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Therapeutic use of ketamine in psychiatric disorders

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Therapeutic use of ketamine in psychiatric disorders

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ORIGINAL RESEARCH
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"This Is Something That Changed My Life": A Qualitative Study of Patients' Experiences in a Clinical Trial of Ketamine Treatment for Alcohol Use Disorders

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Background: The therapeutic benefits of ketamine have been demonstrated for a variety of psychiatric disorders. However, the role of ketamine induced psychoactive experiences in mediating the therapeutic effects is unclear. Despite the growing quantitative research on the efficacy of ketamine treatment, very few studies examined participant experiences of ketamine infusions in a treatment setting.

Aims: The current study aimed to examine participant experiences of ketamine infusions and how these relate to therapeutic mechanisms in a clinical trial setting.

Methods: We conducted semi-structured interviews with 12 participants who received up to three ketamine infusions (0.8 mg/kg) as part of a Phase II double blind, randomised controlled trial. The interviews explored participants' acute experiences of ketamine infusions, experiences of psychotherapy/education, and the lasting effects of the trial. The interviews were transcribed verbatim and analysed using thematic analysis.

Results: Six key themes were identified. (1) Participants reported multifaceted motivations for trial participation. (2) The set and setting was found to be influential in determining acute ketamine experiences. The acute ketamine experiences included: (3) the inherent contradictions of the experience (e.g., dissociation vs feelings of connection), (4) rapidly fluctuating and changing experiences, (5) meaningful, mystical and spiritual experiences. Finally, the final theme (6) relates to the transformational effects of the infusions and the trial.

Conclusion: Provided in a supportive and professional environment, ketamine treatment led to a significant change in relationship with alcohol. Ketamine induced ego dissolution and dissociation were reported to be related to the transformational effects on relationship with alcohol. The extent to which the acute psychoactive effects of ketamine mediate therapeutic effects on drinking outcomes remain to be investigated in the trial data. The acute effects of ketamine reported by our participants transcend its traditional

conceptualisation as a "dissociative anaesthetic"; therefore, we suggest the development or use of new measures alongside ketamine infusions to fully capture the spectrum of these effects which may be crucial in its therapeutic and transformative effects.

Keywords: alcohol use disorder, ketamine, psychedelics, dissociation, thematic analysis, qualitative study, clinical trial

INTRODUCTION

Ketamine is an N-methyl-d-aspartate (NMDA) receptor antagonist, which produces powerful dissociative effects. Ketamine was initially developed in the 1960s as an anaesthetic drug (1), but there has been a recent escalation in interest for its use in treating psychiatric disorders. Ketamine has been characterised as a "dissociative anaesthetic" due to strong sensory dissociation associated with it (1) [for a review of terminology referring to similar classes of drugs including "psychedelics," "hallucinogens," "entheogens," "psychotomimetics" see (2)]. At a sub-anaesthetic dose, ketamine has been shown to display rapid antidepressant effects (3–5) and there is further evidence demonstrating its therapeutic benefits for a variety of psychiatric disorders such as unipolar/bipolar depression, post-traumatic stress disorder, generalised anxiety disorders, obsessive compulsive disorder, and substance use disorders (6). A small number of studies demonstrate the therapeutic effects of ketamine on drug abstinence, drug use, craving and withdrawal [see (7) for a review], and most recently alcohol use disorder (8, 9). Although the safety and efficacy of ketamine has been well-established, few studies thus far have looked at the phenomenological experiences of people who have been given the drug therapeutically and how these relate to mechanisms of therapeutic benefits (10, 11).

Ketamine acutely can induce mystical and psychedelic effects [for a full review of mechanisms of action see (12)]. Whilst these have been thought of as adverse effects in the psychiatric literature, there is evidence to suggest that these effects may be important therapeutically. In an early study of Ketamine Psychedelic Therapy in patients with alcohol use disorders, negative experiences during the ketamine session (i.e., experiences associated with fear, anxiety, horror, and other negative emotions) were positively correlated with the length of remission (13). In a subsequent study where participants with heroin use disorders were randomised to receive either a "psychedelic" dose of ketamine [2.0 mg/kg Intramuscular (IM)] or a "sub-psychedelic" dose (0.2 mg/kg IM), the rate of abstinence over 2 years was higher in the former group than the latter (14) indicating a therapeutic benefit of ketamine-induced psychedelic experiences. Additionally, in a recent report antidepressant response was correlated with dimensions of altered states of consciousness such as feelings of unity, spirituality and insight (15). Moreover, ketamine's therapeutic effects on motivation to quit cocaine and cocaine use were mediated by ketamine's mystical type effects—but not dissociative effects (16, 17). Whilst some studies (18, 19) have described the experiences during treatment, there have been no qualitative studies of the experiences of participants during ketamine treatment for alcohol use disorders, and as far as we are aware of only a handful of studies that have looked at ketamine experiences qualitatively in any treatment setting (10, 11).

The participants in the present study were a subsample of participants from a recently completed randomised controlled trial, Ketamine for the Reduction of Alcoholic Relapse (KARE), which investigated ketamine as a treatment for alcohol use disorders (8). In this trial, three infusions of ketamine, compared to matched placebo, were found to be effective at prolonging abstinence from alcohol in recently detoxified patients with alcohol dependence, with the greatest benefit at 6 months observed in those who had also received psychological therapy. Whilst quantitative data are useful for establishing efficacy of novel treatments, qualitative data about patient experiences may provide insight into potential mechanisms of such treatments, particularly in newly developing fields such as psychedelic treatment. Additionally, qualitative data can provide important additional information alongside psychometric measures from clinical trials such as motivations and experiences of ketamine treatment which can inform the design of future trials. In the current study, we investigated the retrospective subjective experiences of participants who received at least one ketamine infusion and psychotherapy/psychoeducation as part of this clinical trial. Through semi-structured interviews we aimed to explore participants' acute psychological experiences under the ketamine infusions and perceived long-term effects of ketamine treatment and the overall trial.

MATERIALS AND METHODS

Design

The current study involved semi-structured interviews which lasted up to an hour and a half each and were conducted by two members of the team (O.M.M., J.K.). Before commencing the interview, participants were invited to guess which condition they had been allocated to, as they had been blinded up to this point. The interviews comprised of three main sections: questions based on acute and subacute ketamine experiences, experiences of rumination (reported elsewhere), and current drinking levels (see **Appendix** for the interview schedule). Participants were invited to elaborate on their experiences using prompts and were invited to share any other experiences they thought were particularly important.

Participants

Twelve participants (nine males and three females) who had previously taken part in a Phase-II double blinded randomised controlled multisite trial in London and South West England were recruited in this follow-up study. The main inclusion

criteria for the trial were being 18-60 years old, meeting the Diagnostic and Statistical Manual of Mental Disorders (DSM)-V criteria for severe alcohol use disorder or DSM-IV criteria for severe alcohol dependence in the past 12 months, currently abstinent from alcohol, and a negative urine drug screen. Individuals on other relapse prevention medication or antidepressants, those with uncontrolled hypertension, and those with history of psychosis or first-degree family history of psychosis were excluded [Full criteria are reported in McAndrew et al. (8)].

Setting

The aim of the KARE trial was to assess the efficacy of ketamine infusions combined with psychotherapy or alcohol education on reducing relapse rates in recently detoxified alcohol dependent individuals. In this trial, participants were given ketamine (0.8 mg/kg) or saline placebo infusions weekly for 3 weeks alongside seven sessions of either psychological therapy or alcohol education. The therapy or education sessions were always timed immediately before the infusion and ∼24 h after the infusion. Prior to each infusion participants were read a script to prepare them for the ketamine experience, which included a suggestion to consider an intention for the session if they wanted to. The infusion was administered by a blinded anaesthetist through a cannula in the arm. During the infusion participants reclined on a bed in a single room with dimmed lights, listening to soothing music on headphones. Full instructions provided to participants prior to their infusions can be found in the **Supplementary Materials**. The infusion lasted 40 min and a psychologist and a nurse were present throughout the infusion. Participants rated potential side effects before, during and after the infusion on a standard scale developed for ketamine. Participants were followed up at 3 and 6 months after the end of treatment. Further details of the KARE trial are published elsewhere (8). Out of 48 participants who had been allocated to the ketamine group, only 25 were contactable. This is because the consent forms outlining whether they had consented to being contacted about future research were not accessible for all participants at the time due to one of the clinical trial units being closed during the COVID-19 Pandemic. These individuals were invited to take part in this qualitative research and offered £30 reimbursement in online vouchers for their participation. Ethical approval for this study was obtained from the Institutional Ethics Committee at the University of Exeter (Reference no: eCLESPsy001453 v7.1).

Procedure

Participants were contacted with an information sheet and consent form for the study. Each participant was given a participant ID and the data collected as part of the study was stored separately from the consent forms. After giving informed consent, participants who received at least one ketamine infusion were invited to an online interview to gather data on their acute experiences during the ketamine infusions. All interviews were conducted online over Zoom, each interview was audio recorded in its entirety and was transcribed verbatim by Zoom. The recordings were checked by researchers for transcription accuracy. Participants' personal details were removed from the transcripts to preserve anonymity and the audio recordings were deleted once the interviews were transcribed and checked.

Data Analysis

The qualitative data were analysed with Reflexive Thematic Analysis (TA). Reflexive Thematic Analysis as defined by Braun and Clarke (20), seeks to identify patterns of meaning across a dataset. It involves using qualitative methods of data collection and analysis, within a qualitative paradigm (20, 21). It is theoretically flexible and can be used in different frameworks to answer different questions (20). We adopted a realist/essentialist approach, whereby we assumed a straightforward relationship between language and meaning. We initially sought to identify participants' experiences of ketamine at different stages of the trial; pre-trial, acute experiences, and subacute experiences. Our analysis was partly theoretical in that it was conducted within the lens of current research on ketamine and its effects. However, we endeavoured to stay as close as possible to the participants' experiences and in doing so uncovered some effects of ketamine previously not reported in other quantitative studies.

We followed the six stages of analysis identified and developed by Braun and Clarke (20, 22). Two researchers reviewed the transcripts numerous times to familiarise themselves with the data. Initial codes were developed following a line by line reading of the transcripts. After coding transcripts independently, the researchers compared and discussed any discrepancies in coding labels and conceptualisations of the codes. A consensus was reached between the two researchers for each code, disagreements between the two researchers were resolved by discussion with a third researcher. Codes were then analysed further to identify overarching themes underpinning the data and develop a thematic model. Identifying themes was an iterative and collaborative process involving the whole research team.

All researchers involved in the process considered how their knowledge and experience might be impacting on the research at all stages, as they wanted to stay close to the participants experiences. Memos and research notes were kept to record this process of reflection and this was a regular point of discussion in research meetings. Literature on ketamine was partly drawn upon to structure the analysis as we initially explore experiences before trial participation, during acute and subacute effects of ketamine, and the long term effects of ketamine and the trial.

RESULTS

Participant Characteristics

The demographic and clinical characteristics of the sample who took part in the interviews are reported in **Table 1**. Ten participants reported their age, which at the time of interview ranged from 22 to 59 ($M = 46.5$, $SD = 11.1$). One participant identified as Scottish Iranian, and the rest were White. The time from last infusion to interview ranged from 11 months to 3 years and 4 months. All participants except one were in employment at the time of interviewing. Demographic details of the full sample and results of psychometric measurements will be available in the publication of the main trial data. Four of the

twelve interviewed participants had received the psychotherapy as part of the trial and the rest took part in alcohol education sessions. All participants interviewed here correctly guessed their allocation in the ketamine group.

At the time of enrolment in the KARE trial, participants had met a mean of 7.7 ($SD = 1.91$) DSM-V criteria. Current DSM V criteria were not measured at the time of interview, however we recorded current drinking days per month and current craving levels (see **Table 1**). Craving scores on the Alcohol Craving Questionnaire Short Form—Revised ranged from 1.34 to 4.57 ($M = 2.91$, $SD = 0.82$). Out of 12 participants interviewed here, three were completely abstinent at the time of the interview and one was abstinent except a recent binging episode. Following the trial, length of abstinence ranged from nearly 2 weeks to 14 months for those who were no longer abstinent, two participants had completely remained abstinent since their participation in the trial. Reasons for breaking abstinence following the trial included mainly social events, stress and low mood, desire to drink and celebrations. The rates of abstinence from alcohol use in the total sample of the original KARE trial ($N = 96$) will be reported in the publication of the main trial. The characteristics of the sample interviewed closely resembled those of the total sample ($N = 96$). Though a higher proportion of participants interviewed here had received alcohol education compared to psychotherapy, which was allocated on a 1:1 ratio in the trial.

Qualitative Results

Six key themes were identified following our thematic analysis of all interviews, which explored participants' experiences at all stages of the trial (prior to the trial, acute experiences, subacute experiences, and post-trial effects). These themes, which are explored in detail below, include (See **Table 2**):

1. Multifaceted motivations for seeking ketamine in a clinical trial.
2. Set and Setting as influential in determining acute ketamine experiences.
3. The inherent contradictions of the acute ketamine experience.
4. Rapidly fluctuating and changing ketamine experiences.
5. Meaningful, spiritual and mystical experiences.
6. The ketamine infusions and the trial as potentially transformative.

Multifaceted Motivations for Seeking Ketamine in a Clinical Trial

Participants' motivations to take part in the trial were often multifaceted, with participants citing more than one reason for their participation. The key motivations for participation identified included: concern over their own alcohol use, hitting rock bottom, altruism, legitimacy of the trial, and curiosity. Motivations were both internally focused (e.g., participant's recognising their relationship with alcohol meant they needed to take action to benefit their health) and externally influenced (the legitimacy of the trial at a University and hospital encouraged participation).

Concern Over Alcohol Use and Health

Participants were motivated to take part in the trial when they assessed their own health as requiring action: "*I was looking for ways to just become a lot healthier. And to become just absolutely teetotal*" (P08). For the majority of participants, concerns over alcohol use were a key motivator for taking part.

Hitting Rock Bottom

Some participants felt that their alcohol use was beginning to "*spiral out of control*" (P12) and reported feelings of hopelessness and suicidal thoughts related to their level of drinking, which led them to engage with the trial. In this way the trial was described as a "*last chance*": "*I was at my wit's end, at my lowest point. I had no escape, no way out of alcohol to the point of I knew if I carried on, it would kill me*" (P03).

Altruism

For some participants it was also the potential to help others through taking part in this clinical research trial that provided extra motivation for them to sign up: *"My thought behind this process was that if I did these 6 months and it helped others. That's something that I, I, you know, it's a little bit of extra incentive for me*" (P05).

Legitimacy of the Trial and Curiosity

The legitimacy of the trial afforded by it being conducted at a well-known University and a hospital, seemed to provide reassurance for participants and sparked their curiosity to participate:

> "*I sort of tend to be a little bit cautious with these sorts of things, but because it was sort of university and hospital based, I thought well you know, why not give it a go. The risks seem very small*" (P02).

Indeed, many participants reported curiosity related to the trial advertisement, noting in particular, interest in exploring ketamine therapy as part of a clinical trial setting.

Set and Setting as Influential in Determining Acute Ketamine Experiences

Set

Participants' expectations of the infusions, elicited from past experiences of changes in consciousness with and without drugs, had an impact on their acute experiences of ketamine. Similarly, the absence of prior drug experience exerted an influence on participants' acute experiences. For some participants who had not used drugs recreationally in the past, the ketamine experience was particularly novel. For one participant, speaking to a friend who had used hallucinogenic substances prior to their second infusion helped them to feel more "prepared" for the experience:

> "*And he advised me just to relax, he said, just chill out. Just have the confidence that you're gonna you're going to get out of this. And the whole situation will be more, will be better for you. And basically, yeah that's. I was prepared for it*" (P04).

Participants' prior mindset and spiritual beliefs were also reported to affect their acute ketamine experience: "*And for me,*

TABLE 1 | Demographic and clinical characteristics of participants.

ID	Age	Gender	Ethnicity	Site	DSM-V criteria at baseline	Total number of infusions	Total number of psychotherapy/ education sessions	Psychotherapy or alcohol education allocation	Current drinking days per month	Current craving levels (ACQ-SF-R)	Abstinence following the trial	Reasons for breaking abstinence	History of anxiety	History of depression	Time from last infusion to interview
P02	59	Male	White	Exeter	4	3	7	Psychotherapy	20-25	2.74	39 days	Social event	No	No	2 years and 8 months
P03	47	Female	White	Exeter	9	3	7	Psychotherapy	0 (Abstaining)	3.45	Fully abstinent	N/A	Yes	Yes	1 year and 8 months
P04	53	Male	White	Exeter	7	3	7	Alcohol education	8-10	2.58	40 days	Desire to drink	No	Yes	1 year and 1 month
P05	53	Male	White	Exeter	10	3	7	Psychotherapy	0 (Abstaining)	2.08	Fully abstinent	N/A	No	No	11 months
P06	56	Female	White	London	5	3	7	Alcohol education	20	2.45	2 months	Celebration	Yes	Yes	1 year and 8 months
P07		Male	White	London	7	3	7	Alcohol education	0 (Abstaining)	3.55	6 months	Stress and low mood	Yes	Yes	1 year and 1 month
P08	42	Male	Scottish Iranian	London	9	3	7	Alcohol education	8	4.57	1-2 months	Social event	No	Yes	2 years and 3 months
P09	35	Male	White	London	9	3	7	Psychotherapy	2	3.11	1 month	Social event	Yes	Yes	1 year and 2 months
P10		Male	White	Exeter	9	3	7	Alcohol education	3-4 days (Abstinent except for a recent binge)	2.97	14 months	Stress and low mood	Yes	Yes	1 year and 1 month
P11	50	Male	White	Exeter	10	3	7	Alcohol education	14	2.58	12 days	Social event	No	No	2 years and 6 months
P12	22	Male	White	Exeter	7	3	7	Alcohol education	15-20	3.5	2 months	Social event	No	No	2 years and 4 months
P13	48	Female	White	Exeter	7	1	2	Psychotherapy	28	1.34	Not known	N/A	Missing	Missing	3 years and 4 months

DSM-V, Diagnostic and Statistical Manual of Mental Disorders 5th version; ACQ-SF-R, Alcohol Craving Questionnaire Short Form Revised. The participant allocated ID number 01 was subsequently not available for interview.

TABLE 2 | Themes, codes, example quotations.

1. Multifaceted motivations for seeking ketamine in a clinical trial	
Concern over alcohol use and health	"*I was aware I was drinking too much, and it looked like a very interesting way of beginning to address it.*" (P13)
Hitting rock bottom	*"...for me, it was kind of it felt like kind of like the last chance saloon really to kind of do something..."* (P09)
Altruism	"*… I thought what if the ketamine trial proves successful and you know it just saves one life, someone who might die because of alcohol dependency issues, and then it is worth my continuing.*" (P04)
Legitimacy of the trial and curiosity	"*...I used to have a personal trainer and I noticed he posted on Facebook actually the KARE trial was happening. And that's why I saw about it and I just got intrigued by it.*" (P11)
2. Set and Setting as influential in determining acute ketamine experiences	
Set	"*... I've done that before with ketamine but in a gang of friends, which is kind of what you do with friends and it's all a bit sloppy and daft after a big techno night and it's not something I've done much in the last five years before the trial anyway. But you know, I do know that world and they're lovely*" (P06)
Setting	"*I had no idea what would happen... but then after that, the second and third I sort of went into the sessions with more intent to explore and to get answers from certain things... it was nice to just do that and know that you're in a safe environment and you can come out the other side...It filled you with confidence and you know there's no paranoia.*" (P10)
3. Inherent contradictions of acute experience	
Positive effects	
A. Calmness and relaxation	"*It was peaceful. It was calming and I just sat back and... you know, I didn't lose sense of who I was. I always knew who I was, and I had confidence that this would be temporary.*" (P04)
B. Reinforcing effects	"*I wanted this to carry on every week for the rest of my life. I wanted this experience in this, you know, sort of clinical place, I would still be coming now you know what I mean?*" (P05)
Negative experiences	
A. Fear or panic	"*I knew where I was, but I just, it wasn't a pleasant experience like the first one and then the end part, the second one. It was, it was scary. And to the point of when you're on it, you barely breathe, you've quite shallow breathing.*" (P03)
B. Paranoid ideation	"*So it was a sort of mixture of extreme comfort for want of a better word with a sort of paranoia where one's brain is saying, if you guys in the room will leave the room, I'm stuck here for the rest of my life, sort of thing.*" (P02)
C. Paralysis	"*It's almost like a state of paralysis, where you do receive visual and sound information. But I don't know how much sense I was making to the people in the room around me. It feels like when you try and run in a dream, but your legs are move fast enough. In fact, exactly like that."* (P08)
D. Nausea and vomiting	"*I was I didn't feel particularly brilliant, to be honest. And then I started moving and just was aware I was going to be sick. And then I was quite violently sick. So that was my experience.*" (P13)
Otherworldly experiences	"*Well, that infusion took me somewhere that was out outworldly, was out of this world. It was not—it was not within this world.*" (P05)
Dissociation, detachment, and floating	"*… as far as I was concerned that was it. I was done. My human body wasn't—I didn't have a human body. I was something… And even though I knew that I was kind of tethered, I didn't know how I was going to get back to my body.*" (P05)
Ego dissolution	"*The experience was genuinely remarkable in terms of the both the visual effects and…. the sort of removal of ego that accompanied that. I felt that I was one with the whole universe and it sounds hippy dippy but that's how I felt... I think I related to this sort of ego changing, the size of the ego in me as well as a sort of physical sensation.*" (P07)
Changes in experiences over time	"*So, the first one was very trippy and like going into another dimension. And then the second one, because I wanted to go into that dimension, I think I was trying to go there and then I got a bit sort of like, oh, I can hear voices. This is putting me off... And then the third one... I wasn't well at all after that...As I said I couldn't come around from it.*" (P03)
4. Rapidly fluctuating and changing experiences	
Perceptual distortions	
A Visual distortions	"*I remember looking at the light above my head in the window and sort of blinking and as I blinked the of the colours changed. Even though... the picture in my mind, the light in the window was the same.*" (P07)
B Auditory distortions	"*...there were pieces that I was familiar with, but they were just, they were coming—It's like different aspects that made up the piece were coming through a different speeds or different pitches. They were just sounding like unique. … I could still hear them as piano pieces but they weren't the pieces that I knew.*" (P04)
C Hallucinations or visions	"*I saw...this very strong vision of the synapse travelling across the neural pathway, then me typing into my phone, him getting the message him talking to someone else, and like this chain of communication, essentially that got bigger and bigger and bigger and bigger and bigger, to the point where it zoomed right out and you're seeing the earth hanging there in space along with say 20, 25, 30 other inhabited planets all there in the cosmos.*" (P09)
5. Meaningful, spiritual, and mystical experiences	
Ego dissolution	"*It was a sense of completeness sense of, I suppose in a way finality, a source of finish. But also, a sense of enormous growth and a feeling of oneness with other entities, other living beings in particular, but also the world and universe as a whole.*" (P.07)
Epiphanies and Enlightenment	"*I think the first two like, they sort of left me… like they answered a lot of questions. You know, thinking about my children and I have a stepdaughter and… It was things about that. And about, you know what I should be doing and how I should be, you know, I don't know it seemed to be like all the things that are really heavy on my mind and that I stress about whatever it was sort of going through those things...just realising how little importance some things had or were...*" (P10)

(Continued)

TABLE 2 | Continued

Transcendence of time	"*...while we're on the subject of time. I mean, that just goes bananas and I love it... It's almost like... this afternoon, this evening, the way we think of that—That just blows apart and doesn't exist anymore.*" (P06)
Hallucinations or visions	"*I was lying there, and there was this, there was this like a cacophony coming from the hallway, everyone was going like, like he's coming he's coming! And I was like what's going on, you know, like thinking this shouldn't be happening in the hospital, I thought this is a peaceful place and everyone's like rushing out into the hallway to see what's happening. And it's this cartoon very simply drawn constructed of neon light rendering of God, essentially is walking down the corridor...and he came up to me and he was like...you can ask me two questions.*" (P09)
6. The ketamine infusions and the trial as transformational	
Perspective on life	"*It helped family wise, relationship wise in every, every single avenue of my life. It's changed it...doing the ketamine and seeing this other dimension enforced my belief of another life and I now live every single day to the max. When I go for a walk, I'm very observant of my world around me. I take pleasures in life rather than pleasures of...drink...So...it's still with me and I hope it'll stay with me for forever.*" (P03)
Relationship with alcohol	"*I think before the trial all my life was sort of focused around alcohol. I was either drinking it at home or selling it to students or working in an event where there was alcohol, the alcohol was a focus of it. So it was sort of everything and then afterwards, it just sort of stopped...I enjoy a drink every now and then, but under much safer ways really...So it just made me realise I don't need to sort of drink to excess because there's nothing else to do. I can just do other things...and that alcohol isn't everything.*" (P12)
Positive experiences of psychotherapy and alcohol education	"*You definitely need that support system. It feels like that you get with the therapy and the fact that you can take that home with you as a crutch. So yeah, it was, it was very good, obviously painful in some parts, but you know I was at my most... desperate. I wouldn't be here now, if it wasn't for it. I can definitely say that.*" (P03)
Interaction of ketamine with psychotherapy or education	
A. Ketamine interacting with psychotherapy or education	"*If I had just gone to education sessions and gone: 'oh well I work around alcohol all day, I am pretty sure I know all the stuff I need to know about it,' I probably wouldn't have listened so deeply. But the ketamine sort of made me more willing to engage with it*" (P12)
B. No impact of ketamine on psychotherapy or education	"*I don't think there was any correlation there because the effects had fully worn off before we would go into that kind of conversation.*" (P08)
Ketamine and talking sessions as mutually supportive	"*I was kind of more open to understanding those mental and physiological impacts of alcohol because of the mental effects I've had from the ketamine. Um, so I think there was there was a sort of mutually supportive relationship between both elements to the therapy.*" (P07)
Non-specific trial effects	"*It's more the sort of holding hands that one needs, you need somebody who you've sort of divulged all your innermost secrets to. Having done that, it then sort of makes you think twice about buying that bottle of wine. It's that sort of attention that you get that I think is valuable in this sort of thing.*" (P02)

the idea that science and a form of spiritual practise or awareness are two wings of the same bird. So, I think that probably informed how I experienced this" (P09).

Participants' experiences during the trial and expectations following the first infusion also appeared to affect their experiences of the following two infusions. For instance, one participant recounted that concerns by the trial staff about their mood following the first infusion led to a discussion on whether they can continue with the infusions, and although they were able to continue, this experience impacted their next infusions:

> "*The process of getting back on the trial and having to fight for it meant that I was carrying some sort of negative feelings. And that's slightly obscured those positive aspects that I had before [during the first infusion] … I was nervous and that affected the experienced I had.*" (P07).

Setting

The setting in which the trial took place was described as "professional," "controlled," "carefully regulated," and "clinical." As participants reported that the legitimacy of the trial was one of the reasons that motivated their participation in the trial, related to this they reported feeling safe and being comforted by the professionalism of the trial staff as well as the clinical setting in which the trial took place: "*I thought it was amazing how clinical it was and how organised it was and how safe I felt with it. That was brilliant*" (P11).

This professional and regulated setting of the trial was reported to play an important role in determining participants' acute ketamine experiences:

> "*I just thought, right 'How extreme is this experience going to be? Is it going to be a ride from hell or something like that?*" *And it absolutely wasn't and that's down to the laboratory type conditions, the controlled environment*" (P08).

The Inherent Contradictions of the Acute Ketamine Experience

The acute ketamine experiences of our participants were characterised by inherent contradictions. Participants described experiences that were both highly positive and negative and could be conceptualised as a "rollercoaster ride." It is also worth noting the negative experiences were largely transient and that despite these negative experiences, most participants described their acute ketamine experience as overall pleasant: "*I just found I left every session, kind of, you know, feeling happy. Feeling, you know… feeling lighter… Feeling like clearer thoughts*" (P10).

This "rollercoaster" was experienced differently by each participant and whereas for some, experiences were largely positive, for others the rollercoaster led to a real divergence

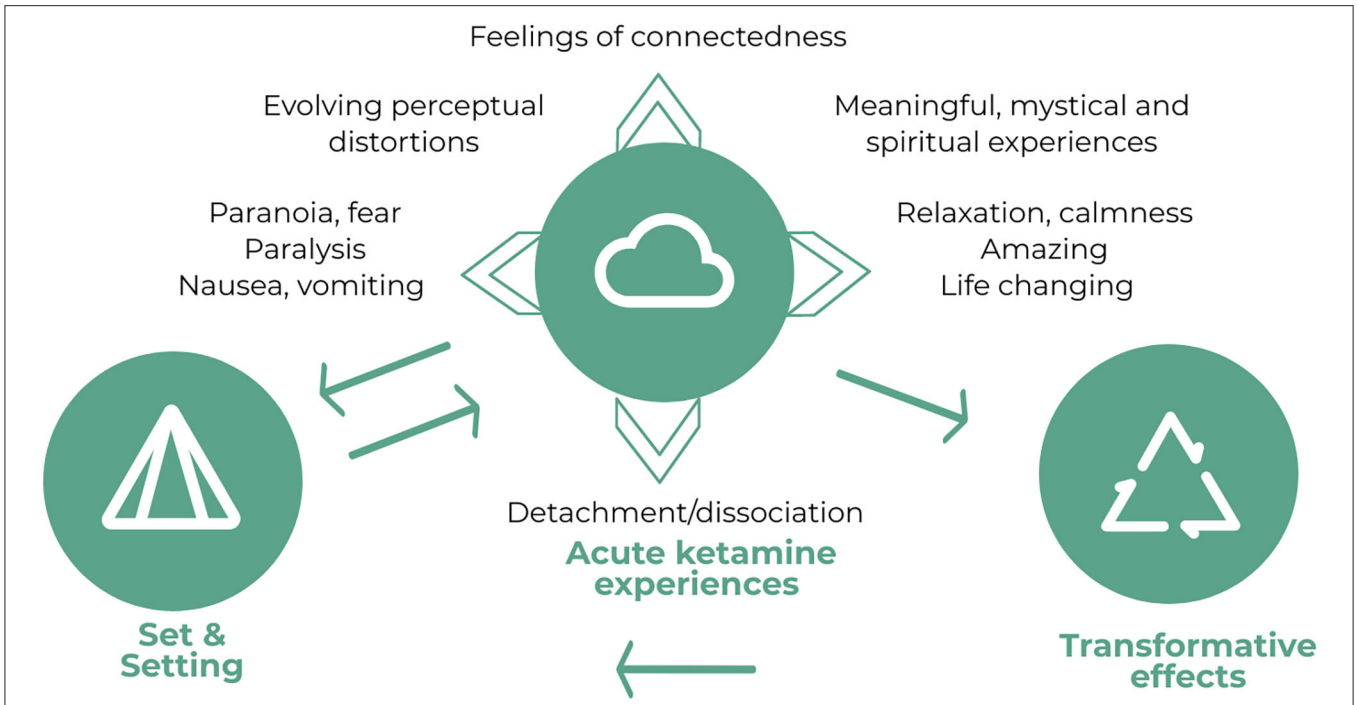

FIGURE 1 | Diagram depicting the relationship between set and setting, the acute ketamine experiences (inherent contradictions of the experience, rapidly fluctuating and changing experiences, and meaningful, spiritual and mystical experiences) and transformative effects of the infusions and the trial. Whilst set and setting are influential in determining the acute ketamine experiences, experiences from the first two infusions and the transformative effects also contribute to the set of the subsequent infusions as expectations. As discussed in theme 4, the acute ketamine experiences, particularly feelings of connectedness and dissociation also appeared to be related to the transformative effects.

of positive and negative effects, all occurring in the context of differing/vivid psychedelic experiences, as we will discuss further below.

Changes in Experiences Over Time

Moreover, exploring participants' experiences across the three infusions highlighted further contradictions—for some participants the infusion experiences were qualitatively similar, others described each infusion having a unique effect:

> "*The first one was in the imagination..., with what I know as a human being, got my mind my will being put on it.... And the second one was just freedom and just wow.... The third one was a little bit too short, and as I came out I was panicky. I was just like 'that's it, we're done'*" (P05).

Some participants perceived the experiences as less vivid/potent as the trial progressed due to the reliability of the effects: "*I think having, having had it a couple of times, I was kind of probably more used to what I was expecting. I suppose it was less of a wow, this is amazing, because I've done it before*" (P07).

This reduction in the strength of effects across the infusions was reported to lead to dissatisfaction due to expectations from previous infusions and a desire to replicate such experiences: "*My body was still starting to disappear, but not as quick so. It's almost like your body gets used to it*" (P03).

Positive Experiences

As seen in **Figure 1**, positive effects identified during the infusions included feelings of calmness and relaxation. Particular experiences were feeling relieved, unhooked, mellowed, carefree, chilled, and peaceful:

> "*It was, um, it was a sort of sense of complete relaxation, a sense of sort of vanishing, you can, it feels like one was being sort of enveloped in a duvet type, you know, that sort of feeling, if you like*" (P02).

Another positive aspect of the experience was the reinforcing effects of ketamine. Participants described the experiences associated with the ketamine infusions using terms such as "beautiful," "fantastic," "brilliant," and "amazing." Several participants reported the experience as "life changing" or "one of the best experiences of my life."

Due to the positive effects of ketamine infusions, feelings of loss and sadness were described in relation to the cessation of the ketamine infusion and the trial. Participants reported wanting the experience to continue, or that they would benefit from a larger number of sessions (e.g., six rather than three); this was related to the changes in experiences across infusions which meant that each infusion led to a deeper understanding:

> "*Because there's the three sessions, really like I wanted to do six thinking back on it because I felt like the third one, I just really*

cracked into something and you know to go a little bit further, I think would have been really good" (P09).

Negative Experiences

On the other hand, the transient negative effects included fear or panic, mild paranoid ideation, paralysis, and nausea and vomiting. Nearly all participants experienced some form of transient psychological or physical distress during the acute ketamine infusion. Participants commonly described fear of permanently losing their sense of self and body. This fear was attributable to a sense that the trial would never end: "*It was the fear factor of I couldn't get out of it. I couldn't come off it*" (P03).

Despite reports of feeling safe and comforted by the professionalism of the trial staff, several participants started to question the veracity of the trial and the motivations of the trial staff whilst under the acute effects of ketamine: "*And I thought, hang on, what have I let myself in for you know? What is this thing? What the hell is going on here?*" (P08).

These thoughts and feelings of paranoia were described to be "strong" and "overwhelming." Additionally, these thoughts were linked with beliefs that they would be stuck in this situation for the rest of their lives:

> "*I can remember thinking, feeling very paranoid that the whole trial was kind of a fake and it was like trying to get me into this situation. And that I was actually going to be in a situation for the rest of my life*" (P04).

The transient physically distressing experiences took the form of paralysis and nausea and vomiting. A few participants described feeling nauseous and sick during the infusions. A number of participants reported varying degrees of paralysis, whereby they were not able to move parts of their body due to feelings of detachment:

> "*And it's almost like a state of paralysis, where you do receive visual and sound information. But I don't know how much sense I was making to the people in the room around me. It feels like when you try and run in a dream, but your legs aren't moving fast enough. In fact, exactly like that*" (P08).

Another set of contradictory experiences involved on one hand experiences of dissociation, detachment, floating, otherworldliness and on the other hand ego dissolution characterised by feelings of connectedness with other beings, decreased self-importance, a sense of the small self-fitting in with the vastness of the universe.

Dissociation, Detachment, or Floating

Nearly all participants reported feelings of dissociation or detachment, either from their environment, their physical body, or their sense of self: "*I kind of lost a sense of who I was. I couldn't—there didn't seem to be no connection with normality and what, how I usually felt*" (P04).

Other experiences of dissociation involved participants feeling detached from their physical bodies or feeling as though their bodies had disappeared: "*… My whole feeling of my body disappeared.… It was like being an amoeba and just floating in space. I had nobody, I had no- I was a soul*" (P03). For some people this experience of was accompanied by feeling of paralysis, which was reported as disturbing, as intense feelings of detachment made them feel like they had no physical connection to their bodies: "*One further thing I remember is I couldn't actually move any part of my body because of the detachment.*" (P04). In an extreme case of detachment from their physical body, one participant reported what they described as a near death experience: "*I was this entity of pure whiteness, and I was above myself.... As far as I was concerned, that was it. I could be dead. I could have been that was it. I could have stayed white forever.*" (P05).

Otherwordly Experiences

Participants also reported experiences which can be described as dissociation from the world; ketamine infusions were commonly described as "out of this world," "otherworldly" or opening one up to a "new realm": "*That infusion took me somewhere that was outworldly, was out of this world. It was not within this world*" (P05).

Ego Dissolution

In direct contrast to these experiences of dissociation or detachment from one's sense of self, physical body or the world around them, experiences of ego dissolution were reported; these were characterised by a diminishing sense of self as distinct from other beings and feelings of unity with the rest of the universe. Some of these experiences were primarily characterised by decreased absorption by one's own issues and concerns and a decrease in sense of self-importance:

> "*I felt a sense of all the things that I decide or wanted or had or didn't have, was kind of understandable in a sort of childish way but actually not what was important... I didn't have any acquisition, or requirements or needs. I was over that. It was a sense of completeness, a sense of, I suppose finality, a source of finish*" (P07).

Whilst for others, this experience of decreased self-importance and decreased self-absorption was linked to a feeling of connectedness with other beings, a sense of the "small self" and/or fitting in within the vastness of the universe:

> "*It was almost like the universe was surrounding me and I was just the most tiny you know, small, small and fundamental particle, you know. From this feeling of like this huge vastness and me being absolutely nothing or very, very, extremely small. And because of that tininess of me, it was almost like all the things that made me no longer existed*" (P04).

Rapidly Fluctuating and Changing Experiences

Perceptual Distortions

All participants reported perceptual distortions, which were variable in nature and changed throughout the experience. These took the form of visual and auditory distortions and hallucinations or visions. Visual distortions were most commonly reported, which included dimensional and spatial distortions, whereby objects and people felt smaller or larger, closer, or further

away, or had a different shape or texture: "*I could feel different textures of surfaces. I could see movement of these surfaces like snakeskin scales or lava. And different shades of colours*" (P07). For some, this involved feeling themselves as smaller or larger in comparison to the room. "*I got a sort of spatial sense of being enormous or being tiny.*" (P07). Aspects of texture and colour were also altered for these participants. Most participants reported changes in colour perception, which was described as "beautiful" and an "explosion of colour."

Others reported auditory distortions, such as voices sounding further away or closer and musical pieces being unrecognisable "*It's like different aspects that made up the piece were coming through at different speeds or different pitches. … I could still hear them as piano pieces but they weren't the pieces that I knew*" (P04); or changing depending on their concurrent psychoactive experience: "*So, when the music tempo picked up, it's sort of moved into a different place within the journey that you were on essentially*" (P11).

These experiences of visual and auditory distortions were reported to change and evolve throughout the infusion, this is key to the rollercoaster of experiences whereby perceptions and reality are rapidly changing:

> "*Sometimes it would become very linear, everything will be at right angles and lines and squares. And other times it would be just like a blur it would just be colours. And it would constantly change and evolve, what I was seeing would evolve and what I was hearing would evolve as well*" (P04).

On the other hand, for some the sensory changes were more extensive than simple distortions, crossing over into what can be described as hallucinations or visions. These were very subjective, ranging from research staff transforming into Alice in Wonderland characters, images of being surrounded by hundreds of people, images of being surrounded by pink blancmange and abstract hallucinations of a biological nature:

> "*So, everybody turned into Alice in the Wonderland for me.… And then the other one I can't remember her name, she is wonderful, but she was the Cheshire cat. So, when she walked in, she had this massive grin*" (P05).

Meaningful, Spiritual, and Mystical Experiences

Ego Dissolution, Epiphanies, and Enlightenment

For several participants, these experiences of ego dissolution during the ketamine infusions were connected to gaining deep and meaningful insights to important aspects of their life (see also theme 4 below). For some, this took the form of gaining insights into a sense of what was important in life:

> "*It was about material things, not wanting those, those aren't really important. And neither is the sense of doubt and self-criticism, you know, it's almost like life's too short. In a way, I felt like life was over. I can let these things go; you know that they are not really that important. Almost like simplistically, don't sweat the small stuff*" (P07).

For one participant the epiphanies involved reflections on life and death:

> "*…Life and death is not a black and white thing. It's not a switch on and switch off when you die. They are a passage and I'm a part of it here and I'm a part of it whenever that other thing happens*" (P06).

Another participant experienced an epiphany about many aspects of their life including an understanding about the need to integrate traumatic experiences within oneself; as we explore in the next theme, for this participant, these new understandings led to significant transformations in their life:

> "*So, if trauma was like a ball so like you've got something about the size of a tennis ball that has a trauma experience. It's attached to your body. You can move it around in the body, but it's still attached to you. It's unpicking that fabric and weaving the fabric into your being. So, it doesn't cease to exist, but its power is gone*" (P09).

Transcendence of Time

Some participants reported experiences where a sense of time as we know it was eliminated. For some, distortions of time produced the fear of the experience lasting for eternity. For others, distortions of time had a more profound effect and put into perspective the normal ordering of events in society: "*Now, this afternoon, this evening, the way we think of that—That just blows apart and doesn't exist anymore*" (P06).

Hallucinations or Visions

For some, hallucinations and visions were related to religious, spiritual, and mystical experiences:

> "*….we are all connected and there is this connection between all beings, people and things to again bring us out of this kind of prison of addiction. The transpersonal effects of the drug bring us out of ourselves and put the problems into perspective*" (P09).

For one participant this took the form of encountering and talking to God. He described these experiences as "holy" and these visions were closely related to epiphanies:

> "*And so essentially, it was like this higher power, this representation of the higher power [referring to God] that had appeared at the start was showing that I had permission to be happy and do I what want, as long as I didn't misuse my resources*" (P09).

It is important to note that every participant reported these acute ketamine effects as being transient in nature, with the only psychoactive effects in the following few hours being mild, such as "strange" feelings, slight feelings of confusion, or mild visual effects whilst going to sleep. Many participants reported that ketamine infusions had positive effects on their mood in the days following the infusions. These included reports of feeling "chilled out," at peace, reflective, happy, energetic, or just generally being in a better mood but for most these positive effects on mood were brief and returned to baseline within a week.

The Ketamine Infusions and the Trial as Potentially Transformational

Perspective on Life

The combination of the ketamine infusions and the trial as a whole were reported to be transformational in many aspects of participants' lives: "*In a non-cheesy way, it actually probably changed my life around and kept me alive*" (P12). The effects of the trial were described as helping "every single avenue" of one's life (P03), as well as a "real fundamental shift in gears" (P09).

It's important to note that not all participants reported these transformational effects of the trial, several participants expressed that the trial did not lead to a fundamental lasting change on their perspective of life. Though one of these participants described the trial as a "major a part of a process" which allowed them to move forward with regards to their mental health.

Relationship With Alcohol

Whilst only three participants were still completely abstinent at the time of interview, all participants who completed the treatment recounted that the trial had transformed their relationship with alcohol in a number of ways. For some, this consisted of a switch from uncontrolled to a more controlled drinking approach, whereby participants were able to remain abstinent for much longer periods and consume much less alcohol: "*I still drink, but I'm quite capable of having 2, 3, 4, 5, 6, 7 days where I'm just not bothered about it, which is not something that happened in the past*" (P04).

For others, the transformational effects involved reduced craving or urge to drink alcohol, which was accompanied by reduced pleasure from alcohol in some: "*I feel I have much less desire to drink now than I used to. And I think what it is, I actually, I think, enjoy it less now*" (P11).

In some cases, the trial and the infusions resulted in changes in drinking motives from drinking to cope with negative emotions or boredom, to drinking for social reasons instead: "*It's more just sociable drinking now, not: 'Oh I've got nothing to do after I finish work, I might as well just go get a bottle of rum and drink that'*" (P12).

For participants who were abstinent from alcohol at the time of interview, the trial led to more fundamental changes in their relationship with alcohol, where alcohol no longer was the primary focus of their life which meant that they were able to prioritise other aspects of their life: "*Whilst I was drinking, drink was the most important thing and drink was the dangerous thing. It was you know, my love and my hate, drink was and now I've got swimming*" (P03). This also involved a switch from wanting to find a reason not to drink, to longer needing a reason not to drink: "*Right now I've got to have a reason. Show me the reason to drink. I don't have a reason, I don't need a reason not to drink anymore*" (P05).

For those who were abstinent from alcohol, some of these transformational effects were closely linked with the deeply meaningful, personally relevant, religious, spiritual and mystical experiences, and dissociative effects during the acute ketamine experiences. For one participant, overcoming the near death like experience of extreme dissociation from their physical body became a coping mechanism for dealing with other problems in life:

> "*So moving onwards in life, every time I get something that's quite testing or you know a problem, I just say, 'well, a couple of months ago, I was just white.… So how bad can this be?'" … At least I'm not white, you know, at least I've got a body, at least I'm alive kind of thing* (P05).

Similarly, for another participant, the experience of disembodiment during their first infusion was connected to their abstinence from alcohol: "*…After the first one, I knew I wasn't going to drink again.*" (P03). Indirectly, this strong experience of dissociation appeared to be related to the participant forgetting the taste of their drink of choice and thus desire to remain abstinent: "*I don't recall what pint tastes like, now a pint was my drink. And I couldn't imagine the taste, so instantly I was not wanting to drink*" (P03).

For another participant, it was the reduction in self-absorption and feelings of connection with the universe that seemed to affect their relationship with alcohol:

> "*… The sense of oneness that I felt and the sense of moving away from focusing on the worries and the small stuff is helpful in terms of improving my relationship with alcohol. Because I think I used alcohol as a self-medication and as a blocking and avoiding mechanism. And I think feeling that those issues are less prevalent or at least less important means I feel less motivated to drink*" (P07).

A number of participants who reported experiences of ego dissolution or epiphanies during the ketamine infusions were not completely abstinent from alcohol at the time of interview. Whilst they all reported changes in their relationship with alcohol as explained above, it is not clear whether these were due to their experiences of ketamine infusions or the education/psychotherapy: "*My attitude towards alcohol has changed, but I couldn't say how much that was down to infusions or education or a combination of the two*" (P04).

Positive Experiences of Psychotherapy and Alcohol Education

Another potentially transformative aspect of the trial was the psychotherapy/psychoeducation sessions provided alongside ketamine infusions. These were described as "illuminating" and "engaging." Participants reported that even if they were vaguely aware of the dangers of alcohol, through the psychoeducation sessions they gained an in depth understanding about the detrimental effects of alcohol on the body and the mind. In some cases, this knowledge appeared to be linked to the transformations in drinking behaviour/attitudes to alcohol: "*… Actually learning the dangers of over drinking to go: 'you know what, I don't really want to be around it that much anymore'*" (P12).

Only four of the participants interviewed had received the psychotherapy as part of the trial, nonetheless these participants recounted the transformational effects of psychotherapy, including opening one up to different kinds of therapy, as a support system that kept them focused on their journey, and as having significant impact on their personality:

"*. . . My persona was a jacket that I could take off and hang up at the door and do the work. And then put that jacket back on. But the jacket would be a slightly different colour and then by the end of the process, it was a different jacket*" (P09).

Interaction of Ketamine With Psychotherapy or Education

One possible transformational effect of ketamine infusions was making participants more receptive, more willing to engage with and more open minded towards the psychotherapy/psychoeducation sessions:

"*If I had just gone to education sessions and gone: 'oh well I work around alcohol all day, I am pretty sure I know all the stuff I need to know about it', I probably wouldn't have listened so deeply. But the ketamine sort of made me more willing to engage with it*" (P12).

Though for others, there was no obvious connection between their ketamine experiences and openness to learning new information as part of the talking sessions.

It is important to discuss whether the transformational effects reported here are due to the ketamine infusions, the psychoeducation/psychotherapy sessions, or non-specific trial effects for instance the care and attention that the participants reported receiving from the trial staff.

Ketamine and Talking Sessions as Mutually Supportive

Several participants described the ketamine and talking interventions as a package, components of which mutually supported each other, and attributed the effects of the trial to both:

"*So, I think that as a package, I hit the golden button, didn't I? . . . . Not only did I get a life changing and mind-altering experience, but then the therapist did plug some new thoughts to me that made me think differently... I feel that it is really important that when you are split open, you know, in such an intense and life changing way that you are given new thoughts and you know that someone gives you something to refill that, so you do change stuff*" (P05).

Nonspecific Trial Effects

Others mentioned that the benefits they experienced may be due to other factors associated with the trial and highlighted that the emotional connection with the therapist and desire to do well for them also played a role:

"*I don't know whether it was the chemicals, the therapy, the keeping of the notes, the loyalty, the wish to sort of be a good pupil if you like in relation to the people involved in the course. . . . And I'm not sure it's the therapy that one needs. It's more the sort of holding hands that one needs, you need somebody who you've sort of divulged all your innermost secrets to. Having done that, it then sort of makes you think twice about buying that bottle of wine*" (P02).

Participants responded positively to the attention and care they received from the trial staff and their genuine interest in helping them: "*I did feel throughout the KARE trial, that one of the really positive aspects of the whole thing was the care and interest in me that I felt from the staff that I met with and engaged with*" (P07).

TABLE 3 | A list of recommendations for future trials of ketamine treatment based on current findings.

1. Preparation

- Include first person accounts of ketamine experience in the preparation for infusions
- Emphasise that the experience may involve paranoid thoughts and altered perception of time, though any affects are transient
- Include a debrief at the end of the ketamine infusions to discuss potential feelings of loss and sadness associated with the end of treatment
- Screen individuals for tendency towards paranoid beliefs

2. Setting

- Clinical and professional setting may be reassuring for ketamine naïve participants
- Trusting relationships with the trial staff appear to be crucial in providing a safe setting

3. Measurements

- Include questionnaires measuring a wide range of the psychoactive effects of ketamine (religious, mystical, spiritual, and dissociative) including Hood's Mysticism Scale, Psychotomimetic States Inventory, and 5-Dimensional Altered Consciousness Rating Scale
- Measure motivations and expectations from treatment using measures such as The Stages of Change Readiness and Treatment Eagerness and The Alcohol Abstinence Self-Efficacy Scale
- Development of a new measurement capturing the wide range of acute experiences reported under ketamine infusions: dissociative, religious, mystical and spiritual, and otherworldly experiences as well as perceptual distortions

4. Dosing and Administration

- Consider titrating doses up according to individual experiences
- Consider multiple sessions based on individualised need/experiences
- Investigate the optimal number of doses

DISCUSSION

"*.. so, it was showing that essentially, we are all connected. And there's this connection between all beings, people, and things to again bring us out of this kind of prison of addiction, the transpersonal effects of the drug to bring us out of ourselves and put the problems into perspective*" (P09).

"*I have to remember this, because this is going to be one of the best experiences of my life*" (P04).

This study set out to explore the subjective experiences of individuals in a clinical trial of ketamine for the treatment of alcohol use disorder. Our use of an open-ended, semi-structured interview allowed us to identify themes which may not have been apparent from using a standardised questionnaire or clinical checklist, and in doing so we were able to uncover a number of previously unreported effects of ketamine. This work has yielded important insights into the motivations for and experiences of ketamine treatment which may be useful for tailoring future treatments and preparing participants for ketamine treatment (see **Table 3**).

Consistent with previous work with psychedelics (23, 24), but rarely considered in ketamine studies, set and setting were found to be important in the acute experience following ketamine administration. Most of the respondents reported being

comforted by the professional and clinical setting in which the trial took place. The setting of this trial represents a contrast with the way the therapeutic environment has been manipulated in studies of classic psychedelic drugs to feel comfortable and incorporate natural features (24–26). Whilst it was previously thought that clinical or medical environments may induce anxiety or unpleasant experiences (2, 25, 27), this did not reflect the experiences of the participants interviewed here.

The mindset or "set" was also found to be important: those who had previous experience of non-ordinary states of consciousness had found these experiences to be useful preparations. These reports parallel research in the context of psychedelics, which showed that readiness to surrender to the experience and being supported by trusted individuals in a therapeutic setting protects against challenging psychological experiences (24). The experiences reported by participants here further underscore the importance of the context in which psychedelic drugs such as ketamine are administered. Whilst previous research investigated the effect of drug by environment interactions on the acute experiences of psychedelic drugs (28, 29), future research is needed to examine the role of set and setting in determining the treatment efficacy of psychedelic drugs (30).

Participants' reported that ketamine induced religious, spiritual, and mystical experiences. This may be relevant to the use of the drug in this group of participants with alcohol use disorder, as connection to a higher power is a key element in some approaches to achieving and maintaining sobriety from alcohol, for example the twelve-step programme. It is possible that ketamine or other psychedelics might once again have a place alongside these treatment approaches (31) for those who have struggling to engage with these aspects of these programmes. Whilst previous research on religious, spiritual, and mystical experiences (RSME) has dismissed such experiences produced by psychedelics as artificial compared with spontaneous RSMEs (32), others argued that the "fruits" (outcomes) of the experience are more important than its "roots" [cause/origins as William James cf. (33)] (33, 34). In fact, a previous study has reported that the RSMEs induced by psychedelic substances were perceived as more mystical than RSMEs produced through other means and had greater positive impact on one's sense of purpose, and greater increases in individuals' spirituality (33). The participant experiences reported here are in line with previous research demonstrating that psychedelic drugs such as ketamine can trigger profound RSMEs when administered in highly controlled and supportive clinical trial settings (25, 30, 35–38). The extent to which such experiences are related to ketamine's treatment effects for addiction remains to be further investigated.

A number of participants reported ego dissolution from ketamine, which comprised feelings of connectedness with the universe, and a sense of the "small-self" fitting in with the vastness of the universe; similar to experiences commonly observed with other classic psychedelic drugs such as psilocybin (1, 30, 38). Whilst feelings of dissociation and detachment that were reported by the majority of participants are consistent with previous reports (39, 40) in the current trial these feelings of detachment from one's sense of self or one's physical body were accompanied by seemingly paradoxical feelings of connectedness with the universe and of decreased self-importance and self-absorption.

Acute ketamine experiences reported by patients—feelings of connectedness, altered time perception, self-diminishment, perceived vastness, and physical sensations—all map on to the experience of "awe" which is an increasingly researched psychological construct (41). Awe has been proposed as a potential mechanism of action underlying the effects of classic psychedelic-assisted psychotherapy (42) and theoretically overlaps with mystical experiences (43), the small self and ego dissolution (44) and challenging experiences (45) under psychedelics. The ketamine induced profound sense of awe, wonder and connectedness may be of particular use in this group of patients, in helping individuals break the cycle of compulsive patterns of thinking that are a feature of alcohol use disorders.

