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Patients' recovery and non-recovery narratives after intravenous ketamine for treatment-resistant depression

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ABSTRACT

Background: Intravenous (IV) ketamine is an effective therapy for treatment-resistant depression. A large data base is confirmatory and steadily expanding. Qualitative studies can inform best practices and suggest new research directions. As part of a clinical trial designed to identify biomarkers of ketamine response, a qualitative study was conducted to characterize experiences with: receiving infusions; recovering or not recovering from depression; and beliefs about why ketamine worked or did not work.

Methods: Adults with treatment-resistant depression received three IV ketamine infusions in a two-week period and were characterized as remitters or non-remitters via symptom reduction 24 h after the third infusion. Qualitative interviews of a subset of participants were audio recorded, transcribed verbatim, and coded using deductive and inductive methods. Themes were derived and compared across a broader construct of recovery status.

Results: Of the 21 participants, nine (43 %) were characterized as having experienced remission and 12 (57 %) non-remission. Of the 12 non-remitters, five were characterized as having experienced partial recovery based on their subjective experiences, reporting substantial benefit from ketamine infusions despite non-remission status based on scale measurements. Attributions for ketamine's effects included biological and experiential mechanisms. Among non-remitters there was risk of disappointment when adding another failed treatment.

Limitations: A more diverse sample may have yielded different themes. Different patients had different amounts of time elapsed between ketamine infusions and qualitative interview.

Conclusions: Qualitative methods may enhance researchers' characterization of IV ketamine's impact on treatment-resistant depression. While requiring confirmation, patients may benefit from a preparatory milieu that prepares them for multiple recovery pathways; decouples the psychedelic experience from clinical outcomes; and addresses potential risks of another failed treatment.

1. Background

For many patients with major depressive disorder (MDD) and bipolar disorder (BD), conventional pharmacotherapy is not effective. Up to one-third of patients with MDD do not respond to conventional antidepressants (Warden et al., 2007) and treatment resistance often occurs for patients with BD depression despite extensive trials with numerous pharmacologic agents (Perlis et al., 2006). While not yet FDA approved, the efficacy of intravenous ketamine for treatment refractory depression is supported by both meta-analyses and guideline statements, and is administered under federal jurisdiction at Veterans Administration hospitals under an approved national protocol guidance (Price et al.,

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2022; McIntyre et al., 2021; Swainson et al., 2021). As research into ketamine therapeutics continues at a rapid rate, a limited number of qualitative studies have also emerged, focusing on topics such as the effect of ketamine treatment on suicidal ideation (Lascelles et al., 2019; Phillips et al., 2016) and alcohol use (Mollaahmetoglu et al., 2021; Jilka et al., 2021). These studies have begun to characterize patient experiences with ketamine treatment, hinting at possible mechanisms of action – such as improved mood and quality of thought (Lascelles et al., 2019) – which patients cite as contributing to their improved mental health. Yet to be studied, however, are the subjective recovery and non-recovery narratives of patients seeking intravenous ketamine infusions for treatment-resistant depression. How do patients with treatment-resistant depression understand and evaluate receiving ketamine infusions, a novel and qualitatively different treatment, in the context of having "failed" conventional care? How do they describe its therapeutic effects, as well as its varied impact on cognition, dissociation, and insight during an acute infusion? What is their understanding of how ketamine infusions can impact depression? How can these narratives inform the clinical provision of intravenous ketamine for patients with treatment-resistant depression?

Such questions prompted initiation of the current qualitative study, which is an exploratory arm of "Bio-K" (NCT03156504), a recently concluded, four site, open-label, single-arm clinical trial in the United States designed to develop biomarkers of ketamine response in patients with treatment-resistant unipolar or bipolar major depression. The current qualitative study sought to explore the recovery and non-recovery narratives of individuals enrolled in Bio-K. Qualitative aims were to characterize these patients' subjective experiences with (1) receiving the infusions; (2) recovering or not recovering from treatment-resistant depression after the infusions; and (3) beliefs about why ketamine worked or did not prove effective for their depression episode. Characterizing patient recovery and non-recovery narratives through these aims can help establish best practices for providers in framing expectations for patients seeking ketamine for treatment-resistant depression, and in supporting patients whose treatment has failed. Many patients with treatment-resistant depression bring fervent hopes that ketamine will finally "solve" a problem that has plagued them for much of their lives (Lascelles et al., 2019). Providing a supportive and recovery-oriented framework through which patients can understand their experience with intravenous ketamine, regardless of its success as measured by a depression rating scale at one time point, is a delicate task that could be enhanced by a better understanding of patient subjective experiences.

