Ketamine: From Anesthetic to Controversial Mental Health Treatment

An overview of its journey from FDA approval to the center of modern medical and legal debates.

Discovery of Ketamine

•1962- Dr. Calvin Steven of Parke-Davis (now Pfizer), first synthesizes ketamine.

•Goal was to create a safer alternative to the anesthetic Phencyclidine (PCP).

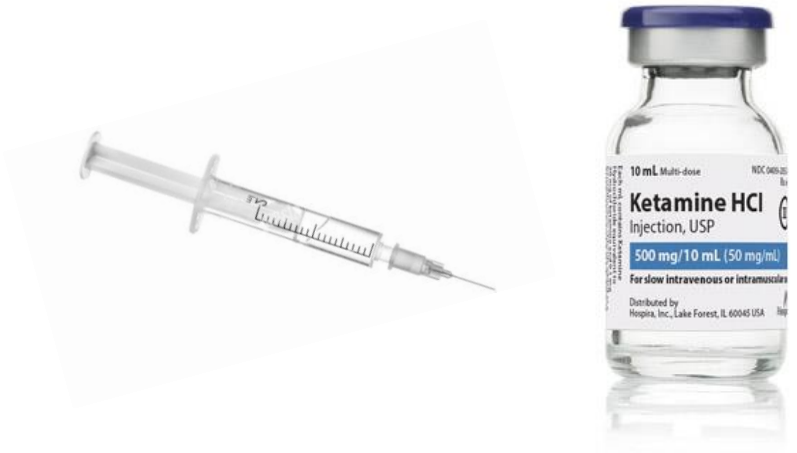
•PCP was a powerful anesthetic but caused severe, long-lasting hallucinations.

•1964-Human trials are conducted on prisoners, revealing its potent, rapid-acting anesthetic effects with a shorter recovery period than PCP.

PARKE-DAVIS

1970- Ketamine First Approved

- FDA approval as fast acting anesthetic delivered intravenously
- Park-Davis (now Pfizer) markets as Ketalar



- Provides anesthesia without suppressing breathing
- Extensively used for battlefield surgeries in Vietnam

Clinical Pharmacology
& Therapeutics

Official literature on new drugs

Ketamine hydrochloride (Ketalar)

Parke Davis

First published: September 1970 | https://doi.org/10.1002/cpt1970115777 | Citations: 4

Abstract

Ketalar is a nonbarbiturate anesthetic chemically designated *dl* 2- (o-chlorophenyl) -2-(methylamino) cyclohexanone hydrochloride. It is formulated as a slightly acid (pH 3.5–5.5) solution for intravenous or intramuscular injection in concentrations containing the equivalent of either 10 or 50 mg. ketamine base per ml. and contains 1: 10,000 Phemerc (benzethonillm chloride) as a preservative. The 10 mg. per ml. solution has been made isotonic with sodium chloride.

Keep Well

Ketamine, The New Anesthetic

BY DR. T. R. VAN DELLEN

Ketamine is a new anesthetic that is injected intravenously or into a muscle. Instantly, it produces a peculiar state of unconsciousness in which the individual does not appear to be asleep but "isolated" from his surroundings.

Under its influence, the brain is unable to make the appropriate response to pain. As a result, the drug produces a profound analgesia without a depressing effect on the heart or respiration. On awakening, the patient suffers virtually no nausea or vomiting. There is complete amnesia for the period of the operation.

According to Dr. Guenter Corssen of Birmingham, Ala., ketamine works best in brief diagnostic and surgical procedures involving the head and neck. Among these are minor operations of the eye, ear and mouth and for plastic surgery. It is also useful in doing highly skilled X-ray procedures of the brain.

Ketamine anesthesia is also a boon when severe burn areas must be cleaned and dressed. The agent will also be useful in setting fractures, manipulating frozen joints and in the management of children undergoing a variety of surgical procedures of the head and neck.

One drawback is that ketamine does not anesthetize the chest or abdomen. As a result, it is not recommended as the sole anesthetic agent in abdominal and thoracic surgery. It can be used as a starter but must be supplemented with other general anesthetics. In addition, ketamine does not produce the muscle relaxation required when doing operations in this area of the body.

Surgery aid OKd by FDA

SEATTLE, Wash. (UPI)—A new, fast-acting anesthetic tested here at Children's Orthopedic Hospital, where it was proved to be of particular value for surgery on youngsters under 16, soon will be available to hospitals throughout the country.

The anesthetic is known generically as ketamine Hydrochloride. The Food and Drug Administration approved its use for persons of all ages after it was widely tested on patients.

Because Children's Orthopedic Hospital and Medical Center in Seattle was one of the first to participate, it will be one of the first hospitals to receive the anesthetic.

Ketamine hydrochloride is a nonbarbiturate and some experts believe it is the safest anesthetic on the market.