Given the reported experiences here, the term "dissociative anaesthetic" appears insufficient to characterise the wide range of acute ketamine experiences captured in this study. In previous clinical trials of ketamine as a mental health treatment, the Clinician Administered Dissociative State Scale (CADSS) (46) was the most commonly used tool to assess the dissociative effects of ketamine (47). However, concerns were raised that the CADSS may be inadequate to measure such experiences as it has only been validated in populations with Post Traumatic Stress Disorder/ dissociative disorders (46) and it does not appear to fully capture the phenomenological experiences of ketamine administration (48). It is important to accurately measure the subjective experience following ketamine, as there is considerable research interest in whether the acute psychoactive effects of ketamine mediate its therapeutic effects. Emerging evidence suggests the mystical, dissociative and psychotomimetic effects characterising the ketamine's acute effects may contribute to its therapeutic benefits (16, 17, 49) parallel to findings in the psilocybin research which links mystical experiences to treatment outcomes (50–52). A recent review suggested this evidence to be inconclusive for ketamine but concluded that this may be due to the measurement tools used [for a review see (47)].

Whilst a number of terms have been used to describe ketamine and similar drugs, including hallucinogen (perceptual alterations), entheogen (producing mystical like experiences), psychotomimetic (modelling symptoms of psychosis), all seem to suffer from the issue of focusing on a single aspect of the experience at the expense of others (2). The term psychedelics may also not be preferable due to strong connotations with Western counterculture of the 1960s (2). Additionally, feelings of connection, epiphanies and the awe aspect of the experiences are not reflected in any of the proposed names. It may be that a new nomenclature for characterising the effects of psychedelic drugs is needed, whereby each drug might be described in terms of the extent to which the described categories of experiences are reported.

Nearly all participants experienced transient periods of psychological and physical distress during the ketamine infusions. Despite reports of trusting relationships with the trial staff, under the effects of ketamine a small of number participants questioned the veracity of the trial or the motivations of the trial

team; these strong and overwhelming paranoid thoughts were linked with beliefs that the experience would never end, which were reported as being frightening. An important suggestion emerging from this work therefore is that in preparation sessions it should be discussed with patients that they may experience such thoughts and their perception of time might be affected during the infusions, though any affects are transient. Whilst individuals with psychosis/schizophrenia and family history of such disorders were excluded from the trial, it may also be worth considering specifically screening for individuals with paranoid beliefs prior to their involvement in a ketamine trial. Crucially, none of the participants reported prolonged psychosis or lasting perceptual alterations beyond the acute infusions.

Some participants described each infusion allowing further insights and understanding, likening the infusions to a three-part story. This was linked to a desire to have more than three infusions, to "go a little bit further." Tachyphylaxis (rapidly developing tolerance) was described even over these three sessions which may suggest future doses might need to be titrated up. Indeed, similar approaches have been used in Ketamine Assisted Psychotherapy and psilocybin treatment, whereby following the first dose, subsequent doses were titrated up according to individual experiences to achieve a "mystical" (52) or "trance" state (53). Additionally, higher doses were found to be predictive of a "peak" [based on (54)] or "mystical" (35) psychedelic experience (28) which has been linked to treatment efficacy (55) and titrating up is common in the private ketamine therapeutic practise in the US (56).

All participants interviewed here reported positive experiences associated with the ketamine infusions overall despite the transient distressing experiences. This suggests that short-lived intense distress can be well-tolerated by study participants in a supportive and therapeutic setting as part of a clinical trial (38). One of the interviewed participants reported an isolated incident of recreational ketamine use following the trial. There are concerns about the abuse potential of ketamine, but this may suggest that when provided in a treatment context to participants who were appropriately screened, supervised, and followed up [see (2) for safety guidelines in human hallucinogen research] the risks are minimised.

Whilst only three of 12 participants were abstinent from alcohol at the time of interview, all participants who completed the three infusions ($N = 11$) described lasting changes in their relationship with alcohol, suggesting a shift from uncontrolled to a more controlled drinking approach: ability to remain abstinent for longer periods, reducing amount of consumption, reduction in craving to drink alcohol and changes in motives for consuming alcohol. This is a particularly valuable insight from qualitative data, which would not be possible to ascertain from the quantitative data on relapse rates alone. Similar findings of controlled drinking following treatment have also been reported in the psychedelic literature (52). This may also indicate future trials may need to consider outcomes beyond abstinence or relapse rates in evaluating ketamine's therapeutic effects for alcohol use disorders. The appropriate outcome measurements may be related to patients' motivations and expectations from the treatment, as well as perceived self-efficacy to remain abstinent, as these factors are shown to be strongly related to long term drinking outcomes (57).

There are a number of limitations to consider in the current study. Firstly, the interviews were conducted on average 2 years following participants' involvement with the KARE trial and the ketamine infusions, therefore their memory of their experiences may be subject to distortion. The acute and long-term benefits of ketamine reported by the participants here may also be explained as a result of other non-specific factors associated with taking part in a clinical trial including the rapport with the therapist, the care and attention received during the trial and wishing to please the trial team as reflected by a number of participants here [e.g., (30)]. Participants may have also felt a wish to report more positive experiences of the infusions or the trial to please the interviewers, however the fact that researchers undertaking the interviews were not previously known to the participants may have minimised this.

The current study reported patient perspectives of ketamine treatment in the context of a clinical trial for alcohol use disorders. The experiences reported here highlight the importance of supportive, safe, and a professional environment in determining individuals' acute ketamine experiences. For majority of the participants, the acute ketamine experience included dissociative effects, transient distress and perceptual distortions; though some also reported more profound religious, spiritual, and mystical experiences such as ego dissolution and epiphanies. Whilst some of these experiences including strong feelings of dissociation as well as feelings of connectedness, appeared to be related to the transformations reported by the participants, the extent to which these acute experiences contribute to ketamine's therapeutic effects for alcohol and/or substance use disorders remains to be fully investigated. The wide range of acute experiences reported here are not captured by ketamine's characterisation as a "dissociative anaesthetic." Keeping this in mind along with issues highlighted with other terminology, a new nomenclature for describing the effects of ketamine and other "psychedelic" drugs, as well as the development of a new measure to appropriately assess ketamine's acute effects are recommended. Beyond the acute effects, potentially transformative effects of ketamine infusions and the trial are reported. For some participants, insights from the acute ketamine experience have had significant positive effects on many aspects of their lives. For the majority, the treatment is reported to have led to significant change in their relationship with alcohol. How ketamine interacts with psychotherapy, as well as the most appropriate psychotherapy to be delivered alongside ketamine treatment remains to be determined; qualitative analyses such as these are vitally important in informing such approaches.

DATA AVAILABILITY STATEMENT

Due to ethical concerns, the research data supporting this publication are not publicly available.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by University of Exeter CLES Psychology Ethics Committee. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

OMM, CJAM, JK, and MG contributed to the conception and design of the study. OMM and JK conducted the qualitative interviews and collected survey data. OMM, CJAM, JK, KJA, and EKA were responsible for qualitative data analysis. CM was responsible for the supervision of the research study and the article. OMM led the drafting of the manuscript with JK and KJA provided critical feedback on the results section. All authors contributed to the manuscript revision, read, and approved the submitted version.

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REFERENCES

1. Domino E, Chodoff P, Corssen G. Pharmacologic effects of ci-581, a new dissociative anesthetic, in man. *Clin Pharmacol Ther.* (1965) 6:279–91. doi: 10.1002/cpt196563279
2. Johnson MW, Richards W, Griffiths RR. Human hallucinogen research: guidelines for safety. *J Psychopharmacol.* (2008) 22:603–20. doi: 10.1177/0269881108093587
3. Aan Het Rot M, Zarate CAJ, Charney DS, Mathew SJ. Ketamine for depression: where do we go from here? *Biol Psychiatry.* (2012) 72:537–47. doi: 10.1016/j.biopsych.2012.05.003
4. Serafini G, Howland RH, Rovedi F, Girardi P, Amore M. The role of ketamine in treatment-resistant depression: a systematic review. *Curr Neuropharmacol.* (2014) 12:444–61. doi: 10.2174/1570159X12666140619204251
5. Garay R, Zarate CAJr, Cavero I, Kim Y-K, Charpeaud T, Skolnick P. The development of glutamate-based antidepressants is taking longer than expected. *Drug Discov Today.* (2018) 23:1689–92. doi: 10.1016/j.drudis.2018.02.006
6. Martinotti G, Chiappini S, Pettorruso M, Mosca A, Miuli A, Di Carlo F, et al. Therapeutic potentials of ketamine and esketamine in obsessive-compulsive disorder (OCD), substance use disorders (SUD) and eating disorders (ED): a review of the current literature. *Brain Sci.* (2021) 11:856. doi: 10.3390/brainsci11070856
7. Jones JL, Mateus CF, Malcolm RJ, Brady KT, Back SE. Efficacy of ketamine in the treatment of substance use disorders: a systematic review. *Front Psychiatry.* (2018) 9:277. doi: 10.3389/fpsyt.2018.00277
8. McAndrew A, Lawn W, Stevens T, Porffy L, Brandner B, Morgan CJ. A proof-of-concept investigation into ketamine as a pharmacological treatment for alcohol dependence: study protocol for a randomised controlled trial. *Trials.* (2017) 18:159. doi: 10.1186/s13063-017-1895-6
9. Dakwar E, Levin F, Hart CL, Basaraba C, Choi J, Pavlicova M, et al. A single ketamine infusion combined with motivational enhancement therapy for alcohol use disorder: a randomized midazolam-controlled pilot trial. *Am J Psychiatry.* (2020) 177:125–33. doi: 10.1176/appi.ajp.2019.19070684
10. Lascelles K, Marzano L, Brand F, Trueman H, McShane R, Hawton K. Effects of ketamine treatment on suicidal ideation: a qualitative study of patients' accounts following treatment for depression in a UK ketamine clinic. *BMJ Open.* (2019) 9:e029108. doi: 10.1136/bmjopen-2019-029108
11. Griffiths C, Walker K, Reid I, da Silva KM, O'Neill-Kerr A. A qualitative study of patients' experience of ketamine treatment for depression: The 'Ketamine and me' project. *J Affect Disord Rep.* (2021) 4:100079. doi: 10.1016/j.jadr.2021.100079
12. Ivan Ezquerra-Romano I, Lawn W, Krupitsky EM, Morgan CJA. Ketamine for the treatment of addiction: evidence and potential mechanisms. *Neuropharmacology.* (2018) 142:72–82. doi: 10.1016/j.neuropharm.2018.01.017
13. Krupitsky EM, Grinenko AY. Ketamine psychedelic therapy (KPT): a review of the results of ten years of research. *J Psychoactive Drugs.* (1997) 29:165–83. doi: 10.1080/02791072.1997.10400185
14. Krupitsky EM, Burakov A, Romanova T, Dunaevsky I, Strassman R, Grinenko AY. Ketamine psychotherapy for heroin addiction: immediate effects and two-year follow-up. *J Subst Abuse Treat.* (2002) 23:273–83. doi: 10.1016/S0740-5472(02)00275-1
15. Sumner RL, Chacko E, McMillan R, Spriggs MJ, Anderson C, Chen J, et al. A qualitative and quantitative account of patient's experiences of ketamine and its antidepressant properties. *J Psychopharmacol.* (2021). doi: 10.1177/0269881121998321. [Epub ahead of print].
16. Dakwar E, Anerella C, Hart CL, Levin FR, Mathew SJ, Nunes EV. Therapeutic infusions of ketamine: do the psychoactive effects matter? *Drug Alcohol Depend.* (2014) 136:153–7. doi: 10.1016/j.drugalcdep.2013.12.019
17. Dakwar E, Nunes EV, Hart CL, Hu MC, Foltin RW, Levin FR. A sub-set of psychoactive effects may be critical to the behavioral impact of ketamine on cocaine use disorder: Results from a randomized, controlled laboratory study. *Neuropharmacology.* (2018) 142:270–6. doi: 10.1016/j.neuropharm.2018.01.005
18. Kolp E, Friedman HL, Young MS, Krupitsky E. Ketamine enhanced psychotherapy: preliminary clinical observations on its effectiveness in treating alcoholism. *Humanist Psychol.* (2006) 34:399–422. doi: 10.1207/s15473333thp3404_7
19. Kolp E, Krupitsky E, Young M, Karl J, Harris F, Laurie-Ann OC. Ketamine enhanced psychotherapy: preliminary clinical observations on its effectiveness in treating death anxiety. *Int J Transpers Stud.* (2007) 26:1–17. doi: 10.24972/ijts.2007.26.1.1
20. Braun V, Clarke V. Conceptual and design thinking for thematic analysis. *Qual Psychol.* (2021). doi: 10.1037/qup0000196
21. Kidder LH, Fine M. Qualitative and quantitative methods: when stories converge. *New Direc Program Eval.* (1987) 1987:57–75. doi: 10.1002/ev.1459
22. Braun V, Clarke V. Using thematic analysis in psychology. *Qual Res Psychol.* (2006) 3:77–101. doi: 10.1191/1478088706qp063oa
23. Hartogsohn I. Constructing drug effects: a history of set and setting. *Drug Sci Policy Law.* (2017) 3:2050324516683325. doi: 10.1177/2050324516683325
24. Carhart-Harris RL, Roseman L, Haijen E, Erritzoe D, Watts R, Branchi I, et al. Psychedelics and the essential importance of context. *J Psychopharmacol.* (2018) 32:725–31. doi: 10.1177/0269881118754710

25. Turton S, Nutt D, Carhart-Harris RL. A qualitative report on the subjective experience of intravenous psilocybin administered in an FMRI environment. *Curr Drug Abuse Rev.* (2014) 7:117–27. doi: 10.2174/1874473708666150107120930
26. Bogenschutz MP, Johnson MW. Classic hallucinogens in the treatment of addictions. *Prog Neuropsychopharmacol Biol Psychiatry.* (2016) 64:250–8. doi: 10.1016/j.pnpbp.2015.03.002
27. Strassman RJ. *DMT: The Spirit Molecule*. Rochester, VT: Park Street Press (2001).
28. Studerus E, Gamma A, Kometer M, Vollenweider FX. Prediction of psilocybin response in healthy volunteers. *PLoS One.* (2012) 7:e30800. doi: 10.1371/journal.pone.0030800
29. Kaelen M, Giribaldi B, Raine J, Evans L, Timmerman C, Rodriguez N, et al. The hidden therapist: evidence for a central role of music in psychedelic therapy. *Psychopharmacology.* (2018) 235:505–19. doi: 10.1007/s00213-017-4820-5
30. Watts R, Day C, Krzanowski J, Nutt D, Carhart-Harris RL. Patients' accounts of increased "connectedness" and "acceptance" after psilocybin for treatment-resistant depression. *J Humanist Psychol.* (2017) 57:520–64. doi: 10.1177/0022167817709585
31. Osmond H. A review of the clinical effects of psychotomimetic agents. *Ann N Y Acad Sci.* (1957) 66:418–34. doi: 10.1111/j.1749-6632.1957.tb40738.x
32. Zaehner RC. *Drugs, Mysticism and Make-Believe*. London, England: Harper Collins (1972).
33. Yaden DB, Le Nguyen KD, Kern ML, Belser AB, Eichstaedt JC, Iwry J, et al. Of roots and fruits: a comparison of psychedelic and nonpsychedelic mystical experiences. *J Humanist Psychol.* (2016) 57:338–53. doi: 10.1177/0022167816674625
34. Stace WT. *Mysticism and Philosophy*. Philadelphia, PA: J. B. Lippincott (1960).
35. Griffiths RR, Richards WA, McCann U, Jesse R. Psilocybin can occasion mystical-type experiences having substantial and sustained personal meaning and spiritual significance. *Psychopharmacology (Berl).* (2006) 187:268–83; discussion 284–92. doi: 10.1007/s00213-006-0457-5
36. Grob CS, Danforth AL, Chopra GS, Hagerty M, McKay CR, Halberstadt AL, et al. Pilot study of psilocybin treatment for anxiety in patients with advanced-stage cancer. *Arch Gen Psychiatry.* (2011) 68:71–8. doi: 10.1001/archgenpsychiatry.2010.116
37. Gasser P, Kirchner K, Passie T. LSD-assisted psychotherapy for anxiety associated with a life-threatening disease: a qualitative study of acute and sustained subjective effects. *J Psychopharmacol.* (2015) 29:57–68. doi: 10.1177/0269881114555249
38. Belser AB, Agin-Liebes G, Swift TC, Terrana S, Devenot N, Friedman HL, et al. Patient experiences of psilocybin-assisted psychotherapy: an interpretative phenomenological analysis. *J Humanist Psychol.* (2017) 57:354–88. doi: 10.1177/0022167817706884
39. Krystal JH, Lp K, Seibyl JP, Freeman GK, Delaney R, Bremner JD, et al. Subanesthetic effects of the noncompetitive NMDA antagonist, ketamine, in humans. Psychotomimetic, perceptual, cognitive, and neuroendocrine responses. *Arch Gen Psychiatry.* (1994) 51:199–214. doi: 10.1001/archpsyc.1994.03950030035004
40. Muetzelfeldt L, Kamboj SK, Rees H, Taylor J, Morgan CJA, Curran HV. Journey through the K-hole: phenomenological aspects of ketamine use. *Drug Alcohol Depend.* (2008) 95:219–29. doi: 10.1016/j.drugalcdep.2008.01.024
41. Yaden DB, Kaufman SB, Hyde E, Chirico A, Gaggioli A, Zhang JW, et al. The development of the Awe Experience Scale (AWE-S): a multifactorial measure for a complex emotion. *J Posit Psychol.* (2019) 14:474–88. doi: 10.1080/17439760.2018.1484940
42. Hendricks PS. Awe: a putative mechanism underlying the effects of classic psychedelic-assisted psychotherapy. *Int Rev Psychiatry.* (2018) 30:331–42. doi: 10.1080/09540261.2018.1474185
43. Barrett FS, Johnson MW, Griffiths RR. Validation of the revised Mystical Experience Questionnaire in experimental sessions with psilocybin. *J Psychopharmacol.* (2015) 29:1182–90. doi: 10.1177/0269881115609019
44. Nour MM, Evans L, Nutt D, Carhart-Harris RL. Ego-dissolution and psychedelics: validation of the ego-dissolution inventory (EDI). *Front Hum Neurosci.* (2016) 10:269. doi: 10.3389/fnhum.2016.00269
45. Barrett FS, Bradstreet MP, Leoutsakos J-MS, Johnson MW, Griffiths RR. The Challenging Experience Questionnaire: characterization of challenging experiences with psilocybin mushrooms. *J Psychopharmacol.* (2016) 30:1279–95. doi: 10.1177/0269881116678781
46. Bremner JD, Krystal J, Putnam FW, Southwick SM, Marmar C, Charney DS, et al. Measurement of dissociative states with the Clinician-Administered Dissociative States Scale (CADSS). *J Trauma Stress.* (1998) 1:125–36. doi: 10.1023/A:1024465317902
47. Grabski M, Borissova A, Marsh B, Morgan CJA, Curran HV. Ketamine as a mental health treatment: are acute psychoactive effects associated with outcomes? A systematic review. *Behav Brain Res.* (2020) 392:112629. doi: 10.1016/j.bbr.2020.112629
48. van Schalkwyk GI, Wilkinson ST, Davidson L, Silverman WK, Sanacora G. Acute psychoactive effects of intravenous ketamine during treatment of mood disorders: Analysis of the Clinician Administered Dissociative State Scale. *J Affect Disord.* (2018) 227:11–6. doi: 10.1016/j.jad.2017.09.023
49. Luckenbaugh DA, Niciu MJ, Ionescu DF, Nolan NM, Richards EM, Brutsche NE, et al. Do the dissociative side effects of ketamine mediate its antidepressant effects? *J Affect Disord.* (2014) 159:56–61. doi: 10.1016/j.jad.2014.02.017
50. Griffiths RR, Johnson MW, Richards WA, Richards BD, McCann U, Jesse R. Psilocybin occasioned mystical-type experiences: immediate and persisting dose-related effects. *Psychopharmacology (Berl).* (2011) 218:649–65. doi: 10.1007/s00213-011-2358-5
51. Garcia-Romeu A, Griffiths RR, Johnson MW. Psilocybin-occasioned mystical experiences in the treatment of tobacco addiction. *Curr Drug Abuse Rev.* (2014) 7:157–64. doi: 10.2174/1874473708666150107121331
52. Bogenschutz MP, Forcehimes AA, Pommy JA, Wilcox CE, Barbosa PC, Strassman RJ. Psilocybin-assisted treatment for alcohol dependence: a proof-of-concept study. *J Psychopharmacol.* (2015) 29:289–99. doi: 10.1177/0269881114565144
53. Dore J, Turnipseed B, Dwyer S, Turnipseed A, Andries J, Ascani G, et al. Ketamine assisted psychotherapy (KAP): patient demographics, clinical data and outcomes in three large practices administering ketamine with psychotherapy. *J Psychoactive Drugs.* (2019) 51:189–98. doi: 10.1080/02791072.2019.1587556
54. Maslow AH. *Religions, Values and Peak Experiences.* Harmond-sworth: Penguin (1976).
55. Roseman L, Nutt DJ, Carhart-Harris RL. Quality of acute psychedelic experience predicts therapeutic efficacy of psilocybin for treatment-resistant depression. *Front Pharmacol.* (2017) 8:974. doi: 10.3389/fphar.2017.00974
56. Bennett R. Paradigms of ketamine treatment. *MAPS Bull Spring.* (2019). 29:48–9. Available online at: https://maps.org/news/bulletin/articles/436-maps-bulletin-spring-2019-vol-29,-no-1/7718-paradigms-of-ketamine-treatment-spring-2019
57. Muller A, Znoj H, Moggi F. How are self-efficacy and motivation related to drinking five years after residential treatment? A Longitudinal Multicenter Study. *Eur Addict Res.* (2019) 25:213–23. doi: 10.1159/000500520

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APPENDIX

SECTION 1: ACUTE EXPERIENCES OF THE KETAMINE INFUSION

1. *Circumstances around deciding to participate*: Thinking back to the time period prior to starting the trial, what was it that made you consider taking part?
2. *Experiences during ketamine infusion*: Thinking back to when you were taking part in the trial, could you describe your experiences whilst being given the infusion? (Prompts—liked and disliked aspects).
   a. Was the experience similar each time you were given a ketamine infusion?
   b. Any more positive or negative experiences you'd like to report?
3. *Long-term experiences*: Could you now please describe your experiences in the week following the infusion?
   a. Prompts: did you find that the effects of the ketamine had any lasting effects after the duration of the infusion?
   b. E.g., immediately after infusion, in the days following infusion, in the weeks following infusion.
4. *Effects on world/alcohol perspective*: Do you think that the trial changed the way you see the world in any way?
   a. Has anything changed around your relationship with alcohol?
   b. Has anything changed with your mood?
5. *Interaction with therapy:* What were your experiences participating in the talking session [therapy/psychoeducation] following the ketamine infusion?
   a. Thinking about whether the ketamine helped or did not help your engagement with the talking session

SECTION 2: RUMINATIVE THINKING STYLES

In the next section, we'd like to ask you some questions about your thinking patterns, particularly about a thinking style called rumination. Have you heard of this term before? Could you tell me what your understanding of rumination is?
Rumination is a repetitive, negative, and self-critical thinking pattern about one's self, feelings, personal concerns and upsetting experiences. It is often difficult to control this thinking pattern once it starts.

6. *Topics of rumination*: Typically, people ruminate about a great number of things. I wonder if you could tell me about some of the main things that you tend to ruminate about and your general experience of ruminating.
7. *Triggers of rumination:* Thinking about when you have these repetitive thoughts, what starts it off?
   a. Prompts: negative mood, upsetting experiences?
8. *What ends the rumination:* Is there anything that tends to end/stop these thoughts?
9. *Effects of rumination on mood*: Thinking about when you're ruminating, do you notice any change in your mood or craving for alcohol?
10. *Changes in rumination*: Have you experienced any changes in your ruminative thinking following the treatment? (specify timeline: following the treatment you received during the trial).
    a. Prompts: Change in how often you tend to ruminate,
    b. Whether you find it easier to control ruminative thoughts
    c. Change in what starts and ends rumination.

Final section involves some questions about your current alcohol and drug use.

SECTION 3: CURRENT ALCOHOL AND DRUG USE (YES/NO)

11. Have you been using alcohol since you finished participating in the trial?
    a. If yes, when did you start? What do you attribute this to?
    b. How frequently? (Days in month)
    c. Last 14 days of alcohol use
12. Have you at used ketamine or any other drugs recreationally since finishing participation in the trial?
    a. Which drugs?
    b. How frequently (days in a month) what dose in a session? (A session is each occasion of use)

DEBRIEF

Is there anything else you would like to report related to your experience taking part in the KARE trial?
Do you have any questions?

frontiers in Psychiatry

CASE REPORT
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Case Report: Unexpected Remission From Extreme and Enduring Bulimia Nervosa With Repeated Ketamine Assisted Psychotherapy

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Background: Bulimia nervosa is a disabling psychiatric disorder that considerably impairs physical health, disrupts psychosocial functioning, and reduces overall quality of life. Despite available treatment, less than half of sufferers achieve recovery and approximately a third become chronically ill. Extreme and enduring cases are particularly resistant to first-line treatment, namely antidepressants and cognitive behavioral therapy, and have the highest rate of premature mortality. Here, we demonstrate that in such cases, repeated sessions of ketamine assisted psychotherapy (KAP) is an effective treatment alternative for improving symptoms.

Case Presentation: A 21-year-old woman presented with extreme and enduring bulimia nervosa. She reported recurrent binge-eating and purging by self-induced vomiting 40 episodes per day, which proved refractory to both pharmacological and behavioral treatment at the outpatient, residential, and inpatient level. Provided this, her physician recommended repeated KAP as an exploratory and off-label intervention for her eating disorder. The patient underwent three courses of KAP over 3 months, with each course consisting of six sessions scheduled twice weekly. She showed dramatic reductions in binge-eating and purging following the first course of treatment that continued with the second and third. Complete cessation of behavioral symptoms was achieved 3 months post-treatment. Her remission has sustained for over 1 year to date.

Conclusions: To our knowledge, this is the first report of repeated KAP used to treat bulimia nervosa that led to complete and sustained remission, a rare outcome for severe and enduring cases, let alone extreme ones. Additionally, it highlights the degree to which KAP can be tailored at the individual level based on symptom severity and treatment response. While its mechanism of action is unclear, repeated KAP is a promising intervention for bulimia nervosa that warrants future research and clinical practice consideration.

Keywords: bulimia nervosa, eating disorder, binge-eating, purging, ketamine, ketamine assisted psychotherapy, psychopharmacology, case report

INTRODUCTION

Bulimia nervosa (BN) is a disabling psychiatric disorder characterized by recurrent binge-eating (consuming objectively large amounts of food with a sense of lost control) and inappropriate compensatory behaviors (self-induced vomiting; laxative, diuretic, or medication misuse; and fasting or excessive exercise) aimed at preventing weight gain (1, 2). Overtime, the severity of these patterns significantly disrupts physical health and psychosocial functioning, as well as impacts families and communities at large (3). Approximately 50 million people worldwide will develop BN at some point in their life (4). Moreover, studies have found BN to be associated with concomitant psychiatric comorbidity [e.g., mood disorders and substance abuse; (5, 6)] in addition to premature mortality due to medical complications (7–9). Death by suicide is also eight times more likely to occur among individuals with BN compared to the general population, with more than a third experiencing lifetime rates of non-suicidal self-injury (10, 11).

While pharmacological (e.g., selective serotonin reuptake inhibitors) and behavioral (e.g., cognitive behavioral therapy) interventions are effective in managing BN (12, 13), many individuals do not respond to first-line treatment, are unsuccessful in later attempts, and fail to change over protracted periods (14, 15). Nearly 30% of sufferers become chronically ill as a result (16). For such chronic refractory cases, the paucity of evidence-based treatments has prompted paradigm shifts toward harm reduction and palliative care *over* recovery (17, 18).

Ketamine, a non-competitive N-methyl-D-aspartate receptor (NMDAr) antagonist, is an emerging therapy for treatment-resistant mood disorders (19, 20). Single-dose studies have consistently shown rapid antidepressant and anti-suicidal effects following ketamine treatment, though are relatively short-lived (1–4 weeks) (21–28). Ketamine assisted psychotherapy (KAP) has therefore been utilized to prolong ketamine's efficacy and maximize therapeutic outcomes (29–34). To date, few studies have used ketamine for the treatment of eating disorders, including one open-label study (35), two case reports (36, 37), and one longitudinal case series (38), all of which administered ketamine without a psychotherapeutic component. Nonetheless, the results are encouraging. Here, we report the case of a young woman suffering from extreme and enduring BN, according to CARE (CAse REport) guidelines (39), who demonstrated remarkable symptom improvement following repeated sessions of KAP.

CASE PRESENTATION

A 21-year-old woman with BN of 9 years presented to the outpatient clinic, Forum Health. She was first diagnosed with BN, binge-eating/purging type, at 12.5 years of age to which the severity of her symptoms steadily increased overtime. On presentation, she reported alarming rates of binge-eating and purging by self-induced vomiting, averaging ∼40 episodes per day for the last 12 months. Based on this frequency, her BN was categorized as "extreme" according to *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5) criterion (14 or more episodes per week). Clinical assessment and scoring on the Eating Disorder Examination Questionnaire [EDE-Q; (40, 41)] additionally confirmed the severity of her illness. No laxative or diuretic abuse was reported. While not active in psychiatric treatment, the patient was taking potassium chloride 20 mEq extended-release twice daily for hypokalemia as well as trazodone 100 mg once daily in the evenings for sleep. At 161.92 cm tall and 46.26 kg in weight [body mass index (BMI) = 17.6 kg per m^2], the patient was amenorrheic and described body image disturbances, intense fear of gaining weight, and obsessive-compulsive tendencies around food (counting calories, binging by order of food group, and inability to discard uneaten items). She further displayed pronounced bilateral parotid sialadenosis (enlargement of the salivary glands) and pseudo-idiopathic edema, otherwise known as pseudo-bartter's syndrome (PBS): a rare and painful complication of BN characterized by hyperaldosteronism, metabolic alkalosis, and hypokalemia (42). As a University student studying cognitive neuroscience, the patient was obliged to take a medical leave due functional decline. "I lost all ability to take care of myself. I could not think clearly or show up for classes. I stopped socializing and running errands. I could hardly maintain basic hygiene."

Her psychiatric history included an adolescent sexual assault by a treating physician (13 years of age [2011]); a suicide attempt by cut throat injury at the level of the hyoid bone, which required emergency transportation and thyroid cartilage repair as well as inpatient hospitalization (13 years of age [2011]); a second suicide attempt by drug overdose involving mixed opioids, barbiturates, and antidepressants that resulted in emergency room hospitalization (15 years of age [2013]); and a blitz rape (surprise attack) by an unknown assailant (19 years of age [2017]). The patient's history also contained reports of major depression, general anxiety, and obsessive-compulsive disorder. There was no family history of eating disorders, including BN.

As an outpatient, she was treated with various pharmacotherapies (fluoxetine 40 mg once daily, citalopram 20 mg once daily, and naltrexone 50 mg twice daily), behavioral interventions (cognitive behavioral therapy, mindfulness-based stress reduction, and eye movement desensitization and reprocessing), and nutritional counseling (dietary modification and time-based feeding). She additionally was prescribed spironolactone 25 mg twice daily, a potassium-sparing diuretic, on multiple occasions to treat PBS following attempts at purging cessation. However, the patient's binge-purge patterns continued. Finally, she received inpatient, residential, and intensive-outpatient eating disorder care (15–16 years of age [2013–2014]), which the patient described as a "traumatic experience" that resulted in immediate relapse upon discharge.

"My parents pulled me out of class and dropped me off at a center, leaving me there for almost 10 months. It was like being in prison. I was completely cut off from my friends and family. I was forced to eat unreasonable amounts of food at each meal.

Abbreviations: BMI, body mass index; BN, bulimia nervosa; DSM-5, diagnostics and statistical manual of mental disorders, 5th edition; EDE-Q, eating disorder examination questionnaire; KAP, ketamine assisted psychotherapy; NMDAr, N-methyl-D-aspartate receptor; PBS, pseudo-bartter's syndrome.

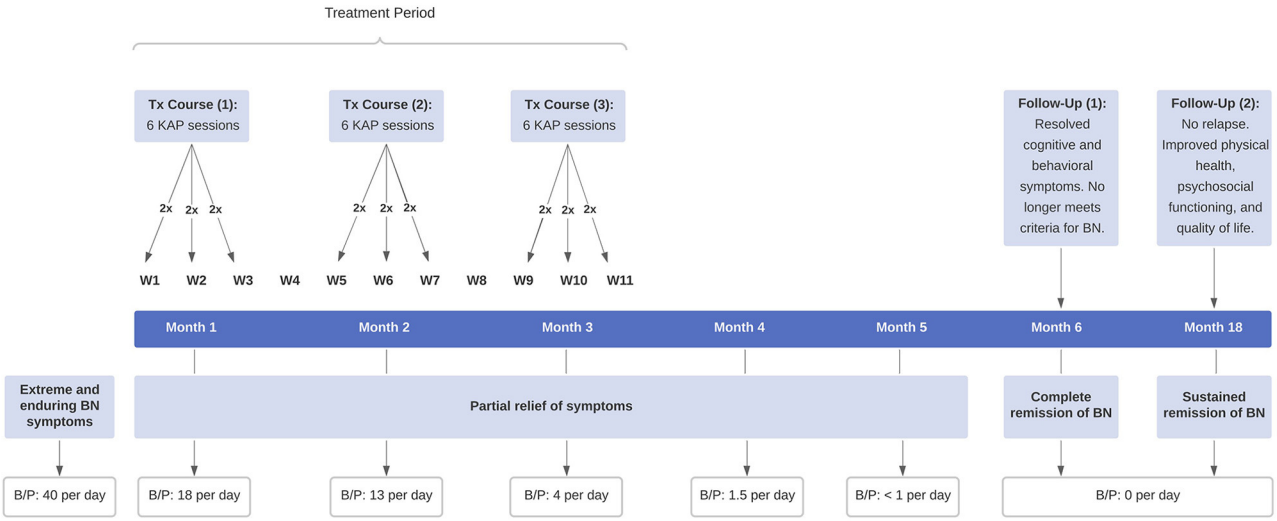

FIGURE 1 | Timeline of clinical events. The patient received three courses of repeated KAP for extreme and enduring BN, consisting of six sessions per course scheduled twice weekly for 3 weeks. KAP, ketamine assisted psychotherapy; BN, bulimia nervosa; B/P, binge-eating and purging.

And I learned new [eating disorder] tricks from other patients that I tried later on. It was not a place conducive to recovery, at least for me. It just made my condition worse."

Her medical history detailed emergency room hospitalizations for hypokalemia (16, 19, and 20 years of age [2014, 2017, 2018]), gastroesophageal reflux disorder (17–21 years of age [2015–2019]), gastric and duodenal ulcers (19 and 21 years of age [2017, 2019]), hypothyroidism (20–21 years of age [2018–2019]), and adrenocortical insufficiency (20–21 years of age [2018–2019]). Porcelain-laminate veneers were also placed on 10 of her teeth due to dental caries and enamel erosion from chronic purging (21 years of age [2019]).

Given the patient's extreme and chronic refractory state, her physician recommended repeated KAP, with the understanding it constituted an exploratory and off-label intervention for her eating disorder. She consented to treatment following a comprehensive medical evaluation and in-depth review of the procedures, risks, and possible side effects. A signed consent form was obtained. Prior to treatment, she met with a clinical psychologist to establish rapport and therapeutic alliance. The patient then underwent one course of repeated KAP, consisting of six sessions scheduled twice weekly for 3 weeks, with a minimum interval between sessions of 48 h (**Figure 1**). Each KAP session involved guided psychotherapy combined with racemic ketamine hydrochloride (0.5 mg per kg bodyweight suspended in 0.9% normal saline) administered intravenously over 40 min. The drug regimen was standard practice in the clinic for sub-anesthetic ketamine infusions, which is most commonly used for treating psychiatric disorders and is supported by a substantial body of literature (43, 44). A person-centered, humanistic approach to psychotherapy was employed to facilitate the process of self-actualization and therapeutic change. KAP sessions were preceded by 30 min of preparatory psychotherapy and delivered in a private room with dimmed lights, ambient music, and textile art on the ceiling. The intervention components and ketamine regimen remained the same for all five consecutive sessions; and blood pressure, heart rate, and oxygen saturation were continuously monitored. Due to the severity of her eating disorder, however, the patient returned to the clinic 1 month later for a second course of repeated KAP and then again 1 month later for a third.

Dissociation, ego dissolution, and perceptual distortions were present during all KAP sessions, as evidenced by the patient's description of "being disconnected from reality," "losing [her] sense of identity and self," and "seeing abstract geometric patterns." She further exhibited mild diplopia (double vision), nystagmus (involuntary oscillations of the eyes), and alogia (lack of speech) during treatment that resolved completely. No other side effects or adverse events were reported. The patient's eating disorder symptoms remitted over the course of treatments, as measured by change in scoring on the EDE-Q as well as entries from a daily tracking log that recorded frequency of binge-eating and purging. On the EDE-Q, her global score dropped from 31.8 at baseline to 15.0 by the end of all three courses (18 sessions), with similar patterns recorded across all four subscales: "Restraint" ($M = 5.0$, $SD = 2.2$ to $M = 1.8$, $SD = 1.3$), "Eating Concern" ($M = 5.8$, $SD = 0.5$ to $M = 2.2$, $SD = 1.5$), "Weight Concern" ($M = 5.8$, $SD = 0.5$ to $M = 4.0$, $SD = 1.9$), and "Shape Concern" ($M = 5.5$, $SD = 0.8$ to $M = 2.5$, $SD = 1.6$) (**Figure 2**). Additionally, the patient's tracking log showed decreases in binge-eating and purging from 40 to 18 episodes per day after the first course of treatment (6 sessions), 18 to 13 episodes per day after the second course of treatment (12 sessions), and 13 to 4 episodes per day after the third course of treatment (18 sessions) (**Figure 3**).

Most notably, the patient stopped her binge-eating and purging behaviors 3 months post-treatment. Given her initial severity and chronic refractory state, this degree of improvement

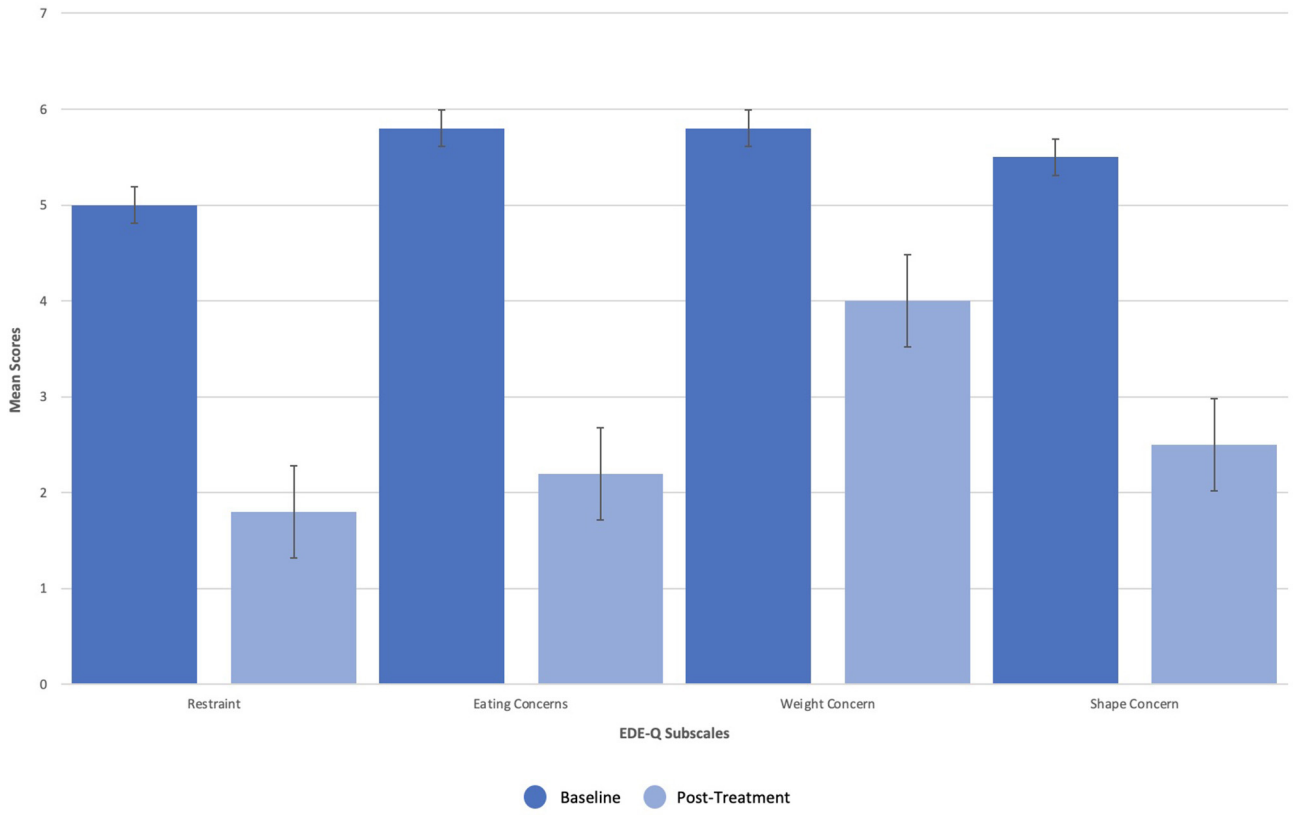

FIGURE 2 | Change in scoring on the Eating Disorder Examination Questionnaire (EDE-Q).

was striking. The patient's daily tracking log additionally showed no signs of relapse 1 year later, accompanied by marked improvement in psychosocial functioning. Specifically, she reported feeling "free" from intrusive BN thoughts and compulsions, "less impulsive" when faced with the urge to binge and purge, and "more confident" about her body in general. The patient has since resumed her academic studies in preparation for a doctoral program.

DISCUSSION

Severe, chronic, and refractory eating disorder symptoms are unfortunately common among patients with BN. In this case, we describe a young woman with extreme and enduring BN, who remained unresponsive to first-line treatment for nearly a decade, despite care at the outpatient, residential, and inpatient level. Her eating disorder was extreme, insofar as she engaged in recurrent binge-eating and purging by self-induced vomiting 40 episodes per day, which significantly exceeds DSM-5 criterion (14 or more episodes per week). Given the severity of her illness, complete and sustained remission with three courses of repeated KAP (18 sessions) was both remarkable and unanticipated. These findings are more robust provided the patient was not active in psychiatric treatment for 1 year prior to clinic admission, excluding her long-standing prescription of potassium chloride for hypokalemia and trazodone for sleep. If ketamine and psychotherapy act synergistically, with therapy priming and enhancing the response to treatment, then its combined effect may explain the striking improvements in symptoms. Serial treatments likely account for the durability of response necessary for sustained remission, which is consistent with literature (45–48).

Provided this is the first report of repeated KAP used as an exploratory and off-label intervention for BN, it is important to consider the a-priori context. Clinical recommendation to pursue repeated KAP was prompted by three factors. First, the patient's psychiatric and medical history that detailed unsuccessful treatment attempts, including pharmacotherapies, behavioral treatments, and nutritional counseling—even at higher levels of eating disorder care; and significant trauma to which accumulating evidence has shown ketamine to yield positive effects for (49–51). Second, her severe functional impairment in three major life domains, including academic work, social and family engagement, and personal responsibilities. The patient was binge-eating and purging nearly to the exclusion of all other activities, spending more time "alone in the bathroom than with [her] friends or family." Finally, an open-label case series on repeated ketamine in severe and enduring anorexia nervosa, showing modest improvements in eating disorder symptoms (38).

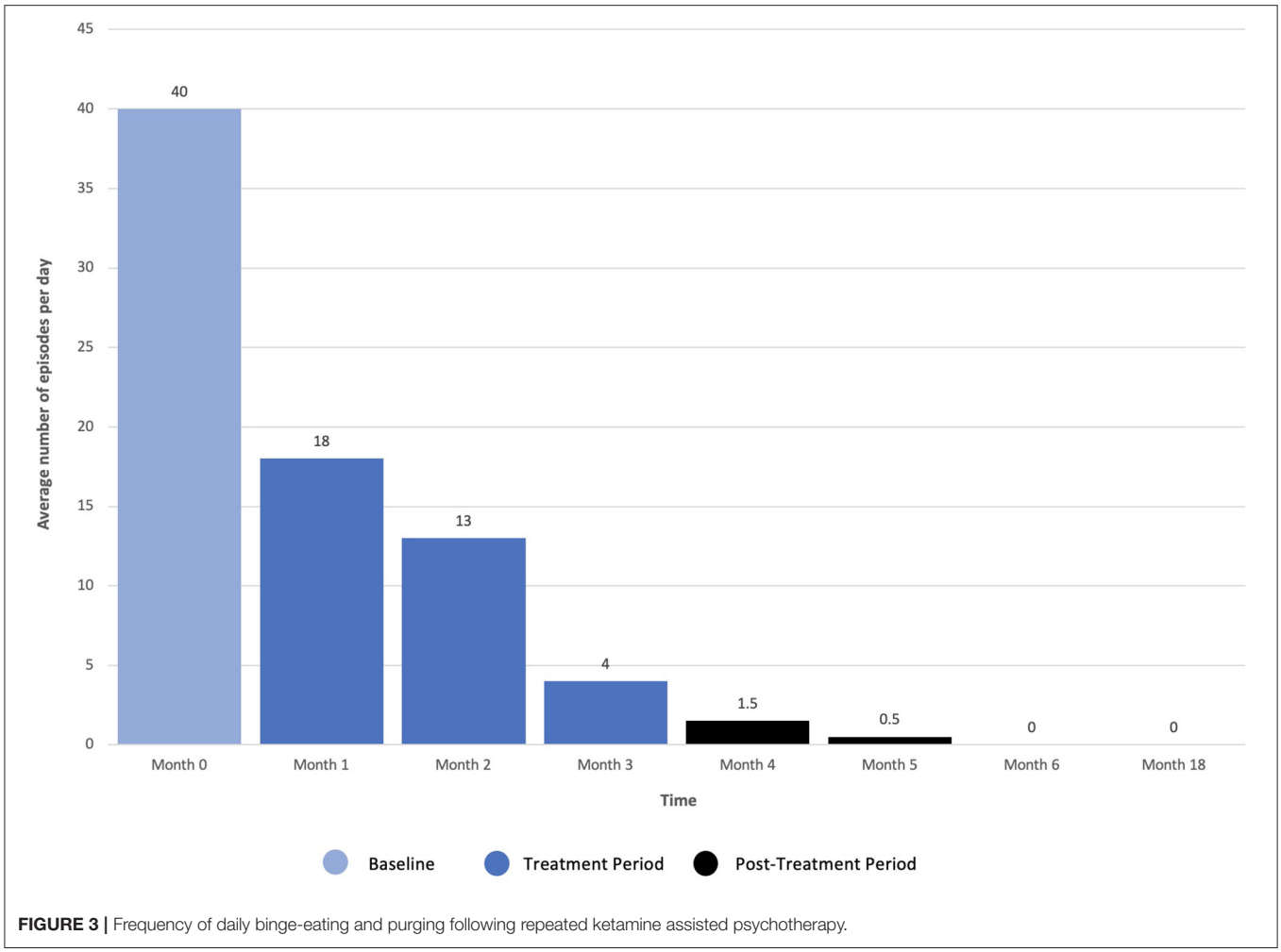

FIGURE 3 | Frequency of daily binge-eating and purging following repeated ketamine assisted psychotherapy.

The patient's impetus for treatment was largely driven by fear of premature mortality—that if she did not attempt something new, she was going to "eat [herself] to death," quite literally. Serious degradation in the patient's physical and mental health status were particularly motivating. Apart from transient psychological (dissociation, ego dissolution, and perceptual distortions) and physiological (mild diplopia, nystagmus, and alogia) side effects of ketamine that resolved completely after each session, the treatment was well-tolerated. Following all three courses of treatment, the patient dramatically reduced her binge-eating and purging behaviors by 90% compared to baseline, as measured by the EDE-Q and daily tracking logs. She also demonstrated considerable improvements in disordered eating psychopathology that were captured by the subscales of the EDE-Q, most notably "Restraint" (e.g., dietary rules and avoidance of food) and "Eating Concerns" (e.g., preoccupation with calories and fear of losing control over eating). Moreover, the patient regained control of her impulsive eating as well as resolved her obsessive-compulsive neurosis, which align with previous BN-specific findings from a study on intermittent ketamine infusions in eating disorders (35). At 3 months follow-up, she achieved complete cessation of binge-eating and purging and no longer met diagnostic criteria for BN. The magnitude of response neither diminished over time, with no signs of relapse at 15 months follow-up, contrary to studies showing rapid decline of effects after treatment (28, 52, 53). With sustained remission, the patient has adopted a healthier relationship with food, established psychosocial stability in her life, and resumed her academic studies in preparation for graduate school.

This is a single case report with inherent limitations in generalizing the findings to other patients with BN. The lack of polypharmacy or medication washout is an additional limitation that may have unknowingly mediated improvements. Furthermore, it is unclear as to whether ketamine or psychotherapy produced greater clinical benefit, if both are coadjuvant and necessary, or if the treatment would have been as effective without psychotherapy and/or fewer sessions. Finally, a person-centered, humanistic approach to psychotherapy was employed, differing from more traditional methods, such as cognitive-behavioral, interpersonal, and psychodynamic therapy. Open pilot studies as well as fully-powered randomized controlled trials with longitudinal assessment are thus required to establish whether the outcome of this case can be replicated, to what degree ketamine and psychotherapy contribute to the

overall success of the treatment, and the comparative efficacy of different psychotherapeutic interventions. Further research is also warranted to optimize KAP duration and frequency for this patient population.

CONCLUSIONS

This study provides compelling evidence that repeated KAP is an effective treatment for extreme and enduring BN, which is exceedingly resistant to first-line therapies and associated with poor prognosis. It further highlights the utility of combined strategies that may prolong ketamine's efficacy, and subsequently maximize therapeutic outcomes at the individual level.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

PH-B assessed, treated, and followed-up with the patient. AR interviewed the patient, conceptualized the case report, drafted the manuscript, and developed all figures. LKJ and SC contributed to the literature review and assisted with manuscript preparation. LG, QT, and MR provided substantial contributions to the interpretation of data as well as manuscript revisions. All authors have read and approved the final manuscript.

