Ketamine Update with Brandon Kitay, M.D.

Annabel Kuhn M.D., Brandon Kitay, M.D., David Puder, M.D.

Dr. Puder doesn't have any conflicts of interest.

Dr. Kitay has the following conflicts of interest: received salary support from Janssen Pharmaceutica, received an honorarium from JNJ for work conducted involving esketamine, salary support and consultant fees from Sage Therapeutics, been on scientific advisory boards, clinical practices in South East Asia, consultant fees and salary support from Otsuka Pharmaceutical.

Esketamine is the first non-monoaminergic based medication which is FDA approved and indicated for treatment refractory depression. A longer duration of undertreated depression is associated with poor longitudinal functional outcomes. Instead of cycling patients through monoaminergic antidepressant trials and cognitive behavioral therapy approaches, according to Dr. Kitay, providers should consider treatments like esketamine much sooner in the treatment course.

Ketamine versus Esketamine (S-ketamine)

- "Ketamine" is the racemic mixture of ketamine which is used intravenously or intramusculalry as a general anesthetic and analgesic. It is not FDA approved for any psychiatric indication, but is used off-label most commonly for treatment-resistant unipolar or bipolar depression.
- Esketamine ("S-ketamine") is the s-enantiomer which is taken out from the racemic mixture. S-ketamine is the proprietary product of Janssen Pharmaceuticals, Inc. that is compounded for intranasal delivery.

Formulations

- S-ketamine is administered intranasally.
- Ketamine is typically administered intravenously for treatment-resistant depression, but it can also be administered intramuscularly or orally. Similar to S-ketamine, ketamine can be compounded by specialty pharmacies into an intranasal formulation as well.
- Ketamine can be compounded into either a pill or a troche (sucking candy). There is some research (although not high quality evidence) that suggests that orally delivered ketamine may be helpful as a maintenance strategy for some patients or as a primary treatment strategy for other patients.
    - We do not advocate for home ketamine administration at this time due to safety concerns. The primary side effect of ketamine is dissociation, which can be detrimental for a patient in an unsupervised setting. Additionally, ketamine can cause increased blood pressure (on average 5-10 mmHg systolic). For patients with hypertension at baseline, ketamine administration can result in hypertensive

urgency or emergency, which requires close evaluation and further intervention by a medical professional.

- Psychodynamically, the bioavailability of oral ketamine is low. Patients are likely not achieving purported therapeutic serum levels for depression when taking oral ketamine as compared to patients receiving intravenous ketamine.

How do providers administer ketamine and S-ketamine?

- Patients can go to a clinic that is staffed by a psychiatrist or by other providers (e.g. anesthesiologists, nurse anesthetists, or a medical professional with experience administering anesthetic agents) who work alongside community psychiatrists.
- Patients arrive and often receive ketamine treatment on an outpatient basis. They are monitored before, during, and after the treatment for a predetermined period of time, and then discharged home.
- Initially, treatments are administered twice weekly for 3- (IV ketamine) or 4-weeks (esketamine) consecutively, and continued at a reduced dosing interval (e.g. q weekly, bi-weekly, or q monthly). Patients may be candidates for “maintenance” therapy (see the “Duration of treatment course” section below).
- Some mental health providers are utilizing ketamine-assisted psychotherapy, in which a patient undergoes psychotherapy during or in the days following intravenous or intramuscular ketamine administrtion.
- S-ketamine was FDA approved with the stipulation that a REMS (Risk Evaluation and Mitigation Strategies) program be established to monitor safe administration by community practitioners. Treatment with clozapine also involves a REMS. Treatment with S-ketamine involves sending de-identified patient and treatment data back to the REMS for assessment of long-term safety. Patients must also consent to not drive on the day of treatment, and remain in a monitored setting for two hours before going home. These are standards that must be upheld in order to receive treatment. This may create an access problem in patients who are unable to find transportation or are unable to remain in the clinic for two hours.
- On the other hand, ketamine is not FDA approved and therefore does not have any guidelines for administration or monitoring. While this alleviates some of the aforementioned barriers to access, it also creates a potential for malpractice, especially since ketamine is an off-label treatment. Standards of care around ketamine administration are developing based on empirical evidence and clinical experience being described in the evidence base that adhere closely to those for esketamine.

