



UW PACC

Psychiatry and Addictions Case Conference

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INTRAVENOUS KETAMINE IN PSYCHIATRY

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GENERAL DISCLOSURES

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GENERAL DISCLOSURES

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SPEAKER DISCLOSURES

- ✓ No conflicts to disclose

PLANNER DISCLOSURES

The following series planners have no relevant conflicts of interest to disclose:

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OBJECTIVES

1. Participants will be able to describe the proposed mechanisms of actions of ketamine infusions in depressive disorders and other mental illness
2. Participants will be able to appreciate the evidence behind the use of ketamine infusions in treatment of severe major depressive disorder
3. Participants will be able to discuss the rationale behind the proposed dosing and administration recommendations for use of ketamine
4. Participants will understand limitations in the use of ketamine as well as potential side effects and risks associated with use of this medication for mental health indications

CASE EXAMPLE

- 36 yo veteran with life-long depression, history of childhood trauma and military service trauma, and severe alcohol use disorder, with chronic suicidal ideation, admitted to Psychiatry floor in March 2016 after a suicide attempt (hanging with wrist lacerations while intoxicated)
- Has had a total of 29 ECT sessions prior to that, ECT was helpful at first but effects tapered off, while causing cognitive side effects
- Several previous hospitalizations including long term detainment in 2012, at least 2 prior suicide attempts (cutting wrist, overdose)
- Has daily psychotherapy during hospitalization, treated with nortriptyline
- Has been on several medications previously (SSRIs, SNRIs, bupropion), feels they “never help enough to matter”
- Continues to endorse a plan to kill himself when he leaves the hospital

CASE EXAMPLE CONTINUED

This treatment occurred prior to the more standard ketamine treatment protocol was adapted at the VA Hospital.

Ketamine infusions initiated – 6 total, 1 on Friday followed by 5 more, qday the following week (Monday through Friday). Below is a record from the last treatment.

This is a repeat ketamine treatment for severe depression.

Pre-treatment : The patient expressed improvement in happiness for the duration of the day (post-treatment) yesterday and feels "normal" today. We did not discuss what "normal" means.

Ketamine bolus 0.1 mg/kg (7.5mg) was given IV (rt hand), followed by 0.2 mg/kg (15mg) over 30 minutes. Total of 22.5 mg was given.

The patient was awake, hemodynamically stable with BP 112-131/81-82 mm Hg, HR 100-106 bpm, Sats 99-100% during the whole treatment.

The patient was able to leave the hospital shortly after, with follow up at ATC and a strong recommendation to engage in DBT. He continued Antabuse. He continued to see his inpatient therapist for weekly individual psychotherapy for several months after discharge. 2 years later, he is described as “thriving,” has had no additional hospitalizations.

DEPRESSION MECHANISM

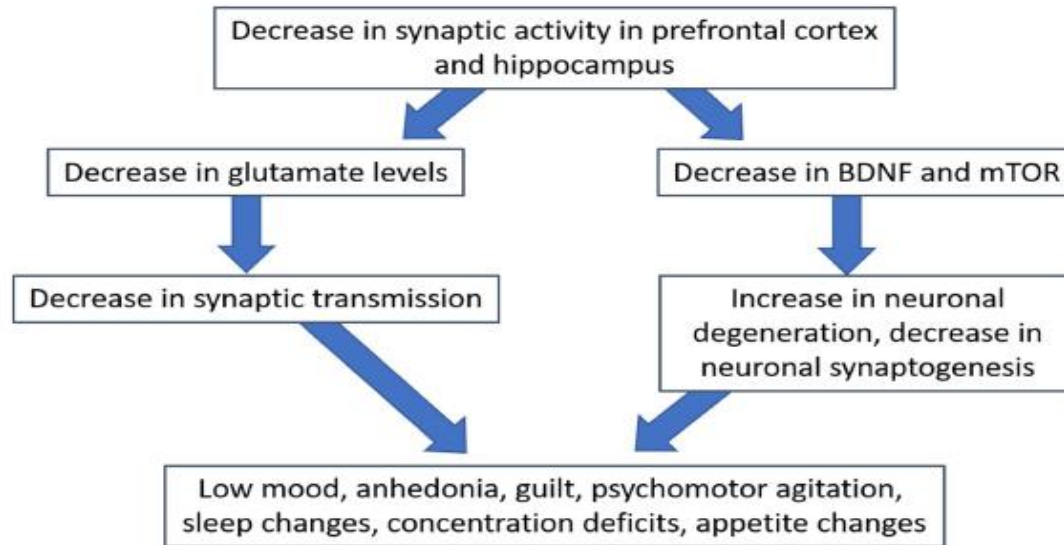


FIGURE 3: Proposed neurophysiology of treatment-resistant depression

Abbreviations: BDNF, brain-derived neurotrophic factor; mTOR, mechanistic target of rapamycin.

