Pharmacotherapy and Ketamine Assisted Psychotherapy for Treatment-Resistant Depression:

A Patient With Lifelong Self-Doubt and Self-Criticism

Albert Yeung, MD, ScD[a,*]; Guy Sapirstein, PhD[b]; Laura D. Crain, MD[c]; Margaret A. Cramer, PhD, ABPP[d]; Fernando Espi Forcen, MD, PhD[d]; Susan Sprich, PhD[d]; and Jonah N. Cohen, PhD[e]

Presented here is a series that highlights the discussion of a complex case by several expert clinicians, faculty members of Massachusetts General Hospital/Harvard Medical School, from distinct fields of study. Cross Talk demonstrates that clinical challenges can often be improved upon by leveraging more, rather than fewer, clinical perspectives.

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[a]Depression Clinical & Research Program, Massachusetts General Hospital, Boston, Massachusetts

[b]Private practice, Boston, Massachusetts

[c]Center for Group Psychotherapy, Massachusetts General Hospital, Boston, Massachusetts

[d]Department of Psychiatry, Massachusetts General Hospital, Boston, Massachusetts

[e]Center for Anxiety and Traumatic Stress Disorders, Massachusetts General Hospital, Boston, Massachusetts

**Corresponding author:* Albert Yeung, MD, ScD, Massachusetts General Hospital, 6F, Bowdoin Sq, Boston, MA 02114 (ayeung@mgh.harvard.edu).

ABSTRACT

Although consensus in the field is lacking, the most common definition for treatment-resistant depression (TRD) requires a minimum of 2 prior treatment failures with confirmed adequate dose and duration. This article presents a clinical example of TRD in a patient with a long history of depression and inadequate response to treatment. The prominent feature is the patient's persistent self-criticism that might have predisposed him to unrelenting depression symptoms, intense anger, self-doubt, and self-disapproval. We explore potential underlying causes for self-criticism, its impact on depression and help-seeking, and plausible treatment approaches.

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According to the Sequenced Treatment Alternatives to Relieve Depression trial, only 30% of participants achieved remission with selective serotonin reuptake inhibitor (SSRI) (citalopram) monotherapy (level 1); another 20% achieved remission after switching to a second antidepressant or psychotherapy or by combining a different class of antidepressant with citalopram (level 2), and the probability of remission decreased with each additional treatment trial.[1] While there is no consensus on a definition of treatment-resistant depression (TRD), many researchers have used "unsatisfactory response to two adequate trials of two different classes of antidepressants at optimum dosage for sufficient duration."[2] A recent estimate of the 12-month prevalence of TRD, based on data from US insurance claims, concluded that 30.9% of people with medication-treated major depressive disorder (MDD) have TRD, which accounts for a large proportion of the national annual health care burden (56.6%), unemployment burden (47.7%), and productivity burden (32.2%) of medication-treated MDD.[3] TRD was found to be associated with higher symptom severity, suicide risk, greater number of lifetime depressive episodes, and comorbid anxiety and anhedonia.[4,5] Comorbid physical illnesses, including autoimmune conditions, hypothyroidism, and cardiac or cerebrovascular diseases, and comorbid psychiatric disorders, such as substance abuse and personality disorders, can also negatively impact the outcomes of treatment of MDD.[6] Certain personality and psychological characteristics may also contribute to TRD. Individuals with delays or deficits in the development of a self-concept, or view of the self, may become highly self-critical. They may develop intense feelings of inferiority, guilt, and worthlessness and feel that they have failed to live up to expectations and standards.[7] Such individuals are highly prone to depression and increased levels of stress, which may reinforce a negative view of one's sense of self. Experiencing a discrepancy between one's actual self and one's ideal or desired self is associated with depression.[8] Also, individuals who are preoccupied with being flawless or perfectionistic and inclined to scrutinize themselves harshly are also prone to depression.[9]

