Policy and Regulatory Challenges for the Medical Use of Ketamine

Seth Mailhot, JD,
Husch Blackwell

Policy and Regulatory Challenges for the Medical Use of Ketamine: State Review

Seth A. Mailhot, Partner

Head, FDA Practice

General Status

- Ketamine can be administered by practitioners who are licensed to prescribe Schedule III controlled substances within medical specialties, including anesthesiology, psychiatry, emergency medicine, primary care, and internal medicine
- Esketamine is restricted to administration by practitioners who are licensed to prescribe Schedule III controlled substances within mental health care, primary care, and internal medicine

Corporate Practice of Medicine (CPOM) Doctrine

- Prohibits corporations from practicing medicine or employing a physician to provide professional medical services
- Public policy concerns:

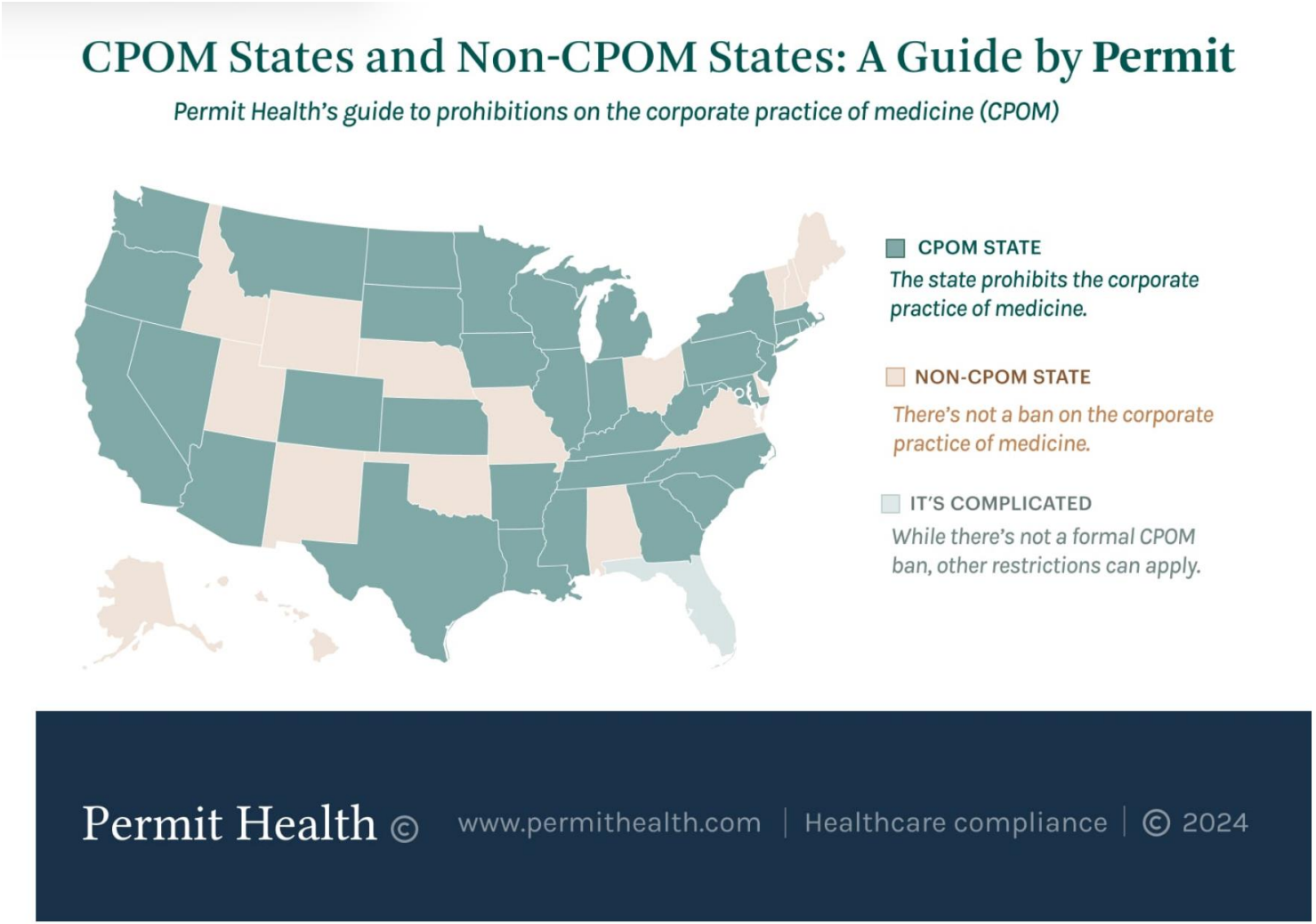
1. allowing corporations to practice medicine or employ physicians will result in the commercialization of the practice of medicine,
2. a corporation's obligation to its shareholders may not align with a physician's obligation to his patients, and
3. employment of a physician by a corporation may interfere with the physician's independent medical judgment

- Impacts the ownership and operation of ketamine clinics

State CPOM Restrictions

- Thirty-two (32) states plus the District of Columbia prohibit the corporate practice of medicine
- Every one of these states provides an exception for professional corporations, which are corporations organized for the specific purpose of rendering a professional service
  - State statutes often specify how the professional corporations should be structured, who can participate as shareholders or owners and who must serve on the board of directors
  - Most states restrict the shareholders, owners, or board of directors of a professional corporation to persons licensed to render the same professional service as the professional corporation
- Many states also provide an exception for employment of physicians by certain entities, although the scope varies by state
- Seventeen (17) states do not have some form of CPOM restriction
- Florida also lacks a formal CPOM restriction but requires special licensure for non-physician owned clinics

State CPOM Restrictions (cont.)



Supervision of Advanced Practice Providers

- Advanced Practice Provider: health care provider who is not a physician but who performs medical activities typically performed by a physician, such as a nurse practitioner or physician assistant
- In some states, Advanced Practice Registered Nurses may prescribe controlled substances without supervision, but in other states supervision may be required
- South Carolina, Georgia, and New York require a written collaboration agreement between the supervising physician and the Advance Practice Provider
- California, Georgia, and Virginia limit the number of prescribing Advance Practice Providers that a physician may supervise at one time
- Georgia limits the distance permitted between the Advance Practice Provider and the supervising physician when the physician's office is out-of-state

State Guidance and Laws Related to Ketamine

- Utah: 58-1-510. “Anesthesia and sedation requirements -- Unprofessional conduct -- Whistleblower protection” places requirements on various sedation levels in an outpatient setting, implicating use of ketamine, including
  - healthcare personnel to have certain training,
  - direct supervision of the patient, and
  - “having at least one individual in the procedure room who has advanced airway training and the knowledge and skills to recognize and treat airway complications and rescue a patient who entered a deeper than intended level of sedation”
- SB197, passed last year, modifies 58-1-510 to allow an anesthesia provider who is providing ketamine for a non-anesthetic purpose to have an individual with airway training on site rather than in the procedure room

State Guidance and Laws Related to Ketamine (cont.)

- Arizona: State Board of Nursing issued an advisory opinion on when Registered Nurses are operating within their scope of practice with respect to administering ketamine for various indications (pain control/analgesia, depression, and sedation), but not anesthesia
- Florida: State Department of Health issued a series of rulings allowing registered nurses with Advanced Cardiovascular Life Support training to administer low doses of ketamine (up to 0.5mg/kg) provided it does not rise to the level of sedation or analgesia
  - Rulings concluded that registered nurses cannot administer ketamine if the administration will result in sedation or analgesia, in contrast to American Nurses Association's Procedural Sedation Consensus Statement

State Guidance and Laws Related to Ketamine (cont.)

- Oregon: State Department of Justice issued an opinion that the infusion of sub-anesthetic doses of ketamine for the treatment of disorders of mood, anxiety, trauma, and stressors resistant to medication and psychotherapy in an outpatient clinic setting is within the scope of practice for Certified Registered Nurse Anesthetists (CRNA)
  - Disorder must be determined by a licensed independent health care practitioner
  - Assumes that the CRNA owns and manages clinic where treatment occurs

QUESTIONS?

HUSCH BLACKWELL

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Seth Mailhot is a Partner and lead of the FDA Regulatory Practice Group in Husch Blackwell's Washington D.C. office. His 14 years working in the U.S. Food and Drug Administration (FDA) has provided him a unique perspective when counseling clients on a broad range of matters involving the FDA.

Seth's practice includes representation of the medical device, pharmaceutical, dietary supplement, tobacco and food industries, and covers both premarket and post-market issues. His practice is focused on development of premarket submission strategies, and FDA enforcement of good manufacturing practices, both domestically and abroad.

Admissions

- California
- District of Columbia
- Massachusetts
- U.S. Patent and Trademark Office

Education

- New England School of Law, J.D., Valedictorian, *summa cum laude*
- University of Massachusetts, B.S., Chemical Engineering