The new anesthetic "profoundly blocks pain and at the same time provides a lighter level of sleep," a hospital spokesman said.

When injected into a vein, the anesthetic takes effect within 10 to 30 seconds and has a lasting effect of about 10 minutes. It therefore may replace sodium pentethal as a means of initiating anesthesia in many instances.

The Salt Lake Tribune A 21
Thursday, October 7, 1971

Dr. T. R. Van Dellen

Ketamine Aids Surgeons in Minor Cases

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Dr. Van Dellen

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Chicago Tribune, Thursday, October 7, 1971

How to Stay Healthy

Ketamine is new anesthetic

BY T. R. VAN DELLEN, M.D.

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The modern anesthesiologist is always at the head of the operating room table. After the patient is asleep, he checks blood pressure, pulse, respiration and reflexes to prevent complications that might stem from the anesthetic. Now and then he warns the surgeon that all is not well and the operation is stopped.

Chloroform, ether and cyclopropane are seldom used today. They have been replaced with safer and more effective local and general anesthetics.

* * *

Questions on medical topics will be answered if a stamped, self-addressed envelope is sent to Dr. Van Dellen, The Columbus Ledger, P.O. Box 711, Columbus, Ga. 31902.

Yesterday's Headlines

From the files of The Columbus Ledger:

60 Years Ago (1911)

Good Roads convention will convene tomorrow morning; session will begin at 10 o'clock in Muscogee County courthouse; several prominent speakers will make addresses.

40 Years Ago (1931)

Clyde Pangborn and Hugh Herndon today completed the first non-stop airplane flight across the Pacific; Americans land Monday at Wenatchee, Wash., after flight from Japan; span the Pacific in about 41 hours.

20 Years Ago (1951)

Lt. Gov. Marvin Griffin will address tourist-boosters from 19 West Georgia counties here Wednesday at the fifth annual meeting of U. S. Highway 27 Association.

2019- Spravato Approved

- FDA approves J&J's Spravato, a Ketamine derived nasal spray for treatment resistant depression.
- Clinical trials show 50-70% of patients achieved significant relief within four weeks (when combined with oral antidepressants).
- Available only via REMS Programs (FDA-mandated safety programs for drugs with serious risks – requires administration and monitoring in a certified healthcare setting.
- Black Boxed Warning

SPRAVATO® (esketamine) is now approved as the first and only treatment used as monotherapy for adults living with treatment-resistant depression

Learn More

SPRAVATO® is the only FDA-approved treatment used as monotherapy or in conjunction with an oral antidepressant for adults with treatment-resistant depression (MDD with inadequate response to at least 2 oral antidepressants of adequate dose and duration)

SPRAVATO® is a unique treatment approach that delivers:

Click Below To See Clinical & Safety Data

- Results as early as 24 hours and out to 28 days
- Long-term safety and efficacy out to 5 years

Patient Support & Savings

IMPORTANT SAFETY INFORMATION

WARNING: SEDATION; DISSOCIATION; RESPIRATORY DEPRESSION; ABUSE AND MISUSE; and SUICIDAL THOUGHTS AND BEHAVIORS

See full prescribing information for complete boxed warning

- Risk for sedation, dissociation, and respiratory depression after administration. Monitor patients for at least two hours after administration (5.1, 5.2, 5.3).
- Potential for abuse and misuse. Consider the risks and benefits of using SPRAVATO® prior to use in patients at higher risk of abuse. Monitor for signs and symptoms of abuse and misuse (5.4).
- SPRAVATO® is only available through a restricted program called the SPRAVATO® REMS (5.5).
- Increased risk of suicidal thoughts and behaviors in pediatric and young adult patients taking antidepressants. Closely monitor all antidepressant-treated patients for clinical worsening and emergence of suicidal thoughts and behaviors. SPRAVATO® is not approved for use in pediatric patients (5.6).

VIEW FULL IMPORTANT SAFETY INFORMATION

SPRAVATO® is contraindicated in patients

Spravato Regulatory History

March 2019

- Initial FDA approval
- Approved for treatment resistant depression in adults
- Must be used conjunction with an oral antidepressant

August 2020

- Approved for depressive symptoms in adults with major depressive disorder or acute suicidal ideation
- Still must be used conjunction with an oral antidepressant

January 2025

- Approved as first monotherapy for treatment resistant depression in adults
- Patients can now receive Spravato without the concurrent use of an oral antidepressant for TRD.

EMS Program: Due to risks of sedation, dissociation, and abuse/misuse, Spravato is available only through a restricted Risk Evaluation and Mitigation Strategy (REMS) program, requiring supervised administration in a certified healthcare setting.

Clinical Trials: 3 suicides during open-label treatment. Study site investigators **did not deem related to Spravato.**

Postmarketing Data From March 2019 to January 2023, **147 deaths were reported,** with **47 of those due to suicide.**

J&J's Comeback Kid: Spravato= Blockbuster

- After a slow start, Spravato is now J&J's fastest-growing medication and is considered a blockbuster.
- **Reached $1Billion in Annual Sales.**
- Forecasts predict 3-5 billion for 2025.