<u>When should providers consider treatment with ketamine or esketamine?</u>

- The majority of the evidence suggests that the best candidate for treatment with ketamine would be someone who has failed at least two optimal medication trials with oral antidepressants. Someone who has failed an adequate course of CBT (cognitive

behavioral therapy) in addition to two failed antidepressant trials would especially be a good candidate.

- When choosing any treatment, providers should consider the patient's core symptoms, the acuity, and the practicality of the treatment.
- Core symptoms and acuity:
    - Consider these two patients: Patient A is severely functionally impaired (i.e., in bed all day, acutely suicidal, on the verge of being hospitalized) and Patient B is relatively functional (i.e., going to work, managing child care responsibilities), although still suffering from symptoms of depression. Either Patient A or patient B would be a good candidate for ketamine or esketamine therapy assuming they have not responded to multiple, adequate medication +/- psychotherapy trials, however practical considerations might influence which patient has access to these potentially beneficial treatments.
- Practical considerations
    - A patient cannot drive on the day of ketamine or esketamine treatment. This could be a barrier to treatment if the patient cannot find other means of transportation.
    - Treatment with esketamine is not always covered by insurance. Treatment with IV ketamine is typically not covered by insurance, as it is not FDA approved.

What are the side effects of esketamine?

- We discuss a study that explores FDA adverse events reporting system (FAERS) database from March 2019-March 2020. The database explores side effects that occur with prolonged courses of S-ketamine treatment (i.e., a longer course of treatment than what is typical for randomized control trials). The study found that there were "2,274 esketamine-related AEs (adverse events) in 962 patients (mean 2.4 AEs per person)" (Gastaldon 2021).
    - One of the most frequently reported adverse events was dissociation (*n* = 212, 9.32%) with mean time-to-onset 20.3 days.
        - The 20.3 day time-to-onset of dissociation was surprising to us because dissociation is thought to be a direct pharmacological side effect of esketamine, and occurs while the patient has the medication in their system. Additionally, esketamine is rapidly metabolized.
        - Dr. Kitay says that in his experience, patients experience dissociation onset within 10-20 minutes of esketamine treatment, and then it subsides after 60-90 minutes.
        - It is possible that in this study, esketamine was given to patients who have a greater propensity for experiencing dissociation independently of the medication due to other underlying comorbidities (i.e., personality disorders, PTSD). For these individuals, the reported dissociation at the

20 day mark is less likely related to esketamine administration and more likely a symptom of an underlying mental health condition. However this is something that is worthy of future study and inquiry.

    - Nausea is also a common side effect of esketamine administration. Dr. Kitay reports that he often pre-medicates his patients with ondansetron or another antiemetic prior to initiating treatment.
- Suicidal ideation was reported as an adverse event (*n* = 64, 2.81%) with mean time-to-onset of 8.3 days (Gastaldon 2021).
- These numbers do not surprise us, as the patients who are being treated with esketamine are experiencing severe depression often with suicidal ideation. It is reasonable that patients would have continued suicidal ideation or recurrence of suicidal ideation within 8 days of onset of esketamine, as this is a symptom of major depressive disorder.

Esketamine and suicidal ideation

- There are two FDA-approved indications for esketamine. According to the esketamine package insert, "SPRAVATO (esketamine) is indicated, in conjunction with an oral antidepressant, for the treatment of treatment-resistant depression (TRD) in adults and depressive symptoms in adults with major depressive disorder (MDD) with acute suicidal ideation (SI) or behavior" (Janssen Pharmaceuticals, Inc. 2020).
- This is important because in clinical trials, esketamine improved depressive symptoms in patients with MDD with SI, but it did not demonstrate a statistically significant impact on SI in itself.
- We can say with much more confidence that esketamine and ketamine can treat the major modifiable risk factor associated with SI, which is the severity of the depressive symptoms in patients with MDD with SI.
- This additional indication also increase potential access to esketamine: patients experiencing MDD with acute SI or behavior that do *not* meet the minimum criteria for treatment resistant depression during the current depressive episode would fall under this indication, this may often include psychiatric inpatients admitted following a suicide attempt.

