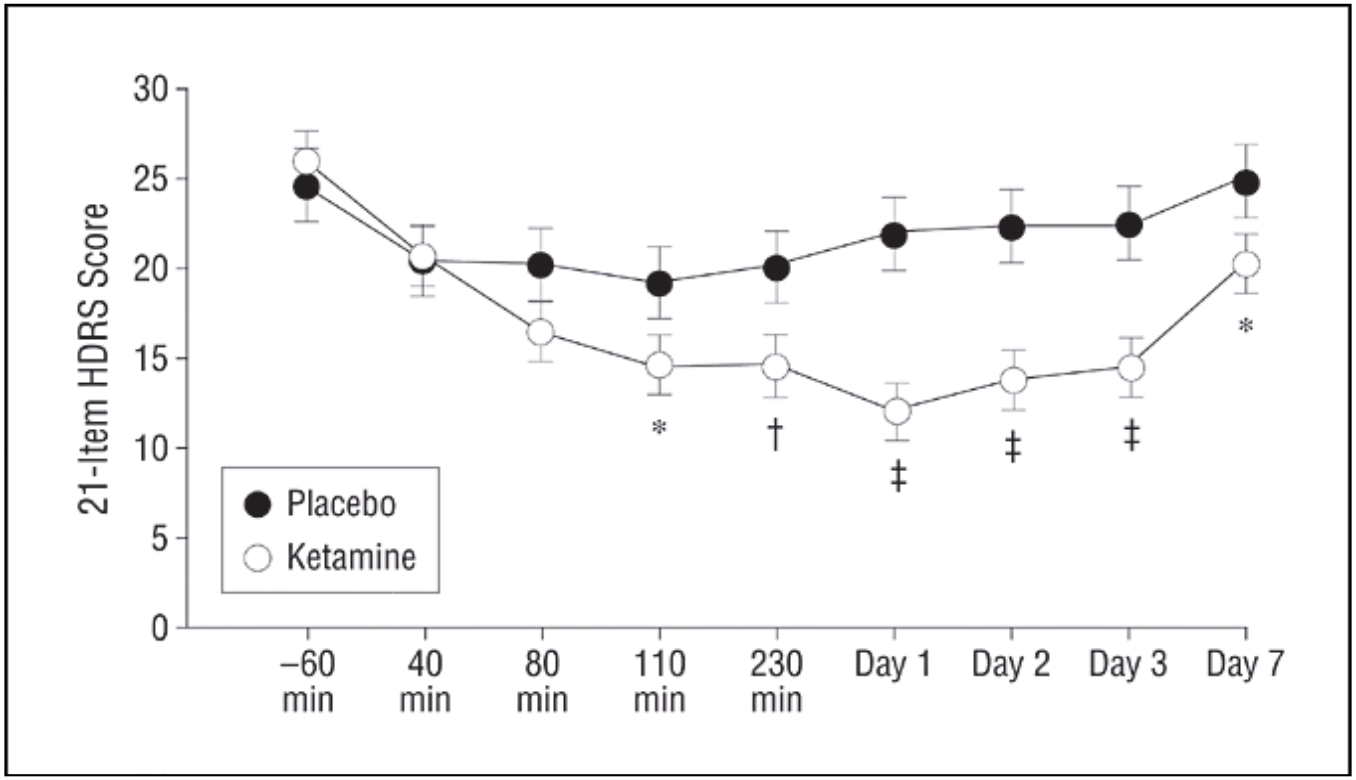
Robert M. Berman, Angela Cappiello, Amit Anand, Dan A. Oren, George R. Heninger, Dennis S. Charney, and John H. Krystal

Berman R, et al. *Biol Psychiatry*. 2000 Feb 15;47(4):351-4.



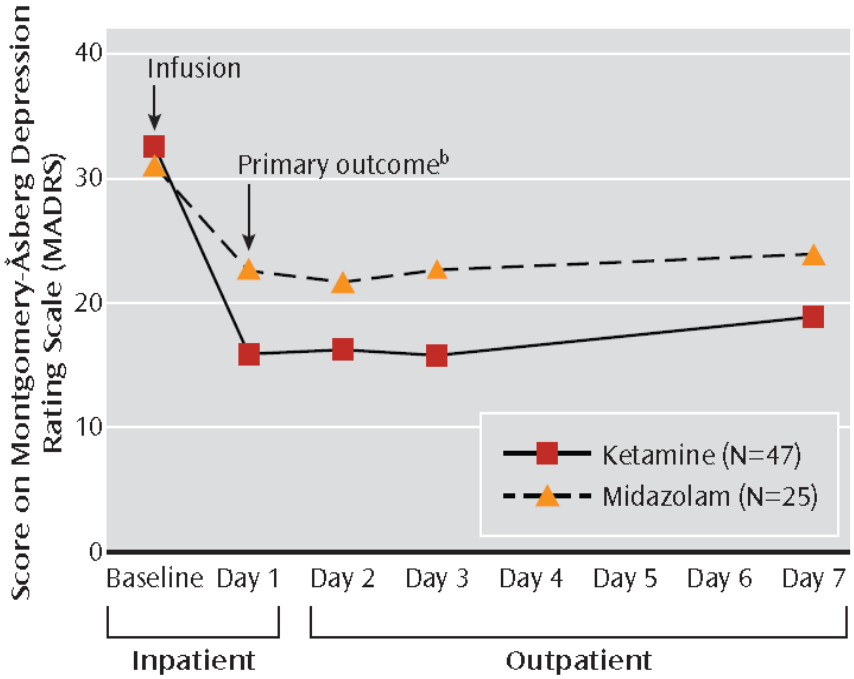
Berman R, et al. *Biol Psychiatry*. 2000 Feb 15;47(4):351-4.

Change in the 21-Item Hamilton Depression Rating Scale (HDRS) Over 1 Week (n = 18)



Zarate, CA et al. *Arch Gen Psychiatry*. 2006;63:856-864.