2. Methods

This study was approved by the University of Michigan Institutional Review Board and designated a standard study (HUM#00136106). While Bio-K was a multi-site study, the qualitative sub-study was conducted only through the University of Michigan, although participants were recruited for this study from multiple sites.

2.1. Study population and settings

A primary aim of the Bio-K clinical trial was to discover preliminary biomarkers of ketamine response in patients with treatment-resistant, non-psychotic unipolar or bipolar major depression. Bio-K inclusion criteria included age 18–65 years; meeting DSM-5 diagnostic criteria for major depressive disorder, bipolar I disorder, or bipolar II disorder; PHQ-9 total score $>$ 15 at baseline; and treatment-resistant depression, as defined by a failure of at least two previous antidepressant or mood stabilizing treatments at adequate dose and duration within the current depressive episode. Failed antidepressant or mood stabilizing treatments could include pharmacotherapy for depression at an adequate dose for at least 8 weeks, or an acute series of at least 6 administrations of electroconvulsive therapy. Exclusion criteria included patients with a BMI $>$ 40; diagnosis of psychotic disorder; benzodiazepine use; current drug or alcohol abuse; prior ketamine use; and intellectual disability. The infusion setting varied slightly between sites, but all took place in private or semi-private (curtained) areas. Participants laid or reclined on a bed in a hospital gown or comfortable clothes while receiving infusions. There was minimal noise in the area. Participants often brought something with which to entertain themselves or pass the time (i.e., book, magazine, etc.) during infusions. Participants were monitored by a nurse, psychiatrist, and study coordinator. Some engaged in light conversation with study staff, while others did not. The study did not include a guided psychotherapy-like process during infusions. Ketamine infusions were either 100 min or 40 min or mixed, using a dose of 0.5 mg/kg to a maximum of 50 mg per infusion, which is typical of what is found in most clinical settings.

Bio-K participants received three acute phase intravenous ketamine infusions, delivered in an 8–11-day period. The primary outcome of the clinical trial was *remission*, as defined by a Montgomery-Åsberg Depression Scale (MÅDRS) score of $\leq$9, 24 h after the final infusion. While this definition of *remission* of the depressive episode was used to stratify outcomes in the clinical trial, here we use the broader term of *recovery* to capture qualitative, patient-generated subjective outcomes beyond the MÅDRS score.

For the qualitative study, participants were recruited by various methods. Bio-K participants were sent a letter or email to see if they would be interested in being part of the qualitative study after their participation was complete in the main study. If the participants expressed interest, the respective site research coordinator or the participant themselves could connect to the research team. The team would follow-up with interested participants via email or phone and have them complete an electronic consent through Qualtrics Software. Once the electronic consent was completed, the participants were scheduled for the in-depth interview through videoconference. Our goal was to recruit only a subset of participants to gain a sample of qualitative experiences. Therefore, while all study participants were invited to participate, we discontinued our recruitment and consenting efforts after reaching approximately 10 participants characterized as remitters and 10 characterized as non-remitters, so as to avoid oversaturation of data. As the interview took place after completion of the main study, the narrative interview was retrospective in nature, referring to how participants have felt since their original infusions for the study.

2.2. Interview protocol and processes

The qualitative study team consisted of two faculty members, three master's level researchers with mental health credentials, and a bachelor's level research assistant. The semi-structured interview protocol (Appendix A) was designed by the faculty members and master's level researchers in consultation with members of the VA Center for Clinical Management Research Qualitative Core and Bio-K Study team. The protocol chiefly focused on eliciting rich narratives about experiences receiving intravenous ketamine treatment and beliefs about depression recovery, non-recovery, and treatment impact. Representative items included, "Can you describe your first experience during the ketamine infusions?", "Walk me through how the treatment has affected you over time, starting with right after," and "What is your understanding of how ketamine works?"

A faculty member (AL) provided qualitative interview training to the rest of the qualitative study team and demonstrated semi-structured interviewing techniques by leading the first few interviews with other team members observing. AL then observed the next few interviews conducted by other team members to ensure adherence to training and protocols. Further interviews were conducted by DL, CS, EA, EV, and IS. The interviewers asked the interview guide questions in order, and certain prompts were required as part of the interview. Interviewers were also permitted to ask follow-up or other probing questions based on interviewee responses.