October 2023: FDA warns providers risks associated with compounded ketamine products for psychiatric disorders, emphasizing that ketamine is not FDA approved for treating any

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

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:

- Ketamine is *not* FDA approved for the treatment of any psychiatric disorder. FDA is aware that compounded ketamine products have been marketed for a wide variety of psychiatric disorders (e.g., depression, anxiety, post-traumatic stress disorder (PTSD), and obsessive-compulsive disorder); however, FDA has not determined that ketamine is safe and effective for such uses.
- Compounded drugs, including compounded ketamine products, are *not* FDA approved, which means FDA has not evaluated their safety, effectiveness, or quality prior to marketing. Therefore, compounded drugs do not have any FDA-approved indications or routes of administration. Although compounded drugs can serve an important medical need for certain patients when an FDA-approved drug is not medically appropriate, they also present a risk to patients and should only be used under the care of a health care provider.
- Use of compounded ketamine products *without* monitoring by a health care provider for sedation (sleepiness), dissociation (disconnection between a person's thoughts, feelings, and sense of space, time, and self), and changes in vital signs (such as blood pressure and heart rate) may put patients at risk for serious adverse events.
- Known safety concerns associated with the use of ketamine products include abuse and misuse, psychiatric events, increases in blood pressure, respiratory depression (slowed breathing), and lower urinary tract and bladder symptoms. For FDA-approved ketamine (see Ketalar prescribing information (https://www.accessdata.fda.gov/spl/data/705c4709-580e-4f02-8a74-bc9aa0641fe2/705c4709-580e-4f02-8a74-bc9aa0641fe2.xml)), the

February 2022 –FDA issued a warning about potential risks associated with compounded ketamine nasal sprays due to adverse event reports and lack of

FDA alerts health care professionals of potential risks associated with compounded ketamine nasal spray

February 16, 2022

Background

FDA has become aware of safety reports involving compounded intranasal ketamine to treat psychiatric disorders which may be putting patients at risk. Compounded drugs are not FDA-approved, which means FDA has not evaluated their safety, effectiveness, or quality prior to marketing.

Ketamine hydrochloride[a] (tradename: Ketalar) is a Schedule III controlled substance that is FDA-approved as an intravenous or intramuscular injection solution for induction and maintenance of general anesthesia. Ketamine is a racemic mixture consisting of two mirror image molecules, R- and S-ketamine. FDA-approved labeling for ketamine contains warnings and precautions on hemodynamic instability, emergence reactions (vivid dreams, hallucinations, or delirium), respiratory depression, and drug-induced liver injury, among others.

Ketamine is not FDA-approved for the treatment of any psychiatric disorder. However, the "S" form of ketamine, which is derived from ketamine and known as Spravato (esketamine), is a Schedule III controlled substance that was approved by FDA in 2019 as a nasal spray for treatment-resistant depression in adults and depressive symptoms in adults with major depressive disorder with acute suicidal ideation or behavior, in conjunction with an oral antidepressant. Because of the potential risks associated with Spravato (esketamine), including sedation, dissociation, and abuse or misuse, its label contains Boxed Warnings, and Spravato is subject to strict safety controls on dispensing and administration under a safety program called a Risk Evaluation and Mitigation Strategy (REMS). The Spravato REMS (https://www.accessdata.fda.gov/scripts/cder/rems/index.cfm?event=IndvRemsDetails.page&REMS=386)[1] program requires Spravato (esketamine) to be dispensed and administered in health care settings that are certified in the REMS. Spravato (esketamine) cannot be dispensed for use outside the certified healthcare setting. Patients must be monitored inside the healthcare setting after administration for a minimum of two hours until patients are safe to leave.

Challenges in Compounded Ketamine Lozenge Production

Problem: Inconsistent Drug Distribution

- **Uneven Mixing:** Difficulty ensuring uniform distribution of ketamine within the lozenge base.
- **"Hot Spots":** Risk of dangerously high concentrations of ketamine in some areas and little to no active ingredient in others.
- **Patient Safety Risk:** Patients may receive supra-therapeutic doses one day and sub-therapeutic doses the next, despite consistent prescription.

Problem: Variable Patient Absorption

- **Sublingual Variability:** Estimated ~30% absorption of sublingual ketamine into the bloodstream.
- **Influencing Factors:** Absorption rates vary significantly based on:
  - Duration the lozenge is held in the mouth.
  - Individual saliva production.
  - Other physiological factors.

Problem: Drug Stability & Potency Degradation

- **Sensitivity:** Ketamine is susceptible to degradation from heat and light.
- **Manufacturing Impact:** Lozenge production processes can unpredictably reduce ketamine potency.