FIGURE 1. Change in Depression Severity Over Time in Patients With Treatment-Resistant Major Depression Given a Single Infusion of Ketamine or Midazolam[a]



[a] Modified intention-to-treat group. MADRS scores range from 0 to 60, with higher scores indicating a greater severity of symptoms.

[b] Reduction in MADRS score 24 hours after infusion was the primary outcome measure and was significantly greater for the ketamine group than for the midazolam group ($p \leq 0.002$).

Murrough, JW et al. *Am J Psychiatry* 2013; 170:1134-1142.

The Good

JAMA Psychiatry | Special Communication

A Consensus Statement on the Use of Ketamine in the Treatment of Mood Disorders

Gerard Sanacora, MD, PhD; Mark A. Frye, MD; William McDonald, MD; Sanjay J. Mathew, MD; Mason S. Turner, MD; Alan F. Schatzberg, MD; Paul Summergrad, MD; Charles B. Nemeroff, MD, PhD; for the American Psychiatric Association (APA) Council of Research Task Force on Novel Biomarkers and Treatments

IMPORTANCE Several studies now provide evidence of ketamine hydrochloride's ability to produce rapid and robust antidepressant effects in patients with mood and anxiety disorders that were previously resistant to treatment. Despite the relatively small sample sizes, lack of longer-term data on efficacy, and limited data on safety provided by these studies, they have led to increased use of ketamine as an off-label treatment for mood and other psychiatric disorders.

OBSERVATIONS This review and consensus statement provides a general overview of the data on the use of ketamine for the treatment of mood disorders and highlights the limitations of the existing knowledge. While ketamine may be beneficial to some patients with mood disorders, it is important to consider the limitations of the available data and the potential risk associated with the drug when considering the treatment option.

CONCLUSIONS AND RELEVANCE The suggestions provided are intended to facilitate clinical decision making and encourage an evidence-based approach to using ketamine in the treatment of psychiatric disorders considering the limited information that is currently available. This article provides information on potentially important issues related to the off-label treatment approach that should be considered to help ensure patient safety.

JAMA Psychiatry. 2017;74(4):399-405. doi:10.1001/jamapsychiatry.2017.0080
Published online March 1, 2017.

Invited Commentary
page 405

Supplemental content at
jamapsychiatry.com

Author Affiliations: Author affiliations are listed at the end of this article.

Group Information: The American Psychiatric Association (APA) Council of Research Task Force on Novel Biomarkers and Treatments members are listed at the end of this article.

Corresponding Author: Gerard Sanacora, MD, PhD, Yale University School of Medicine, 100 York St, Ste 2J, New Haven, CT 06511 (gerard.sanacora@yale.edu).

Sanacora G, et al. *JAMA Psych*. 2017;74:399-405.

Table. Recommended Components of Preprocedural Evaluation for Appropriateness of Ketamine Hydrochloride Treatment

Component	Recommendation
1	A comprehensive diagnostic assessment should be completed to establish current diagnosis and evaluate history of substance use and psychotic disorders
2	Assessment of baseline symptom severity should be completed to allow later assessments of clinical change with treatment[a]
3	A thorough history of antidepressant treatment should be collected and documented to confirm previous adequate trials of antidepressant treatments
4	A thorough review of systems should be performed to evaluate potential risk factors associated with ketamine treatment[b]
5	Decisions on the specific physical examination and laboratory screening assessments should be made according to established guidelines and advisories issued by the American College of Cardiology Foundation/American Heart Association and the American Society of Anesthesiologists and should be based on a patient's individual clinical characteristics[c]
6	A careful review of past medical and psychiatric records and/or corroboration of the past history by family members are strongly encouraged; all current medications and allergies should be reviewed, including histories of opiate and benzodiazepine use; the use of a baseline urine toxicology screen is strongly encouraged to ensure the accuracy of the reported substance use and medication record
7	An informed consent process, including discussion of the risks associated with the treatment,[d] the limits of the available information pertaining to the potential benefits of the treatment, the fact that this is an off-label use of ketamine, and a discussion of alternative treatment options should be completed; this discussion should be complemented with written materials, and the patient should provide written informed consent before initiating treatment

Sanacora G, et al. *JAMA Psych*. 2017;74:399-405.

Depression and Anxiety 33:685–688 (2016)

Editorial

WHITHER KETAMINE AS AN ANTIDEPRESSANT: PANACEA OR TOXIN?

D. Jeffrey Newport, M.D., M.S., M.Div.,[1,2] Alan F. Schatzberg, M.D.,[3] and Charles B. Nemeroff, M.D., Ph.D.[1,4]*

Commentary

Balancing the Promise and Risks of Ketamine Treatment for Mood Disorders

G Sanacora*[,1], H Heimer[2], D Hartman[3], SJ Mathew[4], M Frye[5], C Nemeroff[6] and R Robinson Beale[7]

[1]Yale Depression Research Program, Yale University School of Medicine, New Haven, CT, USA; [2]Cure Alliance for Mental Illness, Providence, RI, USA; [3]Ketamine Advocacy Network, Seattle, WA, USA; [4]Baylor College of Medicine, Houston, TX and Michael E. DeBakey VA Medical Center, Houston, TX, USA; [5]Mayo Clinic, Rochester, MN, USA; [6]University of Miami, Miami FL, USA; [7]Blue Cross of Idaho, Boise, ID, USA

Neuropsychopharmacology (2017) **42,** 1179–1181; doi:10.1038/npp.2016.193; published online 12 October 2016

Ketamine: Quo Vadis?

Charles B. Nemeroff, M.D., Ph.D.

"It was the best of times, it was the worst of times, it was the age of wisdom, it was the age of foolishness, it was the epoch of belief, it was the epoch of incredulity, it was the season of light, it was the season of darkness, it was the spring of hope, it was the winter of despair."

—Charles Dickens, *A Tale of Two Cities*

A Word to the Wise About Intranasal Esketamine

Alan F. Schatzberg, M.D.

