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Psychiatry and Addictions Case Conference
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KETAMINE – THE GOOD AND THE BAD

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UW Medicine
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SPEAKER DISCLOSURES

✓ Any conflicts of interest? NO

Planner disclosures

The following series planners have no relevant conflicts of interest to disclose; other disclosures have been mitigated.

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OBJECTIVES

1. Discuss different types of ketamine
2. Identify therapeutic uses of ketamine
3. Engage the audience in an open discussion of the pros and cons of ketamine treatment in different settings

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KETAMINE IN PSYCHIATRY: THE BASICS

- Substantial effect on depression and suicidal ideation
- Comes in many forms only one of which is strictly regulated (Spravato – esketamine)
- Early RCTs demonstrated benefit from just one IVK infusion, the effect was temporary but extended if infusions were repeated
- Now, intramuscular, oral, subcutaneous, intranasal, and intravenous forms of ketamine are widely prescribed
- Best evidence exists for IVK (racemic ketamine) and esketamine (intranasal, Spravato)
- Oral treatment is widely available and often used – for depression and for chronic pain. Protocols are shared among those in the field.

IV KETAMINE FOR DEPRESSION: EVIDENCE BASE

- Review of 7 double blind placebo-controlled RCTs of ketamine usage in depression demonstrated a statistically significant improvement over placebo or midazolam in MDD and significant improvement over placebo in bipolar depression (Grady).
- *A single dose of ketamine, 0.5 mg/kg infused over 40 minutes produces a quick antidepressant response within 2-4 hours of administration and may reach the highest impact 24 hrs after infusion and last up to 7 days*. Ketamine's efficacy was not affected from day 1 through day 7, but bipolar patients only saw efficacy through day 4 (Romeo, Grady).
- In a midazolam-controlled RCT of IV ketamine for suicidal ideation in MDD in 80 patients, the Scale for Suicidal Ideation (SSI) at day 1 was reduced by 4.96 points (p=0.0003), sustained up to 6 weeks (Grunebaum)
- A meta-analysis of 36 studies with 2903 participants found that ketamine (racemic and esketamine) is associated with improved response (65%), remission (39%) and depression severity (78%) against placebo (Bahji)
- NNT is less than 10 (Calder)

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HOW ABOUT LONG-TERM?

- A systematic review of 2665 patients suggest substantial antidepressant effect though more treatment-resistant cases remit less often. Therapeutic effect doesn't decline with repeated treatments (Alnefeesi)
- A 4-year long retrospective study of 421 patients with TRD – initial 6 treatment course followed by maintenance as indicated – demonstrated improvement in depression (50% response, 20% remission) at 6 weeks, and better at 10 weeks (72% response, 38% remission), and 50% reduction in SI at 6 weeks (Oliver)
- A systematic review of 7 RCTs of esketamine v placebo was safe and more effective at decreasing depressive symptoms. Esketamine with antidepressant decreased the risk of relapse by 51% among stable remitters and 70% among stable responders, in long-term studies. (Jawad)
- A review of available maintenance treatment studies suggests continued benefit in many patients, with little evidence of harm. Better designed studies are needed. (Smith-Apeldoorn)
- Response rates are usually higher than remission rates – a recent meta-analysis found that remission with esketamine was questionable (Ouyang). So… most patients continue the treatment (with gradually reduced frequency).

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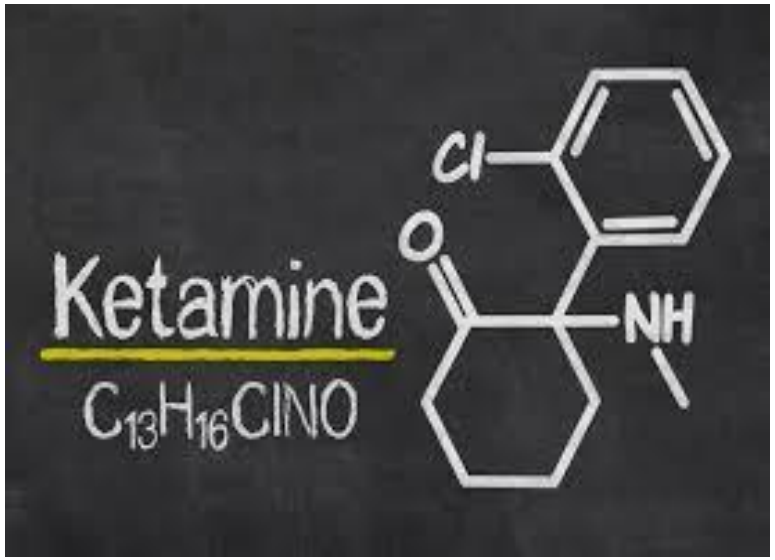
KETAMINE MECHANISM OF ACTION