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REFERENCES

1. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders: DSM-5*. 5th ed. Washington DC: American Psychiatric Association (2013). doi: 10.1176/appi.books.9780890425596
2. Grilo CM, Ivezaj V, White MA. Evaluation of the DSM-5 severity indicator for bulimia nervosa. *Behav Res Ther.* (2015) 67:41–4. doi: 10.1016/j.brat.2015.02.002
3. van Hoeken D, Hoek HW. Review of the burden of eating disorders: mortality, disability, costs, quality of life, and family burden. *Curr Opin Psychiatry.* (2020) 33:521–7. doi: 10.1097/YCO.0000000000000641
4. Qian J, Wu Y, Liu F, Zhu Y, Jin H, Zhang H, et al. An update on the prevalence of eating disorders in the general population: a systematic review and meta-analysis. *Eat Weight Disord.* (2021) 1–4. doi: 10.1007/s40519-021-01162-z
5. Himmerich H, Hotopf M, Shetty H, Schmidt U, Treasure J, Hayes RD, et al. Psychiatric comorbidity as a risk factor for the mortality of people with bulimia nervosa. *Soc Psychiatry Psychiatr Epidemiol.* (2019) 54:813–21. doi: 10.1007/s00127-019-01667-0
6. Dalle Grave R, Sartirana M, Calugi S. *Complex Cases and Comorbidity in Eating Disorders: Assessment and Management*. Springer Nature (2021). p. 79–97. doi: 10.1007/978-3-030-69341-1
7. Arcelus J, Mitchell AJ, Wales J, Nielsen S. Mortality rates in patients with anorexia nervosa and other eating disorders: a meta-analysis of 36 studies. *Arch Gen Psychiatry.* (2011) 68:724–31. doi: 10.1001/archgenpsychiatry.2011.74
8. Huas C, Godart N, Caille A, Pham-Scottez A, Foulon C, Divac SM, et al. Mortality and its predictors in severe bulimia nervosa patients. *Eur Eat Disord Rev.* (2013) 21:15–9. doi: 10.1002/erv.2178
9. Franko DL, Tabri N, Keshaviah A, Murray HB, Herzog DB, Thomas JJ, et al. Predictors of long-term recovery in anorexia nervosa and bulimia nervosa: data from a 22-year longitudinal study. *J Psychiatr Res.* (2018) 96:183–8. doi: 10.1016/j.jpsychires.2017.10.008
10. Preti A, Rocchi MB, Sisti D, Camboni MV, Miotto P. A comprehensive meta-analysis of the risk of suicide in eating disorders. *Acta Psychiatr. Scand.* (2011) 124:6–17. doi: 10.1111/j.1600-0447.2010.01641.x
11. Cucchi A, Ryan D, Konstantakopoulos G, Stroumpa S, Kaçar AS, Renshaw S, et al. Lifetime prevalence of non-suicidal self-injury in patients with eating disorders: a systematic review and meta-analysis. *Psychol Med.* (2016) 46:1345–58. doi: 10.1017/S0033291716000027
12. Mitchell JE, Agras S, Wonderlich S. Treatment of bulimia nervosa: where are we and where are we going? *Int J Eat Disord.* (2007) 40:95–101. doi: 10.1002/eat.20343
13. Vocks S, Tuschen-Caffier B, Pietrowsky R, Rustenbach SJ, Kersting A, Herpertz S. Meta-analysis of the effectiveness of psychological and pharmacological treatments for binge eating disorder. *Int J Eat Disord.* (2010) 43:205–17. doi: 10.1002/eat.20696
14. Wonderlich S, Mitchell JE, Crosby RD, Myers TC, Kadlec K, LaHaise K, et al. Minimizing and treating chronicity in the eating disorders: a clinical overview. *Int J Eat Disord.* (2012) 45:467–75. doi: 10.1002/eat.20978
15. Eddy KT, Tabri N, Thomas JJ, Murray HB, Keshaviah A, Hastings E, et al. Recovery from anorexia nervosa and bulimia nervosa at 22-year follow-up. *J Clin Psychiatry.* (2017) 78:184–9. doi: 10.4088/JCP.15m10393
16. Steinhausen HC, Weber S. The outcome of bulimia nervosa: findings from one-quarter century of research. *Am J Psychiatry.* (2009) 166:1331–41. doi: 10.1176/appi.ajp.2009.09040582
17. Westmoreland P, Mehler PS. Caring for patients with severe and enduring eating disorders (SEED): certification, harm reduction, palliative care, and the question of futility. *J Psychiatr Pract.* (2016) 22:313–20. doi: 10.1097/PRA.0000000000000160
18. Strand M, Sjöstrand M, Lindblad A. A palliative care approach in psychiatry: clinical implications. *BMC Med Ethics.* (2020) 21:29. doi: 10.1186/s12910-020-00472-8
19. Park LT, Falodun TB, Zarate CA Jr. Ketamine for treatment-resistant mood disorders. *Focus.* (2019) 17:8–12. doi: 10.1176/appi.focus.20180030
20. Wilkinson ST, Sanacora G. A new generation of antidepressants: an update on the pharmaceutical pipeline for novel and rapid-acting therapeutics in mood disorders based on glutamate/GABA neurotransmitter systems. *Drug Discov Today.* (2019) 24:606–15. doi: 10.1016/j.drudis.2018.11.007
21. Berman RM, Cappiello A, Anand A, Oren DA, Heninger GR, Charney DS, et al. Antidepressant effects of ketamine in depressed patients. *Biol Psychiatry.* (2000) 47:351–4. doi: 10.1016/S0006-3223(99)00230-9

22. Zarate CA, Singh JB, Carlson PJ, Brutsche NE, Ameli R, Luckenbaugh DA, et al. A randomized trial of an N-methyl-D-aspartate antagonist in treatment-resistant major depression. *Arch Gen Psychiatry.* (2006) 63:856–64. doi: 10.1001/archpsyc.63.8.856
23. Diazgranados N, Ibrahim L, Brutsche NE, Newberg A, Kronstein P, Khalife S, et al. A randomized add-on trial of an N-methyl-D-aspartate antagonist in treatment-resistant bipolar depression. *Arch Gen Psychiatry.* (2010) 67:793–802. doi: 10.1001/archgenpsychiatry.2010.90
24. Zarate CA Jr., Brutsche NE, Ibrahim L, Franco-Chaves J, Diazgranados N, Cravchik A, et al. Replication of ketamine's antidepressant efficacy in bipolar depression: a randomized controlled add-on trial. *Biol Psychiatry.* (2012) 71:939–46. doi: 10.1016/j.biopsych.2011.12.010
25. Murrough JW, Iosifescu DV, Chang LC, Al Jurdi RK, Green CE, Perez AM, et al. Antidepressant efficacy of ketamine in treatment-resistant major depression: a two-site randomized controlled trial. *Am J Psychiatry.* (2013) 170:1134–42. doi: 10.1176/appi.ajp.2013.13030392
26. Lapidus KA, Levitch CF, Perez AM, Brallier JW, Parides MK, Soleimani L, et al. A randomized controlled trial of intranasal ketamine in major depressive disorder. *Biol Psychiatry.* (2014) 76:970–6. doi: 10.1016/j.biopsych.2014.03.026
27. Lai R, Katalinic N, Glue P, Somogyi AA, Mitchell PB, Leyden J, et al. Pilot dose–response trial of iv ketamine in treatment-resistant depression. *World J Biol Psychiatry.* (2014) 15:579–84. doi: 10.3109/15622975.2014.922697
28. Marcantoni WS, Akoumba BS, Wassef M, Mayrand J, Lai H, Richard-Devantoy S. et al. A systematic review and meta-analysis of the efficacy of intravenous ketamine infusion for treatment resistant depression: January 2009–January 2019. *J Affect Disord.* (2020) 277:831–41. doi: 10.1016/j.jad.2020.09.007
29. Krupitsky EM, Grinenko AY. Ketamine psychedelic therapy (KPT): a review of the results of ten years of research. *J Psychoactive Drugs.* (1997) 29:165–83. doi: 10.1080/02791072.1997.10400185
30. Kolp E, Young MS, Friedman H, Krupitsky E, Jansen K, O'Connor L. Ketamine-enhanced psychotherapy: preliminary clinical observations on its effects in treating death anxiety. *Int J Transpers Stud.* (2007) 26:1–7. doi: 10.24972/ijts.2007.26.1.1
31. Calabrese L. Titrated serial ketamine infusions stop outpatient suicidality and avert ER visits and hospitalizations. *Int J Psychiatr Res.* (2019) 2:1–2. Available online at: http://scivisionpub.com/pdfs/titrated-serial-ketamine-infusions-stop-outpatient-suicidality-and-avert-er-visits-and-hospitalizations-918.pdf
32. Dore J, Turnipseed B, Dwyer S, Turnipseed A, Andries J, Ascani G, et al. Ketamine assisted psychotherapy (KAP): patient demographics, clinical data and outcomes in three large practices administering ketamine with psychotherapy. *J Psychoactive Drugs.* (2019) 51:189–98. doi: 10.1080/02791072.2019.1587556
33. Wheeler SW, Dyer NL. A systematic review of psychedelic-assisted psychotherapy for mental health: an evaluation of the current wave of research and suggestions for the future. *Psychol Conscious.* (2020) 7:279. doi: 10.1037/cns0000237
34. Halstead M, Reed S, Krause R, Williams MT. Ketamine-assisted psychotherapy for PTSD related to racial discrimination. *J Clin Case Stud.* (2021) 20:310–30. doi: 10.1177/1534650121990894
35. Mills IH, Park GR, Manara AR, Merriman RJ. Treatment of compulsive behaviour in eating disorders with intermittent ketamine infusions. *QJM.* (1998) 91:493–503. doi: 10.1093/qjmed/91.7.493
36. Dechant E, Boyle B, Ross RA. Ketamine in a patient with comorbid anorexia and MDD. *J Women's Health Dev.* (2020) 3:373–5. doi: 10.26502/fjwhd.2644-28840044
37. Scolnick B, Zupec-Kania B, Calabrese L, Aoki C, Hildebrandt T. Remission from chronic anorexia nervosa with ketogenic diet and ketamine: case report. *Front Psychiatry.* (2020) 11:763. doi: 10.3389/fpsyt.2020.00763
38. Schwartz T, Trunko ME, Feifel D, Lopez E, Peterson D, Frank GK, et al. A longitudinal case series of IM ketamine for patients with severe and enduring eating disorders and comorbid treatment-resistant depression. *Clin Case Rep.* (2021) 9:e03869. doi: 10.1002/ccr3.3869
39. Gagnier J, Kienle G, Altman DG, Moher D, Sox H, Riley DS, et al. The CARE guidelines: consensus-based clinical case report guideline development. *J Clin Epidemiol.* (2013) 67:46–51. doi: 10.1111/head.12246
40. Fairburn CG, Cooper Z, O'Connor M. The eating disorder examination. *Int J Eat Disord.* (1993) 6:1–8.
41. Fairburn CG, Cooper Z, O'Connor M. Eating Disorder Examination (Edition 16.0 D). In: Fairburn CG, editor. *Cognitive Behavior Therapy and Eating Disorders.* New York, NY: Guilford Press (2008). p. 265–308.
42. Nitsch A, Dlugosz H, Gibson D, Mehler PS. Medical complications of bulimia nervosa. *Clevel Clin J Med.* (2021) 88:333–43. doi: 10.3949/ccjm.88a.20168
43. Andrade C. Ketamine for depression, 4: in what dose, at what rate, by what route, for how long, and at what frequency? *J Clin Psychiatry.* (2017) 78:e852–7. doi: 10.4088/JCP.17f11738
44. Peyrovian B, McIntyre RS, Phan L, Lui LM, Gill H, Majeed A, et al. Registered clinical trials investigating ketamine for psychiatric disorders. *J Psychiatr Res.* (2020) 127:1–2. doi: 10.1016/j.jpsychires.2020.03.020
45. Murrough JW, Perez AM, Pillemer S, Stern J, Parides MK, aan het Rot M, et al. Rapid and longer-term antidepressant effects of repeated ketamine infusions in treatment-resistant major depression. *Biol Psychiatry.* (2013) 74:250–6. doi: 10.1016/j.biopsych.2012.06.022
46. Albott CS, Lim KO, Forbes MK, Erbes C, Tye SJ, Grabowski JG, et al. Efficacy, safety, and durability of repeated ketamine infusions for comorbid posttraumatic stress disorder and treatment-resistant depression. *J Clin Psychiatry.* (2018) 79:17m11634. doi: 10.4088/JCP.17m11634
47. Phillips JL, Norris S, Talbot J, Birmingham M, Hatchard T, Ortiz A, et al. Single, repeated, and maintenance ketamine infusions for treatment-resistant depression: a randomized controlled trial. *Am J Psychiatry.* (2019) 176:401–9. doi: 10.1176/appi.ajp.2018.18070834
48. Krystal JH, Abdallah CG, Sanacora G, Charney DS, Duman RS. Ketamine: a paradigm shift for depression research and treatment. *Neuron.* (2019) 101:774–8. doi: 10.1016/j.neuron.2019.02.005
49. McGhee LL, Maani CV, Garza TH, Gaylord KM, Black IH. The correlation between ketamine and posttraumatic stress disorder in burned service members. *J Trauma Acute Care Surg.* (2008) 64:S195–9. doi: 10.1097/TA.0b013e318160ba1d
50. Feder A, Parides MK, Murrough JW, Perez AM, Morgan JE, Saxena S, et al. Efficacy of intravenous ketamine for treatment of chronic posttraumatic stress disorder: a randomized clinical trial. *JAMA Psychiatry.* (2014) 71:681–8. doi: 10.1001/jamapsychiatry.2014.62
51. Feder A, Rutter SB, Schiller D, Charney DS. The emergence of ketamine as a novel treatment for posttraumatic stress disorder. *Adv Pharmacol.* (2020) 89:261–86. doi: 10.1016/bs.apha.2020.05.004
52. aan het Rot M, Collins KA, Murrough JW, Perez AM, Reich DL, Charney DS, et al. Safety and efficacy of repeated-dose intravenous ketamine for treatment-resistant depression. *Biol Psychiatry.* (2010) 67:139–45. doi: 10.1016/j.biopsych.2009.08.038
53. Newport DJ, Carpenter LL, McDonald WM, Potash JB, Tohen M, Nemeroff CB, et al. Ketamine and other NMDA antagonists: early clinical trials and possible mechanisms in depression. *Am J Psychiatry.* (2015) 172:950–66. doi: 10.1176/appi.ajp.2015.15040465

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Association of VEGF With Antianhedonic Effects of Repeated-Dose Intravenous Ketamine in Treatment-Refractory Depression

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Objectives: To first explore the role of plasma vascular endothelial growth factor (VEGF) concentrations in ketamine's antianhedonic effects, focusing on Chinese patients with treatment-refractory depression (TRD).

Methods: Seventy-eight patients with treatment-refractory major depressive disorder (MDD) or bipolar disorder (BD) were treated with six ketamine infusions (0.5 mg/kg). Levels of anhedonia were measured using the Montgomery–Åsberg Depression Rating Scale (MADRS) anhedonia item at baseline, day 13 and 26. Plasma VEGF concentrations were examined at the same time points as the MADRS.

Results: Despite a significant reduction in anhedonia symptoms in individuals with treatment-refractory MDD ($n = 59$) or BD ($n = 19$) after they received repeated-dose ketamine infusions ($p < 0.05$), no significant changes in plasma VEGF concentrations were found at day 13 when compared to baseline ($p > 0.05$). The alteration of plasma VEGF concentrations did not differ between antianhedonic responders and non-responders at days 13 and 26 (all $ps > 0.05$). Additionally, no significant correlations were observed between the antianhedonic response to ketamine and plasma VEGF concentrations (all $ps > 0.05$).

Conclusion: This preliminary study suggests that the antianhedonic effects of ketamine are not mediated by VEGF.

Keywords: ketamine, VEGF, antianhedonic effect, major depressive disorder, response

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INTRODUCTION

Anhedonia, a reduced capacity for pleasure, is regarded as one of the typical characteristics of major depressive disorder (MDD) and bipolar depression (BD) (1) and appears to occur irrespective of other depressive symptoms (2, 3). Anhedonia is a robust predictor of poor outcomes (4) and suicidal ideation independent of neurocognitive dysfunction and affective symptoms (5), suggesting that it appears to be an independent somatic domain in mood disorders (3). As a residual interepisodic symptom, anhedonia has been commonly described in patients suffering

from treatment-refractory depression (TRD) treated with conventional pharmacotherapy (6). Patients with mood disorders, especially those with TRD, frequently endorse disturbance in reward capacity, providing the impetus for exploring novel agents and treatment approaches (7, 8).

Ketamine, as a dissociative anesthetic, is currently evaluated as a rapid-acting antidepressant. In addition to the rapid effect on depressive symptoms, ketamine also has rapid and robust effects on anhedonia symptoms (1, 9, 10) and suicidal ideation (11–13) in treatment-refractory BD and MDD. When compared with placebo, a single ketamine infusion could rapidly ameliorate anhedonia symptoms in individuals suffering from treatment-refractory BD; the reduction in anhedonia symptoms occurred within 40 min and lasted up to 14 days (10). Interestingly, ketamine's antianhedonic effects occur independently of the reduction in depressive symptoms (10).

Accumulating evidence has implicated neurotrophic factors including brain-derived neurotrophic factor (BDNF) (14–16) and vascular endothelial growth factor (VEGF) (15–17) in the MDD and BD pathophysiology. VEGF can potentially mediate the antidepressant effects of ketamine (18, 19) and typical antidepressants (20). Similarly, serum BDNF levels were increased in chronic ketamine users (21) and change in plasma BDNF levels following subanesthetic ketamine infusion are associated with acute and 24 h resting-state functional connectivity (RSFC) changes (22). Findings on the association of VEGF and ketamine's antidepressant effects have been inconsistent (18, 23–25). For example, the expression of VEGF is necessary for the antidepressant-like behaviors of ketamine (18, 19). A recent study supported a role for VEGF in the antidepressant action of ketamine (25), but two recent studies found that ketamine does not change the plasma concentrations of VEGF (23, 24). However, evidence on the role of plasma VEGF concentrations in ketamine's antianhedonic effects is still lacking.

Therefore, the main aim of this current study, which employed a real-world design, is to determine the role of plasma VEGF concentrations in the antianhedonic effects of repeated-dose intravenous ketamine (0.5 mg/kg) administered thrice weekly over 2 weeks, focusing on Chinese subjects experiencing treatment-refractory MDD or BD.

METHODS

Study Design and Population

Data were collected from an open-label, real-world ketamine clinical trial (registration number: ChiCTR-OOC-17012239). IRB approval of the Affiliated Brain Hospital of Guangzhou Medical University was obtained for this study (Ethical Application Ref: 2016030). All participants gave written informed consent. In this study, we specifically report the relationship of plasma VEGF concentrations and antianhedonic effects of subanaesthetic doses of ketamine, focusing on individuals suffering from treatment-refractory MDD or BD. The detailed study design, study population and clinical findings of this single-center open-label ketamine clinical study were described in our early studies (26, 27). Briefly, seventy-eight subjects aged between 18 and 65 years were recruited, with a diagnosis of major depressive episode (MED)–MDD or BD–using DSM-5 criteria. In this study, each patient was required to score $\geq$ 17 points on the 17-item Hamilton Depression Rating Scale (HAMD) (28, 29), experiencing TRD defined as failure to respond to at least two pharmacological therapies for the current MDE (30). Patients with other psychiatric disorders such as drug/alcohol dependence or schizophrenia were excluded, but a comorbidity of obsessive compulsive disorder (OCD) or anxiety disorder was permitted if it was not judged to be the primary presenting problem. Similar to prior studies (26, 27), each participant received six ketamine infusions (0.5 mg/kg over 40 min).

Antianhedonic Response

Similar to several early studies (31, 32), the Montgomery–Åsberg Depression Rating Scale (MADRS) anhedonia item including items 1 (apparent sadness), 2 (reported sadness), 6 (concentration difficulties), 7 (lassitude), and 8 (inability to feel) was also used in this study to assess anhedonia symptoms at baseline, day 13 and 26 (at the 1 day and 2 week follow-ups after completing the last infusion, respectively). Antianhedonic response was defined as at least a 50% reduction in MADRS anhedonia item scores on day 13.

Measurement of Plasma VEGF Concentrations

All blood samples of seventy-eight subjects with treatment-refractory MDD or BD were collected preinfusion and again at days 13 and 26. Consistent with a recent study (24), a Human VEGF Immunoassay enzyme-linked immunosorbent assay (ELISA) kit (R&D Systems, Minneapolis, USA) was used to measure the plasma concentrations of VEGF.

Statistical Analysis

All statistical analyses were conducted using SPSS 24.0 statistical software focusing on Chinese patients suffering from treatment-refractory MDD or BD, with a significance level of 0.05 (two-sided). We performed a two-sample *t*-test and/or a Mann–Whitney U test as well as a chi-square test and/or a Fisher's exact test to compare the differences in baseline plasma concentrations of VEGF and demographic and clinical features between the two groups (patients with and without antianhedonic response), if necessary. A linear mixed model was conducted for changes in anhedonia symptoms as measured by MADRS and the plasma concentrations of VEGF over time between the two groups, with Bonferroni correction for the time points examined. Correlation analyses were conducted to determine the relationship of the effects of ketamine on anhedonia symptoms and the plasma concentrations of VEGF.

RESULTS

Table 1 presents the demographic and clinical data of the patients suffering from treatment-refractory MDD ($n = 59$) or BD ($n = 19$) who received repeated ketamine infusions and provided a blood sample at baseline. Antianhedonic non-responders had a significantly higher history of psychiatric hospitalization than antianhedonic responders ($p < 0.05$).

TABLE 1 | Demographic and clinical characteristics of subjects suffering from TRD.

Variables	Total sample ($n = 78$)		Antianhedonic responders ($n = 38$)		Antianhedonic non-responders ($n = 40$)		Statistics		
	N	%	*N*	%	*N*	%	χ^2	df	*p*-value
Male	39	50.0	20	52.6	19	47.5	0.2	1	0.65
Married	39	50.0	21	55.3	18	45.0	0.8	1	0.34
Employed	29	37.2	17	44.7	12	30.0	1.8	1	0.18
No history of psychiatric hospitalization	53	67.9	31	81.6	22	55.0	6.3	1	**0.01**
Having a family history of psychiatric disorders	32	41.0	13	34.2	19	47.5	1.4	1	0.23
On ADs two or more	10	12.8	4	10.5	6	15.0	0.3	1	0.56
On APs	46	59.0	21	55.3	25	62.5	0.4	1	0.52
On mood stabilizers	24	30.8	10	26.3	14	35.0	0.7	1	0.41
On benzodiazepines	31	39.7	14	36.8	17	42.5	0.3	1	0.61
On anxiolytics	36	46.2	18	47.4	18	45.0	0.04	1	0.83
On anticholinergics	12	15.4	6	15.8	6	15.0	0.01	1	0.92
Current smoking	18	23.1	9	23.7	9	22.5	0.02	1	0.90
Current drinking	4	5.1	1	2.6	3	7.5	—[a]	—[a]	0.33
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**	**T/Z**	**df**	***p*-value**
Age (years)	34.6	11.8	35.1	11.5	34.1	12.2	0.4	76	0.70
Education (years)	12.3	3.5	12.0	3.3	12.5	3.6	−0.6	76	0.55
BMI (kg/m^2)	22.7	3.4	23.3	3.7	22.1	3.1	1.6	76	0.12
Age of onset (years)	25.8	11.4	27.2	12.3	24.4	10.5	1.1	76	0.29
Duration of illness (months)	109.5	104.2	98.8	104.6	119.6	104.3	−1.0	—[b]	0.31
FLUeq (mg/day)	36.7	23.0	38.5	24.1	35.1	22.2	−0.6	—[b]	0.53
CPZeq (mg/day)	172.3	125.6	144.9	102.6	195.3	139.9	−1.4	—[b]	0.16
Baseline MADRS total scores	31.5	7.4	31.0	7.0	31.9	7.8	−0.5	76	0.62
Baseline MADRS anhedonia item scores	19.9	4.6	19.5	4.6	20.3	4.7	−0.8	76	0.45
Baseline plasma VEGF concentrations (ng/ml)	30.7	48.2	34.0	47.2	27.5	49.5	−0.7	—[b]	0.46

[a]*Fisher's exact test;* [b]*Mann-Whitney U test. Bolded values are p < 0.05. Ads, Antidepressants; Aps, antipsychotics; BMI, body mass index; CPZeq, chlorpromazine equivalent milligrams; FLUeq, Fluoxetine equivalents equals; MADRS, Montgomery–Åsberg Depression Rating Scale; VEGF, vascular endothelial growth factor; TRD, treatment-refractory depression.*

TABLE 2 | Comparison of MADRS anhedonia item scores and plasma VEGF concentrations between antianhedonic responders and non-responders in subjects suffering from TRD using linear mixed models.

Variables	Group-by-time interaction		Time main effect		Group main effect	
	F	*p*-value	F	*p*-value	F	*p*-value
MADRS anhedonia item scores	55.2	**<0.001**	148.8	**<0.001**	72.6	**<0.001**
Plasma VEGF concentrations (ng/ml)	2.4	0.09	4.0	**0.02**	0.1	0.79

Bolded values are p < 0.05. MADRS, the Montgomery-Åsberg Depression Rating Scale; VEGF, vascular endothelial growth factor; TRD, treatment-refractory depression.

Thirty-eight patients (48.7%, 95% Cl = 37.4–60.1%) fulfilled the criteria for antianhedonic response. As depicted in **Table 2**, significant time main effects were found regarding MADRS anhedonia item scores and plasma VEGF concentrations (all *ps* < 0.05). No significant group main effects or group-by-time interactions were detected regarding plasma VEGF concentrations (all *ps* > 0.05; **Table 2**). Despite significant reductions in MADRS anhedonia item scores at days 13 and 26 (all *ps* < 0.05; **Figure 1**), no significant changes in plasma VEGF concentrations were observed at day 13 when compared to baseline ($p > 0.05$) (**Figure 1**). No significant differences in plasma VEGF concentrations were found between antianhedonic responders and non-responders at days 13 and 26 (all *ps* > 0.05) (**Figure 1**).

As shown in **Table 3**, correlation analysis of plasma VEGF concentrations and anhedonia symptoms as measured by the MADRS anhedonia item did not yield any significant relationships (all *ps* > 0.05).

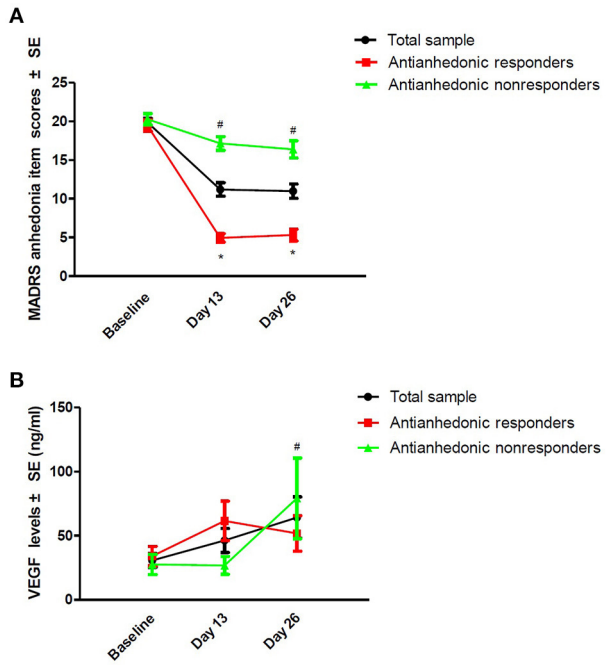

FIGURE 1 | Change in anhedonia symptoms **(A)** and plasma VEGF concentrations **(B)** in subjects suffering from TRD. #Significant difference was found when compared to baseline at the indicated times ($p < 0.05$). *Significant difference was found between antianhedonic responders and non-responders at the indicated times ($p < 0.05$). MADRS, the Montgomery-Asberg Depression Rating Scale; SE, standard error; TRD, treatment-refractory depression; VEGF, vascular endothelial growth factor.

TABLE 3 | Relationship of baseline plasma VEGF concentrations and anhedonia symptoms in subjects suffering from TRD.

Variables		MADRS anhedonia item scores			Change in MADRS anhedonia item scores	
		At baseline	At day 13	At day 26	At day 13	At day 26
Baseline plasma VEGF concentrations (ng/ml)	*r*	−0.01	−0.13	−0.04	0.13	0.03
	p	0.94	0.24	0.74	0.23	0.77
Change in plasma VEGF concentrations at day 13 (ng/ml)	*r*	−0.06	−0.17	−0.24	0.13	0.19
	p	0.62	0.17	0.06	0.29	0.13
Change in plasma VEGF concentrations at day 26 (ng/ml)	*r*	−0.25	0.01	−0.11	−0.16	−0.04
	p	0.08	0.95	0.45	0.24	0.80

MADRS, the Montgomery-Åsberg Depression Rating Scale; VEGF, vascular endothelial growth factor; r, Pearson coefficient of correlation; TRD, treatment-refractory depression.

DISCUSSION

To our knowledge, this is the first report to determine whether plasma VEGF concentrations are involved in the rapid antianhedonic effects of ketamine. The major finding in the present study was that (1) consistent with previous studies (1, 2, 9, 10), ketamine exerted significant and rapid antianhedonic effects; (2) plasma VEGF concentrations showed no significant changes at day 13, and no significant difference in plasma VEGF concentrations was found in antianhedonic responders compared to non-responders at days 13 and 26; and (3) plasma VEGF concentrations showed no significant correlation with the observed antianhedonic effects in individuals treated with six ketamine infusions.

In this study, the observed rapid reduction in anhedonia symptoms after six ketamine infusions replicates findings from numerous earlier studies (1, 2, 9, 10). Of them, the Snaith–Hamilton Pleasure Scale (SHAPS) was used to evaluate the levels of anhedonia in some studies (1, 9, 10) but not all (2). In addition to the SHAPS, the Beck Depression Inventory (BDI) anhedonia item was used in Ballard et al. study (2). Similarly, a recent study examined the effects of esketamine on anhedonia symptoms by using MADRS item 8 (inability to feel) (30). In this study, the MADRS anhedonia item rather than a specific scale for anhedonia was used to evaluate anhedonia symptoms. Thus, a specific scale for anhedonia, such as the SHAPS and the Profile of Mood States (POMS), should be used to confirm these findings. Importantly, future studies should adopt a more specific assessment approach.

Preclinical trials have shown that rapid increases in VEGF in the medial prefrontal cortex (mPFC) are required for the behavioral action of ketamine (33). Neuronal VEGF–Flk-1 signaling in the mPFC was associated with the antidepressant actions of ketamine (19). VEGF also appeared to be critical for the behavioral effects of various antidepressants (20, 34, 35) and lamotrigine (36) in rodent models of depression. In a recent clinical study, a single infusion of ketamine increased the plasma mRNA levels of VEGF, supporting a role for VEGF in the action of ketamine (25). However, our data failed to demonstrate that plasma VEGF concentrations were significantly associated with ketamine's rapid antianhedonic effects in subjects with TRD. Similarly, a recent study also found that VEGF does not play a critical role in the observed antidepressant response to ketamine in depressed patients (24). However, the association of VEGF and ketamine's antisuicidal effects is unclear.

There were several limitations in the current study. First, since patient samples were limited to Chinese subjects suffering from treatment-refractory MDD or BD, the findings may not be fully generalizable. In addition, the pooling of individuals diagnosed with MDD and BD made the sample nonhomogeneous. Second, patients continued receiving psychotropic medication in this open-label real-world study, which may have affected the plasma VEGF concentrations and partly explained the contradictory findings between our study and early reports (25). Third, we did not directly measure brain VEGF levels since blood VEGF levels may not be related to brain VEGF concentrations (37). Fourth,

other key neurobiological mediators of the ketamine response, such as phosphorylation of glycogen synthase kinase-3 (p-GSK-3) or mammalian target of rapamycin (mTOR) (38, 39), should be measured in future studies. Finally, the possible comorbid diagnosis such as a comorbidity of OCD or anxiety disorder was not reported in this study. Although treatment strategies for OCD, substance use disorders (SUD) and eating disorders (ED) are complex and difficult, ketamine and esketamine appeared to be effective in treating them (40).

CONCLUSIONS

This preliminary study suggests that the antianhedonic effects of ketamine are not mediated by VEGF.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding authors.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Affiliated Brain Hospital of Guangzhou Medical University. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

YPN: study design. WZ, YLZ, and CYW: data collection. WZ and LMG: analysis and interpretation of data. WZ: drafting of the manuscript. BZ, DFW, and YPN: critical revision of the manuscript. All the authors contributed to the final draft of the manuscript and approved the final version for publication.

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REFERENCES

1. Rodrigues NB, McIntyre RS, Lipsitz O, Cha DS, Lee Y, Gill H, et al. Changes in symptoms of anhedonia in adults with major depressive or bipolar disorder receiving IV ketamine: results from the Canadian rapid treatment center of excellence. *J Affect Disord.* (2020) 276:570–5. doi: 10.1016/j.jad.2020.07.083
2. Ballard ED, Wills K, Lally N, Richards EM, Luckenbaugh DA, Walls T, et al. Anhedonia as a clinical correlate of suicidal thoughts in clinical ketamine trials. *J Affect Disord.* (2017) 218:195–200. doi: 10.1016/j.jad.2017.04.057
3. Słupski J, Cubała WJ, Górska N, Słupska A, Gałuszko-Wegielnik M. Copper and anti-anhedonic effect of ketamine in treatment-resistant depression. *Med Hypotheses.* (2020) 144:110268. doi: 10.1016/j.mehy.2020.110268
4. Vrieze E, Demyttenaere K, Bruffaerts R, Hermans D, Pizzagalli DA, Sienaert P, et al. Dimensions in major depressive disorder and their relevance for treatment outcome. *J Affect Disord.* (2014) 155:35–41. doi: 10.1016/j.jad.2013.10.020
5. Winer ES, Nadorff MR, Ellis TE, Allen JG, Herrera S, Salem T. Anhedonia predicts suicidal ideation in a large psychiatric inpatient sample. *Psychiatry Res.* (2014) 218:124–8. doi: 10.1016/j.psychres.2014.04.016
6. Cao B, Zhu J, Zuckerman H, Rosenblat JD, Brietzke E, Pan Z, et al. Pharmacological interventions targeting anhedonia in patients with major depressive disorder: a systematic review. *Prog Neuropsychopharmacol Biol Psychiatry.* (2019) 92:109–17. doi: 10.1016/j.pnpbp.2019.01.002
7. McCabe C, Cowen PJ, Harmer CJ. Neural representation of reward in recovered depressed patients. *Psychopharmacology.* (2009) 205:667–77. doi: 10.1007/s00213-009-1573-9
8. Young CB, Chen T, Nusslock R, Keller J, Schatzberg AF, Menon V. Anhedonia and general distress show dissociable ventromedial prefrontal cortex connectivity in major depressive disorder. *Transl Psychiatry.* (2016) 6:e810. doi: 10.1038/tp.2016.80
9. Lally N, Nugent AC, Luckenbaugh DA, Niciu MJ, Roiser JP, Zarate CA. Neural correlates of change in major depressive disorder anhedonia following open-label ketamine. *J Psychopharmacol.* (2015) 29:596–607. doi: 10.1177/0269881114568041
10. Lally N, Nugent AC, Luckenbaugh DA, Ameli R, Roiser JP, Zarate CA. Anti-anhedonic effect of ketamine and its neural correlates in treatment-resistant bipolar depression. *Transl Psychiatry.* (2014) 4:e469. doi: 10.1038/tp.2014.105
11. Witt K, Potts J, Hubers A, Grunebaum MF, Murrough JW, Loo C, et al. Ketamine for suicidal ideation in adults with psychiatric disorders: a systematic review and meta-analysis of treatment trials. *Aust N Z J Psychiatry.* (2020) 54:29–45. doi: 10.1177/0004867419883341
12. Wilkinson ST, Ballard ED, Bloch MH, Mathew SJ, Murrough JW, Feder A, et al. The Effect of a single dose of intravenous ketamine on suicidal ideation: a systematic review and individual participant data meta-analysis. *Am J Psychiatry.* (2018) 175:150–8. doi: 10.1176/appi.ajp.2017.17040472
13. Zheng W, Zhou YL, Wang CY, Lan XF, Zhang B, Zhou SM, et al. Association between plasma levels of BDNF and the antisuicidal effects of repeated ketamine infusions in depression with suicidal ideation. *Ther Adv Psychopharmacol.* (2020) 10:1–10. doi: 10.1177/2045125320973794
14. Caviedes A, Lafourcade C, Soto C, Wyneken U. BDNF/NF-κB signaling in the neurobiology of depression. *Curr Pharm Des.* (2017) 23:3154–63. doi: 10.2174/1381612823666170111141915
15. Amidfar M, Réus GZ, de Moura AB, Quevedo J, Kim YK. The Role of neurotrophic factors in pathophysiology of major depressive disorder. *Adv Exp Med Biol.* (2021) 1305:257–72. doi: 10.1007/978-981-33-6044-0_14
16. Scola G, Andreazza AC. The role of neurotrophins in bipolar disorder. *Prog Neuropsychopharmacol Biol Psychiatry.* (2015) 56:122–8. doi: 10.1016/j.pnpbp.2014.08.013
17. Tsai SJ, Hong CJ, Liou YJ, Chen TJ, Chen ML, Hou SJ, et al. Haplotype analysis of single nucleotide polymorphisms in the vascular endothelial growth factor (VEGFA) gene and antidepressant treatment

response in major depressive disorder. *Psychiatry Res.* (2009) 169:113–7. doi: 10.1016/j.psychres.2008.06.028
18. Choi M, Lee SH, Chang HL, Son H. Hippocampal VEGF is necessary for antidepressant-like behaviors but not sufficient for antidepressant-like effects of ketamine in rats. *Biochim Biophys Acta.* (2016) 1862:1247–54. doi: 10.1016/j.bbadis.2016.04.001
19. Deyama S, Bang E, Wohleb ES, Li XY, Kato T, Gerhard DM, et al. Role of neuronal VEGF signaling in the prefrontal cortex in the rapid antidepressant effects of ketamine. *Am J Psychiatry.* (2019) 176:388–400. doi: 10.1176/appi.ajp.2018.17121368
20. Warner-Schmidt JL, Duman RS. VEGF is an essential mediator of the neurogenic and behavioral actions of antidepressants. *Proc Natl Acad Sci U S A.* (2007) 104:4647–52. doi: 10.1073/pnas.0610282104
21. Ricci V, Martinotti G, Gelfo F, Tonioni F, Caltagirone C, Bria P, et al. Chronic ketamine use increases serum levels of brain-derived neurotrophic factor. *Psychopharmacology.* (2011) 215:143–8. doi: 10.1007/s00213-010-2121-3
22. Woelfer M, Li M, Colic L, Liebe T, Di X, Biswal B, et al. Ketamine-induced changes in plasma brain-derived neurotrophic factor (BDNF) levels are associated with the resting-state functional connectivity of the prefrontal cortex. *World J Biol Psychiatry.* (2020) 21:696–710. doi: 10.1080/15622975.2019.1679391
23. Medeiros GC, Greenstein D, Kadriu B, Yuan P, Park LT, Gould TD, et al. Treatment of depression with ketamine does not change plasma levels of brain-derived neurotrophic factor or vascular endothelial growth factor. *J Affect Disord.* (2021) 280:136-9. doi: 10.1016/j.jad.2020.11.011
24. Zheng W, Zhou YL, Wang CY, Lan XF, Zhang B, Zhou SM, et al. Association of plasma VEGF levels and the antidepressant effects of ketamine in patients with depression. *Ther Adv Psychopharmacol.* (2021) 11:1–7. doi: 10.1177/20451253211014320
25. McGrory CL, Ryan KM, Gallagher B, McLoughlin DM. Vascular endothelial growth factor and pigment epithelial-derived factor in the peripheral response to ketamine. *J Affect Disord.* (2020) 273:380–3. doi: 10.1016/j.jad.2020.04.013
26. Zheng W, Zhou YL, Liu WJ, Wang CY, Zhan YN, Li HQ, et al. Rapid and longer-term antidepressant effects of repeated-dose intravenous ketamine for patients with unipolar and bipolar depression. *J Psychiatr Res.* (2018) 106:61–8. doi: 10.1016/j.jpsychires.2018.09.013
27. Zheng W, Zhou YL, Liu WJ, Wang CY, Zhan YN, Li HQ, et al. Neurocognitive performance and repeated-dose intravenous ketamine in major depressive disorder. *J Affect Disord.* (2019) 246:241–7. doi: 10.1016/j.jad.2018.12.005
28. Hamilton M. A rating scale for depression. *J Neurol Neurosurg Psychiatry.* (1960) 23:56–62. doi: 10.1136/jnnp.23.1.56
29. Xie GR, Shen QJ. Use of the Chinese version of the hamilton rating scale for depression in general population and patients with major depression (In Chinese). *Chin J Nerv Ment Dis.* (1984) 10:364.
30. Delfino RS, Del-Porto JA, Surjan J, Magalhães E, Sant LCD, Lucchese AC, et al. Comparative effectiveness of esketamine in the treatment of anhedonia in bipolar and unipolar depression. *J Affect Disord.* (2021) 278:515–8. doi: 10.1016/j.jad.2020.09.056
31. McIntyre RS, Loft H, Christensen MC. Efficacy of vortioxetine on anhedonia: results from a pooled analysis of short-term studies in patients with major depressive disorder. *Neuropsychiatr Dis Treat.* (2021) 17:575–85. doi: 10.2147/NDT.S296451
32. Cao B, Park C, Subramaniapillai M, Lee Y, Iacobucci M, Mansur RB, et al. The efficacy of vortioxetine on anhedonia in patients with major depressive disorder. *Front Psychiatry.* (2019) 10:17. doi: 10.3389/fpsyt.2019.00017
33. Deyama S, Bang E, Kato T, Li XY, Duman RS. Neurotrophic and antidepressant actions of brain-derived neurotrophic factor require vascular endothelial growth factor. *Biol Psychiatry.* (2019) 86:143–52. doi: 10.1016/j.biopsych.2018.12.014
34. Greene J, Banasr M, Lee B, Warner-Schmidt J, Duman RS. Vascular endothelial growth factor signaling is required for the behavioral actions of antidepressant treatment: pharmacological and cellular characterization. *Neuropsychopharmacology.* (2009) 34:2459–68. doi: 10.1038/npp.2009.68
35. Warner-Schmidt JL, Duman RS. VEGF as a potential target for therapeutic intervention in depression. *Curr Opin Pharmacol.* (2008) 8:14–9. doi: 10.1016/j.coph.2007.10.013
36. Sun R, Li N, Li T. VEGF regulates antidepressant effects of lamotrigine. *Eur Neuropsychopharmacol.* (2012) 22:424–30. doi: 10.1016/j.euroneuro.2011.09.010
37. Levy MJF, Boulle F, Steinbusch HW, van den Hove DLA, Kenis G, Lanfumey L. Neurotrophic factors and neuroplasticity pathways in the pathophysiology and treatment of depression. *Psychopharmacology.* (2018) 235:2195–220. doi: 10.1007/s00213-018-4950-4
38. Yang C, Zhou ZQ, Gao ZQ, Shi JY, Yang JJ. Acute increases in plasma mammalian target of rapamycin, glycogen synthase kinase-3β, and eukaryotic elongation factor 2 phosphorylation after ketamine treatment in three depressed patients. *Biol Psychiatry.* (2013) 73:e35–6. doi: 10.1016/j.biopsych.2012.07.022
39. Denk MC, Rewerts C, Holsboer F, Erhardt-Lehmann A, Turck CW. Monitoring ketamine treatment response in a depressed patient via peripheral mammalian target of rapamycin activation. *Am J Psychiatry.* (2011) 168:751–2. doi: 10.1176/appi.ajp.2011.11010128
40. Martinotti G, Chiappini S, Pettorruso M, Mosca A, Miuli A, Di Carlo F, et al. Therapeutic potentials of ketamine and esketamine in obsessive-compulsive disorder (OCD), substance use disorders (SUD) and eating disorders (ED): a review of the current literature. *Brain Sci.* (2021) 11:856. doi: 10.3390/brainsci11070856

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CASE REPORT
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A Cohort-Based Case Report: The Impact of Ketamine-Assisted Therapy Embedded in a Community of Practice Framework for Healthcare Providers With PTSD and Depression

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Amid an international pandemic and a worsening mental health crisis, ketamine-assisted therapy is emerging as a promising solution for those deemed "treatment resistant." Post-traumatic stress disorder (PTSD) and depression are on the rise, with accelerating direct (e.g., burden of suffering) and indirect (e.g., disability/role impairment and impact on family) costs. Psychedelic-assisted therapies show significant promise in the treatment of a number of clinically challenging conditions, including depression, anxiety, PTSD, addiction, and end-of-life distress. Ketamine is currently the only safe, effective and legal widely available psychedelic-like medicine. To address the echo pandemic of health care provider distress, a multi-disciplinary team was charged with developing a ketamine-assisted psychotherapy program, delivered in a community of practice (CoP) group model and evaluated in a quality improvement framework. Program evaluation occurred through mixed methods. Quantitative mental health assessments included the PHQ-9 for depression, the PCL-5 for PTSD, GAD-7 for generalized anxiety disorder (GAD), and B-IPF for work/life functionality. Participant narrative feedback was collected to evaluate outcomes and for quality improvement purposes. Mean mental health scores were collected across three cohorts, totaling 94 patients. The mean aggregate scores of participants meeting the mental health assessment cut-off criteria (screening positive) were analyzed to assess clinical significance. Mean aggregate results comparing baseline vs. outcome measures (measured within 1–2 weeks after completion of the 12-week program) were clinically significant, demonstrating significant improvements in depression, post-traumatic stress disorder, generalized anxiety disorder and work/life functionality. In summary, 91% saw improvements in generalized anxiety, 79% saw improvements in depression, 86% of those who screened positive for PTSD now screen negative, and 92% had significant life/work functionality improvements. Qualitative feedback was overwhelmingly positive, with several unsolicited self-reports of transformation. Participant and team feedback enables the program to continue

improving with each iteration. Results speak to the effectiveness of ketamine for psychedelic-assisted therapy, supported by a CoP framework. Outcomes are relevant for mental health programming, education and healthcare policy.

Keywords: ketamine-assisted psychotherapy, healthcare providers (HCP), resilience, psychedelic therapy, group therapy, community of practice, post-traumatic stress disorder (PTSD), depression

INTRODUCTION

The impetus for embedding ketamine-assisted therapy (KaT) within a group-oriented community of practice (CoP) revolves around the growing mental health crises in Canada, with healthcare providers (HCP) disproportionately impacted (1). Due to high stimulus and trauma-laden work environments, they are at a higher risk for mental health challenges (2). Even before the pandemic, 40–60% of HCPs were experiencing burnout at some point in their career (3), and the addition of COVID-19 is causing a devastating impact on morale, absenteeism, retention and patient care (1). Given HCP training and lived experience, their input helps identify occupational health and safety gaps and options for remediation.

A CALL FOR INNOVATION

Modern psychiatry was strongly influenced by the emergence of so-called *Biological Psychiatry* and the *Decade of the Brain (1990's)*. The belief at the time was that we were on the threshold of a new psychiatry, where we could reduce mental illness to defined perturbations of neuroreceptors, trusting that our novel *anti*depressants and *anti*psychotics would provide definitive treatment.

By any standard, this has been a failed experiment. Despite an exponential increase in prescribing over the recent decades, even before the pandemic, the costs of mental health disability were higher than ever before and steadily rising (4), with depression as the leading cause (5). Treatment wise, it is common knowledge that the placebo response to antidepressants is equal to, or greater than the effect of the medication (6). Further, among those who respond, many are left with subsyndromal symptoms, with only a minority realizing full remission. Not surprisingly, there is a growing cohort of *treatment resistant* patients. Perhaps our patients are not treatment resistant at all, perhaps we are simply using the wrong treatments.

Modern psychiatry is failing to get to the source of the *distress* that is a product of living in an increasingly frenetic and disconnected world. Instead, we label distress as *disorder,* failing to recognize that many of our disorders are simply an adaptation to increasingly hostile and toxic environments. The failure of frontline therapies for a growing number of people is accelerating the re-emergence of psychedelic-assisted therapies.

The Re-emergence Psychedelic Agents

Psychedelic-assisted therapies are demonstrating positive outcomes in the treatment of depression, PTSD, addiction, and end-of-life distress (7). They are radically different from traditional therapy, requiring specific training to support the client preparing for, navigating and integrating transformation from non-ordinary states of consciousness. Unique to psychedelic therapy, is the interruption of autonomic nervous system's fight-flight-freeze reactions, allowing recipients to re-orient themselves to traumatic events and disempowering belief systems of the past returning to a parasympathetic state.

To safely incorporate these new therapies, the current biomedical model of Canada's public healthcare system will need significant capacity-building. Currently, ketamine is the only legal and widely available psychedelic-like medicine. Ketamine is an FDA-approved drug, mainly used as an anesthetic in high doses with persons with MDD and PTSD (8). When ketamine is administered in sub-anesthetic doses, it produces a phenomenological psychedelic effect similar in some ways to psilocybin and Lysergic acid diethylamide (LSD) (9), enabling therapists to help people work with and through the belief systems and emotions associated with trauma. KaT shows significantly positive outcomes treating PTSD, depression, and addictions (10–12). As a result, working with ketamine provides an opportunity to provide psychedelic-assisted therapy, enabling a translation of knowledge to other psychedelic medicines as they become available. Finally, developing and delivering psychedelic-assisted therapy programs in multidisciplinary holistic teams will maximize therapeutic impact and minimize safety risks.

DEVELOPING THE INNOVATIVE TREATMENT PLAN

An interdisciplinary and multi-agency team innovated by combining KaT, using ketamine as a psychedelic-like agent, with an evidence-informed CoP program, serves HCPs facing depression and PTSD. The program was a registered quality improvement project. The community based, evidence and equity informed framework is designed to minimize safety risks and to support and maintain recovery. The team's guiding principles include holistic, trauma-informed care, inclusivity, cultural/personal safety and constant quality improvement. Aligned with Canada's Strategy for Patient-Oriented Research led by the Canadian Institutes of Health Research our program is about engaging HCPs in the research process. This engagement helps to ensure that studies focus on HCP-identified priorities, which ultimately lead to better treatments and patient outcomes. The treatment program is 12-weeks in length (2 h each week, three, 4-h sessions for KaT; ∼40 h in total) and runs through Vancouver Island University.

BUILDING THE INTERDISCIPLINARY TEAM

The team includes medical doctors, researchers, HCPs with lived experience of depression and PTSD, nurses, clinical counselors, spiritual health practitioners, Indigenous Elders and Knowledge Holders, Somatic Energy Practitioners, Functional Medicine Experts, Sleep Experts, Aromatherapy experts, and Physical Movement Experts. This style of team is rare in the Western Medical Model, necessitating apprenticeship/mentoring to build the team and orient new members.

Alongside Indigenous knowledge holders and cultural safety experts, the team engages in ongoing training and practices that promote equity and trauma informed care. The team models the program's guiding principles, including the adoption of shared intentions and agreements. These include, honesty, authenticity, vulnerability, and the mirroring of unconditional positive regard. The realization of these practices and principles bring forth a remarkable real humanity and palpable caring within the team. This, in turn, creates an environment of safety and trust that is often espoused, but rarely realized in mainstream health care settings.

Those wishing to join the team are encouraged to first go through the program as participants in the CoP program, and if eligible, in the KaT portion as well. Once participants transition to alumni, they can apply to be a mentee on the team, working closely with a mentor before they become a full facilitating team member.

INTAKE AND SCREENING PROCESS

HCPs with depression and PTSD were the priority population. Prior to acceptance into the program, participants first undergo a thorough three step intake process. The initial intake is completed by a registered psychiatric nurse who introduces participants to the program concepts through regulation practices, inner attunement, and authentic expression. For instance, the intake begins with a breathing technique that promotes relaxation, encouraging them to listen to what is arising in their physical awareness, and to speak to their fears and hopes of the process.

If determined a good fit by the participant-candidate and the team member, they proceed to meet with the team psychiatrist. If cleared by the team's psychiatrist, they then proceed to a meeting with a medical doctor who specializes in psychedelic-assisted therapy, ensuring no contraindications to ketamine use.

Inclusion Criteria

Referral from a primary care provider (or provider with a longitudinal relationship with client) *AND* history of previous treatment failure *AND* diagnosis of treatment resistant depression (11, 13), chronic anxiety (14), obsessive-compulsive disorder (OCD) (15), suicidality (16), PTSD (11), or Substance Use Disorder (10, 17).

Exclusion Criteria

Hypersensitivity to ketamine, presence of active psychotic symptoms, diagnosis of dementia/delirium, high risk for coronary artery disease, uncontrolled cardiopulmonary disease/cardiovascular disease/hypertension, aneurysm, history of intracerebral hemorrhage, hepatic cirrhosis, hepatorenal disease, recent changes in medications related to mood disorders, or pregnancy or if breastfeeding within 11 h of ketamine administration (18). Extreme emotional lability can be disruptive to the group milieu and is a relative exclusion criterion.

Participant Feedback

"The 3 intakes were very helpful in connecting with the various members of the team, and clarifying my intentions to participate. I appreciated the opportunity to ask questions, and have a one-to-one conversation with each intake team/facilitator."

TREATMENT MECHANISM: COMMUNITY OF PRACTICE

The CoP curriculum is informed by the literature, describing what humans need to thrive and maintain resilience amidst adversity (2). The concept of a CoP was coined by Lave and Wenger (19) and defined by (20) as "groups of people who share a concern or a passion for something they do and learn how to do it better as they interact regularly (p. 1)." The program was developed from a research-informed resilience development framework (2) call *Roots to Thrive*, which focuses on the development of:

- congruence (21), representing one's orientation to self and authentic expression in the world, and
- sense of coherence (22), representing one's orientation to the world, bolstering meaning, understanding, and confidence in one's resources.

The context for developing these qualities favors a focus on the somatic nature of healing and present moment experience, within a CoP that mirrors unconditional positive regard (23) rather than sharing extended narratives and events of personal history. Aligning with Polyvagal Theory, when social relationships become a source of connection and security, they regulate the nervous system and encourage authentic ways of being (2, 24). The mechanisms of healing that are integrated into the CoP include:

- connection to self and others through the experience of secure attachment,
- addressing trauma within an environment of unconditional positive regard,
- regulating the nervous system,
- co-regulating through relationship,
- alignment with one's desires and calling.

Based on ongoing participant feedback, the most important healing components of the program revolve around the team's ability to model vulnerability themselves and to provide unconditional positive regard, which is quickly mirrored among participants.

Participant Feedback

"The small groups have been amazing. I look forward to weekly sessions. Getting to know these beautiful people in a different way

has created a connection that I never knew could exist. How could we know each other without knowing all of our stories? The trust that was felt in our group occurred in the first session and has increased every week. I realized that I don't need to know their stories nor do they need to know mine to have a strong trusting relationship. I love that our facilitators are also sharing with us, they continue to work on themselves through this process."

The Community of Practice Structure

The weekly CoP runs one evening a week for 2 h. The entire cohort (ranging from 50 to 100 participants) first meets in a large group format, then they move to the same breakout group each week for sharing. Each small group contains between six and nine participants and is facilitated by a clinician and therapist dyad. Except for the psychedelic medicine-assisted component of the 12-week program, all patient provider interactions are completed virtually. Additional sessions are provided by a Functional Medicine Practitioner, an Emotional Freedom Technique (EFT/Tapping) Practitioner, a Body Movement Practitioner (such as Yoga), and one to one support as needed from a variety of specialists on the team.

Each week, participants meet in a large group format for 30–40 min beginning with an opening message by the program's Indigenous Elder, followed by Program Logistics. A team member provides an evidence-informed *Coming To Know* teaching, which cultivates the understanding, meaning, confidence, and engagement necessary for the deeper work (at the level of the body) to unfold. All then engage in a Pause Practice (guided meditation or somatic self-regulation practice), which encourages transition from "figuring it out" at the level of the mind to a somatic or felt sense, honoring the inner healing intelligence within the body.

Within the breakout groups at the first meeting, each small group adopts a set of intentions and agreements. Members are accountable to one another, which is important for developing accountability, trust and a sense of relational security. Participants are paired with a *Buddy,* to connect and integrate with once a week, using a structured conversational format promoting authentic and embodied sharing.

During the small group break-out session, participants begin with a *Short Check-In*, where they name one to two physical sensations and emotions they feel in that moment. They then transition to a *Long Check-In*, where they speak to an open-ended reflective question that encourages contemplation, somatic reflection, and emotional expression. Participants receive an *Integration Practice* to incorporate over the following week, ending in a *Short Check-Out,* where they again name one to two physical sensations and emotions that they are experiencing in that moment.

All members are encouraged to engage according to their own comfort level, working within their unique window of tolerance for vulnerability. With practice, participants gain trust and confidence in the process and their small group. The mechanisms of healing in the CoP structure include co-regulation of the nervous system, somatic awareness, authentic expression, expanding one's window of tolerance for vulnerability and stress, and the giving and receiving of unconditional positive regard through compassionate witnessing (a verbal reflection practice from other group members to the person who shared, focusing on empathy and resonance).

Participant Feedback

"I am already experiencing moments of sadness when I think of these 12 sessions ending and I hope for it to continue in some form past the formal end of the program. I see that for integration to truly take place, I would need for the process to last longer than 12 weeks."

Upon completion of the program, participants receive an exit interview to reflect on the process and for continuity of care. For those wanting ongoing support after the 12-weeks, participants are invited to join an Alumni CoP Program, enabling ongoing peer and team support and additional access to KaT.

Participant Feedback

"I truly believe them when they tell me to 'reach out anytime,' 'we are always here for you' – the words, actions and energies all align leaving me with a deep sense of trust, and a willingness to open further in the safety of the container. I feel truly seen."

"The delicate and thoughtful way in which the container of the group was developed was helpful and satisfying. I was amazed at how quickly I felt safe and willing to share my vulnerable pieces with the group. I have appreciated the offerings of various tools for my tool box."

TREATMENT MECHANISM: THREE KAT SESSIONS

The KaT component of the 12-week program brings CoP members together to receive ketamine in a group format, with a skilled therapist-clinician dyad per six participants. In addition, floating cultural and spiritual safety experts and knowledge holders, somatic energy practitioners, medical doctors, and a psychiatrist oversee all of the group administrations, attending where needed.