Ketamine and Other NMDA Antagonists: Early Clinical Trials and Possible Mechanisms in Depression

D. Jeffrey Newport, M.D., M.S., M.Div., Linda L. Carpenter, M.D., William M. McDonald, M.D., James B. Potash, M.D., M.P.H., Mauricio Tohen, M.D., Dr.P.H., M.B.A., Charles B. Nemeroff, M.D., Ph.D., The APA Council of Research Task Force on Novel Biomarkers and Treatments

Am J Psychiatry 172:10, October 2015

Newport J, et al. *Am J Psychiatry. 2015;*172-10.

Conclusions: The antidepressant efficacy of ketamine, and perhaps D-cycloserine and rapastinel, holds promise for future glutamate-modulating strategies; however, the ineffectiveness of other NMDA antagonists suggests that any forthcoming advances will depend on improving our understanding of ketamine's mechanism of action. The fleeting nature of ketamine's therapeutic benefit, coupled with its potential for abuse and neurotoxicity, suggest that its use in the clinical setting warrants caution.

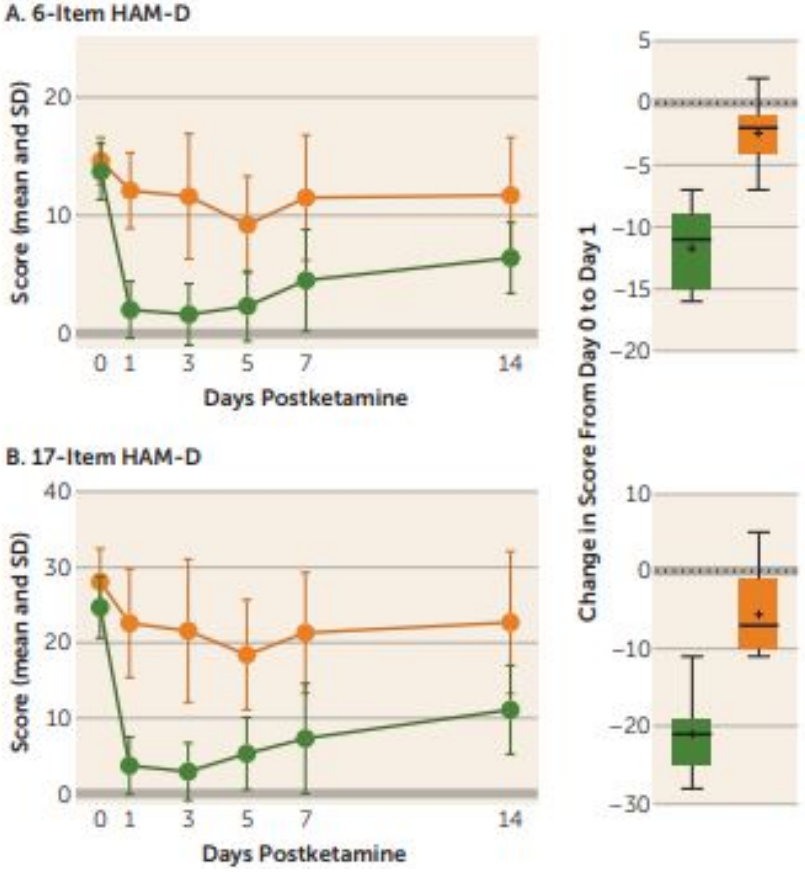
Newport J, et al. *Am J Psychiatry. 2015;*172-10.

Attenuation of Antidepressant Effects of Ketamine by Opioid Receptor Antagonism

Nolan R. Williams, M.D., Boris D. Heifets, M.D., Ph.D., Christine Blasey, Ph.D., Keith Sudheimer, Ph.D., Jaspreet Pannu, B.S., Heather Pankow, B.S., Jessica Hawkins, B.S., Justin Birnbaum, M.D., David M. Lyons, Ph.D., Carolyn I. Rodriguez, M.D., Ph.D., Alan F. Schatzberg, M.D.

Williams N, et al. *Am J Psychiatry*. 2018;175:12.

FIGURE 1. Time Course of Primary and Secondary Outcome Measures for Ketamine-Responsive Patients With Treatment-Resistant Depression (N=7) in Two Conditions in a Crossover Study of Ketamine's Antidepressant Effect After Pretreatment With Naltrexone or Placebo[a]



Williams N, et al. *Am J Psychiatry*. 2018;175:12.

Molecular Psychiatry (2019) 24:1779–1786
https://doi.org/10.1038/s41380-019-0503-4

IMMEDIATE COMMUNICATION

Attenuation of antidepressant and antisuicidal effects of ketamine by opioid receptor antagonism

Nolan R. Williams[1] · Boris D. Heifets[2] · Brandon S. Bentzley[1] · Christine Blasey[1,3] · Keith D. Sudheimer[1] · Jessica Hawkins[1] · David M. Lyons[1] · Alan F. Schatzberg[1]

Received: 29 December 2018 / Revised: 30 April 2019 / Accepted: 17 May 2019 / Published online: 29 August 2019

Abstract

We recently reported that naltrexone blocks antidepressant effects of ketamine in humans, indicating that antidepressant effects of ketamine require opioid receptor activation. However, it is unknown if opioid receptors are also involved in ketamine's antisuicidality effects. Here, in a secondary analysis of our recent clinical trial, we test whether naltrexone attenuates antisuicidality effects of ketamine. Participants were pretreated with naltrexone or placebo prior to intravenous ketamine in a double-blinded crossover design. Suicidality was measured with the Hamilton Depression Rating Scale item 3, Montgomery–Åsberg Depression Rating Scale item 10, and Columbia Suicide Severity Rating Scale. In the 12 participants who completed naltrexone and placebo conditions, naltrexone attenuated the antisuicidality effects of ketamine on all three suicidality scales/subscales (linear mixed model, fixed pretreatment effect, $p < 0.01$). Results indicate that opioid receptor activation plays a significant role in the antisuicidality effects of ketamine.

Williams N, et al. *Mol Psychiatry*. 2019; 24:1779-1786.