Various pharmacologic strategies and neurotherapeutic devices are used for treating TRD.[10] Pharmacologic approaches include optimization, drug substitution, combination, and augmentation. Optimization involves using medications that have worked for the patient in the past or increasing the

dose of the existing antidepressant and lengthening the duration of therapy. Drug substitution involves changing from one antidepressant to another antidepressant, which could be in the same class or have a different mechanism of action. Combination involves the addition of a second antidepressant to the therapy regimen to obtain a complementary clinical effect. Augmentation involves adding a non-antidepressant agent, such as lithium, anticonvulsants, antipsychotics, thyroxine, bupropion, pindolol, or pramipexole, to the antidepressant. Neurotherapeutic treatments include transcranial magnetic stimulation, vagal nerve stimulation, and electroconvulsive therapy (ECT) for treatment of TRD. ECT is considered the gold standard treatment, with an estimated 65% efficacy.[11] If ECT fails, neurosurgery is available for severe TRD. However, its use is usually restricted to academic centers due to the invasiveness of the procedure. In addition to pharmacologic and neurotherapeutic devices, psychotherapies including cognitive therapy, interpersonal therapy, and psychodynamic psychotherapy are frequently provided as part of the treatment of TRD.

Ketamine, a dissociative anesthetic drug and an antagonist at glutamate *N*-methyl-D-aspartate (NMDA) receptors, is considered a novel antidepressant. Ketamine, 0.5 mg/kg, intravenous infusion over the course of 40 minutes, has been demonstrated to be an effective treatment for TRD in both research and clinical settings.[12,13] Observational studies have reported that ketamine administrated via intramuscular and oral routes is also effective for patients with depression and anxiety.[14–16] More recently, esketamine nasal spray, the *S*(+) enantiomer of ketamine, was approved by the FDA in 2019 for treatment of TRD in conjunction with an oral antidepressant.[17] The bioavailability of intravenous, intramuscular, intranasal, oral, and rectal ketamine is 100%, 93%, 8%–45%, 17%–29%, and 11%–25%, respectively.[18] While the available data provide only short-term outcomes, ketamine is now a novel treatment for TRD. It can be delivered by different routes, tailoring to the clinical setting, the desired speed of onset of action, and the patient's preference.

In recent years, there has been a resurgence in the interest of psychedelic assisted psychotherapy (PAP) using psychedelics (hallucinogens) such as lysergic acid diethylamide (LSD), mescaline, 3,4-methylenedioxy methamphetamine (MDMA), and psilocybin. These are serotonin 2A receptor (5-HT_{2A}R) agonists with promising results for treatment of end-of-life psychological distress, addiction, MDD, and posttraumatic stress disorder (PTSD).[19] Psychedelics induce altered consciousness that is associated with feelings of bliss, ecstasy, unconditional love, interconnectedness, and oneness with all things, and the occurrence of such a consciousness state appears to predict positive mental health outcomes.[20] PAP can be conceptualized as experiential treatment in which specific pharmacologic actions temporarily induce modifications in brain functioning and conscious experience. When appropriately mediated, these can be deeply meaningful experiences that elicit emotional, cognitive, and behavioral changes. In general, PAP requires very few drug treatment sessions, accompanied by drug-free sessions before and/or after drug sessions, usually referred to as preparatory and integrative psychotherapy, respectively. With ketamine, positive results were obtained with 1 to 12 administrations; with MDMA, just 3; and with psilocybin and LSD only 2, while ibogaine may be effective after a single administration.[21] During drug treatment sessions, patients are continuously monitored and supported by trained mental health professionals following available guidelines.[22] During medication sessions, patients usually wear eyeshades, listen to instrumental evocative music, and are encouraged to stay introspective and open to feelings, be attentive to thoughts and memories, and feel free to engage in psychotherapy at any time.[21] The (usually 2) cotherapists monitor the patient's vital signs including blood pressure, pulse rate, respiration rate, and oxygen saturation; attend to the patient's comfort and needs; address adverse events such as nausea, vomiting, and hypertension; and administer medication treatment when indicated. In addition, they provide therapy when the patient is ready to share and engage in conversation, offer emotional support if the patient manifests strong anxiety or fear, and manage overt agitation to prevent escalation or physical injury.