MECHANISMS OF KETAMINE ACTION

- Phencyclidine derivative
- Opioid receptor agonist
- 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 by decrease in eEF2 kinase activity, eEF2 dephosphorylation, and phosphorylation of adenosine monophosphate activated protein kinase



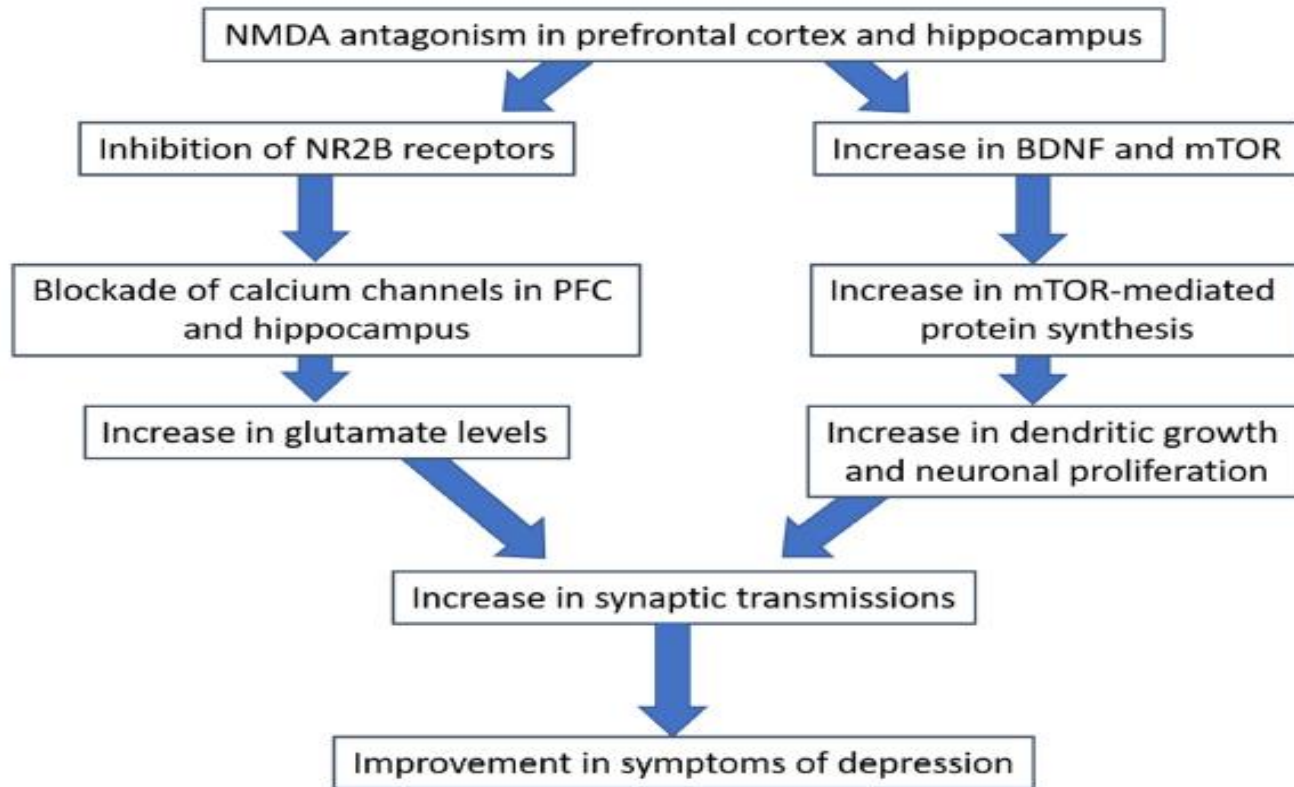


FIGURE 1: Proposed effect of NMDA antagonism on neurotransmission

Abbreviations: NMDA, N-methyl-D-aspartate; BDNF, brain-derived neurotrophic factor; mTOR, mechanistic target of rapamycin; PFC, prefrontal cortex.

