Ketamine: Menace, Pancea, or Window in Time

Ryan Shackelford, MD

*Bicycle Day, Blomerth 2019
Ketamine is NOT a Psychedelic!!??

Slide Coming
Ketamine Assisted Psychotherapy

WHY?

WHAT?

WHY?
Let everything happen to you:
Beauty and terror
Just keep going
No feeling is final.

Rainer Maria Rilke
**Table 1. Adverse Events With the Use of Ketamine to Treat Depression**

- Transient elevations in blood pressure and pulse (some requiring administration of antihypertensives)
- Increased anxiety
- Increased psychotic symptoms
- Feeling drowsy or sleepy
- Dizziness or faintness
- Poor coordination or unsteadiness
- Dizziness when standing up
- Blurred vision
- Feeling strange or unreal
- Abnormal sensations
- Slurred speech
- Headache
- Dry mouth
- Trouble concentrating
- Numbness or tingling
- Diminished mental capacity

*Source: Reference 24.*
Ketamine Mechanism of Actions

• **NMDA Non-competitive Receptor Antagonist**
• **Anti-Nociceptive:** NMDA antagonism blocks opioid hyperalgesia
• **Anti-inflammatory:** reduces pro-inflammatory mediators
• **Anti-depressant:** increased synaptic plasticity
How Ketamine Reduces Depression

- NMDA Receptor mediated inhibition of GABA interneurons ➔ reduced inhibitory control over prefrontal glutamate neurons and glutamate burst.

- Prefrontal glutamate burst = dissociation

- Depression/Anti-Suicidal properties emerge rapidly but peak and persist long after dissociation has resolved.
Plasticity

- Brain Derived Neurotrophic Factor drives growth of interneuron dendrites and soma - structural plasticity

- Glutamate transmission promotes BDNF synthesis and release in frontocortical-hippocampal and mesocorticolimbic dopaminergic pyramidal interneurons.

- Connectivity of the Default Mode Network
Safety

- **6,630 cases**, subanesthetic dose by a psychiatrist, **zero** MSAE (Feifel, 2020)

- **883 cases**, procedural sedation, **1** case of laryngospasm (Bellolio, 2016)

- **70,000** ER cases, procedural sedation, **1** case of acute cardiac event (Strayer, 2008)
Safety

- 2017 JAMA Guidelines recommend ACLS trained staff and equipment
- Acute cardiac (MI, CVA, BP event) or respiratory (laryngospasm) events
- Reviewed 91 studies, 2 studies reported serious medical adverse event (MSAE)
- 3,575 cases, 4 total serious adverse medical events (Hovda, 2022)
# Incidence of Medical Serious Adverse Events

## Table 1

<table>
<thead>
<tr>
<th># Who Received Ketamine</th>
<th>Total MSAE's:</th>
<th>Incidence (as a %) of MSAEs</th>
<th>Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total</strong></td>
<td>3575</td>
<td>4</td>
<td>0.1118881119</td>
</tr>
<tr>
<td><strong>Racemic</strong></td>
<td>1975</td>
<td>1</td>
<td>0.05063291139</td>
</tr>
<tr>
<td><strong>Esketamine</strong></td>
<td>1600</td>
<td>3</td>
<td>0.1875</td>
</tr>
<tr>
<td><strong>Arketamine</strong></td>
<td>19</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
## Description of MSAE’s

<table>
<thead>
<tr>
<th>Route</th>
<th>Dose</th>
<th># MSAEs</th>
<th>MSAE description</th>
</tr>
</thead>
<tbody>
<tr>
<td>IV 40 min infusion</td>
<td>0.5mg/kg racemic</td>
<td>1</td>
<td>1. <strong>Hypotension</strong> (BP 73/40 for 1 minute) and <strong>bradycardia</strong> (HR &lt;30 bpm for 30 seconds, followed by spontaneous recovery), likely secondary to vasovagal episode during venipuncture. No further intervention required.</td>
</tr>
</tbody>
</table>
| IN                 | 54mg or 84mg Esketamine     | 3       | 1. **Autonomic nervous system imbalance** with blood pressure fluctuations (range 50/30 to 140/100 mm HG) over approximately 33 minutes, resolved without intervention or sequelae.  
2. **Generalized muscle rigidity and loss of consciousness** with no response to painful stimuli in setting of elevated blood pressure (200/130), treated with PO captopril, IM furosemide, and IV fluids and resolved without sequelae.  
3. **Hypothermia** to 92.3 degrees Fahrenheit, warmed and discharged from ED |
History of Ketamine