Ketamine, an NMDA receptor antagonist, is not considered a classic psychedelic. Yet, it has similar dissociative effects that have been observed to bring relief from negativity, increase openness, promote communication, provide access to difficult materials with less fear, offer relief from obsessive and depressive concerns, and integrate a sense of newness and healing.[19] These properties make ketamine an excellent candidate for PAP, and, currently, ketamine is the only legal psychedelic medicine available to mental health providers for the treatment of TRD. Ketamine assisted psychotherapy (KAP) has been used for patients suffering from a variety of disorders, including MDD, PTSD, bipolar I and II disorder, obsessive-compulsive disorder (OCD), and substance use. While the literature on KAP is small, it shows promise as a novel intervention to be explored further in many treatment-resistant clinical conditions.[23] Similar to PAP, KAP clinicians meet with patients for 1–3 preparatory sessions to educate them about potential effects of ketamine, inform them about what happens during medication sessions and how best to engage in treatment, and guide them to select the psychological issues they want to focus on during medication treatment. In the first session, ketamine is usually given at a low sublingual dose to gauge the patient's response, such as emotional changes, access to memories, or gaining new insights. In subsequent ketamine sessions, the doses will be titrated to optimize the patient's therapeutic outcomes, which are frequently related to the levels of consciousness change. The therapists will then meet with the patient for "integration" sessions to process their experience in the ketamine sessions, as well as generate meanings and insights to be integrated into their cognitive framework.

CASE HISTORY AND TREATMENT COURSE

Dr Albert Yeung and Dr Guy Sapirstein: John was a 61-year-old white, male accountant who owned a tax and financial consulting company. He described himself as a workaholic. He had made some bad business decisions in the past, and, as a result, was not where he wanted to be financially. Nonetheless, he currently had a good-sized clientele and felt that if his business continued with the current trend, he would do well financially. John had a long history of depression with extensive treatment.

John's past medical history was significant for hip replacements on both sides. He took a statin for elevated cholesterol. He complained of frequent urination and mild urine leakage and had seen a urologist, who reassured him that examinations and tests showed negative findings. He exercised regularly.

John reported an onset of depression at 21 years old when he was in college. Since then, he had been consistently depressed, with brief remissions between his depression episodes. He had been treated with various SSRIs and serotonin-norepinephrine reuptake inhibitor with partial improvement, but he continued to be distressed by his symptoms and did not like the side effects of antidepressants, which included weight gain and sexual dysfunction.

He had received electroconvulsive treatment for a significant depressive episode at 46 years old. This episode started months after his divorce and his brother's suicide (described later), and the depression responded poorly to medications. Since the onset of depression, he had received cognitive behavioral therapy from different therapists for varying durations ranging from several months to several years but did not find therapy helpful. He denied history of bipolar, psychotic, or substance use disorder.

In the past 5 years, he had been treated by his former psychiatrist with a combination of duloxetine, bupropion, and lamotrigine, all at therapeutic range and for adequate duration, with only partial improvement in his depression. He had been treated with mixed amphetamine salts for suspected attention deficit disorder for a brief period but could not tolerate the tachycardia side effects. In 2020, he received adjunctive transcranial magnetic stimulation treatment for 40 sessions with no significant benefits. He stopped all of his medications in March 2021 due to weight gain and sexual dysfunction side effects. In April 2021, his anxiety and depression symptoms exacerbated, with decreased motivation, interest, and lower productivity. He requested to be transferred to Dr Yeung's care when his former psychiatrist informed the patient that he would be retiring.