Problem: Lack of Quality Control Oversight

- **No Federal Mandate:** Absence of federal requirements for batch testing compounded products for uniformity and potency.

FDA

FDA Briefing Document

Psychopharmacologic Drugs Advisory Committee (PDAC) and Drug Safety and Risk Management (DSaRM) Advisory Committee Meeting

February 12, 2019

Agenda Topic: The committees will discuss the efficacy, safety, and risk-benefit profile of New Drug Application (NDA) 211243, esketamine 28 mg single-use nasal spray device, submitted by Janssen Pharmaceuticals, Inc., for the treatment of treatment-resistant depression

"A total of 28 hepetobiliary events occurred among the 20 cases … ranging from asymptomatic elevation in liver enzymes to irreversible structural damage to the liver or biliary system and/or clinical signs of liver failure…. We find an association between ketamine and a range of hepatobiliary events in the context of off-label, repeated use."

- "Ketamine dependence and tolerance are possible following prolonged administration. A withdrawal syndrome with psychotic features has been described following discontinuation of long-term ketamine use."

- "It appears that treatment with esketamine leads to dissociation … noted immediate effects such as dissociation (for a majority of subjects, with rates as high as 75 percent) and sedation upon dosing, that do not dissipate with time according to the safety data reviewed."

- "None of the studies prospectively examined long-term persistence of cognitive

FDA Overlooked Red Flags In Drugmaker's Testing of New Depression Medicine

Dr. Jess Fiedorowicz, director of the Mood Disorders Center at the University of Iowa and a member of the FDA advisory committee that reviewed the drug, described its benefit as "almost certainly exaggerated" after hearing the evidence.

The FDA typically requires that applicants provide at least two clinical trials demonstrating the drug's efficacy, "each convincing on its own." Janssen provided just one successful short-term, double-blind trial of esketamine. Two other trials it ran to test efficacy fell short.

To reach the two-trial threshold, the FDA broke its precedent for psychiatric drugs and allowed the company to count a trial conducted to study a different topic: relapse and remission trends. But, by definition, every patient in the trial had already taken and seen improvement from esketamine.

What's more, that single positive efficacy trial showed just a 4-point improvement in depression symptoms compared with the placebo treatment on a 60-point scale some clinicians use to measure depression severity. Some committee members noted the trial wasn't really blind since participants could recognize they were getting the drug from side effects like a temporary out-of-body sensation.

Finally, the FDA lowered the bar for "treatment-resistant depression." Initially, for inclusion, trial participants would have had to have failed two classes of oral antidepressants.

Are we repeating mistakes of the past? A review of the evidence for esketamine

Published online by Cambridge University Press: **27 May 2020**

Mark A. Horowitz and Joanna Moncrieff

Show author details

Summary

Esketamine has been licensed for 'treatment-resistant depression' in the USA, UK and Europe. Licensing trials did not establish efficacy: two trials were negative, one showed a statistically significant but clinically uncertain effect, and a flawed discontinuation trial was included, against Food and Drug Administration precedent. Safety signals – deaths, including suicides, and bladder damage – were minimised.

Epidemiology and Psychiatric Sciences

cambridge.org/eps

Epidemiology for Clinical Psychopharmacology

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Esketamine; evidence-based medicine; FDA; regulatory policies; treatment-resistant depression

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Esketamine for treatment resistant depression: a trick of smoke and mirrors?

C. Gastaldon, D. Papola, G. Ostuzzi and C. Barbui

Department of Neuroscience, Biomedicine and Movement Sciences, Section of Psychiatry, World Health Organization Collaborating Centre for Research and Training in Mental Health and Service Evaluation, University of Verona, Verona, Italy

Abstract

In March 2019, the US Food and Drug Administration (FDA) approved a nasal spray formulation of esketamine for the treatment of resistant depression in adults. Esketamine is the S-enantiomer of ketamine, a occasionally, hallucinations. USA or in any other countr commentary critically reviev to draw implications for clir

Re-analysis of the primary efficacy data of the three phase III short-term studies (four comparisons in total, as for one three-arm trial each arm was considered separately *v.* placebo) revealed an overall mean difference of −4.08 (95% CI −6.20 to 1.97, I^2 = 0%, three studies, 641 participants), suggesting that, in comparison with placebo, esketamine may improve depressive symptoms reducing by 4 points the MADRS score (Fig. 1). Of the four comparisons reported in Fig. 1, only one revealed a significant difference between esketamine and placebo.

In March 2019, the US Food
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depression (TRD) refers to a
depressant (AD) trials of ad
mine is indicated in TRD in
review by the European Med
positive feedback and may b

Esketamine is the S-enan
mine has not been approved
used off-label in cases of s
Zhang and Hashimoto, 2019
it produces desired mental and behavioural changes, such as euphoria, and perceptual changes, such as dissociation and, occasionally, hallucinations (Caddy *et al.*, 2015). These effects, together with a risk of abuse and misuse, made ketamine a widespread street drug, also known as 'Special K' (Zhu *et al.*, 2016).

