

Ketamine: An antidote for suicidal thoughts



Belgium, Circa 1960



Belgium, Circa 1960



Ketamine got its
start in Belgium in
the 1960s as an
anesthesia medicine
for animals

Vietnam, Circa 1970



Vietnam, Circa 1970



It was used in treating injured soldiers on the battlefields in the Vietnam War

Yale University, Circa 1980



Investigators
started giving
ketamine to healthy
individuals to
produce transient
symptoms of
schizophrenia

New York, Circa 1990



Emergency responders may give ketamine to an agitated patient who, they have rescued from a suicide attempt.

"Someone is trying to jump off a bridge and they give him ketamine in the ambulance to calm him down and 9 months later, he says, 'I haven't felt suicidal for 9 months.'

That's how doctors began to realize that the drug had powerful effects against depression and suicidal thoughts.

Can we really use ketamine for the treatment of depression?



Circa 2000 to 2013 Different parts of world

Antidepressant effects of ketamine in depressed patients

(Robert M Berman et al. Biological Psychiatry, 2000, 47 (4), 351-354)

- **Methods:** Seven subjects with major depression completed 2 test days that involved intravenous treatment with ketamine hydrochloride (0.5 mg/kg) or saline solutions under randomized, double-blind conditions.

Antidepressant effects of ketamine in depressed patients

(Robert M Berman et al. Biological Psychiatry, 2000, 47 (4), 351-354)

- **Results:** Subjects with depression evidenced significant improvement in depressive symptoms within 72 hours after ketamine but not placebo infusion.
- **Conclusions:** These results suggest a potential role for NMDA receptor-modulating drugs in the treatment of depression.

Two Case Studies of Patients with Major Depressive Disorder Given Low-Dose Ketamine Infusions.

(Correll GE and Futter GE. Pain Medicine. 2006, 7, 1)

- One patient had an 18 month history of depression unsuccessfully treated with Citalopram, Mirtazapine, Venlafaxine and ECT.
- She was given a 5 day course of Ketamine, IV, at 0.27 mg/kg/hr. Her BDI improved from 36 to 11 in four days and she remained well 12 months later on Citalopram 40 mg.

Two Case Studies of Patients with Major Depressive Disorder Given Low-Dose Ketamine Infusions.

(Correll GE and Futter GE. Pain Medicine. 2006, 7, 1)

- The second patient had a 16 year history of depression unsuccessfully treated with Fluoxetine, Nefazodone, Mirtazapine, Venlafaxine, Amisulpride, Lithium and ECT.
- He was given a 5 day course of Ketamine. IV, at 0.3 mg/kg/hr. His BDI improved from 52 to 9 in four days.
- He relapsed twice, after 2.5 months and 8.5 months and had two further 5-day infusions which were successful.
- At 12 months he remained well on Lithium 500mg/day.

A Randomized Trial of an N-methyl-D-aspartate Antagonist in Treatment-Resistant Major Depression.

(Carlos A. Zarate, et al. *Arch Gen Psychiatry*, 2006; 63: 856-864)

- A randomized, placebo-controlled, double-blind crossover study of 18 patients with treatment resistant major depression, given a single intravenous infusion of Ketamine 0.5 mg/kg over 40 minutes.
- 71% met response criteria the day following ketamine infusion as compared with 0% of subjects treated with placebo.

Intravenous ketamine therapy in a patient with a
treatment-resistant major depression.

(Michael Liebrenz et al. *Swiss Med Wkly* 2007;137:234-236)

- A 55-year-old male subject with a treatment-resistant major depression and a co-occurring alcohol and benzodiazepine dependence received an intravenous infusion of 0.5 mg/kg ketamine over a period of 50 minutes.
- Over the previous five years the subject had been treated with citalopram, paroxetine, mianserin, mirtazapine, venlafaxine, trimipramine, trazodone, and escitalopram.

Intravenous ketamine therapy in a patient with a
treatment-resistant major depression.

(Michael Liebrenz et al. *Swiss Med Wkly* 2007;137:234-236)

- Augmentation therapy had comprised methylphenidate, valproic acid, lithium, olanzapine, quetiapine, buspirone, and chlorprothixene.
- Throughout 2002 the subject had received cognitive behavioural therapy. All of these were tolerated well, but failed to achieve remission.
- After the ketamine infusion, his BDI improved from 26 to 9 in two days.

Serial infusions of low-dose ketamine for major depression.

(Rasmussen KG et al . J Psychopharmacol. 2013 May;27(5):444-50)

- Ten depressed patients were treated with twice weekly ketamine infusions of ketamine 0.5 mg/kg administered over 100 min until either remission was achieved or four infusions were given.
- Side effects were assessed with the Young Mania Rating Scale (YMRS) and the Brief Psychiatric Rating Scale (BPRS).
- Patients were followed naturalistically at weekly intervals for four weeks after completion of the infusions.