Policy and Regulatory Challenges for the Medical Use of Ketamine

A.J. Day, PharmD, RPh,
National Community Pharmacists Association

Policy and regulatory challenges for the medical use of ketamine

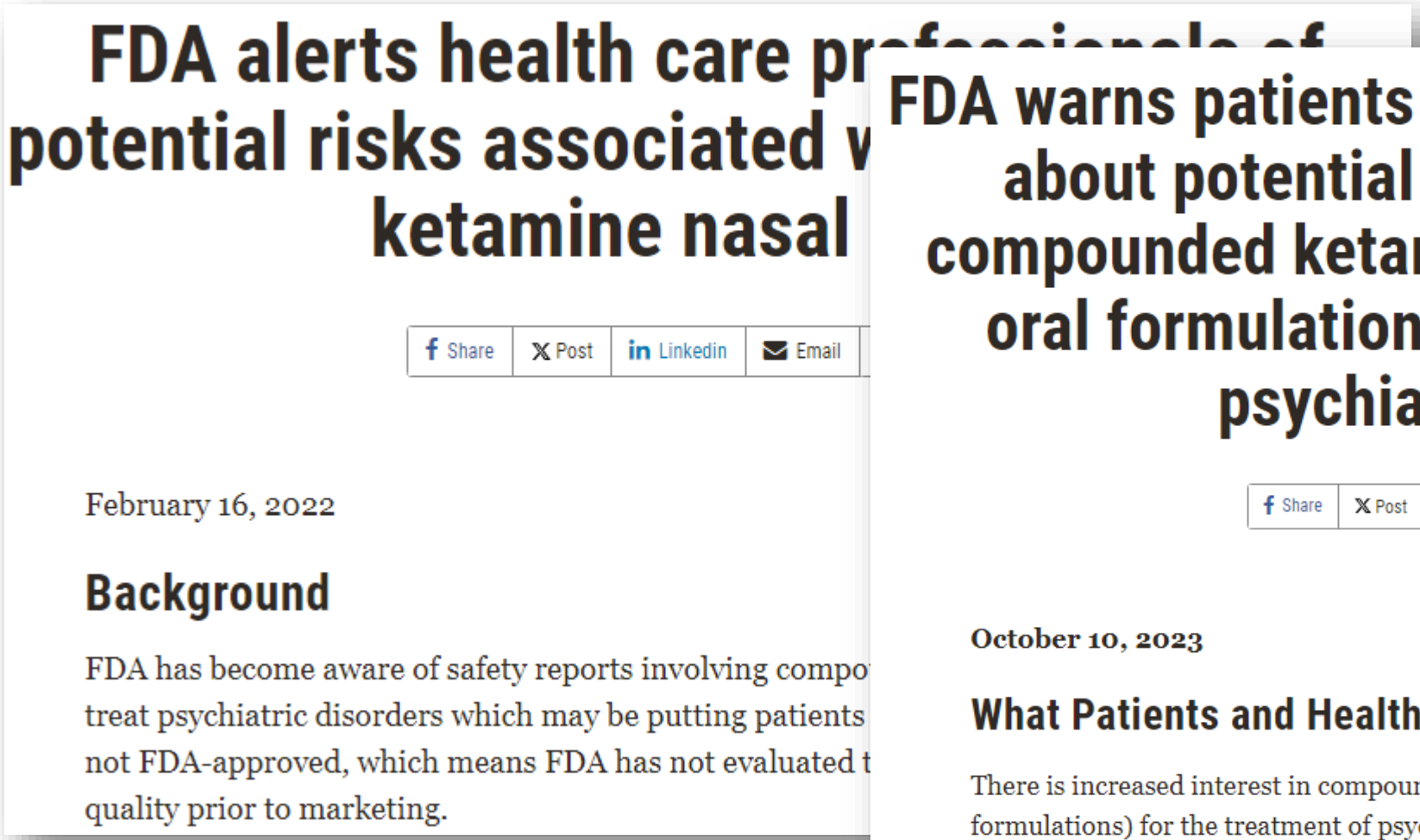
June 27, 2024

A.J. Day, PharmD

National Community Pharmacists Association

Compounding Steering Committee Member

FDA Compounding Risk Alerts



FDA alerts health care pr… potential risks associated w… ketamine nasal

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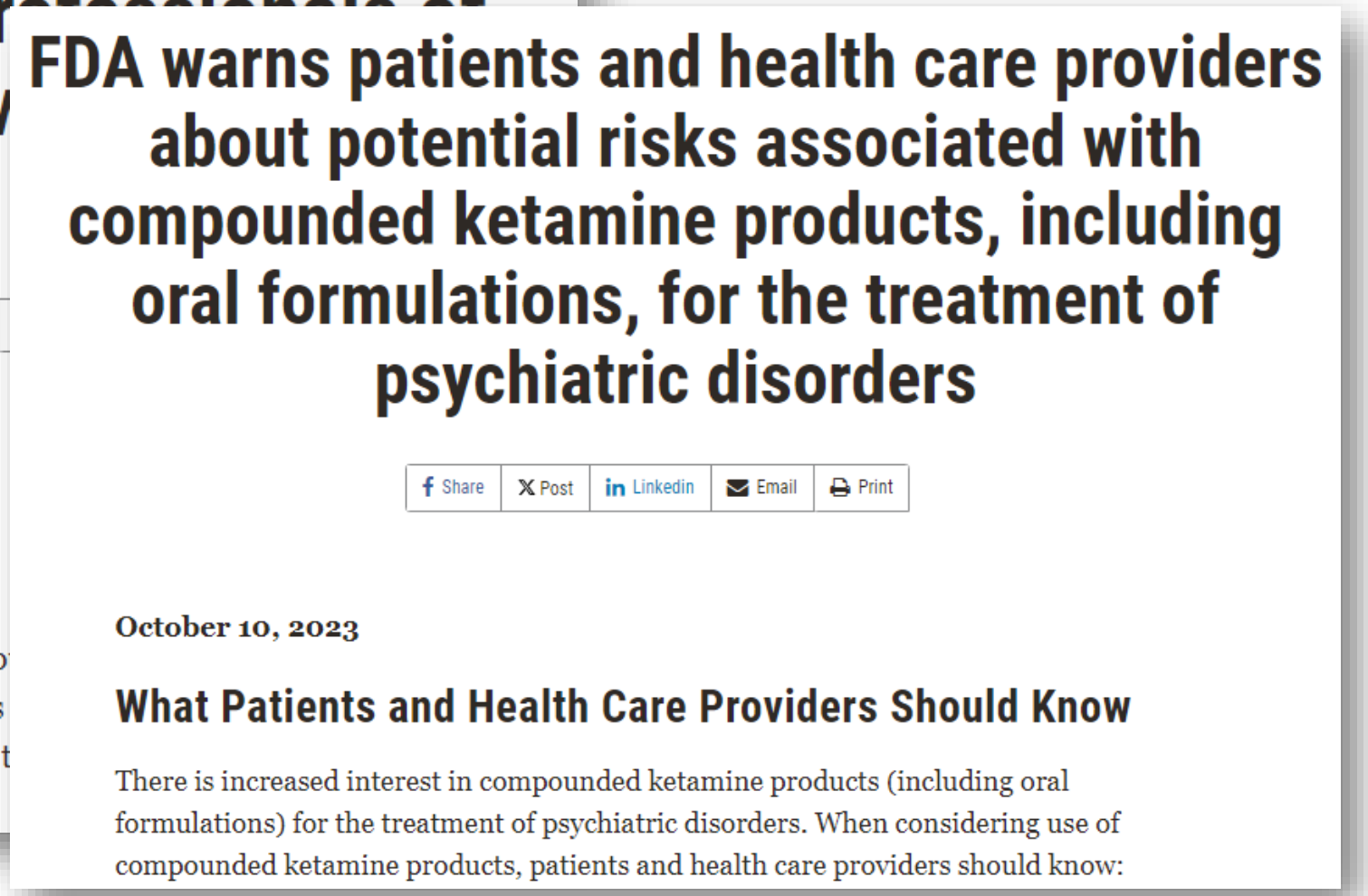
February 16, 2022

Background

FDA has become aware of safety reports involving compo… treat psychiatric disorders which may be putting patients … not FDA-approved, which means FDA has not evaluated t… quality prior to marketing.



FDA warns patients and health care providers about potential risks associated with compounded ketamine products, including oral formulations, for the treatment of psychiatric disorders

Share | Post | Linkedin | Email | Print

October 10, 2023

What Patients and Health Care Providers Should Know

There is increased interest in compounded ketamine products (including oral formulations) for the treatment of psychiatric disorders. When considering use of compounded ketamine products, patients and health care providers should know:

https://www.fda.gov/drugs/human-drug-compounding/fda-warns-patients-and-health-care-providers-about-potential-risks-associated-compounded-ketamine
https://www.fda.gov/drugs/human-drug-compounding/fda-alerts-health-care-professionals-potential-risks-associated-compounded-ketamine-nasal-spray

Industry Confusion

- FDA Risk Alerts state
  - Ketamine is not FDA approved for the treatment of any psychiatric disorder
  - Compounded drugs are not FDA approved
  - Use of compounded ketamine without monitoring by health care provider…may put patients at risk for serious adverse events
  - Known safety concerns associated with the use of ketamine products…

- FDA Risk Alerts do **NOT** state
  - Using compounded ketamine is illegal in any way
  - Off-label use of ketamine is not allowed
  - Patient-administered ketamine is not allowed

Industry Confusion – Feb 2022 Risk Alert

References

[1] Approved Risk Evaluation and Mitigation Strategies (REMS). Accessed February 8, 2022. Available at Spravato (esketamine).

[2] Olney, J. W., Labruyere, J., & Price, M. T. (1989). Pathological changes induced in cerebrocortical neurons by phencyclidine and related drugs. Science, 244(4910), 1360–1362.

[3] Drug Approval Package: Spravato (2019). Pharmacology Review(s). Accessed February 8, 2022. Available at https://www.accessdata.fda.gov/drugsatfda_docs/nda/2019/211243Orig1s000TOC.cfm.