Against this background, in this commentary, the evidence on esketamine submitted to the FDA was reviewed, aiming to draw implications for clinical practice, research and regulatory science. The FDA website was searched using the term 'esketamine' (up to June 2019), and all documents were downloaded and independently inspected by two investigators. Phase III studies were identified and, using standard Cochrane meta-analytical methods (Higgins and Green, 2011), efficacy and acceptability data were extracted and re-analysed.

Critical inspection of the FDA documentation revealed a total of four phase III trials (Ochs-Ross *et. al.*, 2019; Daly *et al.*, 2019; Fedgchin *et al.*, 2019; Popova *et al.*, 2019). Three were short-term placebo-controlled efficacy trials conducted in participants suffering from TRD. The main characteristics of the three efficacy studies are summarised in Table 1.

TRANSFORM-2 is the only short-term efficacy trial that found a significant difference between esketamine + AD and placebo + AD. This trial showed that participants receiving esketamine had a reduction of 21.4 points at the Montgomery–Asberg Depression Rating Scale (MADRS) (standard deviation (SD) 12.32) *v.* a reduction of 17.0 (SD. 13.88) in the placebo group at day 28, with a mean difference between the two groups of 4.4 points. TRANSFORM-1 and TRANSFORM-3 failed to show a significant difference in terms of efficacy between esketamine + AD and placebo + AD.

The fourth study is a withdrawal placebo-controlled clinical trial (SUSTAIN-1,

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

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S2215-0366(19)30394-3
See Comment page 975

With a novel mechanism of action compared with existing marketed antidepressants, esketamine has been of keen interest to mental health clinicians and researchers. On March 5, 2019, the US Food and Drug Administration (FDA) approved intranasal esketamine for treatment-resistant depression.[1] To make a proper risk–benefit analysis before prescribing, mental health clinicians should look beyond the fact of approval and consider the data

documents from the Feb 12, 2019, Psychopharmacologic Drugs Advisory Committee.[2] These documents reveal the following concerns regarding the safety of esketamine.

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. Consequently, clinicians might find that esketamine demonstrates less efficacy among real-world patients with higher levels of treatment resistance.

Second, one of the two non-significant trials involved older patients (65 years or older; study 3005 [NCT02422186], p=0·06), raising the question of esketamine's efficacy within this important demographic (this trial remains unpublished).

Third, in the sole positive short-term phase 3 trial (3002),[2] the mean decrease from baseline on the Montgomery-Åsberg Depression Rating Scale was

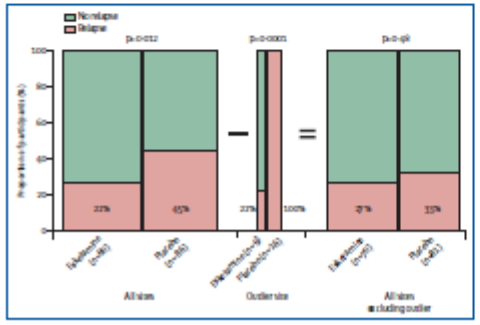


Figure: Relapse rates for esketamine versus placebo and the effect of outlier site on overall result
Column width is proportional to sample size.

difference is clinically meaningful,[2] clinicians who have heard esketamine referred to as a game changer might be disappointed to calculate that 81% of the response to esketamine was observed with placebo.

Fourth, participation in the randomised withdrawal trial (3003) was restricted to patients who had been previously randomly assigned to esketamine (not placebo) in a short-term trial and achieved stable remission (FDA slides 20, 29),[2] resulting in an enriched population that was statistically more likely to respond to the drug.

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." (FBD p 25). Although the FDA reassured its Advisory Committee that it had inspected this site and "didn't find any reason to question the data integrity" (transcript pp 200-01),[2] the issue arose only following a question by a committee member and was not presented in the slides. Without access to patient-level data, one cannot recalculate time to relapse and the hazard ratio, but one can do a sensitivity analysis using the relapse data provided (FBD p 25). As shown in the figure, removing the outlier site changes the results from significant (Fisher's exact test p=0·012) to non-significant (p=0·48).

Sixth, using the primary outcome results of these three esketamine trials (FDA slide 24),[2] meta-analysis yields a standardised mean difference of 0·28 (95% CI 0·11–0·44), similar to that of the only other drug approved by the FDA for treatment-resistant depression, the olanzapine-fluoxetine combination (0·26 [95% CI 0·04–0·45]),[4] and less than the standardised mean differences of two drugs approved by the FDA for adjunctive treatment of depression, aripiprazole (0·35 [0·23–0·48]) and quetiapine (0·40 [0·26–0·53]).[4] Thus, esketamine's novel mechanism of action does not appear to confer efficacy beyond that of cheaper alternatives.