In July 2021, John resumed taking duloxetine 30 mg/d. Several months later, he reluctantly agreed to increase the duloxetine dose to 60 mg, but refused to increase further due to concerns about side effects. He reported some improvement but still suffered from significant residual symptoms of depression.

John complained of current symptoms of anxiety and depression. He said he struggled to get started in the morning but that later in the day he was usually able to work efficiently. He complained of having a sense of emptiness and self-doubt and said he questioned how he was conducting his life and whether there were things he could change. He also reported constant "existential angst." John worried frequently and excessively; for example, when his daughter was on vacation, he worried whether she would be able to have a good time. He had somatic complaints including mild pain and frequent urination. He said he was distractible. He tended to procrastinate and struggle with deadlines and noted having to work frantically until the last minute to meet tax filing deadlines for his clients. He suspected having attention deficit disorder but did not want to try stimulants given his earlier side effects with mixed amphetamine salts. He said that he tended to check his emails for errors multiple times (up to 5 times) before sending them out; this happened 3–4 times a day, and he questioned whether he had OCD. He denied history of bipolar episodes, psychosis, or substance use disorder.

During his visits, he was generally talkative and energetic. He complained of being dysphoric but denied symptoms of fatigue, difficulty concentrating, or loss of appetite. A recurring theme was that he felt like an underachiever despite considering himself exceptionally talented, skilled, and committed to work. He became agitated when he talked about this. He was highly frustrated that he needed to push himself to get started in the morning even though he was usually able to work efficiently later in the day. He denied ever having suicidal/homicidal thoughts, hallucinations, or other psychotic symptoms.

Psychosocial History

John was married at 28 years old and divorced 17 years later. He had 2 adult daughters from this marriage and reported that his older daughter had a history of bipolar disorder and borderline personality disorder. John lived with his younger daughter, who was in her early twenties and had a history of anxiety and depression.

He was brought up Catholic, but he did not consider himself religious. John's parents were married to each other until their respective deaths in their nineties. John reported having a good relationship with his parents and denied being abused himself, although his father was emotionally volatile and hit his older brothers in multiple circumstances and believed in corporal punishment. John reported being "unplanned" as the youngest of 6 children. His mother was described as a very devoted parent who suffered from long-standing anxiety. John's brother had killed himself about 15 years earlier after struggling with depression and suicidality. His brother was not married, had a PhD, and reported feeling that he never managed to actualize himself.

John related that until 8–10 years of age, his life was "bliss," but then he became increasingly anxious. He described a "dichotomy" of living "a charmed existence" outwardly but experiencing anxiety and what he termed "OCD" internally. His father reportedly noticed that he became more isolated around

CASE HISTORY AND TREATMENT COURSE (continued)

10 years old. John reported being held up at gunpoint at about 13 years old. Although he endorsed feeling very afraid, he did not report any lingering effects from that event. In the summer before his senior year, he and his girlfriend had a "pregnancy scare" that sent him into a depression. He recalled feeling that his "sovereignty was blown away" and felt he had been "irresponsible."

Throughout his childhood he had "placed his father on a pedestal," although he did not experience their relationship as being emotionally intimate. He continually experienced self-doubt, which he hypothesized might be a result of being, in his words, "the baby."

John had been involved in 3 main romantic relationships. The first was with a girlfriend in high school, with whom he broke up after 8 months. John described his marriage with his ex-wife as "charmed at first sight." They grew apart after about 12 years and eventually divorced after being together for about 17 years. At the end of the relationship, his ex-wife disclosed she was in love with a woman and identified as lesbian. They get along well to this day. John's current relationship had been about a year long, and he hoped it would be permanent, despite having almost broken up with her recently since she was "annoying him."