KETAMINE MECHANISM OF ACTION

- Ketamine reduces brain activation in regions associated with 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



KETAMINE FOR DEPRESSION: EVIDENCE BASE

- Review of 7 double blind placebo-controlled RCTs of ketamine usage in depression demonstrates 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).
- A meta-analysis of 9 studies (226 patients with MDD and bipolar depression) confirmed ketamine's efficacy in MDD, bipolar depression, in drug-free and medication-treated patients (Fond)
- “Using ketamine may be helpful for patients that have exhausted other therapeutic options.” (Grady)

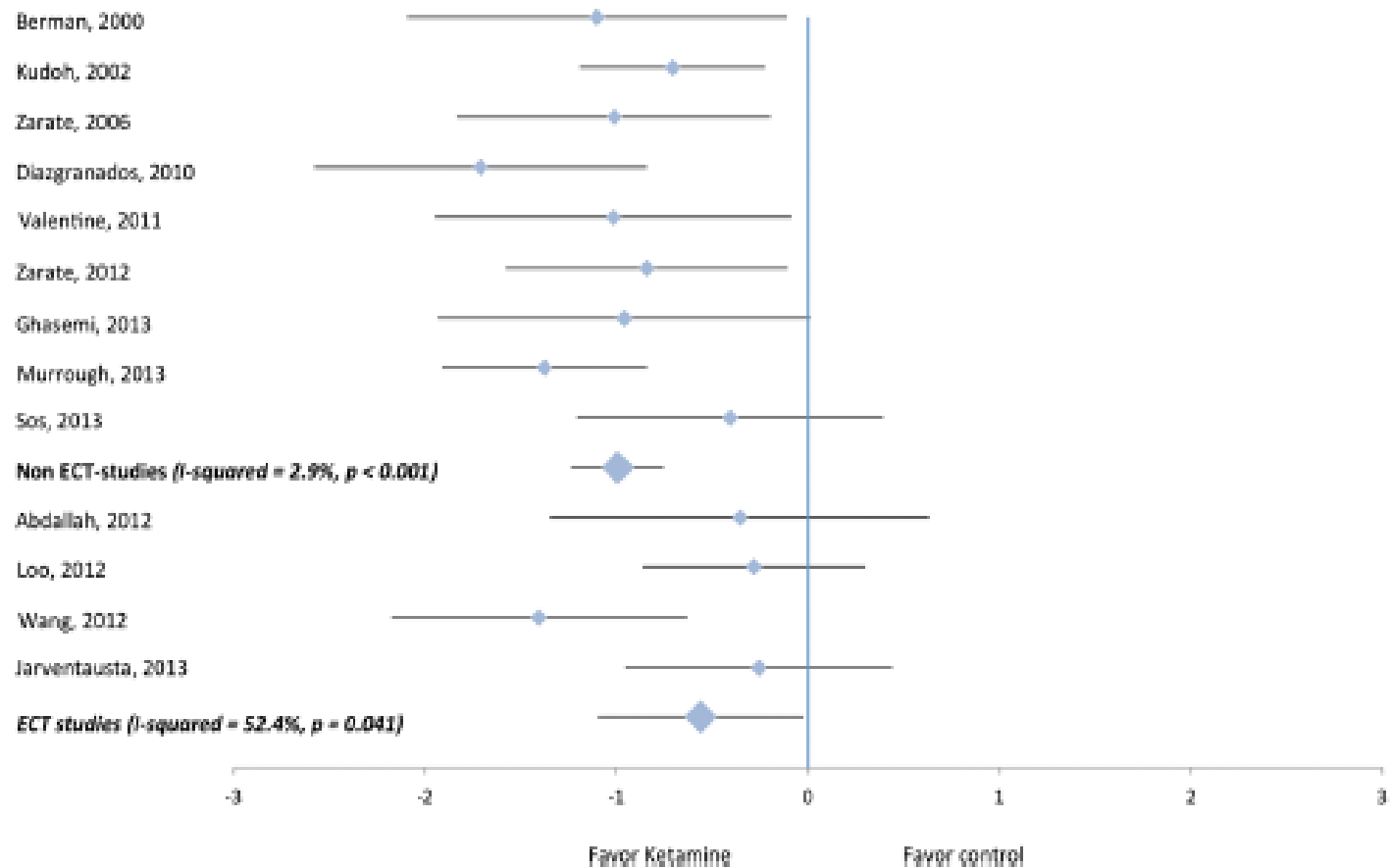


Fig. 2 Global ketamine's efficacy on depressive symptomatology in non-ECT and ECT studies. All depression assessments were made 24 h after administration in non-ECT studies