Last, rapid onset of response was not formally demonstrated. One trial (3001)[2] lent supportive data, but "The onset of clinical response cannot be formally evaluated (for 84 mg or 56 mg) since previous endpoints in the testing hierarchy were not significant." (JBD p 234).[2]

FDA had "loosened its rules" over esketamine approval because the drug-maker "could not provide two positive efficacy trials."

Half of the participants (48.3 percent overall) experienced dissociation and one-third dizziness. Increased blood pressure, hypoesthesia (sensory numbness), nausea, and sedation were each present in between 10 and 30 percent of participants."

"A known drug of misuse, associated with significant harm, is **increasingly promoted despite scant evidence of efficacy and without long-term safety studies.**"

Spravato Safety Concerns and Potential Personal Injury Claims

Allegations or concerns about inadequate warnings regarding serious side effects.

- Respiratory Depression/Arrest: Reports of these serious adverse events; Janssen updated U.S. labels in October 2023.

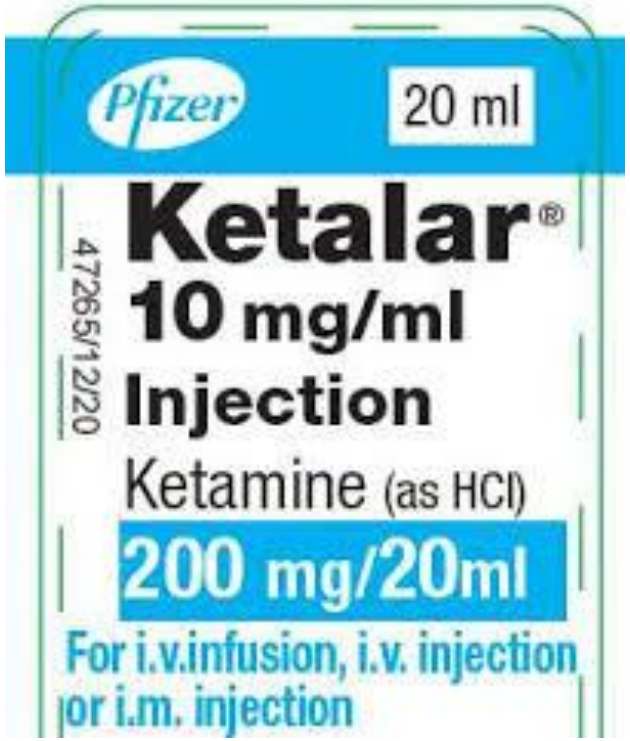
- Suicidal Ideation/Behavior: Spravato carries a boxed warning. While suicides occurred in trials and post-marketing, investigators often deemed them unrelated to the drug itself.

- **Litigation** Status: While some law firms are investigating these claims no current widespread personal injury lawsuits

Ketalar- Off-Label Use and Medical Malpractice

Lawsuits arising from ketamine's off-label use for conditions like depression and chronic pain.
Key Issues Raised:

- **Standard of Care:** Allegations of physicians failing to meet the standard of care when prescribing or administering ketamine for unapproved uses.
- **Informed Consent:** Claims of failure to adequately inform patients about the off-label nature, risks (e.g., hallucinations, dissociative behavior), and alternative treatments.
- **Monitoring:** Lawsuits related to insufficient patient monitoring during and after ketamine administration, leading to adverse events.
- **Overdose:** Cases where prescribed ketamine amounts are alleged to be "gross overdoses," leading to severe adverse



Editorials

Esketamine for treatment resistant depression

BMJ 2019 ; 366 doi: https://doi.org/10.1136/bmj.l5572 (Published 23 September 2019)
Cite this as: *BMJ* 2019;366:l5572

Opinion

A drug not a miracle—why we need a new system for monitoring ketamine

It appears that history is repeating: a known drug of abuse, associated with significant harm, with scant evidence of efficacy, is being submitted for licensing, without adequate long-term safety studies. 'Scrupulous monitoring' has not been previously adequate in preventing the rise in prescribed drug dependence.

Esketamine for treatment resistant depression is not recommended by NICE

BMJ 2020 ; 368 doi: https://doi.org/10.1136/bmj.m329 (Published 28 January 2020)
Cite this as: *BMJ* 2020;368:m329

Linked Editorial

Esketamine for treatment resistant depression

Elisabeth Mahase

Author affiliations

An esketamine nasal spray may not be made available on the NHS for patients with treatment resistant depression because of uncertainties over its clinical and cost effectiveness, says draft guidance from the National Institute for Health and Care Excellence.[1]

NICE reviewed the effectiveness of esketamine in combination with a selective serotonin reuptake inhibitor or serotonin-norepinephrine reuptake inhibitor for adults with treatment resistant depression that have not responded to at least two different antidepressants in the current moderate to severe depressive episode.