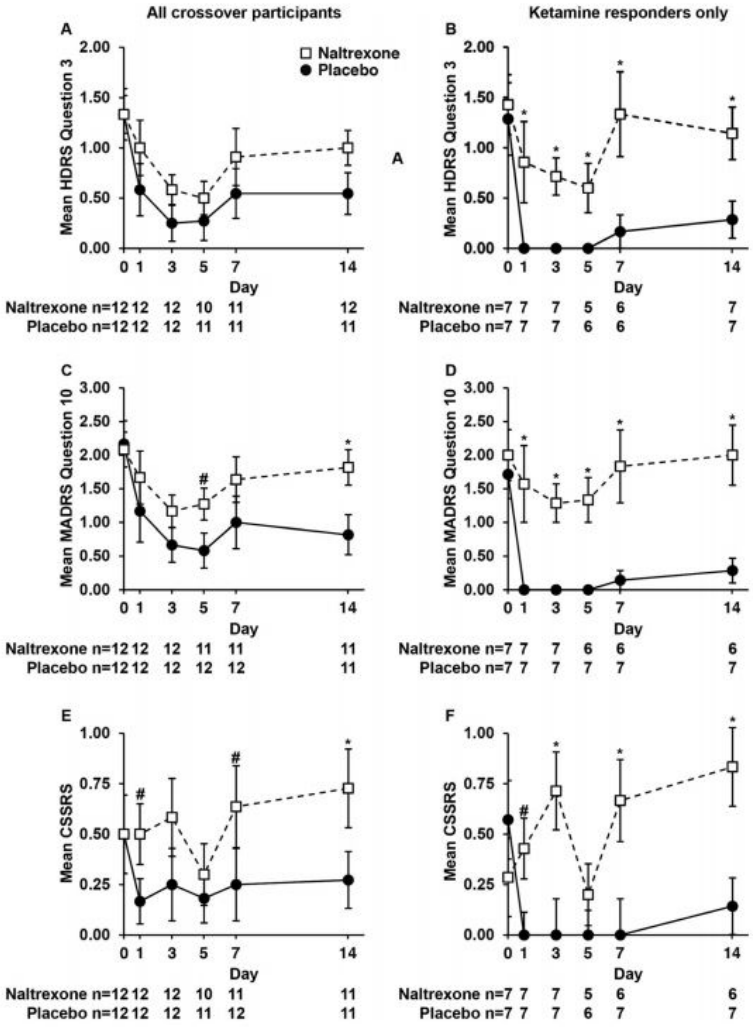


Fig. 1 Naltrexone blocks the antisuicidality effects of ketamine as measured by **a**, **b**: item 3 of the HDRS, **c**, **d**: item 10 of the MADRS, and **e**, **f**: CSSRS. This effect was especially pronounced in the group of participants who responded to ketamine (right column) compared with the entire group of 12 crossover participants (left column). $^{\#}p < 0.10$, $^{*}p < 0.05$ after Bonferroni correction for multiple comparisons

Williams N, et al. *Mol Psychiatry*. 2019; 24:1779-1786.

The Bad

KLARISANA AUSTIN UPDATE

3) Will my dose be just set at the “standard” NIH protocol which is unvalidated or will it be changed in a dynamic fashion? We believe that the ideal dose is VERY individualized and requires a fair amount of effort on the part of the clinician treating you. We feel it is important to have a Psychotropic Therapeutic Response (PTR) where a true paradigm shift in a patient’s thought patters can be achieved. For some people this is 50mg over an hour and others it is 200mg over an hour. It takes a lot of time and effort on that part of clinic staff to fine tune the dosing strategy for each patient. Some centers cut costs by having a standard “one size fits all” protocol such as everybody gets 0.5 mg/kg of ketamine over forty minutes for a total of six infusions. We find that this assembly line model is too simplistic and counterproductive when we are talking about achieving a a true therapeutic response.

4) Does the center offer the possibility to receive facilitated psychotherapy whereby a therapist works with you while you are receiving ketamine. This can be a powerful modality to allow the therapist to explore elements of the subject’s mind which would not be accessible while not on ketamine.

JAMA Psychiatry | Original Investigation

Effect of Repetitive Transcranial Magnetic Stimulation on Treatment-Resistant Major Depression in US Veterans
A Randomized Clinical Trial

Jerome A. Yesavage, MD; J. Kaci Fairchild, PhD; Zhibao Mi, PhD; Kousick Biswas, PhD; Anne Davis-Karim, PharmD; Ciaran S. Phibbs, PhD; Steven D. Forman, MD, PhD; Michael Thase, MD; Leanne M. Williams, PhD; Amit Etkin, MD, PhD; Ruth O'Hara, PhD; Gerald Georgette, RN; Tamara Beale, MA; Grant D. Huang, MPH, PhD; Art Noda, MS; Mark S. George, MD; for the VA Cooperative Studies Program Study Team

JAMA Psychiatry. 2018;75(9):884-893. doi:10.1001/jamapsychiatry.2018.1483
Published online June 27, 2018.

Yesavage J, et al. *JAMA Psychiatry*. 2018;75:884-893.

Key Points

Question Is repetitive transcranial magnetic stimulation an efficacious treatment for treatment-resistant major depression in patients who are veterans?

Findings In this randomized clinical trial of 164 US veterans with depression, the overall remission rate was 39%, with no significant difference between the active and sham groups. Patients with comorbid posttraumatic stress disorder showed the least improvement.

Meaning These findings may reflect the importance of close clinical surveillance, rigorous monitoring of concomitant medication, and regular interaction with clinic staff in bringing about significant improvement in this treatment-resistant population.

Yesavage J, et al. *JAMA Psychiatry*. 2018;75:884-893.

