KETAMINE:
NEW FRONTIERS IN PHARMACOTHERAPY

C. SCOTT JENNISCH, MD
IOWA PSYCHIATRY, LLC
MANAGING PARTNER

DISCLOSURES:

SPEAKERS BUREAU: SUNOVION, ALLERGAN, TAKEDA, LUNDBECK/OTSUKA
PARTIAL OWNERSHIP, IOWA KETAMINE CLINIC, LLC
OBJECTIVES:

WHY DO WE NEED MORE TREATMENT OPTIONS?

REVIEW THE HISTORY OF KETAMINE

CLINICAL APPLICATION – INFORMATION TO USE ON MONDAY

RISKS PROFILE AND REASONS FOR CAUTION

EXPERIENCE AT IOWA KETAMINE CLINIC, LLC

WHAT DOES THE FUTURE HOLD?

TO NOT EMBARRASS MYSELF IN FRONT OF DR. CORYELL

THE NEED FOR MORE TREATMENT OPTIONS

STAR*D data1 – cumulative remission rate of 67%

Onset of action/time to remission with current treatments1

Suicide rates are rising2 – 1999-2016 increased:

Nationwide by 25%, Iowa by 36%

Depression is the leading cause of disability worldwide with an 18% increase

Effective treatment alters the course of illness1

End organ damage4,5,6,7 – hippocampus, information processing, genetic,

changes and inflammatory markers

HISTORY:

First developed in 1962 and was first approved for human use in the 1970s.

During the Vietnam War, ketamine was used as an anesthetic to help wounded soldiers.

In the late 1970s, use of ketamine began to rise. Marcia Mode wrote Journeys into the Bright World and John Lilly wrote The Scientist.

In the 1990s, ketamine began to be popularly abused in the club scene.

The most common way for people to get ketamine is through theft of legal, pharmaceutical or from bombing veterans' clinics.

In 1999, ketamine became a scheduled II controlled substance.
KETAMINE QUIZ

KETAMINE IS A SHORT ACTING MEDICATION?
TRUE OR FALSE?

KETAMINE IS ON THE WHO MODEL LIST OF ESSENTIAL MEDICATIONS?
TRUE OR FALSE?
KETAMINE WILL GIVE A FALSE POSITIVE FOR PCP ON A URINE DRUG SCREEN?
TRUE OR FALSE?

STREET NAMES FOR KETAMINE INCLUDE ALL OF THE FOLLOWING:
SPECIAL K, K, VITAMIN K, KIT KAT, CAT VALIUM, FIGHTING IRISH, AND K-HOLE?
TRUE OR FALSE?

KETAMINE IS A HORSE TRANQUILIZER?
TRUE OR FALSE?
MECHANISM OF ACTION:

- NMDA RECEPTOR ANTAGONIST
- G PROTEIN MIGRATION
- MAPK/ERK PATHWAY
- OPIOID SYSTEM ACTIVATION

3. Biological Psychiatry Jan 2018;83:2-4  

SIDE EFFECT PROFILE:

CARDIOVASCULAR: Blood pressure and pulse rate are frequently elevated following administration of ketamine hydrochloride alone. Premature, hypotension and bradycardia have been observed. Arrhythmia may also occur.

RESPIRATION: Although respiration is frequently stimulated, severe depression of respiration or apnea may occur following rapid intravenous administration of ketamine hydrochloride. Cardiorespiratory and other forms of anaphylactic reactions have occurred during ketamine hydrochloride administration. Epileptic seizures have been reported following ketamine hydrochloride administration. ECG changes may occur during ketamine hydrochloride administration. It may give rise to a cardiac arrhythmia.

EYE: Diplopia and nystagmus have been noted following ketamine hydrochloride administration. It may cause a slight elevation in intraocular pressure.

GENITOURINARY: Severe irritative and inflammatory urinary tract and bladder symptoms including cystitis have been reported in individuals with a history of chronic ketamine use or abuse.

PSYCHOLOGICAL: Hallucinations, derealization, deafferentation, dissociation, and altered consciousness may occur. Seizures, agitation, and anxiety may occur. Delusions may occur during ketamine administration. It may also cause a sense of floating or derealization.

NEUROLOGICAL: Insomnia, anxiety, and confusion have been observed. Cerebellar ataxia and tremor may occur. Disorientation, disinhibition, and disorientation may occur.

GASTROINTESTINAL: Anorexia, nausea, and vomiting may occur. Nausea and vomiting are common. Treatment of nausea and vomiting is necessary.

SYSTEMATIC ANALYSIS OF 60 PRIOR STUDIES ON THE USE OF KETAMINE TO TREAT DEPRESSION, WHICH INCLUDED 899 PATIENTS IN TOTAL.