Interviews on average lasted approximately 40 min. All interviews were conducted by one lead interviewer and at least one note-taker who had the opportunity to ask follow-up or clarifying questions at the end of the interview. The note-taker wrote brief memos about each interview at its conclusion. All interviews took place over a HIPAA-compliant videoconference to facilitate rapport, but only the audio track was recorded.

2.3. Data analysis

Automatic transcriptions were created, which were cleaned and edited by a research assistant who compared the transcript to the audio recording to correct errors. Dedoose Version 8.2.14, a web application for managing, analyzing, and presenting qualitative research data, was used to store and compile the codes. The study team used inductive qualitative data analysis techniques (Patton, 2018). The coding team consisted of three members of the broader qualitative study team (AL, DL, EA), including the lead faculty member. Coding team members reviewed the transcripts and held an initial discussion about the data. The coding team then obtained a second consultation with members of the VA Center for Clinical Management Research Qualitative Core for discussion of coding and analysis. Following this consultation, preliminary coding schemes were developed based on study aims and transcript review. To create a codebook, the entire coding team refined the coding scheme through iterative independent coding of the same two transcripts, which were selected based on their differentness from one another relating to extent of depression remission. The coding team discussed codes and code definitions until agreement was reached. The entire coding team then continued to refine the coding scheme through iterative independent coding of the same three additional transcripts, and again discussed codes and code definitions until agreement was reached. The first two transcripts were re-coded to reflect new codes that were developed in analysis of the following three transcripts, and five further transcripts were double-coded by two coding team members. The remaining 11 transcripts were single-coded by one of the coding team members. Two single-coded transcripts were then audited by a coding team member to check for consistency of coding approach. In sum, 12 transcripts (57 %) were coded by more than one team member, and nine transcripts (43 %) were coded by one team member. Coded transcript excerpts were examined by the entire coding team to derive themes and illustrative quotations connected to study aims, but the methodology also permitted interview responses to generate the themes that emerged spontaneously from the data. Coding team members wrote memos after each team meeting and throughout the coding process.

After coding was complete, each participant was assigned a remission-related "attribute" based on the Bio-K Study's primary outcome; the MÅDRS score. The MÅDRS is a 10-item clinician rating of depressive symptoms commonly used in ketamine research in treatment-resistant depression (Montgomery and Åsberg, 1979; Sanacora et al., 2003). Each item is scored on a 7-point scale (0 to 6) (range 0–60), with anchors at even-numbered scale points. Higher scores represent more intense depression. Its psychometric properties are well established (Williams and Kobak, 2008; Yüksel and Öngür, 2010). Scores of 44, 32, 23, 15, and 7 are suggested to designate very severe, severe, moderate, mild, and recovered depressions, respectively (Sanacora et al., 2003). In the current qualitative study, as with the Bio-K study, those with a MÅDRS score of ≤9 were characterized as remitters, and those with a score of >9 were characterized as non-remitters. Among non-remitters, those with at least a 50 % reduction in the MÅDRS score were then characterized as partial remitters. Adding remission-related "attributes" to participants took place only after all coding was complete so as not to risk overt biases in coding, although most transcripts did give some sense of the participant's remission status through their narratives.

3. Results

3.1. Participants

All 75 participants in the main Bio-K Study were invited to participate in the qualitative study (47 women and 28 men). Of these, 36 individuals expressed initial interest in the study and 21 (15 women and six men) ultimately participated in interviews. Ninety percent of the qualitative sample were white and 10 % were African-American. Their average age was 44, with a range of 27 to 66. Please see Table 1 for demographics. The average time between the date of the Bio-K infusions and the qualitative interview was 29 months and 10 days (approximately 2.4 years), with a range from 11 months, 7 days to 50 months, nine days (approximately 4.1 years). Those with a MÅDRS score of ≤9 were characterized as remitters (nine; 43 %), and those with a score of >9 were characterized as non-remitters (12; 57 %). Among the non-remitters, those with at least a 50 % reduction in the MÅDRS score were then characterized as partial remitters (three; 14 % of sample or 25 % of non-remission sample). At the time of the interview, 18 participants (86 %) had obtained further ketamine treatment after their Bio-K infusions from commercial clinics in the community or were prescribed ketamine by a provider.