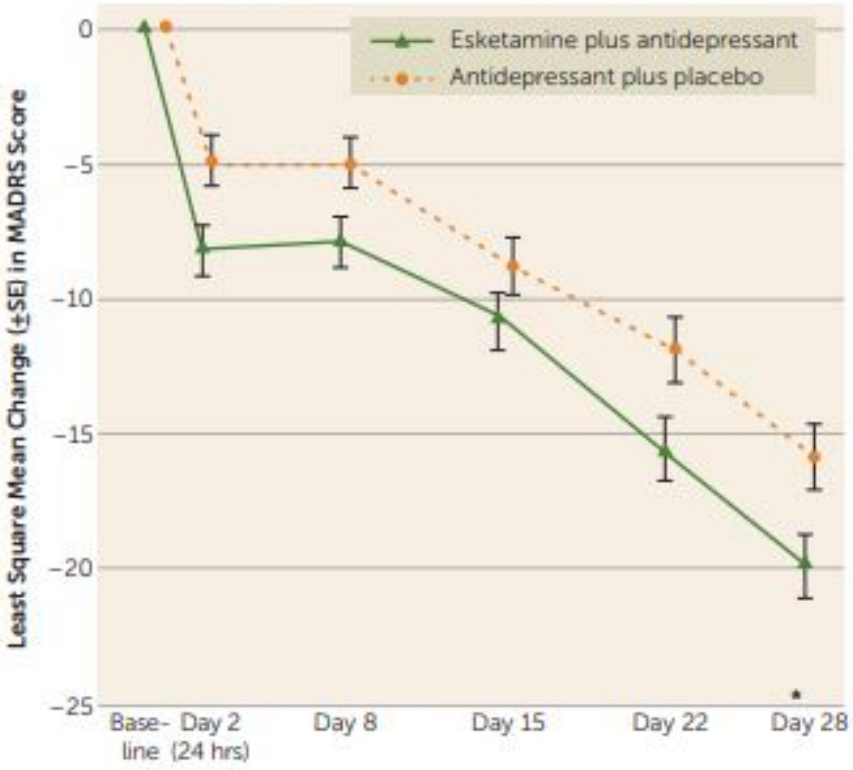
Esketamine

Efficacy and Safety of Flexibly Dosed Esketamine Nasal Spray Combined With a Newly Initiated Oral Antidepressant in Treatment-Resistant Depression: A Randomized Double-Blind Active-Controlled Study

Vanina Popova, M.D., Ella J. Daly, M.D., Madhukar Trivedi, M.D., Kimberly Cooper, M.S., Rosanne Lane, M.A.S., Pilar Lim, Ph.D., Christine Mazzucco, M.Sc., David Hough, M.D., Michael E. Thase, M.D., Richard C. Shelton, M.D., Patricio Molero, M.D., Ph.D., Eduard Vieta, M.D., Ph.D., Malek Bajbouj, M.D., Husseini Manji, M.D., Wayne C. Drevets, M.D., Jaskaran B. Singh, M.D.

Popova V, et al. *Am J Psychiatry*. 2019; 176:6.

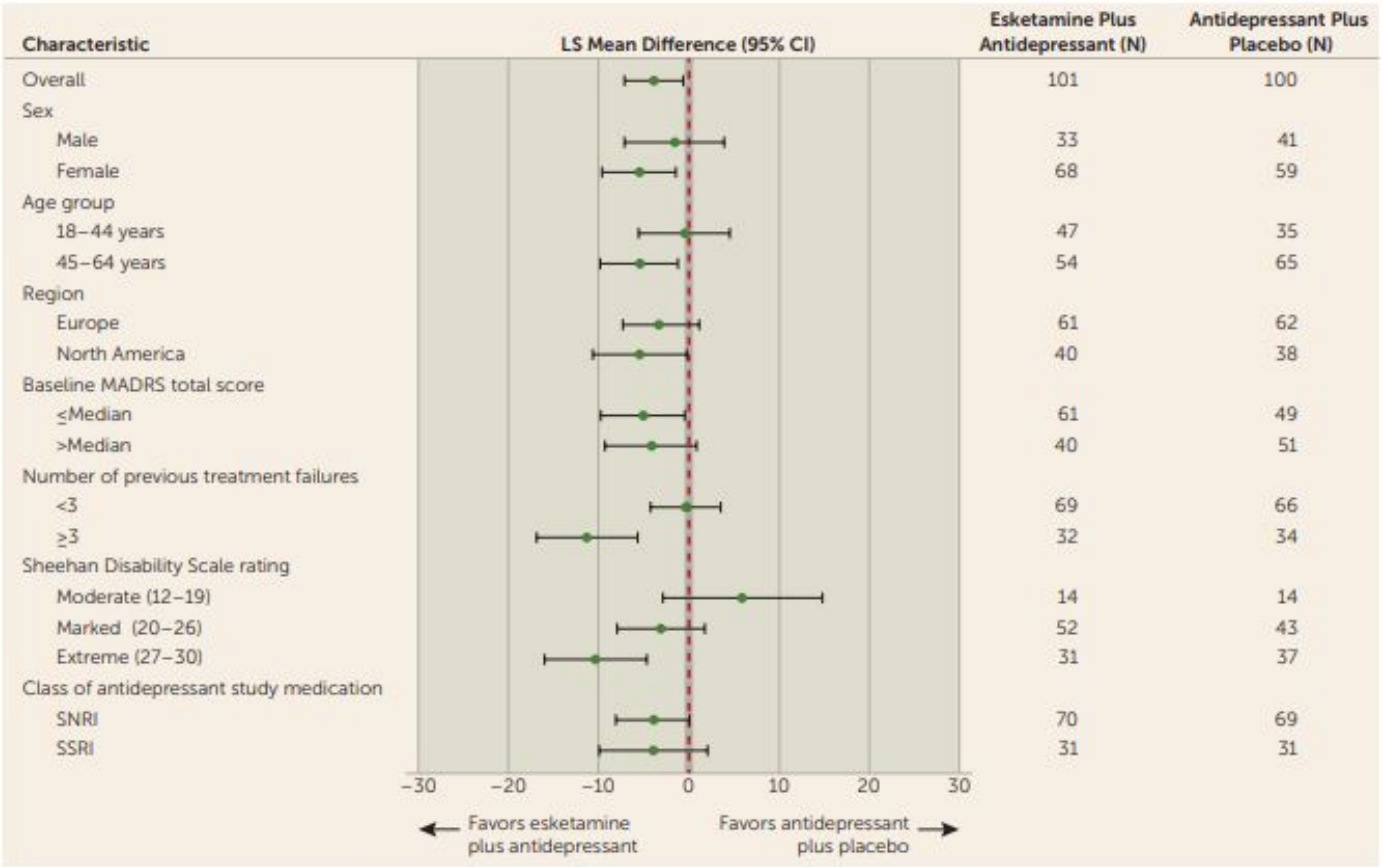
FIGURE 1. Least square mean change in Montgomery-Åsberg Depression Rating Scale (MADRS) score over time in the double-blind treatment phase of a randomized controlled trial of esketamine nasal spray for treatment-resistant depression[a]