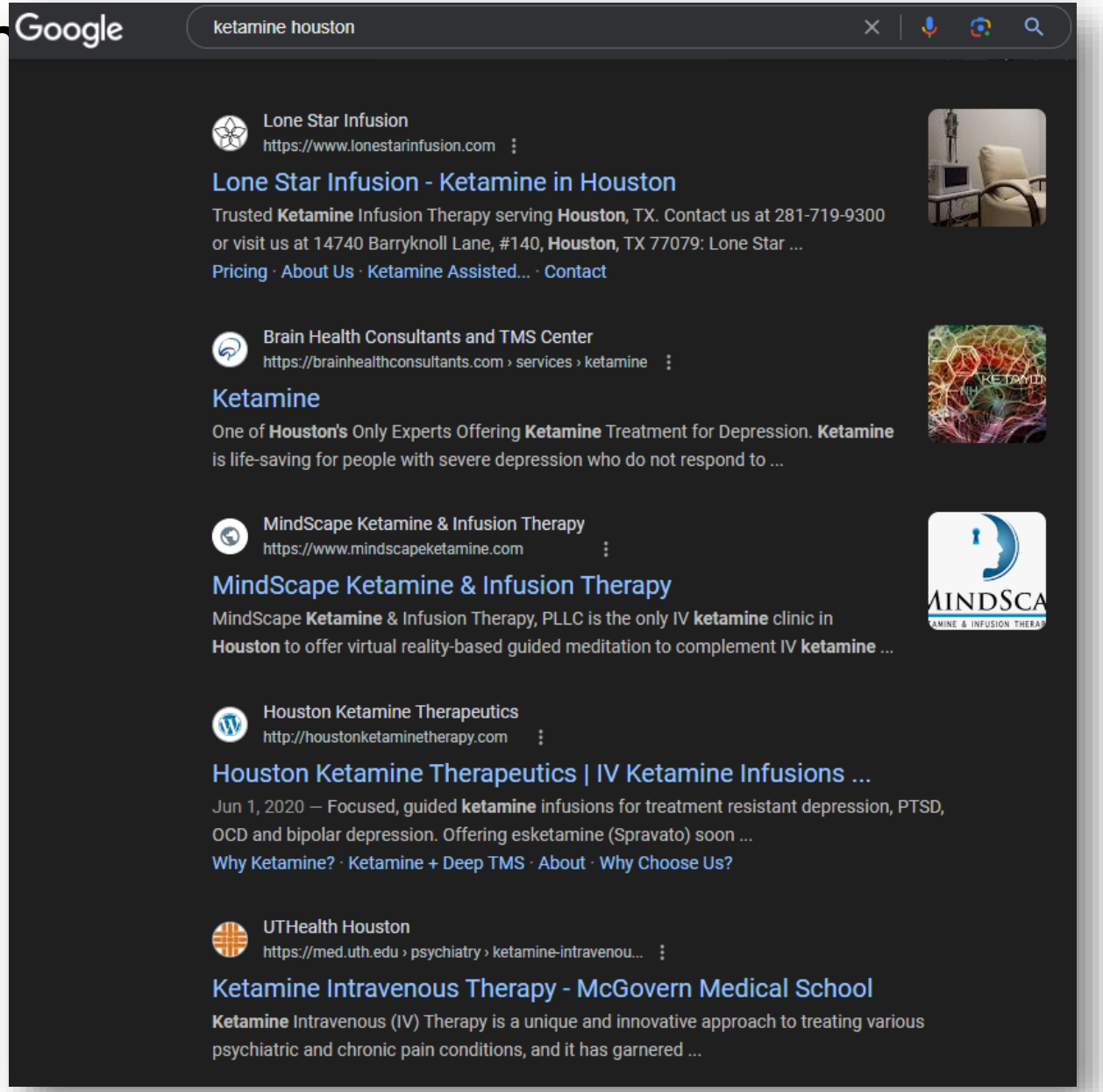
To further clarify the role of PCP receptors, we tested two other PCP receptor ligands, tiletamine and ketamine. Both agents are anesthetics used in veterinary medicine, and ketamine is used in human anesthesia (*15*). Each drug was administered in aqueous solution (*12*) as a single dose (1, 5, 10, and 20 mg/kg sc for tiletamine and 5, 10, 20, and 40 mg/kg sc for ketamine) to adult rats (n = 6 per treatment group). Examination of the brains 4 hours later revealed vacuole formation in cingulate and retrosplenial cerebrocortical neurons after tiletamine treatment at 10 and 20 mg/kg and ketamine treatment only at 40 mg/kg. Lower doses of either drug were not associated with cerebrocortical pathological changes.

- Administered PCP, PCP-like substance, tiletamine, and ketamine subcutaneously to rats
- Only 40 mg/kg SC ketamine showed cerebrocortical pathological changes
- ~3,000 mg dose for 75 kg human patient

Stakeholder Confusion

Questions from FDA
Compounding Risk Alerts

- Is the issue “compounded ketamine”?
- Or ketamine in general?



30-year History Compounding with Ketamine

Journal of Affective Disorders 314 (2022) 59–67

Contents lists available at ScienceDirect

Journal of Affective Disorders

journal homepage: www.elsevier.com/locate/jad

Research paper

At-home, sublingual ketamine telehealth is a safe and effect
for moderate to severe anxiety and depression: Findings fro
prospective, open-label effectiveness trial

Thomas D. Hull [a,*,1], Matteo Malgaroli [b,1], Adam Gazzaley [c], Teddy J. Akiki [c]
Leonardo Vando [f], Kristin Arden [f], Jack Swain [f], Madeline Klotz [f], Casey Pale

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[c] University of California, San Francisco, United States of America
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[e] Houston Methodist Behavioral Health, United States of America
[f] Mindbloom, United States of America

A B S T R A C T

Background: At-home Ketamine-assisted therapy (KAT) with psychosocial support and remote monitoring through telehealth platforms addresses access barriers, including the COVID-19 pandemic. Large-scale evaluation of this approach is needed for questions regarding safety and effectiveness for depression and anxiety.

Methods: In this prospective study, a large outpatient sample received KAT over four weeks through a telehealth provider. Symptoms were assessed using the Patient Health Questionnaire (PHQ-9) for depression, and the Generalized Anxiety Disorder scale (GAD-7) for anxiety. Demographics, adverse events, and patient-reported dissociation were also analyzed. Symptom trajectories were identified using Growth Mixture Modeling, along with outcome predictors.

Results: A sample of 1247 completed treatment with sufficient data, 62.8 % reported a 50 % or greater improvement on the PHQ-9, $d = 1.61$, and 62.9 % on the GAD-7, $d = 1.56$. Remission rates were 32.6 % for PHQ-9 and 31.3 % for GAD-7, with 0.9 % deteriorating on the PHQ-9, and 0.6 % on the GAD-7. Four patients left treatment early due to side effects or clinician disqualification, and two more due to adverse events. Three patient subpopulations emerged, characterized by Improvement (79.3 %), Chronic (11.4 %), and Delayed Improvement (9.3 %) for PHQ-9 and GAD-7. Endorsing side effects at Session 2 was associated with delayed symptom improvement, and Chronic patients were more likely than the other two groups to report dissociation at Session 4.

Conclusion: At-home KAT response and remission rates indicated rapid and significant antidepressant and anxiolytic effects. Rates were consistent with laboratory- and clinic-administered ketamine treatment. Patient screening and remote monitoring maintained low levels of adverse events. Future research should assess durability of effects.

Alliance for Pharmacy Compounding

Best Practices for Preparing and Dispensing Compounded Ketamine by Pharmacies

April 1, 2024

This document is not specific to particular indications or dosage forms for compounded ketamine, and it is not intended to be an exhaustive statement on the practice of compounding ketamine. It should not be relied upon as advice. Pharmacies should seek legal counsel before compounding ketamine.

These best practices apply to the following circumstances in which manufactured ketamine is prescribed or administered off label and when compounded ketamine is being prescribed and/or administered off-label for certain indications:

1. Commercially available intravenous/intramuscular or compounded IV/IM ketamine administered in-clinic to a specific patient for the treatment of a specific, legitimate medical indication. (The patient is monitored for potential adverse effects by a practitioner during the treatment.)
2. Compounded ketamine nasal sprays, rapid dissolve tablets, troches, suppositories, or other dosage forms prescribed and dispensed to a specific patient for the treatment of a specific, legitimate medical indication.

https://a4pc.org/files/APC-Ketamine-Best-Practices-April-2024.pdf

Best Practices for Preparing and Dispensing Compounded Ketamine by Pharmacies

- Pharmacist Legal Obligations
  - DEA & controlled substance laws, federal & state-specific
  - Pharmacist's corresponding responsibility
- Diversion Concerns
  - Prescription Drug Monitoring Program (PDMP) utilization for every filling of each Rx
  - Thorough patient & prescriber verification to ensure legitimacy and appropriateness of Rx
    - Verify patient-prescriber relationship
    - Consider prescriber scope of practice
  - Caution with high volumes, multiple refills, early-refill requests. Watch for patterns
  - Monitor pharmacy inventory
  - Prompt and thorough investigations for any concerns. Report to appropriate authorities

Best Practices for Preparing and Dispensing Compounded Ketamine by Pharmacies

- Dosing Limits
  - Evaluate each Rx carefully, considering best practices and RPh corresponding responsibility.
  - Establish appropriate dosing considerations for ketamine based on clinical guidelines, available evidence, and knowledge of patient's specific needs.
  - Use professional judgement, clinical literature, and communication with the prescriber when assessing dosing for each condition, considering individual patient factors and treatment goals. Do not utilize arbitrary limits.
- Dosage Forms
  - Consider utilizing alternative dosage forms, such as capsules containing abuse-deterrent excipients, to enhance safety
  - Consider dispensing all ketamine products in a child-resistant container, even if the resident state does not require it

Best Practices for Preparing and Dispensing Compounded Ketamine by Pharmacies

- Documentation
  - Properly document all aspects of compounding & dispensing process, particularly for outlying events involving dosing, directions for use, and other concerns
  - Document drug-drug interactions, early-refill conversations with providers, and anything that may constate a “red flag”, along with all other DUR documentation
- Patient Education
  - Provide comprehensive counseling to patients, which may include written and verbal communication
  - Supply written educational materials to reinforce key points and serve as a reference for patients
  - Education patients on side effects, emphasizing restrictions on driving or combining with other medications or alcohol

Best Practices for Preparing and Dispensing Compounded Ketamine by Pharmacies

- Constructive Transfer
  - DEA considerations
- Ketamine Onboarding Checklist for 503B Wholesaling
  - (Outside the scope of traditional pharmacy practice)

Other Common Discussions

- Ketamine is not esketamine
  - Patient access to the right therapy, with oversight from treating physicians, is vital

- Operational Protocols
  - Pharmacies have SOP’s for the compounding laboratory
  - Physicians have treatment protocols for patients
  - Some physicians have patients and pharmacy review & sign treatment protocols, and each entity gets a copy
    - Risks, benefits, FAQs

Thank you for the opportunity to speak at this event today

Policy and Regulatory Challenges for the Medical Use of Ketamine

Discussion:

- **Gail Bormel, RPh, JD,** U.S. Food and Drug Administration
- **A.J. Day, PharmD, RPh,** National Community Pharmacists Association
- **Lisa Harding, MD,** Yale University
- **Seth Mailhot, JD,** Husch Blackwell
- **Lisa Robin,** Federation of State Medical Boards
- **Jenni Wai, RPh, MBA,** Ohio Board of Pharmacy