3.2. Themes

3.2.1. Experience during ketamine infusions

In this sample, 12 participants (67 % of remission/partial remission group and 44 % of non-remission group) had what might be referred to as a "psychedelic-like" or dissociative experience during the infusion, such as perceptual distortions, sense of flying, or euphoria. Five in the remission/partial remission group (42 % of remission/partial remission group) and 6 in the non-remission group (67 % of non-remission group) were characterized as having had positive or pleasant experiences during infusion, and three in the remission/partial remission group (25 % of remission/partial remission group) and zero from the non-remission group were characterized as having had negative or unpleasant experiences during infusion. Twelve participants (67 % of remission/partial remission group and 44 % of non-remission group) described gaining existential insights or shifting perspectives on life related to forgiveness, compassion, or acceptance during infusions. Not all who described psychedelic experiences also had existential insights, and not all who had existential insights also had psychedelic experiences. All participants commented on the treatment milieu. Eight participants felt that any conversation with staff would interfere with the treatment process or burgeoning insights, 7 felt that they would have benefited from some type of guided discovery process, and 6 were neutral or equivocal. See Table 2 for representative quotations related to experiences during infusions.

3.2.2. Ketamine's place in a treatment trajectory

Thirteen participants (56 % of remission/partial remission group and 67 % of non-remission group) described feeling optimism and hope when initiating intravenous ketamine treatment. They often saw

Table 1
Demographics

N = 21	Remission status		
	Remitter	Non-remitter	Partial remitter
% (total)	42.86 (9)	42.86 (9)	14.29 (3)
Age — M (SD)	39.67 (9.59)	40.78 (14.60)	53.67 (9.07)
Sex — % (total)			
Male	44.44 (4)	0 (0)	66.67 (2)
Female	55.55 (5)	100 (9)	33.33 (1)
Race — % (total)			
White	100 (9)	77.78 (7)	100 (3)
Black or African American		22.22 (2)	

Table 2
Experience during ketamine infusions.

MADRS category	Representative quotation
Remitter	When I would like close my eyes it was like a black and white scene of like circles and squares kind of and just like moving horizontally across like my plane of vision, but my eyes were closed. [P3]
Partial remitter	[It] probably had a somewhat of a sedating effect. So my usual anxiety, which I certainly felt during those visits immediately before the infusions, lifted somewhat … Felt a little bit calmer, I think I remember [name of provider] asking me if I felt ecstatic or manic and wanted to go off and save the world and I never had that sort of euphoric effect. [P14]
Non-remitter	For some reason I thought about my grandmother, who I was very close to and helped raise me, and I felt like I was reaching out to her … Because I think part of the depression, that part with the constant ruminating, the part where you experience guilt for a lot of stuff you didn't have control over but letting your family down, so I think that might have been part of it. Because sometimes when I'm really stuck in a really bad depression, I think about having let my family down, let myself down. And particularly her [the grandmother] because she really basically saved me … with the ketamine, and I felt kind of weightless and just kind of floating and I didn't feel obviously any guilt. I didn't feel anything any of that stuff at that time. I don't know if I was trying to rescue her or if she was trying to rescue me and I just felt like I was reaching out to her. [P9]

ketamine as a more radical approach, which they felt was warranted due to the refractory nature of their depression. In the remission/partial remission group, a sense of excitement and even exuberance followed the realization that their depression was lifting. Many recovery narratives included changes not only in their mood, but also in their outlook, sense of interpersonal connectedness, energy, and thinking.

On the other hand, in the non-remission group, the realization that their depression was unchanged was met with profound disappointment. Non-recovery narratives discussed ketamine as if it were one link in a chain of failed treatments, each of which seeming to provide further evidence that their depression was untreatable. There was evidence of risk when adding yet another failed treatment to that chain, in that failing treatment in and of itself contributed to a sense of hopelessness.

Table 3
Ketamine's place in a treatment trajectory.

MADRS category	Representative quotation
Remitter	It was after the third treatment that I noticed a little bit of a lift in my mood, and it was like almost magical you know, to go from feeling almost catatonic and barely able to move and not wanting to live, to just maybe a sense of hope there's just a lighter, light lift to my mood. … After the first and second one I was concerned that it wasn't going to work, and this was the last resort. I mean there was nothing else. I've done every other treatment. I've done ECT, I've done everything else. So, if this didn't work, you know, it was bit ominous not to be feeling better. But like said I really trusted [study doctor] and you know, he was very good about [saying] this is our experience, sometimes it doesn't work after the first two, three, it takes everybody takes different time period … So, when I did feel that little bit of a lift after the third one, then I was very hopeful that it was going to work. [P21]
Partial remitter	I know people like myself who have tried a million things and it's frustrating. All you know if they feel hopeless, and you know I tell them that there's still stuff try, they could look into that. [P2]
Non-remitter	They told me at the time that it would open up new pathways in my brain. And so that's kind of what I was expecting to happen … I felt so disappointed that it didn't do anything for me so that made it really kind of a very negative experience. Just like the ECT and the magnet therapy, I was extremely disappointed afterwards when it didn't work [P20]
Non-remitter	Well, I can see that it looks like it's an – you know I'm reading more about it being an option for people, but I just feel disappointed that it didn't do anything for me, and I really wanted it to. [Participant was choked up and beginning to cry] [P8]

See Table 3 for representative quotations.