Drugs.com
Know more. Be sure.

Spravato User Reviews & Ratings

"I completely changed into another person. I went into a major psychosis and ended up in the psych ward five times at the end of December to mid February. It was horrific and terrifying."

"On Spravato I felt like I was going to die. It took 4 minutes to kick in. I couldn't feel my face, couldn't speak, couldn't breathe, the room was spinning … I was sweating / felt like I was sinking, mind racing, nauseous. I felt like I was strapped to a Ferris wheel that wouldn't stop spinning / falling really fast…. I couldn't move…. It was really scary."

"The drug experience is horrible. After I spray it in my nose and it begins to take effects I pray it will end. The feeling is so horrible. I want to throw up, I can't physically move, I can't assess where I am, I can't 'sense' anything but I am aware of how bad I feel and pray it ends."

" "I became very aggressive and hostile. The actual process of taking the drug was a miserable experience. The taste was horrible and made me horribly nauseated."

About 10 minutes or so [after the second dose], I began to feel like I was falling, spinning and losing my mind, completely out of control. I sat there for almost 4 hours absolutely terrified. Terrified that I would never feel 'normal' again, that I would die, I would lose everything I cared about. I cried in fear and begged the person who gave me the medicine to make it stop."

Ketalar- Illegal Administration & Distribution

Nature: Criminal indictments and civil actions against individuals or clinics involved in the illegal handling of ketamine.

- **Unlicensed Administration:** Doctors administering ketamine without proper DEA registration or supervision.
- **Fraudulent Billing:** Illegally billing Medicare or other federal healthcare programs for ketamine services.
- **Improper Prescribing:** Schemes involving pre-signed prescription pads or prescribing ketamine without patient examination.
- **Diversion:** Misuse or unauthorized distribution of controlled substances, including ketamine.
- **Fatal Overdoses:** Investigations and indictments related to deaths linked to illegally obtained or improperly administered ketamine (e.g., Matthew Perry case, other overdose incidents).

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Matthew Perry Death Suit Could Blow Past Calif. Damage Cap

By Y. Peter Ka

Law360 (Au
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"Conduct rewarded is conduct repeated," he said, "When doctors get away with substandard or reckless care and are not held accountable, they'll do it again. So the best way to shape change is to enforce the rules we have."

Guy R, Gruppie, a senior partner at Murchison & Cumming LLP in Los Angeles and a specialist in defending against wrongful death cases, told Law360 that a civil suit filed by Perry's estate could take advantage of the work done by federal prosecutors.

"The plaintiffs' side of the case would be inclined to very carefully watch the prosecution and see how that all goes down and take advantage of any pleas or evidence that come up that way, and they will be able to bootstrap, to some degree, the medical evidence generated by the L.A. County coroner,"

Law360 (August 23, 2024, 10:10 PM EDT) -- The federal indictment recently unsealed accusing two doctors and others of peddling the ketamine that caused Matthew Perry's death will serve as prime fodder for any wrongful death suit by the actor's estate, experts say, and California's medical malpractice damages cap may not even be a factor.

Attorneys told Law360 that the doctors' alleged actions were shocking and were diametrically opposed to their Hippocratic oath to do no harm.

"I would consider these guys to be rogue doctors, this is not the expectation of what a normal, reasonable and functioning physician would do," said Stuart Ratzan, founding partner of plaintiffs firm Ratzan Weissman & Boldt in Miami, "This is way outside the boundaries of what a reasonably careful doctor would do. This is all about stashing cash. When greed takes over, bad things happen."

Ratzan drew parallels with the nation's opioid crisis and how some doctors have taken advantage of vulnerable patients with addiction problems. Although the crisis has spawned guidelines and restrictions on drugs across the country, Ratzan said it boils down to enforcement and accountability, so a criminal conviction and successful wrongful death suit would go a long way towards preventing similar incidents in the future.

"Conduct rewarded is conduct repeated," he said, "When doctors get away with substandard or reckless care and are not held accountable, they'll do it again. So the best way to shape change is to enforce the rules we have."

Ketalar- False Advertising and Billing Practices

Nature: Allegations against ketamine clinics for misleading advertising and improper billing.

Key Issues:

- **Off-Label Claims:** Advertising off-label and unapproved uses of ketamine for various mental health and pain conditions without clear disclaimers.
- **Safety Misrepresentation:** Making misleading representations regarding the safety of ketamine treatments, especially for at-home use without onsite monitoring.
- **Billing Fraud:** Inappropriate billing for ketamine services, including lack of compliance with documentation standards and coding guidelines, leading to payment retractions.