Online Promotion and Access to Ketamine

Michael DiStefano, PhD, MBE
University of Colorado – Anschutz

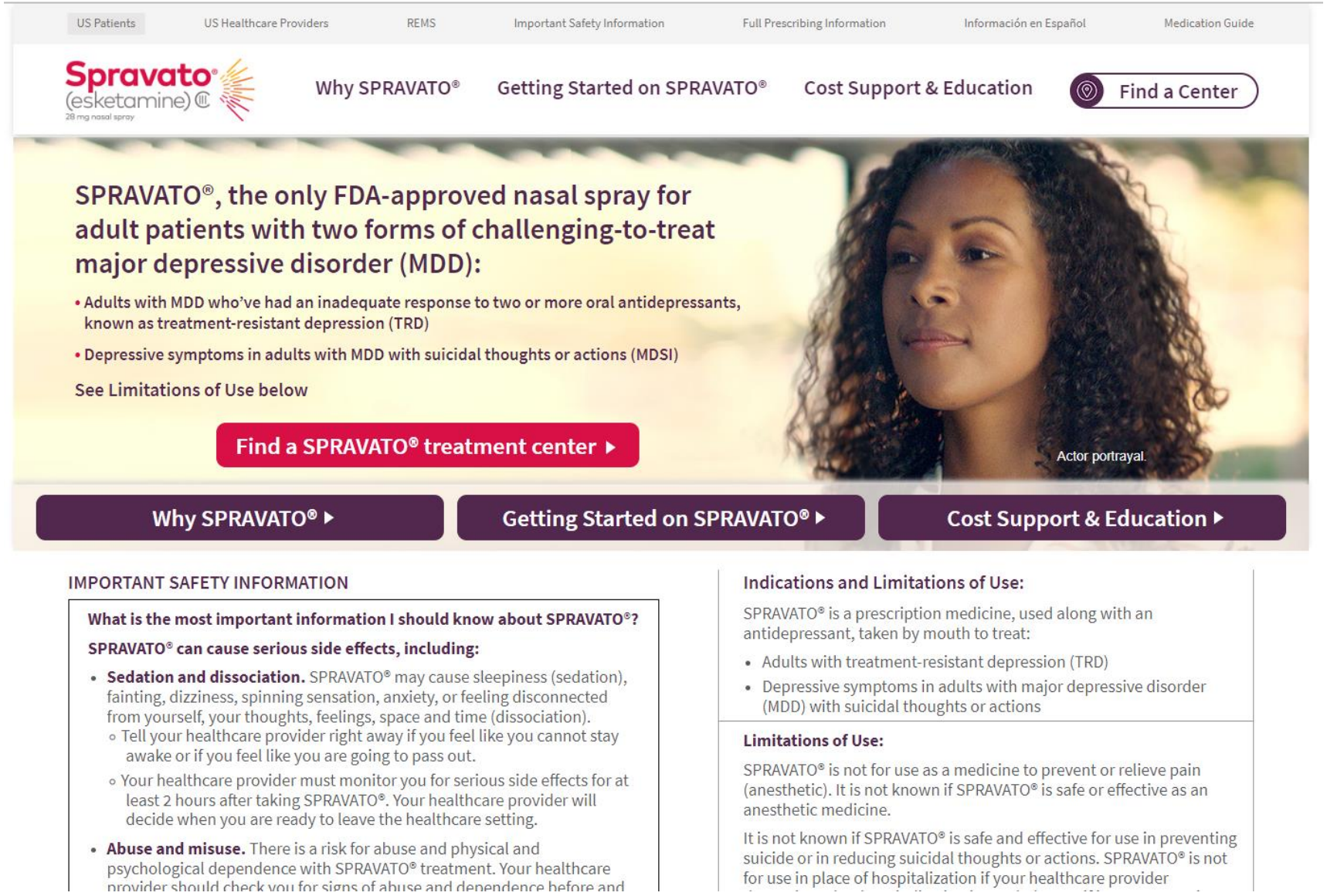
Ketamine: False and Misleading Advertising

A Survey of Maryland Ketamine Clinics

Matthew A. Crane, Michael J. DiStefano, Thomas J. Moore

Disclaimer

This presentation and associated documents reflect the views of the authors and should not be construed to represent the views or policies of the US Food and Drug Administration, the Department of Health and Human Services, or the US Government.



Source: https://www.spravato.com/

MEDICATION GUIDE

SPRAVATO® (sprah vah' toe) CIII
(esketamine)
nasal spray

What is the most important information I should know about SPRAVATO?

SPRAVATO can cause serious side effects, including:

- **Sedation and dissociation.** SPRAVATO may cause sleepiness (sedation), fainting, dizziness, spinning sensation, anxiety, or feeling disconnected from yourself, your thoughts, feelings, space and time (dissociation).
  - Tell your healthcare provider right away if you feel like you cannot stay awake or if you feel like you are going to pass out.
  - Your healthcare provider must monitor you for serious side effects for at least 2 hours after taking SPRAVATO. Your healthcare provider will decide when you are ready to leave the healthcare setting.
- **Abuse and misuse.** There is a risk for abuse and physical and psychological dependence with SPRAVATO treatment. Your healthcare provider should check you for signs of abuse and dependence before and during treatment with SPRAVATO.
  - Tell your healthcare provider if you have ever abused or been dependent on alcohol, prescription medicines, or street drugs.
  - Your healthcare provider can tell you more about the differences between physical and psychological dependence and drug addiction.
- **SPRAVATO Risk Evaluation and Mitigation Strategy (REMS).** Because of the risks for sedation, dissociation, and abuse and misuse, SPRAVATO is only available through a restricted program called the SPRAVATO Risk Evaluation and Mitigation Strategy (REMS) Program. SPRAVATO can only be administered at healthcare settings certified in the SPRAVATO REMS Program. Patients treated in outpatient healthcare settings (e.g. medical offices and clinics) must be enrolled in the program.
- **Increased risk of suicidal thoughts and actions.** Antidepressant medicines may increase suicidal thoughts and actions in some people 24 years of age and younger, **especially within the first few months of treatment or when the dose is changed. SPRAVATO is not for use in children.**
  - Depression and other serious mental illnesses are the most important causes of suicidal thoughts and actions. Some people may have a higher risk of having suicidal thoughts and actions. These include people who have (or have a family history of) depression or a history of suicidal thoughts and actions.

  How can I watch for and try to prevent suicidal thoughts and actions in myself or a family member?
  - Pay close attention to any changes, especially sudden changes, in mood, behavior, thoughts, or feelings, or if you develop suicidal thoughts or actions.
  - Tell your healthcare provider right away if you have any new or sudden changes in mood, behavior, thoughts, or feelings.
  - Keep all follow-up visits with your healthcare provider as scheduled. Call your healthcare provider between visits as needed, especially if you have concerns about symptoms.

  Tell your healthcare provider right away if you or your family member have any of the following symptoms, especially if they are new, worse, or worry you:
  - suicide attempts
  - thoughts about suicide or dying
  - worsening depression
  - other unusual changes in behavior or mood

Maryland Ketamine Clinics

Table 1. Services Offered by 17 Maryland Ketamine Advertisers and Associated Cost

Services listed	No. of clinics advertising service[a]	Cost disclosed, $[b]	Cost range, $[b]
Infusion[c]	13	7	360-2500
Ketamine-assisted psychotherapy[d]	9	2	150-500
Consultation[e]	9	9	0-390
Esketamine[f]	6	2	250-300
Intramuscular injection	2	1	450
Oral[g]	2	1	89
Intranasal[h]	1	1	300

[a] Not all advertisers provided a specific inventory of services offered.

[b] Not all advertisers provided cost for the services offered. The range provided represents data from clinics that did provide these data.

[c] Cost per infusion varied by different dimensions. Some advertisers offered a first-visit discount. Others charged different costs by different indications (eg, a mood disorder would be priced differently compared with a chronic pain disorder).

[d] Ketamine-assisted psychotherapy (also known as KAP or ketamine assisted-therapy [KAT]) refers to the use of ketamine as an adjunct to psychotherapy sessions.

[e] Consultations were free at times and at other times a fee was charged to determine whether ketamine therapy would be appropriate.

Our success rate with all therapies including Ketamine, concussion, and Lyme disease is above 90%. For patients with dementia and cognitive issues, we anticipate stabilization while looking for root causes, and in cases of mild cognitive impairment, we anticipate reversal and improved functioning.

Today, Ketamine is being prescribed for more than just depression. Ketamine is now being used to treat alcohol abuse, drug addiction, sleeping disorders, pain both acute and chronic as well as anxiety even Asthma.

During a Ketamine treatment, you generally will not feel any side effects during or after, and appointments usually take less than an hour. You can feel secure and comfortable during your visit.

Addiction and Risk

How does ketamine treat anxiety?

[redacted] Ketamine and Wellness uses ketamine, a nonaddictive medication, to treat anxiety. Ketamine interacts with brain receptors capable of regulating your behavioral responses, so it works well to treat symptoms of depression, post-traumatic stress disorder (PTSD), and other mood disorders.

Is there potential for addiction?

Some may have heard that ketamine is used as a "party drug" and worry about addiction potential. Studies and clinical experience have shown that in very low doses, like those used in this treatment, in a medical setting with lack of access at home, and infrequent dosing, there is virtually no potential for addiction or abuse.

Addiction and Risk

Other risks

Misuse (drug abuse) of ketamine has been reported in the past. Reports have indicated that ketamine can cause various symptoms, including but not limited to flashbacks, hallucinations, feelings of unhappiness, restlessness, anxiety, insomnia, or disorientation. Individuals with a history of drug misuse or dependence can develop a dependency on ketamine.

As Ketamine is used for sedation in surgery, the doses used in this study may cause sleepiness and may put you to sleep. There is a potential risk of dosing error or unknown drug interaction that may cause significant sedation and may require medical intervention including intubation (putting in a breathing tube).

Addiction and Risk

- 5 sites minimized risk of abuse
- 3 sites claimed ketamine is non-addictive
- 7 sites did not disclose risks of adverse effects or risk of addiction or misuse

Regulatory Language

Ketamine Treatment

Depression can be a severe, recurring, disabling, and life-threatening condition. When current medical treatments are only partially effective, ketamine may be used to provide rapid-acting antidepressant effect. Ketamine is approved by the Food and Drug Administration (FDA) to treat depressions.

Learn More

Nasal spray Esketamine (SPRAVATO®) is an FDA-approved medication for treatment resistant depressive disorders. Other forms of Ketamine such as injectables (IV Infusion, Under the muscle) can reduce severe depressive symptoms including suicidal thoughts within a few hours to some days. Repeated Ketamine treatment overtime have shown effectiveness towards reversing the course of depression, anxiety, PTSD and OCD symptoms.

What is Ketamine?

Ketamine is a well-researched, dissociative anesthetic that was approved by the FDA in 1970. Since then, ketamine has been used extensively for pediatric and adult treatment in surgery, emergency departments, ambulances, trauma medicine, and war zones. It is a commonly used medication in veterinary medicine. The World Health Organization lists ketamine as one of the most essential medications due to its therapeutic effects and wide margin of safety.

Over the last decade, Yale University and the National Institutes of Health identified additional benefits of ketamine in the treatment of mood disorders and chronic pain. The use of ketamine for depression has been named “the biggest discovery in mental health in decades.”