THE MOST COMMON SIDE-EFFECTS WERE ANXIETY, HEADACHE, DISTRESS, DISASSOCIATION, ELEVATED BLOOD PRESSURE, AND BLURRED VISION. MOST SIDE-EFFECTS SPONTANEOUSLY RESOLVED SHORTLY AFTER KETAMINE WAS ADMINISTERED.

"Our findings suggest a selective reporting bias with limited assessment of long-term use and safety and after repeated dosing..."
**DOSING:**

**INDUCTION:**
- Ketamine 1–4.5 mg/kg IV
- Ketamine 3–9 mg/kg intranasal

**DEPRESSION:**
- Ketamine 0.5 mg/kg per 40 minutes IV\(^1\)
- Esketamine 28 mg, 56 mg, 84 mg intranasal\(^2\)

\(^1\) Int J Neuropsychopharmacol. 2016;19(4):pyv124
\(^2\) AMA Psychiatry. 2018;75(2):139-143

**KETAMINE INFUSION MDD:**

**DOUBLE-BLIND, PLACEBO-CONTROLLED TRIAL OF KETAMINE THERAPY IN TREATMENT-RESISTANT DEPRESSION:**

**PRIMARY OBJECTIVE** is to investigate whether all doses (0.1 mg/kg, 0.2 mg/kg, 0.5 mg/kg, and 1.0 mg/kg) of ketamine are superior to active placebo (midazolam 0.045 mg/kg) therapy in the acute treatment of patients with treatment resistant depression within 72 hours (Day 3), when added to ongoing and stable antidepressant therapy. (N=99)

ClinicalTrials.gov Identifier: NCT01920555 / Maurizio Fava, MD, Massachusetts General Hospital
KETAMINE INFUSION MDD:

RESULTS:
GROUPS: ALL GROUPS
STATISTICAL TEST TYPE: SUPERIORITY
STATISTICAL METHOD: MIXED MODELS ANALYSIS
P VALUE: <0.01
MEAN DIFFERENCE (FINAL VALUES): -4.79
95% CONFIDENCE INTERVAL: -7.35 to -2.24

KETAMINE INFUSION MDD:

KETAMINE AUGMENTATION FOR OUTPATIENTS WITH TREATMENT-RESISTANT DEPRESSION: PRELIMINARY EVIDENCE FOR TWO-STEP INTRAVENOUS DOSE ESCALATION.
FOURTEEN PATIENTS WITH TREATMENT-RESISTANT DEPRESSION WERE ELIGIBLE TO RECEIVE AUGMENTATION WITH SIX OPEN-LABEL INTRAVENOUS KETAMINE INFUSIONS OVER 3 WEEKS. FOR THE FIRST THREE INFUSIONS, KETAMINE WAS ADMINISTERED AT A DOSE OF 0.5 mg/kg OVER 45 MINUTES; THE DOSE WAS INCREASED TO 0.75 mg/kg OVER 45 MINUTES FOR THE SUBSEQUENT THREE INFUSIONS. THE PRIMARY OUTCOME MEASURE WAS RESPONSE AS MEASURED ON HAMILTON DEPRESSION RATING SCALE-28 (HDSS).
AFTER THE COMPLETION OF THREE KETAMINE INFUSIONS, 7.1% (1/14) RESPONDED; AFTER ALL SIX KETAMINE INFUSIONS, 41.7% (5/12) COMPLETERS RESPONDED AND 16.7% (2/12) REMITTED. INTENT-TO-TREAT RESPONSE AND REMISSION RATES AT THE END OF THE FINAL INFUSION WERE 35.7% (5/14) AND 14.3% (2/14). HOWEVER, ALL BUT ONE RESPONDER RELAPSED WITHIN 2 WEEKS AFTER THE FINAL INFUSION.
REPEATED, ESCALATING DOSES OF INTRAVENOUS KETAMINE AUGMENTATION WERE PRELIMINARILY FOUND TO BE FEASIBLE, EFFICACIOUS AND WELL TOLERATED.

KETAMINE INFUSION MDD:

SINGLE-DOSE INFUSION KETAMINE AND NON-KETAMINE N-METHYL-D-ASPARTATE RECEPTOR ANTAGONISTS FOR UNIPOLAR AND BIPOLAR DEPRESSION: A META-ANALYSIS OF EFFICACY, SAFETY AND TIME TRAJECTORIES.
NINE RCT, KETAMINE STUDIES: N = 234. KETAMINE REDUCED DEPRESSION SIGNIFICANTLY MORE THAN PLACEBO/PLACEDOSE PLACEDOSE BEGINNING AT 40 MIN, PEAKING AT DAY (95% CI -1.28 to -0.73, P<0.001), AND LOSING SUPERIORITY BY DAYS 10-12.
COMPARED WITH PLACEBO/PLACEDOSE PLACEDOSE, KETAMINE Led TO SIGNIFICANTLY GREATER RESPONSE (40 MIN TO DAY 7) AND REMISSION (80 MIN TO DAYS 3-5).
ALL-CAUSE DISCONTINUATION WAS SIMILAR BETWEEN KETAMINE (P = 0.34) AND PLACEDOSE. ALTHOUGH SOME ADVERSE EFFECTS WERE MORE COMMON WITH KETAMINE THAN PLACEDOSE, THESE WERE TRANSIENT AND CLINICALLY INSIGNIFICANT.
KETAMINE INFUSION MDD:

Systematic review of seven trials compared ketamine with a control in 172 patients with unipolar or bipolar major depression. A single dose of ketamine (0.5 mg/kg) or the control was administered intravenously (six trials) or intranasally (one trial). Response at multiple posttreatment time points occurred in more patients who received ketamine than the control:

- Two hours – 51% versus 2% of patients
- One day – 53% versus 7%
- Seven days – 31% versus 7%

By day 14, response was present in only 11 percent of the patients who received ketamine.


ELECTROCONVULSIVE THERAPY:

Significant treatment effect of add-on ketamine anesthesia: electroconvulsive therapy in depressive patients. A meta-analysis1

16 studies with 346 patients/329 controls. Antidepressant treatment effect of add-on ketamine significantly higher than other anesthetics (P<0.001). Significance persisted at 1–2 weeks and 3–4 weeks. Side effect profiles and recovery rate significantly worse than control group (P<0.05).

Ketamine in electroconvulsive therapy for depressive disorder: a systematic review and meta-analysis2

16 studies including 938 patients. Ketamine and ECT showed no better response and remission rates with increased adverse events, including cardiovascular and psychiatric symptoms.


ELECTROCONVULSIVE THERAPY:

Rapid antidepressant effects of repeated doses of ketamine compared with electroconvulsive therapy

Blind, randomized study, 18 patients were divided into two groups which received either three intravenous infusions of ketamine hydrochloride (0.5 mg/kg over 45 min) or ECT on 3 test days (every 48 h). The primary outcome measure was the Beck Depression Inventory and Hamilton Depression Rating Scale, which was used to rate overall depressive symptoms at baseline, 24 h after each treatment, 24 h and one week after the last (third) ketamine or ECT. Ketamine (0.5 mg/kg, intravenous infusions) significantly improved in subjects receiving the first dose of ketamine compared with the ECT group. This antidepressant advantage significantly disappeared at the second ECT. Depression symptoms after the second dose ketamine were also lower than the second ECT, ketamine being as effective as ECT in improving depressive symptoms at 24 h, and having lower rate of antidepressant effects compared with the ECT.

OTHER PSYCHIATRIC CONSIDERATIONS:

- Bipolar Affective Disorder
- Suicidal Ideation
- OCD
- PTSD
- GAD/Social Anxiety Disorder
- Hospice Care
- Chemical Dependency
- Traumatic Brain Injury, Autism Spectrum Disorder, Eating Disorders

SUICIDAL IDEATION:

Ketamine may be useful for short-term treatment of suicidal ideation. A meta-analysis of patient-level data from eight randomized trials compared a single intravenous infusion of ketamine (0.5 mg/kg) with a control condition in 167 patients with active or passive suicidal ideation at study entry. Most of the patients were diagnosed with unipolar major depression (77 percent); other diagnoses included bipolar disorder and posttraumatic stress disorder. Approximately 60 percent of patients were concurrently treated with psychotropic medications. Greater improvement with ketamine began within one day of treatment, and resolution of suicidal ideation by day seven occurred in more patients who received ketamine than controls (60% versus 32%).


CHILD/ADOLESCENT:

Intranasal ketamine in pediatric bipolar disorder with the fear of harm phenotype: A retrospective chart review of 12 treatment-refractory youth – ages 6-19. Substantial reduction in mania, fear of harm, aggression, depression, anxiety, behavioral symptoms, attention/executive function, and sleep problems. The medication was well tolerated.

Clinical experience using intranasal ketamine in the longitudinal treatment of juvenile bipolar disorder with the fear of harm phenotype: A retrospective chart review of 12 patients (6-18 years), nearly all patients had a marked reduction in CGI rated as “much” or “very much” improved with minimal adverse events that decreased over time without loss of benefit.

Intravenous ketamine for adolescents with treatment-resistant depression: An open-label study. 13 participants aged 14-18 received 6 IV ketamine treatments (0.5 mg/kg) over two weeks. Four responders. Three suicides occurred within six weeks. Increase in patient and treatment monitoring.