	Base-line	Day 2 (24 hrs)	Day 8	Day 15	Day 22	Day 28
Esketamine plus antidepressant (N)	114	109	109	107	103	101
Antidepressant plus placebo (N)	109	102	105	102	104	100

Popova V, et al. *Am J Psychiatry*. 2019; 176:6.

FIGURE 2. Forest plot of treatment differences on change in Montgomery-Åsberg Depression Rating Scale (MADRS) score from baseline to day 28 in the double-blind treatment phase of a randomized controlled trial of esketamine nasal spray for treatment-resistant depression[a]



[a] Data are differences of least square (LS) means (95% CI) from a mixed model for repeated measures, by subgroup. Subgroups of ≤15 patients or considered confounded on data review are not presented. Number of previous treatment failures refers to number of antidepressants taken with nonresponse in addition to one prospective antidepressant. SNRI=serotonin-norepinephrine reuptake inhibitor; SSRI=selective serotonin reuptake inhibitor.

Popova V, et al. *Am J Psychiatry*. 2019; 176:6.

JAMA Psychiatry | Original Investigation

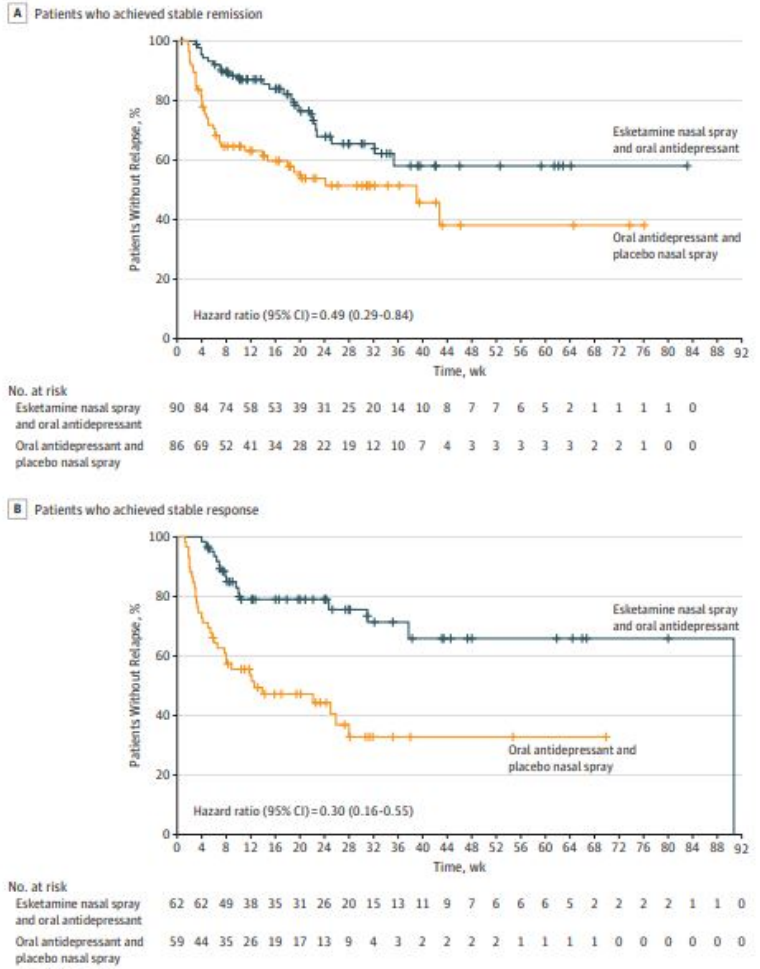
Efficacy of Esketamine Nasal Spray Plus Oral Antidepressant Treatment for Relapse Prevention in Patients With Treatment-Resistant Depression

A Randomized Clinical Trial

Ella J. Daly, MD; Madhukar H. Trivedi, MD; Adam Janik, MD; Honglan Li, MD, PhD; Yun Zhang, PhD; Xiang Li, PhD; Rosanne Lane, MAS; Pilar Lim, PhD; Anna R. Duca, BSN; David Hough, MD; Michael E. Thase, MD; John Zajecka, MD; Andrew Winokur, MD, PhD; Ilona Divacka, MBA, MD; Andrea Fagiolini, MD; Wiesław J. Cubała, MD, PhD; István Bitter, MD, PhD; Pierre Blier, MD, PhD; Richard C. Shelton, MD; Patricio Molero, MD, PhD; Husseini Manji, MD; Wayne C. Drevets, MD; Jaskaran B. Singh, MD

Daly E, et al. *JAMA Psychiatry*. 2019. 1189. [Epub ahead of print]

Figure 2. Kaplan-Meier Estimates of Time to Relapse



One patient who achieved stable response was incorrectly randomized as a patient who achieved stable remission at the end of the optimization phase. One patient did not meet stable remission or stable response criteria and was incorrectly randomized as a patient with stable response. The most common cause of censoring participants was based on being relapse free at study end (see Table 2 legend). Vertical lines indicate censored observations.