Regulatory Language

- 1 site stated the FDA had approved ketamine as a treatment for depression
- 10 sites did not disclose that ketamine use for mental health conditions is off-label and not FDA-approved for these indications
- All 3 sites offering unapproved oral or intranasal forms of ketamine did not disclose this unapproved status

Takeaways

- Maryland consumers and patients are not consistently provided important facts relevant to their decision to pursue ketamine treatment.
- Information provided at times ranges from false to misleading or deceptive.
- At least 800 ketamine clinics nationwide

Thank you


Research Letter | Health Policy

November 7, 2023

False or Misleading Claims in Online Direct-to-Consumer Ketamine Advertising in Maryland

Matthew A. Crane, BS[1]; Michael J. DiStefano, PhD[2]; Thomas J. Moore, AB[3]

Crane MA, DiStefano MJ, Moore TJ. False or Misleading Claims in Online Direct-to-Consumer Ketamine Advertising in Maryland. *JAMA Netw Open.* 2023;6(11):e2342210. doi:10.1001/jamanetworkopen.2023.42210

REAGAN-UDALL FOUNDATION FOR THE FDA

Online Promotion and Access to Ketamine

Boris Heifets, MD,
Stanford University School of Medicine

Setting expectations about ketamine therapy for mental health indications

Boris D. Heifets, MD, PhD

Associate Professor
Department of Anesthesiology, Perioperative and Pain Medicine
(*by courtesy*) Department of Psychiatry and Behavioral Sciences
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Associate Professor
Department of Anesthesiology, Perioperative & Pain Medicine,
And by courtesy, Psychiatry & Behavioral Sciences
Stanford University School of Medicine, Stanford, CA, USA

Grant Support:

RO1MH130591 (PI)

"Mapping neural circuit activity mediating MDMA's prosocial effects"

P50DA042012 (multi-PI)

Overall PI: Karl Deisseroth MD, PhD

"Neural circuit dynamics of drug action: revealing, uncoupling, and restoring altered brain states"

R01MH133553 (co-I)

PI: Carolyn Rodriguez MD, PhD

"Examining Mu Opioid Mechanisms of Ketamine's Rapid Effects In OCD"

Foundation for OCD Research (co-I)

PI: Carolyn Rodriguez MD, PhD

"Pilot study of 3,4-methylenedioxymethamphetamine (MDMA) in OCD"

American Foundation for Suicide Prevention (co-I)

PI: Alan Schatzberg MD
"Opiate Suicide Study in Patient with Major Depression"

Financial relationships :

I own stock in:

- **Osmind Mental Health** (Scientific Advisor)
- **Journey Clinical** (Scientific Advisor)

I consult for (past 24 months):

- **Clairvoyant Therapeutics, Inc.**
- **Arcadia Medicine, Inc.**

My presentation includes discussion of off-label or investigational use of ketamine. All references are to peer-reviewed clinical and preclinical research unless otherwise noted.

Key points

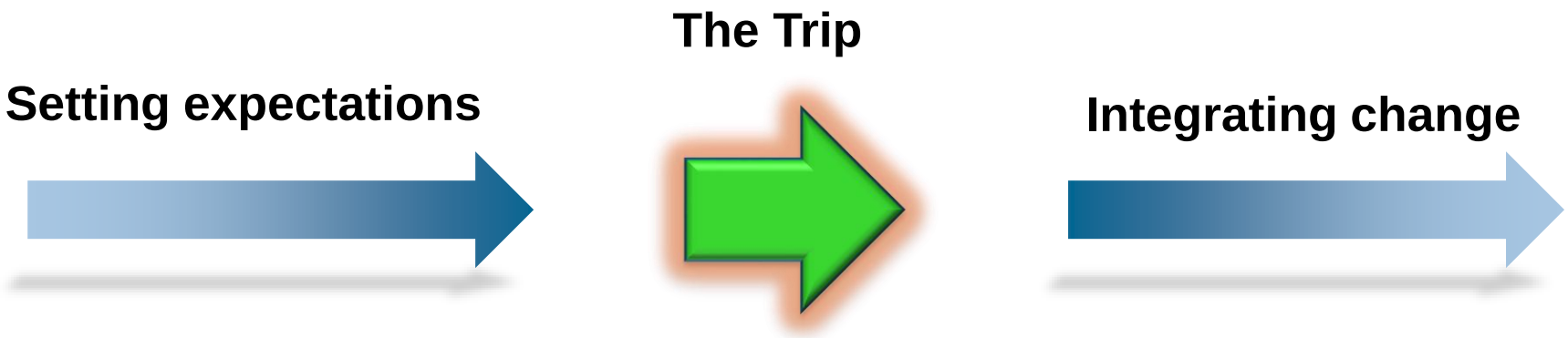
1. Patient expectations shape ketamine's measured efficacy

2. What kind of information do patients get about safety and efficacy?

3. 'Real World Evidence': hard to collect data on safety

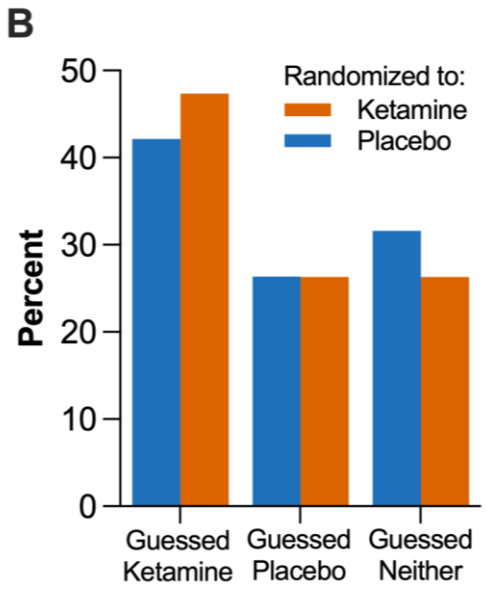
Potent therapy, by definition, carries risk

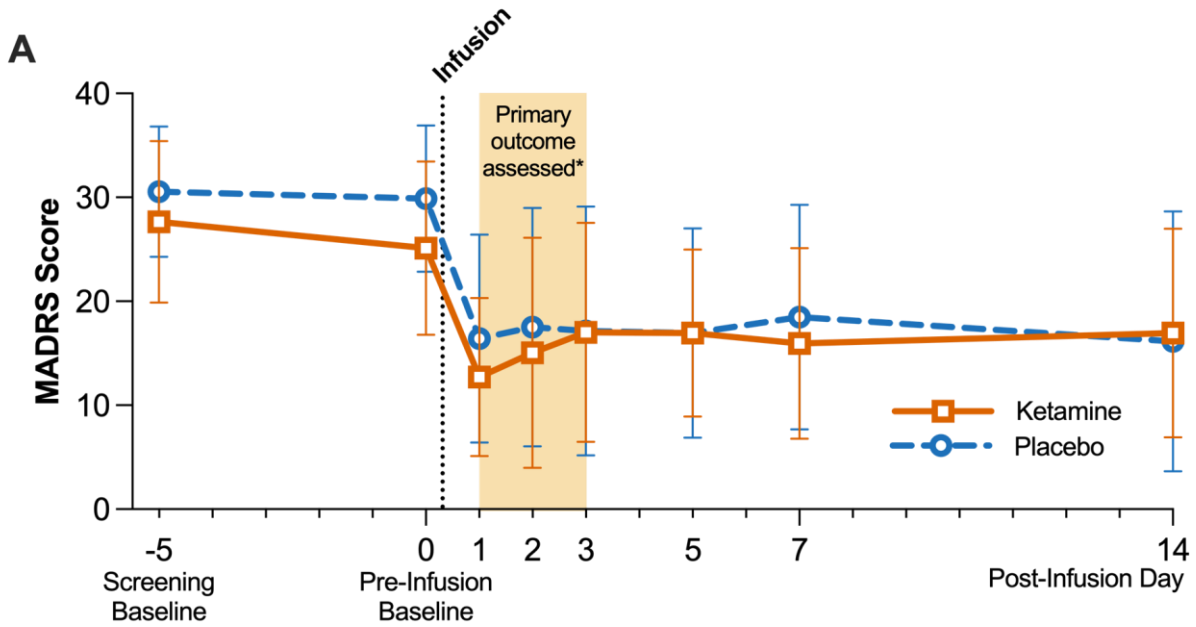
Is it the drug, the trip, …or non-drug factors?

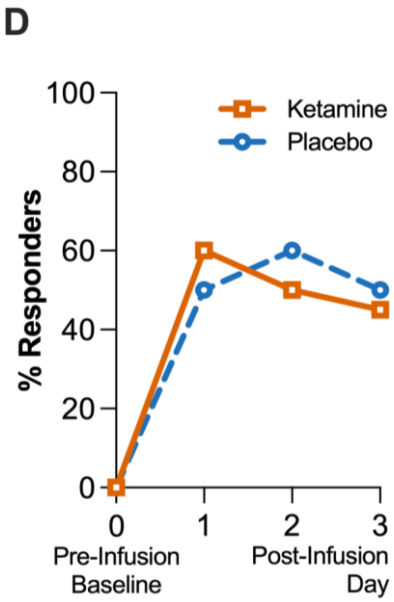


Does ketamine work for depression in unconscious patients?