3.2.3. Beliefs about ketamine's mechanisms of action

To characterize participants' understanding of ketamine's mechanisms of action, they were asked *why* ketamine might impact a person's depression. Some of these beliefs were attributed to what clinical staff had already told them about how ketamine works, and others were based on their own experiences. Seven participants in the remission/partial remission group (78 %) and eight in the non-remission group (67 %) described beliefs that were characterized as principally *physical or biological*; for example, affecting brain chemicals or pathways. One in the remission/partial remission group (11 %) and four in the non-remission group (33 %) described beliefs that were characterized as *experiential*; for example, flowing from new perspectives or insights. One in the remission/partial remission group (11 %) described both biological and experiential beliefs. Recovery narratives framed improvements in wellbeing in various ways; for example, rearranging "how I was thinking about things or over-analyzing things" or giving them hope by being able to think more clearly. See Table 4 for representative quotations.

3.2.4. Qualitative versus quantitative assessment of remission status

One unexpected finding related to a contrast between quantitative and qualitative methods to assess recovery. Of the nine participants who were defined by their MÅDRS score as being in the non-remission group, five could be characterized as having experienced full or partial depression recovery based on subjective experiences taking place after the infusion. For example, one participant in the non-remission group described going off their anxiety medications completely and noticing such an improvement in functioning that they continued to seek out ketamine treatment over time. The inverse relationship was not found; in other words, none of the participants characterized as having had remission by their MÅDRS score were characterized as having non-recovery by their qualitative interview. See Table 5 for representative quotations that illustrate contrasting questionnaire and qualitative findings. (See Table 1.)

Table 4
Beliefs about ketamine's mechanisms of action.

MADRS category	Representative quotation
Remitter	You know, when you talk about depression and people talk about like breaking it down and talking about our bodies needing to be in deep rest and I think in our current culture, our current society we're so incredibly overwhelmed with all of these 'you have to be the perfect mom, you have to be the perfect career person, you have to be the perfect wife, you have to be the perfect fill-in-all-of these-blanks,' and it's overwhelming … what I feel like the ketamine did was by dissociating it gave my brain a break that it wasn't otherwise getting in any other part of my life and it forced that break … like you're leaving earth for an hour and then coming back. And so I think there is a lot of wisdom to that. Just that ability to disconnect from all of the pressures and all of the things that are placed on us every day. [P11]
Partial remitter	I guess using an analogy, if something was plugged up in your brain chemicals that weren't allowing the chemicals, the serotonin or whatever else that's up there that makes you feel better, I was hoping that this medication would have gave it a jolt and get it moving again. [P7]
Non-remitter	When I feel really low or really anxious … I feel like I can feel myself getting on that kind of on ramp of negative thinking that's very familiar… repeating the same negative beliefs, it seems like (laughs) and I feel like I have more awareness of that [since the ketamine] and when that happens. Which it still does, and I could feel the rigidity of that. I feel stuck when I feel really depressed and I felt very stuck, and so [ketamine] increased brain flexibility. It felt like an opportunity to feel like a little less stuck even just being aware of like, oh, this is just this familiar line of thinking happening again in my brain. Felt like an increased flexibility, rather than just going down that path, without being aware of it at all. [P6]

Table 5
Contrasting qualitative and quantitative assessment of remission status.

Categorizations	Representative quotation
MADRS: non-remitter; qualitative: recovery	I found it was working. I have since gone off my anxiety meds completely. And you know it's not a magic wand it doesn't change everything, but I have definitely noticed an improvement in my generalized anxiety and my moods, so I have pursued [ketamine] for treatment. [P1]
MADRS: non-remitter; qualitative: partial recovery	It didn't help as much as I hoped. I think at the time, I really had a sense that, like some people had a couple infusions and then we're like way better forever. And that is not what happened to me, but it did make a really marked improvement and like functioning and being able to do things again. [P6]
MADRS: non-remitter; qualitative: partial recovery	After a negative emotion or a negative thought, or I was put into a bad situation at work, my first thought wasn't a suicidal thought. That wasn't my automatic trigger in my head. A lot of my suicide symptoms alleviated themselves. Unfortunately, they started to come back recently, but my energy levels were up. I think I was able to stay optimistic, especially during that first lockdown [during the COVID-19 pandemic] so I pretty much wrapped up my first set of ketamine treatments right as the shelter in place happened or stayed home orders, so I think that put me in a really good spot to get through those first few months. [P13]