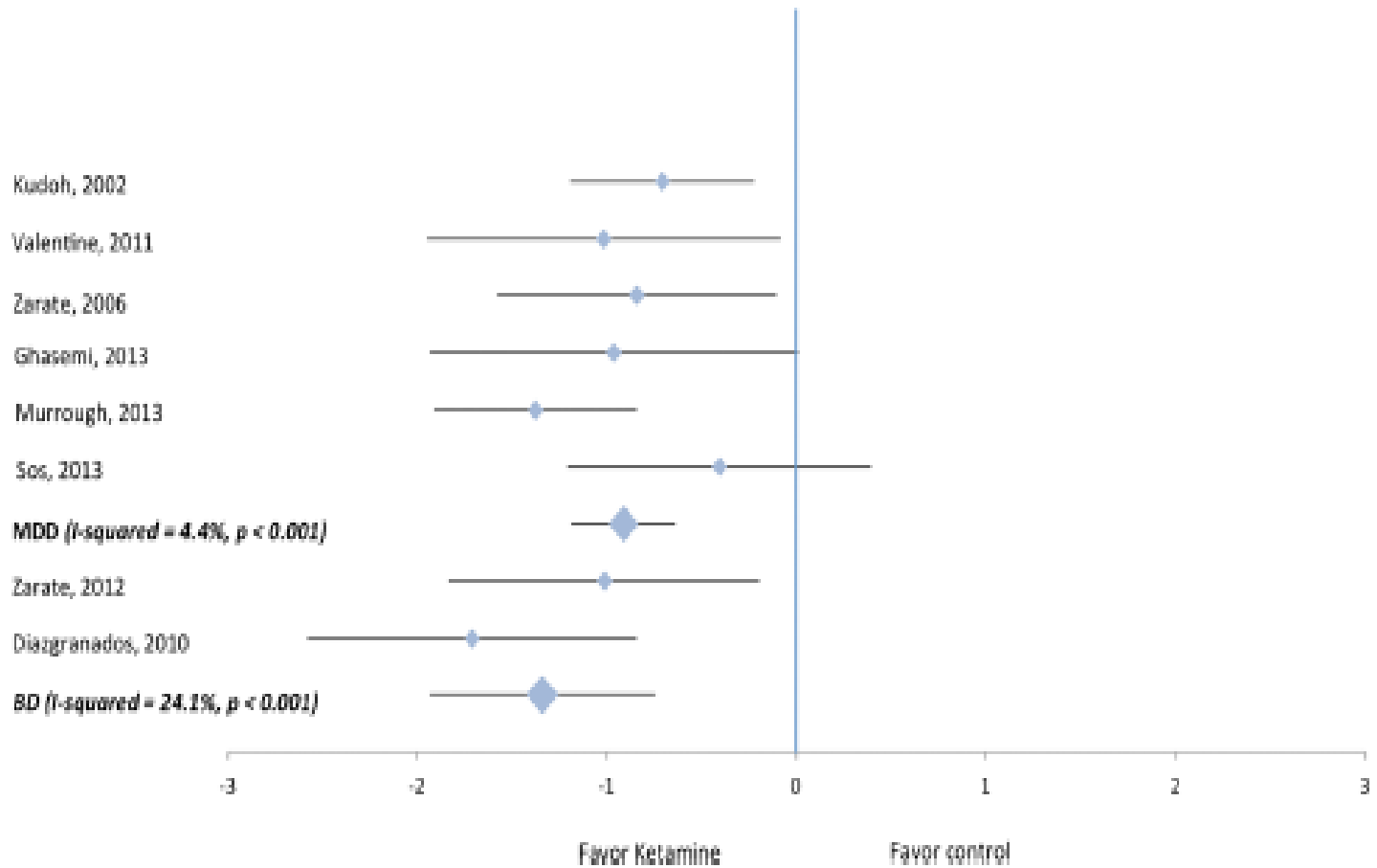


Fig. 3 Subgroup analysis: ketamine's efficacy in major depressive disorder (MDD) and bipolar depression (BD)