Ketamine vs Placebo during surgical anesthesia in Patients with Major Depressive Disorder







When the blind is maintained,
expectation + a big "event"
may have a
dramatic treatment effect

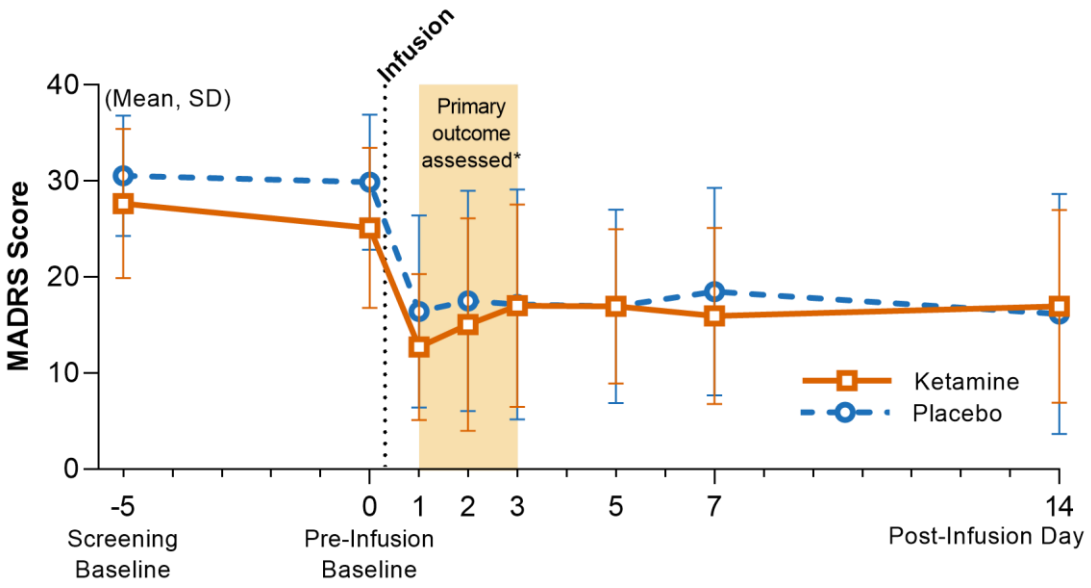
Theresa Lii
Ashleigh Smith
Robin Okada
Cynthia Nyongesa
Josie Flohr
Laura Hack
Alan Schatzberg

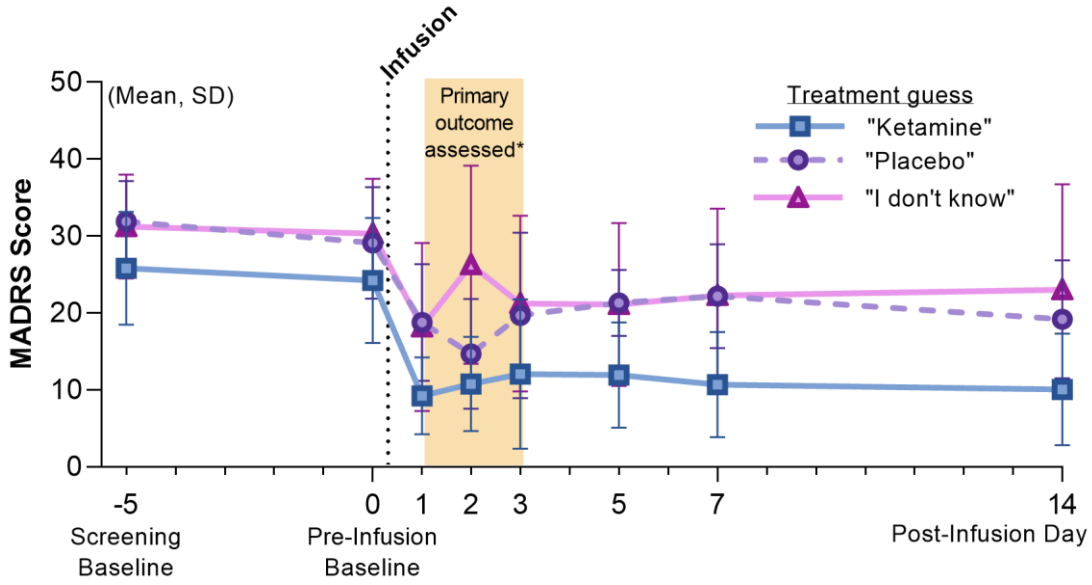
Lii et al, 2023 *Nat Mental Health*

Expectations and outcomes

Patients who experienced improvements in mood thought they received ketamine…

but on average did not improve more than placebo.





Theresa Lii Ashleigh Smith Robin Okada Cynthia Nyongesa Josie Flohr Laura Hack Alan Schatzberg

Lii et al, 2023 *Nat Mental Health*

Key points

1. Patient expectations shape ketamine's measured efficacy

2. **What kind of information** do patients get about safety and efficacy?

3. 'Real World Evidence': hard to collect data on safety

MENTAL

Getting the In
Ketamine's Myst

Achieve Your Bre
With Psychedelic

Reduce your anxiety or depression a
clinician-prescribed, guided experien

- 87% of clients report improvement in depr
- 85% of clients report improvement in anxi

AM I A CANDIDATE?

AS SEEN IN: The New York Times

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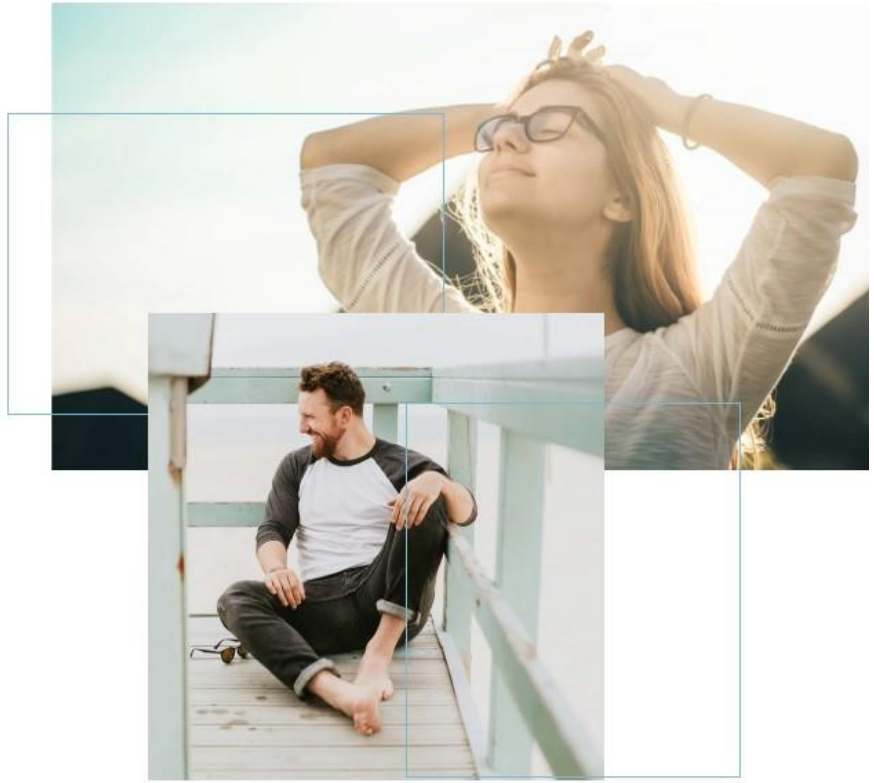
wondermed™

Introducing Wonder Calm

The future of anxiety treatment

This low-dose, oral ketamine treatment combats anxiety from the comfort of your home.

Get Started



Your personalized treatment program gives you the power to heal your mind, enabling sustainable life change and a return to a life of productivity and joy.

Wonder Calm is available exclusively through Wondermed.

Psychedelic Media Exposure Questionnaire (PMEQ)

Study 1 Stanford Pain Clinic Registry (N=6,891 contacted)
- N = 472 Completed Survey
- N = 197 (41.7%) identified ketamine as a psychedelic

Study 2: Reddit / X sample
- N = 159 Completed Survey
- N = 76 (47.8%) identified ketamine as a psychedelic

Audrey Evers (Stanford)
Chris Kelly, PhD (Icahn / Mt Sinai)
Shayla Love (Science Journalist)
Et al.
Manuscript in preparation

Psychedelic Media Exposure Questionnaire (PMEQ): **items sourced from news and advertisements**

- Psychedelic therapy is like 10 years of therapy in 1-day
- Psychedelic therapy is far better than antidepressant medication
- Psychedelics are a cure for mental illness
- Psychedelics shut down the default mode network in the brain
- Psychedelics rewire your brain
- Psychedelics are among the safest drugs
- Psychedelics open another plane of spiritual existence
- Psychedelics have the potential to help people

- Psychedelics can make you psychotic or manic
- Psychedelics are dangerous
- Governments have used psychedelics for mind control

0, Strongly Disagree
1, Disagree
2, Neither Agree Nor Disagree
3, Agree
4, Strongly Agree

On average, general views fall in the moderate (neither agree nor disagree). More extreme statements (Psychedelics are a cure for mental illness) had lower agreement.

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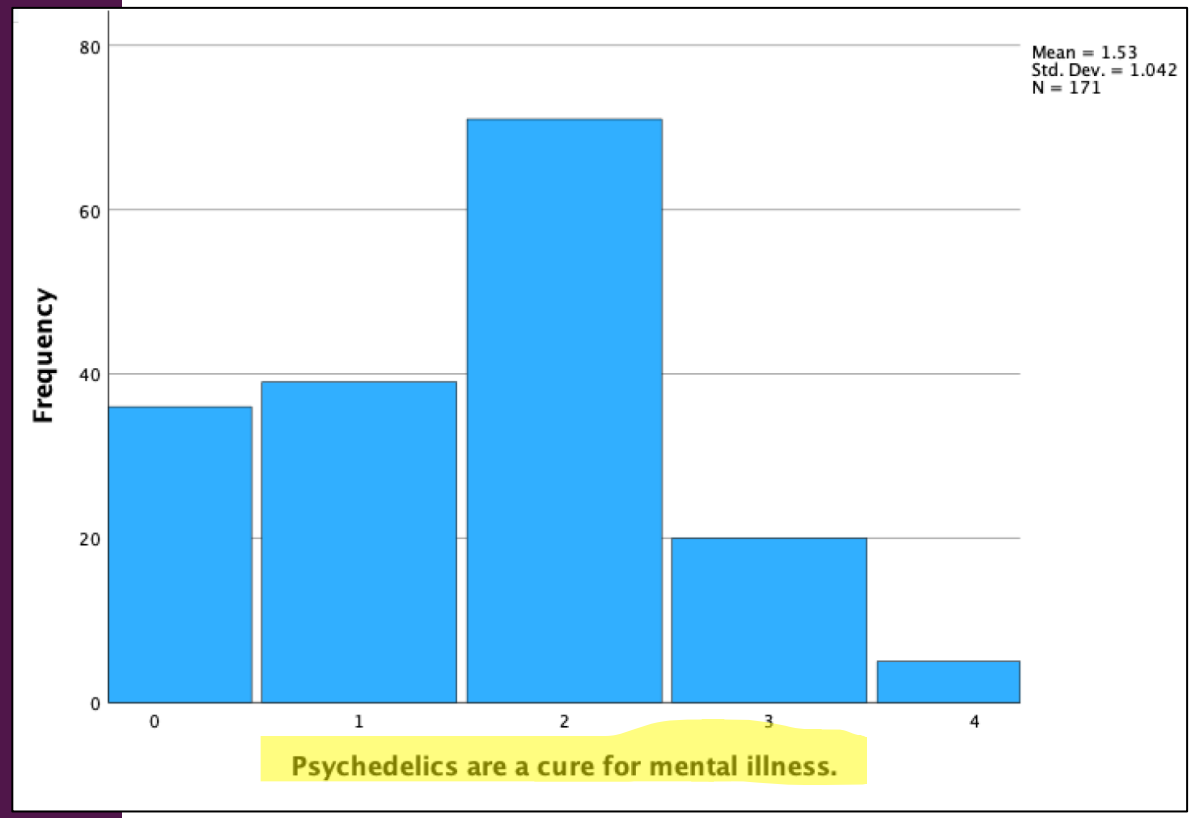