Ketamine Assisted Psychotherapy

After reading encouraging news about psychedelics and ketamine assisted psychotherapy (KAP), John sought KAP as an adjunctive treatment for his depression while he continued taking duloxetine 60 mg. Before medication sessions, John had a 1-hour session with each of the 2 cotherapists (A.Y., G.S.) to review the medical aspects and potential side effects of ketamine and to clarify the psychological issues he wanted to focus on. John reported wanting to focus on his persistent frustration and depressed mood. He was also informed that we would be using a combination of psychodynamic and client-centered orientations when working with him. In the first ketamine session, John was given a 100-mg lozenge, followed by another 100-mg lozenge after 20 minutes when he requested a stronger dose. He tolerated the two doses well with no notable adverse events. In the early part of his ketamine session, he spoke about being "paranoid" toward the two therapists and was trying to remain in a non-altered state of consciousness. After that, John tried to relax and focus inward and was quiet most of the time. Toward the end of the ketamine session, he appeared stuck in a loop of negative self-evaluation and asked the therapists whether he was "doing it right." He was reassured to go with the flow and explore whatever space he found himself in. John was discharged to his escort after it was ascertained that he was stable on his feet and felt safe to return home.

During the integration phase immediately following the first KAP treatment, John reported a variety of different and inconsistent thoughts and experiences, some of which were positive and others, negative. Initially, he qualified the experience, saying that he did not "leave the room," indicating he was mostly present and minimally dissociated. He then reported that, overall, the experience was positive. As he continued to reflect, he began to indicate the challenges he experienced. He spoke about being worried that he was "doing things wrong" and reiterated how much he was trying to "let go." He mentioned vague concerns and referenced anxiety several times, often without elaborating. He did mention worrying that he was going to "lose himself" and disclosed a moment of paranoia about whether he had enough trust in his therapists.

In his second KAP session, he received 50 mg IM, followed by a booster of 30 mg IM 15 minutes later, with the goal of attaining a deeper level of consciousness change and easing of ego boundaries. He tolerated the two doses well and reported no side effects. He appeared quite relaxed throughout the experience, apparently staying in an inner space with no interactions with the therapists until the end when the ketamine effects diminished. During the recovery period after the second ketamine treatment, he repeatedly stated that the experience was very positive and relaxing, and that he was trying hard to let go and "go with the flow" and not get anxious. He frequently mentioned the high school girlfriend with whom he had broken up ("the one that got away") and recalled a niece who had died a year ago from cancer. Another theme was, in his words, "universality"; he saw faces: women (mother, high school girlfriend, current girlfriend, a TV character) and men (he and his father) "morphing" from one to another. He remembered having a dream in which he conversed with his father, who was a threatening figure (in the dream).

During the second post-ketamine integration session, John reported no enduring change and stated that he did not benefit from the KAP sessions. He spoke about his ambivalence surrounding allowing himself to relax and enjoy his life. For example, he said he understood that he could go away and travel for several weeks, manage his business remotely, and relax with his girlfriend, but, despite that knowledge, he expressed reservations about traveling. In that conversation, he related that he felt similarly about KAP and going away on vacation and was hesitant about both. He spoke about needing time for self-exploration and self-reflection and was encouraged to consider whether KAP or a long vacation would be more conducive to that process.

Observations About the Ketamine Assisted Psychotherapy Sessions

During ketamine treatment, John appeared to be making the case that he was trying to do it right (eg, "trying to go with the flow"). This statement, which he made several times, could be seen as transferential in nature, as though the therapists were assuming he did not try "hard enough" (which he often thought of himself, or possibly what he felt his father thought), or as being defensive (making an argument to convince himself that he did the best he could). Additionally, the statements underscore the question of whether he can acknowledge the existence of an internalized conflict around his core beliefs about himself: on the one hand, that he has worked hard and been successful, and on the other hand, the belief that he has not lived up to his self-defined potential. It is also possible

CASE HISTORY AND TREATMENT COURSE (continued)

that additional content was censored during his KAP sessions through blocking off his access to certain feelings; for example, when he expressed the fear, "Am I going to lose myself?"