Daly E, et al. *JAMA Psychiatry*. 2019. 1189. [Epub ahead of print]

Esketamine for treatment-resistant depression: seven concerns about efficacy and FDA approval

Lancet Psychiatry 2019

Published Online
October 31, 2019
https://doi.org/10.1016/
S2215-0366(19)30394-3

Turner EH. *Lancet Psychiatry*. 2019;6:977-979.

First, the clinical trials used an arguably lax "regulatory definition of treatment-resistant depression",[2] specifically "failure of treatment of... any two antidepressants" (FDA Briefing Document (FBD) p 15),[2] enabling inclusion of patients in whom only selective serotonin reuptake inhibitors had failed. Indeed, among the 702 patients who entered the three short-term phase 3 trials, 22% had treatment failure with just one class of antidepressants (Janssen briefing packet (JBD) p 67),[2] 60% had treatment failure with two classes of antidepressants, and only 18% had treatment failure with three or four classes. Additionally, trial patients were not required to have undergone psychotherapy unsuccessfully.

Turner EH. *Lancet Psychiatry*. 2019;6:977-979.

Fifth, inconsistent with the FDA requirement for "substantial evidence of effectiveness" (FBD p 9), the results of study 3003 are not robust:[2] "One concern in this study was that one site in Poland drives the overall study result due to a 100% rate of placebo arm relapses."

Turner EH. *Lancet Psychiatry*. 2019;6:977-979.

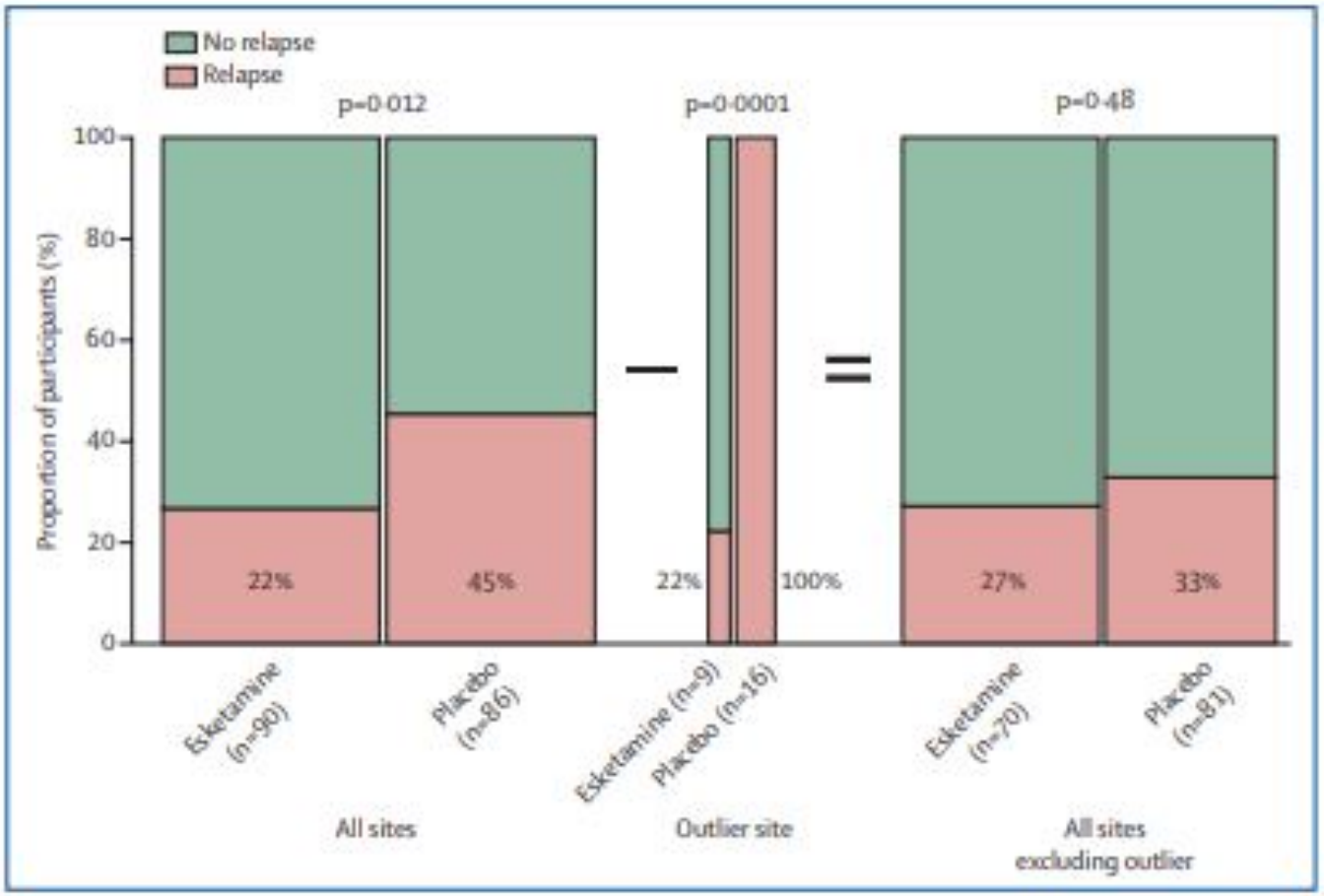


Figure: Relapse rates for esketamine versus placebo and the effect of outlier site on overall result
Column width is proportional to sample size.

Turner EH. *Lancet Psychiatry*. 2019;6:977-979.

There were six deaths in the esketamine for treatment-resistant depression development program as of January 8, 2019, all in esketamine-treated subjects.

Three of these deaths were by suicide – two well after the patient's last dose of esketamine (12 and 20 days), and one 4 days after the patient's last dose of esketamine.

Given the small number of cases, the severity of the patients' underlying illness, and the lack of consistent pattern among these cases, it is difficult to consider these deaths as drug-related.

Of the remaining three cases, one involved a motorcycle accident 26 hours after the patient's last dose of esketamine.