Yale's $1.5M Ketamine VA Settlement Spotlights Private-Public Partnership Complexities

Clinical Relevance: Ethics matter in publicly funded research

- Yale and one of its psychiatry professors settled a lawsuit with Veterans Affairs for $1.5 million over undisclosed ketamine patents.
- The settlement brings ethical questions about public-private research partnerships to the forefront.
- The case could set a precedent for transparency in managing publicly funded research.

‘Take Care of Maya’ trial: Doctor who prescribed ketamine treatments testifies in $220 million case

Dr. Bronner's settles lawsuit over employee's ketamine massage death

Dr. Bronner's employee, Denise Lozano, died after getting what her family says was a company-sponsored ketamine massage.

In January 2022, Dr. Bronner's became one of the first companies in the country to offer employees ketamine-assisted mental health therapy through its health benefits package.

"Let's face it, the world would be a far better place if more people experienced psychedelic medicines," said David Bronner, the company's CEO ("Cosmic Engagement Officer"), in a New York Times article about the ketamine therapy program.

But a wrongful death lawsuit filed in December alleges the company has also fostered a risky culture of drug use among some leaders and employees, claiming they routinely use potent psychedelics as an unregulated form of "healing" and for recreational purposes.

The complaint filed in San Diego County Superior Court was brought by the family of Denise Lozano, a former Dr. Bronner's employee who, in 2022, died of an accidental overdose at the age of 50.

"Denise's life was cut short unnecessarily, unjustifiably, and without the dignity that she had earned from the people she trusted and that proclaimed to love her the most, the Dr. Bronner's family," the lawsuit states.

SC Man Receives $45K Settlement Over Ketamine Incident

A Charleston County man has received a $45,000 settlement to his lawsuit alleging he suffered a serious health reaction to ketamine administered by medics.

According to *WSOC*, Randy Botton filed the lawsuit nearly three years ago, claiming he experienced acute respiratory failure after being injected with ketamine by Charleston County EMS in 2021. Botton was celebrating his upcoming wedding at Folly Beach when he fell and hit his head, prompting an ambulance response.

The lawsuit states that on the way to the hospital, medics pulled over after Botton allegedly became combative and injected him with 300 milligrams of ketamine, followed by another 200 milligrams about 15 minutes later.

- Ketamine Considerations for Prehospital Use

- Ketamine's Versatility Makes it a Powerful Tool for EMS
- Ketamine May Aid in Prehospital Management of Severe Asthma
- The EMS Handoff: Why Ketamine?
- CO Panel Issues Guidelines for Injecting Ketamine
- Ketamine Use in the Prehospital Settings Should Remain, Says National Association of EMS Physicians

The suit says medics had been informed Botton was intoxicated—information that should have raised concerns about mixing alcohol with ketamine.

Wrongful Death Lawsuit Filed after 2018 Ketamine Injection

November 8, 2022 JEMS Staff 1 MIN READ SHARE TO:

A Colorado family has filed a wrongful death lawsuit after a paramedic injected a woman with ketamine during an incident in 2018, according to a report.

Responders were called about a distressed person trespassing on private property in Colorado Springs on the night of Jan. 18, 2018, NBC News reported. They found 29-year-old Jerica LaCour lying on the ground and crying uncontrollably after she had been drinking.

The family's lawsuit claims a paramedic for AMR administered 400 milligrams of ketamine to LaCour despite objections from a firefighter-EMT also on scene. LaCour stopped breathing after being injected, the lawsuit alleges.

Last year, Colorado's health department announced that EMS providers should not use a condition involving erratic behavior as a reason to use ketamine. The announcement came two years after the fatal arrest of Elijah McClain.

‘Weaponization of medicine’: police use of ketamine draws scrutiny after Elijah McClain’s death

The sedative is used more often on Black people – and justified after the fact with questionable claims of ‘excited delirium’

String players perform during a vigil for Elijah McClain in New York City. McClain played the violin. Photograph: Byron Smith/Getty Images

In the summer of 2019, 23-year-old Elijah McClain was stopped by the Aurora, Colorado, police while walking home, after someone called 911 saying he looked suspicious.

The incident quickly turned violent, with three police officers piling on the 140lbMcClain, twice putting him in a chokehold that has since been banned. After vomiting, coming in and out of consciousness and pleading for breath, paramedics arrived and injected McClain with an excessive dose of ketamine, a powerful sedative.

A FORMER PARAMEDIC with the Emergency Medical Services in Woodbury, a suburb of St. Paul, Minnesota, has filed a whistleblower lawsuit claiming that police pressured him to administer ketamine, a fast-acting sedative, during an arrest. He claims that the incident is part of a larger trend among the region's law enforcement. The paramedic, 32-year-old Joseph Baker, said that he hopes to take a stand against police using ketamine "to gain compliance."

"It's not an appropriate use of our jobs as paramedics," he told The Intercept, in his first interview since the lawsuit was filed on August 17, in the District Court of Minnesota. In Woodbury, the police, EMS, and firefighters all collaborate as part of the city's Public Safety Department.