- 1950’s discovery of PCP
- 1962 discovery of Ketamine
- 1964 tested on “volunteer” prisoners describing a dissociative phenomenon
- 60-70’s expanded use as dissociative anesthetic with analgesia as well as field anesthetic in Vietnam
- 70’s expanded experimental use in counterculture led to fears of psychedelics
- 80’s abuse in veterans and as a rave drug
- 80/90’s supplanted by propofol and others due to psychotomimetic concerns
- 1999 Ketamine classified as a schedule 3 substance US Controlled Sub Act
- Early 2000’s re-emergence interest in treating depression (J H Krystal group Yale)

https://journals.lww.com/ejanaesthesiology/fulltext/2017/09000/history_of_anaesthesia__the_ketamine_story__past,.2.aspx
# Ketamine vs Ketamine Assisted Therapy

<table>
<thead>
<tr>
<th></th>
<th>Ketamine/Esketamine</th>
<th>Ketamine Assisted Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Route</strong></td>
<td>Typically IV or *IN (Spravato)</td>
<td>Typically IM or PO</td>
</tr>
<tr>
<td><strong>Dose</strong></td>
<td>IV 0.5mg/kg over 40min; 28mg</td>
<td>Low (psycholytic)/High (transformative)</td>
</tr>
<tr>
<td><strong>Schedule</strong></td>
<td>6x in first 2 weeks then tapering</td>
<td>After 2-3 integration sessions</td>
</tr>
<tr>
<td><strong>Goal</strong></td>
<td>Indicated for treatment of MDD, experimental data support treatment of other conditions</td>
<td>Off-label treatment, goal is successful psychotherapy treatment</td>
</tr>
<tr>
<td></td>
<td>*Only FDA approved treatment</td>
<td></td>
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</tbody>
</table>
History of Ketamine Assisted Psychotherapy

Phil Wolfson, MD

Salvador Roquet, MD

Evgeny Krupitsky, MD PhD
Ketamine Assisted Psychotherapy

WHY?
How Effective Are We?

- SSRI’s Mean Weighted Effect Size for Depression = 0.31 - 0.41 (Turner, 2008)

- CBT (0.68), Psychodynamic Psychotherapy (0.86), ISTDP (0.97) (Shedler, 2010)

- Drop out rates 40-50% (Wierzbicki, 1993)

- Relapse rates of 35-70% (Wiborg, 1996)

Just Stop It!
Fortress of Solitude
Person of the Therapist

• <50% of therapists report a sense of mastery.

• 76% of therapists report lacking skill and confidence in 3 crucial areas:
  • Engaging patients to be actively involved
  • Understanding the therapy process moment to moment
  • Knowing how and when to employ specific techniques for specific problems

• Drop out rates vary substantially between therapists

• Regardless of how they do it, effective therapists do the same things

(Orlinsky and Ronnestad, 2005)
Neurobiology of Attachment

• Age 0-1: primary task is creation of a secure attachment bond of emotional communication.

• The Primary Caregiver “co-regulates” the infants ANS/Emotions - "affective communication embedded in emotional gaze episodes; psychobiologically attuned caregiver appraises non-verbal expressions of arousal and regulates affective states - both negative and positive."

(Schore, 2011)
Neurobiology of Attachment

• Affective Attunement/Harmony is “a balance between being responsive and allowing independence as well as repair or re-engagement when mis-attunement happens”. DW’s The Good Enough Mother.

• Ideally, eventually the infant gains self-regulatory capacity but “the extent that they can tolerate their emotions w/o undue physiologic arousal will determine the need for level of defense mechanism protection.”