- Phencyclidine derivative
- Opioid receptor agonist (indirect)
- Non-competitive NMDA receptor antagonist
- AMPA receptor agonist
- Dissociative anesthetic
- Sedative, hallucinogenic, antidepressant, drug of abuse
- Exerts antidepressant effect via neurotransmitter changes and intracellular signaling/neurotrophic factor modulation
- Increases levels of BDNF through modulation of eEF2 kinase



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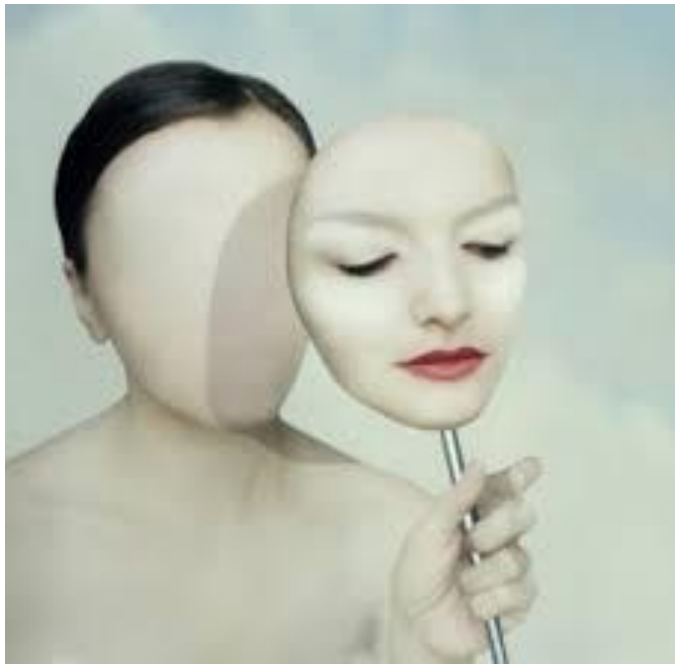
KETAMINE MECHANISM OF ACTION

- Ketamine reduces self-monitoring, increases emotional blunting (which reduces limbic responses to emotional stimuli)
- Most effects in subgenual ACC, PCC, PFC, and hippocampus
- Dissociation caused by reducing subgenual ACC blood flow disconnects “excessive effects of an aversive visceromotor state on cognition and the self”
- Ketamine shifts focus away from internal states of anxiety, depression, somatization, and more toward the perceptual changes induced by ketamine
- Ketamine increases neural activation in the bilateral cingulate cortices, insula, and right thalamus, activating reward processing areas



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COMMON SIDE EFFECTS WITH KETAMINE

- Increases HR and BP – these changes are transient and not clinically significant, usually
- Dissociation, derealization, perceptual changes are common
- Usually, pleasant changes in mood
- Sleepiness/fatigue after the treatment
- Rarely patients may experience more anxiety, dysphoria, exacerbation of suicidal ideation
- Other concerns have not come to pass with treatment within guidelines (cystitis, liver injury, cognitive impairment, psychosis, abuse, addiction)
- To be fair, data on cognition with ketamine treatment is still inconclusive (Vaccarino)
- Monitoring and support are essential to safe treatment no matter the formulation

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IVK AND SPRAVATO COMPARISON:

A SYSTEMATIC REVIEW OF 24 TRIALS WITH 1877 PARTICIPANTS SHOWED THAT RACEMIC KETAMINE RELATIVE TO ESKETAMINE DEMONSTRATED GREATER OVERALL RESPONSE AND REMISSION RATES WITH LOWER DROPOUTS (BAHJI)

IV Ketamine infusions

- Not FDA-approved, usually cash payment
- Most clinics in the area run by CRNAs or anesthesiologists
- Can be used for MDD, bipolar depression, PTSD, promising for substance abuse
- Initial course: 6 treatments, 2/week
- Usual improvement is after 1-3 treatments
- Dose can be increased from 0.5 to 1 mg/kg provided it's well-tolerated
- Infusion is 40 minutes
- Maintenance option exists
- No rules on combination with other antidepressants

Spravato (intranasal esketamine)

- FDA-approved, usually insurance covered
- Only used for MDD
- Initial course: 8 treatments, 2/week; then 1/week, then every 2 weeks once patients are ready.
- Usual improvement is after 4 treatments
- Dose is increased from 56 mg for 2 treatments to 84 mg for subsequent treatments
- Patients observed for 2 hours after self-administration
- Maintenance option exists and is once again covered by insurance
- Used to be required combined with an antidepressant; no longer; some insurance companies still require it.

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ORAL KETAMINE?