4. Discussion

In this sample, both remission and non-remission groups had varying levels and types of psychedelic experience, pleasantness or unpleasantness, and existential insights during infusions. Their attributions related to ketamine's mechanism of action, whether primarily experiential or biological, also varied. Consistent with previous research (Luckenbaugh et al., 2014), this finding suggests that it is important to set expectations for prospective patients such that even if no special insights or psychedelic experiences take place, it is quite possible to have a treatment response to intravenous ketamine. Decoupling the psychedelic experience with clinical outcomes has an added benefit of avoiding needlessly high doses of ketamine to achieve dissociative effects, since dissociation is neither necessary nor sufficient for a beneficial effect (McIntyre et al., 2021; Luckenbaugh et al., 2014). Conversely, as some patients describe gaining meaningful insights during infusions, and having these insights continue to inspire over time even in non-recovery from depression, clinicians should be ready to convey support for those attributions and not downplay their potential meaning in patients' lives. As patients had varying levels of interest in guided conversation from staff, their preferences should also be discussed at the outset of treatment and revisited once they are familiar with the infusion process. In the absence of published manuals or pivotal trials of ketamine-assisted psychotherapy, our findings do not provide additional support for psychotherapy during or immediately after IV ketamine.

We observed that among participants who did not recover from depression, unsuccessful intravenous ketamine treatment in and of itself contributed to disappointment and perhaps even hopelessness. Several described a long chain of ineffective treatments, cautious hope upon learning about ketamine, and crushing disappointment upon realizing it did not work for them. One could argue that among people with treatment-resistant depression, *disappointment* should be considered a key risk of pursuing any novel treatment, and that this risk should be discussed alongside medically oriented risks such as high blood pressure or confusion. Discussing possible disappointment upfront using open-ended questions and guided discovery could help vulnerable patients appropriately set their expectations and gather the supports they may need if treatment proves to be unsuccessful.

Patient recovery narratives included information about changes not just to mood, but to outlook, connectedness, energy, and thinking. One unexpected finding related to a contrast between questionnaire and qualitative methods to assess remission status, whereby a subset of patients categorized as having experienced non-remission by MÅDRS score attributed significant recovery gains to ketamine in their qualitative interviews, such as with decreased suicidal ideation. The discrepancy between the two assessment methods highlights the importance of eliciting patient narratives when attempting to capture the full range of outcomes associated with a novel treatment. It could be that for some patients, quality of life may increase even if psychiatric symptoms do not improve. The *two continua model* of mental illness and mental health suggests that these are related but distinct continua: one indicates the presence or absence of mental health, the other the presence or absence of mental illness (Iasiello et al., 2019; Westerhof and Keyes, 2009). Prior qualitative studies of ketamine treatment also begin to suggest the value of exploring multiple recovery continua; for example, through finding that changes in suicidal ideation can occur independently from changes in mood (Ballard et al., 2017; Ballard et al., 2018; Phillips et al., 2016; Wilkinson et al., 2018).

The current study should be understood in the context of some limitations. Our sample consisted only of individuals with treatment-resistant depression and was homogenous with respect to race and ethnicity. People with differing identities, or with diagnoses to include substance abuse, chronic pain, or PTSD, may have discussed different themes. Our retrospective narrative study presents significant heterogeneity with respect to how many ketamine treatment participants received and how much time had elapsed since the original ketamine infusions; for example, the average time between the date of the Bio-K infusions and the qualitative interview was 29 months and 10 days, with a range from 11 months, 7 days to 50 months, nine days. There is some heterogeneity with respect to pursuit of further treatment as well, with 86 % of participants having sought out additional ketamine treatments in the community after participation in Bio-K. We see this as potentially coloring participants' recollections of their original series of infusions, although not a confounding variable per se, given our qualitative aims of achieving a better understanding of patient narratives across varying experiences.

The current qualitative study characterizes narratives among people receiving ketamine infusions for treatment-resistant depression, whether or not they experienced remission from depression. While we consider measurement-based care to be critical for all, we found evidence of intravenous ketamine launching a process of recovery that goes beyond the result of a short-term depression rating scale, highlighting the importance of multiple research methodologies to characterize the effects of a novel intervention, and illustrating the value of a comprehensive approach to assessment of depression recovery.