(Schore, 2011)
TRIANGLE OF CONFLICT

Symptom Reduction

Beginning of Treatment

End of Treatment

Character Change

Feelings

Anxiety Rises

Defense Response

Defense

Anxiety

Ask about Feelings
Why We Fail

- Inability to effectively handle resistance/defenses
- Inability to effectively mobilize will/UTA
- Inability to effectively help patient identify and regulate anxiety
- Inability to help patients link current difficulties with past unresolved conflicts
- Inability to identify and utilize conflict within ourselves
## Unconscious Alliance Vs Resistance

### Start of Treatment

<table>
<thead>
<tr>
<th>Resistance</th>
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<table>
<thead>
<tr>
<th>UTA</th>
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Unconscious Alliance Vs Resistance

Middle Phase of Treatment

<table>
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Breakthrough
Working Through Phase of Therapy
# Low vs High Dose Ketamine KAP

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<th>High Dose KAP</th>
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<tr>
<td><strong>Dose (IM)</strong></td>
<td>0.5mg/kg (20-50mg)</td>
<td>1.0mg/kg (60-120mg+)</td>
</tr>
<tr>
<td><strong>Patient Experience</strong></td>
<td>Lighter body, visuals, mild dissociation, stays in contact with body and therapist to some degree</td>
<td>More complete dissociation, may lose all contact to reality w/o ability to express, psychedelic, timelessness, ineffability</td>
</tr>
<tr>
<td><strong>Therapy</strong></td>
<td>More amenable to basic emotional processing and somatic therapies during acute phase and more complex processing immediately following</td>
<td>Supportive during acute phase then prompting and recording after - traditional guide.</td>
</tr>
<tr>
<td><strong>Pros</strong></td>
<td>Less highly defended and anxious but still capable of higher thought and processing</td>
<td>Transformative experience with deep connection to self/others</td>
</tr>
<tr>
<td><strong>Cons</strong></td>
<td>Highly resistant/syntonic defenses may not come down</td>
<td>High risk of medical complication or intense unpleasant experience</td>
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## MDMA vs KAP Protocols

<table>
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<tr>
<th>Protocol</th>
<th>Intake/Screening</th>
<th>Preparatory Sessions x 3</th>
<th>MDMA Session w/ overnight stay</th>
<th>Integration Sessions x 3</th>
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<td>MDMA Protocol (MAPP 1)</td>
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<tr>
<td>Ketamine Assisted Therapy Protocol - Sojourn Psychotherapy</td>
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- **MDMA Protocol (MAPP 1)**
  - Intake/Screening
  - Preparatory Sessions x 3
  - MDMA Session w/ overnight stay
  - Integration Sessions x 3

- **Ketamine Assisted Therapy Protocol - Sojourn Psychotherapy**
  - Trial Therapy/Screening
  - Therapy Sessions
  - KAP Session if necessary
  - Therapy Sessions
Management of Complications

• Avoid Complications with:
  • Properly establishing the Set and Setting
  • Screening for Contraindications
    • CV Risk Factors
    • Active Mania/Psychosis/SUD
    • Pregnancy
    • Previous history of anesthetic reactions

• Nausea - +/- pre-medicate with Zofran
• Agitation - Behavioral, Benzo (emergence), Haldol
• Hypertension/Hypotension - ACLS/911
• Laryngospasm - jaw thrust, bag mask, 911
Helpful Therapy Components

- Anxiety assessment and regulation
- Internal focus
- General therapeutic session focus
- Ritual (smudging, sound healing)
- Guided breathing/meditation
- Therapeutic playlist
- Somatic processing
Qualities of Successful MAP Therapists

• Skill and presence
• Empathic/active listening
• Non-directive approach (keep going!)
• An understanding and skill to make use of the Unconscious
• An awareness of self and ability to tolerate strong affect in self and other
• Facility in working with non-ordinary states/dissociative states
Keys to Mind Set

- Up front assessment of anxiety
- Free floating
- Signal anxiety
- Acknowledgment of unknown
- Acknowledgment of goal/purpose
- Ability to join people in a receptive state
Keys to Setting

- Physical Space
  - Home like
  - Quiet, private, safe
  - Connections to nature
- Music is critical
- Light sensitivity
- Mask promotes an inner journey focus
Menace?

Absolutely Not
Panacea?

Sadly, No
Case Report Example

- 70’s yo F w/ chronic depression/anxiety
- Internalized shame and aggression fueling self-attack, anxiety, depression, reactivity
  - KAP session 1 followed by reunification with son ➔ fantastic week w/ minimal depression (PHQ=3)
  - KAP session 2 followed by rejecting experience with spouse ➔ terrible week of depression (PHQ9 = 8)
- It provided an opportunity where she could tolerate her feelings and emotional closeness but it did not change her patterns of anxiety and defense around rejection... **only effective psychotherapy can do that.**
Ketamine is a Window
10. Schore, A. Science of the Art of Psychotherapy. 2011