- Review of available evidence (4 RCTs, 1 case series, 6 case reports, 5 open-label trials, 6 retrospective chart reviews, 2336 pts with unipolar/bipolar depression) found it to be a promising treatment. Most studies were low quality.
- Difficult to compare dosing regimens – most started with 0.5 mg/kg but titrated up as tolerated (range was 0.25 to 1.5 mg/kg).
- Variable treatment schedules, from 1/week to 1/every 2 days to 3/day.
- Most studies report benefit, treatment is well-tolerated (Meshkat)

ORAL KETAMINE: PROS AND CONS

Pros:

- Cheaper
- More convenient, more accessible
- Can be very effective
- Fewer adverse events than IVK
- Longer duration of action – hours rather than minutes with IV.
- Recommendations for dosing vary greatly: 1:1 conversion from IV to PO recommended by U of Rochester, 2.0-2.5 mg/kg dosing recommended by Dr. Andrade
- Moderate doses tid advocated by Colorado Hospital Association for treatment of pain only while hospitalized

Cons

- Bioavailability is poor, 10-20%
- Potential for misuse and abuse
- Difficulty monitoring changes in HR/BP
- Managing hypertension and other side effects is a challenge over telehealth
- Insufficient data to determine the best regimen and dose
- Long-term use in addicted people can lead to dementia, bladder disease, liver failure
- Are there solutions to these practical considerations?

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SUBLINGUAL KETAMINE – A MORE RELIABLE ALTERNATIVE?

- Lucinda Grande MD from Lacey WA proposes a protocol for using SL ketamine for treatment of chronic pain and TRD
- Average dose is 60-120 mg but variability is substantial
- SL ketamine provides better absorption than oral, with bioavailability of 16%
- Patients usually dose daily, with the goal of achieving relief and avoiding dissociative symptoms
- *Many patients decrease the use of opioids they have been reliant on*
- A number of side effects and risks were described though to be fair, they seem less severe than the risks of opioid medications
- Dr. Grande speaks somewhat cavalierly of hallucinations occurring when doses are too high – “reducing the dose seems to take care of that”

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IM KETAMINE – AN (EASIER?) ALTERNATIVE TO IVK

- Bioavailability is somewhat less than IVK, metabolism may be different enough that dosing must be increased compared to IVK
- A retrospective study of 452 patients with MDD, GAD, PTSD from a private psychiatric clinic described dosing between 0.55 to 2.15 mg/kg (usual IVK dose would stop around 1-1.2 mg/kg)
- Median depression scores improved 38% and median anxiety scores improved 50%, median improvements maintained with continued treatment
- Median treatment number was 4 but ranged from 1 to 48 IM ketamine treatments
- Adverse events occurred in 2.3% of treatments, none severe (Ahuja)

SUBCUTANEOUS KETAMINE: NEXT OPTION?

- A small but well-designed multiple-crossover, double-blind study compared IV, IM, and SC administration of ketamine at doses from 0.1 to 0.5 mg/kg, at intervals of a week or longer
- 15 participants (all with TRD, some failing ECT, one also failing DBS), 12 responders. Bipolar d/o, schizophrenia were exclusions.
- All routes resulted in comparable efficacy for depression
- This study demonstrated similar plasma concentrations between IM, IV, SC routes – however IV treatment was only a 5-minute push rather than a 40-minute infusion.
- Subq route had fewest side effects (Loo)

OTHER USES OF KETAMINE: KAP

- In authors' own words, *"Depending upon dose, ketamine promotes a time-out from ordinary, usual mind, relief from negativity, and an openness to the expansiveness of mind with access to self in the larger sense. These effects enhance a patient's ability to engage in meaningful psychotherapy during and after administration. Ketamine is potent for respite, analysis, and meditative presence, and potent for recovery from depression and the lingering effects of trauma."*
- Using in-office ketamine in various forms (sublingual, oral, intranasal, intramuscular) to provide psychedelic-enhanced psychotherapy – where psychedelic effect is not a side effect but rather a desirable feature, to reach trance and transformation
- Sessions started with preparation for psychedelic experience, treatments with active medication, followed by integration. More sessions appeared to lead to better outcomes.
- Substantial effect on anxiety and depression reported in this study (BDI scores decreased by 11 points on average, HAM-A scores decreased by 5.5 points on average) (Dore et al).

IS THERE A RISK OF ADDICTION?

- Personally, I can attest to having had 2 patients who appeared to be dependent on ketamine (pathologically)
- However, I've also used ketamine for treatment of alcohol dependence (in conjunction with other treatments) - successfully
- A systematic review of literature that included up to 2174 patients only found a very small number of patients (4) to exhibit dependence on the drug (Ingrosso)

WHAT IF A PATIENT DOESN'T RESPOND TO KETAMINE?

- ECT, TMS, VNS, psychedelic research trials, medications, psychotherapy are still good options
- ECT is still the gold standard of treating TRD and has a more robust body of evidence in bipolar depression than ketamine
- Most people still haven't tried options like MAOIs, Auvelity, antipsychotic augmentation, lithium augmentation, etc.
- A recent review found that Li was better than esketamine with risk/benefit ratio 1.8 compared to esketamine 0.71 (Vazquez)
- Another interesting review found IVK to be equivalent to Li in terms of efficacy and acceptability, more so than esketamine or aripiprazole (Terao)