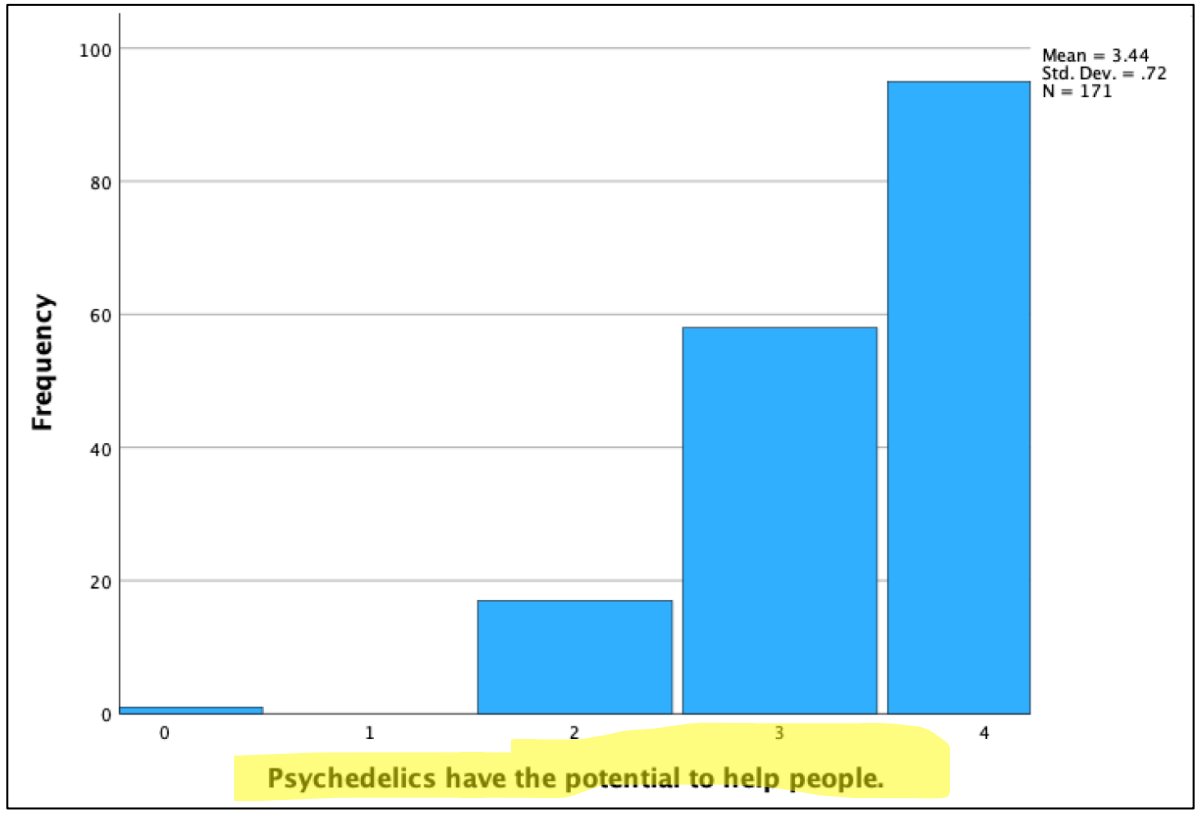

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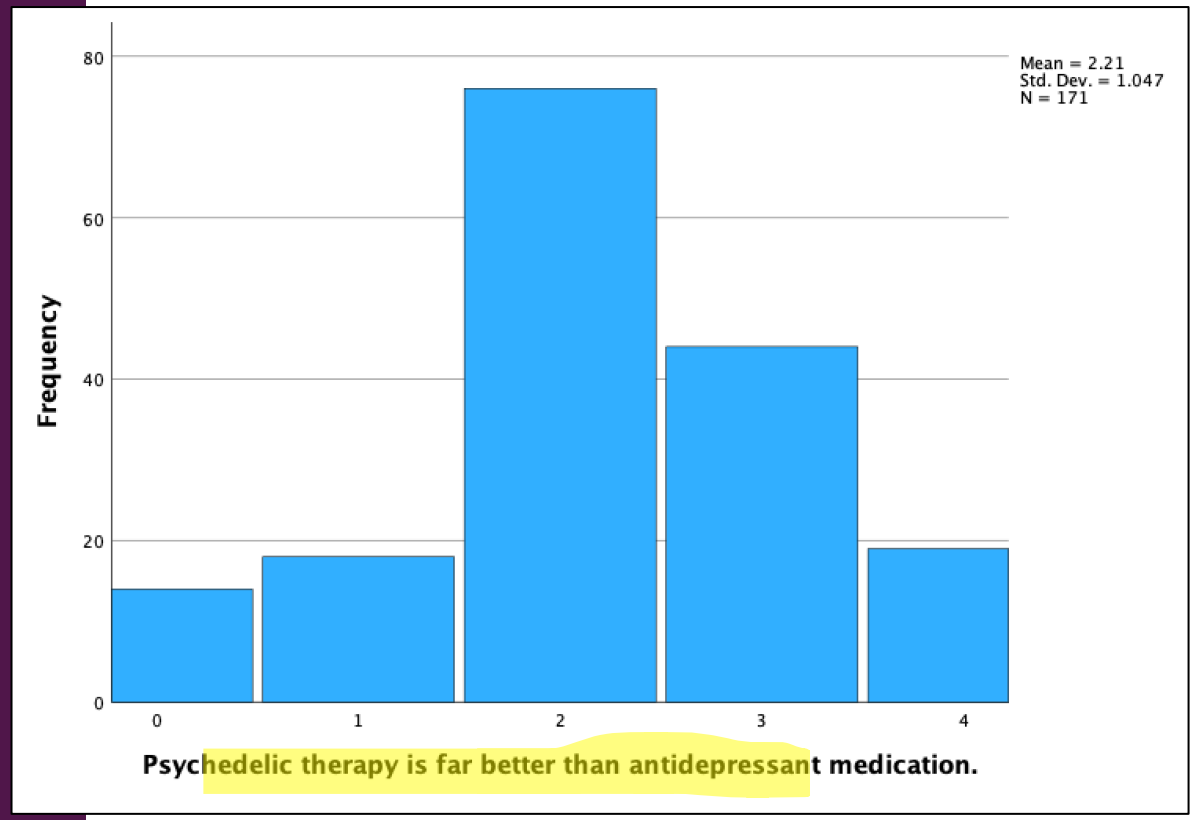