Due to the brief and ambivalent engagement of the patient during treatment, it is difficult to ascertain the effects (positive and/or negative and/or neutral) the treatment had on him. It does appear that the short-term effects of the treatment were positive (by self-description immediately following the administration of ketamine). Despite his positive appraisal of the treatment at the time of the meeting, it is important to note the concerns John expressed: fears of "letting go," slight paranoia about the therapists, and insistence that he "tried to go with the flow" (implying he was not always successful in doing so). These concerns suggest that even at the time of treatment he was aware of his struggle to adequately relax his defensive structure and allow his affect to spontaneously enter his conscious awareness in an undefended form. Perhaps his desire to please the therapists led to understating the degree of discomfort and concern until well after the ketamine sessions.

Psychodynamic Perspective

Dr Laura D. Crain

Given his deep suffering, this patient sought out KAP hoping for rapid relief. Instead, he finds the pace of the ketamine-induced state to be fast and overstimulating such that he struggles to usefully integrate his experiences. He leaves the treatment saying that he finds himself "needing time for self-exploration and self-reflection." In my experience, moments of insight are rarely dramatic, and are followed by long periods of integration and working through, on the road to psychic change.

Regardless of what treatment we employ, it is helpful to be grounded in a formulation. We learn that John is the "unplanned" baby of 6 from a large Catholic family. There is significant unresolved trauma in his life. He tells us that he was once held at gunpoint, but we don't hear what he remembers about that experience or what it meant to him. He feels empty, no good, an underachiever. His father physically abused his older brothers and spared him; if he had more insight, the patient might be aware of survivor guilt in the wake of his brother's suicide. Instead, John reports his idea that his brother's suicide was caused by brother's failure to self-actualize; despite his own achievements, he feels identified with this brother. His worst depression occurred after two major losses: when his wife left him for a woman, undoubtedly a devastating blow, and then a year or two later, after his brother's suicide. There is a lot that this patient cannot yet access from his unconscious.

We could wonder if John has ever felt enough feelings during his life, or, upon reflection about his life, would be able to feel truly alive enough to sufficiently mourn his losses. This man has deep psychic wounds that could be revealed and worked through over time; a longer-term insight-oriented psychotherapy will be the opportunity for self-exploration and self-reflection that he needs. In the best case, ketamine helps to push the unknown to the surface, but, in the worst case, ketamine may represent this patient going into action mode—looking for a magic potion—to avoid a simpler talking cure that would enable him to bear painful feelings and insights.

Family Systems Perspective

Dr Margaret A. Cramer

The central feature of this individual's experience is that, though he has tried virtually every treatment for depression, nothing has helped him. Despite a well-functioning life that includes a successful business, steady relationship, good health, regular exercise, and relatively mild depressive symptoms, he reports being distressed consistently for 40 years.

John's early family relationships may contain clues to his long-standing suffering: Father was on a "pedestal," yet was volatile and believed in corporal punishment; the first 10 years of his life were "bliss," but then, inexplicably, filled with anxiety. Adulthood is burdened with convictions/worries that he isn't "doing it right" or trying hard enough, or is underachieving.

The current treatment regimen can be understood as a re-enactment of the patient's internalized family relational protocols. A successful life but an enduring experience as not living up to his potential creates a safe space where he achieves but never really enjoys, one that keeps him safe from, and from becoming, his volatile father. This compromise contains and expresses his rage at a critical but longed for parent. The patient imagines, for example, that his doctors are accusing him of not working hard enough in treatment, yet in a trick of mind that turns passive into active, the patient also becomes the harsh father who frustrates his treaters, enlisting them to try endlessly but to no avail. His doctors, too, aren't good enough.

To help free John from the internalized family constellation alive in the treatment, his providers might attempt a paradoxical intervention. They might shift the focus of treatment from cure to learning coping skills to deal with his life as it is. By assuring the patient that he is not at risk of serious improvement while also assuring him of their continued availability, the internalized pressure that governs this patient's life and the need for his compromised experience of it might begin to lift and, with it, open the possibility of the life satisfaction that has eluded him for so long.