Serial infusions of low-dose ketamine for major depression.

(Rasmussen KG et al . J Psychopharmacol. 2013 May;27(5):444-50)

- Five of 10 patients achieved remission status. There were no significant increases on the BPRS or YMRS.
- Two of the remitting patients sustained their improvement throughout the four week follow-up period.
- Ketamine infusions at a lower rate than previously reported have demonstrated similar efficacy and excellent tolerability and may be more practically available for routine clinical care.
- Serial ketamine infusions appear to be more effective than a single infusion.
- Further research to test relapse prevention strategies with continuation ketamine infusions is indicated.

Intramuscular ketamine in acute depression: A report of two cases

Case 1: **India, Circa 2013**

- A 23/M, with OCD for 5 years on fluoxetine (40 mg) and bupropion (300 mg) attempted suicide by slashing his throat.
- His bupropion was hiked to 450 mg and fluoxetine to 60 mg. ECT was not considered in view of his ensuing exams.
- He was given Inj. ketamine (0.5 mg/kg) IM.
- He had no side-effects.

(Harihar C, Dasari P, Srinivas JS. Indian J Psychiatry 2013;55:186-8)

Intramuscular ketamine in acute depression: A report of two cases

Case 1: **India, Circa 2013**

- After 2 hours, his HDRS score dropped down from 21 to 4.
- Three days later, he received a similar dose.
- His HDRS scores dropped from 10 to 7 within 2 hours.
- During the subsequent weeks, the improvement was maintained, and suicidal thoughts never returned.
- He appeared in his examinations and did well to his satisfaction.

(Harihar C, Dasari P, Srinivas JS. Indian J Psychiatry 2013;55:186-8)

Intramuscular ketamine in acute depression: A report of two cases

Case-2

India, Circa 2013

- A 21/M suffering from recurrent depressive episodes since last 5 years, reported recent worsening of his symptoms along with suicidal ideas.
- He was on bupropion 450 mg and fluoxetine 20 mg.
- As he was not willing for ECT, he was taken up for ketamine.

(Harihar C, Dasari P, Srinivas JS. Indian J Psychiatry 2013;55:186-8)

Intramuscular ketamine in acute depression: A report of two cases

Case-2

India, Circa 2013

- A dose of 0.5 mg/kg of IM ketamine was given.
- After 2 hours, his HDRS score dropped from 21 to 6.
- He did not have any side effects.
- After 3 days, he was given a second dose of ketamine.
- After 2 hours, his HDRS dropped from 13 to 6.
- He reported nausea which subsided with oral domperidone.

(Harihar C, Dasari P, Srinivas JS. Indian J Psychiatry 2013;55:186-8)

2013

2013

Ketamine for Treatment
Resistant Depression & OCD



Ketamine for Treatment Resistant Depression & OCD

- 72 treatment-resistant patients with depression.
- Didn't have any improvements after trying at least three different biological treatments
- Were either given an intravenous infusion of ketamine for 40 minutes or an active placebo of midazolam,



Ketamine for Treatment Resistant Depression & OCD

- After 24 hours, 63.8 percent of the ketamine group had improved symptoms, compared to 28 percent of the placebo group.
- Seven days later, 45.7 percent of the ketamine group still had improved symptoms, compared to 18.2 percent of the placebo group.
- Neither group had any major side effects.



Ketamine for Treatment Resistant Depression & OCD

- A second trial in 15 patients diagnosed with obsessive-compulsive disorder (OCD), conducted at Columbia University in New York City, found that the drug was significantly superior to placebo (saline, in this case) in reducing OCD symptoms according to the Yale-Brown rating scale and patient self-assessments.
- Both studies were reported here at the American Psychiatric Association annual meeting.

Efficacy of single and repeated administration of ketamine in unipolar and bipolar depression: a meta-analysis of randomized clinical trials
Circa 2020
(Joanna Kryst et al. Pharmacol Rep. 2020 June)

- Our meta-analysis revealed rapid and robust antidepressant effects of single-dose ketamine in patients with treatment-resistant depression (TRD). By pooling data from RCTs, we showed for the first time that repeated ketamine administration is effective in sustaining initial antidepressant effects observed after single dosing.

Can we really use IV or Oral
Ketamine for the treatment of
Bipolar Depression?



Ketamine for Bipolar Depression: A Systematic Review

(Anees Bahji, Carlos A Zarate, Jr, and Gustavo H Vazquez, Int J Neuropsychopharmacol. 2021 Jul; 24(7): 535-541.)

- We identified 6 studies, with 135 participants (Circa 2021)
- All studies used 0.5 mg/kg of add-on intravenous racemic ketamine, with the number of doses ranging from 1 to 6; All participants continued a mood-stabilizing agent.
- The overall proportion achieving a response (defined as those having a reduction in their baseline depression severity of at least 50%) was 61% for those receiving ketamine and 5% for those receiving a placebo.