CRediT authorship contribution statement

Adrienne Lapidos designed the qualitative study, led development of the protocol, conducted qualitative interviews, led qualitative data analysis, led literature search process, and was the lead writer of the manuscript.

Daniela Lopez-Vives contributed to the development of the protocol, conducted qualitative interviews, contributed to qualitative coding, contributed to qualitative data analysis, led literature searches and analyses, and made substantial edits to the manuscript.

Cortney E. Sera contributed to the development of the protocol, conducted qualitative interviews, contributed to data analysis, contributed to the literature search process, made edits to the manuscript and participated in developing the manuscript.

Elizabeth Ahearn conducted qualitative interviews, contributed to qualitative coding, contributed to qualitative data analysis, contributed to literature searches and analyses, and participated in developing the manuscript.

Erica Vest conducted qualitative interviews, contributed to literature searches and analyses, and participated in developing the manuscript.

Ivana Senic conducted qualitative interviews and participated in developing the manuscript.

Jennifer L. Vande Voort is a lead investigator for the main (Bio-K) study, contributed to the design of the qualitative study, and made substantial edits to the manuscript.

Mark Frye is a lead investigator for the main (Bio-K) study, contributed to the design of the qualitative study, and participated in developing the manuscript.

Fernando S. Goes is a lead investigator for the main (Bio-K) study and made substantial edits to the manuscript.

Eric Achtyes is a lead investigator for the main (Bio-K) study and made substantial edits to the manuscript.

John Greden is a lead investigator for the main (Bio-K) study and made substantial edits to the manuscript.

Sagar V. Parikh is a lead investigator for the main (Bio-K) study, conceived of the qualitative study, co-designed the qualitative study, contributed to the development of the protocol, guided and contributed to the literature search process, and was the co-lead writer of the manuscript.

Declaration of competing interest

Adrienne Lapidos, Daniela Lopez-Vives, Cortney E. Sera, Elizabeth Ahearn, Erica Vest, Ivana Senic, and John Greden have no conflicts of interest to declare.

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Dr. Achtyes has served on advisory boards or consulted for Alkermes, Atheneum, Janssen, Karuna, Lundbeck/Otsuka, Roche, Sunovion and Teva and reports previous stock holdings in AstraZeneca, Johnson & Johnson, Moderna, and Pfizer.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jad.2022.11.090.

References

Ballard, E.D., Wills, K., Lally, N., Richards, E.M., Luckenbaugh, D.A., Walls, T., Ameli, R., Niciu, M.J., Brutsche, N.E., Park, L., Zarate, C.A., 2017. Anhedonia as a clinical correlate of suicidal thoughts in clinical ketamine trials. J. Affect. Disord. 218, 195–200. https://doi.org/10.1016/j.jad.2017.04.057.

Ballard, E.D., Yarrington, J.S., Farmer, C.A., Richards, E., Machado-Vieira, R., Kadriu, B., Niciu, M.J., Yuan, P., Park, L., Zarate, C.A., 2018. Characterizing the course of suicidal ideation response to ketamine. J. Affect. Disord. 241, 86–93. https://doi.org/10.1016/j.jad.2018.07.077.

Iasiello, M., van Agteren, J., Keyes, C.L., Cochrane, E.M., 2019. Positive mental health as a predictor of recovery from mental illness. J. Affect. Disord. 251, 227–230. https://doi.org/10.1016/j.jad.2019.03.065.

Jilka, S., Odoi, C.M., Wilson, E., Meran, S., Simblett, S., Wykes, T., 2021. Ketamine treatment for depression: qualitative study exploring patient views. BJPsych Open 7 (1). https://doi.org/10.1192/bjo.2020.165.

Lascelles, K., Marzano, L., Brand, F., Trueman, H., McShane, R., Hawton, K., 2019. Effects of ketamine treatment on suicidal ideation: a qualitative study of patients' accounts following treatment for depression in a UK ketamine clinic. BMJ Open 9 (8), e029108. https://doi.org/10.1136/bmjopen-2019-029108.

Luckenbaugh, D.A., Niciu, M.J., Ionescu, D.F., Nolan, N.M., Richards, E.M., Brutsche, N. E., Guevara, S., Zarate, C.A., 2014. Do the dissociative side effects of ketamine mediate its antidepressant effects? J. Affect. Disord. 159, 56–61. https://doi.org/10.1016/j.jad.2014.02.017.