Cognitive Behavioral Therapy Perspective

Dr Susan Sprich

Given the discrepancy between the patient's relatively mild depression symptoms and his high subjective distress, I would suggest referring him for an evaluation to assess for attention-deficit/hyperactivity disorder (ADHD) and OCD, as either of these diagnoses might explain the gap between how hard he is working and his sense that he is not as successful as he should be. If the patient meets criteria for ADHD, this might be useful as a framework for him to understand this discrepancy. John might benefit from CBT aimed at providing more structure around his tasks, prioritization, coping with procrastination, and other skills designed to help with executive functioning. If he has OCD, it might cause him to work harder than other people to accomplish the same amount. In this case, he could benefit not only from psychopharmacologic intervention, but also from CBT (exposure plus response prevention).

Another way that CBT might be helpful with this patient is in helping him identify his core beliefs and chip away at core beliefs that are not serving him well. If John has a belief that "if I'm not perfect, I'm a failure" or something along those lines, he might be minimizing his success because he isn't "perfect" by whatever definition he might be using. I would also recommend that the patient consider participating in one of the third-wave CBT therapies like dialectical behavior therapy (DBT)[24] or acceptance and commitment therapy (ACT).[25] Both focus on radically accepting both the past and present to help individuals move forward effectively. ACT has a strong emphasis on labeling thoughts as thoughts and not giving them too much power and on encouraging people to clarify their values and make sure that they are spending their time in a way that aligns with their values. Doing this would likely alleviate some of the patient's distress. If he could learn and practice mindfulness, he could be more accepting and present. He could learn to label thoughts and emotions and simply let them be, rather than trying to control them, which often causes distress.

Ketamine Assisted Psychotherapy Perspective

Dr Fernando Espi Forcen

Data for ketamine and KAP are emergent and deserve further study. More research on the routes of administration is necessary as only IV ketamine and intranasal esketamine have received sufficient study in randomized controlled trials. Furthermore, more research on KAP (versus ketamine only) is particularly necessary as psychedelic assisted psychotherapy (eg, KAP) is a highly promising yet currently understudied area of inquiry.

In this case, the use of ketamine, and KAP more specifically, was a clinically reasonable treatment choice as John had tried a number of psychopharmacologic and psychosocial treatments and 2 modalities of neuromodulation. The clinicians showed reasonable judgment by starting with oral lozenges to assess tolerance and adding the booster later in the session to ensure an appropriate dose to treat the patient. Since John tolerated ketamine lozenges well, intramuscular (IM) ketamine was reasonable for the second KAP session. IM ketamine has greater bioavailability than ketamine lozenges; therefore, the dose used here was higher than the dose used in the first session. IM ketamine is more incisive and, as such, ideal for KAP. Patients receiving only ketamine for depression generally receive 6 to 12 treatments, whereas in KAP 1 or 2 sessions could potentially be sufficient to continue integration therapy without ketamine. Ketamine is generally well tolerated, and its side effects such as nausea, hypertension, and headache can be easily controlled in a clinical setting.

In contrast to traditional antidepressants that enhance serotonin, norepinephrine, and dopamine activity, ketamine's proposed mechanism of action is antagonism of the NMDA receptors. The NMDA receptor is a receptor of glutamate, a major excitatory neurotransmitter. Dysfunction of the NMDA receptor affects cognition and behavior, as in various pathogenic and iatrogenic conditions, such as NMDAR encephalitis, amyotrophic lateral sclerosis, and dextromethorphan intoxication. NMDA receptor antagonism has been shown to improve depression.