Ketamine for Bipolar Depression: A Systematic Review

(Anees Bahji, Carlos A Zarate, Jr, and Gustavo H Vazquez, Int J Neuropsychopharmacol. 2021 Jul; 24(7): 535-541.)

- The overall response rates varied from 52% to 80% across studies.
- Ketamine was reasonably well tolerated; however, 2 participants (1 receiving ketamine and 1 receiving placebo) developed manic symptoms.
- Some participants developed significant dissociative symptoms at the 40-minute mark following ketamine infusion in 2 trials.

Oral Ketamine for Unipolar and Bipolar Depression

- 42-year-female, a case of bipolar mood disorder
- Was on Lithium, Lamotrigine, and Escitalopram
- Presented with severe depression and suicidal ideations
- Mirtazapine (15 mg) at bedtime was added
- Was a bit reluctant for ECT
- Was willing to try out Ketamine, so was started on oral ketamine therapy

Continue 2 ...

Oral Ketamine for Bipolar Depression

- Gradually drank 2 ml of ketamine (100 mg) mixed in 300 ml of juice over a period of 45 minutes. (Pulse and BP were monitored at baseline and after 15, 30, and 45 minutes)
- Felt immediate relief in depressive symptoms and suicidal ideations
- Therapy was continued - 3 times a week for first two weeks, then twice a week for next two weeks and then once a week for next two weeks.
- The improvement was maintained

Ketamine as an anesthetic agent for ECT



Antidepressant Effect of Ketamine During ECT

(Ostroff et al. Am J Psychiatry 162 (7): 1385. July 2005)

- An opportunistic case report of a woman with severe treatment-resistant depression who was referred for ECT shortly after ceasing anti-epileptic drugs.
- She was given ketamine as an anaesthetic for the ECT, but failed to have a convulsion, on two occasions.
- In spite of this she experienced an immediate and unexpected improvement in her mood both times.

Rapid antidepressant effect of ketamine anaesthesia during electroconvulsive therapy of treatment-resistant depression: comparing ketamine and propofol anaesthesia.

(Okamoto N et al J ECT. 2010 Sep;26(3):223-7)

- 31 inpatients with treatment-resistant depression.
- An anaesthesiologist who was unaware of the mental symptoms of the subjects assigned them to receive propofol or ketamine anaesthetic according to the preferences of the patients, and the patients underwent 8 ECT sessions for 4 weeks.

Rapid antidepressant effect of ketamine anesthesia during electroconvulsive therapy of treatment-resistant depression : comparing ketamine and propofol anesthesia.

(Okamoto N et al J ECT. 2010 Sep;26(3):223-7)

- The HDRS scores improved earlier in the ketamine group, with decreases in HDRS scores that were significantly greater in the ketamine group.
- The results suggested that it is possible to improve symptoms of depression earlier by using ketamine anaesthesia.

Safety and Tolerability



Targeting the glutamatergic system to develop
novel, improved therapeutics for mood disorders

(Sanacora et al, Nat Rev Drug Discov. 2008 May; 7(5): 426-437)

- Clinically, ketamine is a popular agent for emergency department procedural sedation in children, with ample evidence to support its safety and efficacy.
- Although its psychotomimetic side effects have led to its misuse and abuse, there is no evidence that ketamine causes physical dependence in humans.

Targeting the glutamatergic system to develop
novel, improved therapeutics for mood disorders

(Sanacora et al, Nat Rev Drug Discov. 2008 May; 7(5): 426-437)

- In addition, recent studies found no evidence that repeated, albeit limited (typically less than four exposures), exposure to ketamine increases the risk of more severe or more protracted psychosis, perceptual changes resembling dissociation, severe emotional distress or euphoria in healthy subjects or in patient populations.

Psychiatric safety of ketamine in psychopharmacology research

(Edward P et al Psychopharmacology, 2007, 192 (2), 253-260)

- 450 subjects received at least one dose of active ketamine.
- In 833 subjects active ketamine and 621 placebo infusions were administered.
- 10 adverse mental status events were documented in 9 (2%) subjects that were deemed related to ketamine administration.
- All but one adverse reaction resolved by the end of the test session.

Ketamine

India, Circa 2023

- Some psychiatrists are already using ketamine (IV, IM, SC, Orally, Intranasally) for selected patients.
- Doctors can do this legally because ketamine is an FDA approved anaesthetic drug.
- The rapid short-term benefits in suicidal patients and benefit in treatment resistant depression might outweigh the risks associated with its use.

A Member of Ketamine Fan Club

SIGNING OFF



Thank You

A Member of Ketamine Fan Club