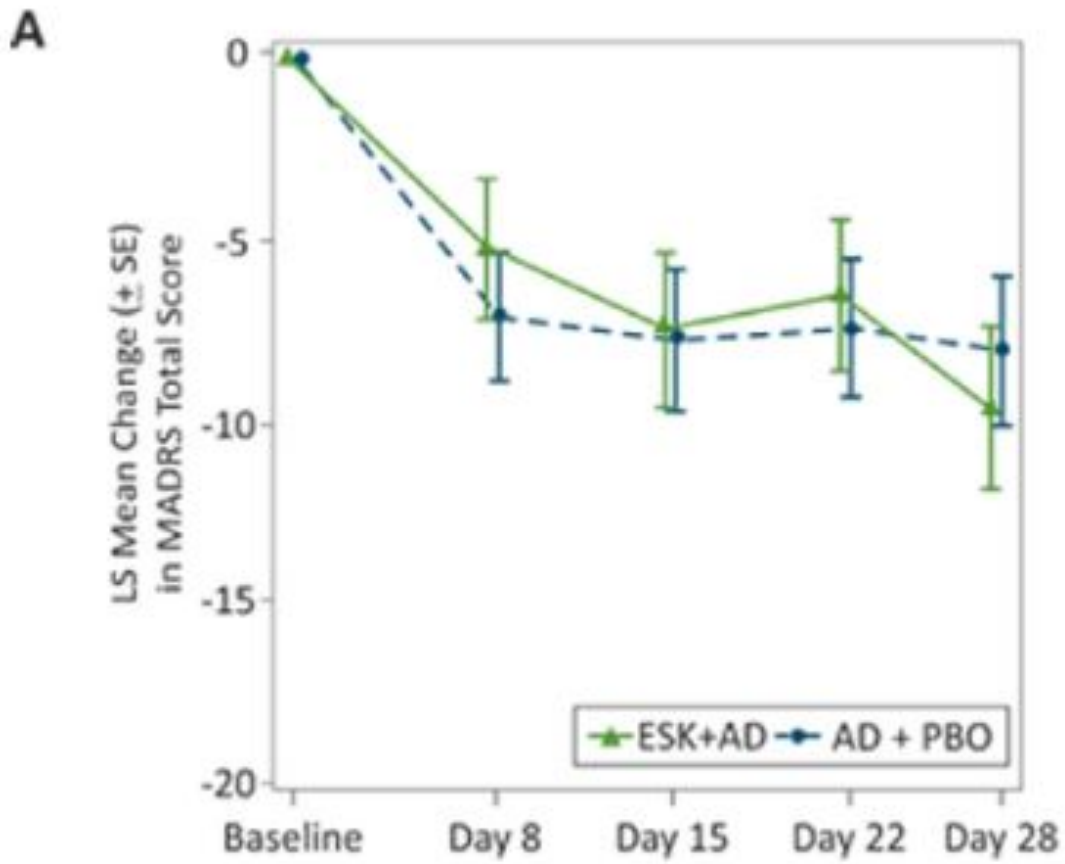
FDA Briefing Document. Psychopharmacologic Drugs Advisory Committee (PDAC) and Drug Safety and Risk Management Advisory Committee Meeting February 12, 2019

Regular Research Article

Efficacy and Safety of Esketamine Nasal Spray Plus an Oral Antidepressant in Elderly Patients With Treatment-Resistant Depression—TRANSFORM-3

Rachel Ochs-Ross, M.D., Ella J. Daly, M.D., Yun Zhang, Ph.D., Rosanne Lane, M.A.S., Pilar Lim, Ph.D., Randall L. Morrison, PhD, David Hough, M.D., Husseini Manji, M.D., Wayne C. Drevets, M.D., Gerard Sanacora, M.D., Ph.D., David C. Steffens, M.D., M.H.S., Caleb Adler, M.D., Rupert McShane, M.D., Raphaël Gaillard, M.D., Ph.D., Samuel T. Wilkinson, M.D., Jaskaran B. Singh, M.D.

Ochs-Ross R, et al. *Am J Geriatr Psychiatry*. 2020; 28:121-141.



Ochs-Ross R, et al. *Am J Geriatr Psychiatry*. 2020; 28:121-141.

Health

Anti-depressant spray not recommended on NHS

28 January 2020 Share

A fast acting ketamine-like anti-depressant spray that can lift mood within hours has been rejected by the NHS healthcare watchdog.

The National Institute for Health and Care and Excellence (NICE) says there are too many uncertainties about the correlation between the price and clinical benefits of esketamine.

It is licensed as a therapy for people with hard-to-treat depression.

But it costs about £10,000 per patient for a single course of treatment.

Hi Doctor,

I am a refractory depressed patient who did much research before embarking on ketamine infusions. I'm also a chronic pain patient on opioids for 20 years.

I sought treatment in a clinic run by an anesthesiologist. This pursuit was after fully discussing with my psychiatrist who ran an internal pilot program testing infusions on depressed patients.

After my series of six infusions over a 3-week period I was ecstatic. I had all the recommended responses, NDE and near birth experiences and a clearer sense that death is nothing to fear and we are all just a part of the quantum physics "everything and nothingness."

The problem? I felt like I was high for a 2-week period and then in the third week my depression and suicide ideation returned WORSE THAN EVER! My new-found lack of fear of death proved to take away an important boundary protecting me from suicide. I had to seek ketamine nasal spray to step down and stop ideation.

I now understand I'm hooked on ketamine. I dream about more infusions taking me away from it all. I loved the feeling of freedom and peace. I'm dismayed I was never warned about the action (hello addiction!). Having taken myself off opioids previously without medical support I now have a new project to overcome these new craving.

Just wanted to let you know hear from someone who got trapped in a new "cure"…

SMART Goals

Specific, Measurable, Attainable, Relevant, Timely

- Data show that rapid antidepressant action is, in fact, possible
- It is important to examine the evidence for ketamine and esketamine
- There are outstanding issues related to both long-term use and abuse liability
- The MOA remains controversial

Questions & Answers

Don’t forget to fill out your evaluations to collect your credit.