In addition to its NMDA receptor antagonism, ketamine has other mechanisms of action that may contribute to its antidepressant effect. Ketamine antagonizes μ and has an agonist/antagonist action of κ-opioid receptor, antagonizes the nicotinic receptors, and agonizes the dopamine D_2 receptors. Another mechanism of ketamine that might explain its antidepressant effect is neuroplasticity. Ketamine appears to promote synaptogenesis in the medial prefrontal cortex and hippocampus, elevating the formation rate of dendritic spines in these areas that are traditionally affected by chronic stress and depression.[26] The auxiliary mechanisms should be further studied to determine their clinical significance.

Apart from the basic science aspects and neurobiological mechanisms, there may be a therapeutic role derived from the ketamine phenomenological experience. The psychedelic effects of ketamine, such as dissociation from mind and body, calmness, peacefulness, and euphoria—taken in the appropriate setting—may help the patient expand perception and insight.

Integrative Discussion

Dr Jonah N. Cohen

Treatment-resistant depression is associated with significant suffering and health care burden. Treatments

of TRD included psychotherapy, neurotherapeutics, and pharmacotherapy, including ketamine. Clinical presentations of TRD are heterogeneous, with different symptom profiles, varying sociocultural and developmental backgrounds, and diverse characterological organizations. Drs Yeung and Sapirstein present the case of John, a man with lifelong depression who is treated with KAP and ongoing pharmacotherapy. John's case is an excellent example of how using different therapeutic frameworks is essential in the conceptualization and treatment of TRD.

Drs Crain and Cramer examine some of the developmental, interpersonal, and intrapsychic underpinnings of John's lifelong depression. Dr Crain explores John's unresolved traumas (eg, brother's suicide, his wife's departure) and the importance of mourning and metabolizing his losses. Dr Cramer discusses how John leads a successful life but feels as though he has failed to live up to his potential, a compromise John has made to keep himself feeling psychological safe but also in pain. Like Drs Crain and Cramer, I believe an appreciation for the developmental and characterological elements of John's TRD is essential in formulating the drivers of his suffering. John must learn to relate to others and to himself in new and healthier ways. To do this, John must mourn profound interpersonal disappointments and mourn the loss of an idealized view he has had for himself. John must also navigate the tension between experiencing his clinicians as capable of disappointing him but also as capable of reliably caring for him. Of course, this is a long and challenging therapeutic journey, and when someone has suffered as long and as intensely as John has, one should think pragmatically and creatively.

Dr Sprich discusses essential diagnostic considerations that may help to explain aspects of John's TRD. John's procrastination and other challenges around executive functioning may be related to ADHD or an obsessional process, which opens up other treatment possibilities such as cognitive behavioral therapy for ADHD or OCD, highly effective and often shorter-term interventions. Moreover, Dr Sprich recommends ACT and/or DBT and discusses the role of acceptance in these therapies, which converge with Drs Cramer and Crain's focus on mourning painful realities where there is a delta between the actual and the ideal.

Finally, Dr Forcen discusses the power of ketamine and KAP. Ketamine has a different mechanism of action than traditional antidepressants, making it a good option when more traditional options have led to a suboptimal therapeutic response. Dr Forcen also discusses how ketamine may enhance neuroplasticity and insight. Crucially, KAP might help facilitate insights and affective shifts in John's relationship to others and himself in a shorter period than more traditional longitudinal psychotherapies. On the other hand, John experienced some challenges surrendering to KAP, and one must be cautious in making overpromises. Overall, effective treatment, particularly for clinical presentations such as TRD, requires putting aside theoretical allegiances in exchange for a flexible and creative therapeutic approach.

CLINICAL POINTS

- Ketamine is a dissociative anesthetic drug and a novel antidepressant for treatment-resistant depression (TRD).
- Ketamine frequently leads to altered consciousness, with decreased negativity, increased openness, and more access to difficult materials with less fear. In ketamine assisted psychotherapy (KAP), a therapist provides guidance to patients during such a consciousness state.
- Maladaptive psychological characteristics such as poorly developed self-concept may contribute to TRD. KAP may bring about meaningful emotional, cognitive, and behavioral changes to amend such characteristics.

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