PREDICTORS OF KETAMINE RESPONSE:

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sociodemographic</td>
<td>None</td>
</tr>
<tr>
<td>Clinical</td>
<td>Family history of alcohol disorder in a first-degree relative (FH)</td>
</tr>
<tr>
<td></td>
<td>Lucksenbaugh et al. 2012 [18]. MDD and BD (N = 33)</td>
</tr>
<tr>
<td></td>
<td>Nicu et al. 2014 [19]. MDD (N = 52)</td>
</tr>
<tr>
<td></td>
<td>High BMI</td>
</tr>
<tr>
<td></td>
<td>No prior suicide history</td>
</tr>
<tr>
<td>Peripheral biochemistry</td>
<td>Low baseline adiponectin levels</td>
</tr>
<tr>
<td></td>
<td>High baseline peripheral B12 levels</td>
</tr>
<tr>
<td>Neurochemistry</td>
<td>Low baseline delta sleep ratio</td>
</tr>
<tr>
<td></td>
<td>Low Glx/Glutamate ratio</td>
</tr>
<tr>
<td>Cognition</td>
<td>Poor baseline neurocognitive score</td>
</tr>
</tbody>
</table>

CONTRAINDICATIONS:

- Active psychotic symptoms, manic symptoms, or a history of a primary psychotic disorder
- Uncontrolled hypertension
- Pregnancy - relative
- History of ketamine abuse or dependence
- History of severe, ongoing alcohol or substance abuse or dependence
- Known hypersensitivity to ketamine or its components

IOWA KETAMINE CLINIC, LLC:

- One of two ketamine clinics in the state of Iowa
- Opened in September 2017
- Treatment for psychiatric conditions – no pain management
- Approximately 75 patients treated to date
- Response rate 75% in MDD (PHQ-9, -15) (GAD-7, -10.5)
- Maintenance treatment 20% in MDD
ESKETAMINE:

ALSO KNOWN AS (S)-KETAMINE, KETANEST AND KETANEST S, AN ENANTIOMER OF KETAMINE
INTRODUCED IN GERMANY IN 1997
JOHNSON & JOHNSON/JANSSEN DEVELOPED A NASAL SPRAY FORMULATION FOR MDD
BREAKTHROUGH DESIGNATION FROM THE FDA FOR TREATMENT RESISTANT DEPRESSION AND MDD WITH SUICIDAL IDEATION
ONGOING PHASE III CLINICAL TRIALS

ESKETAMINE NASAL SPRAY - AUGMENTATION:

ADULTS WITH TREATMENT RESISTANT DEPRESSION (TRD) – 28 DAYS
RESPONSE TO ESKETAMINE 69%, PLACEBO 52%
RELAPSE PREVENTION IN ADULTS WITH TRD IN REMISSION AFTER 16 WEEKS
51% LOWER RISK OF RELAPSE (27% RELAPSE IN GROUP, 45% PLACEBO RELAPSE)
LONG-TERM SAFETY STUDY:
TREATMENT EMERGENT ADVERSE EVENTS – DIZZINESS (33%), DISSOCIATION (27%),NAUSEA (25%), HEADACHE (25%), DROWSINESS (17%), 6.9% RATE OF TEAE
ELDERLY
MADRS CHANGE NOT STATISTICALLY SIGNIFICANT

ESKETAMINE NASAL SPRAY - AUGMENTATION:

Efficacy and Safety of Intranasal EKetamine Adjunctive to Oral Antidepressant Therapy in Treatment-Resistant Depression: A Randomized Clinical Trial

JAMA Psychiatry. 2018;75(2):139

Efficacy and Safety of Intranasal EKetamine Adjunctive to Oral Antidepressant Therapy in Treatment-Resistant Depression: A Randomized Clinical Trial

Efficacy and Safety of Intranasal EKetamine Adjunctive to Oral Antidepressant Therapy in Treatment-Resistant Depression: A Randomized Clinical Trial

ESKETAMINE NASAL SPRAY - AUGMENTATION:

Efficacy and Safety of Intranasal EKetamine Adjunctive to Oral Antidepressant Therapy in Treatment-Resistant Depression: A Randomized Clinical Trial

JAMA Psychiatry. 2018;75(2):139
REASON FOR CAUTION:

- Vulnerable patient population
- Safety profile of long term use unknown
- Considered experimental/off label
- Potential for abuse

FUTURE DEVELOPMENTS:

- Esketamine
- Rapastinel
- Brexanolone/Sage – 217
- ALKS-5461 – Buprenorphine 2 mg / Samidorphan 2 mg
- Psychedelics - psilocybin

SUMMARY:

- Unmet need abounds
- We can do better
- Ketamine has much promise...
- But there is much we do not know
- Future developments are promising
- We have hope to offer our patients
THANK YOU!

QUESTIONS?

"And how do I tell me I'm waiting over a gunshot hell?"