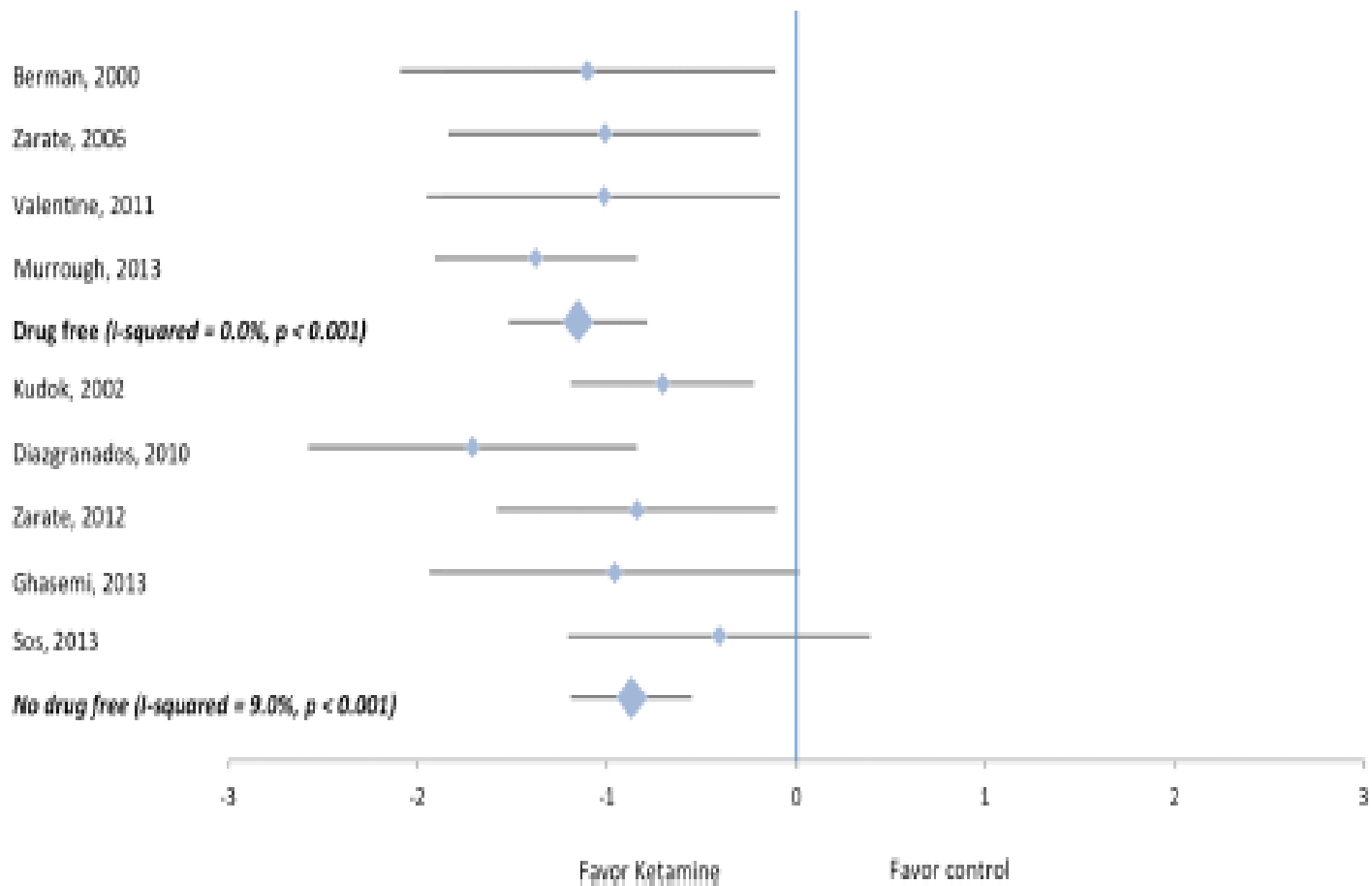


Fig. 4 Sensitivity analysis: ketamine's efficacy in drug-free patients versus patients taking antidepressants or mood-stabilizing agents