Duration of treatment course with esketamine/ketamine

- One of the major drawbacks of esketamine and ketamine is that the effect of these medications is transient in nature. Depressive symptoms can recur pretty quickly in patients who were previously effectively treated with esketamine and then discontinue use. Is this inherent to the demographics or neurobiology of the patients, or to the therapy? At this point in time we do not know, and so when to terminate a course of ketamine and esketamine remains a collaborative, patient centered decision. Theoretically, a patient could be prescribed IV ketamine or esketamine as a maintenance therapy for their lifetime.

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- We do know from an esketamine withdrawal study that ongoing therapy at a reduced dosing interval following induction decreases the risk of relapse by 70% in “stable responders” (those that only experience a 50% improvement or more in symptoms) and 51% in “stable remitters” (those that experience complete resolution or subclinical symptoms). Clinically, it is important to consider the risk and consequences of relapse in whether ongoing therapy is appropriate for an individual patient. Unfortunately, at this point in time, we do not know the long-term side effects of chronic ketamine use. Might chronic ketamine use impact cognition? Could it make people more vulnerable to psychosis? Evidence to date suggests that it does not impact cognition. Our best data comes from ketamine abuse studies, most of which come from southeast Asia where chronic ketamine abuse is more common than it is in the United States. Those studies have shown that individuals with chronic daily ketamine use are at higher risk for developing psychosis, bladder symptoms and interstitial cystitis. Reassuringly, these occurred in individuals who take much higher and more frequent doses than what is given to patients who are prescribed esketamine.

What is the mechanism of action of ketamine?

Ketamine rapidly increases synaptic plasticity of glutamatergic neurons. The greatest density of glutamatergic neurotransmission occurs in the cortex, which is a higher order brain area and is not well pharmacologically targeted. According to a study from a research team at Yale, ketamine can rapidly increase synaptic plasticity (for review of pre-clinical and clinical ketamine studies, see Krystal 2019). This study involved tracing and labeling dendrites in the prefrontal cortex of mice who were experiencing “chronic unpredictable stress”, which is a research model for depression. In mice with chronic unpredictable stress, their dendrites look sick—narrow with very few dendritic spines. Fewer dendritic spines means fewer opportunities for synaptic neurotransmission or connectivity between local and distal brain regions. But 24-48 hours after a single dose of intraperitoneal ketamine, the dendrites appear much healthier with many more dendritic spines. This suggests that ketamine is enhancing synaptic plasticity—the propensity to form new connections in the brain. This seems to occur quickly and in areas of the brain that are involved in the cortico-limbic model of depression.