KaT is typically provided at week 4, 5, and 7. The short window of time between sessions provides a liminal space that magnifies the psychedelic mechanism, which could also be described as a loosening of the mind/ego structures that lead to the sense of stuckness that characterizes many mental health conditions.

KaT sessions include at least one or more one-to-one preparatory sessions. Participants plan for the ketamine sessions to take 4 h. Participants arrive at the healthcare center and are welcomed by the medical team for check-in and vital signs. They are then invited to settle into the room where the session will take place. Each room is set up with mats on the floor in a circular formation. A ceremonial process takes place, similar to the CoP structure, while also honoring local Indigenous and cultural traditions and participant preferences. Consent forms are collectively reviewed and signed. Ketamine is administered as either oral lozenges for the first session and intramuscularly for the second and third sessions. Participants are provided with eye coverings and synchronized headphones, ensuring that they are all listening to the same uniquely constructed,

ketamine-specific playlist. When the effects of the ketamine begin to wane around the 90-min mark, the initial sharing begins. Upon completion and ceremonial close, vital signs are repeated, and participants are escorted to the person driving them home.

Post-KaT, to facilitate integration within the first 36 h where neuroplasticity is most pronounced (25), participants attend group sessions in addition to their weekly CoP. These additional post-KaT sessions promote further integration of insights and new ways of being in their day-to-day lives.

Participant Feedback

"Although nervous at first of the unknown, I have found the sessions absolutely mind shifting. The work that I have done in these sessions have made me able to process my trauma and move forward in a way that I never thought would be possible. It brought

COHORT 1-3	PRE INDIVIDUAL (number of people)	POST INDIVIDUAL (number of people)	PRE AGGREGATE (score)	POST AGGREGATE (score)
Generalized Anxiety Disorder (GAD)	55 screened positive	(91%) went into a milder category or had significant clinical improvements (>5).	12 (moderate)	6 (mild anxiety)
Depression (PHQ-9)	62 screened positive	49 (79%) went into a milder category or had significant clinical improvements (>5).	13 (moderate)	7 (mild depression)
PTSD (PCL-5)	37 screened positive	32 (86%) screened negative.	47 (positive score)	20 (PTSD not evident)
Life Work Functionality (B-IPF)	65 had impairments	(92%) had significant clinical improvements.	42 (moderate impairment)	18 (mild impairment)

FIGURE 1 | Cohort 1, 2, and 3 Combined Quantitative Results. The enclosed data includes the participants who screened positive for PTSD, depression, or generalized anxiety disorder upon entry into the RTI-KaT program. The pre-results were taken within 1 month of the program beginning and post-results were taken directly after the 12-week program was completed. If data was missing, it was not included.

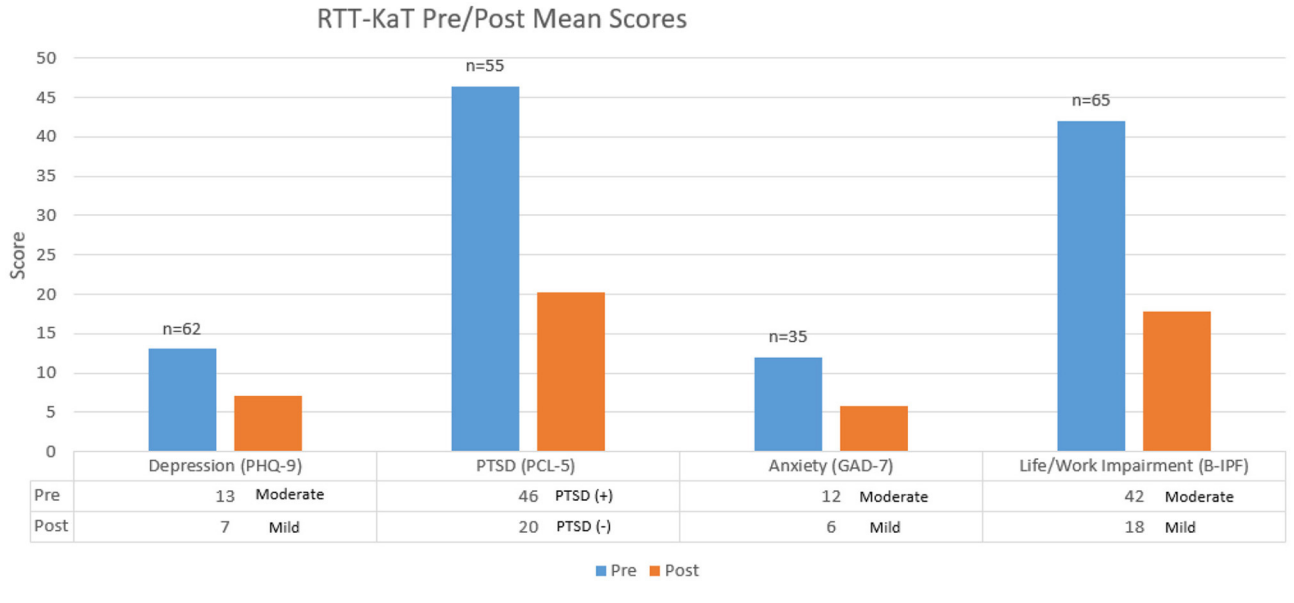

FIGURE 2 | Cohort 1, 2, and 3 aggregate: mean scores. The "*n*" represents the number of participants who screened positive for PTSD, depression, or generalized anxiety disorder upon entry into the RTT-KaT program. The pre-results were taken within 1 month of the program beginning and post results were taken directly after the 12-week program was completed. If data was missing, it was not included.

forward things that I didn't know were affecting me. The days after the KaT sessions, I processed the experience even further."

Ketamine Administration

Participants are given a dose of between 1 and 1.5 mg/kg by intramuscular injection. The dosing range promotes a psychedelic mechanism and is determined in conversation with the participant, based on their goals, intentions, and comfort with non-ordinary states of consciousness. In session two and three, the dosing is adjusted to remain aligned with participant's goals and comfort level. Dissociation is a normal (and often helpful) side effect for many. Some also experienced nausea, vomiting, and/or hypertension, which was resolved through pharmaceutical and non-pharmaceutical approaches.

TREATMENT RESULTS

Over 1 year, three cohorts totaling 94 participants completed the 12-week treatment program. With each cohort, quality improvement results were directly translated to the frontline of care and to ongoing program development efforts. As illustrated in **Figures 1**, **2**, mean aggregate results of those who screened positive for GAD, Depression, PTSD, or Life/Work Impairments were clinically significant, demonstrated by a shift in score of five or greater after the 12-week treatment program.

- Of those who screened positive for generalized anxiety disorder symptoms (GAD), such as feeling on edge, not being able to stop worrying, trouble relaxing, unable to sit still, irritability, a sense of impending doom, 91% had reduced scores, dropping into a milder category or had significant clinical improvements.
- Of those who screened positive for symptoms of depression, such as feeling hopeless, little interest in doing things, sleeping too much or too little, loss of appetite and energy, trouble concentrating, feeling like a failure, and thoughts of being better off dead, 79% had reduced scores that dropped them into a milder category or had significant clinical improvements.
- Of those who screened positive for PTSD, such as re-experiencing past, emotional numbness, avoidance of people and activities that remind them of past trauma, difficulty sleeping, jumpy, easily irritated and angered, 86% left the program screening negative for PTSD.
- Of those who screened positive for Life/Work Impairments in romantic relationships, family relationships, work, friendships and socializing, parenting, education, and self-care, 92% had significant clinical improvements.

Participant Feedback

Upon Completion in response to "What are you noticing about yourself and your relationships?":
"I have been led through some of my fears while experiencing a new found deep sense of love for life. I am able to connect with my partner from a more intimate authentic place. I am also noticing a greater depth of connection with those I work with and for."

"I've stopped using Edibles [Cannabis]. I've felt more empowered, like I have my voice. I'm more connected to myself. I am quicker to reach out. I find love easier in connection. I'm less anxious at work and have more ease as I enjoy my colleagues more and trust they enjoy me. I'm noticing more space within myself. I'm not engaging in the push-pull in my relationships as much."

Limitations and Suggestions for Future Research

This cohort-based case study was completed within a registered quality improvement project with the local health authority, which was exempt from REB review. Running through a program of research with a control group (comparing the CoP alone with the CoP + KaP) will promote further understanding of impact factors.

CONCLUSION

Access to ketamine assisted therapy is limited, the cost of treatment, and durability of results are common challenges. Using a group/CoP model reduces cost, enhances capacity and thereby access, accelerates recovery and may reduce relapse by providing ongoing integration support over the 12 weeks of the program and beyond. Based on the learnings and positive outcomes of this program, we anticipate that the demand for communities of practice as a treatment and supportive integration mechanism will become a gold standard in the delivery of psychedelic-assisted therapies. Finally, we would like to recognize the HCPs that courageously stepped forward to co-develop this program in the process of navigating their own healing journeys.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

The project was registered as a Quality Improvement Project with the local health authority, exempt from formal ethical review under TCPS 2 (2018), Article 2.5. The patients provided their written consent to participate in the program.

AUTHOR CONTRIBUTIONS

All authors provided substantial contributions to the conception or design of the work, or the acquisition, analysis or interpretation of data for the work, drafted the work or revising it critically for important intellectual content, provided approval for publication of the content, and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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REFERENCES

1. Lai J, Ma S, Wang Y, Cai Z, Hu J, Wei N, et al. Factors associated with mental health outcomes among health care workers exposed to coronavirus disease 2019. *JAMA Netw Open*. (2020) 3:3976. doi: 10.1001/jamanetworkopen.2020.3976
2. Dames S. *Root Strength: A Health and Care Professionals' Guide to Minimizing Stress and Maximizing Thriving*. Cambridge, MA: Elsevier Publishing (2021).
3. O'Leary OF, Dinan TG, Cryan JF. Faster, better, stronger: towards new antidepressant therapeutic strategies. *Eur J Pharmacol*. (2015) 753:32–50. doi: 10.1016/j.ejphar.2014.07.046
4. Patel V, Saxena S, Lund C, Thornicroft G, Baingana F, Bolton P, et al. The lancet commission on global mental health and sustainable development. *Lancet*. (2018) 10157:1553–98. doi: 10.1016/S0140-6736(18)31612-X
5. The World Health Organization (WHO). *Depression*. (2021). Available online at: https://www.who.int/news-room/fact-sheets/detail/depression
6. Kirsch I. Antidepressants and the placebo effect. *Z Psychol*. (2014) 222:128–34. doi: 10.1027/2151-2604/a000176
7. Carhart-Harris RL, Goodwin GM. The therapeutic potential of psychedelic drugs: past, present, and future. *Neuropsychopharmacology*. (2017) 42:2105–13. doi: 10.1038/npp.2017.84
8. Dore J, Turnipseed B, Dwyer S, Turnipseed A, Andries J, Ascani G, et al. Ketamine assisted psychotherapy (KAP): Patient demographics, clinical data and outcomes in three large practices administering ketamine with psychotherapy. *J Psychoactive Drugs*. (2019) 51:189–98. doi: 10.1080/02791072.2019.1587556
9. Tupper KW, Wood E, Yensen R, Johnson MW. Psychedelic medicine: a re-emerging therapeutic paradigm. *CMAJ Can Med Assoc J*. (2015) 187:1054–9. doi: 10.1503/cmaj.141124
10. Ezquerra-Romano I, Lawn W, Krupitsky E, Morgan CJA. Ketamine for the treatment of addiction: evidence and potential mechanisms. *Neuropharmacology*. (2018) 142:72–82. doi: 10.1016/j.neuropharm.2018.01.017
11. Feder A, Parides MK, Murrough JW, Perez AM, Morgan JE, Saxena S, et al. Efficacy of intravenous ketamine for treatment of chronic post-traumatic stress disorder: a randomized clinical trial. *JAMA Psychiatry*. (2014) 71:681–8. doi: 10.1001/jamapsychiatry.2014.62
12. Fond G, Loundou A, Rabu C, Macgregor A, Lançon C, Brittner M, et al. Ketamine administration in depressive disorders: a systematic review and meta-analysis. *Psychopharmacology*. (2014) 231:3663–76. doi: 10.1007/s00213-014-3664-5
13. Chilukuri H, Reddy NP, Pathapati RM, Manu AN, Jollu S, Shaik AB. Acute antidepressant effects of intramuscular versus intravenous ketamine. *Indian J Psychol Med*. (2014) 36:71–6. doi: 10.4103/0253-7176.127258
14. Taylor J, Landeros-Weisenberger A, Coughlin C, Mulqueen J, Johnson JA, Gabriel D, et al. Ketamine for social anxiety disorder: a randomized, placebo-controlled crossover trial. *Neuropsychopharmacol*. (2018) 43:325–33. doi: 10.1038/npp.2017.194
15. Bloch MH, Wasylink S, Landeros-Weisenberger A, Panza KE, Billingslea E, Leckman JF, et al. Effects of ketamine in treatment-refractory obsessive-compulsive disorder. *Biol Psychiatry*. (2012) 72:964–70. doi: 10.1016/j.biopsych.2012.05.028
16. Wilkinson ST, Ballard ED, Bloch MH, Mathew SJ, Murrough JW, Feder A, et al. The effect of a single dose of intravenous ketamine on suicidal ideation: a systematic review and individual participant data meta-analysis. *Am J Psychiatry*. (2018) 175:150–8. doi: 10.1176/appi.ajp.2017.17040472
17. Jones JL, Mateus CF, Malcolm RJ, Brady KT, Back SE. Efficacy of ketamine in the treatment of substance use disorders: a systematic review. *Front Psychiatry*. (2018) 9:277. doi: 10.3389/fpsyt.2018.00277
18. Briggs GG, Freeman RK, Yaffe SJ. *Drugs in Pregnancy and Lactation: A Reference Guide to Fetal and Neonatal Risk*. Place of publication not identified: Wolters Kluwer Health (2016).
19. Lave J, Wenger E. *Situated Learning: Legitimate Peripheral Participation*. Cambridge, Cambridge University Press (1991).
20. Wenger-Treyner E, Wenger-Treyner B. *Introduction to Communities of Practice: A Brief Overview of the Concept and it's Uses*. Available online at: https://wenger-trayner.com/introduction-to-communities-of-practice/
21. Rogers CR. A theory of therapy, personality, and interpersonal relationships: as developed in the client-centered framework. In: Koch S, editor. *Psychology: A Study of a Science. Formulations of the Person and the Social Context*. New York, NY: McGraw Hill (1959). p. 184–256.
22. Antonovsky A. *Health, Stress and Coping*. San Francisco, CA: Jossey-Bass (1979).
23. Rogers C. *Client-Centered Therapy*, 3rd ed. Boston: Houghton-Mifflin (1956).
24. Porges SW. *The Polyvagal Theory: Neurophysiological Foundations of Emotions, Attachment, Communication, and Self-regulation*. New York, NY: W.W. Norton (2011).
25. Collo G, Cavalleri L, Merlo Pich E. Structural plasticity induced by ketamine in human dopaminergic neurons as mechanism relevant for treatment-resistant depression. *Chronic Stress*. (2019) 3:2470547019842545. doi: 10.1177/2470547019842545

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Corrigendum: A cohort-based case report: The impact of ketamine-assisted therapy embedded in a community of practice framework for healthcare providers with PTSD and depression

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In the published article, there was an error in Figure 2 as published. The PTSD labels in the pre- and post- rows of the figure were incorrectly positioned underneath the Anxiety score, and vice versa. The corrected version of Figure 2 and its caption is published below.

The authors apologize for this error and state that this does not change the scientific conclusions of the article in any way. The original article has been updated.

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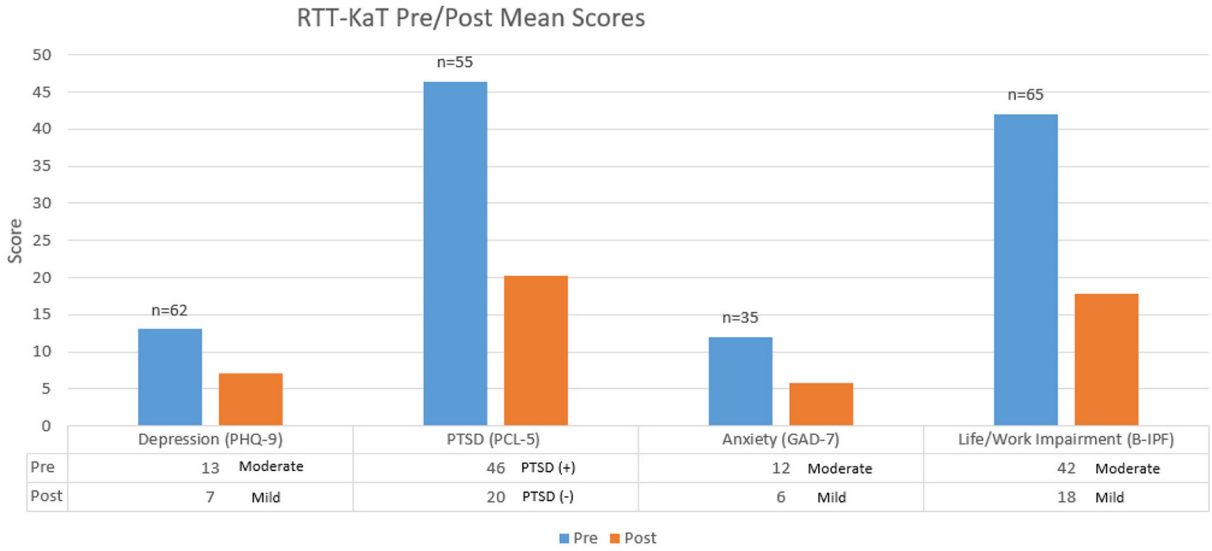

FIGURES 2
Cohort 1, 2, and 3 aggregate: mean scores. The "*n*" represents the number of participants who screened positive for PTSD, depression, or generalized anxiety disorder upon entry into the RTT-KaT program. The pre-results were taken within 1 month of the program beginning and post results were taken directly after the 12-week program was completed. If data was missing, it was not included.

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Pre-treatment Pain Symptoms Influence Antidepressant Response to Ketamine in Depressive Patients

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Background: Pain strongly coexists with depression. Ketamine has great analgesic and antidepressant effects, acting as a promising role in treating depression with pain. Few studies have evaluated impact of pain symptoms on antidepressant effect of ketamine infusions. Thus, present study investigated whether pain symptoms in individuals with depression moderate response to ketamine.

Methods: One hundred and four individuals with major depressive disorder and bipolar depression received six intravenous infusions of ketamine. The Montgomery–Åsberg Depression Rating Scale (MADRS) was administered at baseline, the next morning after each infusion and 2 weeks (Day 26) after the last infusion. Pain symptoms were collected at baseline using the short-form McGill Pain Questionnaire (SF-MPQ).

Results: The prevalence of pain in patients with depression was 48.8%. Mix model analyses showed that pre-treatment pain symptoms assessed by each domain of SF-MPQ significantly moderated antidepressant response to six infusions of ketamine from baseline to day 26 (all $p < 0.05$). Then follow-up simple slopes analyses suggested that all patients across groups showed a significant symptomatic improvement after ketamine infusions (all $p < 0.05$), and patients with severe pain (across all domains of SF-MPQ) had greater improvement in depressive symptoms than those with mild pain or non-pain (all $p < 0.05$).

Conclusion: A significant and rapid improvement in depressive symptoms was observed in patients with depression and pain after ketamine treatment. Ketamine may be a novel and promising antidepressant preferentially for the therapy of depression with severe pain.

Keywords: ketamine, depression, pain, bipolar depression, treatment resistant, moderate

INTRODUCTION

Both depression and pain are widespread and debilitating conditions, contributing to substantial disability as well as large socioeconomic burden worldwide (1, 2). The foregoing conditions are reported to be strongly comorbid in clinical settings (3). For example, it has been reported that the prevalence of pain among individuals affected by depression ranges from 43.3 to 80% (4–6). Moreover, comorbidity of pain and depression is reported to result in greater function impairment, increased health care costs and decreased quality of life (7–9) when compared to the effect of either condition occurring alone in affected individuals. Additionally, symptoms of pain have been associated with a greater treatment resistance in persons with depression (10, 11). Evidence from the Sequenced Treatments for Alternatives to Relieve Depression (STAR*D) study demonstrates that baseline pain severity is associated with more severe depressive symptoms and poorer treatment response to conventional antidepressants in individuals with major depressive disorder (MDD) (5). Improving treatment outcomes in individuals affected by depression with pain symptoms becomes the top therapeutic priority from an individual and socio-economic perspective.

In recent decades, intensified efforts are underway to develop new antidepressants. Ketamine is a non-selective N-methyl-D-aspartic acid receptor (NMDAR) antagonist with anesthetic and analgesic effects, which can effectively relieve acute and chronic pain (12–15). Ketamine has also been reported to have rapid antidepressant and anti-suicidal effects in patients with MDD or bipolar depression (BD) in recent years (16–18). The foregoing highly replicated finding is observed in both open-label studies and randomized, placebo-controlled trials (18–20). Although a single infusion of ketamine at a subanesthetic dose (0.5 mg/kg) can quickly improve depressive symptoms, its antidepressant effect only lasts a few days (19). Repeat-dose infusions of ketamine can extend the antidepressant effect and achieve treatment response for weeks (18, 21, 22). Moreover, our previous publication reported that only 14% of patients with MDD and BD achieved response after the first ketamine infusion while up to 68% of patients responded to six infusions of ketamine (23).

Ketamine has also been reported to be effective in individuals with the comorbidity of depression pain (24, 25). A recent study reported that oral therapy of ketamine for 6 weeks can successfully alleviate depressive symptoms in chronic pain patients (26). Moreover, our recent publication reported that subanesthetic infusions of ketamine can both reduce depressive symptoms and pain symptoms in individuals with treatment resistant depression (TRD) (27).

Taken together, ketamine may be a promising treatment for individuals experiencing comorbid depression and pain. However, there is limited clinical research that has evaluated the role of pre-treatment pain symptoms in response to repeated ketamine infusions in individuals with depression. Thus, the study herein aimed to determine whether pre-treatment pain symptoms moderate the antidepressant efficacy of repeated intravenous ketamine infusions in individuals with MDD or BD. Considering the powerful effect of ketamine on alleviating pain, we hypothesize that pre-treatment pain severity may differently moderate the response to ketamine infusions in patients with depression when compared to conventional antidepressant treatment.

MATERIALS AND METHODS

Present study was a single-arm open-label clinical trial of six ketamine infusions conducted in The Affiliated Brain Hospital of Guangzhou Medical University from November 2016 to July 2018 which aimed to explore the antidepressant efficacy of adjunctive ketamine in patients with MDD or BD. The protocol was approved by the Clinical Research Ethics Committee of The Affiliated Brain Hospital of Guangzhou Medical University with a clinical trial number, ChiCTROOC-17012239. All participants provided informed consent before entering our study. Patient selection and study design are introduced briefly in our current study, as they have been described in detail in our previous study (23).

Participants

Participants who satisfied the following inclusion criteria were permitted to participate in our study: (1) aged 18∼65 years old; (2) were suffering from MDD or BD without psychotic symptoms according to the structured clinical interview for Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-5); (3) were experiencing moderate to severe depressive symptoms defined as a score of ≥17 on the 17-item Hamilton Depression Rating scale (HAMD-17) (28), and were suffering from current suicidal ideation with a score of ≥2 on Beck Scale for Suicide Ideation-part I (29) or had a history of TRD who did not respond to two or more classes of antidepressants with adequate dosage and treatment duration (30). The exclusion criteria included (1) substance use disorder; (2) any serious or unstable physical disease or neurological illness; (3) any other severe mental disorders (i.e., dementing disorders or schizophrenia); (4) pregnant or breast-feeding. In addition, patients' oral psychiatric medications were required to be administered at a stable dose for more than 4 weeks before the trial and maintained throughout the infusion period.

Study Design

Participants received six intravenous infusions of ketamine for 2 weeks (three times per week, Monday-Wednesday-Friday). After an overnight fast, enrolled patients received an intravenous (IV) infusion of ketamine dosed at 0.5 mg/kg diluted in 0.9% saline, which was delivered at least 40 min. IV ketamine infusions were performed on days 1, 3, 5, 8, 10, and 12 during the trial.

Rating Scales

Depressive symptoms were measured by the Montgomery–Åsberg Depression Rating Scale (MADRS) (31), which was administered at baseline, the next morning (24 h) after each infusion, and 2 weeks (Day 26) after the last infusion. Pain severity was assessed by the short-form McGill Pain

Questionnaire (SF-MPQ) (32). The SF-MPQ was used to assess pain severity with sufficient reliability and validity, which had three sections: (1) A visual analog scale (VAS) was used to evaluate the intensity of subjective pain with scores from 0 (non-pain) to 10 (worst imaginable pain). (2) The pain rating index (PRI) consisted of sensory index and affective index, providing with a total of 15 items scored from 0 (non-pain) to 3 (severe pain). (3) Present pain intensity (PPI) was used to measure current pain intensity from 0 (no pain) to 5 (excruciating).

Statistical Analyses

The retrospective exploratory analysis was conducted in SPSS 22.0 statistical software. All tests were two-sided with significance at $p < 0.05$. Student's *t*-test for continuous variables and the chi-square test categorical variables were used to compare demographic variables and clinical data between the groups (pain vs. non-pain). Analysis of variance was performed to compare differences in pre-treatment depressive severity between severe pain, mild pain, and non-pain groups. Bonferroni test was used in *post hoc* comparisons. With respect to missing data, a mixed model was performed to assess change in MADRS scores from baseline to day 26. The interaction effect between ketamine treatment and pre-treatment pain severity was calculated to evaluate whether overall changes in depressive symptoms measured by MADRS score from baseline to day 26, were moderated by pre-treatment pain symptoms, as measured by VAS, sensory index, affective index, PPI and their total score. Follow-up simple slopes comparisons were performed for significant interactions, comparing difference of slopes between mild, severe pain and non-pain groups. Patients exhibiting no pain symptoms at pre-treatment were characterized as "non-pain," patients exhibiting the mean or below the average score (i.e., VAS, sensory index, affective index, PPI, or total pain) were characterized as "mild pain" and patients exhibiting above the average score were characterized as "severe pain." Therefore, five separate models were conducted in our statistical analyses. Age, gender, body mass index (BMI), education, duration of illness, diagnosis, and pre-treatment depression severity were included as covariates in each model. In addition, pre-treatment MADRS score was evaluated for multicollinearity with pre-treatment pain symptoms before entering the model.

TABLE 1 | A summary of depressive patient's demographic and clinical characteristics.

Variables	Non-pain (*N* = 54)		Pain (*N* = 50)		X^2	*P*
	N	%	*N*	%		
Gender (male)	26	48.1	26	52.0	0.154	0.845
Employment status (working)	27	50.0	18	36.0	2.073	0.150
Smoking	9	16.7	9	18.0	0.032	0.857
TRD	45	83.3	44	88.0	0.458	0.499
With suicidality	44	81.5	35	70.0	1.874	0.171
Psychiatric comorbidity (yes)①	13	24.1	7	14.0	1.696	0.193
Having family history of psychiatric disorders	18	33.3	24	48.0	2.320	0.128
Previous hospitalization (yes)②	17	31.5	14	28.0	0.150	0.698
Current pharmacotherapies						
≥2 antidepressant	8	14.8	10	20.0	0.488	0.485
Mood stabilizer	16	29.6	14	28.0	0.034	0.855
Benzodiazepine	28	51.9	22	44.0	0.641	0.423
Antipsychotic	31	57.4	24	48.0	0.922	0.337
	Mean	**SD**	**Mean**	**SD**	***t***	***P***
Age (years)	32.7	10.9	36.0	12.1	−1.450	0.150
Education (years)	13.1	2.9	11.4	3.3	2.761	0.007
Duration of illness (months)	95.0	76.0	116.9	104.7	−1.226	0.223
BMI (kg/m^2)	22.2	3.6	23.4	3.5	−1.692	0.094
Dose of antidepressant (mg/day)③	36.6	23.4	39.0	22.0	−0.525	0.601
Pre-treatment MADRS score	31.5	8.2	32.9	6.7	−1.206	0.231
Pre-treatment VAS score	–	–	5.2	2.0	NA	NA
Pre-treatment sensory index	–	–	4.1	3.1	NA	NA
Pre-treatment affective index	–	–	4.7	2.9	NA	NA
Pre-treatment present pain intensity	–	–	2.4	1.0	NA	NA
Pre-treatment total pain	–	–	16.5	7.2	NA	NA

MDD, Major Depressive Disorder; TRD, Treatment-resistant Depression; BMI, body mass index; MADRS, Montgomery-Åsberg Depression Rating Scale; VAS, visual analog scale; NA, not applicable.

①Comorbidity of an Axis I anxiety disorder, obsessive-compulsive disorder, phobia, or panic disorder.

②Previous hospitalization due to mental health problems.

③Fluoxetine equivalent dose.

RESULTS

A total of 104 depressive patients with pre-treatment pain data received six infusions of ketamine. 16 patients dropped out at day 26. Thus, depressive symptoms assessed by MADRS were available for 104 patients at pre-treatment and for 88 patients at day 26. 48.8% of patients ($N = 50$) were suffering pain before ketamine treatment. Baseline sociodemographic and clinical characteristics are presented in **Table 1**.

According to mean scores of VAS, sensory index, affective index, PPI, and total pain, there were 23, 32, 24, 26, and 24 patients with mild pain, respectively, as well as 27, 18, 26, 24, and 26 patients with severe pain, respectively. As shown in **Table 2**, pre-treatment MADRS scores were significantly different among non-pain, mild pain and severe pain groups. *Post hoc* comparisons using the Bonferroni test indicated that the mean pre-treatment MADRS score of patients with severe sensory index (mean = 37.6 ± 5.1) was significantly higher than patients with mild sensory index (mean = 30.5 ± 6.6, $p = 0.008$) or patients without pain (mean = 31.5 ± 8.2, $p = 0.004$). However, the mean pre-treatment MADRS score did not significantly differ between patients with mild sensory index and patients without pain ($p = 1.000$). Similar findings were observed when comparation were performed among patients with mild/severe affective index and non-pain, with mild/severe PPI and non-pain, as well as

TABLE 2 | Comparisons of baseline depressive severity among severe, mild, and non-pain group.

Variable	Non-pain	Mild pain	Severe pain	*F*	*P*[a]
Visual analog scale	*N* = 54	*N* = 23	*N* = 27		
Pre-treatment MADRS score	31.5 ± 8.2	30.4 ± 6.3	35.3 ± 6.9	3.271	0.042[b]
Sensory index	*N* = 54	*N* = 32	*N* = 18		
Pre-treatment MADRS score	31.5 ± 8.2	30.5 ± 6.6	37.6 ± 5.1	6.082	0.003[c]
Affective index	*N* = 54	*N* = 24	*N* = 26		
Pre-treatment MADRS score	31.5 ± 8.2	29.8 ± 7.2	36.1 ± 5.3	5.264	0.007[c]
Present pain intensity	*N* = 54	*N* = 26	*N* = 24		
Pre-treatment MADRS score	31.5 ± 8.2	29.8 ± 5.4	36.6 ± 6.9	6.109	0.003[c]
Total pain	*N* = 54	*N* = 24	*N* = 26		
Pre-treatment MADRS score	31.5 ± 8.2	28.8 ± 5.8	37.0 ± 5.5	9.107	<0.001[c]

MADRS, Montgomery-Åsberg Depression Rating Scale.
[a]p-value represents overall F-test. Post hoc comparisons listed as significant p < 0.05 using Bonferroni test.
[b]None of Bonferroni tests are statistically significant.
[c]Comparisons of severe vs. mild and non-pain are significant.

TABLE 3 | Results from mixed models for the moderating effects of pain symptom on changes in overall depressive symptoms from pre-treatment to post-infusion.

Parameter	*B*	SE	*t*	*P*	95% C.I. for B	
					Lower	Upper
Visual analog scale						
Ketamine	−0.992	0.072	−13.700	<0.001	−1.134	−0.850
Pre-treatment pain	2.659	0.653	4.074	<0.001	1.378	3.940
Ketamine × Pre-treatment pain	−0.332	0.065	−5.089	<0.001	−0.461	−0.204
Sensory index						
Ketamine	−1.017	0.072	−14.065	<0.001	−1.159	−0.875
Pre-treatment pain	2.836	0.724	3.916	<0.001	1.415	4.258
Ketamine × Pre-treatment pain	−0.336	0.073	−4.601	<0.001	−0.479	−0.192
Affective index						
Ketamine	−1.021	0.073	−14.040	<0.001	−1.164	−0.878
Pre-treatment pain	2.503	0.664	3.768	<0.001	1.199	3.807
Ketamine × Pre-treatment pain	−0.294	0.066	−4.446	<0.001	−0.423	−0.164
Present pain intensity						
Ketamine	−0.989	0.072	−13.678	<0.001	−1.131	−0.847
Pre-treatment pain	2.815	0.669	4.206	<0.001	1.501	4.129
Ketamine × Pre-treatment pain	−0.346	0.067	−5.166	<0.001	−0.477	−0.214
Total pain						
Ketamine	−0.986	0.072	−13.633	<0.001	−1.128	−0.844
Pre-treatment pain	2.933	0.657	4.462	<0.001	1.643	4.224
Ketamine × Pre-treatment pain	−0.344	0.066	−5.214	<0.001	−0.474	−0.215

mild/severe total pain and non-pain, consistently suggesting that pre-treatment MADRS score in patients with severe pain was higher than patients with mild pain or non-pain (all $p < 0.05$). Mean pre-treatment MADRS scores in patients with severe VAS (mean = 35.3 ± 6.9) was also higher than patients with mild VAS (mean = 30.4 ± 6.3), but this difference didn't reach a statistical significance ($p = 0.093$). Similarly, mean pre-treatment MADRS scores in patients with severe VAS was higher than patients without pain (mean = 31.5 ± 8.2), but this difference did not reach a statistical significance either ($p = 0.068$).

Table 3 presents standardized coefficients, standard errors and *P*-value for each model. In summary, total pain significantly moderated changes in depressive symptoms from baseline to day 26 ($B = -0.344$, $t = -5.214$, $P < 0.001$). Follow-up simple slopes analyses showed that patients with mild total pain ($B = -1.246$, $t = -12.051$, $P < 0.001$), severe total pain ($B = -1.706$, $t = -13.684$, $P < 0.001$), and non-pain ($B = -1.004$, $t = -12.976$, $P < 0.001$) all reported significant reductions in depressive symptoms from baseline to day 26. **Figure 1** shows that patients with severe pain obtained a more robust symptomatic improvement than mild pain or non-pain patients (slope: severe pain > mild pain, non-pain).

A similar pattern was observed when VAS ($B = -0.332$, $t = -5.089$, $P < 0.001$), sensory index ($B = -0.336$, $t = -4.601$, $P < 0.001$), affective index ($B = -0.294$, $t = -4.446$, $P < 0.001$), and PPI ($B = -0.346$, $t = -5.166$, $P < 0.001$) were, respectively, included as moderators, such that all significantly moderated antidepressant effect of IV ketamine treatment. Participants with mild VAS ($B = -1.266$, $t = -11.070$, $P < 0.001$) and severe VAS ($B = -1.675$, $t = -14.629$, $P < 0.001$) both reported significant reductions in depressive symptoms from baseline to day 26.

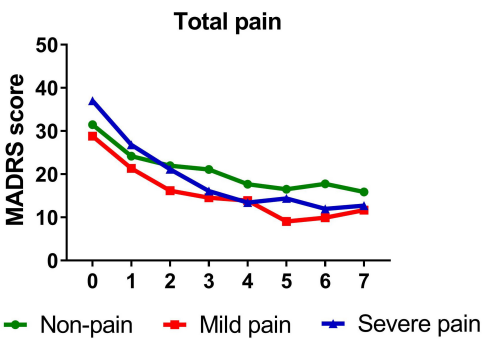

FIGURE 1 | Overall change in MADRS score across six infusions. Pain severity was defined by total score of SF-MPQ. Patients exhibiting no pain symptom were characterized as "non-pain," patients exhibiting the mean or below the mean total pain score were characterized as "mild pain" and patients exhibiting above the mean total pain score were characterized as "severe pain." MADRS, Montgomery-Åsberg Depression Rating Scale; SF-MPQ, short-form McGill Pain Questionnaire. Numbers on *X*-axis: 0 represents baseline, 1~6 represent the next morning after each infusion, 7 represents 2 weeks after infusions (Day 26).

Figure 2 shows that patients with severe pain obtained a more robust symptomatic improvement than mild pain or non-pain patients (slope: severe pain > mild pain, non-pain).

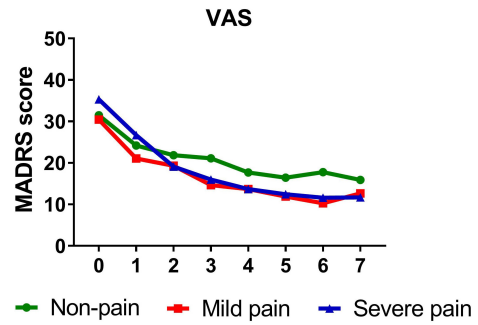

FIGURE 2 | Overall change in MADRS score across six infusions. Pain severity was defined by VAS. Patients exhibiting no pain symptom were characterized as "non-pain," patients exhibiting the mean or below the mean VAS score were characterized as "mild pain" and patients exhibiting above the mean VAS score were characterized as "severe pain." MADRS, Montgomery-Åsberg Depression Rating Scale; VAS, visual analog scale. Numbers on *X*-axis: 0 represents baseline, 1∼6 represent the next morning after each infusion, 7 represents 2 weeks after infusions (Day 26).

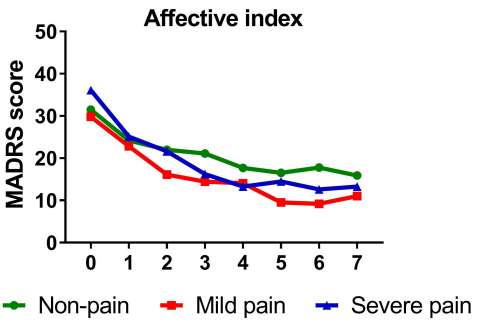

FIGURE 4 | Overall change in MADRS score across six infusions. Pain severity was defined by affective index. Patients exhibiting no pain symptom were characterized as "non-pain," patients exhibiting the mean or below the mean affective index were characterized as "mild pain" and patients exhibiting above the mean affective index were characterized as "severe pain." MADRS, Montgomery-Åsberg Depression Rating Scale. Numbers on *X*-axis: 0 represents baseline, 1∼6 represent the next morning after each infusion, 7 represents 2 weeks after infusions (Day 26).

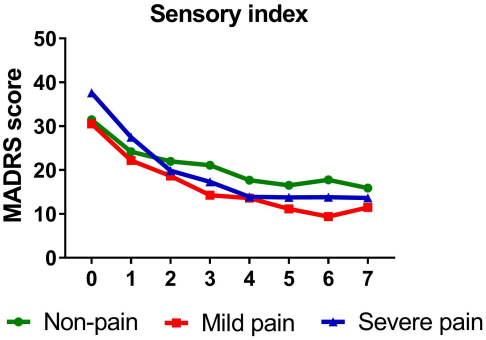

FIGURE 3 | Overall change in MADRS score across six infusions. Pain severity was defined by sensory index. Patients exhibiting no pain symptom were characterized as "non-pain," patients exhibiting the mean or below the mean sensory index were characterized as "mild pain" and patients exhibiting above the mean sensory index were characterized as "severe pain." MADRS, Montgomery-Åsberg Depression Rating Scale. Numbers on *X*-axis: 0 represents baseline, 1∼6 represent the next morning after each infusion, 7 represents 2 weeks after infusions (Day 26).

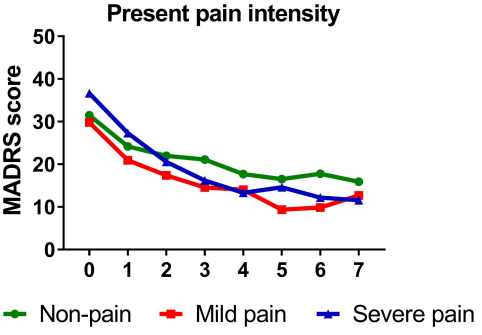

FIGURE 5 | Overall change in MADRS score across six infusions. Pain severity was defined by present pain intensity. Patients exhibiting no pain symptom were characterized as "non-pain," patients exhibiting the mean or below the mean present pain intensity were characterized as "mild pain" and patients exhibiting above the mean present pain intensity were characterized as "severe pain." MADRS, Montgomery-Åsberg Depression Rating Scale. Numbers on *X*-axis: 0 represents baseline, 1∼6 represent the next morning after each infusion, 7 represents 2 weeks after infusions (Day 26).

Similarly, participants with mild ($B = -1.389$, $t = -14.811$, $P < 0.001$)/severe ($B = -1.642$, $t = -10.612$, $P < 0.001$) sensory index, with mild ($B = -1.386$, $t = -12.281$, $P < 0.001$)/severe ($B = -1.568$, $t = -13.334$, $P < 0.001$) affective index, or with mild ($B = -1.263$, $t = -11.703$, $P < 0.001$)/severe ($B = -1.711$, $t = -14.048$, $P < 0.001$) PPI all reported significant reductions in depressive symptoms from baseline to day 26. **Figures 3–5** show that patients with mild or severe pain obtained a more robust symptomatic improvement than non-pain patients (slope: severe pain, mild pain > non-pain).

DISCUSSION

To our best knowledge, this is the first study to explore the impact of pre-treatment pain symptoms on antidepressant effect of repeated intravenous infusions of ketamine in individuals with depression. The main findings are: (1) the rate of pain in depressive patients was high (48.8%); (2) patients with greater pain severity also had higher pre-treatment depressive scores assessed by MADRS; (3) the benefits of repeated infusions of ketamine were observed in patients affected by MDD/BD, both with and without pain; and (4) patients affected by MDD/BD with higher pre-treatment pain exhibited more robust symptomatic improvement, suggesting pre-treatment pain severity moderated ketamine's antidepressant effect, which is inconsistent with outcomes observed with conventional antidepressants.

Nearly a half of patients with depressive symptoms in our study reported pain symptoms, which was consistent with previous reports (6, 27). This finding suggests a high proportion of patients may be resistant to antidepressant treatment, as pain symptoms could negatively impact insight of depression and

adherence to medication, which may lead to adverse results (3). In accordance with previous studies (3, 5, 33), our findings suggest that patients with greater pain severity suffered from more severe depression. Increased pain severity was associated with more pain-related functional limitations (34), which may interfere with daily activities and consequently affect depression severity (3).

Our study revealed that significant and rapid reductions in depressive symptoms were observed across groups after receiving six infusions of IV ketamine, suggesting that ketamine has a robust antidepressant effect which has been supported by a wealth of studies (35–38). However, the moderational effect of pain symptoms on observed antidepressant effect of ketamine treatment in persons with depression requires further investigation.

It has been reported that pain adversely affects the treatment response to conventional antidepressants in persons with depression. For example, results from the STAR*D study indicated that MDD patients with physical pain symptoms were less likely to remit and took longer to achieve remission when they were treated by selective serotonin reuptake inhibitor (SSRI) antidepressants (5). A previous randomized controlled trial also showed that baseline pain symptoms reduced the antidepressant benefits after 3 months of treatment, and an increase in levels of baseline pain severity was associated with a decrease in the likelihood of improvement of depressive symptoms (3).

Ketamine, a novel, rapid-acting antidepressant, has been reported to have therapeutic effects in both pain and depressive symptoms, and may be an ideal treatment option for individuals with depression and comorbid pain symptoms (26, 27). For example, a double randomized controlled study showed that daily oral ketamine for 6 weeks is more effective in improving depressive symptoms in chronic pain patients comorbid with mild to moderate depression when compared to diclofenac (26). A separate study conducted by our group has shown that persons with TRD and comorbid pain symptoms are more likely to achieve response and remission than those without pain after receiving six ketamine infusions (27). The study herein extends the foregoing finding, with evidence of ketamine successfully reducing depressive symptoms in both patients with and without pain. Moreover, the study herein found that higher level of pre-treatment pain severity was associated with greater antidepressant effect of ketamine in patients with depression, which is discordant with outcomes observed with conventional antidepressants. The foregoing findings suggest that the antidepressant effect of ketamine may arise from a different neural mechanism from conventional monoamine-based antidepressants.

There may be neurobiological mechanisms underlying the enhanced ketamine's antidepressant effect in patients with depression and severe pain. Excessive activation of inflammation has been implicated in the pathogenic mechanism of the comorbidity of depression and pain. In animal models of depression with concomitant neuropathic pain, the increased expression of pro-inflammatory cytokines is observed in brain regions that are responsible for processing emotion and pain (39, 40). Similar findings also are reported by clinical research. For example, microglial activation has been found in brain regions related to pain and emotion including the prefrontal cortex and hippocampus in patients who exhibited pain and depression (41). In addition, peripheral increased cytokines such as tumor necrosis factor (TNF)-α and interleukin (IL)-6 have been reported in individuals with the comorbidity of depression and pain (41). Our previous publication revealed that depressive patients with pain had higher plasma levels of IL-6 and granulocyte-macrophage colony stimulating factor (GM-CSF) than those without pain, suggesting pain increases inflammatory response in patients affected by depression (27).

Ketamine has anti-inflammatory effects, which may be implicated in its therapeutic effect on pain and depressive symptoms (42). Moreover, ketamine's analgesic effect can also enhance its anti-depressive effect via alleviating immune response in depressive patients with pain (27). Therefore, inflammation may by a contributing factor to the observed moderational effect of pain on depressive symptom reduction in individuals with MD/BD.

Regarding to the adverse effects, ketamine IV three times a week in our study showed well-tolerated and safe during the infusions as the psychotomimetic and dissociative symptoms, and blood pressure and pulse elevations were very mild and transient, which have been described in detail in our previous publication (43). In recent years, most studies have conducted repeated ketamine infusions (mainly two or three times weekly) to prolong antidepressant effects. Increased infusions of ketamine may increase adverse effects. For example, it is reported that six infusions of ketamine had greater side effects as compared to single ketamine (44). But few studies have compared the side effects of twice- and thrice-weekly ketamine treatment schedules directly. Only one study has evaluated the efficacy and safety of twice- and thrice-weekly intravenous infusion of ketamine, indicating that both treatment schedules achieved similar antidepressant effect but there was no significant difference in adverse events between the two groups due to small sample size (45). Despite of that, both twice- and thrice-weekly intravenous infusion of ketamine showed acceptable short-term side effects such as psychotomimetic and dissociative symptoms, and other general adverse events (headache, nausea, dizziness, etc.) (18, 46). In addition, a longer-term follow-up study (range, 8 months to 6 years) that carried an open-label ketamine infusion three times weekly over a 12-day period showed that no persistent physical symptoms or increased substance use were found in participants, suggesting longer-term safety of ketamine treatment (46). However, considering few studies, including current study, have measured the abuse potential of ketamine, substantially more follow-up studies on the long-term safety are needed.

Several limitations should be noted. First, this was a retrospective analysis of data from an open-label clinical study without placebo controls. And the potential subjective bias of patients and researchers may affect the interpretation of the results because of the lack of blind method. Second, the sample size of this study is relatively small, which may lead to sampling bias. Moreover, due to the limited sample size, patients with either MDD or BD analyzed as a whole in this study may increase heterogeneity. Third, we only recruited depressive patients with

treatment-resistant and with suicidality, which may limit the generalizability of these results for depression patients. Fourth, baseline demographic characteristics of patients with mild, severe and non-pain were not shown because they were divided into multiple groups according to different domains of SF-MPQ. Fifth, we did not measure biological indicators such as plasma cytokines which may enhance persuasive evidence. Thus, it is necessary for further study to measure biological indicators in these depressive patients.

In summary, our study showed that depressive patients with varying degrees of pain exhibited a significant and rapid improvement in depressive symptoms after six infusions of ketamine treatment, and pre-treatment pain symptoms moderated ketamine's antidepressant effect. Overall, our findings suggest that ketamine may be a novel and promising antidepressant preferentially for the therapy of depression with severe pain.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Clinical Research Ethics Committee of The Affiliated Brain Hospital of Guangzhou Medical University. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

YN and YZ designed the study and wrote the protocol. YN provided research supervision. XL and YZ wrote the manuscript. RM helped to revise the manuscript. All authors participated in the data collection and contributed and approved the final manuscript.