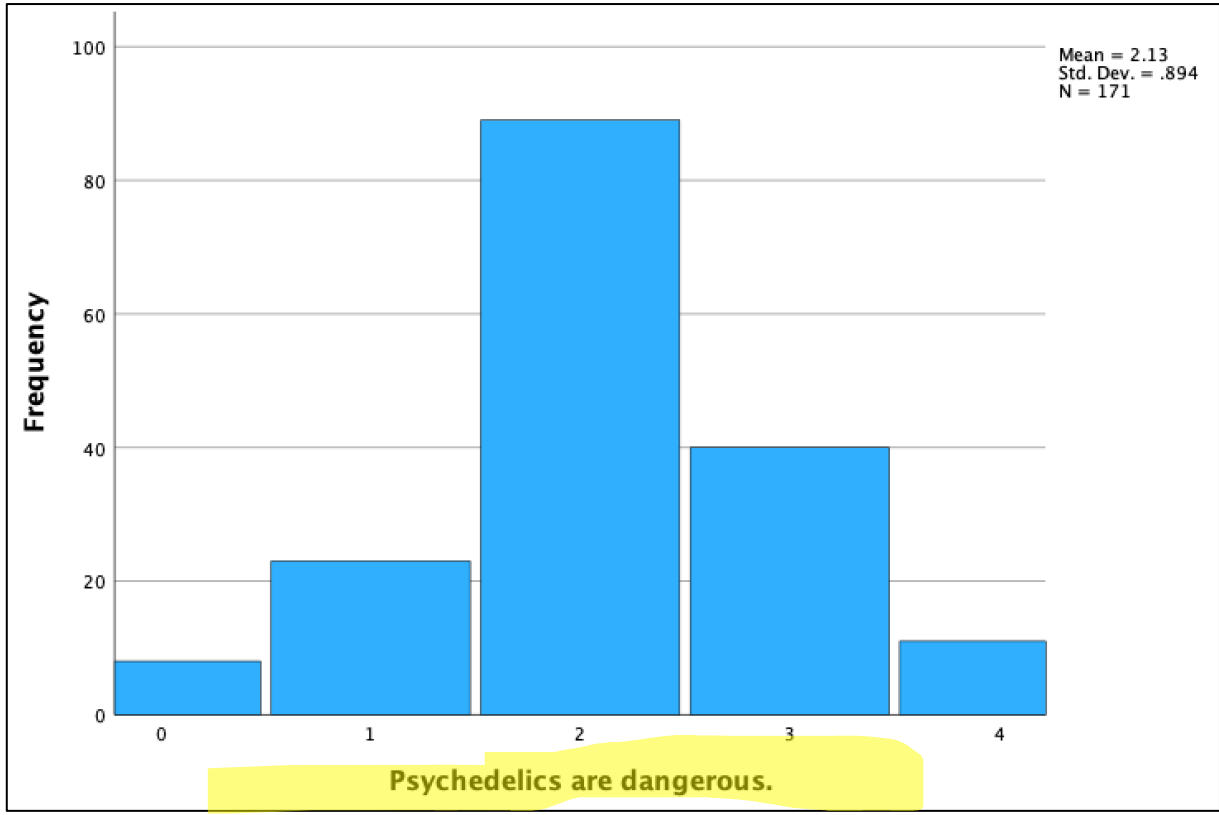

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Key points

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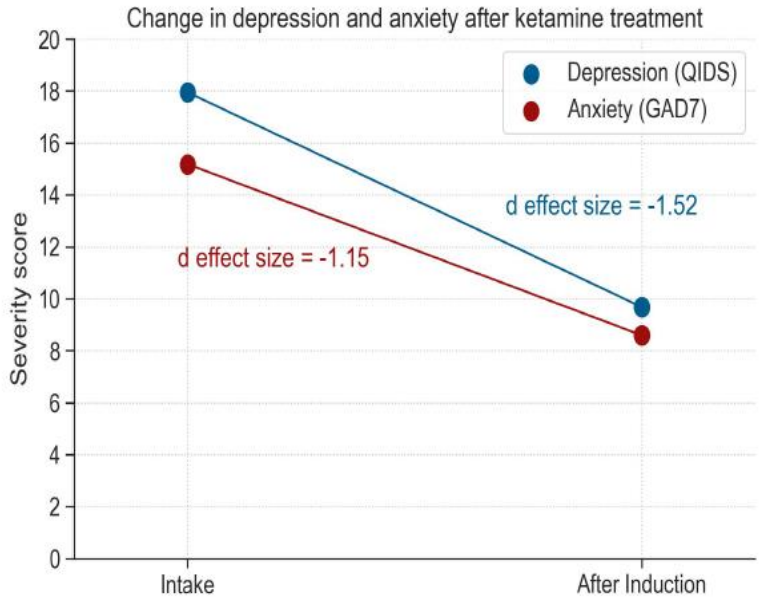
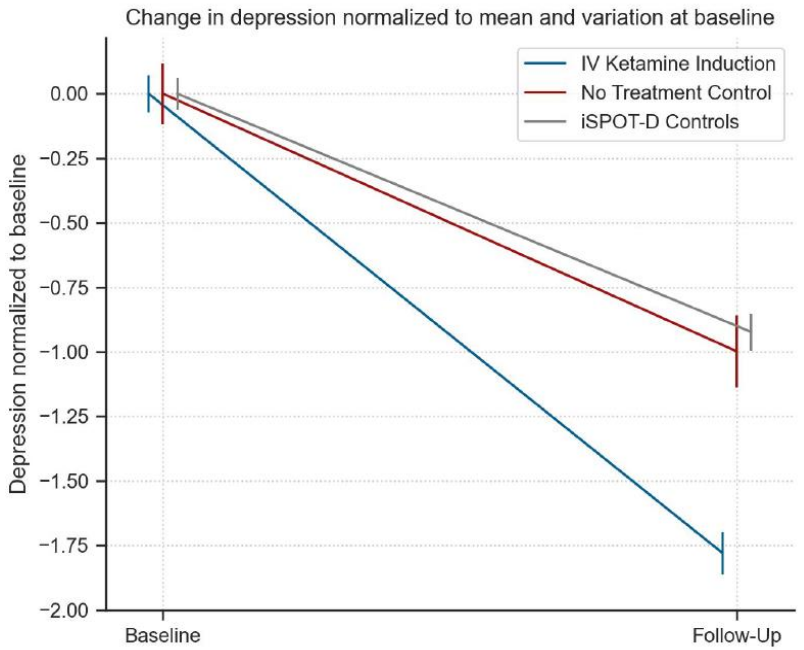
Ketamine: real world evidence of efficacy

Ketamine improves depression and anxiety symptoms N= 714



Comparison with two control datasets N= 276 and N=1,008



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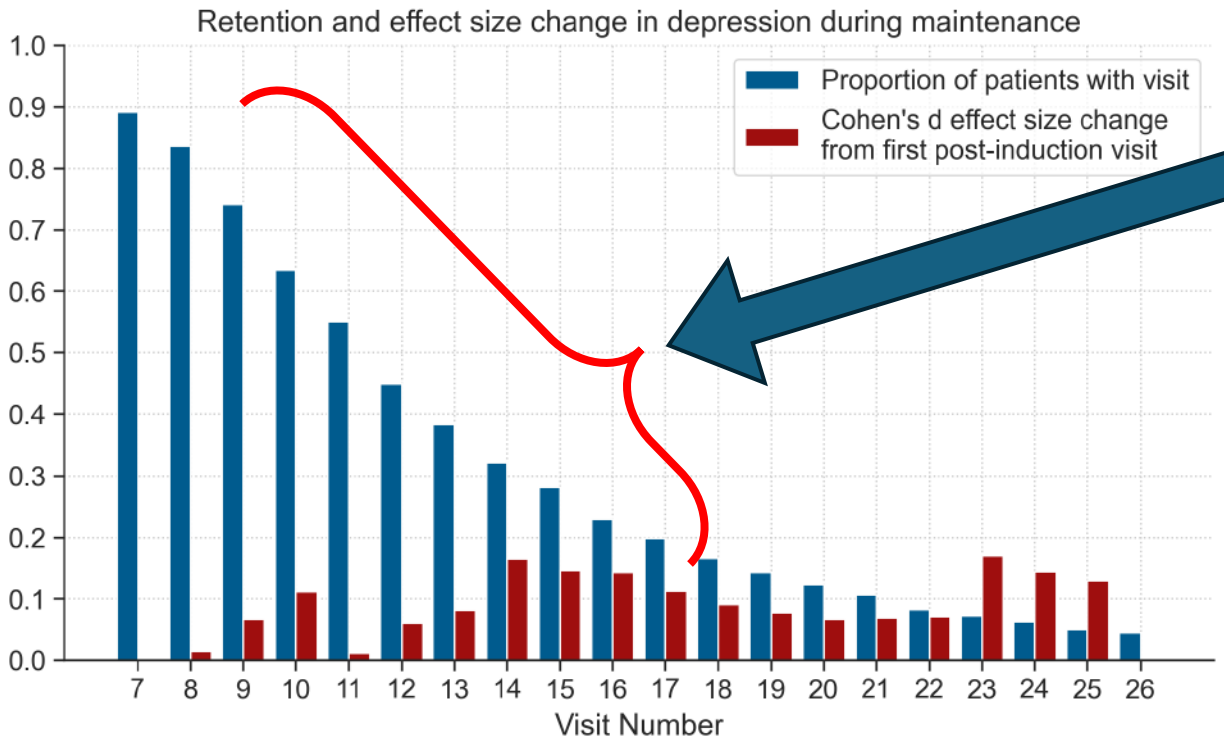
Ketamine: real world evidence of safety?



What happened to the patients who left care?

Without a clinician in the loop, are safety claims reliable?

Safety concerns for ketamine

- **Diversion**
- **Misuse / abuse**
- **Medical complications of long-term use**

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Hietamies et al, 2023 *J Affective Disorders*

Can we learn about ketamine risk from others' experience?

We have a way; where's the will to tackle drugs?

Philip Yeung + FOLLOW

Published: 12:00am, 9 Apr, 2010

Why you can trust SCMP

Hong Kong is fast becoming a K-society, K as in ketamine; it is everywhere you look. The fact that it is a soft drug doesn't make it any less dangerous. Ketamine has several properties that make it a drug of choice for the masses. This drug is not about exclusivity; social workers in the know say that four people can get high by sharing just HK$20 worth of ketamine. Its cheapness explains its socially penetrative power. Schoolchildren can use their pocket money to get high without their parents being any the wiser. As a result, about 80 per cent of young drug addicts are taking ketamine.

South China Morning Post, Apr 9, 2010

Commission on Narcotic Drugs
Fifty-eighth session
Vienna, 9-17 March 2015
Item 6 (b) of the provisional agenda*
Implementation of the international drug control treaties:
Changes in the scope of control of substances

Further information provided by the People's Republic of China on the proposed scheduling of ketamine

On 8 March 2014, pursuant to article 2, paragraph 1, of the Convention on Psychotropic Substances of 1971, the Government of China notified the Secretary-General of the United Nations that China recommended that ketamine should be placed in Schedule I of the 1971 Convention (see E/CN.7/2015/7, annex III).

Following its thirty-sixth meeting, the World Health Organization's Expert Committee on Drug Dependence has recommended that ketamine not be placed under international control at this time (see E/CN.7/2015/7, annex IV).

On 4 March 2015, the Government of the People's Republic of China referring to its note verbale dated 8 March 2014, informed the Secretary-General of the United Nations, that China wished to change the proposal for scheduling ketamine from under Schedule I to under Schedule IV of the 1971 Convention, based on further consideration guided by the principle of a comprehensive and balanced approach with regard to the needs, on one side, to prevent the ever-growing and wide abuse, diversion and illicit trafficking of ketamine, and on the other side, to ensure its availability for therapeutic use.

Key points

1. Patient **expectations** shape ketamine's measured efficacy

2. **What kind of information** do patients get about safety and efficacy?

3. 'Real World Evidence': **hard to collect data** on safety

Thank you! Questions?

@theBorisLab

Heifetslab

https://heifetslab.stanford.edu

Boris D. Heifets, MD, PhD

Associate Professor
Department of Anesthesiology, Perioperative and Pain Medicine
(*by courtesy*) Department of Psychiatry and Behavioral Sciences
Stanford University School of Medicine

Online Promotion and Access to Ketamine

Discussion:

- **Ilisa Bernstein, PharmD, JD,** Bernstein Rx Solutions
- **Michael DiStefano, PhD, MBE,** Colorado University Anschutz, Skaggs School of Pharmacy and Pharmaceutical Sciences
- **Boris Heifets, MD,** Stanford University School of Medicine
- **Richard Quaresima,** Federal Trade Commission

Break

The meeting will resume at 3:10 pm ET

REAGAN-UDALL FOUNDATION FOR THE FDA

Potential Future Use of Ketamine

Discussion:

- **Eric Hermes, MD,** Veterans Health Administration
- **Caroline Huang, PhD,** U.S. Food and Drug Administration
- **Michelle Kim Leff, MD, MBA,** Substance Abuse and Mental Health Services Administration
- **Lisa Robin,** Federation of State Medical Boards
- **Gerard Sanacora, MD, PhD,** Yale University

Understanding Current Use of Ketamine for Emerging Areas of Therapeutic Interest

Thank you for attending!

The meeting recording, transcript, and other materials will be available on the FDA Foundation website next week.

Funding Disclosure: This activity is one part of a multi-part Foundation project related to substance use disorder. The multi-part project is supported by the Food and Drug Administration (FDA) of the U.S. Department of Health and Human Services (HHS) as part of an overall award of $1,720,109 of federal funds (100% of the project). The contents are those of the author(s) and do not necessarily represent the official views of, nor an endorsement, by FDA, HHS, or the U.S. Government. For more information, please visit FDA.gov.

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