ADDITIONAL KETAMINE BENEFITS

- In a placebo-controlled RCT of newly initiated escitalopram with a single ketamine infusion v a single saline infusion demonstrated that most escitalopram+ketamine patients responded to treatment (92.3% v 57.1%, $p=0.04$) and remitted (76.9% v 14.3%, $p=0.001$) with shorter time to response and remission. Half of 30 enrolled patients were treatment-resistant.
- “Single-dose i.v. ketamine augmentation of escitalopram was safe and effective in severe MDD, holding promise for speeding up early oral antidepressant efficacy.” (Hu)
- In a midazolam-controlled RCT of IV ketamine for suicidal ideation in MDD in 80 patients, there was a reduction on Scale for Suicidal Ideation (SSI) at day 1, greater by 4.96 points ($p=0.0003$). Proportion of responders at day 1 was 55% after ketamine and 30% after midazolam. Benefit was sustained for up to 6 weeks with pharmacotherapy.
- “Adjunctive ketamine demonstrated greater reduction of clinically significant suicidal ideation in depressed patients within 4 hours compared to midazolam, partially independent of antidepressant effect.” (Grunebaum)

SAFETY OF KETAMINE INFUSIONS: POTENTIAL CONCERNS

- Abuse/addiction
- Cardiovascular complications
- Cystitis and other urinary tract sequelae
- Cognitive Impairment
- Psychiatric complications (psychosis, suicidality)



SAFETY OF KETAMINE INFUSIONS: EXPERIENCE

- Single-site retrospective analysis of 684 ketamine infusions (including geriatric patients and patients with hypertension) **did not demonstrate significant blood pressure increases** – systolic 3.28mmHg, diastolic 3.17mmHg (Riva-Posse).
- Hong Kong chronic ketamine users (3-9 years) compared to healthy controls: **cognitive impairments in visual memory, verbal memory, selective attention, and response inhibition**. Abstinence did not lead to resolution of these deficits (Xiaoyin).
- Hong Kong chronic users of ketamine: lower and upper urinary tract pathology, hepatobiliary (epigastric pain, dilated bile ducts, liver injury) and gastrointestinal problems (gastritis, peptic ulceration, intestinal metaplasia), neuropsychiatric complications (psychosis, depression, anxiety, cortical atrophy). **Gradual improvement can be expected after abstinence from ketamine use, but not always in neuropsychiatric sx** (Hong).
- Report on poorly monitored intranasal ketamine prescription describes addiction and eventual death by suicide (Schak).

MAINTENANCE KETAMINE TREATMENT

Very little data available, as most studies focused on short term results, and most ketamine clinics don't publish/report their results.

1. Retrospective case series of 30 patients treated with acute course of IV ketamine, 6-8 infusions. 11 patients with TRD had ongoing maintenance treatments (age 31-69 years, 10 female, 1 male). After 1 year, 4 patients continued treatment (1 of them transitioned to intranasal form), 7 patients discontinued treatment. In 4 of these 7, there was perceived loss of effect. In 1 case, there were side effects. 2 cases – reason for discontinuation was unknown. **Conclusion: “maintenance ketamine treatments may be an effective way of maintaining treatment response in some ketamine responders.”** (Archer)
2. Retrospective study of 54 patients who received ketamine, of those 14 received ketamine on a long-term basis (12-45 procedures over 14-126 weeks, with no evidence of cognitive decline, increased proclivity to delusions, or emergence of cystitis). 1 patient relapsed when treatment frequency was decreased and didn't improve with repeat acute course. 9 patients relapsed after discontinuation of infusions but improved when twice weekly infusions resumed. 1 patient relapsed but couldn't regain full response after resumption of treatments. 3 patients did not relapse. **7 of 14 long term patients reported that the antidepressant effect of ketamine started to fade 3 weeks following exposure** (Wilkinson).