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REFERENCES

1. Murray CJ, Vos T, Lozano R, Naghavi M, Flaxman AD, Michaud C, et al. Disability-adjusted life years (DALYs) for 291 diseases and injuries in 21 regions, 1990-2010: a systematic analysis for the global burden of disease study 2010. *Lancet.* (2012) 380:2197–223. doi: 10.1016/S0140-6736(12)61689-4
2. GBD 2019 Viewpoint Collaborators. Five insights from the global burden of disease study 2019. *Lancet.* (2020) 396:1135–59. doi: 10.1016/S0140-6736(20)31404-5
3. Bair MJ, Robinson RL, Eckert GJ, Stang PE, Croghan TW, Kroenke K. Impact of pain on depression treatment response in primary care. *Psychosom Med.* (2004) 66:17–22. doi: 10.1097/01.psy.0000106883.94059.c5
4. Ohayon MM, Schatzberg AF. Using chronic pain to predict depressive morbidity in the general population. *Arch Gen Psychiatry.* (2003) 60:39–47. doi: 10.1001/archpsyc.60.1.39
5. Leuchter AF, Husain MM, Cook IA, Trivedi MH, Wisniewski SR, Gilmer WS, et al. Painful physical symptoms and treatment outcome in major depressive disorder: a STAR*D (sequenced treatment alternatives to relieve depression) report. *Psychol Med.* (2010) 40:239–51. doi: 10.1017/S0033291709006035
6. Aguera-Ortiz L, Failde I, Mico JA, Cervilla J, Lopez-Ibor JJ. Pain as a symptom of depression: prevalence and clinical correlates in patients attending psychiatric clinics. *J Affect Disord.* (2011) 130:106–12. doi: 10.1016/j.jad.2010.10.022
7. Elliott TE, Renier CM, Palcher JA. Chronic pain, depression, and quality of life: correlations and predictive value of the SF-36. *Pain Med.* (2003) 4:331–9. doi: 10.1111/j.1526-4637.2003.03040.x
8. Rayner L, Hotopf M, Petkova H, Matcham F, Simpson A, Mccracken LM. Depression in patients with chronic pain attending a specialised pain treatment centre: prevalence and impact on health care costs. *Pain.* (2016) 157:1472–9. doi: 10.1097/j.pain.0000000000000542
9. IsHak WW, Wen RY, Naghdechi L, Vanle B, Dang J, Knosp M, et al. Pain and depression: a systematic review. *Harv Rev Psychiatry.* (2018) 26:352–63. doi: 10.1097/HRP.0000000000000198
10. Bair MJ, Robinson RL, Katon W, Kroenke K. Depression and pain comorbidity: a literature review. *Arch Intern Med.* (2003) 163:2433–45. doi: 10.1001/archinte.163.20.2433
11. DeVeaugh-Geiss AM, West SL, Miller WC, Sleath B, Gaynes BN, Kroenke K. The adverse effects of comorbid pain on depression outcomes in primary care patients: results from the ARTIST trial. *Pain Med.* (2010) 11:732–41. doi: 10.1111/j.1526-4637.2010.00830.x
12. Bell RF. Ketamine for chronic non-cancer pain. *Pain.* (2009) 141:210–4. doi: 10.1016/j.pain.2008.12.003
13. Abbasi S, Bidi N, Mahshidfar B, Hafezimoghadam P, Rezai M, Mofidi M, et al. Can low-dose of ketamine reduce the need for morphine in renal colic? A double-blind randomized clinical trial. *Am J Emerg Med.* (2018) 36:376–9. doi: 10.1016/j.ajem.2017.08.026
14. Zhao J, Wang Y, Wang D. The effect of ketamine infusion in the treatment of complex regional pain syndrome: a systemic review and meta-analysis. *Curr Pain Headache Rep.* (2018) 22:12. doi: 10.1007/s11916-018-0664-x
15. Corriger A, Voute M, Consortium O, Lambert C, Pereira B, Pickering G. Ketamine for refractory chronic pain: a one-year follow-up study. *Pain.* (2021). doi: 10.1097/j.pain.0000000000002403 [Epub ahead of print].
16. Kishimoto T, Chawla JM, Hagi K, Zarate CA, Kane JM, Bauer M, et al. Single-dose infusion ketamine and non-ketamine N-methyl-d-aspartate receptor antagonists for unipolar and bipolar depression: a meta-analysis of efficacy, safety and time trajectories. *Psychol Med.* (2016) 46:1459–72. doi: 10.1017/S0033291716000064
17. Wilkinson ST, Ballard ED, Bloch MH, Mathew SJ, Murrough JW, Feder A, et al. The effect of a single dose of intravenous ketamine on suicidal ideation: a systematic review and individual participant data meta-analysis. *Am J Psychiatry.* (2018) 175:150–8. doi: 10.1176/appi.ajp.2017.17040472

18. McIntyre RS, Rodrigues NB, Lee Y, Lipsitz O, Subramaniapillai M, Gill H, et al. The effectiveness of repeated intravenous ketamine on depressive symptoms, suicidal ideation and functional disability in adults with major depressive disorder and bipolar disorder: results from the Canadian rapid treatment center of excellence. *J Affect Disord.* (2020) 274:903–10. doi: 10.1016/j.jad.2020.05.088
19. Zarate CA Jr, Brutsche NE, Ibrahim L, Franco-Chaves J, Diazgranados N, Cravchik A, et al. Replication of ketamine's antidepressant efficacy in bipolar depression: a randomized controlled add-on trial. *Biol Psychiatry.* (2012) 71:939–46. doi: 10.1016/j.biopsych.2011.12.010
20. Marcantoni WS, Akoumba BS, Wassef M, Mayrand J, Lai H, Richard-Devantoy S, et al. A systematic review and meta-analysis of the efficacy of intravenous ketamine infusion for treatment resistant depression: January 2009 – January 2019. *J Affect Disord.* (2020) 277:831–41. doi: 10.1016/j.jad.2020.09.007
21. Murrough JW, Perez AM, Pillemer S, Stern J, Parides MK, Aan Het Rot M, et al. Rapid and longer-term antidepressant effects of repeated ketamine infusions in treatment-resistant major depression. *Biol Psychiatry.* (2013) 74:250–6. doi: 10.1016/j.biopsych.2012.06.022
22. McIntyre RS, Rosenblat JD, Nemeroff CB, Sanacora G, Murrough JW, Berk M, et al. Synthesizing the evidence for ketamine and esketamine in treatment-resistant depression: an international expert opinion on the available evidence and implementation. *Am J Psychiatry.* (2021) 178:383–99. doi: 10.1176/appi.ajp.2020.20081251
23. Zheng W, Zhou YL, Liu WJ, Wang CY, Zhan YN, Li HQ, et al. Rapid and longer-term antidepressant effects of repeated-dose intravenous ketamine for patients with unipolar and bipolar depression. *J Psychiatr Res.* (2018) 106:61–8. doi: 10.1016/j.jpsychires.2018.09.013
24. Bigman D, Kunaparaju S, Bobrin B. Use of ketamine for acute suicidal ideation in a patient with chronic pain on prescribed cannabinoids. *BMJ Case Rep.* (2017) 2017:bcr2017222059. doi: 10.1136/bcr-2017-222059
25. Weber G, Yao J, Binns S, Namkoong S. Case report of subanesthetic intravenous ketamine infusion for the treatment of neuropathic pain and depression with suicidal features in a pediatric patient. *Case Rep Anesthesiol.* (2018) 2018:9375910. doi: 10.1155/2018/9375910
26. Jafarinia M, Afarideh M, Tafakhori A, Arbabi M, Ghajar A, Noorbala AA, et al. Efficacy and safety of oral ketamine versus diclofenac to alleviate mild to moderate depression in chronic pain patients: a double-blind, randomized, controlled trial. *J Affect Disord.* (2016) 204:1–8. doi: 10.1016/j.jad.2016.05.076
27. Zhou Y, Wang C, Lan X, Li H, Chao Z, Ning Y. Plasma inflammatory cytokines and treatment-resistant depression with comorbid pain: improvement by ketamine. *J Neuroinflammation.* (2021) 18:200. doi: 10.1186/s12974-021-02245-5
28. Hamilton M. A rating scale for depression. *J Neurol Neurosurg Psychiatry.* (1960) 23:56–62. doi: 10.1136/jnnp.23.1.56
29. Zhan Y, Zhou Y, Zheng W, Liu W, Wang C, Lan X, et al. Alterations of multiple peripheral inflammatory cytokine levels after repeated ketamine infusions in major depressive disorder. *Transl Psychiatry.* (2020) 10:246. doi: 10.1038/s41398-020-00933-z
30. Liu W, Zhou Y, Wang C, Zheng W, Zhan Y, Lan X, et al. Baseline insomnia as a predictor of antidepressant efficacy to repeated intravenous ketamine for unipolar and bipolar depression: a preliminary study. *J Affect Disord.* (2020) 271:1–8. doi: 10.1016/j.jad.2020.03.048
31. Montgomery SA, Asberg M. A new depression scale designed to be sensitive to change. *Br J Psychiatry.* (1979) 134:382–9. doi: 10.1192/bjp.134.4.382
32. Melzack R. The short-form McGill pain questionnaire. *Pain.* (1987) 30:191–7. doi: 10.1016/0304-3959(87)91074-8
33. Fava M, Alpert JE, Carmin CN, Wisniewski SR, Trivedi MH, Biggs MM, et al. Clinical correlates and symptom patterns of anxious depression among patients with major depressive disorder in STAR*D. *Psychol Med.* (2004) 34:1299–308. doi: 10.1017/s0033291704002612
34. Von Korff M, Ormel J, Katon W, Lin EH. Disability and depression among high utilizers of health care. A longitudinal analysis. *Arch Gen Psychiatry.* (1992) 49:91–100. doi: 10.1001/archpsyc.1992.01820020011002
35. Murrough JW, Iosifescu DV, Chang LC, Al Jurdi RK, Green CE, Perez AM, et al. Antidepressant efficacy of ketamine in treatment-resistant major depression: a two-site randomized controlled trial. *Am J Psychiatry.* (2013) 170:1134–42. doi: 10.1176/appi.ajp.2013.13030392
36. Yang Y, Cui Y, Sang K, Dong Y, Ni Z, Ma S, et al. Ketamine blocks bursting in the lateral habenula to rapidly relieve depression. *Nature.* (2018) 554:317–22. doi: 10.1038/nature25509
37. Wang C, Zhou Y, Zheng W, Liu W, Zhan Y, Li H, et al. Association between depression subtypes and response to repeated-dose intravenous ketamine. *Acta Psychiatr Scand.* (2019) 140:446–57. doi: 10.1111/acps.13096
38. Zheng W, Zhou YL, Liu WJ, Wang CY, Zhan YN, Lan XF, et al. A preliminary study of adjunctive ketamine for treatment-resistant bipolar depression. *J Affect Disord.* (2020) 275:38–43. doi: 10.1016/j.jad.2020.06.020
39. Burke NN, Geoghegan E, Kerr DM, Moriarty O, Finn DP, Roche M. Altered neuropathic pain behaviour in a rat model of depression is associated with changes in inflammatory gene expression in the amygdala. *Genes Brain Behav.* (2013) 12:705–13. doi: 10.1111/gbb.12080
40. Burke NN, Finn DP, Roche M. Chronic administration of amitriptyline differentially alters neuropathic pain-related behaviour in the presence and absence of a depressive-like phenotype. *Behav Brain Res.* (2015) 278:193–201. doi: 10.1016/j.bbr.2014.09.044
41. Burke NN, Finn DP, Roche M. Neuroinflammatory mechanisms linking pain and depression. *Mod Trends Pharmacopsychiatry.* (2015) 30:36–50. doi: 10.1159/000435931
42. Niesters M, Martini C, Dahan A. Ketamine for chronic pain: risks and benefits. *Br J Clin Pharmacol.* (2014) 77:357–67. doi: 10.1111/bcp.12094
43. Zhou YL, Liu WJ, Wang CY, Zheng W, Lan XF, Weng SY, et al. Cardiovascular effects of repeated subanaesthetic ketamine infusion in depression. *J Psychopharmacol.* (2021) 35:159–67. doi: 10.1177/0269881120936909
44. Shiroma PR, Thuras P, Wels J, Albott CS, Erbes C, Tye S, et al. A randomized, double-blind, active placebo-controlled study of efficacy, safety, and durability of repeated vs single subanesthetic ketamine for treatment-resistant depression. *Transl Psychiatry.* (2020) 10:206. doi: 10.1038/s41398-020-00897-0
45. Singh JB, Fedgchin M, Daly EJ, De Boer P, Cooper K, Lim P, et al. A double-blind, randomized, placebo-controlled, dose-frequency study of intravenous ketamine in patients with treatment-resistant depression. *Am J Psychiatry.* (2016) 173:816–26. doi: 10.1176/appi.ajp.2016.16010037
46. Wan LB, Levitch CF, Perez AM, Brallier JW, Iosifescu DV, Chang LC, et al. Ketamine safety and tolerability in clinical trials for treatment-resistant depression. *J Clin Psychiatry.* (2015) 76:247–52. doi: 10.4088/JCP.13m08852

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ORIGINAL RESEARCH
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Plasma VEGF Concentrations and Ketamine's Effects on Suicidal Ideation in Depression With Suicidal Ideation

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Objectives: Accumulating evidence supports a role for vascular endothelial growth factor (VEGF) in the pathogenesis of depression, but its relationship with the antisuicidal effects of ketamine is not clear. Our objective was to determine whether there was an association between the plasma VEGF (pVEGF) concentrations and the antisuicidal response to serial ketamine infusions.

Methods: Six ketamine infusions (0.5 mg/kg) over a 12-day period were administered to sixty depressed individuals suffering from suicidal ideation. The Hamilton Depression Rating Scale (HAMD) suicide item, the Montgomery-Åsberg Depression Rating Scale (MADRS) suicide item, and the Beck Scale for Suicide Ideation (SSI-part I) were used to assess suicidal ideation at baseline, 1 day after the first infusion (day 1), 1 day following the last infusion (day 13), and again 2 weeks post-infusion (day 26). For this purpose, plasma was obtained at baseline, day 13 and 26.

Results: The rates of antisuicidal response to ketamine were 61.7% (37/60), 81.7% (49/60), and 73.3% (44/60) at days 1, 13, and 26, respectively. The linear mixed model revealed significant time effects on suicidal ideation and pVEGF concentrations over time (all $Ps < 0.05$). Antisuicidal responders did not have significantly altered pVEGF concentrations compared with non-responders on day 13 and day 26 (all $Ps > 0.05$). No significant correlation was found between the baseline pVEGF concentration and suicidal ideation as measured by the SSI part 1, HAMD suicide item and MADRS suicide item on days 1, 13, and 26 (all $ps > 0.05$).

Conclusion: This preliminary finding does not support a role for VEGF in the antisuicidal effects of serial ketamine treatments in individuals with depression and suicidal ideation. Further research is needed to confirm and expand these findings.

Keywords: ketamine, VEGF, suicidal ideation, depression, response

INTRODUCTION

Approximately 0.8 million individuals worldwide die by suicide every year (1), which is becoming a substantial public health concern. Suicide is a complex and multifaceted phenomenon where numerous potential mechanisms could be implicated (2). Suicidal ideation is common in individuals with major depressive disorder (MDD) (3) and bipolar depression (BD) (4), especially among inpatients. Better therapy for suicidal ideation in MDD and BD is a critical target in preventing deaths due to suicide (5). However, very few treatments can rapidly alleviate suicidal ideation (6). Although accumulating evidence has indicated that treatment with dialectical behavioral therapy (7), cognitive behavioral therapy (CBT) (8, 9), and lithium (10) can effectively alleviate suicidal ideation, the onset of clinically relevant antisuicidal effects generally takes 2–4 weeks. Thus, novel pharmacotherapeutic approaches are urgently needed for subjects with depression and suicidal ideation.

As a non-selective *N*-methyl-D-aspartic acid receptor (NMDAR) antagonist, ketamine has shown quick and dramatic antisuicidal effects in randomized controlled trials (RCTs) (11, 12) and meta-analyses (13, 14) for MDD and BD. In addition to its rapid antisuicidal effects, ketamine at a single intravenous dose has a rapid effect in reducing the level of ahedonia (15–18) and ameliorating depressive symptoms (19, 20) in MDD and BD. After controlling for the effects of ketamine on depression, ketamine's antisuicidal ideation remained significant (13, 21). Antidepressant and antisuicidal responses to a single ketamine infusion could be prolonged with repeated ketamine infusions (22, 23). For example, a recent study found that the antisuicidal response rates increased from 57.0 to 65.1% after five additional infusions of ketamine in depressed patients experiencing suicidal ideation (22). However, a certain proportion of depressed patients experiencing suicidal ideation do not adequately respond to single or repeated ketamine infusions, but the reasons for this are unclear.

Vascular endothelial growth factor (VEGF), as an angiogenic cytokine, has been associated with the antidepressant response to electroconvulsive therapy (ECT) (24) and serotonin selective reuptake inhibitors (SSRIs) (25). Patients experiencing suicidal ideation had lower cerebrospinal fluid VEGF concentrations than healthy controls (26). In contrast, antidepressant therapy can induce hippocampal expression of VEGF (27). Recently, Deyama et al. found that the rapid antidepressant response to ketamine was associated with neuronal VEGF-Flk-1 signaling in the medial prefrontal cortex (mPFC) (28). Finding on the relationship between VEGF and ketamine's antidepressant effect in depressed patients were inconsistent (29, 30). For instance, McGrory et al. found that VEGF plays an essential role in the antidepressant action of ketamine (30). However, another study reported a negative finding (29). No study has yet reported on the association of plasma VEGF (pVEGF) concentrations and the antisuicidal effects of repeated-dose intravenous ketamine in Chinese subjects with depression who are experiencing suicidal ideation.

The aim of the current study was to: (1) detect the change in pVEGF concentrations after repeated-dose intravenous ketamine in depressed patients experiencing suicidal ideation and (2) to demonstrate the relationship between pVEGF concentrations and the antisuicidal effects of repeated doses of intravenous ketamine. We hypothesized that pVEGF concentrations would be increased after six ketamine infusions, and pVEGF would play an improtant role in the antidepressant actions of ketamine in individuals with depression and suicidal ideation.

METHODS

Study Population and the Procedure

The data for this study were obtained from a single-center clinical trial (Registration Number: ChiCTR-OOC-17012239) in which unipolar and bipolar depressed patients received six ketamine infusions at the Affiliated Brain Hospital of Guangzhou Medical University from September 2016 to December 2017 (31, 32). All patients gave written informed consent and the study was approved by the Affiliated Brain Hospital of Guangzhou Medical University Institutional Review Board (Ethical Application Ref: 2016030). In the present study, we specifically report the association between pVEGF concentration and the effect of ketamine on suicidal ideation, focusing on depressed patients with suicidal ideation. The inclusion criteria were as follows: (1) sixty depressed patients were 18–65 years old with suicidal ideation as defined by the Beck Scale for Suicide Ideation (SSI)-part I $\geq$ 2 (33, 34); (2) patients fulfilling the diagnostic criteria listed in the DSM-5, for MDD or BD without psychotic symptoms; (3) each participant experiencing a major depressive episode of at least moderate severity, as defined by the 17-item Hamilton Depression Rating Scale (HAMD) $\geq$ 17 (35, 36); (4) full understanding of the study procedure. The exclusion criteria of the current study were consistent with those used in previous studes (31, 32). Briefly, participants diagnosed with other psychiatric disorders such as schizophrenia, substance use disorder or alcohol use disorder were excluded, but a comorbidity of obsessive compulsive disorder, anxiety disorder or eating disorder was permitted when it was not judged to be the primary presenting problem. All subjects received six intravenous infusions of ketamine at subanaesthetic doses over 12 days. During the study period, the participants continued their psychotropic medications.

Antisuicidal Response

The SSI part I, the Montgomery-Åsberg Depression Rating Scale (MADRS) suicide item, and the HAMD suicide item were used to evaluate the severity of suicidal ideation at baseline, 1 day after the first infusion (day 1), 1 day after the completion of six ketamine infusions (day 13), and at the 2-week follow-up after the completion of six ketamine infusions (day 26). Antisuicidal responses to repeated-dose intravenous ketamine at day 13 were defined by the SSI part I $<$ 2 (22, 37).

Measurement of pVEGF Concentrations

A commercially available enzyme-linked immunosorbent assay (ELISA) kit (R&D Systems, Minneapolis, USA) was used to examine the pVEGF concentrations according to the manufacturer's recommendations. The plasma was obtained at

baseline and then on days 13 and 26. The measurement of the pVEGF concentrations was in line with those used in a recent study (29).

Statistical Analysis

Data from this study were analyzed by using SPSS 24.0 statistical software. Significance was considered at $p < 0.05$. The demographic and clinical characteristics and pVEGF concentrations at baseline were compared between the antisuicidal responders and the non-responders using the chi-squared test and/or Fisher's exact test for categorical variables and Student's *t*-test and/or the Mann–Whitney U test for continuous variables, as appropriate. Changes in the pVEGF concentrations and the suicidal symptoms evaluated by the HAMD suicide item, MADRS suicide item, and SSI part I over time and the subgroup differences (antisuicidal responders vs.

TABLE 1 | Baseline characteristics of antisuicidal responders and non-responders calculated by SSI part I scores on day 13.

Variables	Total sample ($n = 60$)		Antisuicidal responders ($n = 49$)		Antisuicidal non-responders ($n = 11$)		Statistics		
	N	%	*N*	%	*N*	%	X^2	df	*p*
Male	27	45.0	22	44.9	5	45.5	—[a]	—[a]	1.00
Employed	23	38.3	21	42.9	2	18.2	—[a]	—[a]	0.18
Married	34	56.7	27	55.1	7	63.6	—[a]	—[a]	0.74
On ADs two or more	8	13.3	8	16.3	0	0	—[a]	—[a]	0.33
On APs	35	58.3	29	59.2	6	54.5	—[a]	—[a]	1.00
On mood stabilizers	16	26.7	13	26.5	3	27.3	—[a]	—[a]	1.00
On benzodiazepines	27	45.0	21	42.9	6	54.5	—[a]	—[a]	0.52
On anxiolytics	27	45.0	22	44.9	5	45.5	—[a]	—[a]	1.00
On anticholinergics	8	13.3	8	16.3	0	0	—[a]	—[a]	0.33
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**	**T/Z**	**df**	***p***
Age (years)	35.3	12.4	34.8	12.0	37.4	14.4	−0.6	58	0.54
Education level (years)	12.2	3.5	12.5	3.4	10.7	3.9	0.8	58	0.14
BMI	22.2	3.5	22.1	3.3	22.8	4.5	−0.7	58	0.51
Illness duration (months)	91.5	80.0	81.5	69.1	135.9	110.2	−2.1	58	**0.04**
FLUeq (mg/day)	35.6	20.7	35.8	21.7	34.5	16.2	0.2	58	0.85
CPZeq (mg/day)	169.1	117.6	168.7	125.8	170.8	74.5	−0.5	—[b]	0.64
Baseline pVEGF concentrations (ng/ml)	38.4	55.7	44.5	59.7	11.6	15.7	−1.8	—[b]	0.07
Baseline SSI-part I scores	5.0	2.4	4.8	2.5	5.2	2.2	0.34	58	0.73
Baseline HAMD suicide item scores	2.2	0.8	2.2	0.8	2.5	0.8	−1.5	58	0.15
Baseline MADRS suicide item scores	2.9	1.3	2.8	1.2	3.5	1.5	−1.8	58	0.07

Bolded values are $p < 0.05$.
[a]*Fisher's Exact Test.*
[b]*Mann-Whitney U test.*
Ads, Antidepressants; APs, antipsychotics; BMI, body mass index; CPZeq, chlorpromazine equivalent milligrams; FLUeq, Fluoxetine equivalents equals; pVEGF, plasma vascular endothelial growth factor; df, degrees of freedom; HAMD, the Hamilton Depression Rating Scale; MADRS, the Montgomery-Åsberg Depression Rating Scale; SSI, the Beck Scale for Suicide Ideation; SD, standard deviation; TRD, treatment refractory depression.

TABLE 2 | Comparison of suicidal ideation scores and pVEGF concentrations between antisuicidal responders and non-responders in depressed patients with suicidal ideation using linear mixed model analysis.

Variables	Group-by-time interaction		Time main effect		Group main effect	
	F	*p*	*F*	*p*	*F*	*p*
HAMD suicide item scores	6.8	**<0.001**	33.2	**<0.001**	11.9	**0.001**
MADRS suicide item scores	4.6	**0.004**	30.1	**<0.001**	10.2	**0.002**
SSI-part I scores	4.1	**0.008**	28.8	**<0.001**	11.2	**0.002**
pVEGF concentrations (ng/ml)	0.6	0.55	3.5	**0.04**	0.3	0.57

Bolded values are $p < 0.05$.
pVEGF, plasma vascular endothelial growth factor; SSI, the Beck Scale for Suicide Ideation; MADRS, the Montgomery-Åsberg Depression Rating Scale; HAMD, the Hamilton Depression Rating Scale.

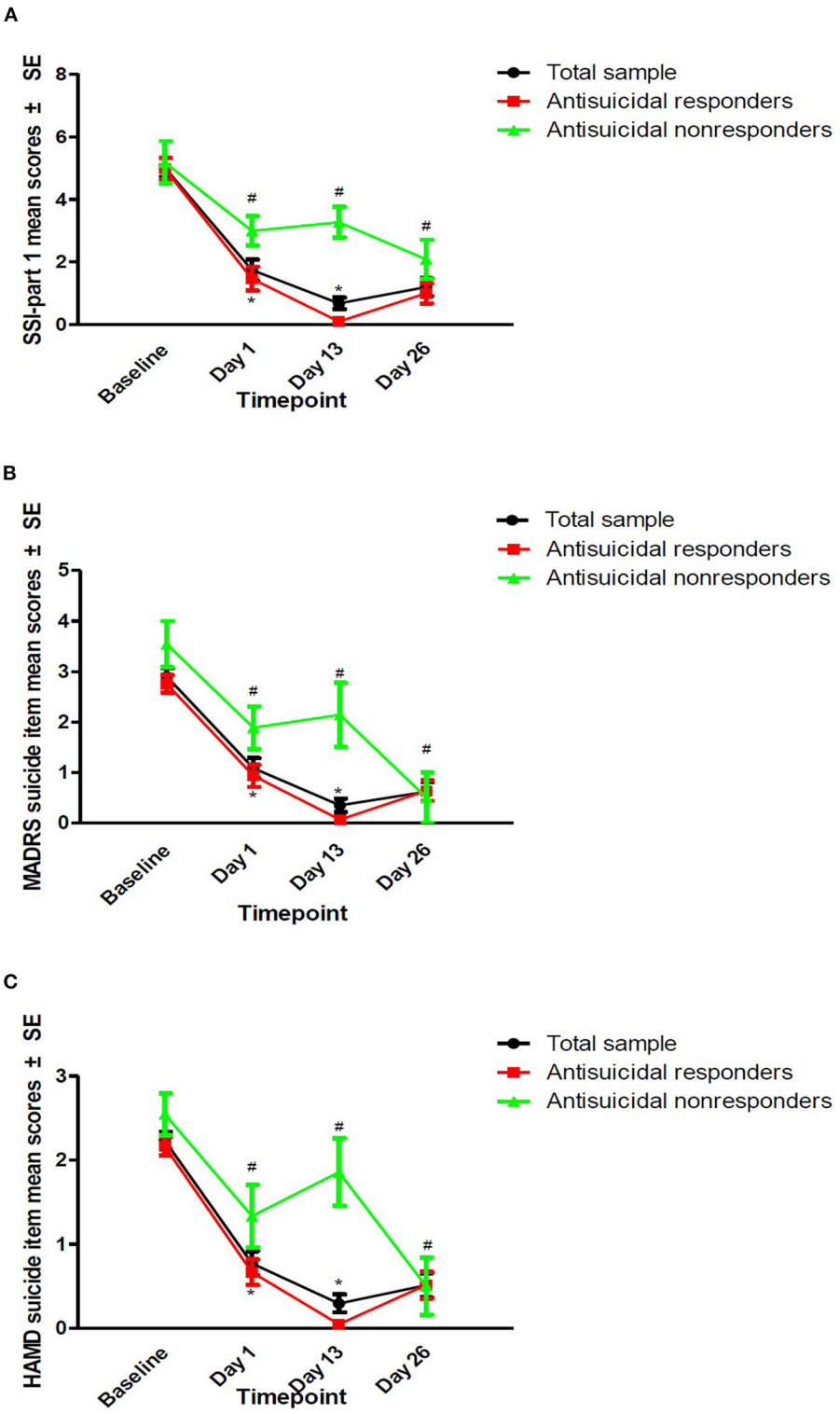

FIGURE 1 | The antisuicidal effects of ketamine were measured by SSI part I, the MADRS suicide item, and the HAMD suicide item. The antisuicidal effects of ketamine as measured by SSI part I **(A)**, the MADRS suicide item **(B)**, and the HAMD suicide item **(C)**. #A significant difference was found compared to the baseline at the indicated times ($P < 0.05$). *A significant difference was found between antisuicidal responders and non-responders at the indicated times ($P < 0.05$). SSI, the Beck Scale for Suicide Ideation; MADRS, the Montgomery-Åsberg Depression Rating Scale; HAMD, the Hamilton Depression Rating Scale.

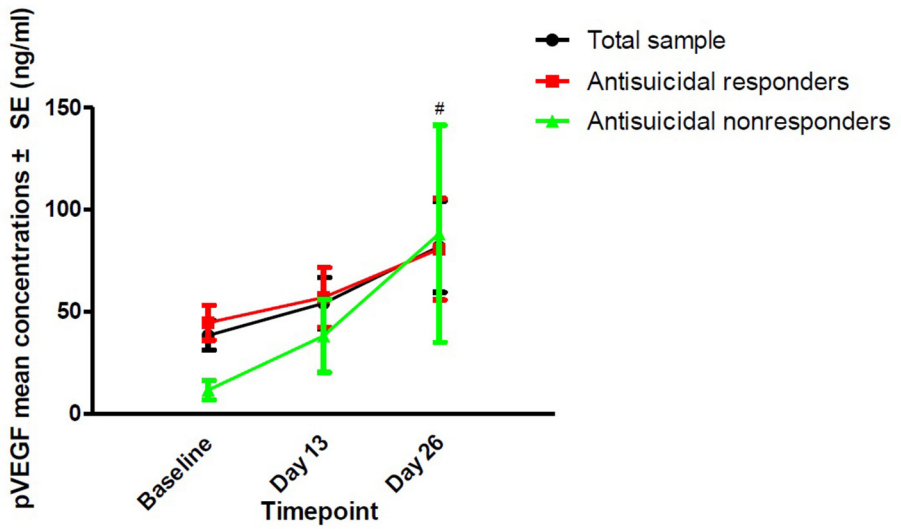

FIGURE 2 | The change in pVEGF concentrations in depressed patients with suicidal ideation at the indicated times. #No significant difference at the indicated times was found when compared to baseline ($P > 0.05$). No significant difference at the indicated times was found between antisuicidal responders and non-responders ($P > 0.05$). pVEGF, plasma vascular endothelial growth factor.

TABLE 3 | Correlation analysis between suicidal ideation and baseline pVEGF concentrations in depressed patients with suicidal ideation at the indicated times.

Variables		HAMD suicide item scores			MADRS suicide item scores			SSI-part I scores		
		Day 1	Day 13	Day 26	Day 1	Day 13	Day 26	Day 1	Day 13	Day 26
Baseline pVEGF concentrations (ng/ml)	*r*	−0.07	−0.18	0.16	−0.05	−0.19	0.13	0.17	−0.22	0.24
	p	0.62	0.22	0.30	0.74	0.19	0.41	0.20	0.09	0.07
Variables		**Change in HAMD suicide item scores**			**Change in MADRS suicide item scores**			**Change in SSI-part I scores**		
		Day 1	**Day 13**	**Day 26**	**Day 1**	**Day 13**	**Day 26**	**Day 1**	**Day 13**	**Day 26**
Change in pVEGF concentrations (ng/ml)	*r*	0.10	−0.14	0.09	0.09	−0.10	0.07	0.10	−0.24	−0.02
	p	0.53	0.36	0.54	0.59	0.51	0.67	0.53	0.11	0.91

pVEGF, plasma vascular endothelial growth factor; r, Pearson coefficient of correlation; SSI, the Beck Scale for Suicide Ideation; MADRS, the Montgomery-Åsberg Depression Rating Scale; HAMD, the Hamilton Depression Rating Scale.

non-responders) were investigated using linear mixed models. The association of pVEGF concentrations with the antisuicidal effects of ketamine was examined by correlation analysis.

RESULTS

pVEGF concentrations were obtained from 60 patients suffering from depression and suicidal ideation. A comparison between the demographic and clinical characteristics of antisuicidal responders and non-responders is presented in **Table 1**. Antisuicidal responders had marginally significantly higher baseline pVEGF concentrations than antisuicidal non-responders ($P = 0.07$; **Table 1**).

The rates of antisuicidal responses to ketamine were 61.7% (37/60), 81.7% (49/60), and 73.3% (44/60) on days 1, 13, and 26, respectively. The linear mixed model with SSI part I, MADRS suicide items and HAMD suicide items showed a significant main effect of time and group and a group-by-time interaction (all *Ps* < 0.05; **Table 2**). Antisuicidal responders had a significantly greater reduction in suicidal ideation than non-responders (as measured by the SSI part I, the MADRS suicide item and the HAMD suicide item) at days 1 and 13 (all *Ps* < 0.05; **Figure 1**). The linear mixed model with pVEGF concentrations showed a significant main effect of time ($P < 0.05$; **Table 2**) but not for the main effect of group and group-by-time interaction (all *Ps* > 0.05; **Table 2**). Although a significant change in pVEGF concentrations was found at day 26 as compared to baseline ($P < 0.05$), the antisuicidal responders compared to nonresponders did not have significantly altered pVEGF concentrations at day 13 and day 26 (all *Ps* > 0.05; **Figure 2**).

As depicted in **Table 3**, no significant association of baseline pVEGF concentrations and reductions in suicidal ideation following ketamine treatment (as measured by the SSI part I, the

MADRS suicide item, and the HAMD suicide item) were found on day 1, day 13, or day 26 (all $Ps > 0.05$; **Table 2**).

DISCUSSION

The current study first illuminated the association of pVEGF concentrations with the effect of ketamine on suicidal ideation. Our findings indicate that antisuicidal responders had marginally significantly greater pVEGF concentrations at baseline than antisuicidal non-responders. Despite a significant reduction in suicidal ideation during serial ketamine infusions over time, the pVEGF concentrations were not significantly altered in antisuicidal responders compared with non-responders on day 13 and day 26. Similarly, no notable association was detected between the pVEGF concentrations and the effects of repeated-dose intravenous ketamine on suicidal ideation as measured by SSI part I, the MADRS suicide item, and the HAMD suicide item.

Accumulating evidence suggests that VEGF is associated with brain function, including neurogenesis, learning and memory, by regulating hippocampal synaptic activity and plasticity (38–41). Dysregulated VEGF concentrations have been involved in major mental disorders, such as MDD and BD (42). Low pVEGF concentrations are associated with a higher suicide risk among suicide attempters (43). Therapy with antidepressants such as SSRIs (27, 44) and ketamine (30) can increase the expression of VEGF. Consistent with previous studies (11–14), in this study, ketamine had a rapid and robust effect in reducing suicidal ideation. Repeated administration of intravenous ketamine (0.5 mg/kg) did not significantly increase pVEGF concentrations, even after a 2-week follow-up, corroborating the results of previous studies (45).

As reported by Deyama et al.'s study, the antidepressant-like and neurotrophic actions of brain-derived neurotrophic factor (BDNF) require VEGF signaling (44). Thus, VEGFR2 signaling appears to be indispensable for cellular and behavioral responses to antidepressant treatments (27). The findings of several animal trials support a role for VEGF in the biological actions of antidepressants (i.e., fluoxetine) (46) and mood stabilizers (i.e., lamotrigine) (47). Similarly, VEGF could mediate the antidepressant actions of electroconvulsive seizures (48, 49) and a single ketamine infusion (28) but not six ketamine infusions (29). However, in this study, we found that VEGF was not involved in the antisuicidal effects of repeated-dose intravenous ketamine in Chinese patients with depression and suicidal ideation, which should be confirmed by RCTs.

This study is associated with several limitations. First, the relatively small sample size is the first study limitation, partly accounting for the negative results. Second, the lack of a control group in the protocol of the present study was another limitation, affecting the interpretation and external validity of the findings. Third, when compared to the samples from controlled clinical trials, the sample of the current study based on a real-world design is potentially more heterogeneous. Furthermore, the pooling of subjects suffering from MDD and BD made the sample non-homogeneous. Fourth, although substance use disorder is a significant predictor of non-adherence among individuals suffering from mood disorders (50), patients suffering from substance use disorder were excluded in this study. Finally, all subjects continued to receive psychotropic medications, which may have potentially affected their pVEGF concentrations and explained the contradictory findings between this study and previous studies (30, 45). Finally, as reported by Levy et al., blood VEGF concentrations may not be associated with VEGF concentrations in the brain (51). However, VEGF concentrations in the brain could not be directly detected in the current study.

CONCLUSIONS

This preliminary study does not support a role for VEGF in the antisuicidal effects of serial ketamine treatments in individuals with depression and suicidal ideation. Further research is needed to confirm and expand these findings.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Affiliated Brain Hospital of Guangzhou Medical University Institutional Review Board (Ethical Application Ref: 2016030). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

Y-PN: study design. WZ, Y-LZ, C-YW, and X-FL: data collection. WZ and L-MG: analysis and interpretation of data. WZ: drafting of the manuscript. BZ and Y-PN: critical revision of the manuscript. All authors: approval of the final version for publication.

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REFERENCES

1. Chesney E, Goodwin GM, Fazel S. Risks of all-cause and suicide mortality in mental disorders: a meta-review. *World Psychiatry.* (2014) 13:153–60. doi: 10.1002/wps.20128
2. Orsolini L, Latini R, Pompili M, Serafini G, Volpe U, Vellante F, et al. Understanding the complex of suicide in depression: from research to clinics. *Psychiatry Investig.* (2020) 17:207–21. doi: 10.30773/pi.2019.0171
3. Cai H, Jin Y, Liu S, Zhang Q, Zhang L, Cheung T, et al. Prevalence of suicidal ideation and planning in patients with major depressive disorder: a meta-analysis of observation studies. *J Affect Disord.* (2021) 293:148–58. doi: 10.1016/j.jad.2021.05.115
4. Dong M, Lu L, Zhang L, Zhang Q, Ungvari GS, Ng CH, et al. Prevalence of suicide attempts in bipolar disorder: a systematic review and meta-analysis of observational studies. *Epidemiol Psychiatr Sci.* (2019) 29:e63. doi: 10.1017/S2045796019000593
5. Ballard ED, Wills K, Lally N, Richards EM, Luckenbaugh DA, Walls T, et al. Anhedonia as a clinical correlate of suicidal thoughts in clinical ketamine trials. *J Affect Disord.* (2017) 218:195–200. doi: 10.1016/j.jad.2017.04.057
6. Griffiths JJ, Zarate CA, Jr., Rasimas JJ. Existing and novel biological therapeutics in suicide prevention. *Am J Prev Med.* (2014) 47 (3 Suppl. 2):S195–203. doi: 10.1016/j.amepre.2014.06.012
7. Linehan MM, Comtois KA, Murray AM, Brown MZ, Gallop RJ, Heard HL, et al. Two-year randomized controlled trial and follow-up of dialectical behavior therapy vs therapy by experts for suicidal behaviors and borderline personality disorder. *Arch Gen Psychiatry.* (2006) 63:757–66. doi: 10.1001/archpsyc.63.7.757
8. Hawton K, Witt KG, Salisbury TLT, Arensman E, Gunnell D, Hazell P, et al. Psychosocial interventions following self-harm in adults: a systematic review and meta-analysis. *Lancet Psychiatry.* (2016) 3:740–50. doi: 10.1016/S2215-0366(16)30070-0
9. Brown GK, Ten Have T, Henriques GR, Xie SX, Hollander JE, Beck AT. Cognitive therapy for the prevention of suicide attempts: a randomized controlled trial. *JAMA.* (2005) 294:563–70. doi: 10.1001/jama.294.5.563
10. Cipriani A, Hawton K, Stockton S, Geddes JR. Lithium in the prevention of suicide in mood disorders: updated systematic review and meta-analysis. *BMJ.* (2013) 346:f3646. doi: 10.1136/bmj.f3646
11. Price RB, Iosifescu DV, Murrough JW, Chang LC, Al Jurdi RK, Iqbal SZ, et al. Effects of ketamine on explicit and implicit suicidal cognition: a randomized controlled trial in treatment-resistant depression. *Depress Anxiety.* (2014) 31:335–43. doi: 10.1002/da.22253
12. Chen MH, Lin WC, Tu PC, Li CT, Bai YM, Tsai SJ, et al. Antidepressant and antisuicidal effects of ketamine on the functional connectivity of prefrontal cortex-related circuits in treatment-resistant depression: A double-blind, placebo-controlled, randomized, longitudinal resting fMRI study. *J Affect Disord.* (2019) 259:15–20. doi: 10.1016/j.jad.2019.08.022
13. Wilkinson ST, Ballard ED, Bloch MH, Mathew SJ, Murrough JW, Feder A, et al. The effect of a single dose of intravenous ketamine on suicidal ideation: a systematic review and individual participant data meta-analysis. *Am J Psychiatry.* (2018) 175:150–8. doi: 10.1176/appi.ajp.2017.17040472
14. Xiong J, Lipsitz O, Chen-Li D, Rosenblat JD, Rodrigues NB, Carvalho I, et al. The acute antisuicidal effects of single-dose intravenous ketamine and intranasal esketamine in individuals with major depression and bipolar disorders: a systematic review and meta-analysis. *J Psychiatr Res.* (2021) 134:57–68. doi: 10.1016/j.jpsychires.2020.12.038
15. Lally N, Nugent AC, Luckenbaugh DA, Ameli R, Roiser JP, Zarate CA. Anti-anhedonic effect of ketamine and its neural correlates in treatment-resistant bipolar depression. *Transl Psychiatry.* (2014) 4:e469. doi: 10.1038/tp.2014.105
16. Lally N, Nugent AC, Luckenbaugh DA, Niciu MJ, Roiser JP, Zarate CA Jr. Neural correlates of change in major depressive disorder anhedonia following open-label ketamine. *J Psychopharmacol.* (2015) 29:596–607. doi: 10.1177/0269881114568041
17. Zheng W, Gu LM, Sun CH, Zhou YL, Wang CY, Lan XF, et al. Comparative effectiveness of repeated ketamine infusions in treating anhedonia in bipolar and unipolar depression. *J Affect Disord.* (2022) 300:109–13. doi: 10.1016/j.jad.2021.12.105
18. Zheng W, Gu LM, Zhou YL, Wang CY, Lan XF, Zhang B, et al. Association of VEGF with antianhedonic effects of repeated-dose intravenous ketamine in treatment-refractory depression. *Front Psychiatry.* (2021) 12:780975. doi: 10.3389/fpsyt.2021.780975
19. Berman RM, Cappiello A, Anand A, Oren DA, Heninger GR, Charney DS, et al. Antidepressant effects of ketamine in depressed patients. *Biol Psychiatry.* (2000) 47:351–4. doi: 10.1016/S0006-3223(99)00230-9
20. Kishimoto T, Chawla JM, Hagi K, Zarate CA, Kane JM, Bauer M, et al. Single-dose infusion ketamine and non-ketamine N-methyl-d-aspartate receptor antagonists for unipolar and bipolar depression: a meta-analysis of efficacy, safety and time trajectories. *Psychol Med.* (2016) 46:1459–72. doi: 10.1017/S0033291716000064
21. Ballard ED, Ionescu DF, Vande Voort JL, Niciu MJ, Richards EM, Luckenbaugh DA, et al. Improvement in suicidal ideation after ketamine infusion: relationship to reductions in depression and anxiety. *J Psychiatr Res.* (2014) 58:161–6. doi: 10.1016/j.jpsychires.2014.07.027
22. Zhan Y, Zhang B, Zhou Y, Zheng W, Liu W, Wang C, et al. A preliminary study of anti-suicidal efficacy of repeated ketamine infusions in depression with suicidal ideation. *J Affect Disord.* (2019) 251:205–12. doi: 10.1016/j.jad.2019.03.071
23. Murrough JW, Perez AM, Pillemer S, Stern J, Parides MK, aan het Rot M, et al. Rapid and longer-term antidepressant effects of repeated ketamine infusions in treatment-resistant major depression. *Biol Psychiatry.* (2013) 74:250–6. doi: 10.1016/j.biopsych.2012.06.022
24. Minelli A, Maffioletti E, Bortolomasi M, Conca A, Zanardini R, Rillosi L, et al. Association between baseline serum vascular endothelial growth factor levels and response to electroconvulsive therapy. *Acta Psychiatr Scand.* (2014) 129:461–6. doi: 10.1111/acps.12187
25. Kao CF, Liu YL, Yu YW, Yang AC, Lin E, Kuo PH, et al. Gene-based analysis of genes related to neurotrophic pathway suggests association of BDNF and VEGFA with antidepressant treatment-response in depressed patients. *Sci Rep.* (2018) 8:6983. doi: 10.1038/s41598-018-25529-y
26. Isung J, Aeinehband S, Mobarrez F, Mårtensson B, Nordström P, Asberg M, et al. Low vascular endothelial growth factor and interleukin-8 in cerebrospinal fluid of suicide attempters. *Transl Psychiatry.* (2012) 2:e196. doi: 10.1038/tp.2012.123
27. Nowacka MM, Obuchowicz E. Vascular endothelial growth factor (VEGF) and its role in the central nervous system: a new element in the neurotrophic hypothesis of antidepressant drug action. *Neuropeptides.* (2012) 46:1–10. doi: 10.1016/j.npep.2011.05.005
28. Deyama S, Bang E, Wohleb ES, Li XY, Kato T, Gerhard DM, et al. Role of neuronal VEGF signaling in the prefrontal cortex in the rapid antidepressant effects of ketamine. *Am J Psychiatry.* (2019) 176:388–400. doi: 10.1176/appi.ajp.2018.17121368
29. Zheng W, Zhou YL, Wang CY, Lan XF, Zhang B, Zhou SM, et al. Association of plasma VEGF levels and the antidepressant effects of ketamine in patients with depression. *Therap Adv Psychopharmacol.* (2021) 11:20451253211014320. doi: 10.1177/20451253211014320
30. McGrory CL, Ryan KM, Gallagher B, McLoughlin DM. Vascular endothelial growth factor and pigment epithelial-derived factor in the peripheral response to ketamine. *J Affect Disord.* (2020) 273:380–3. doi: 10.1016/j.jad.2020.04.013
31. Zheng W, Zhou YL, Liu WJ, Wang CY, Zhan YN, Li HQ, et al. Investigation of medical effect of multiple ketamine infusions on patients with major depressive disorder. *J Psychopharmacol.* (2019) 33:494–501. doi: 10.1177/0269881119827811
32. Zheng W, Zhou YL, Liu WJ, Wang CY, Zhan YN, Li HQ, et al. Rapid and longer-term antidepressant effects of repeated-dose intravenous ketamine for patients with unipolar and bipolar depression. *J Psychiatr Res.* (2018) 106:61–8. doi: 10.1016/j.jpsychires.2018.09.013
33. Vande Voort JL, Ballard ED, Luckenbaugh DA, Bernert RA, Richards EM, Niciu MJ, et al. Antisuicidal response following ketamine infusion is associated with decreased nighttime wakefulness in major depressive disorder and bipolar disorder. *J Clin Psychiatry.* (2017) 78:1068–74. doi: 10.4088/JCP.15m10440
34. Zhou Y, Liu W, Zheng W, Wang C, Zhan Y, Lan X, et al. Predictors of response to repeated ketamine infusions in depression with suicidal ideation: an ROC curve analysis. *J Affect Disord.* (2020) 264:263–71. doi: 10.1016/j.jad.2020.01.001
35. Hamilton M. A rating scale for depression. *J Neurol Neurosurg Psychiatry.* (1960) 23:56–62. doi: 10.1136/jnnp.23.1.56

36. Xie GR, Shen QJ. Use of the Chinese version of the Hamilton Rating Scale for Depression in general population and patients with major depression (In Chinese). *Chin J Nerv Ment Dis.* (1984) 10:364.
37. Rasmussen KG, Lineberry TW, Galardy CW, Kung S, Lapid MI, Palmer BA, et al. Serial infusions of low-dose ketamine for major depression. *J Psychopharmacol.* (2013) 27:444–50. doi: 10.1177/0269881113478283
38. Cao L, Jiao X, Zuzga DS, Liu Y, Fong DM, Young D, et al. VEGF links hippocampal activity with neurogenesis, learning and memory. *Nat Genet.* (2004) 36:827–35. doi: 10.1038/ng1395
39. Storkebaum E, Lambrechts D, Carmeliet P. VEGF: once regarded as a specific angiogenic factor, now implicated in neuroprotection. *Bioessays.* (2004) 26:943–54. doi: 10.1002/bies.20092
40. Fournier NM, Lee B, Banasr M, Elsayed M, Duman RS. Vascular endothelial growth factor regulates adult hippocampal cell proliferation through MEK/ERK- and PI3K/Akt-dependent signaling. *Neuropharmacology.* (2012) 63:642–52. doi: 10.1016/j.neuropharm.2012.04.033
41. Calvo CF, Fontaine RH, Soueid J, Tammela T, Makinen T, Alfaro-Cervello C, et al. Vascular endothelial growth factor receptor 3 directly regulates murine neurogenesis. *Genes Dev.* (2011) 25:831–44. doi: 10.1101/gad.615311
42. Clark-Raymond A, Halaris A. VEGF and depression: a comprehensive assessment of clinical data. *J Psychiatr Res.* (2013) 47:1080–7. doi: 10.1016/j.jpsychires.2013.04.008
43. Isung J, Mobarrez F, Nordström P, Asberg M, Jokinen J. Low plasma vascular endothelial growth factor (VEGF) associated with completed suicide. *World J Biol Psychiatry.* (2012) 13:468–73. doi: 10.3109/15622975.2011.624549
44. Deyama S, Bang E, Kato T, Li XY, Duman RS. Neurotrophic and Antidepressant Actions of Brain-Derived Neurotrophic Factor Require Vascular Endothelial Growth Factor. *Biol Psychiatry.* (2019) 86:143–52. doi: 10.1016/j.biopsych.2018.12.014
45. Medeiros GC, Greenstein D, Kadriu B, Yuan P, Park LT, Gould TD, et al. Treatment of depression with ketamine does not change plasma levels of brain-derived neurotrophic factor or vascular endothelial growth factor. *J Affect Disord.* (2021) 280:136–9. doi: 10.1016/j.jad.2020.11.011
46. Greene J, Banasr M, Lee B, Warner-Schmidt J, Duman RS. Vascular endothelial growth factor signaling is required for the behavioral actions of antidepressant treatment: pharmacological and cellular characterization. *Neuropsychopharmacology.* (2009) 34:2459–68. doi: 10.1038/npp.2009.68
47. Sun R, Li N, Li T. VEGF regulates antidepressant effects of lamotrigine. *Eur Neuropsychopharmacol.* (2012) 22:424–30. doi: 10.1016/j.euroneuro.2011.09.010
48. Segi-Nishida E. Exploration of new molecular mechanisms for antidepressant actions of electroconvulsive seizure. *Biol Pharm Bull.* (2011) 34:939–44. doi: 10.1248/bpb.34.939
49. Warner-Schmidt JL, Duman RS. VEGF as a potential target for therapeutic intervention in depression. *Curr Opin Pharmacol.* (2008) 8:14–9. doi: 10.1016/j.coph.2007.10.013
50. Pompili M, Venturini P, Palermo M, Stefani H, Seretti ME, Lamis DA, et al. Mood disorders medications: predictors of nonadherence - review of the current literature. *Expert Rev Neurother.* (2013) 13:809–25. doi: 10.1586/14737175.2013.811976
51. Levy MJF, Boulle F, Steinbusch HW, van den Hove DLA, Kenis G, Lanfumey L. Neurotrophic factors and neuroplasticity pathways in the pathophysiology and treatment of depression. *Psychopharmacology.* (2018) 235:2195–220. doi: 10.1007/s00213-018-4950-4

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Cognitive Function Mediates the Anti-suicide Effect of Repeated Intravenous Ketamine in Adult Patients With Suicidal Ideation

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Objective: Prior research has shown that ketamine has anti-suicide effects. Additional evidence also suggests that ketamine may offer pro-cognitive effects. Herein, we propose that the anti-suicide effects of ketamine are partially mediated *via* pro-cognitive effects. We aimed to determine whether improvement in cognitive function mediated change in suicidal ideation was associated with ketamine treatment.

Methods: Unipolar or bipolar depressive patients (n = 86) with suicidal ideation received six infusions of ketamine (0.5 mg/kg) over 2 weeks. The current severity of suicidal ideation and depression symptoms were assessed with the Beck Scale for Suicide Ideation (SSI) and the Montgomery–Asberg Depression Rating Scale (MADRS), respectively, at baseline, days 13 and 26. Cognitive domains, including processing speed, working memory, visual learning, and verbal learning were measured with the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) Consensus Cognitive Battery at the same time points.

Results: Mediation analysis showed a significant total effect of ketamine treatment on SSI score (coef = –1.853, 95%CI [–2.2, –1.5]). The direct and total indirect (MADRS total score and any of cognitive domains) effects of ketamine on suicidal ideation both were statistically significant (direct: coef = –1.064 to –1.352; total indirect: coef = –0.501 to –0.788). MADRS total score and processing speed (but not other cognitive domains) were significant partial mediators of the association between ketamine treatment and improvements in suicidal ideation.

Conclusion: Depressive symptoms severity and processing speed performance partially mediated improvements in suicidal ideation after repeated ketamine infusions in persons with unipolar or bipolar depressive disorder.

Keywords: suicidal ideation, ketamine, depression, processing speed, cognition

INTRODUCTION

Suicide is a serious mental health problem with the number of global suicide mortality of over 800,000 per year and suicide attempts of around 16 million per year (1). Mental disorders are the most frequent diagnoses of suicidal behavior, notably depression (2). Currently, treatment options to improve aspects of suicidality are limited. Conventional interventions including antidepressants, cognitive behavioral therapy, and electroconvulsive therapy, are reported to reduce suicidal ideation and behavior in persons with depression, but this effect takes weeks, leaving a considerable proportion of patients suffering from suicide risk for a long time (3, 4). Moreover, only lithium has demonstrated the ability to lower suicide completion in persons with mood disorders (5).

Fortunately, in the past two decades, numerous RCTs have confirmed ketamine, a glutamate N-methyl-D-aspartate (NMDA) receptor antagonist, has rapid-onset antidepressant effects (6–10). Replicated evidence also indicates that ketamine can rapidly reduce aspects of suicidality (11–17). Suicidal ideation reductions typically manifest within a few hours, and some patients respond as soon as 40 min after the initial infusion (11–17). Currently, nasal esketamine, the S-enantiomer of ketamine has been approved by Food and Drug Administration for the treatment of depressive symptoms in adults with major depressive disorder (MDD) with acute suicidal ideation or behavior (18–20).

Most clinical studies showed a significant decrease in suicidal ideation and overall depressive symptom severity simultaneously following ketamine treatment, suggesting the ketamine's antisuicide effects are, to a certain extent, mediated by the improvements in overall depressive symptom severity (11, 14). However, Ionescu et al. in an open-label ketamine trial observed a significant decrease in suicidal ideation following six ketamine infusions. The anti-suicide effects approached significance after controlling for total depressive symptom severity, indicating the ketamine's anti-suicide effects were independent of the antidepressant effects (13). There is a need to determine whether ketamine's anti-suicide effects are dissociable from its antidepressive effects.

In addition, cognitive dysfunction is recognized a core symptom in depression (21), and the potential pro-cognitive effects in the domains of working memory, visual learning memory, and processing speed with ketamine in treatment-resistant depression (TRD) is suggested by the recent reports (22–25). Our previous study assessed the cognitive effect of six infusions of ketamine in adults with TRD and/or suicidal ideation, and simple improvements in processing speed and verbal learning were observed 1 day following six infusions of ketamine (23). Currently, studies have suggested a close association between vulnerability to suicidal behavior and cognitive alterations (26–28). Deficits in executive function, working memory, decision-making, and impulsivity were associated with current or/and histories of suicidal ideation/behavior in patients with MDD (26–28). Altered value-based and cognitive control processes may be important factors of suicidal vulnerability (29). Available evidence suggests underlying the suicidal processing and help to identify the target of therapeutic interventions aimed at reducing the long-term risk of suicidal acts.

Relatively few studies have evaluated the mediational role of cognition in suicidality in persons with mood disorders. We observed previously that improvements in working memory were associated with anti-suicide outcomes after repeated ketamine infusions in depressed patients with baseline suicidal ideation (30). The foregoing observation supports the previous hypothesis that the anti-suicide effects of ketamine are mediated, in part *via* pro-cognitive effects (30).

However, our previous study takes no account of the effect of improvements in depressive symptoms on the anti-suicide effects following ketamine treatment and lacks the result of other cognitive domains except working memory. Herein, we sought to determine whether improvements in depressive symptoms and/or cognition mediated change in suicidal ideation in adult patients received six sub-anesthetic doses of ketamine, and examine predictors of ketamine's anti-suicide effects.

MATERIALS AND METHODS

Participants and Study Design

The present data were obtained from a larger single-center open label study comprising a total of 136 adults patients with MDD or bipolar depressive disorder received six sub-anesthetic doses of ketamine (23, 31). This study was approved by the Clinical Research Ethics Committee of the Affiliated Brain Hospital of Guangzhou Medical University and is registered on Chinese Clinical Trial Registry under the identifier ChiCTR-OOC-17012239.

Eligibility criteria and treatment protocol have been outlined previously (23, 31). Briefly, all the subjects were adults (age $\geq$ 18 years) male or female with a diagnosis of MDD or bipolar disorder supported by the Diagnostic and Statistical Manual of Mental Disorders (DSM-5.0) criteria; moderate-to-severe depressive symptom severity assessed by the 17-item Hamilton Depression Rating Scale (HAMD-17, total scores $\geq$ 17); and with a suicidal tendency confirmed by a Beck Scale for Suicide Ideation (SSI) part I score $\geq$ 2 at screening. Participants were excluded if they had a presence of alcohol or substance dependence or any serious or unstable medical conditions identified through physical examination, vital signs, weight, electrocardiogram, blood tests, and urinalysis. Participants were also excluded if had psychotic symptoms or bipolar depressive patients had a mania or hypomania episode in the preceding 6 months.

All the participants received six infusions of intravenous ketamine (0.5 mg/kg) over 2 weeks (infusion on Monday-Wednesday-Friday). Ketamine was administered as an adjunctive to current psychotropic medications which were required to maintain the same dose during the 2-week period. Ketamine hydrochloride injection mixed with 0.9% sodium chloride injections was administered by IV pump over 40 min by a study physician and research nurse. Vital signs (blood pressure, pulse, and oxygen saturation) were monitored throughout the infusion

and post-infusion to ensure a return to pre-infusion levels. Additional detailed information regarding these participants has been described in our previous studies (23, 31).

Measurements

Depressive symptoms, suicidal ideation, and cognitive function were assessed at baseline, 1 day following the sixth infusion (i.e., day 13), and again 14 days following the sixth infusion (i.e., day 26). The Montgomery–Asberg Depression Rating Scale (MADRS) was used to characterize depressive symptoms by clinicians. The total scores range 0–60 and higher scores indicated more severe depressive symptom (32). Current severity of suicidal ideation was assessed *via* the SSI part I, a 5-item scale rating from 0 (least severe) to 2 (most severe) and score range 0–10 (33). Cognitive function was assessed with the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) Consensus Cognitive Battery (MCCB) (34). There were seven cognitive domains in the MCCB, but four of them, including processing speed [using the Category Fluency test, Trail Making A test, and Brief Assessment of Cognition in Schizophrenia (BACS)], working memory [using WAIS-III, letter–number sequencing (LNS) subtest, WMS-III, Spatial Span], visual learning (using Brief Visuospatial Memory Test-Revised, BVMT-R), and verbal learning (using Hopkins Verbal Learning Test-Revised, HVLT-R) were selected in the study. Each domain score was standardized to a T score with a mean of 50 and a standard deviation of 10.