McIntyre, R.S., Rosenblat, J.D., Nemeroff, C.B., Sanacora, G., Murrough, J.W., Berk, M., Stahl, S., 2021. Synthesizing the evidence for ketamine and esketamine in treatment-resistant depression: an international expert opinion on the available evidence and implementation. Am. J. Psychiatr. 178 (5), 383–399.

Mollaahmetoglu, O.M., Keeler, J., Ashbullby, K.J., Ketzitzidou-Argyri, E., Grabski, M., Morgan, C.J.A., 2021. "This is something that changed my Life": a qualitative study of patients' experiences in a clinical trial of ketamine treatment for alcohol use disorders. Front Psychiatry 12. https://doi.org/10.3389/fpsyt.2021.695335.

Price, R.B., Kissel, N., Baumeister, A., 2022. International pooled patient-level meta-analysis of ketamine infusion for depression: in search of clinical moderators [published online ahead of print, 2022 Sep 7]. Mol. Psychiatry. https://doi.org/10.1038/s41380-022-01757-7 doi:10.1038/s41380-022-01757-7.

Montgomery, S.A., Åsberg, M.A.R.I.E., 1979. A new depression scale designed to be sensitive to change. Br. J. Psychiatry 134 (4), 382–389.

Patton, M.Q., 2018. Evaluation science. Am. J. Eval. 39 (2), 183–200. https://doi.org/10.1177/1098214018763121.

Perlis, R.H., Ostacher, M.J., Patel, J.K., Marangell, L.B., Zhang, H., Wisniewski, S.R., Ketter, T.A., Miklowitz, D.J., Otto, M.W., Gyulai, L., Reilly-Harrington, N.A., Nierenberg, A.A., Sachs, G.S., Thase, M.E., 2006. Predictors of recurrence in bipolar disorder: primary outcomes from the systematic treatment enhancement program for bipolar disorder (STEP-BD). Am. J. Psychiatr. 163 (2), 217–224. https://doi.org/10.1176/appi.ajp.163.2.217.

Phillips, J., Norris, S., Talbot, J., Owoeye, O., Blier, P., 2016. Direct effect of ketamine on suicidal ideation independent of its effects on depressive symptoms. Eur. Neuropsychopharmacol. 26, S472. https://doi.org/10.1016/s0924-977x(16)31473-0.

Sanacora, G., Rothman, D.L., Mason, G., Krystal, J.H., 2003. Clinical studies implementing glutamate neurotransmission in mood disorders. Ann. N. Y. Acad. Sci. 1003 (1), 292–308. https://doi.org/10.1196/annals.1300.018.

Swainson, J., McGirr, A., Blier, P., et al., 2021. The Canadian network for mood and anxiety treatments (CANMAT) task force recommendations for the use of racemic ketamine in adults with major depressive disorder. Can. J. Psychiatr. 66 (2), 113–125. https://doi.org/10.1177/0706743720970860.

Warden, D., Rush, A.J., Trivedi, M.H., Fava, M., Wisniewski, S.R., 2007. The STAR*D project results: a comprehensive review of findings. Curr. Psychiatry Rep. 9 (6), 449–459. https://doi.org/10.1007/s11920-007-0061-3.

Westerhof, G.J., Keyes, C.L.M., 2009. Mental illness and mental health: the two continua model across the lifespan. J. Adult Dev. 17 (2), 110–119. https://doi.org/10.1007/s10804-009-9082-y.

Wilkinson, S.T., Ballard, E.D., Bloch, M.H., Mathew, S.J., Murrough, J.W., Feder, A., Sos, P., Wang, G., Zarate, C.A., Sanacora, G., 2018. The effect of a single dose of intravenous ketamine on suicidal ideation: a systematic review and individual participant data meta-analysis. Am. J. Psychiatr. 175 (2), 150–158. https://doi.org/10.1176/appi.ajp.2017.17040472.

Williams, J.B.W., Kobak, K.A., 2008. Development and reliability of a structured interview guide for the Montgomery-Åsberg depression rating scale (SIGMA). Br. J. Psychiatry 192 (1), 52–58. https://doi.org/10.1192/bjp.bp.106.032532.

Yüksel, C., Öngür, D., 2010. Magnetic resonance spectroscopy studies of glutamate-related abnormalities in mood disorders. Biol. Psychiatry 68 (9), 785–794. https://doi.org/10.1016/j.biopsych.2010.06.016.