KETAMINE IN ECT

- May decrease seizure threshold (or at least not change it)
- May be used as sedative monotherapy, or as an add-on
- A meta-analysis of 16 studies including 928 patients found that depressive scores were lower after 1st ECT when ketamine was used as monotherapy
- Depressive scores were lower after 2nd, 3rd, 4th, and 7th ECTs when ketamine was an add-on anesthetic
- Overall, ketamine in ECT showed no better response and remission rate, no significant difference in cognitive performance/impairment in ketamine v non-ketamine groups
- There were increased adverse events related to cardiovascular and psychiatric systems during the whole ECT course – may place patients at higher risk for postictal agitation (Ren)
- Not included in study above was an RCT from Canada, comparing ketamine v propofol during ECT, which was terminated early. Ketamine patients achieved a 50% MADRS reduction after 2 treatments, and 83% of propofol patients achieved the same outcome after 4 treatments, all patients eventually achieved remission (MADRS≤10) (Gamble)

KETAMINE IN SUBSTANCE USE DISORDERS

- 7 studies identified: 2 on alcohol dependence, 2 on cocaine dependence, 3 on opioid dependence
- **Cocaine use:** after 1 infusion, ketamine increased motivation to quit cocaine and reduced cravings, significant reduction in frequency and amount of cocaine use in follow-up
- **Opioid use:** RCT of 70 heroin-dependent participants compared high dose ketamine v low dose ketamine with psychotherapy. 50% of subjects receiving multiple ketamine treatments were abstinent at 1 year follow up compared to 22% of single session treatments, and reduced cravings. RCT of saline v. IV ketamine prior to rapid opiate antagonist induction showed that ketamine could suppress physiologic response to opiate withdrawal.
- **Alcohol use:** after 3-month residential treatments, patients volunteered for ketamine-assisted psychotherapy and were compared to patients who completed follow up as usual. 1 year abstinence rates were 66% in the ketamine group compared to 24% in the comparison group. For 23 patients hospitalized for severe alcohol withdrawal, there was a trend toward reduced benzodiazepine requirements post ketamine initiation. (Jones)

KETAMINE IN PTSD

- Open-label study of repeated ketamine infusions in patients with comorbid PTSD and MDD received 6 intravenous ketamine infusions over 12 days
- Remission rate was 80% for PTSD, and response rate for TRD was 93%.
- Median time to relapse of PTSD sx was 41 days
- Median time to relapse of TRD sx was 20 days
- The most significant side effect reported were transient increases in dissociative sx (Albott)

QUESTIONS THAT REMAIN

- 60-100 ketamine clinics operating in the United States do not follow the minimal recommendations of the APA task force consensus report
- There is no regulation of ketamine use in depression, and no post-marketing surveillance. Should anyone provide systematic oversight?
- What about patients who have comorbid psychiatric disorders?
- Is ketamine as a drug of abuse problem being addressed in ketamine clinics?
- Can new antidepressants be developed without abuse liability of ketamine, based on its mechanism of action? (Nemeroff)
- What is the effective dose? Efficacy has been reported at doses less than 0.5 mg/kg.
- What is the optimum route of drug administration?
- At which point should the treatments adjourn? Is there room for maintenance treatment or is it not useful enough to even think about?



GUIDANCE FROM THE APA

- Follow the appropriate preprocedural evaluation (basic labs, EKG at minimum).
- Most commonly used dosing was 0.5 mg/kg per 40 minutes IV to achieve plasma concentrations of 70-200 ng/ml.
- Should be administered by a licensed clinician who can administer a DEA schedule III medications with ACLS certification. Clinicians should be familiar with behavioral management of patients experiencing acute mental status changes and behavioral emergencies.
- Treatment setting should be in places where basic cardiovascular and respiratory function could be monitored, as well as rapid stabilizations of a patient in case of cardiovascular or behavioral emergency.
- Site-specific SOP should be developed to include preprocedural evaluation, informed consent, assessment of baseline vital signs, incorporation of time out procedure, delineation of criteria for stopping the infusion.
- Twice-weekly dosing is as effective as more frequent dosing for a period of up to 4 weeks.
- Limited evidence exists for maintenance/long term treatment with ketamine infusions.

TAKE-HOME POINTS

- *Proof of concept and subsequent randomized controlled trials comparing short term treatment with ketamine infusions for depression display benefit for acute, severe depression in MDD and bipolar disorder*
- *There is little evidence at the moment for maintenance ketamine treatment, and the effect on depressive symptoms is short lived, but for some patients instrumental in jumpstarting their recovery*
- *Ketamine effect on suicidal ideation has not been studied as systematically but there is some direct and indirect evidence that it helps suicidality*
- *Ketamine has potential for painful long-term sequelae if used injudiciously, and remains a concern as a drug of abuse, however in studies of maintenance patients no significant long term side effects have yet been found.*
- *Important to follow institutional guidelines in administering ketamine infusions. There is no room to recommend maintenance ketamine infusions yet.*