Statistical Analyses

Data were analyzed with IBM Statistical Package for the Social Sciences (SPSS) statistical software for Windows, version 22. All the tests were two-sided with statistical significance at $p < 0.05$. Change in MADRS total score, SSI score, and the four cognitive domain performance following ketamine treatment was assessed using a linear mixed model with measurement point (i.e., baseline, days 13 and 26) as factors. The patients' characteristics including age, gender, education, duration of illness, body mass index (BMI), and concomitant medications (combined use of mood stabilizer/benzodiazepine/antipsychotic or not, and use of one or two antidepressants) were included as covariates.

Then, mediation analysis using the process v2.15 in SPSS was used to investigate whether overall depressive symptom and cognitive function mediated the anti-suicide effect in patients following six ketamine infusions. In this model measurement point (i.e., baseline, days 13 and 26) was the independent variable (X), anti-suicide effect (i.e., SSI score) was the dependent variable (Y), depressive symptom severity (i.e., MADRS total score) was the first mediator (M1), and cognitive function (i.e., processing speed, working memory, visual learning, verbal learning T score) was the second mediator (M2). Patients' characteristics, including age, gender, education, duration of illness, BMI, primary diagnosis, and concomitant medications (combined use of mood stabilizer/benzodiazepine/antipsychotic or not, and use of one or two antidepressants) were treated as covariates. Unstandardized beta coefficients (Coef) and *P*-value are reported.

Finally, a binomial logistic regression using forward LR method was completed to determine the effect of baseline cognitive function, depressive symptom severity, and suicidal ideation on the likelihood patients would achieve responder/remitter outcome to six infusions of ketamine, controlling of the foregoing patients' characteristics. Responders were defined as a 50% or greater decrease in SSI score compared with baseline. Remitters were classified as patients who had a score of zero on the SSI at day 13.

TABLE 1 | Baseline demographic characteristics of patients (n = 86).

Variables	*N*	%
Gender (male)	39	45.3
Employment status (working)	46	53.5
Smoking	16	18.6
Diagnosis (MDD)	66	76.7
Psychiatric comorbidity (yes)①	14	16.3
Having family history of psychiatric disorders	31	36.0
Previous hospitalization (yes)②	25	29.1
Current pharmacotherapies		
At least 1 antidepressant③	86	100
≥ 2 antidepressant	16	18.6
Mood stabilizer④	25	29.1
Benzodiazepine⑤	40	46.5
Antipsychotic⑥	45	52.3
	Mean	***SD***
Age (years)	33.5	11.2
Education (years)	12.6	3.2
Duration of illness (months)	102.5	89.3
Body mass index (kg/m^2)	22.6	3.5
Dose of antidepressant (mg/day)⑦	38.1	21.0

MDD, Major Depressive Disorder.
①Comorbidity of an Axis I anxiety disorder, obsessive-compulsive disorder, phobia, or panic disorder.
②Previous hospitalization due to mental health problems.
③25 Escitalopram (10–20 mg/day), 12 Duloxetine (60–120 mg/day), 5 Fluvoxamine (150–300 mg/day), 6 Fluoxetine (20–40 mg/day), 11 Paroxetine (20–60 mg/day), 11 Sertraline (100–200 mg/day), 16 Venlafaxine (75–300 mg/day).
④6 Lithium carbonate (300–1,200 mg/day), 7 Lamotrigine (25–250 mg/day), 12 Valproate (1,000–1,500 mg/day).
⑤12 Lorazepam (1–4 mg/day), 9 Alprazolam (0.2–0.8 mg/day), 14 Oxazepam (15–30 mg/day), 5 Estazolam (1–2 mg/day).
⑥20 Olanzapine (2.5–20 mg/day), 11 Quetiapine (100–800 mg/day), 2 Risperidone (4 mg/day), 10 Ziprasidone (40–80 mg/day), 2 Amisulpride (600 mg/day).
⑦Fluoxetine equivalent dose.

RESULTS

Demographic and Clinical Characteristics

The project included 104 MDD or bipolar depression with suicidal ideation received ketamine treatment, and 86 of them received six infusions and completed MADRS, SSI, and MCCB at baseline and day 13 whose data were included in this study. In total, 11.6% of them (N = 10) failed to complete the final visit (day 26). Demographic and clinical characteristics are reported in **Table 1**.

Mixed Model and Mediation Results

Six infusions of ketamine were significantly associated with reductions in SSI score and MADRS total score, which have

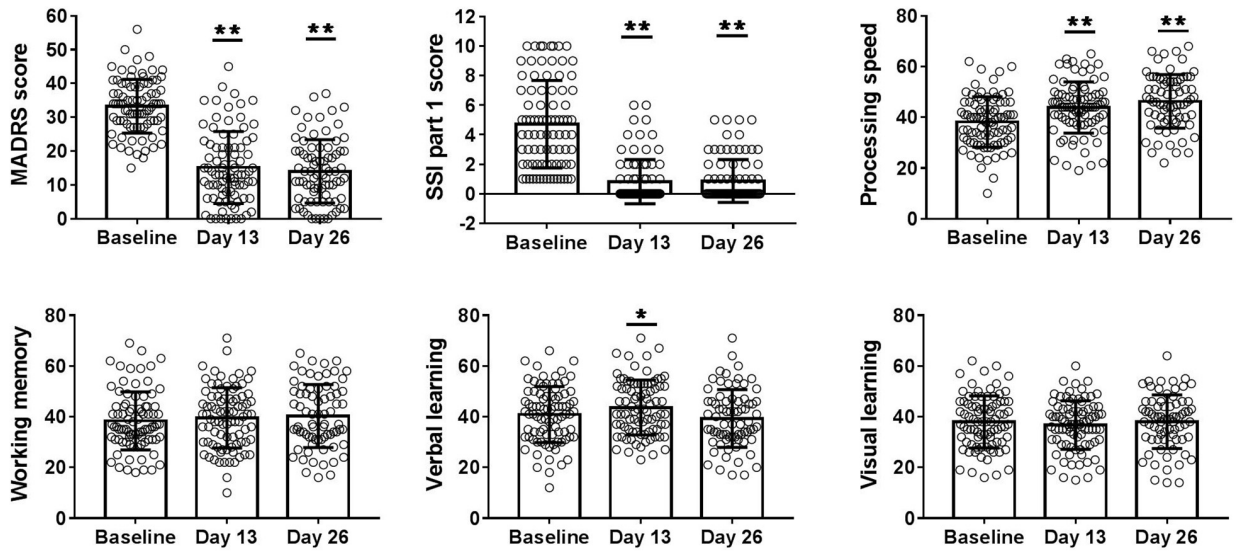

FIGURE 1 | Overall change in MADRS score, SSI part 1 score, T score of processing speed, working memory, visual learning, and verbal learning from baseline to days 13 and 26. A main effect of ketamine treatment was observed in depressive symptoms, suicide ideation, processing speed, and verbal learning performance. MADRS, Montgomery-Asberg Depression Rating Scale; SSI part 1, the first five items of Beck Scale for Suicide Ideation. $^{*}P < 0.05$, $^{**}P < 0.001$. All *p*-values represent the results of retrospective analyses compared with baseline.

been reported previously. There was a significant main effect of ketamine treatment on SSI score (baseline: 4.7 ± 3.0; day 13: 0.9 ± 1.9; day 26: 1.0 ± 1.9; $F = 79.643$, $P < 0.001$; **Figure 1**), indicating that six infusions of ketamine were significantly associated with improvement in suicide ideation. The mean MADRS score significantly decreased from baseline (33.2 ± 7.9) to day 13 (15.2 ± 10.6) and day 26 (14.0 ± 9.4), denoting significant improvement in depressive symptom ($F = 173.769$, $P < 0.001$; **Figure 1**).

Overall change in cognitive function across six infusions of ketamine is presented in **Figure 1**. The mean T score of processing speed (baseline: 38.4 ± 10.4; day 13: 44.1 ± 10.8; day 26: 46.1 ± 12.1; $F = 28.537$, $P < 0.001$) and verbal learning (baseline: 40.9 ± 11.0; day 13: 43.0 ± 11.8; day 26: 39.3 ± 11.4; $F = 4.283$, $P = 0.015$) significantly increased from baseline to days 13 and 26, denoting significant improvements in these domains of cognitive performance. However, no significant improvement in working memory (baseline: 38.4 ± 11.5; day 13: 39.5 ± 11.9; day 26: 40.3 ± 12.5; $F = 1.950$, $P = 0.146$) and visual learning (baseline: 37.9 ± 10.3; day 13: 36.7 ± 9.6; day 26: 38.1 ± 10.6; $F = 0.876$, $P = 0.418$) was found in the linear mixed models.

Path analysis was conducted to explore whether improvements in overall depressive symptom severity and cognition acted as the mediator between the ketamine treatment and improvements in suicidal ideation. There was a significant total effect of ketamine treatment on SSI score (coef = –1.853, 95%CI [–2.2, –1.5]). The direct and total indirect effects of ketamine on suicidal ideation both were statistically significant: processing speed as M2 (direct: coef = –1.064, 95%CI [–1.5, –0.6]; total indirect: coef = –0.788, 95%CI [–1.2, –0.4]), working memory as M2 (direct: coef = –1.270, 95%CI [–1.8, –0.8]; total indirect: coef = –0.583, 95%CI [–1.0, –0.2]), verbal learning as M2 (direct: coef = –1.352, 95%CI [–1.8, –0.9]; total indirect: coef = –0.501, 95%CI [–0.9, –0.1]), and visual learning as M2 (direct: coef = –1.300, 95%CI [–1.8, –0.8]; total indirect: coef = –0.552, 95%CI [–0.9, –0.2]). MADRS total score and processing speed T score were significant partial mediators of the relationship between ketamine treatment and improvements in suicidal ideation, however, the foregoing effect was not demonstrated in measures of working memory, verbal learning, or visual learning (**Table 2** and **Figure 2**).

Binomial Logistic Regression Results

The response rate on the SSI at day 13 was 80.2%, and remission rate was 64.0%. In the binomial logistic regression model of responder outcome, when the four baseline cognitive domains were included as independent variables, baseline speed processing was the only variable that predicted achieving an anti-suicide response to six infusions of ketamine ($B = 0.062$, $P = 0.028$). When baseline MADRS score and SSI score, as well as the four baseline cognitive domains were included as independent variables simultaneously in the responder outcome model, the statistical results did not change, baseline processing speed still was the only significant predictor of the anti-suicide response ($B = 0.062$, $P = 0.028$). In the binomial logistic regression model of remitter outcome, when the four baseline cognitive domains were included as independent variables, only baseline processing speed was a significant predictor of remission ($B = 0.075$, $P = 0.004$). When baseline MADRS score and SSI score, as well as the four baseline cognitive domains were included as independent variables simultaneously in the remitter outcome model, baseline SSI score was a significant predictor of remission ($B = –0.275$, $P = 0.001$), while baseline speed processing was excluded in the model.

TABLE 2 | Mediation effects of depressive symptom and cognition on changes in suicidal ideation across treatment.

Parameter	Coef	SE	LLCI	ULCI
Total effect of ketamine on SSI	−1.853	0.202	−2.249	−1.457
Processing speed was M2				
Total direct effect of ketamine on SSI	−1.064	0.241	−1.539	−0.590
Total indirect effect of ketamine on SSI	−0.788	0.199	−1.198	−0.399
Ketamine → MADRS → SSI	−0.528	0.176	−0.856	−0.169
Ketamine → MADRS → Processing speed → SSI	−0.078	0.043	−0.168	−0.001
Ketamine → Processing speed → SSI	−0.182	0.091	−0.401	−0.034
Working memory was M2				
Total direct effect of ketamine on SSI	−1.270	0.248	−1.758	−0.781
Total indirect effect of ketamine on SSI	−0.583	0.191	−0.976	−0.214
Ketamine → MADRS → SSI	−0.559	0.184	−0.935	−0.196
Ketamine → MADRS → Working memory → SSI	−0.047	0.031	−0.130	−0.005
Ketamine → Working memory → SSI	0.023	0.040	−0.031	0.144
Verbal learning was M2				
Total direct effect of ketamine on SSI	−1.352	0.243	−1.831	−0.873
Total indirect effect of ketamine on SSI	−0.501	0.195	−0.882	−0.116
Ketamine → MADRS → SSI	−0.538	0.182	−0.908	−0.201
Ketamine → MADRS → Verbal learning → SSI	−0.068	0.040	−0.160	−0.008
Ketamine → Verbal learning → SSI	0.105	0.070	−0.001	0.267
Visual learning was M2				
Total direct effect of ketamine on SSI	−1.300	0.250	−1.792	−0.809
Total indirect effect of ketamine on SSI	−0.552	0.187	−0.908	−0.191
Ketamine → MADRS → SSI	−0.551	0.184	−0.895	−0.193
Ketamine → MADRS → Visual learning → SSI	−0.055	0.035	−0.146	−0.001
Ketamine → Visual learning → SSI	0.054	0.041	−0.003	0.177

MADRS, Montgomery-Asberg Depression Rating Scale; SSI, Beck Scale for Suicide Ideation; M2, the second mediator.

DISCUSSION

Herein, we observed six infusions of ketamine in unipolar or bipolar depressive disorders with suicidal ideation were associated with improved mood, suicidal ideation, and cognitive function (i.e., processing speed, verbal learning). Mediational analysis indicated that the anti-suicide effects were partially mediated by improvements in depressive symptom and processing speed. The mediational effect of working memory, verbal learning, or visual learning on the change in SSI was not statistically significant. Herein, we speculate that for some individuals, ketamine's anti-suicide effects may be subserved by improvements in processing speed. Baseline processing speed was a significant predictor of anti-suicide effect, indicating greater baseline processing speed performance was associated with an increase likelihood of achieving anti-suicide effect over six ketamine infusions.

Cognitive function in mood disorder can be broadly categorized as cold cognition and hot cognition. The former refers to information processing in the absence of any emotional influence, yet the latter is influenced by emotion (35). Usually, cold cognition is considered to include memory, attention, executive function, working memory while hot cognition includes catastrophic reactions to real and/or perceived slights, anhedonia, suicidal ideation, negativistic rumination, negative recall bias, and disproportionate attention to negative stimuli (36). Over the past years, an increasing number of literatures have established that cognitive deficits are closely related to suicidality (26–28). In subgroups of individuals with suicidal ideation and behavior represent deficits in cognitive function (i.e., executive function, impulsivity, attention) (26–28). A conceptual framework of cognitive function in mood disorder was provided by McIntyre and colleagues in a review indicating implicit suicidal ideation as a domain of hot cognition (35). These give us indication that improvements in cognitive function may be closed to the anti-suicide effect by the antidepressant treatment, with no exception to ketamine.

The hot and cold cognitive functions could benefit from subanesthetic dose of ketamine. Ketamine's benefit on hot cognition is embodied in the improvement in suicidal ideation, anhedonia, and overall mood symptoms (7, 9, 14, 37). Furthermore, ketamine's enhancement in positive bias and decline in negative emotional perception in MDD further supports its favorable effect on hot cognition (38). The cold cognition benefit is implicated by improvement in working memory, visual memory, and processing speed after ketamine treatment, although some studies reported it was mediated by depressive symptom improvement (22–25).

Our results suggested that repeated ketamine infusions have a pro-cognitive effect independent of decrease in depression severity. Mediational analysis indicated that the improvement in the processing speed was partly independent of decrease in the MADRS score, and the direct effect (coef = 2.732) was greater than the indirect effect (coef = $-0.118 \times -9.968 = 1.220$). The foregoing is in accordance with the results of two other studies with repeated ketamine infusions. McIntyre et al. reported improvement in Trail Making Test-B, measurement processing speed and executive function, was fully independent of improvement in depressive symptom after four infusions in individuals with MDD and bipolar depression (25). Shiroma et al. (24) observed a mood independent pro-cognitive effect on processing speed, attentional set-shifting and spatial working memory among patients with TRD following six doses of ketamine treatment (24).

The results of mediation analysis suggested that the specific effect of ketamine on suicidal ideation also was positively related to pro-cognitive effect. In addition, the present results showed ketamine's specific decrease in suicidal ideation was larger in individuals with greater processing speed at baseline. In a randomized controlled trial of a single infusion of ketamine, Price et al. reported patients with higher severity of baseline suicidal cognition manifest greater anti-suicide effects, which were partly mediated by a decrease in non-suicide-related depressive symptom (11).

In a naturalistic follow-up study of participants with suicidal ideation found that better cognitive flexibility, assessed by the Wisconsin Card Sorting Test which also reflected executive function, predicted less suicidal ideation after 6 months (39). Our previous clinical study found early increase in levels of kynurenic acid, an NMDA receptor agonist leading to neuroprotection by elevation of extracellular glutamate, could predict anti-suicide response following six infusions of ketamine treatment (40). This is partially supported that patients who have a higher intrinsic "restorative" capacity of neuronal plasticity may be more likely to benefit from ketamine.

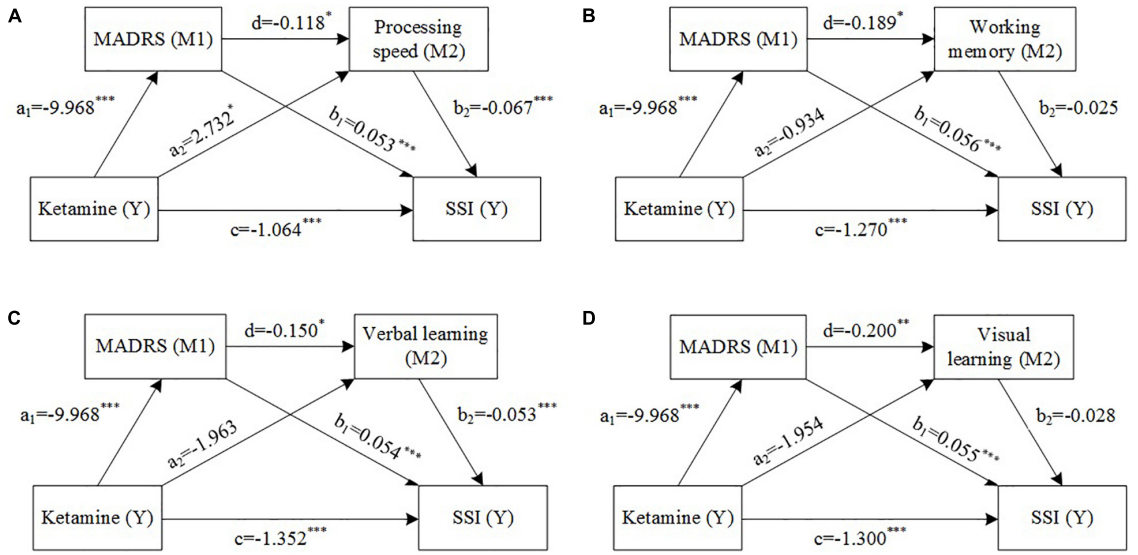

FIGURE 2 | Mediation models with depressive symptom severity (M1) and cognition [M2, **(A)** processing speed, **(B)** working memory, **(C)** visual learning, **(D)** verbal learning] as mediators between ketamine treatment and suicide ideation. Estimated path coefficients are referred to **(A–D)**. $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$.

In addition, the neuromechanism of ketamine on brain may be involved in the relationship between its pro-cognitive effects and anti-suicide as well as antidepressant effects. Ketamine as an NMDA receptor agonist has a unique mechanism of action involving glutamate modulation *via* increased NMDA and α-amino- 3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor throughput, leading to potentiation of BDNF and mechanistic target of rapamycin (mTOR) signaling pathways, and these finally contribute to the augmented synaptogenesis and synapse stabilization (41, 42). Ketamine's glutamatergic modulation of numerous brain regions and neural circuits, as shown in neuroimaging studies, was considered to involve in its antidepressant and anti-suicide action, and also pro-cognitive effect (43–46). The prefrontal cortex (PFC) global connectivity could be normalized in responders and the extent of the PFC global connectivity increase was associated with response after a single dose of ketamine (43, 44). Another study found increased hippocampal volumes and decreased nucleus accumbens volumes 24 h post-single dose of ketamine (45). Our previous study also showed increased volumes of the left amygdale and the right hippocampus after six infusions of ketamine (46). These brain regions and neural circuits correlated to ketamine's treating response also involve hot and cold cognitive functions in patients with MDD, as mentioned in the previous study (36). Herein, we propose that ketamine's antidepressant effects are mediated, in part, by targeting neural circuits that subserve the relevant to cognitive processing and emotional processing (35). It stands to reason that given ketamine's known effect on neural structures and functions, its anti-suicide effects may be in part *via* pro-cognitive effects. The results from this study provide some clues for future work aimed to understand the neural mechanism for the effect of ketamine on suicidal ideation, and these evidences augmented with neuroimaging would be an important pathway for future work.

The present findings should be considered the following limitations. First, the results were obtained from a single arm open label study without a control arm. This may introduce expectation bias both to assessments from the clinician and patients. Second, several lines of evidence suggested that executive function, particularly the decision-making was related to suicidality. Decision-making performance was measured usually using the Iowa Gambling Task (IGT), and poorly performed by patients with current or history of suicide attempt/ideation was observed compared with the healthy controls (28, 29). This study only assessed four cognitive domains, although the Category Fluency test, Trail Making A test, and BACS could well reflect the executive function, lack of decision-making tasks was a significant limitation to describe a complete association between cognition and suicidal ideation. This limitation led to an incomplete relationship between cognitive function and anti-suicide effects of ketamine. Third, patients with severe suicidal ideation or suicidal behavior were excluded for safety reason, therefore, making it difficult to generalize present results to that population. Thus, our findings should not be extrapolated to outcomes of suicidal behavior, particularly attempted or completed suicide. Fourth, all subjects were taking their prior prescribed medications, including benzodiazepine, lithium, and antipsychotics, which may moderate changes in cognition. While changes to medication were not permissible during the study, the effect of psychiatric medication could confuse the observed outcomes. Therefore, the current findings could not be extrapolated to medication-free patients. An additional limitation is we were looking at reduction in suicidal ideations future studies should be looking at reductions in suicide and we do not know if reductions in suicidal ideations would necessarily predict reduction in suicide.

CONCLUSION

The present results provide insights into potential moderators and psychological mechanisms of ketamine's anti-suicide effects, which are associated with pro-cognitive effects. Further study is warranted to explore the mechanisms underpinning ketamine's anti-suicide effects which might reflect glutamate-mediated synaptogenesis and neural circuits serving cognitive function. Future research should also endeavor to combine ketamine with psychosocial strategies (e.g., cognitive behavioral therapy) to determine whether there's a more robust improvement in measures of suicidality and cognitive function.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Clinical Research Ethics Committee of The Affiliated Brain Hospital of Guangzhou Medical University. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

YZ, YN, and RM developed research hypothesis and study design. YZ conducted data analysis and wrote the final draft of the manuscript. CW, XL, WL, KW, and ZC involved with data collection. All authors contributed to the final manuscript proofreading, edits, and approval for submission.

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REFERENCES

1. World Health Organization [WHO]. *Preventing Suicide: A Global Imperative*. Geneva: World Health Organization (2014).
2. Bachmann S. Epidemiology of suicide and the psychiatric perspective. *Int J Environ Res Public Health.* (2018) 15:1425. doi: 10.3390/ijerph15071425
3. Ballard ED, Snider SL, Nugent AC, Luckenbaugh DA, Park L, Zarate CA Jr. Active suicidal ideation during clinical antidepressant trials. *Psychiatry Res.* (2017) 257:303–8. doi: 10.1016/j.psychres.2017.07.065
4. D'Anci KE, Uhl S, Giradi G, Martin C. Treatments for the prevention and management of suicide: a systematic review. *Ann Intern Med.* (2019) 171:334–42. doi: 10.7326/M19-0869
5. McIntyre RS, Berk M, Brietzke E, Goldstein BI, López-Jaramillo C, Kessing LV, et al. Bipolar disorders. *Lancet.* (2020) 396:1841–56. doi: 10.1016/S0140-6736(20)31544-0
6. aan het Rot M, Collins KA, Murrough JW, Perez AM, Reich DL, Charney DS, et al. Safety and efficacy of repeated-dose intravenous ketamine for treatment-resistant depression. *Biol Psychiatry.* (2010) 67:139–45. doi: 10.1016/j.biopsych.2009.08.038
7. Murrough JW, Iosifescu DV, Chang LC, Al Jurdi RK, Green CE, Perez AM, et al. Antidepressant efficacy of ketamine in treatment-resistant major depression: a two-site randomized controlled trial. *Am J Psychiatry.* (2013) 170:1134–42. doi: 10.1176/appi.ajp.2013.13030392
8. Murrough JW, Perez AM, Pillemer S, Stern J, Parides MK, aan het Rot M, et al. Rapid and longer-term antidepressant effects of repeated ketamine infusions in treatment-resistant major depression. *Biol Psychiatry.* (2013) 74:250–6. doi: 10.1016/j.biopsych.2012.06.022
9. Singh JB, Fedgchin M, Daly EJ, De Boer P, Cooper K, Lim P, et al. A double-blind, randomized, placebo-controlled, dose-frequency study of intravenous ketamine in patients with treatment-resistant depression. *Am J Psychiatry.* (2016) 173:816–26. doi: 10.1176/appi.ajp.2016.16010037
10. McIntyre RS, Rosenblat JD, Nemeroff CB, Sanacora G, Murrough JW, Berk M, et al. Synthesizing the evidence for ketamine and esketamine in treatment-resistant depression: an international expert opinion on the available evidence and implementation. *Am J Psychiatry.* (2021) 178:383–99. doi: 10.1176/appi.ajp.2020.20081251
11. Price RB, Iosifescu DV, Murrough JW, Chang LC, Al Jurdi RK, Iqbal SZ, et al. Effects of ketamine on explicit and implicit suicidal cognition: a randomized controlled trial in treatment-resistant depression. *Depress Anxiety.* (2014) 31:335–43. doi: 10.1002/da.22253
12. Murrough JW, Soleimani L, DeWilde KE, Collins KA, Lapidus KA, Iacoviello BM, et al. Ketamine for rapid reduction of suicidal ideation: a randomized controlled trial. *Psychol Med.* (2015) 45:3571–80. doi: 10.1017/S0033291715001506
13. Ionescu DF, Swee MB, Pavone KJ, Taylor N, Akeju O, Baer L, et al. Rapid and sustained reductions in current suicidal ideation following repeated doses of intravenous ketamine: secondary analysis of an open-label study. *J Clin Psychiatry.* (2016) 77:e719–25. doi: 10.4088/JCP.15m10056
14. Grunebaum MF, Galfalvy HC, Choo TH, Keilp JG, Moitra VK, Parris MS, et al. Ketamine for rapid reduction of suicidal thoughts in major depression: a midazolam-controlled randomized clinical trial. *Am J Psychiatry.* (2018) 175:327–35. doi: 10.1176/appi.ajp.2017.17060647
15. Zhan Y, Zhang B, Zhou Y, Zheng W, Liu W, Wang C, et al. A preliminary study of anti-suicidal efficacy of repeated ketamine infusions in depression with suicidal ideation. *J Affect Disord.* (2019) 251:205–12. doi: 10.1016/j.jad.2019.03.071
16. McIntyre RS, Rodrigues NB, Lee Y, Lipsitz O, Subramaniapillai M, Gill H, et al. The effectiveness of repeated intravenous ketamine on depressive symptoms, suicidal ideation and functional disability in adults with major depressive

disorder and bipolar disorder: Results from the Canadian Rapid Treatment Center of Excellence. *J Affect Disord.* (2020) 274:903–10. doi: 10.1016/j.jad.2020.05.088

17. Feeney A, Hock RS, Freeman MP, Flynn M, Hoeppner B, Iosifescu DV, et al. The effect of single administration of intravenous ketamine augmentation on suicidal ideation in treatment-resistant unipolar depression: Results from a randomized double-blind study. *Eur Neuropsychopharmacol.* (2021) 49:122–32. doi: 10.1016/j.euroneuro.2021.04.024
18. Canuso CM, Singh JB, Fedgchin M, Alphs L, Lane R, Lim P, et al. Efficacy and safety of intranasal esketamine for the rapid reduction of symptoms of depression and suicidality in patients at imminent risk for suicide: results of a double-blind, randomized, placebo-controlled study. *Am J Psychiatry.* (2018) 175:620–30. doi: 10.1176/appi.focus.17105
19. Fu DJ, Ionescu DF, Li X, Lane R, Lim P, Sanacora G, et al. Esketamine nasal spray for rapid reduction of major depressive disorder symptoms in patients who have active suicidal ideation with intent: double-blind, randomized study (ASPIRE I). *J Clin Psychiatry.* (2020) 81:19m13191. doi: 10.4088/JCP.19m13191
20. Xiong J, Lipsitz O, Chen-Li D, Rosenblat JD, Rodrigues NB, Carvalho I, et al. The acute antisuicidal effects of single-dose intravenous ketamine and intranasal esketamine in individuals with major depression and bipolar disorders: a systematic review and meta-analysis. *J Psychiatr Res.* (2021) 134:57–68. doi: 10.1016/j.jpsychires.2020.12.038
21. McIntyre RS, Cha DS, Soczynska JK, Woldeyohannes HO, Gallaugher LA, Kudlow P, et al. Cognitive deficits and functional outcomes in major depressive disorder: determinants, substrates, and treatment interventions. *Depress Anxiety.* (2013) 30:515–27. doi: 10.1002/da.22063
22. Shiroma PR, Albott CS, Johns B, Thuras P, Wels J, Lim KO. Neurocognitive performance and serial intravenous subanesthetic ketamine in treatment-resistant depression. *Int J Neuropsychopharmacol.* (2014) 17:1805–13. doi: 10.1017/S1461145714001011
23. Zhou Y, Zheng W, Liu W, Wang C, Zhan Y, Li H, et al. Neurocognitive effects of six ketamine infusions and the association with antidepressant response in patients with unipolar and bipolar depression. *J Psychopharmacol.* (2018) 32:1118–26. doi: 10.1177/0269881118798614
24. Shiroma PR, Thuras P, Wels J, Albott CS, Erbes C, Tye S, et al. Neurocognitive performance of repeated versus single intravenous subanesthetic ketamine in treatment resistant depression. *J Affect Disord.* (2020) 277:470–7. doi: 10.1016/j.jad.2020.08.058
25. McIntyre RS, Rosenblat JD, Rodrigues NB, Lipsitz O, Chen-Li D, Lee JG, et al. The effect of intravenous ketamine on cognitive functions in adults with treatment-resistant major depressive or bipolar disorders: Results from the Canadian rapid treatment center of excellence (CRTCE). *Psychiatry Res.* (2021) 302:113993. doi: 10.1016/j.psychres.2021.113993
26. Richard-Devantoy S, Berlim MT, Jollant F. A meta-analysis of neuropsychological markers of vulnerability to suicidal behavior in mood disorders. *Psychol Med.* (2014) 44:1663–73. doi: 10.1017/S0033291713002304
27. Richard-Devantoy S, Berlim MT, Jollant F. Suicidal behaviour and memory: a systematic review and meta-analysis. *World J Biol Psychiatry.* (2015) 16:544–66. doi: 10.3109/15622975.2014.925584
28. Alacreu-Crespo A, Guillaume S, Sénèque M, Olié E, Courtet P. Cognitive modelling to assess decision-making impairments in patients with current depression and with/without suicide history. *Eur Neuropsychopharmacol.* (2020) 36:50–9. doi: 10.1016/j.euroneuro.2020.04.006
29. Richard-Devantoy S, Olié E, Guillaume S, Bechara A, Courtet P, Jollant F. Distinct alterations in value-based decision-making and cognitive control in suicide attempters: toward a dual neurocognitive model. *J Affect Disord.* (2013) 151:1120–4. doi: 10.1016/j.jad.2013.06.052
30. Chen X, Wang M, Hu Y, Zhan Y, Zhou Y, Zheng W, et al. Working memory associated with anti-suicidal ideation effect of repeated-dose intravenous ketamine in depressed patients. *Eur Arch Psychiatry Clin Neurosci.* (2021) 271:431–8. doi: 10.1007/s00406-020-01221-z
31. Zheng W, Zhou YL, Liu WJ, Wang CY, Zhan YN, Li HQ, et al. Rapid and longer-term antidepressant effects of repeated-dose intravenous ketamine for patients with unipolar and bipolar depression. *J Psychiatr Res.* (2018) 106:61–8. doi: 10.1016/j.jpsychires.2018.09.013
32. Montgomery SA, Asberg M. A new depression scale designed to be sensitive to change. *Br J Psychiatry.* (1979) 134:382–9. doi: 10.1192/bjp.134.4.382
33. Beck AT, Kovacs M, Weissman A. Assessment of suicidal intention: the scale for suicide ideation. *J Consult Clin Psychol.* (1979) 47:343–52. doi: 10.1037//0022-006x.47.2.343
34. Nuechterlein KH, Green MF, Kern RS, Baade LE, Barch DM, Cohen JD, et al. The MATRICS Consensus Cognitive Battery, part 1: test selection, reliability, and validity. *Am J Psychiatry.* (2008) 165:203–13. doi: 10.1176/appi.ajp.2007.07010042
35. Lee Y, Syeda K, Maruschak NA, Cha DS, Mansur RB, Wium-Andersen IK, et al. A new perspective on the anti-suicide effects with ketamine treatment: a procognitive effect. *J Clin Psychopharmacol.* (2016) 36:50–6. doi: 10.1097/JCP.0000000000000441
36. Roiser JP, Sahakian BJ. Hot and cold cognition in depression. *CNS Spectr.* (2013) 18:139–49. doi: 10.1017/S1092852913000072
37. Lally N, Nugent AC, Luckenbaugh DA, Niciu MJ, Roiser JP, Zarate CA Jr. Neural correlates of change in major depressive disorder anhedonia following open-label ketamine. *J Psychopharmacol.* (2015) 29:596–607. doi: 10.1177/0269881114568041
38. Murrough JW, Collins KA, Fields J, DeWilde KE, Phillips ML, Mathew SJ, et al. Regulation of neural responses to emotion perception by ketamine in individuals with treatment-resistant major depressive disorder. *Transl Psychiatry.* (2015) 5:e509. doi: 10.1038/tp.2015.10
39. Miranda R, Gallagher M, Bauchner B, Vaysman R, Marroquín B. Cognitive inflexibility as a prospective predictor of suicidal ideation among young adults with a suicide attempt history. *Depress Anxiety.* (2012) 29:180–6. doi: 10.1002/da.20915
40. Zhou Y, Zheng W, Liu W, Wang C, Zhan Y, Li H, et al. Antidepressant effect of repeated ketamine administration on kynurenine pathway metabolites in patients with unipolar and bipolar depression. *Brain Behav Immun.* (2018) 74:205–12. doi: 10.1016/j.bbi.2018.09.007
41. Zanos P, Moaddel R, Morris PJ, Georgiou P, Fischell J, Elmer GI, et al. NMDAR inhibition-independent antidepressant actions of ketamine metabolites. *Nature.* (2016) 533:481–6. doi: 10.1038/nature17998
42. Matveychuk D, Thomas RK, Swainson J, Khullar A, MacKay MA, Baker GB, et al. Ketamine as an antidepressant: overview of its mechanisms of action and potential predictive biomarkers. *Ther Adv Psychopharmacol.* (2020) 10:2045125320916657. doi: 10.1177/2045125320916657
43. Abdallah CG, Averill CL, Salas R, Averill LA, Baldwin PR, Krystal JH, et al. Prefrontal connectivity and glutamate transmission: relevance to depression pathophysiology and ketamine treatment. *Biol Psychiatry Cogn Neurosci Neuroimaging.* (2017) 2:566–74. doi: 10.1016/j.bpsc.2017.04.006
44. Abdallah CG, Averill LA, Collins KA, Geha P, Schwartz J, Averill C, et al. Ketamine treatment and global brain connectivity in major depression. *Neuropsychopharmacology.* (2017) 42:1210–9. doi: 10.1038/npp.2016.186
45. Abdallah CG, Jackowski A, Salas R, Gupta S, Sato JR, Mao X, et al. The nucleus accumbens and ketamine treatment in major depressive disorder. *Neuropsychopharmacology.* (2017) 42:1739–46. doi: 10.1038/npp.2017.49
46. Zhou YL, Wu FC, Liu WJ, Zheng W, Wang CY, Zhan YN, et al. Volumetric changes in subcortical structures following repeated ketamine treatment in patients with major depressive disorder: a longitudinal analysis. *Transl Psychiatry.* (2020) 10:264. doi: 10.1038/s41398-020-00945-9

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Ketamine for Bipolar Depression: Biochemical, Psychotherapeutic, and Psychedelic Approaches

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Bipolar disorder (type 1) is a serious and chronic psychiatric illness that can be difficult to treat. Many bipolar patients have refractory depressive episodes. Racemic ketamine, a glutamate modulator with prominent dissociate and psychedelic properties, has been demonstrated to have rapid acting antidepressant and anti-obsessional effects which may be useful for treating the symptoms of bipolar depression. Most of the existing research literature on unipolar and bipolar depression has looked at racemic ketamine in the sub-psychedelic dose range given by infusion as a stand-alone treatment (without concurrent psychotherapy). This article expands on the existing research by articulating three different paradigms for ketamine treatment: biochemical, psychotherapeutic, and psychedelic. The authors use composite clinical vignettes to illustrate different ways of working with ketamine to treat bipolar depression, and discuss a variety of clinical considerations for using ketamine with this population, including route, dose, frequency, chemical mitigators, and adverse events. Note that the conceptual paradigms could be applied to any ketamine treatment, with broad applicability beyond bipolar treatment.

Keywords: bipolar, depression, intramuscular, ketamine, psychedelic, psychotherapy, racemic, suicidal

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INTRODUCTION

Bipolar disorder (type 1) is a serious and chronic mood disorder that affects nearly 3% of the population globally (1). It is associated with high rates of disability, suicidal ideation, and completed suicides (2). Conventional treatment for this population typically includes oral antidepressant and mood stabilizing or antipsychotic medication, and possibly anxiolytic or hypnotic medications (3). Even with these medications, many patients with bipolar disorder (type 1) struggle with refractory and recurrent depressive episodes (4). Further, the medications can cause bothersome side effects which interfere with patient compliance. In other words, the medications that are widely used at this time may not sufficiently meet the needs of these individuals (5).

Ketamine treatment may be helpful in addressing the unmet needs of patients who are living with bipolar disorder (type 1). Scientific studies have demonstrated that racemic ketamine is clinically effective in reducing the symptoms of bipolar depression (6, 7). It works rapidly, often taking effect in a matter of minutes. It is generally well tolerated and has a short half-life, which translates into fewer side effects than traditional antidepressant medications. Most of the existing research to date on the use of racemic ketamine for depression (unipolar and bipolar) has looked

at a sub-psychedelic dose of ketamine given by infusion as a stand-alone treatment, without concurrent psychotherapy [See (8) for a meta-analysis of previous research studies].

However, ketamine is a versatile tool which can be used in variety of ways (9). Here we articulate three paradigms for ketamine treatment: biochemical, psychotherapeutic, and psychedelic. The biochemical model focuses on the biological effects of the medication alone. The psychotherapeutic model utilizes ketamine as a lubricant for the psychotherapy process. The psychedelic model makes use of the prominent dissociative and psychedelic properties of ketamine to purposefully induce a temporary altered state of consciousness for psychospiritual exploration.

Using composite clinical vignettes, we illustrate the three approaches to ketamine treatment for refractory depression in patients with bipolar disorder (type 1). These composite cases are based on patients in our clinical practices (10, 11). We also describe a variety of clinical considerations for using ketamine with this population, including notes on route, dose, frequency, chemical mitigators, adverse events, etc. These observations were informed by our clinical practice, consultation with our colleagues, conference material, and patient reports, and should be viewed as preliminary observations from the field which necessitate further research.

CLINICAL VIGNETTES

Biochemical Paradigm

Alex was an artistic 21-year-old male college student with a slender build (6'4" and 180 lbs). He was diagnosed in childhood with Marfan Syndrome and aortic dilation which did not require surgery. Alex, who was studying architecture and art history, began struggling with periods of elation, risk-taking and withdrawn depression. He had several encounters with the local police due to disorderly conduct. Eventually he was diagnosed with bipolar disorder (type 1) by the psychiatrist at the university health center, and started on lithium and escitalopram.

During an intense period of immobilizing depression, Alex's parents brought him to our mental health clinic for consultation. He presented with severe depression including apathy, poverty of speech, and ruminative suicidal ideation without a specific plan. We assessed him and did some psychological preparation him, then we referred Alex to an anesthesiologist for ketamine treatment because of concerns about his cardiac health. Alex received six ketamine infusions (0.5 mg/kg per infusion) in a 3-week period, in addition to weekly psychotherapy. He reported that each ketamine infusion had some similarities to light alcohol intoxication. Alex began showing signs of improvement following the fifth infusion: he became more verbal and engaged in therapy and expressed a desire to complete his education. Alex continued in individual psychotherapy while he completed his senior year, where he worked on recognizing prodromal symptoms, eating and sleeping regularly, time management, and setting limits.

Psychotherapeutic Paradigm

Bijan was an ambitious 47-year-old male businessman (5'9" and 210 lbs). He had three children and was divorced. Bijan had been diagnosed with bipolar disorder (type 1) in his twenties during a psychiatric hospitalization for psychotic and suicidal behavior. He had taken a variety of psychiatric medications over the years, but suffered with significant side effects (including digestive issues, weight gain, and erectile dysfunction) which caused him to stop taking his medications periodically, which in turn would cause his symptoms to intensify.

Bijan was seen for weekly individual psychotherapy and bi-weekly medication management. He was stabilized on bupropion and quetiapine, which did not provide complete symptom relief, but which had a tolerable side effect profile. After several months of treatment, we added three sessions of ketamine-facilitated psychotherapy using injectable ketamine (0.7 mg/kg per injection) spaced several weeks apart. Bijan said that the medicines felt pleasant and relaxing. His ketamine sessions felt like an amplification of his regular talk therapy material: he began to wonder about the impact of his illness on his career and his marriage, he realized that he behaved aggressively or erratically when he was off his medications, and he realized that he had a lot of unexpressed feelings about his divorce. He reported that the ketamine sessions helped to stave off acute depression and gave him more space to think and feel.

Psychedelic Paradigm

Charlie was an articulate and affable 64-year-old male professor (5'10 and 170 lbs). He was the author of several textbooks, a popular academic mentor, and enjoyed doing outdoor sports and playing music in his free time. He reported that he had a long history of depressive episodes that began in childhood. As a young man, Charlie had bouts of over-spending, gambling, and hypersexual behavior, and was diagnosed with bipolar disorder (type 1) in his early thirties. At that time, he started taking valproic acid (with PRN olanzapine) and going to psychotherapy. A few years later, he began practicing mindfulness meditation to help him cope with his mood swings and cravings.

Charlie came to us for psychotherapy to explore his feelings about retirement, concerns about aging, and strategies for managing his recurrent depressive episodes. He stated that he was plagued with feelings of inadequacy for as long as he could remember and believed that he was fundamentally damaged in some way. Charlie was seen for approximately 6 months of psychotherapy with 1-2 meetings per week. His mood began to deteriorate following the unexpected death of a close colleague. Charlie was given two sessions of injectable ketamine in the psychedelic dose range which were fully dissociative and resulted in a loss of interest in external stimuli. except for hypersensitivity to sound. In the first session (1.1 mg/kg), he saw himself on a floating conveyor belt, passing pedestals which represented important accomplishments and challenges in his life. The conveyor belt ended at a wall of light; he sensed that there was something important beyond the wall. Four weeks later, Charlie had the second session (1.4 mg/kg). He reported that his body dissolved, and his awareness was released from his body. His spirit floated in a pool of rainbow light and had a profound sense of peacefulness and wellbeing to the core. Charlie was able to remember and make use of this feeling in the months of psychotherapy that followed.

DISCUSSION

Differential Diagnosis

Before commencing ketamine treatment with any patient, it is important to establish and confirm the patient's clinical diagnosis, as the differential diagnosis guides the treatment plan. We have encountered many patients over the years who were misdiagnosed. For example, we have frequently seen patients who were previously diagnosed with refractory unipolar depression, depression with anxiety, depression with attention deficit disorder, or depression with psychotic features, but who were better understood as having undiagnosed (and untreated) bipolar disorder. We have also seen patients who were previously diagnosed with bipolar disorder who were better understood as having adjustment disorder, sleep disturbance, substance use disorder, or complex PTSD. Sometimes these are overlapping or co-morbid conditions (12).

Trauma

Of special interest here is the potential overlap between bipolar spectrum disorders and complex post-traumatic stress disorder (CPTSD), which can look very similar upon initial presentation (13). While ketamine undoubtedly can be helpful for some patients with PTSD or CPTSD (14), we are also aware of numerous cases where patients were unexpectedly thrown into revisiting traumatic material during their ketamine treatment and were distressed by the experience. At this point, we have reservations about giving a powerful dissociative chemical such as ketamine to patients with a history of dissociative trauma, especially in the absence of substantial psychological support. Further, for patients who have both a bipolar spectrum disorder and PTSD or CPTSD, we have found that it is useful and important to stabilize the organic mood disorder with medications as much as possible first, before delving into an exploration of traumatic material. Working with traumatic memories can be destabilizing, and can feel unbearable when amplified by endogenous mood instability.

Mood Stabilizing Medication

It is advisable for bipolar patients to have a mood stabilizing or antipsychotic medication in their regimen before beginning ketamine treatment. Part of the purpose is to provide as much symptom relief and overall mood stability as possible. This is also important to prevent elevations into hypomania or mania (affective switching) following ketamine administration (15, 16). However, prescribing these kinds of medications is a delicate art to achieve the clinically significant effect without excessive sedation or cognitive impairment.

Psychosis

Historically, there has been concern about administering ketamine to patients who have a history of psychosis. This concern can be traced back to research that was done at Yale in the 1990s, where ketamine was used to induce altered states of conscious for the purpose of studying schizophrenia (17). The next generation of ketamine researchers went on to erroneously and pejoratively apply the term "psychotomimetic" to any expansive or mystical-type experiences that the subjects reported in the studies that were conducted on ketamine infusion for depression (18). This error, which was replicated for many years, represents a fundamental misunderstanding of the nature of psychedelic experience. It is unfortunate that this conflation of "psychotic" and "psychedelic" has caused some clinicians and researchers to exclude patients with refractory bipolar depression from ketamine. We think this exclusion criteria is largely unwarranted, especially when patients are stabilized with medication (see above). Further, new research is investigating ketamine as a possible treatment for the negative symptoms of schizophrenia (19).

Chemical Mitigators of Ketamine

There are several chemicals which are potent ketamine mitigators: benzodiazepines (20, 21), alcohol (22), opiates and opioids (23), and barbiturates. These substances clearly attenuate the therapeutic benefit of ketamine treatment for most patients, as well as the subjective experience. Benzodiazepines are of particular interest here, as they are often prescribed to bipolar patients. There are several different strategies that the psychiatrist might employ in this situation, such as considering the feasibility of reducing the patient's benzodiazepine use, increasing the ketamine dose slightly to compensate for the presence of the benzodiazepines, and/or discussing frankly with the patient about the possible interaction. We have observed in multiple cases that ketamine treatment is greatly enhanced by stopping or reducing benzodiazepine use for several days prior to ketamine administration, but we are also aware of the discomfort and dangers associated with reducing or stopping benzodiazepines. Therefore, it is a matter of clinical judgment about how to approach this dilemma.

There are a number of other chemicals that may be mild ketamine mitigators, including antipsychotic medications (24), lamotrigine (25), cannabis (26), and kava. (There is also a question based on clinical observation of a small number of patients about possible interactions with NSAID pain relievers and/or antihistamines (27). In our clinical experience, patients vary tremendously in their sensitivity to these interactions. The amount and timing of exposure to any of these chemicals also likely plays a role. Whenever a patient does not respond as robustly as desired to ketamine treatment, we look for possible exposure to a chemical mitigator. With respect to mitigating medications, we recommend similar strategies and considerations as for benzodiazepines (see above), keeping in mind the potential risks and benefits of altering the patient's medication regimen.

Contraindications

A complete discussion of all potential chemical interactions and medical contraindications for ketamine treatment is beyond the scope of this article, but it is important to note concern about combining ketamine with substances that cause hypertension, sedation, or respiratory depression.

Substance Abuse

A substantial portion of bipolar patients also have substance use issues (28). We are very wary of giving ketamine to patients

who are using other drugs outside of their prescribed regimens, although we have colleagues who are working with ketamine as an adjunctive treatment for substance use disorders, where the substance use is the focus of clinical treatment (29). We are aware that some of our colleagues require urine screens before ketamine administration, for the patient's safety and/or the provider's liability.

Different Approaches to Ketamine Treatment

Racemic ketamine is a powerful and versatile tool that can be utilized in a variety of ways in clinical treatment for certain mental health indications (30). Currently there is much disagreement in the field about "the right way" to use ketamine in psychiatry and psychotherapy (31). In our experience, we have found that different individuals appear to benefit from different approaches to ketamine treatment at different points in the arc of their illness management.

Biochemical Paradigm

The "biochemical" model focuses on the biological effects of ketamine and treats ketamine's prominent dissociative/psychedelic properties as a problematic side effect (32). Further, in this model, little attention is paid to the patient's mental state ("set") or the environment ("setting") (33, 34). The patient is viewed as a passive vessel which receives the pharmaceutical. Much of the early research on ketamine treatment for depression was done in this paradigm, typically with 0.5 mg/kg of ketamine administered by intravenous infusion over 40 min. In this paradigm, patients often receive six ketamine infusions within the span of 2 or 3 weeks (35). The ketamine infusions are spaced relatively close together to create a cumulative series. It is essential to understand that the need for six treatments is predicated on getting a low dose of ketamine, which is sub-psychedelic by design.

We think that this approach is well-suited to patients (such as Alex) who have cardiac issues or who are medically complicated. In our opinion, it is prudent to send those patients to an anesthesia provider in our community who can provide a very high level of medical monitoring and care, if needed. In addition, patients who are living with mood disorder and physical pain may be good candidates for treatment with an anesthesia provider because of their expertise in pain management. Sometimes, patients choose to see an anesthesia provider in their community for logistical reasons.

It is important to note that many anesthesia providers offer ketamine infusions for mood disorders as a stand-alone treatment, without recommending or requiring concurrent psychotherapy or behavioral strategies. We have concerns about this practice; we believe that patients who are being treated for a mental health reason should have consultation and/or treatment with a mental health professional (36).

In our vignette, Alex got both ketamine infusions and separate but concurrent psychotherapy (asynchronous treatment), and then continued in psychotherapy after the termination of the ketamine treatment. This pattern of treatment is typical of the patients in our clinical practices who are referred out for ketamine infusions. Research done by Wilkinson et al. (37) and supports this asynchronous combination of modalities, and clearly further research is needed.

Psychotherapeutic Paradigm

The "psychotherapeutic" model utilizes ketamine as a lubricant or a catalyst for the psychotherapy process, with an emphasis on the verbal expression and emotional metabolism of the patient's thoughts and feelings during the ketamine administration (synchronous treatment). Psychotherapy is an integral part of this approach. (This approach has some conceptual similarities to the studies on using MDMA to treat PTSD) (38). This type of work can be done with 0.3–0.9 mg/kg of bioavailable ketamine, given by any route that the provider prefers (e.g., intramuscular injection, compounded transbuccal lozenge, nasal spray, intravenous infusion) (39). This dosing strategy is also sub-psychedelic by design. While there may be some alteration of consciousness during this kind of treatment, it is important to keep the dose low enough so that the patient is able to articulate their ideas and engage in meaningful self-reflection.

This approach is well-suited to patients (such as Bijan) who are in an established psychotherapy relationship, and who are motivated to deepen their understanding of themselves and their difficulties. We have observed that patients who engage in ketamine assisted psychotherapy (KAP) tend to revisit material that they have explored previously in psychotherapy, and they often spontaneously experience a consolidation of their insight or commitment to behavioral change. With the help of on-going psychotherapy, these patients can be supported in implementing the changes that they envisioned. Some patients benefit from a few KAP sessions, while others need a longer series. We tend to space KAP sessions 3 to 6 weeks apart, with regular talk therapy in between, to allow time to digest the psychological material, but we are aware that some of our colleagues are using KAP on a bi-weekly or weekly schedule on a time-limited basis with select patients (40) [See (41, 42) for further discussion of KAP].

Psychedelic Paradigm

The "psychedelic" model makes use of ketamine's prominent dissociative and psychedelic properties, and uses the medicine to intentionally induce a profound and temporary altered state of consciousness which is characterized by vivid, dream-like visions (43). This type of experience requires specialized psychological support before, during, and following the ketamine administration. The physical setting also contributes to the overall experience; many clinicians use ceremonial elements to separate the psychedelic session from regular daily life (44, 45). (This approach has some conceptual similarities to the studies on using psilocybin to treat end-of-life anxiety) (46). This kind of ketamine treatment is frequently done using an intramuscular injection in the dose range of 1.0–1.5 mg/kg (47). Higher doses (up to 2.0 mg/kg) are occasionally used, although we have not observed a stronger or more durable benefit in our patients, and the experiences tend to become more fragmented and/or amnestic (48). While early ketamine researchers were fearful of ketamine's psychedelic properties, subsequent research has suggested that the experience of awe (49) or other kinds of

psychedelic experience during ketamine administration may be correlated with more potent antidepressant effects (50, 51) [See (52, 53) for further discussion on the use of psychedelic ketamine journeys in clinical treatment].

Not every patient is well-suited for full-blown dissociative and psychedelic experience at the beginning of ketamine treatment, or ever. It is helpful if patients (such as Charlie) have cultivated the ability to observe their own mental processes before beginning psychedelic treatment (e.g., through meditation or psychotherapy). Patients who have expressed a genuine curiosity about existential issues (e.g., the nature of reality) tend to find value in this kind of exploration. It is important to have a solid therapeutic alliance in place, which takes time and effort, before attempting this kind of treatment. Finally, there is a tendency in the current zeitgeist to idealize psychedelic experience. However, both the patient and the provider need to recognize that this is not a shortcut, and more medicine is not necessarily better medicine.

Different Approaches for Different Treatment Objectives

In the vignettes, all the bipolar patients received some combination of ketamine and psychotherapy, in addition to conventional oral pharmacotherapy. The first patient (Alex) represents a medically complicated young adult, and the focus of his treatment was to reduce the severity of his depressive symptoms. He also had psychotherapy that extended beyond his ketamine treatment, primarily to learn new skills that would help him to function. The second patient (Bijan) not only needed treatment for his refractory bipolar depression, but also had an openness to reflecting on the impact of his illness on his intimate relationships and professional life. In this case, the ketamine was used in service of facilitating personal insight, which lead to make concrete behavioral changes. The third patient (Charlie) needed treatment for his depressive spiral. His psychedelic ketamine experience allowed him to grapple with his feelings of defectiveness despite outward material success, and he did a deep piece of psychological work on his sense of self and relationship with his lifelong illness. It would appear that ketamine and psychotherapy together produced results which could not be achieved through ketamine or regular psychotherapy alone.