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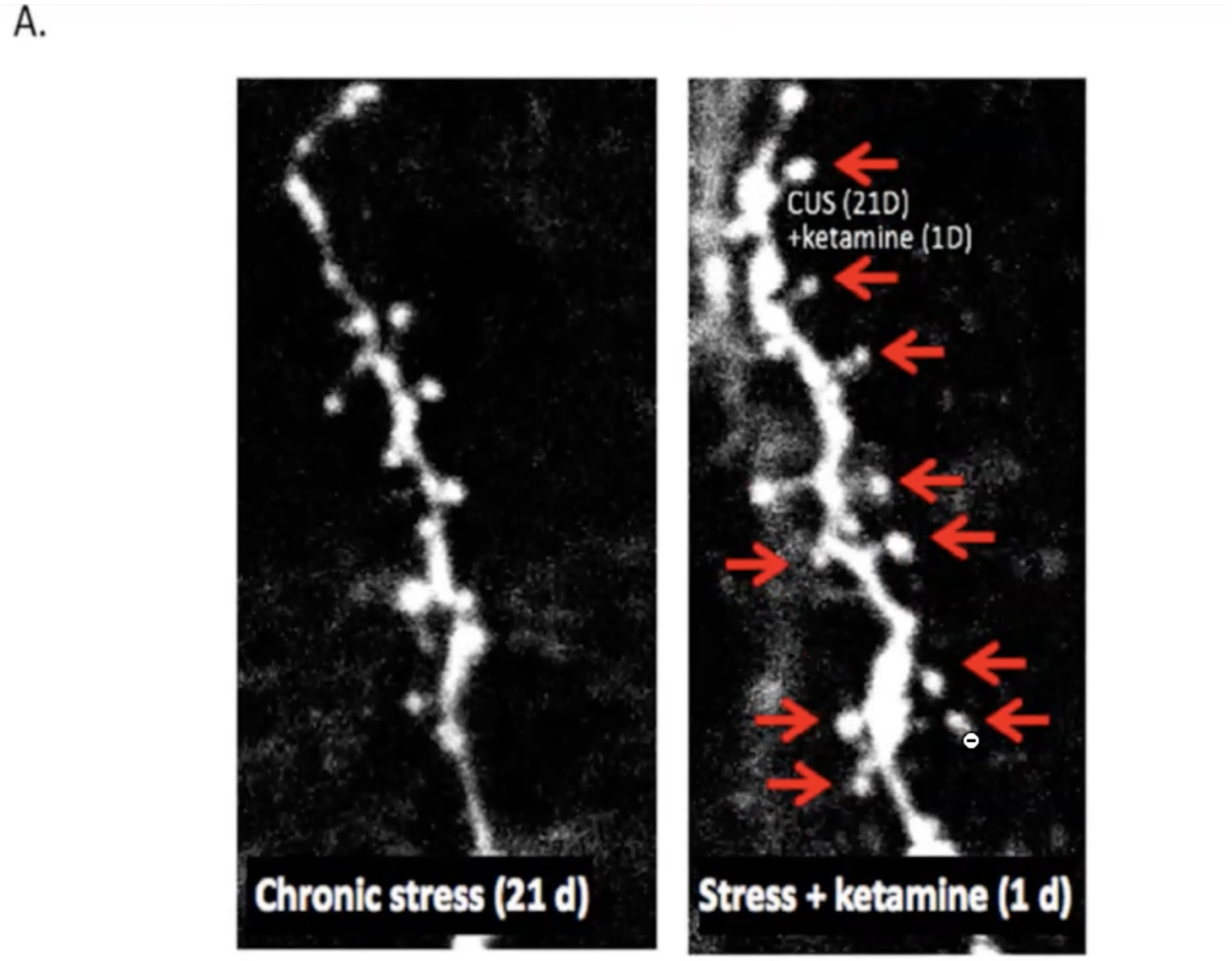

Above is Figure 1 (D, A.) from (Krystal 2019). This is a single dendrite in the cortex of a mouse. It is illuminated by a fluorescent biomarker. The left and right panels are from the same dendrite in the same animal. The mice are put under chronic, unpredictable stress for 21 days. For example, the mice may be subjected to restricted movement, increasing scarcity of food, or bullying stress in which mice are put into a cage with a more dominant animal. The dendrite of the mouse who has experienced this chronic, unpredictable stress is on the left and it appears skinny, narrow, and not robust. The image on the right side shows the same dendrite in the same animal one day after treatment with intraperitoneal ketamine. The arrows on the right side point out dendritic spines which are considered areas for connections. There are more opportunities for connections in the dendritic spines in the dendrite on the right compared to the dendrite on the left.

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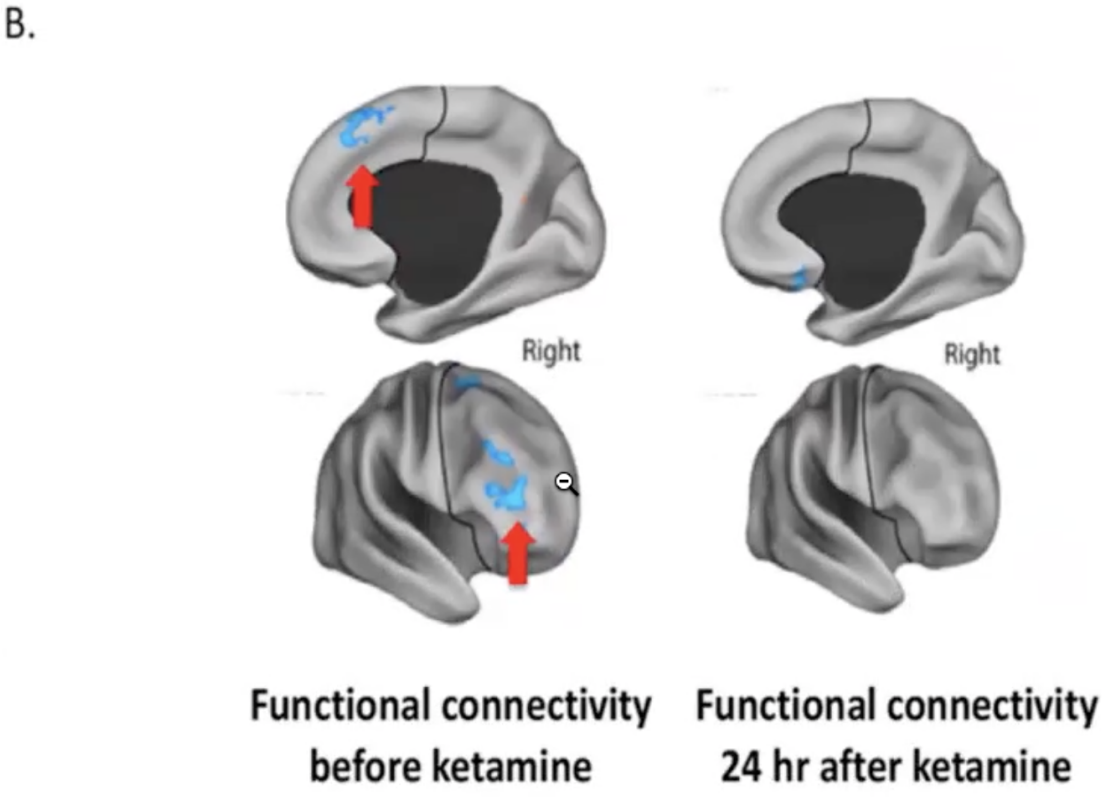