It is worth noting that when clinicians in the field talk about the treatment of bipolar patients (type 1), they often focus on the diagnosis phase and acute symptom management. However, it is useful to remember that patients who live with a lifelong and potentially debilitating illness often benefit from different kinds of support at different points in their lives: identifying the disorder, containing clinical symptoms, understanding the impact of their condition on daily living, and grieving for the losses that are inevitably associated with chronic illness (54).

Route and Dose

In the vignettes above, the ketamine doses ranged from 0.5 to 1.4 mg/kg, and produced a range of subjective experiences. One patient received ketamine by infusion from an anesthesiologist, and the other patients received ketamine by injection from a physician in the presence of a psychotherapist. Note that in our clinical practices, we prefer to use injectable (intramuscular) ketamine because it is inexpensive, easy to administer, and has high bioavailability (55). The total ketamine dose can be divided into multiple injections, if desired. The route of administration and dose in ketamine treatment are independent variables; any dose of ketamine can be given by any route.

Frequency in the Induction Phase

The induction phase is the initial phase of ketamine treatment. There is an inverse relationship between dose and frequency. Patients typically need to be seen more often for lower dose ketamine treatment, and the sessions need to be close together in time so that the effects are cumulative, until the initial series is completed. When patients receive a moderate or higher therapeutic dose of ketamine, the sessions need to be spaced out so that patients have time to process the material that arose.

Time of Day

We have observed that ketamine treatment tends to interfere with sleep for our bipolar patients, although this phenomenon has not been formally researched to date. Specifically, many of our bipolar patients have reported difficulty falling asleep for up to twelve hours following ketamine administration, even with hypnotic medication in their regimen (56). This phenomenon seems particularly pronounced in bipolar patients who have the diurnal variation of depressed mood in the mornings and improved (or elevated) mood in the evenings (57), and ketamine dose may also be a factor (a higher dose of ketamine may be more disruptive to sleep than a lower dose). For this reason, we prefer to do ketamine sessions with our bipolar patients in the early part of the day, preferably before 12 noon, whenever possible.

Synchrony

In all of the vignettes, the patients received ketamine paired with concurrent psychotherapy. In this context, "concurrent" means overlapping in a span of time, although not necessarily in the same session or location. Alex received asynchronous ketamine and psychotherapy, meaning that the infusion and psychotherapy appointments were separate. Bijan and Charlie received synchronous ketamine and psychotherapy, meaning that the ketamine was administered during the psychotherapy session. This is a useful distinction as the ketamine field expands.

Frequency in the Maintenance Phase

One area of ketamine treatment that has not been well documented is maintenance treatment. Currently, many of our colleagues utilize a reactive model and wait for patients to relapse before offering another round of treatment. However, we know that bipolar disorder (type 1) is typically a lifelong, incurable, and cyclical illness. We wonder if a prophylactic model would make sense for this population, which would look like having ketamine treatment at regular intervals in an effort to maintain wellness and/or resolve refractory symptoms before they become clinically significant. Further research is needed to determine the appropriate intervals for this strategy, keeping in mind that excessive ketamine exposure may lead to cystitis (see below).

Enantiomers of Ketamine

We prefer to use racemic ketamine in our clinical practices for a variety of reasons (58). Racemic ketamine is a generic medication in the United States. As such, it is broadly available as a medical supply, and it is extremely inexpensive. We can choose the route, dose, and frequency of treatment to suit the individual needs of our patients. Further, the two enantiomers of ketamine appear to have slightly different effects on people: the S-enantiomer (esketamine) appears to be more activating, and the R-enantiomer (arketamine) appears to be more sedating (59). We have had several patients who received esketamine and racemic ketamine treatment at different times, and they reported that esketamine felt too stimulating or "speedy" for them (60). We are tentatively hypothesizing that racemic ketamine treatment provides a good balance of the activating and soothing properties of ketamine, and that this balance appears especially well suited to treating bipolar patients, and that this may be different from patients with unipolar depression. From our perspective, the only drawback to choosing racemic ketamine for psychiatric treatment is that it is an off-label use at the current time.

Side Effects and Adverse Events

As noted in other places, ketamine is generally well tolerated, but there are a number of potential side effects. Common transient or treatable side effects of ketamine treatment include elevated pulse and/or blood pressure, headache, nausea, anxiety, changes in vision, changes in muscle tension, and/or unwanted feelings of dissociation (61). Ketamine use over time has been linked to cystitis and bladder dysfunction (62, 63). Serious adverse events associated with ketamine treatment in a legal setting include respiratory distress and seizure (64).

Suicidality

Many individuals with bipolar spectrum disorders experience suicidal ideation as a symptom of their illness. There is some evidence that ketamine treatment can be helpful in rapidly alleviating suicidal ideation in unipolar and bipolar patients, including studies on racemic ketamine infusions (65) and esketamine nasal spray (66). In our clinical practices, we have had success in alleviating suicidal ideation using racemic ketamine in a variety of dosing strategies and routes of administration. It sometimes works very quickly ($<$10 min following the introduction of ketamine), and the biochemical effect is often temporary (lasting a few hours to a few days) unless the ketamine treatment is paired with psychotherapy. Suicidal patients who respond robustly to ketamine treatment typically have chronic, ruminative, and/or ego dystonic suicidal ideation which has an obsessive quality to it. This observation raises a question as to whether the ketamine is acting on the self-harmful thought content or the ruminative thought process?

We have also observed that ketamine treatment occasionally increases suicidal ideation in a small fraction of severely depressed individuals (unipolar or bipolar), and this observation has been corroborated by a recent study of ketamine treatment in "real world" clinical treatment (67, 68). We are also aware of several completed suicides that occurred during or following a course of ketamine treatment (69). It is unclear why some patients feel significantly worse in response to ketamine treatment, but ketamine providers need to be aware of this possibility and be extremely cautious about prescribing ketamine for use outside of their direct clinical supervision. Further, individuals with chronic and refractory mental health conditions are inherently a high risk group for adverse psychiatric events, and ketamine is powerful psychoactive medicine that works differently than "traditional" antidepressant or mood stabilizing medications. For these reasons, it is imperative that clinicians who want to work with ketamine for mental health indications seek out specialized training.

CONCLUSIONS

Bipolar disorder (type 1) is a difficult disease to treat. Here we added to the existing literature on this topic by offering our observations from the field on the use of racemic ketamine to treat patients with refractory bipolar depression. We discussed a number of practical considerations for working with this population, including the importance of the differential diagnosis at the beginning of treatment; information about the route of administration, dose, frequency, and timing of ketamine treatment; interactions with other medications; reasons to use racemic ketamine instead of a single enantiomer, and adverse events.

Most of the existing research literature on the use of ketamine to treat depressive disorders (unipolar and bipolar) looked at racemic ketamine in the sub-psychedelic dose range given by infusion as a stand-alone treatment. However, ketamine is a versatile tool that can be used in a variety of ways. Here we articulate three paradigms for ketamine treatment: biochemical, psychotherapeutic, and psychedelic. These approaches differ from each other in the ketamine dose, frequency, and intention for the ketamine session. We used three composite clinical vignettes to illustrate how these paradigms could be utilized in treating bipolar patients with refractory depression, noting that different individuals may be well suited to different treatment strategies. Although our discussion focused on ketamine for patients with bipolar disorder (type 1), these paradigms could be applied more broadly to the field. It is also worth noting that the paradigms are discussed separately for the sake of clarity, but in reality, there is some overlap between the paradigms, e.g., a patient who receives ketamine in the psychedelic dose range also benefits from the biochemical effects of the medicine and also receives substantial psychotherapeutic support before, during, and after the medicine session.

One of the challenges in ketamine treatment is that beneficial effect appears to be temporary, especially if one focuses on the "biochemical" effect alone (70, 71). However, in our years of clinical practice, we have come to believe that ketamine and psychotherapy are synergistic and can potentiate each

other (as described in our vignettes). It appears that the beneficial of ketamine treatment can be extended in some patients by combining conventional pharmacotherapy, ketamine, and psychotherapy. The addition of psychotherapy can add a space for psychological exploration, relational healing, and learning new skills. We hope to reduce the chance of ketamine dependence by offering ketamine in combination with other interventions.

Finally, we acknowledge that this article contains observations from our clinical practices combined with conceptual ideas. It is important to remember that there is a circular and symbiotic relationship between observations from the field and experimental studies, which continuously inform the other. We hope that this article will inspire other clinicians and researchers to broaden their understanding of ketamine treatment and undertake new research studies.

DATA AVAILABILITY STATEMENT

The datasets presented in this article are not readily available because we used composite vignettes to protect patient privacy.

AUTHOR CONTRIBUTIONS

RB conceived of and wrote the bulk of this article, with input from CY and GB. CY and RB created the list of references. All authors edited the report and approved the report before submission.

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REFERENCES

1. National Institute of Mental Health. *Bipolar Disorder Fact Sheet.* Available online at: https://www.nimh.nih.gov/health/statistics/bipolar-disorder (accessed January 25, 2022).
2. Miller J, Black D. Bipolar disorder and suicide: a review. *Curr Psychiatry Rep.* (2020) 22:6. doi: 10.1007/s11920-020-1130-0
3. Jain R, Kong A, Gillard P, Harrington A. Treatment patterns among patients with bipolar disorder in the United States: a retrospective claims database analysis. *Adv Ther*. (2022) 1–18. doi: 10.1007/s12325-022-02112-6
4. Fountoulakis K. Refractoriness in bipolar disorder: definitions and evidence-based treatment. *CNS Neurosc Therap*. (2012) 18:227–37. doi: 10.1111/j.1755-5949.2011.00259.x
5. Baldessarini R, Vázquez G, Tondo L. Bipolar depression: a major unsolved challenge. *Int J Bipolar Disorder*. (2020) 8:1. doi: 10.1186/s40345-019-0160-1
6. Zarate C, Brutsche N, Ibrahim L, Franco-Chaves J, Diazgranados N, Cravchik A, et al. Replication of ketamine's antidepressant efficacy in bipolar depression: a randomized controlled add-on trial. *Biol Psychiatry*. (2012) 71:939–46. doi: 10.1016/j.biopsych.2011.12.010
7. Wilkowska A, Włodarczyk A, Gałuszko-Wegielnik M, Wiglusz M, Cubała W. Intravenous ketamine infusions in treatment-resistant bipolar depression: an open=label naturalistic observational study. *Neuropsychiatr Dis Treat*. (2021) 17:2637–46. doi: 10.2147/NDT.S325000
8. Bahji A, Zarate C, Vazquez G. Ketamine for bipolar depression: a systematic review. *Int J Neuropsychopharmacol*. (2021) 24:535–41. doi: 10.1093/ijnp/pyab023
9. Walsh Z, Mollaahmetoglu O, Rootman J, Golsof S, Keeler J, Marsh B, et al. Ketamine for the treatment of mental health and substance use disorders: comprehensive systematic review. *BJPsych Open*. (2022) 8:E19. doi: 10.1192/bjo.2022.5
10. Duffy M. Writing about clients: developing composite case material and its rationale. *Couns Values*. (2010) 54:135–53. doi: 10.1002/j.2161-007X.2010.tb00011.x
11. Sink C. Critical reflections on the ethical and professional considerations in writing about clients. *Couns Values*. (2011). doi: 10.1002/j.2161-007X.2010.tb00013.x
12. Parker G. Comorbidities in bipolar disorder: models and management. *Med J Aust*. (2010) 193:S18–20. doi: 10.5694/j.1326-5377.2010.tb03892.x
13. Cogan C, Paquet C, Lee J, Miller K, Crowley M, Davis J. Differentiating the symptoms of posttraumatic stress disorder and bipolar disorders in adults: utilizing a trauma-informed assessment approach. *Clin Psychol Psychother*. (2021) (1):251–60. doi: 10.1002/cpp.2504
14. Feder A, Costi S, Rutter S, Collins A, Govindarajulu U, Jha M, et al. A randomized controlled trial of repeated ketamine administration for chronic posttraumatic stress disorder. *Am J Psychiatry*. (2021) 178:193–202. doi: 10.1176/appi.ajp.2020.20050596
15. McInnes L, James-Myers M, Turner M. Possible affective switch associated with intravenous ketamine treatment in a patient with bipolar I disorder. *Biol Psychiatry*. (2016) 79:e71–2. doi: 10.1016/j.biopsych.2015.07.003
16. Bhatt K, Yoo J, Bridges A. Ketamine-induced manic episode. *Prim Care Companion CNS Disord*. (2021) 23:20l02811. doi: 10.4088/PCC.20l02811
17. Krystal J, Karper L, Seibyl J, Freeman G, Delaney R, Bremner J, et al. Subanesthetic effects of the noncompetitive NMDA antagonist ketamine in humans: psychotomimetic, perceptual, cognitive, and neuroendocrine responses. *Arch Gen Psychiatry*. (1994) 51:199–214. doi: 10.1001/archpsyc.1994.03950030035004
18. Zarate C, Singh J, Carlson P, Brutsche NE, Ameli R, Luckenbaugh DA, et al. A randomized trial of an N-methyl-D-aspartate antagonist in treatment-resistant major depression. *Arch Gen Psychiatry*. (2006) 63:856–64. doi: 10.1001/archpsyc.63.8.856
19. Veraart J, Smith-Apeldoorn S, Spijker J, Kamphuis J, Schoevers R. Ketamine treatment for depression in patients with a history of psychosis or current psychotic symptoms: a systematic review. *J Clin Psychiatry*. (2021) 82:20r13459. doi: 10.4088/JCP.20r13459
20. Albott C, Shiroma P, Cullen K, Johns B, Thuras P, Wels J, et al. The antidepressant effect of repeat dose intravenous ketamine is delayed by concurrent benzodiazepine use. *J Clin Psychiatry*. (2017) 78:e308–9. doi: 10.4088/JCP.16l11277
21. Andrashko V, Novak T, Bunovsky M, Klirova M, Sos P, Horacek, J. The antidepressant effect of ketamine is dampened by concomitant benzodiazepine medication. *Front Psychiatry*. (2020) 11:844. doi: 10.3389/fpsyt.2020.00844
22. Gable R. Acute toxic effects of club drugs. *J Psychoactive Drugs*. (2004) 36:303–13. doi: 10.1080/02791072.2004.10400031
23. Thomas K. *Ketamine Adverse Reactions and Drug-Drug Interactions [Lecture]*. KRIYA Conference 2019: Hillsborough, NC (2019).
24. Duncan G, Miyamoto S, Leipzig J, Lieberman J. Comparison of the effects of clozapine, risperidone, and olanzapine on ketamine-induced alterations in regional brain metabolism. *J Pharmacol Exp Therap*. (2000) 293:8–14.
25. Anand A, Charney D, Oren D, Berman R, Hu X, Krystal J. Attenuation of the neuropsychiatric effects of ketamine with lamotrigine: support for hyperglutamatergic effects of N-methyl-D-aspartate receptor antagonists. *Arch General Psychiatry*. (2000) 57:270–6. doi: 10.1001/archpsyc.57.3.270
26. Hallak J, Dursun S, Bosi D, de Macedo L, Machado-de-Sousa J, Abrão J, et al. The interplay of cannabinoid and NMDA glutamate receptor

systems in humans: preliminary evidence of interactive effects of cannabidiol and ketamine in healthy human subjects. *Prog Neuropsychopharmacol Biol Psychiatry.* (2011) 35:198–202. doi: 10.1016/j.pnpbp.2010.11.002
27. Bennett R. Long term ketamine treatments. [Lecture] In: *KRIYA Conference.* (2016). Hillsborough, NC (2016).
28. Levin F, Hennessy G. Bipolar disorder and substance abuse. *Biol Psychiatry.* (2004) 56:738–48. doi: 10.1016/j.biopsych.2004.05.008
29. Dakwar E, Nunes E, Hart C, Foltin R, Mathew S, Carpenter K, et al. single ketamine infusion combined with mindfulness-based behavioral modification to treat cocaine dependence: a randomized clinical trial. *Am J Psychiatry.* (2019) 176:923–30. doi: 10.1176/appi.ajp.2019.18101123
30. Bennett R. Overview of ketamine treatment. [Lecture] In: *KRIYA Conference.* (2016). Hillsborough, NC (2016).
31. Bennett R. *Ketamine for Depression: What Psychologists Need to Know*. Doctoral dissertation, Argosy University, Alameda (2014). Available online at: https://www.kriyainstitute.com/wp-content/uploads/Bennett-Ketamine-2014.pdf (accessed January 25, 2022).
32. Sanacora G, Frye M, McDonald W, Mathew SJ, Turner MS, Schatzberg AF, et al. A consensus statement on the use of ketamine in the treatment of mood disorders. *JAMA Psychiatry.* (2017) 74:399–405. doi: 10.1001/jamapsychiatry.2017.0080
33. Leary T, Metzner R, Alpert R. *The Psychedelic Experience: A Manual Based Upon the Tibetan Book of the Dead*. New York, NY: Kensington (1964).
34. Carhart-Harris R, Roseman L, Haijen E, Erritzoe D, Watts R, Branchi I, et al. Psychedelics and the essential importance of context. *J Psychopharmacol.* (2018) 32:725–31. doi: 10.1177/0269881118754710
35. Diamond P, Farmery A, Atkinson S, Haldar J, Williams N, Cowen P, et al. Ketamine infusions for treatment resistant depression: a series of 28 patients treated weekly or twice weekly in an ECT clinic. *J Psychopharmacol.* (2014) 28:536–44. doi: 10.1177/0269881114527361
36. Bennett R. Ethical guidelines for ketamine clinicians. *J Psychedelic Psychiatry.* (2020) 2:19–23. Available online at: https://www.journalofpsychedelicpsychiatry.org/ethical-ketamine-guidelines (accessed June 1, 2021).
37. Wilkinson S, Wright D, Fasula M, Fenton L, Griepp M, Ostroff R, et al. Cognitive behavior therapy may sustain antidepressant effects of intravenous ketamine in treatment-resistant depression. *Psychother Psychosom.* (2017) 86:162–7. doi: 10.1159/000457960
38. Slomski A. MDMA-assisted therapy highly effective for PTSD. *JAMA.* (2021) 326:299. doi: 10.1001/jama.2021.11748
39. Rosenblat J, Carvalho A, Li M, Lee Y, Subramanieapillai M, McIntyre R. Oral ketamine for depression: a systematic review. *J Clin Psychiatry.* (2019) 80:18r12475. doi: 10.4088/JCP.18r12475
40. Ryan W. Ketamine assisted psychotherapy: theory and chart review[Lecture]. In: *KRIYA Conference.* (2017). Hillsborough, NC (2017).
41. Mathai D, Mora V, Garcia-Romeu A. Toward synergies of ketamine and psychotherapy. *Front Psychol.* (2022) 13:868103. doi: 10.3389/fpsyg.2022.868103
42. Wolfson P, Hartelius G, editors. *The Ketamine Papers.* Santa Cruz, CA: MAPS (2016).
43. Jansen K. *Ketamine: Dreams and Realities, Second Edition*. San Jose, CA: MAPS (2004).
44. Romeu A, Richards W. Current perspectives on psychedelic therapy: use of serotonergic hallucinogens in clinical interventions. *Int Rev Psychiatry.* (2018) 30:291–316. doi: 10.1080/09540261.2018.1486289
45. Greenway K, Garel N, Goyette N, Turecki G, Richard-Devantoy S. Adjunctive music improves the tolerability of intravenous ketamine for bipolar depression. *Int Clin Psychopharmacol.* (2021) 36:218–20. doi: 10.1097/YIC.0000000000000363
46. Ross S, Bossis A, Guss J, Agin-Liebes G, Malone T, Cohen B, et al. Rapid and sustained symptom reduction following psilocybin treatment for anxiety and depression in patients with life-threatening cancer: a randomized controlled trial. *J Psychopharmacol.* (2016) 30:1165–80. doi: 10.1177/0269881116675512
47. Bennett R. Paradigms for ketamine treatment. [Lecture] In: *KRIYA Conference.* (2016). Hillsborough, NC (2016).
48. Kolp E. *Personal Communication on Ketamine Dose.* (2017).
49. Levine S. Lessons learned from five thousand ketamine infusions. *[Lecture] In: Ketamine Conference.* Oakland, CA: Kaiser Permanente (2016).
50. Luckenbaugh D, Niciu M, Ionescu D, Nolan N, Richards E, Brutsche N, et al. Do the dissociative side effects of ketamine mediate its antidepressant effects? *J Affect Disord.* (2014) 159:56–61. doi: 10.1016/j.jad.2014.02.017
51. Mathai D, Meyer M, Storch E, Kosten T. The relationship between subjective effects induced by a single dose of ketamine and treatment response in patients with major depressive disorder: a systematic review. *J Affect Disord.* (2020) 264:123–9. doi: 10.1016/j.jad.2019.12.023
52. Krupitsky E, Grinenko A. Ketamine psychedelic therapy: a review of the results of ten years of research. *J Psychoactive Drug.* (1997) 29:165–83. doi: 10.1080/02791072.1997.10400185
53. Kolp E, Friedman H, Krupitsky E, Jansen K, Sylvester M, Young M, et al. Ketamine psychedelic psychotherapy: focus on its pharmacology, phenomenology, and clinical applications. *Int J Transpers Stud.* (2014) 33:84–140. doi: 10.24972/ijts.2014.33.2.84
54. Boss P, Couden B. Ambiguous loss from chronic physical illness: clinical interventions with individuals, couples, and families. *J Clin Psychol.* (2002) 58:1351–60. doi: 10.1002/jclp.10083
55. Bonnett C, Jain R, Ross C, Wallington D, Schock T. Intramuscular ketamine to treat major depressive disorder: a case series of forty patients. *J Psychiatry Ment Health.* (2021) 6:145. doi: 10.16966/2474-7769.145
56. Bennett R. Observations from clinical practice. [Lecture] In: *KRIYA Conference.* (2017). Hillsborough, NC (2017).
57. Squire L. *Encyclopedia of Neuroscience*. Amsterdam: Elsevier (2009).
58. Bahji A, Vazquez G, Zarate C. Comparative efficacy of racemic ketamine and esketamine for depression: a systematic review and meta-analysis. *J Affect Disord.* (2021) 278:542–55. doi: 10.1016/j.jad.2020.09.071
59. Jelen L, Young A, Stone J. Ketamine: a tale of two enantiomers. *J Psychopharmacol.* (2020) 35:109–23. doi: 10.1177/0269881120959644
60. Bennett R. *Personal Communication on Patient Experience* (2017).
61. Alberich S, Martinez-Cengotitabengoa M, Lopez P, Zorrilla I, Núñez N, Vieta E, et al. Eficacia y seguridad de la ketamina en depresion bipolar: una revision sistematica. (Efficacy and safety of ketamine in bipolar depression: a systemic review*). Rev Psiquiatr Salud Ment.* (2017) 10:104–12. doi: 10.1016/j.rpsm.2016.05.005
62. Tsai Y, Kuo H. Ketamine cystitis: its urological impact and management. *Urol Sci.* (2015) 26:153–7. doi: 10.1016/j.urols.2014.11.003
63. Xie X, Liang J, Huang R, Luo C, Yang J, Xing H, et al. Molecular pathways underlying tissue injuries in the bladder with ketamine cystitis. *FASEB J.* (2021) 35:e21703. doi: 10.1096/fj.202100437
64. Feifel D, Dadiomov D, Lee K. Safety of repeated administration of parenteral ketamine for depression. *Pharmaceuticals.* (2020) 13:151. doi: 10.3390/ph13070151
65. Calabrese L. Titrated serial ketamine infusions stop outpatient suicidality and avert ER visits and hospitalizations. *Int J Psychiatry Res.* (2019) 2:1–2. doi: 10.33425/2641-4317.1033
66. Canuso C, Ionescu D, Li X, Qiu X, Lane R, Turkoz I, et al. Esketamine nasal spray for the rapid reduction of depressive symptoms in major depressive disorder with acute suicidal ideation or behavior. *J Clin Psychopharmacol.* (2021) 41:516–24. doi: 10.1097/JCP.0000000000001465
67. Schwartz H, Katzman J. Integration challenges in ketamine assisted psychotherapy. [Lecture] In: KRIYA Conference (2019). Hillsborough, NC (2019).
68. McInnes L, Qian J, Gargeya R, DeBattista C, Heifets B. A retrospective analysis of ketamine intravenous therapy for depression in real-world care settings. *J Affect Disord.* (2022) 301:486–95. doi: 10.1016/j.jad.2021.12.097
69. Bennett R, Yavorsky C. *Mind the Ketamine Education Gap - Better Training Can Prevent Adverse Outcomes in Psychiatric Patients.* MedPage Today (2021). Available online at: https://www.medpagetoday.com/psychiatry/depression/91719?trw=no (accessed June 1, 2021).

70. Hibicke M, Landry A, Kramer H, Talman Z, Nichols C. Psychedelics, but not ketamine, produce persistent antidepressant-like effects in a rodent experimental system for the study of depression. *ACS Chem Neurosci.* (2020) 11:864–71. doi: 10.1021/acschemneuro.9b00493
71. Romeo B, Choucha W, Fossati P, Rotge J. Meta-analysis of short and mid-term efficacy of ketamine in unipolar and bipolar depression. *Psychiatry Res.* (2015) 230:682–8. doi: 10.1016/j.psychres.2015.10.032

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The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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BRIEF RESEARCH REPORT
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Efficacy and Safety of Intranasal Esketamine in Patients With Treatment-Resistant Depression and Comorbid Chronic Post-traumatic Stress Disorder: Open-Label Single-Arm Pilot Study

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Introduction: Major depressive disorder (MDD) is more likely to resist to usual treatment when it is associated with post-traumatic stress disorder (PTSD). Capitalizing on the effect of ketamine in both treatment-resistant depression (TRD) and PTSD, we conducted a study in order to assess the efficacy of intranasal (IN) Esketamine in patients having TRD with comorbid PTSD.

Materials and Methods: In this open-label, single arm, retrospective pilot study, 11 patients were treated with IN Esketamine (56 or 84 mg) with a longitudinal follow-up of 6 months. IN Esketamine was administered twice weekly during the first month, once weekly during the second month, and then once every 1 or 2 weeks. Patients were assessed with Montgomery-Åsberg Depression Rating Scale (MADRS), Patient Health Questionnaire 9 items, Global Assessment of Functioning (GAF), and Clinical Global Impression-Suicide Scale (CGI-SS).

Results: We included 9 women and 2 men (mean age 47.3 ± 11.1 years). The mean (SD) MADRS scores decreased significantly from 38.6 (6.4) at baseline to 18.2 (10.03) after 6 months of IN Esketamine; 7 patients were responders and 3 patients were in remission. The percentage of patients who were moderately to severely suicidal declined from 63.6% at baseline to 27.3% after 1 month of IN Esketamine sessions. No serious adverse reactions were observed.

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Conclusion: This study reports the outcomes of 11 severely ill patients with comorbid TRD and PTSD after IN Esketamine treatment. Esketamine significantly improved depression symptoms, suggesting that it is likely to be a treatment of choice in this specific population.

Keywords: Esketamine, treatment-resistant depression, post-traumatic stress disorder, assisted-therapy, trauma-focused psychotherapy

INTRODUCTION

Major depressive disorder (MDD) is a common psychiatric disorder and is considered as one of the leading causes of disability worldwide (1). More than one third of depressed patients fail to fully respond to antidepressant treatments at adequate doses and duration, and are regarded as treatment-resistant depression (TRD) patients (2). Treatment resistance is characterized by an absence of symptomatic remission after the use of two successive trials of antidepressants of different pharmacological classes, well conducted in terms of dosage and duration while ensuring quality compliance (3, 4). A wide range of sociodemographic (female sex, age, financial insecurity, low level of education, etc.) and clinical factors, such as psychiatric and somatic comorbidities, are associated with treatment resistance (3). Post-traumatic Stress Disorder (PTSD) is one of those comorbidities (5, 6). It is a chronic and disabling condition arising after exposure to a severe traumatic event, characterized by persistent reexperiencing, avoidance, and hyperarousal symptoms. Risk for PTSD depends on trauma exposure severity, cumulative number of traumas, and trauma type; interpersonal traumas (physical and sexual assault in the context of relationship) carrying the highest risk (7). Patients with comorbid depression and PTSD have greater functional impairment (8) and their likelihood of suicidality is increased by more than three times compared to individuals with only one of these disorders (9).

Treatment strategies for TRD include antidepressants [e.g., selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), tricyclics and monoamine oxidase inhibitors], psychotherapy and brain stimulation techniques [e.g., electroconvulsive therapy (ECT) and repetitive transcranial magnetic stimulation (rTMS)] (10). Because some patients do not respond to those treatments, additional therapeutic strategies are strongly needed (11). In recent years, a growing body of evidence has implicated the glutamatergic system in the pathogenesis of depression, *N*-methyl-D-aspartate (NMDA) glutamate receptors being identified as a potential pharmacotherapeutic target for MDD, including TRD (12–14). Intravenous ketamine, a non-competitive receptor antagonist of NMDA glutamate receptors, was found to exhibit a robust and rapid onset of efficacy in patients with TRD when administered at subanesthetic doses (0.5 mg/kg) (15–19). Glutamate is also involved in stress responsivity, the formation of traumatic memories, and the pathophysiology of PTSD (20). So ketamine was proposed as a potential treatment for chronic PTSD (21–23) or for comorbid PTSD with TRD (24), although the results regarding ketamine efficacy in this indication are contradictory (25).

Nevertheless, ketamine is known for its abuse potential and profound adverse effects, such as psychotomimetic symptoms, neurotoxicity, cognitive impairment, and hypertension. These effects appear to be less frequent with its S-enantiomer or Esketamine, making it preferable to use (26). Oral Esketamine administration yields a low bioavailability of around 20%, which stimulated the development of its intranasal (IN) form (27). Indeed, the bioavailability and the kinetics of effects of ketamine vary considerably according to the route of administration (e.g., bioavailability: oral: 20%; intramuscular: 90%; rectal: 25%; intranasal: 50%; epidural: 77%; kinetics of effects: oral: delay 15–30 min, duration: 60–90 min; intramuscular: delay: 10–15 min, duration: 30–120 min; intravenous: delay: 1–2 min, duration: 20–60 min) (28). Granted marketing authorization by the European Medicines Agency (EMA) for the treatment of TRD in December 2019 (29), Esketamine nasal spray is used as an antidepressant for TRD. It delivers a 28 mg Esketamine dose *via* two sprays (one per nostril) (29, 30). Phase-3 short-term trials of Esketamine nasal spray (28, 56, or 84 mg) plus an oral antidepressant have demonstrated a statistically significant reduction in depressive symptoms [reduction from baseline Montgomery–Åsberg Depression Rating Scale (MADRS) total score] in patients with TRD compared with an oral antidepressant plus placebo nasal spray (31), and a sustained decreased risk of relapse among stable remitters and responders in long-term trials (29, 32, 33). Long-term safety data showed that most treatment-emergent adverse events (AEs) were mild or moderate in intensity, and resolved on the same day (33). However, the optimum dose, duration, and frequency of use are not fully understood yet (34) and potential indications still need to be clarified. There is no head-to-head data to compare ketamine or Esketamine formulation in terms of tolerance or efficacy. Nevertheless, a recent case series demonstrated that 10 consecutive patients who had responded to IV racemic ketamine for TRD successfully maintained their antidepressant response when switched to IN Esketamine (35).

On the basis of the reported efficacy of intravenous ketamine on PTSD and TRD, we hypothesized that IN Esketamine could be effective in TRD patients with comorbid PTSD. This study is the first one to examine the efficacy and the safety of repeated IN Esketamine administration over a 6-month period on symptoms of depression in this specific population. We further discuss the possible mechanisms of action and the potential synergistic effect with psychotherapeutic intervention.

MATERIALS AND METHODS

Participants

We have led an open-label, single arm, retrospective pilot study on 11 adult patients (aged 18–65 years) who have received from Esketamine nasal spray between February 2020 and November 2021 in one psychiatric department specialized in TRD. Patients underwent a psychiatric evaluation by a board-certified psychiatrist (MR or CB) to confirm diagnosis of major depression and comorbid PTSD according to the criteria in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5). All participants met the criteria for TRD (3) and PTSD (DSM-5). Written informed consent was obtained from all participants before participation. Under French ethical law (public Health code), retrospective studies based on the exploitation of routine care data do not have to be submitted to an ethics committee. This research was performed in accordance with the Declaration of Helsinki.

Procedures

All participants received Esketamine nasal spray co-administered with a newly initiated oral antidepressant in either a full or partial hospitalization setting, as recommended by the Summary of Product Characteristics (SmPC) approved by ANSM [European Medicines Agency (36)]. All patients had baseline blood tests and an electrocardiogram to determine medical stability before the initiation of Esketamine. Post-administration monitoring was undertaken by a healthcare professional for ≥120 min. Throughout their treatment with Esketamine, the patients benefited from individualized follow-up by the same referring nurse. Esketamine was initiated at 56 mg and adjusted on an individual basis during the treatment period in accordance with the following treatment guidelines (29, 36): Weeks 1–4: 56 or 84 mg twice weekly; Weeks 5–8: 56 or 84 mg once weekly; and Week 9 and onward: 56 or 84 mg once every 1 or 2 weeks (**Supplementary Figure 1**). However, psychiatrists were free to adjust treatment dosage and frequency on an individual basis, depending on the patient's response and tolerance to treatment. During Esketamine treatment, voluntary patients were offered trauma-focused psychotherapy [cognitive behavioral therapy (CBT) or eye movement desensitization and reprocessing (EMDR)] once every 1 or 2 weeks. Psychotherapy sessions took place within one week of Esketamine administration.

Measures

Scores were collected every month. The primary outcome was changes in depression score, assessed with the MADRS, between treatment initiation at baseline (Day 1) and 6 months of treatment (M6). A MADRS score of 30 is considered a definition of severe depression (37). At 6 months, patients who achieved a 50% or greater reduction in their MADRS scores were considered as responders, while patients who obtained a MADRS score inferior to 12 were remitters. Secondary outcomes included changes in scores on Patient Health Questionnaire-9 (PHQ-9), Global Assessment of Functioning (GAF) and Clinical Global Impression-Suicide Scale (CGI-SS) between baseline, and M6. Side effects and tolerability were assessed after each Esketamine administration. We also assessed PTSD symptoms as an exploratory variable in patients who were undergoing psychotherapy using the PTSD Checklist for DSM-5 (PCL-5) between psychotherapy initiation and the 6th month of psychotherapy (38). A PCL-5 score of 32 was deemed to have the greatest likelihood of correctly categorizing a participant as having PTSD as per the DSM-5 guidelines (38).

Statistical Analysis

Changes in quantitative outcome measures from the baseline to 6 months after Esketamine initiation were examined using non-parametric Friedman tests, due to the small sample size. Statistical analyses were conducted using SPSS, version 28 (IBM, Armonk, NY, United States).

RESULTS

Sample Characteristics

As shown in **Supplementary Table 1**, we included 9 female and 2 male patients with comorbid TRD and PTSD (mean age 47.27 ± 11.07 years, range 24–59). The majority of patients were in a relationship (n = 8), on sick leave (n = 5) or unemployed (n = 4). Nine patients (82%) have already attempted suicide in their lifetime. Patients suffered from chronic PTSD related to rape (n = 2), sexual abuse in childhood (n = 4) or other traumatic experiences (one suicide of family member, one brutal love breakup, and three workplace bullying). Nine patients also had other comorbidities, namely, anxiety disorders (n = 4), chronic pain (n = 3), addiction (n = 1), and eating disorder (n = 1).

Psychotropic Treatment

Treatment with IN Esketamine was initiated at 56 mg, followed by a titration up to a target dose of 84 mg. At 6 months, all patients were still receiving a dose of 84 mg per session except for one patient who was receiving 56 mg due to poor tolerance (nausea). However, the rhythm of the sessions was conducted in accordance with the recommended Esketamine administration protocol for all patients. The mean number of Esketamine sessions administered in 6 months were 25.0 (5.3) ranging from 13 to 28. Concomitant medication prescriptions included SSRIs (n = 2), serotonin/norepinephrine reuptake inhibitors (n = 7), α2 antagonists (n = 1), tricyclics (n = 1), atypical antipsychotics (n = 9), mood stabilizers (n = 10), and benzodiazepines (n = 6). Treatment (other than Esketamine) was not changed during the follow-up period.

To test the effect of concomitant antidepressant treatments on our primary outcome (change in MADRS between baseline and 6 months of Esketamine treatment), we converted antidepressant treatments into fluoxetine equivalent (39). No significant correlation (ρ = –0.598, p = 0.068) was found between relative

improvement (between baseline and 6 months of esketamine) and antidepressants dose (fluoxetine-equivalents).

Evolution of Symptoms

At the baseline, the mean Maudsley staging score was 10.4 (1.6) (range: 7–12), with moderate (n = 5) to severe (n = 6) level of resistance (40). The evolution of depressive symptoms (through MADRS and PHQ-9) and global functioning (through GAF) are illustrated in **Figure 1**. The mean MADRS score significantly decreased during the treatment period (−13.5 points at 3 months and −20.4 at 6 months, $p < 0.001$, see **Table 1**). As reported in **Table 1**, the PHQ-9 scores significantly decreased over the treatment period ($p = 0.012$), whereas the GAF scores significantly increased ($p = 0.001$). The number of patients who achieved response (defined by a reduction of at least 50.0% of the MADRS total score) increased with time from one (9.1%) after one month of treatment, to five (45.5%) after 3 months and seven (63.6%) after 6 months. Regarding remission (defined as a MADRS total score $\leq$ 12), three patients (27.3%) reached remission at 3 and 6 months [including one (9.1%) who achieved remission one month after treatment initiation]. One patient did not respond to treatment and stopped after 25 sessions.

As for suicidality, the percentage of patients who were at least moderately to severely suicidal (CGI-SS score $\geq$ 3) went from 63.6% before treatment to 27.3% after 1 month of Esketamine treatment, and then to 20% after 3 months. However, the decrease was not statistically significant (**Table 1**).

Evolution of Post-traumatic Symptoms Under Psychotherapy

Seven patients received psychotherapy in parallel with the administration of IN Esketamine: either cognitive and behavioral therapy focused on trauma (n = 3), or EMDR (n = 1) or both (n = 3). Psychotherapy occurred on average (SD) 3.6 (2.8) months after starting Esketamine treatment. Their post-traumatic symptoms were assessed through the PCL-5 before and after psychotherapy with a mean interval of 5.6 (5.5) months. The mean score went from 58.6 (3.9) before treatment to 32.7 (16.0) after treatment. The mean (SD) relative improvement was 45.3% (25.5).

Discontinuation Rates

Among the eleven patients included in the analyses, three patients stopped IN Esketamine before 6 months: one patient stopped 2 months after Esketamine initiation (i.e., 13 sessions) because of remission, one patient stopped after 4 months (16 sessions) due to travel difficulties and a third patient stopped due to lack of efficacy of IN Esketamine (25 sessions) and started treatment with a non-selective monoamine oxidase inhibitor.

Adverse Effects and Tolerability

The most frequent AEs were dissociation (n = 7), somnolence (n = 4), nausea (n = 4), sedation (n = 3), dizziness (n = 3), anxiety (n = 2), and increased blood pressure or hypertension (n = 1). Most side effects were moderate and did not require discontinuation of treatment. One patient had nausea and required anti-emetic treatment before sessions. For this patient, the increase of Esketamine dosage to 84 mg had to be delayed. The dissociative effects consisted of disinhibition with verbalization of traumatic events (n = 4) or derealization (n = 3). We did not observe any serious adverse effects throughout the study. In particular, no safety issue due to repeated Esketamine administration occurred in our study.

DISCUSSION

This pilot study provides the first data evaluating IN Esketamine treatment in patients with dual diagnosis of TRD and PTSD, suggesting that this treatment, in association with antidepressants and with psychotherapy, could rapidly reduce depressive symptoms in this population with a long-lasting effect up to 6 months. In our sample, two thirds of TRD patients achieved response and one third reached remission after 6 months of IN Esketamine treatment. The risk of suicide was importantly reduced, although not statistically significant: the percentage of moderately to severely suicidal patients was divided by 3 in 6 months of treatment. PTSD symptoms have also importantly improved for patients that had both Esketamine and trauma-focused therapy, with a mean (SD) reduction of 45.3% (25.5) of PCL-5 after 6 months of therapy. This latter result is exploratory and only concerns a sub-group of patients but seems clinically meaningful considering the severity, the resistance and the functional outcome of the disease presented by our population.

In previous studies, Esketamine has been shown to be effective in TRD. In our study, we found that patients with comorbid TRD and PTSD have similar to higher rates of response than patients with TRD alone in previous studies [63.6% in our study versus 45.6, 52.2, and 61.4% in TRANSFORM-1 (41) and TRANSFORM-2 (31) studies]. However, they have lower rates of remission (27.3% in our study versus 33.3, 34.8, and 46.5% in TRANSFORM-1 and TRANSFORM-2 studies). This difference may be explained by the persistence of residual symptoms that could be specific to the PTSD comorbidity. Several studies found that racemic ketamine could decrease PTSD symptoms (21–23, 42) but this effect was recently challenged (25). Still, the only study that previously explored the efficacy of racemic ketamine on comorbid TRD and PTSD found a quick and significant reduction of symptoms, but with a limited effect over time (median time to relapse of 41 days) (24). Our study therefore confirms these results with IN Esketamine.

This action of Esketamine in patients with both depressive and PTSD symptoms might be explained by common pathophysiological features. Indeed, in both depression and PTSD, patients are more sensitive to negative emotional stimuli which trigger an increased activation of amygdala and anterior cingulate cortex and a decreased activation of the prefrontal cortex (43, 44). Interestingly, low doses of ketamine have been shown to reverse that pattern in patients with MDD (45). On the other hand, PTSD is a risk factor for TRD (5, 6) and patients with TRD perceive their onset-related events as serious psychological distress symptoms (46). It was also shown that patients with TRD who have experienced traumatic events

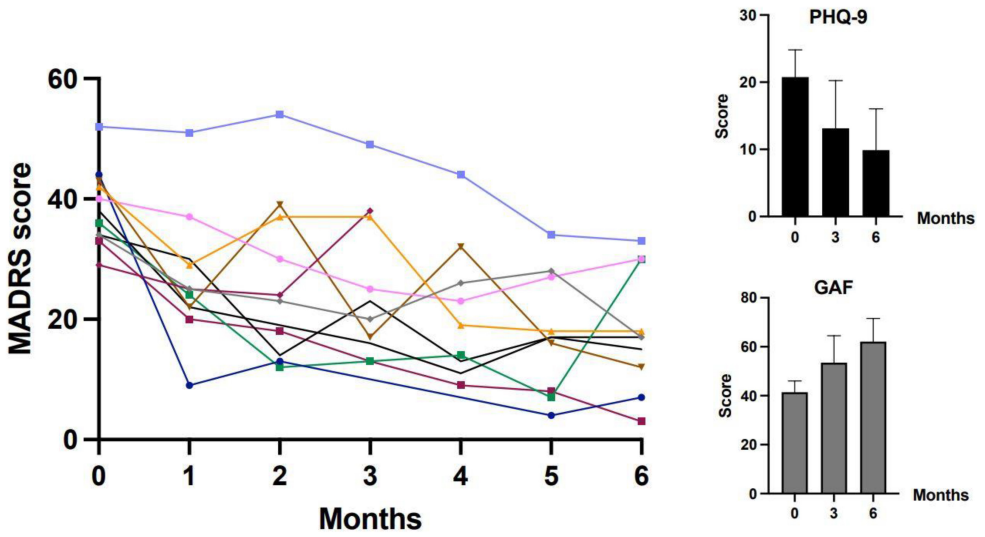

FIGURE 1 | The evolution of depressive symptoms (through MADRS and PHQ-9) and global functioning (through GAF) during treatment. MADRS, Montgomery-Åsberg Depression Rating Scale; PHQ-9, Patient Health Questionnaire-9; GAF, Global Assessment of Functioning. The main figure (on the left) shows MADRS scores for individual participants. The two figures on the right report means and standard deviations for PHQ-9 and GAF.

TABLE 1 | Evolution of mood and functioning outcomes during treatment.

Mean (SD)	MADRS		PHQ-9		GAF		CGI-SS	
Baseline	38.6 (6.4)	*n* = 11	20.8 (4.1)	*n* = 08	41.5 (4.6)	*n* = 11	2.8 (1.0)	*n* = 11
1 month	26.7 (10.6)	*n* = 11	14.9 (5.3)	*n* = 09	54.3 (10.3)	*n* = 08	2.3 (1.0)	*n* = 11
2 months	25.7 (13.1)	*n* = 11	14.1 (5.5)	*n* = 09	52.0 (10.0)	*n* = 08	1.9 (0.9)	*n* = 10
3 months	25.1 (12.3)	*n* = 10	13.1 (7.1)	*n* = 08	53.5 (11.0)	*n* = 08	1.9 (1.0)	*n* = 10
4 months	21.2 (11.4)	*n* = 09	9.3 (4.3)	*n* = 06	57.6 (8.7)	*n* = 07	1.8 (1.0)	*n* = 08
5 months	17.6 (9.8)	*n* = 10	12.1 (8.5)	*n* = 08	63.9 (11.7)	*n* = 09	1.4 (0.7)	*n* = 10
6 months	18.2 (10.0)	*n* = 10	9.9 (6.2)	*n* = 08	62.1 (9.5)	*n* = 10	1.7 (1.1)	*n* = 10
p-value	$p < 0.001$		$p = 0.012$		$p = 0.001$		$p = 0.060$	

Mean (standard deviation) and sample size (n) are reported. P-values are results of Friedman tests. MADRS, Montgomery-Åsberg Depression Rating Scale; PHQ-9, Patient Health Questionnaire-9; GAF, Global Assessment of Functioning.

are relieved by trauma-focused psychotherapy (47), so one could postulate that part of the efficacy of ketamine on TRD may be related to a beneficial action on underlying traumas. Finally, ketamine facilitates fear memory extinction (48, 49) which could help patients with PTSD to have less avoidance behaviors and to enter in a psychotherapeutic process. The main mechanism of action of Esketamine is to block NMDA receptors on GABA interneurons and to activate the alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors. This action might increase neurotrophic signaling, thereby restoring synaptic function and improving neural plasticity and synaptogenesis (50) in particular in the prefrontal cortex (51, 52). Ketamine reverses structural and functional deficits induced by chronic stress exposure (53), which could help both patients with PTSD and with depression. Indeed, in individuals with chronic PTSD, persistent, recurrent intrusions could represent a form of chronic stress that prolongs and worsens maladaptive biological changes, including synaptic atrophy, dysregulation of glutamatergic transmission, and disrupted connectivity in corticolimbic circuitry (54, 55). Finally, ketamine normalizes the disrupted connectivity between the prefrontal cortex, the default mode network and other key brain regions, that is observed in depression (56, 57) and could similarly restore cerebral connectivity in these regions in PTSD (58).

Importantly, the present study also demonstrated that repeated IN Esketamine sessions were safe and well-tolerated, with transient dissociative symptoms that disappeared within 2 h. Indeed, over 6 months, we did not observe any serious adverse effects. These data are consistent with previous ecological observations which did not identify new safety signals (59) compared to the initial data that allowed Esketamine approval. This is a crucial result since previous studies suggested that Esketamine could trigger higher dissociative symptoms than racemic ketamine when administered in acute trauma phases (60). On the contrary, the dissociative effects could induce a surprisingly positive impact. Indeed a trance state, as described during ketamine-assisted psychotherapy (61) was observed in our study for 6 patients (54.5%). It promoted communication and allowed some of them to verbalize their traumatic experience for the first time. Therapists then observed that these patients

were getting rid of fear more easily, enabling them to create new positive associations. Such an effect could have directly emerged from the disinhibition and the fear extinction induced by ketamine (48, 49) or from an increased neuroplasticity (51, 52) that could have reduced the rigidity of traumatic memories, making them finally accessible to psychotherapy. Ketamine-assisted psychotherapy has shown to be a relevant approach in other chronic, severe or resistant diseases, e.g., in alcohol use disorder (62), heroin addiction (63), and TRD without comorbid PTSD (64). Previous articles developed clinical guides of ketamine-assisted psychotherapy (65, 66). However, its modalities, notably in the treatment of PTSD, remain to be better defined. More specifically, the optimal moment to start psychotherapy and how it should be articulated with Esketamine sessions in order to have the most benefit should be specified. Here we tentatively suggest that the first sessions may allow the patients to get used to subjective changes induced by Esketamine and to benefit from early anxiolytic and antidepressant effects. In this sense, it could be more appropriate to start trauma-focused psychotherapy a bit later. In contrast, patients could be accompanied before and during the first Esketamine sessions with techniques that have been developed to improve tolerance and avoid "bad-trip" during psychotropic-assisted therapy (67).

Despite encouraging results, our study had several limitations, notably the small number of patients included and the absence of sample size calculation. The open-label design and the absence of placebo control does not allow us to firmly conclude in terms of efficacy. In addition, there is an overlap between depressive symptoms and some PTSD symptoms and our study cannot accurately describe the respective effect of Esketamine on each of them or tease apart the respective contributions of the pharmacological and the psychotherapeutic treatment in the observed improvement. Moreover, we cannot eliminate a confounding effect of different drugs or other comorbid disorders since there was no control group. Quantitative measures of the intensity of dissociation during Esketamine administration would have allowed us to explore whether it was predictive of response or remission of PTSD symptoms. In the future, the efficacy of Esketamine-assisted therapy may be further assessed with a more structured protocol including a control group.

CONCLUSION

This pilot study is the first one to assess Esketamine efficacy on comorbid TRD and PTSD. Our results suggest rapid and sustained effects of Esketamine both on depressive and PTSD symptoms at 6 months even if patients were severely ill and importantly disabled by their disorders. The properties of Esketamine seem to combine particularly well with trauma-focused therapies and those two approaches probably have a synergistic effect. Esketamine could therefore be a treatment of choice in TRD patients with comorbid PTSD.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

MR, WE-H, OG, RG, VM, and LB conceived and conceptualized the study. MR, ChB, CaB, and DR collected data. VM and DR performed formal analysis of data collected. MR and VM wrote the preliminary draft. WE-H and LB revised and edited the final draft. All authors reviewed and approved the final draft of the manuscript and made substantial contributions to this study.