Above is Figure 1 (D, B.) from (Krystal 2019). This image shows results from a functional connectivity study in humans. On the left, we see hypoconnectivity in the dorsolateral prefrontal cortex (DLPFC) in the brain of a patient living with depression. The right side demonstrates lack of hypoconnectivity in the DLPFC, meaning that there is enhanced activity in that area of the brain. This is similar to what we are seeing in the animal models.

What is ketamine-assisted psychotherapy?

It is critical to contextualize a patient's enhanced synaptic plasticity following ketamine treatment in order to induce long-term changes. While some practitioners perform ketamine-assisted psychotherapy while the patient is experiencing dissociation, there is insufficient evidence supporting that dissociation is *required* for therapeutic benefit. A more mechanistically driven hypothesis would be that ketamine-assisted psychotherapy would be most beneficial during a "plasticity window", which is a time after ketamine administration and when a psychotherapy based on learning models might be maximally engaged. Combining ketamine-assisted psychotherapy with CBT (cognitive behavioral therapy), for example, can help patients contextualize and utilize enhanced synaptic plasticity. There is work being done to develop novel protocols that capitalize on information from functional imaging studies and morphological studies to identify the best time to utilize ketamine-assisted psychotherapy. If a patient is receiving a single acute dose of ketamine, ketamine-assisted psychotherapy can be done within

1-2 days after administration. Combining ketamine and CBT could enhance the response to ketamine and increase long-lasting changes that are unique to psychotherapy.

Social considerations in choosing ketamine therapy

Many people, including those living with treatment-resistant depression, have interpersonal stressors and comorbid psychiatric conditions. Chronic conflicts with a significant other, family, friends, or colleagues may contribute to symptoms of depression. Individuals living with treatment-resistant depression may also have personality factors or comorbid mental health conditions such as PTSD. At this time, we cannot predict whether a patient will respond to ketamine therapy. Even in the setting of external stressors, patients deserve the opportunity to try an interventional treatment such as ketamine or esketamine. However, some individuals do not experience improvement in symptoms following a course of ketamine, possibly because there are core conflicts that are driving these symptoms. In this case, a patient would be referred to psychotherapy. Ketamine offers resilience, but it is not a long-term solution for conflicts in which psychotherapy and other social interventions may be more beneficial.

Conclusion

Esketamine and ketamine are safe and effective treatment options for individuals living with treatment resistant depression. Esketamine is an FDA-approved treatment for the treatment of treatment-resistant depression in adults with major depressive disorder (MDD). It is also FDA approved for treatment of depressive symptoms in adults with MDD who are experiencing acute suicidal ideation (SI) or behavior. Esketamine administration is closely regulated and monitored by the FDA. Ketamine is administered intravenously for treatment-resistant depression, but it is not FDA approved and therefore administration is not regulated. Coupling psychotherapy with ketamine treatment may improve patient outcomes.

Acknowledgments:

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