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SUPPLEMENTARY MATERIAL

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REFERENCES

1. GBD 2017 Disease and Injury Incidence and Prevalence Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990-2017: a systematic analysis for the global burden of disease study 2017. *Lancet.* (2018) 392:1789–858. doi: 10.1016/S0140-6736(18)32279-7
2. Fava M, Davidson KG. Definition and epidemiology of treatment-resistant depression. *Psychiatr Clin North Am.* (1996) 19:179–200. doi: 10.1016/S0193-953X(05)70283-5
3. Rush AJ, Thase ME, Dubé S. Research issues in the study of difficult-to-treat depression. *Biol Psychiatry.* (2003) 53:743–53. doi: 10.1016/s0006-3223(03)00088-x doi: 10.1016/S0006-3223(03)00088-X
4. Holtzmann J, Richieri R, Saba G, Allaïli N, Bation R, Moliere F, et al. [How to define treatment-resistant depression?]. *Presse Med.* (2016) 45:323–8. doi: 10.1016/j.lpm.2016.02.002
5. Kessler RC, Sonnega A, Bromet E, Hughes M, Nelson CB. Posttraumatic stress disorder in the national comorbidity survey. *Arch Gen Psychiatry.* (1995) 52:1048–60. doi: 10.1001/archpsyc.1995.03950240066012
6. Kaplan MJ, Klinetob NA. Childhood emotional trauma and chronic posttraumatic stress disorder in adult outpatients with treatment-resistant

depression. *J Nerv Ment Dis.* (2000) 188:596–601. doi: 10.1097/00005053-200009000-00006
7. Kessler RC, Aguilar-Gaxiola S, Alonso J, Benjet C, Bromet EJ, Cardoso G, et al. Trauma and PTSD in the WHO world mental health surveys. *Eur J Psychotraumatol.* (2017) 8(Suppl. 5):1353383. doi: 10.1080/20008198.2017.1353383
8. Post LM, Zoellner LA, Youngstrom E, Feeny NC. Understanding the relationship between co-occurring PTSD and MDD: symptom severity and affect. *J Anxiety Disord.* (2011) 25:1123–30. doi: 10.1016/j.janxdis.2011.08.003
9. Karatzias T, Hyland P, Bradley A, Cloitre M, Roberts NP, Bisson JI, et al. Risk factors and comorbidity of ICD-11 PTSD and complex PTSD: findings from a trauma-exposed population based sample of adults in the United Kingdom. *Depress Anxiety.* (2019) 36:887–94. doi: 10.1002/da.22934
10. Bennabi D, Charpeaud T, Yrondi A, Genty JB, Destouches S, Lancrenon S, et al. Clinical guidelines for the management of treatment-resistant depression: French recommendations from experts, the French association for biological psychiatry and neuropsychopharmacology and the fondation FondaMental. *BMC Psychiatry.* (2019) 19:262. doi: 10.1186/s12888-019-2237-x
11. Johnston KM, Powell LC, Anderson IM, Szabo S, Cline S. The burden of treatment-resistant depression: a systematic review of the economic and quality of life literature. *J Affect Disord.* (2019) 242:195–210. doi: 10.1016/j.jad.2018.06.045
12. Kadriu B, Musazzi L, Henter ID, Graves M, Popoli M, Zarate CA. Glutamatergic neurotransmission: pathway to developing novel rapid-acting antidepressant treatments. *Int J Neuropsychopharmacol.* (2019) 22:119–35. doi: 10.1093/ijnp/pyy094
13. Mathews DC, Henter ID, Zarate CA. Targeting the glutamatergic system to treat major depressive disorder. *Drugs.* (2012) 72:1313–33. doi: 10.2165/11633130-000000000-00000
14. Li CT, Yang KC, Lin WC. Glutamatergic dysfunction and glutamatergic compounds for major psychiatric disorders: evidence from clinical neuroimaging studies. *Front Psychiatry.* (2019) 9:767. doi: 10.3389/fpsyt.2018.00767
15. Zarate CA, Singh JB, Carlson PJ, Brutsche NE, Ameli R, Luckenbaugh DA, et al. A randomized trial of an N-methyl-D-aspartate antagonist in treatment-resistant major depression. *Arch Gen Psychiatry.* (2006) 63:856–64. doi: 10.1001/archpsyc.63.8.856
16. Schwenk ES, Viscusi ER, Buvanendran A, Hurley RW, Wasan AD, Narouze S, et al. Consensus guidelines on the use of intravenous ketamine infusions for acute pain management from the American society of regional anesthesia and pain medicine, the American academy of pain medicine, and the American society of anesthesiologists. *Reg Anesth Pain Med.* (2018) 43:456–66. doi: 10.1097/AAP.0000000000000806
17. Zheng W, Gu LM, Sun CH, Zhou YL, Wang CY, Lan XF, et al. Comparative effectiveness of repeated ketamine infusions in treating anhedonia in bipolar and unipolar depression. *J Affect Disord.* (2022) 300:109–13. doi: 10.1016/j.jad.2021.12.105
18. Zheng W, Zhou YL, Liu WJ, Wang CY, Zhan YN, Li HQ, et al. Rapid and longer-term antidepressant effects of repeated-dose intravenous ketamine for patients with unipolar and bipolar depression. *J Psychiatr Res.* (2018) 106:61–8. doi: 10.1016/j.jpsychires.2018.09.013
19. Li Z, Ruan M, Chen J, Fang Y. Major depressive disorder: advances in neuroscience research and translational applications. Neurosci Bull. 2021 37(6):863-880. *Erratum Neurosci Bull.* (2021).
20. Nair J, Singh Ajit S. The role of the glutamatergic system in posttraumatic stress disorder. *CNS Spectr.* (2008) 13:585–91.
21. Feder A, Parides MK, Murrough JW, Perez AM, Morgan JE, Saxena S, et al. Efficacy of intravenous ketamine for treatment of chronic posttraumatic stress disorder: a randomized clinical trial. *JAMA Psychiatry.* (2014) 71:681–8.
22. Feder A, Costi S, Rutter SB, Collins AB, Govindarajulu U, Jha MK, et al. A randomized controlled trial of repeated ketamine administration for chronic posttraumatic stress disorder. *Am J Psychiatry.* (2021) 178:193–202.
23. Duek O, Li Y, Kelmendi B, Amen S, Gordon C, Milne M, et al. Modulating amygdala activation to traumatic memories with a single ketamine infusion. *medRxiv*[Preprint]. (2021). 2021.07.07.21260166
24. Albott CS, Lim KO, Forbes MK, Erbes C, Tye SJ, Grabowski JG, et al. Efficacy, safety, and durability of repeated ketamine infusions for comorbid posttraumatic stress disorder and treatment-resistant depression. *J Clin Psychiatry.* (2018) 79:17m11634.
25. Abdallah CG, Roache JD, Gueorguieva R, Averill LA, Young-McCaughan S, Shiroma PR, et al. Dose-related effects of ketamine for antidepressant-resistant symptoms of posttraumatic stress disorder in veterans and active duty military: a double-blind, randomized, placebo-controlled multi-center clinical trial. *Neuropsychopharmacology.* (2022) 47:1574–81.
26. Muller J, Pentyala S, Dilger J, Pentyala S. Ketamine enantiomers in the rapid and sustained antidepressant effects. *Ther Adv Psychopharmacol.* (2016) 6:185–92.
27. Li L, Vlisides PE. Ketamine: 50 years of modulating the mind. *Front Hum Neurosci.* (2016) 10:612. doi: 10.3389/fnhum.2016.00612
28. Dinis-Oliveira RJ. Metabolism and metabolomics of ketamine: a toxicological approach. *Forensic Sci Res.* (2017) 2:2–10. doi: 10.1080/20961790.2017.1285219
29. European Medicines Agency. *Spravato 28 mg Nasal Spray (Esketamine), Solution. Summary of Product Characteristics*. (2021). Available online at: https://www.ema.europa.eu/en/documents/product-information/spravato-epar-product-information_en.pdf (accessed June 23, 2021).
30. U.S. Food and Drug Administration. *SPRAVATO® (Esketamine) Nasal Spray, CIII. Prescribing Information*. (2020). Available online at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/211243lbl.pdf (accessed June 23, 2021).
31. Popova V, Daly EJ, Trivedi M, Cooper K, Lane R, Lim P, et al. Efficacy and safety of flexibly dosed esketamine nasal spray combined with a newly initiated oral antidepressant in treatment-resistant depression: a randomized double-blind active-controlled study. *Am J Psychiatry.* (2019) 176:428–38. doi: 10.1176/appi.ajp.2019.19020172
32. Daly EJ, Trivedi MH, Janik A, Li H, Zhang Y, Li X, et al. Efficacy of esketamine nasal spray plus oral antidepressant treatment for relapse prevention in patients with treatment-resistant depression: a randomized clinical trial. *JAMA Psychiatry.* (2019) 76:893–903. doi: 10.1001/jamapsychiatry.2019.1189
33. Wajs E, Aluisio L, Holder R, Daly EJ, Lane R, Lim P, et al. Esketamine nasal spray plus oral antidepressant in patients with treatment-resistant depression: assessment of long-term safety in a phase 3, open-label study (SUSTAIN-2). *J Clin Psychiatry.* (2020) 81:19m12891. doi: 10.4088/JCP.19m12891
34. Salahudeen MS, Wright CM, Peterson GM. Esketamine: new hope for the treatment of treatment-resistant depression? A narrative review. *Ther Adv Drug Saf.* (2020) 11:2042098620937899. doi: 10.1177/2042098620937899
35. Banov MD, Landrum RE, Moore MB, Szabo ST. Switching to intranasal esketamine maintains the antidepressant response to intravenous racemic ketamine administration: a case series of 10 patients. *J Clin Psychopharmacol.* (2021) 41:594–9. doi: 10.1097/JCP.0000000000001456
36. European Medicines Agency. *SPRAVATO 28 mg, Solution Pour Pulvérisation Nasale. Résumé des Caractéristiques Produit*. (2017). Available online at: https://www.ema.europa.eu/en/documents/product-information/spravato-epar-product-information_fr.pdf (accessed June 23, 2021).
37. Montgomery SA, Asberg M. A new depression scale designed to be sensitive to change. *Br J Psychiatry.* (1979) 134:382–9.
38. Ashbaugh AR, Houle-Johnson S, Herbert C, El-Hage W, Brunet A. Psychometric validation of the English and French versions of the posttraumatic stress disorder checklist for DSM-5 (PCL-5). *PLoS One.* (2016) 11:e0161645. doi: 10.1371/journal.pone.0161645
39. Hayasaka Y, Purgato M, Magni LR, Ogawa Y, Takeshima N, Cipriani A, et al. Dose equivalents of antidepressants: evidence-based recommendations from randomized controlled trials. *J Affect Disord.* (2015) 180:179–84. doi: 10.1016/j.jad.2015.03.021
40. Fekadu A, Donocik JG, Cleare AJ. Standardisation framework for the Maudsley staging method for treatment resistance in depression. *BMC Psychiatry.* (2018) 18:100. doi: 10.1186/s12888-018-1679-x
41. Fedgchin M, Trivedi M, Daly EJ, Melkote R, Lane R, Lim P, et al. Efficacy and safety of fixed-dose esketamine nasal spray combined with a new oral antidepressant in treatment-resistant depression: results of a randomized, double-blind, active-controlled study (TRANSFORM-1). *Int J Neuropsychopharmacol.* (2019) 22:616–30. doi: 10.1093/ijnp/pyz039

42. McGhee LL, Maani CV, Garza TH, Gaylord KM, Black IH. The correlation between ketamine and posttraumatic stress disorder in burned service members. *J Trauma.* (2008) 64(2 Suppl.):S195–8; discussion S197–8. doi: 10.1097/TA.0b013e318160ba1d
43. Hayes JP, Vanelzakker MB, Shin LM. Emotion and cognition interactions in PTSD: a review of neurocognitive and neuroimaging studies. *Front Integr Neurosci.* (2012) 6:89. doi: 10.3389/fnint.2012.00089
44. Groenewold NA, Opmeer EM, de Jonge P, Aleman A, Costafreda SG. Emotional valence modulates brain functional abnormalities in depression: evidence from a meta-analysis of fMRI studies. *Neurosci Biobehav Rev.* (2013) 37:152–63. doi: 10.1016/j.neubiorev.2012.11.015
45. Li C-T, Chen M-H, Lin W-C, Hong C-J, Yang B-H, Liu R-S, et al. The effects of low-dose ketamine on the prefrontal cortex and amygdala in treatment-resistant depression: a randomized controlled study. *Hum Brain Mapp.* (2016) 37:1080–90. doi: 10.1002/hbm.23085
46. Kimura A, Hashimoto T, Niitsu T, Iyo M. Presence of psychological distress symptoms associated with onset-related life events in patients with treatment-refractory depression. *J Affect Disord.* (2015) 175:303–9. doi: 10.1016/j.jad.2015.01.027
47. Minelli A, Zampieri E, Sacco C, Bazzanella R, Mezzetti N, Tessari E, et al. Clinical efficacy of trauma-focused psychotherapies in treatment-resistant depression (TRD) in-patients: a randomized, controlled pilot-study. *Psychiatry Res.* (2019) 273:567–74. doi: 10.1016/j.psychres.2019.01.070
48. Wei M-D, Wang Y-H, Lu K, Lv B-J, Wang Y, Chen W-Y. Ketamine reverses the impaired fear memory extinction and accompanied depressive-like behaviors in adolescent mice. *Behav Brain Res.* (2020) 379:112342. doi: 10.1016/j.bbr.2019.112342
49. Philippens IHCHM, Draaisma L, Baarends G, Krugers HJ, Vermetten E. Ketamine treatment upon memory retrieval reduces fear memory in marmoset monkeys. *Eur Neuropsychopharmacol.* (2021) 50:1–11. doi: 10.1016/j.euroneuro.2021.04.004
50. Duman RS, Aghajanian GK, Sanacora G, Krystal JH. Synaptic plasticity and depression: new insights from stress and rapid-acting antidepressants. *Nat Med.* (2016) 22:238–49.
51. Li N, Lee B, Liu R-J, Banasr M, Dwyer JM, Iwata M, et al. mTOR-dependent synapse formation underlies the rapid antidepressant effects of NMDA antagonists. *Science.* (2010) 329:959–64. doi: 10.1126/science.1190287
52. Pham TH, Gardier AM. Fast-acting antidepressant activity of ketamine: highlights on brain serotonin, glutamate, and GABA neurotransmission in preclinical studies. *Pharmacol Ther.* (2019) 199:58–90. doi: 10.1016/j.pharmthera.2019.02.017
53. Li N, Liu R-J, Dwyer JM, Banasr M, Lee B, Son H, et al. Glutamate N-methyl-D-aspartate receptor antagonists rapidly reverse behavioral and synaptic deficits caused by chronic stress exposure. *Biol Psychiatry.* (2011) 69:754–61. doi: 10.1016/j.biopsych.2010.12.015
54. Averill LA, Purohit P, Averill CL, Boesl MA, Krystal JH, Abdallah CG. Glutamate dysregulation and glutamatergic therapeutics for PTSD: evidence from human studies. *Neurosci Lett.* (2017) 649:147–55. doi: 10.1016/j.neulet.2016.11.064
55. Krystal JH, Abdallah CG, Averill LA, Kelmendi B, Harpaz-Rotem I, Sanacora G, et al. Synaptic loss and the pathophysiology of PTSD: implications for ketamine as a prototype novel therapeutic. *Curr Psychiatry Rep.* (2017) 19:74. doi: 10.1007/s11920-017-0829-z
56. Abdallah CG, Roache JD, Averill LA, Young-McCaughan S, Martini B, Gueorguieva R, et al. Repeated ketamine infusions for antidepressant-resistant PTSD: methods of a multicenter, randomized, placebo-controlled clinical trial. *Contemp Clin Trials.* (2019) 81:11–8.
57. Evans JW, Szczepanik J, Brutsché N, Park LT, Nugent AC, Zarate CA. Default mode connectivity in major depressive disorder measured up to 10 days after ketamine administration. *Biol Psychiatry.* (2018) 84:582–90. doi: 10.1016/j.biopsych.2018.01.027
58. Akiki TJ, Averill CL, Abdallah CG. A network-based neurobiological model of PTSD: evidence from structural and functional neuroimaging studies. *Curr Psychiatry Rep.* (2017) 19:81. doi: 10.1007/s11920-017-0840-4
59. Samalin L, Rothärmel M, Mekaoui L, Gaudré-Wattinne E, Codet MA, Bouju S, et al. Esketamine nasal spray in patients with treatment-resistant depression: the real-world experience in the French cohort early-access programme. *Int J Psychiatry Clin Pract.* (2022) 1–11. doi: 10.1080/13651501.2022.2030757
60. Schönenberg M, Reichwald U, Domes G, Badke A, Hautzinger M. Effects of peritraumatic ketamine medication on early and sustained posttraumatic stress symptoms in moderately injured accident victims. *Psychopharmacology (Berl).* (2005) 182:420–5. doi: 10.1007/s00213-005-0094-4
61. Dore J, Turnipseed B, Dwyer S, Turnipseed A, Andries J, Ascani G, et al. Ketamine assisted psychotherapy (KAP): patient demographics, clinical data and outcomes in three large practices administering ketamine with psychotherapy. *J Psychoactive Drugs.* (2019) 51:189–98. doi: 10.1080/02791072.2019.1587556
62. Grabski M, McAndrew A, Lawn W, Marsh B, Raymen L, Stevens T, et al. Adjunctive ketamine with relapse prevention-based psychological therapy in the treatment of alcohol use disorder. *Am J Psychiatry.* (2022) 179:152–62. doi: 10.1176/appi.ajp.2021.21030277
63. Krupitsky E, Burakov A, Romanova T, Dunaevsky I, Strassman R, Grinenko A. Ketamine psychotherapy for heroin addiction: immediate effects and two-year follow-up. *J Subst Abuse Treat.* (2002) 23:273–83. doi: 10.1016/s0740-5472(02)00275-1
64. Wilkinson ST, Rhee TG, Joormann J, Webler R, Ortiz Lopez M, Kitay B, et al. Cognitive behavioral therapy to sustain the antidepressant effects of ketamine in treatment-resistant depression: a randomized clinical trial. *Psychother Psychosom.* (2021) 90:318–27.
65. Bottemanne H, Baldacci A, Muller C, Boyreau A, Claret A. [Ketamine augmented psychotherapy (KAP) in mood disorder: user guide]. *Encephale.* (2021) 48:304–12. doi: 10.1016/j.encep.2021.08.011
66. Kolp E, Friedman HL, Krupitsky E, Jansen K, Sylvester M, Young MS, et al. Ketamine psychedelic psychotherapy: focus on its pharmacology, phenomenology, and clinical applications. *Int J Transpers Stud.* (2014) 33:84–140. doi: 10.24972/ijts.2014.33.2.84
67. Johnson M, Richards W, Griffiths R. Human hallucinogen research: guidelines for safety. *J Psychopharmacol.* (2008) 22:603–20. doi: 10.1177/0269881108093587

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Intramuscular ketamine vs. escitalopram and aripiprazole in acute and maintenance treatment of patients with treatment-resistant depression: A randomized double-blind clinical trial

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Objective: Ketamine, an N-methyl D-aspartate (NMDA) receptor antagonist, can promote rapid action in the management of individuals with treatment-resistant depression (TRD) at sub-anesthetic doses. However, few studies have investigated the long-term use of ketamine administered intravenously (IV) and intranasally (IN). We report the design and rationale of a therapeutic trial for assessing the efficacy, safety, and tolerability of repeated-dose intramuscular (IM) ketamine vs. active treatment (escitalopram and aripiprazole) in TRD patients.

Methods: A comparative, parallel-group, randomized double-blind trial assessing the efficacy, safety, and tolerability of acute (4 weeks) and maintenance (24 weeks) use of IM ketamine (0.75 mg/kg) vs. active control (escitalopram 15 mg and aripiprazole 5 mg) in individuals with moderate-severe intensity TRD (no psychotic symptoms) with or without suicide risk will be conducted. Patients with TRD (18–40 years) will be randomized and blinded to receive ketamine IM or active treatment at a 1:1 ratio for 4 weeks (active treatment) and 24 weeks (maintenance treatment). Subjects will be assessed using clinical scales, monitored for vital signs (VS) after application of injectable medication, and undergo neuropsychological tests. The primary outcome will be changed on the Montgomery-Åsberg Depression Rating Scale (MADRS) during the course of the trial. The study is in running.

Results: This study can potentially yield evidence on the use of IM ketamine in the treatment of depressive disorders as an ultra-rapid low-cost

therapy associated with less patient discomfort and reduced use of medical resources, and can elucidate long-term effects on different outcomes, such as neuropsychological aspects.

Conclusions: The trial can help promote the introduction of a novel accessible approach for the treatment of complex disease (TRD) and also allow refinement of its long-term use.

Clinical trial registration: https://clinicaltrials.gov/ct2/show/NCT04234776, identifier: NCT04234776.

KEYWORDS

ketamine, treatment-resistant depression, N-methyl-D-aspartate receptor antagonist, randomized clinical trial, intramuscular (IM)

Introduction

In 2015, an estimated 300 million people had depression (4.4% of the world's population) (1). Depression is a common recurrent serious mental disorder associated with morbimortality and a burden of 50 million years lived with disability (YLD), constituting the mental disease with the highest global disability (2, 3). The economic impact of depression on productivity ran into billions of dollars (presenteeism and absenteeism) in terms of Gross National Product (GDP) (4). The disease is the largest contributor to suicide (some 800,000 deaths/year), a figure which is probably underestimated (5, 6).

Depressive disorders are heterogeneous diseases categorized by international systems of disease classification and whose treatment approaches are well-defined (7–10). However, only 1/3 of patients experience symptom remission after the first intervention (11, 12). Therapeutic goals have changed over time, and include symptoms remission, recovery of function, improvement in quality of life, and cognitive remission, as well as new antidepressants called "atypical", have been developed in recent decades, such as duloxetine, agomelatine, vortioxetine, among others, in an attempt to optimize therapeutic results (13–15).

A number of definitions of treatment-resistant depression (TRD) exist, but there is a consensus on non-response after the use of 2 or more antidepressants of different classes (with adjustment of adherence, dose, and duration of use) (16, 17). Since the introduction of the concept in 1974, numerous studies have investigated treatment strategies adopting different definitions of the meaning of the illness (18). Treatment-resistant depression accounts for 12–20% of depressed patients and ∼20% of TRD cases are staged as chronic, with various unfavorable clinical outcomes and both social and economic impacts (19–21).

Although numerous TRD treatment strategies exist, many interventions have limited efficacy, undesirable side effects and are high cost or inaccessible, besides presenting other barriers to implementation (22, 23). A new effective, less invasive treatment could significantly relieve the suffering and anguish of patients and their families compared to complex interventions for TRD, for example, neurostimulation treatments (24).

The clinical effects of ketamine involve anesthetic, analgesic, antidepressant, and anti-inflammatory actions (25). The drug is derived from phencyclidine and was developed in the 1960s (26). It has two enantiomers: S-ketamine and R-ketamine, with the racemic preparation containing concentrations of 1:1 (27). The drug undergoes hepatic biotransformation by the liver into different metabolites, norketamine being the most important, a product of demethylation by the P450 cytochrome that is excreted by the kidneys (28). Readily distributed by the tissues, including the brain, ketamine is very lipid soluble and exhibits plasma protein binding (12%) with a half-life of around 10 min (29). Ketamine is an N-methyl D-aspartate (NMDA) receptor antagonist with additional weaker actions on sigma receptors, as well as noradrenalin, serotonin, and dopamine transporters among others (30, 31). A signaling cascade may play a role in the regulation, and synaptic plasticity of the mammalian target of rapamycin (mTOR), and in mediating the rapid effects of ketamine (32). Effective, rapid antidepressant effects *via* non-conventional mechanisms represent one of the most important breakthroughs in the field of psychiatry over the last 50 years (33, 34).

Berman et al. carried out the first clinical trial using intravenous (IV) ketamine at a dose of 0.5 mg/kg in a small sample, observing a meaningful reduction on the Hamilton Depression Scale (HAM-D) after 3 days (35). Subsequently, a growing number of methodologically-refined studies (involving single IV applications) were conducted (36–39). A systematic review of 22 studies [randomized clinical trials (RCTs) and non-RCTs] involving 629 participants investigating the role of ketamine [IV 0.5 mg/kg for unipolar depression (UD) and bipolar depression (BD)] found a rapid effect in most of the studies reviewed, observing greatest magnitude of effect in RCTs at 210–230 min post-application (40). In another systematic review, McGirr et al. investigated the efficacy of ketamine (IV 0.5

mg/kg) in the treatment of depressive episodes of 73 individuals in parallel arms and 110 in cross-over designs (34 participants with BD and 149 with UD), where the primary outcome was clinical remission of symptoms at 24 h, 3 and 7 days vs. placebo: results at 24 h [Odds Ratio (OR) of 7.06 and number needed to treat (NNT) of 5], at 3 days (OR of 3.86 and NNT of 6) and, at 7 days (OR of 4 and NNT of 6) (41).

The strategy of repeated ketamine infusions has been explored over the past decade (24). Six 12-day infusions [10 patients (non-medicated)] with DRT who previously responded to 1 dose (MADRS $\geq$ 50%) had a mean (SD) reduction in scores after the last infusion of 85% (12%) (42). S-ketamine IV was administered to 6 depressed patients (6 infusions over 4 weeks) to investigate clinical efficacy (HAMD-21: after 120 min of application) obtaining scores from the first to the last measurement in 5 subjects of 19 $\rightarrow$ 11, 19 $\rightarrow$ 10, 35 $\rightarrow$ 25, 22 $\rightarrow$ 1, and 21 $\rightarrow$ 2 (43). Subjects with RDT ($n = 24$) undergoing up to 6 ketamine infusions (IV, 0.5 mg/kg, 3 times a week, 12 days) had a response rate of 70.8% with a mean decrease in score MADRS 2 h after the first infusion (18.9 $\pm$ 6.6; $p < 0.001$); sustained during applications (44). A multi-center, double-blind, randomized, placebo-controlled trial of ketamine (IV 0.5 mg/kg) 2 and 3 times weekly confirmed the efficacy of the 2 regimens, with mean change on the MADRS (baseline to day 15, vs. placebo groups [ketamine twice weekly: -18.4 (SD = 12.0); placebo: -5.7 (SD = 10.2); $p < 0.001$; ketamine 3 times weekly: -17.7 (SD = 7.3); placebo: -3.1 (SD = 5.7); $p < 0.001$] (45).

The safety of ketamine has been confirmed for some decades, with anesthetic doses of 4–5 mg/kg intramuscularly (IM) proving effective [93–100% of children (1,022 pediatric cases)] for airways, emesis, or agitation (46). In a small number of patients, the drug can temporarily affect heart rate, and blood pressure and promote myocardial ischemia, although these risks can be attenuated by the use of sub-anesthetic doses and careful patient selection (27, 41, 44, 47). Dissociative states, a common side effect of the drug, are transient (lasting ~40 min, 2 h after use) and are not associated with persistent psychosis or mood swings (48). Of 158 patients given ketamine, 21 (13.3%) withdrew from the study, compared to 10 (7.4%) out of the 135 patients receiving control interventions (OR 1.95, 95%CI 0.86–4.42, $z = 1.59$, $p = 0.11$) (39). Claims that NMDA receptor blocking can cause "brain damage" and that ketamine affects the urinary retract remain the subject of controversy (49). The most common (≥20%) adverse events following the use of the drug include, headache, anxiety, dissociation, nausea, dizziness, and drowsiness on days of the administration, with these effects dissipating within 2 h, while more serious side effects leading to hospitalization or suicide attempts are rare (40, 50, 51). Anti-depressant effects of ketamine are short-lived (days or weeks), although longer-term benefits can be maintained by use of repeat doses, warranting further studies on the prolonged effects of the drug (44, 52). Intranasal (IN) esketamine was approved for use in 2019 by both the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) (53). Other administration routes have also been investigated: IN, subcutaneous (SC), and oral (54–56).

With 93% bioavailability, the plasma concentration of IM ketamine is linear (mg/kg) (57, 58). A woman with depression and metastatic ovarian cancer experienced rapid remission (MADRS < 7) 1 h after receiving the first injection (1 mg/kg IM ketamine) (59). The same dosing repeated over 10 months (1× per week) kept MADRS scores low over the period (60). In 2 cases of bipolar depression with suicide risk, 4 applications of IM ketamine (0.75 mg) every 2 days, there was a reduction of 75.5%-83.3%-85.7% (case 1) and 71.4%-77.2%-60.8% (case 2) in the BDI, BAI, and BSI, respectively (61). Twenty-seven subjects in 3 parallel groups (9 subjects each) had ketamine administered IM and IV (G1 = 0.5 mg/kg IV, G = 0.5 mg/kg IM, and G3 = 0.25 mg/kg IM) with the HAM-D reduced by 58.86, 60.29, and 57.36%, respectively (62). IM ketamine has a recently similar response as potent ECT in 6–9 sessions for 3 weeks (HAM-D and BDI-suicide ideation) (63).

The anti-depressant efficacy of IM ketamine can offer several advantages: less cost (IN esketamine), less discomfort, ease of administration, and reduced reliance on the care team and resources than IV ketamine. The safety and tolerability of this route can provide greater accessibility and represent an adjunct in the treatment of depression and management of suicide risk. Although, the studies currently available on the IM route for ketamine are scarce and have methodological shortcomings: incipient samples, open studies, administration of few doses, subjective outcomes, no comparison with active substances, varying doses, case studies, etc. (59–64).

Methods

Design and study populations

A comparative, parallel-group, randomized, double-blind trial is to be conducted involving an anti-depressant intervention. The experimental group (EG) will use the experimental substance [ketamine IM 0.75 mg/kg, oral placebo (morning), and oral placebo (evening)], while the control group (CG) will use an active treatment administered orally [escitalopram 15 mg (morning), aripiprazole 5 mg (evening) and placebo IM]. The study will be carried out by the Institute of Psychiatry of the University of São Paulo Medical School (HCFMUSP), in conjunction with the Center for Mind Health Studies (NUPE) in the Vale do Itajaí, Santa Catarina state, Brazil. The study is called the KETAMIM project and is Registered Under No. NCT04234776 on the www.ClinicalTrials.gov platform. The study phases and methodological aspects comply with the recommendations of the CONSORT (Consolidated Standard of Reporting Trials) statement and with Good

Clinical Practice guidelines (GCP) (65, 66). The study is in running.

The study shall entail 5 phases: (1) Dissemination (P0): patients referred by health professionals, dissemination in the press or online media; (2) Pre-treatment (PI): ∼2 weeks for the baseline assessment of candidates for study entry; (3) Therapeutic trial (PII): 4 weeks for ketamine use 3 times weekly and of daily oral medications, as well as placebos for both groups, characterizing acute treatment of the disease; (4) Maintenance (PIII): 24 weeks for weekly ketamine use and maintenance of standard treatment and respective placebos; (5) Post-treatment (PIV): 4 weeks for assessing patients after use of ketamine, maintenance oral medication or placebo.

A total of 88 patients with TRD (≥2 failed trials using anti-depressants, plus ECT as an alternative or otherwise) of moderate-severe intensity [according to criteria of Diagnostic and Statistical Manual of Mental Disorders (DSM-5)], and the diagnosis confirmed by the Portuguese version of the clinical interview of the DSM-IV, will be recruited (67). Patients will be block randomized using a computer-generated list into one of the two interventions (1:1 ratio), EG or CG (68). A nurse blinded to the allocation will administer ketamine or saline IM, placebo orally, or the active treatment, respectively.

Inclusion and exclusion criteria

The following individuals will be eligible for study inclusion: Subjects residing in Itajaí valley (Santa Catarina state, Brazil); adults (age 18–40 years) with a primary diagnosis of TRD based on clinical evaluation and confirmed by the SCID-IV [research version (TRD defined as failure of 2–5 clinical trials with anti-depressants including ECT)]; moderate-severe intensity disease [clinical criteria and/or score ≥14 on the Hamilton Depression Rating Scale (17-item HAM-D)]; with no psychotic symptoms; not presenting an imminent risk of suicide (as indicated by clinical evaluation and HAM-D) and/or murder; with anxiety disorders (secondary); with compensated clinical comorbidities and; literate and able to understand the tasks requested (69). Patients and/or legal guardians must be aware of the nature of the study and give consent by signing the Free and Informed Consent form. All patients will undergo a physical and neurological examination, laboratory tests, and an electrocardiogram (ECG) to ascertain their comorbid clinical and/or uncompensated conditions. **The following individuals will be excluded from the study:** Subjects exhibiting imminent risk of suicide, presenting bipolar spectrum disorders or other diagnosed psychiatric conditions (primary); psychoactive substance dependence within the last year; intellectual deficit; allergy to ketamine; and glaucoma. Fertile women must be in use of a clinically acceptable method of birth control [oral contraceptive and/or condom (only unfollowed topic in GCP)]. In the event of clinical doubt regarding pregnancy, a test for beta-human chorionic gonadotropin (βHCG) hormone will be ordered. Patients who become pregnant during the study period will be excluded and referred for obstetric care. The medication wash-out period required before visit 0 will be 1 week for antipsychotics, antidepressants [except fluoxetine (4 weeks)], and for mood stabilizers. No other medications with psychiatric action will be allowed during the study, except for Lorazepam and Zolpidem for patients in the use of a benzodiazepine or hypnotic agent.

Study hypotheses

The principal hypothesis of this study is that ketamine IM provides similar efficacy to active treatment in patients with TRD due to a comparison between the experimental intervention (ketamine IM) vs. active treatment (escitalopram and aripiprazole). Other objectives of the study include confirming the safety and tolerability of the use of ketamine IM during acute and maintenance treatment.

Measures and outcome variables

The study will assess (given in Table 1):

1) Sociodemographic variables: gender, marital status, ethnicity, number of children, income, education, and employment.
2) Clinical characteristics over the life course: clinical and psychiatric comorbidities, smoking, family history of mood disorders, prior pharmacological treatment and ECT, number of mood episodes, previous psychiatric admissions, suicide attempts, currently receiving psychotherapy, and history of sexual, or physical abuse.
3) Clinical history: visits to the emergency room, attempted suicides, or psychiatric hospitalizations.
4) The Montgomery-Åsberg Depression Rating Scale (MADRS) (70, 71): will be applied as a primary outcome measure 3× per week for the first month (PII), 1× per week for 6 months (PIII), and 1× per week (PIV) for 1 month.
5) The Hamilton Rating Scale for Depression (HAM-D) (72, 73): will be applied once in PI to assess symptom severity and again 3× per week for 1 month (PII), 1× per week for 6 months (PIII), and 1× per week (PIV) for 1 month.
6) Vital signs (VS): pulse oximetry, heart monitoring, breathing rate, heart rate, and blood pressure will be checked continuously using non-invasive methods. VS to be monitored 3× per week for the 1st month (PII) and 1× week (PIII) for 2 h continuously after completion of each application.
7) Global Clinical Impression (GCI) scale: this will be applied 3× a week for 1 month (PII), 1× week for 6 months

TABLE 1 Outcome measurements over time.

Scales	Baseline	P1	End of P1	P2	End of P2	P3	P4
SCID	x						
MADRS		x		x		x	x
HAM-D	x	x		x		x	x
CGI-S	x	x		x		x	x
DTS	x		x		x		
Physical and neurological exams	x						
Clinical tests and ECG	x						
VS		x		x		x	
UKU-SERS		x		x		x	
BPRS-12		x		x		x	
CADSS		x		x		x	
YOUNG		x		x		x	
WHOQOL-Bref							
SDS	x		x		x		x
Neuropsychological assessment	x				x		

SCID, Structured Clinical Interview for DSM Disorders; MADRS, Montgomery–Åsberg Depression Rating Scale; HAM-D, Hamilton Depression Scale; CGI-S, Clinical Global Impression—Severity; DTS, Depressed Thoughts Scale; VS, Vital Signs; UKU-SERS, Udvalg for Kliniske Undersøgelser Side Effect Rating Scale; BPRS-12, Brief Psychiatric Rating Scale; CADSS, Clinician-Administered Dissociative States Scale; YOUNG, Young Mania Rating Scale; WHOQOL, World Health Organization Quality-of-Life scale; SDS, Sheehan Disability Scale.

(PIII), and 1× week (PIV) to assess disease severity, global improvement of the condition and hence, treatment efficacy (74).

8) Depression Thoughts Scale (DTS): the DTS will be applied at visit one (V-1), V11, and V-39 to assess for thought distortions (75, 76).
9) Clinician-Administered Dissociative States Scale (CADSS): this will provide a measure of the dissociative effects of ketamine and will be applied 3× per week for the 1st month (PII), and 1× per week for 6 months (PIII), ∼1 h after application of injections (77).
10) Young's Mania Rating Scale (YMRS): this scale will be employed in this study to assess manic switching as an adverse effect of the medications and applied 3× week for the 1st month (PII) and 1× week for 6 months (PIII), ∼1 h after application of injections (78).
11) Brief Psychiatric Rating Scale (BPRS): Sub-item 12 of the scale will be used for detecting the presence of psychotic symptoms arising after application of ketamine, applied 3× week for 1 month (PII) and 1× week (PIII), ∼1 h after application of injections (79).
12) Udvalg Kliniske Undersoegelser Side Effect Rating Scale (UKU-SERS): this will be used to determine the presence of side effects of the medications used and will be applied 3× week for the 1st month (PII) and 1× week (PIII) thereafter, around 1 h after application of injections (79).
13) World Health Organization Quality of Life, brief version (WHOQOL-Bref): this scale will be applied at V-1, V-11, and V-35 (80).
14) Sheehan Disability Scale (SDS): this scale will be applied at V-1, V-11, and V-35 (81).

Randomization and allocation

Randomization will be based on a computer-generated scheme, balanced by the use of randomly permutated blocks and stratified by the statistician of the Institute of Psychiatry of the FMUSP to receive ketamine IM or active treatment at a 1:1 ratio (82).

Intervention

Two groups will be formed: a study group and an active control group. The study group will receive dextroketamine chloralhydrate IM (0.75 mg/kg) plus 2 placebo tablets orally, one in the morning and the other at night. The active control group will receive saline solution IM plus one of the alternative therapies for TRD: escitalopram 15 mg (morning) or aripiprazole 5 mg (night) (10). Injections will be applied alternately to gluteal muscles in the external upper quadrants. For 4 weeks (1 month), applications will be applied on Mondays, Wednesdays, and Fridays (giving a total of 12 interventions). For the ensuing 6 months, applications will be weekly (giving a total of 24 interventions). For 4 weeks (1 month), participants will continue to receive the tablets (active treatment or placebo) and be monitored. Safety parameters: vital

signs will be monitored continuously by the researchers for 2 h post-application: fingertip pulse oximetry, heart rate, breathing rate, blood pressure, and electrocardiography. Abnormal blood pressure will be defined as low <90/60 mmHg and high >140/90 mmHg. Abnormal heart rate will be defined as <60 or >100 bpm. Abnormal breathing rate will be defined as <10 cycles/min or >20 cycles/min. Low oxygen saturation will be defined as levels <95%. Collateral symptoms such as nausea and vomiting will be managed using ondansetron 8 mg sublingually (SL). Individuals presenting episodes of anxiety, hallucinations, or intense dissociative effects will be given clonazepam SL 0.25 mg. An emergency team will be deployed in the event of serious acute events such as heart arrhythmia or prolonged hypertension. Patients will be placed under observation in a quiet comfortable environment and will be cleared to leave after 2 h, accompanied by a competent adult.

Blinding

The researchers performing the clinical monitoring and application of the outcomes will be blinded, and the study participants will also be blinded. A nurse, not involved in data collection, will distribute the medications and apply the injections according to the randomization process.

Sample size calculation

The sample size was calculated based on a similarly designed RCT (45). Assuming a statistical power of 90% with a clinically significant minimum effect of 0.5 (Cohen's d) and alpha 5%, a total of 88 subjects will be needed (44 in the EG and 44 in the CG). Given this is a long-duration study, a drop-out rate of 10–20% was estimated.

Statistical analysis

All analyzes will be performed using the Statistical Package for the Social Sciences-SPSS® (82). Specific and sociodemographic variables will be expressed generally and between intervention groups in relative and absolute frequencies, means, medians, standard deviation, and 95% confidence interval. Continuous variables will be evaluated by the *T*-student or U-Mann Whitney-test according to their distribution and the qualitative ones by the X^2-test. The distribution of variables will be evaluated using the Shapiro Wilk. The global significance level adopted is 0.05. To determine the effects of intervention throughout the study (main outcome and other scales), repeated measures ANOVA (two-way) will be applied, considering the temporal effect of visits (v-0 to v-final) and the intervention effect (EG × CG). In identifying the significant interaction effect, one-way repeated measures ANOVA test or its non-parametric alternative (Friedmann test) will be performed to verify that the effect is independent of treatment. Contingency tables and X^2-tests will be applied to compare responders and non-responders in the intervention groups. Analysis using intent-to-treat (ITT) will be employed to assess the results (83). Vital signs will be assessed using two repeated measures ANOVA (two-way). First, considering the effect of the intervention immediately (3 evaluations at each visit) and the second, evaluating the effect of the intervention on VS over time (acute and maintenance treatment).

Cognitive assessments

Neuropsychological tests will be applied at P0 and upon conclusion of PIII: to evaluate changes resulting from treatments:

(1) Digit span (subtest of Wechsler Intelligence Scale): measures attention span capacity and working memory; **(2) Wisconsin Card Sorting Test-64:** evaluate mental flexibility and ability to form abstract concepts in rapidly changing situations; **(3) Stroop Color-Word Test** (84): analyzes the maintenance of inhibitory control, from the suppression of the usual response in favor of an unusual response; **(4) Wechsler Abbreviated Scale of Intelligence (WASI):** the IQ is obtained from the sum of the gross results of the subtests converted to results weighted according to the individual's age (85); **(5) Verbal Fluency Test:** measures the ability to spontaneously produce words under semantic restriction and mind control (86); **(6) Rey's Complex Figure:** analyzes the visual-constructive ability, the ability to plan and problem-solving strategies (87) and; **(7) Trail-Making Test:** The purpose of this test is to assess alternate attention.

Reasons for withdrawal or termination

Subjects who meet one or more of the criteria outlined below will be withdrawn from the study:

1) Intolerance to medications;
2) Abnormal results on lab tests;
3) Serious adverse event;
   The above-mentioned items will be assessed individually by the team according to medical criteria. Prolonged arterial hypertension, serious allergies, abnormal heart rate, or worsening of pre-existing diseases, among others, will be checked. Manic switching, imminent risk of suicide, attempted suicide, severe psychotic symptoms, aggressiveness, etc. will constitute grounds for study withdrawal.
4) Relapse or lack of response in Phases II or III. Lack of response will be defined as reduction or maintenance

of scores on the index scale of ≤25%, whereas relapse will be the attainment of scores <50% in individuals who had achieved remission or response during the study.

5) Two consecutive visits missed;
6) Withdrawal of consent for the study.

Patients who discontinue the study shall be given guidance to continue outpatient psychiatric treatment.

Discussion

We describe a protocol for an RCT to assess the efficacy, safety, and tolerability of ketamine vs. active treatment in the acute and maintenance stages of TRD. This study represents the first such trial with this design to date. A total of 12 applications of ketamine IM (0.75 mg/kg) will be administered in the active phase and 24 in the maintenance phase to volunteers randomized into the EG. The sample size for the study was determined by drawing on a similar study found in the literature. The objectives of the planned study, besides the primary outcome of improving symptoms (as measured by the MADRS), is to assess the safety (VS) and tolerability of ketamine at sub-anesthetic doses and side effects, such as the development of depressive thoughts, functioning, quality of life, and neuropsychological effects, in addition to evaluating treatment efficacy in the acute and maintenance phases. The anti-depressant effects of ketamine appear to be dose-dependent and over the last 20 years have been studied using "sub-anesthetic" doses (0.5–1 mg/kg) for the treatment of depression (51). For this trial, it was decided to use ketamine at a dose that lies in the middle of this range (0.75 mg/kg), together with an administration route (IM) that provides similar bioavailability as IV, the most studied route to date. Studies comparing the different routes for ketamine in depression remain incipient (58). Although TRD is an amalgam of modern psychiatry, the impact of the disease and its myriad symptoms remain a major public health problem (19, 20). The issues involved in the efficacy and safety of ketamine IM include the wide use and accessibility of this low-cost substance, known to medicine for decades, yet lacking a clear prescription in current guidelines. The rapid anti-depressant and anti-suicidal action of the drug, together with its glutamatergic neurotransmitter regulation, has led to the recognition of ketamine as a new paradigm in modern psychiatry (34). Patients with compensated clinical comorbidities are to be included in the sample, conferring greater external validity to the findings. The study described must be interpreted according to its limitations regarding generalization of results: sample size, criteria for eligibility (exclusion of individuals with other decompensated psychiatric and clinical comorbidities). Difficulties blinding to ketamine given its dissociative effects, despite the various measures taken to safeguard this bias, may constitute a further limitation.

Conclusions

The study will investigate the efficacy, safety, and tolerability of the use of ketamine IM in the treatment of TRD *via* a double-blind, parallel-group randomized, placebo-controlled trial. Clinical information, monitoring to control vital signs and standardized scales will help further understanding of the relationship of the disease with ketamine use. Future studies investigating the potential benefits of repeated ketamine infusions, non-parenteral administration alternatives, the safety of long-term use, reduced potential for abuse, and alternatives with fewer systemic effects can contribute to the management of TRD, a chronic and complex disease.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving human participants were reviewed and approved by Research Ethics Committee of the University of São Paulo (Permit No. 2.530.851). The patients/participants provided their written informed consent to participate in this study.

Author contributions

Study conception and design: MC, FF, AC, and RM. Drafting of the manuscript: MC and RM. Statistic review: AG. Study execution: MC, DM, MAS, MSS, VA, JA, and AT. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

1. World Health Organization. *Depression and Other Common Mental Disorders: Global Health Estimates*. Geneva: World Health Organization (2017).

2. Kessler RC, Bromet EJ. The epidemiology of depression across cultures. *Annu Rev Public Health.* (2013) 34:119–38. doi: 10.1146/annurev-publhealth-031912-114409

3. GBD 2015 Disease and Injury Incidence and Prevalence Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 310 diseases and injuries, 1990-2015: a systematic analysis for the Global Burden of Disease Study 2015. *Lancet*. (2016) 388:1545–602. doi: 10.1016/S0140-6736(16)31678-6

4. Evans-Lacko S, Knapp M. Global patterns of workplace productivity for people with depression: absenteeism and presenteeism costs across eight diverse countries. *Soc Psychiatry Psychiatr Epidemiol.* (2016) 51:1525–37. doi: 10.1007/s00127-016-1278-4

5. World Health Organization. *Preventing Suicide: A Global Imperative*. Geneva: World Health Organization (2014).

6. Rihmer Z, Gonda X. Pharmacological prevention of suicide in patients with major mood disorders. *Neurosci Biobehav Rev.* (2013) 37:2398–403. doi: 10.1016/j.neubiorev.2012.09.009

7. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders-5*. Washington, DC: American Psychiatric Association (2013).

8. World Health Organization. *International Classification of Diseases, 11th Revision (ICD-11)*. Geneva: World Health Organization (2018).

9. Millan MJ, Goodwin GM, Meyer-Lindenberg A, Ove Ögren S. Learning from the past and looking to the future: emerging perspectives for improving the treatment of psychiatric disorders. *Eur Neuropsychopharmacol.* (2015) 25:599–656. doi: 10.1016/j.euroneuro.2015.01.016

10. Kennedy SH, Lam RW, McIntyre RS, Tourjman SV, Bhat V, Blier P, et al. Canadian network for mood and anxiety treatments (CANMAT) 2016 clinical guidelines for the management of adults with major depressive disorder: section 3. *Pharmacol Treat Can J Psychiatry*. (2016) 61:540–60. doi: 10.1177/0706743716659417

11. Rush AJ, Trivedi MH, Wisniewski SR, Nierenberg AA, Stewart JW, Warden D, et al. Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: a STAR*D report. *Am J Psychiatry*. (2006) 163:1905–17. doi: 10.1176/ajp.2006.163.11.1905

12. Rush AJ, Trivedi MH, Stewart JW, Nierenberg AA, Fava M, Kurian BT, et al. Combining medications to enhance depression outcomes (CO-MED): acute and long-term outcomes of a single-blind randomized study. *Am J Psychiatry*. (2011) 168:689–701. doi: 10.1176/appi.ajp.2011.10111645

13. McIntyre RS. Using measurement strategies to identify and monitor residual symptoms. *J Clin Psychiatry*. (2013) 74:14–8. doi: 10.4088/JCP.12084su1c.03

14. Pompili M, Serafini G, Innamorati M, Venturini P, Fusar-Poli P, Sher L, et al. Agomelatine, a novel intriguing antidepressant option enhancing neuroplasticity: a critical review. *World J Biol Psychiatry*. (2013) 14:412–31. doi: 10.3109/15622975.2013.765593

15. Girardi P, Pompili M, Innamorati M, Mancini M, Serafini G, Mazzarini L, et al. Duloxetine in acute major depression: review of comparisons to placebo and standard antidepressants using dissimilar methods. *Hum Psychopharmacol.* (2009) 24:177–90. doi: 10.1002/hup.1005

16. Berlim MT, Turecki G. Definition, assessment, and staging of treatment-resistant refractory major depression: a review of current concepts and methods. *Can J Psychiatry*. (2007) 52:46–54. doi: 10.1177/070674370705200108

17. Bennabi D, Aouizerate B, El-Hage W, Doumy O, Moliere F, Courtet P, et al. Risk factors for treatment resistance in unipolar depression: a systematic review. *J Affect Disord*. (2015) 171:137–41. doi: 10.1016/j.jad.2014.09.020

18. Ruhé HG, van Rooijen G, Spijker J, Peeters FP, Schene AH. Staging methods for treatment resistant depression. A systematic review. *J Affect Disord.* (2012) 137:35–45. doi: 10.1016/j.jad.2011.02.020

19. McIntyre RS, Filteau MJ, Martin L, Patry S, Carvalho A, Cha DS, et al. Treatment-resistant depression: definitions, review of the evidence, and algorithmic approach. *J Affect Disord.* (2014) 156:1–7. doi: 10.1016/j.jad.2013.10.043

20. Mrazek DA, Hornberger JC, Altar CA, Degtiar I. A review of the clinical, economic, and societal burden of treatment-resistant depression: 1996-2013. *Psychiatr Serv.* (2014) 65:977–87. doi: 10.1176/appi.ps.201300059

21. Lepine BA, Moreno RA, Campos RN, Couttolenc BF. Treatment-resistant depression increases health costs and resource utilization. *Braz J Psychiatry*. (2012) 34:379–88. doi: 10.1016/j.rbp.2012.05.009

22. Little A. Treatment-resistant depression. *Am Fam Physician*. (2009) 80:167–72.

23. Philip NS, Carpenter LL, Tyrka AR, Price LH. Pharmacologic approaches to treatment resistant depression: a re-examination for the modern era. *Expert Opin Pharmacother*. (2010) 11:709–22. doi: 10.1517/14656561003614781

24. Szymkowicz SM, Finnegan N, Dale RM. A 12-month naturalistic observation of three patients receiving repeat intravenous ketamine infusions for their treatment-resistant depression. *J Affect Disord*. (2013) 147:416–20. doi: 10.1016/j.jad.2012.10.015

25. Zanos P, Moaddel R, Morris PJ, Riggs LM, Highland JN, Georgiou P, et al. Ketamine and ketamine metabolite pharmacology: insights into therapeutic mechanisms. *Pharmacol Rev.* (2018) 70:621–60. doi: 10.1124/pr.117.015198

26. Hillhouse TM, Porter JH. A brief history of the development of antidepressant drugs: from monoamines to glutamate. *Exp Clin Psychopharmacol.* (2015) 23:1–21. doi: 10.1037/a0038550

27. Reich DL, Silvay G. Ketamine: an update on the first twenty-five years of clinical experience. *Can J Anaesth.* (1989) 36:186–97. doi: 10.1007/BF03011442

28. Zarate CA Jr, Brutsche N, Laje G, Luckenbaugh DA, Venkata SL, Ramamoorthy A, et al. Relationship of ketamine's plasma metabolites with response, diagnosis, and side effects in major depression. *Biol Psychiatry*. (2012) 72:331–8. doi: 10.1016/j.biopsych.2012.03.004

29. Haas DA, Harper DG. Ketamine: a review of its pharmacologic properties and use in ambulatory anesthesia. *Anesth Prog.* (1992) 39:61–8.

30. Andrade C. Ketamine for depression, 3: does chirality matter? *J Clin Psychiatry*. (2017) 78:e674–7. doi: 10.4088/JCP.17f11681

31. Stahl SM. Mechanism of action of ketamine. *CNS Spectr.* (2013) 18:171–4. doi: 10.1017/S109285291300045X

32. Dwyer JM, Duman RS. Activation of mammalian target of rapamycin and synaptogenesis: role in the actions of rapid-acting antidepressants. *Biol Psychiatry*. (2013) 73:1189–98. doi: 10.1016/j.biopsych.2012.11.011

33. Li N, Liu RJ, Dwyer JM, Banasr M, Lee B, Son H, et al. Glutamate N-methyl-D-aspartate receptor antagonists rapidly reverse behavioral and synaptic deficits caused by chronic stress exposure. *Biol Psychiatry*. (2011) 69:754–61. doi: 10.1016/j.biopsych.2010.12.015

34. Zarate C, Duman RS, Liu G, Sartori S, Quiroz J, Murck H. New paradigms for treatment-resistant depression. *Ann N Y Acad Sci.* (2013) 1292:21–31. doi: 10.1111/nyas.12223

35. Berman RM, Cappiello A, Anand A, Oren DA, Heninger GR, Charney DS, et al. Antidepressant effects of ketamine in depressed patients. *Biol Psychiatry*. (2000) 47:351–4. doi: 10.1016/S0006-3223(99)00230-9

36. Diazgranados N, Ibrahim L, Brutsche NE, Newberg A, Kronstein P, Khalife S, et al. A randomized add-on trial of an N-methyl-D-aspartate antagonist in treatment-resistant bipolar depression. *Arch Gen Psychiatry*. (2010) 67:793–802. doi: 10.1001/archgenpsychiatry.2010.90

37. Zarate CA, Jr., Brutsche NE, Ibrahim L, Franco-Chaves J, Diazgranados N, Cravchik A, et al. Replication of ketamine's antidepressant efficacy in bipolar depression: a randomized controlled add-on trial. *Biol Psychiatry*. (2012) 71:939–46. doi: 10.1016/j.biopsych.2011.12.010

38. Sos P, Klirova M, Novak T, Kohutova B, Horacek J, Palenicek T. Relationship of ketamine's antidepressant and psychotomimetic effects in unipolar depression. *Neuro Endocrinol Lett.* (2013) 34:287–93.

39. Murrough JW, Iosifescu DV, Chang LC, Al Jurdi RK, Green CE, Perez AM, et al. Antidepressant efficacy of ketamine in treatment-resistant major depression: a two-site randomized controlled trial. *Am J Psychiatry.* (2013) 170:1134–42. doi: 10.1176/appi.ajp.2013.13030392

40. Caddy C, Giaroli G, White TP, Shergill SS, Tracy DK. Ketamine as the prototype glutamatergic antidepressant: pharmacodynamic actions, and a systematic review and meta-analysis of efficacy. *Ther Adv Psychopharmacol.* (2014) 4:75–99. doi: 10.1177/2045125313507739

41. McGirr A, Berlim MT, Bond DJ, Fleck MP, Yatham LN, Lam RW, et al. systematic review and meta-analysis of randomized, double-blind, placebo-controlled trials of ketamine in the rapid treatment of major depressive episodes. *Psychol Med.* (2015) 45:693–704. doi: 10.1017/S0033291714001603

42. aan het Rot M, Collins KA, Murrough JW, Perez AM, Reich DL, Charney DS, et al. Safety and efficacy of repeated-dose intravenous ketamine for treatment-resistant depression. *Biol Psychiatry.* (2010) 15:139–45. doi: 10.1016/j.biopsych.2009.08.038

43. Segmiller F, Rüther T, Linhardt A, Padberg F, Berger M, Pogarell O, et al. Repeated S-ketamine infusions in therapy resistant depression: a case series. *J Clin Pharmacol.* (2013) 53:996–8. doi: 10.1002/jcph.122

44. Shiroma PR, Johns B, Kuskowski M, Wels J, Thuras P, Albott CS, et al. Augmentation of response and remission to serial intravenous subanesthetic ketamine in treatment resistant depression. *J Affect Disord.* (2014) 155:123–9. doi: 10.1016/j.jad.2013.10.036

45. Singh JB, Fedgchin M, Daly EJ, De Boer P, Cooper K, Lim P, et al. A double-blind, randomized, placebo-controlled, dose-frequency study of intravenous ketamine in patients with treatment-resistant depression. *Am J Psychiatry.* (2016) 173:816–26. doi: 10.1176/appi.ajp.2016.16010037

46. Green SM, Hummel CB, Wittlake WA, Rothrock SG, Hopkins GA, Garrett W. What is the optimal dose of intramuscular ketamine for pediatric sedation? *Acad Emerg Med.* (1999) 6:21–6. doi: 10.1111/j.1553-2712.1999.tb00089.x

47. Jin JF, Zhu LL, Chen M, Xu HM, Wang HF, Feng XQ, et al. The optimal choice of medication administration route regarding intravenous, intramuscular, and subcutaneous injection. *Patient Prefer Adherence.* (2015) 9:923–42. doi: 10.2147/PPA.S87271

48. Luckenbaugh DA, Niciu MJ, Ionescu DF, Nolan NM, Richards EM, Brutsche NE, et al. Do the dissociative side effects of ketamine mediate its antidepressant effects? *J Affect Disord.* (2014) 159:56–61. doi: 10.1016/j.jad.2014.02.017

49. Rasmussen KG. Has psychiatry tamed the "ketamine tiger?" Considerations on its use for depression and anxiety. *Prog Neuropsychopharmacol Biol Psychiatry.* (2016) 64:218–24. doi: 10.1016/j.pnpbp.2015.01.002

50. Daly EJ, Singh JB, Fedgchin M, Cooper K, Lim P, Shelton RC, et al. Efficacy and safety of intranasal esketamine adjunctive to oral antidepressant therapy in treatment-resistant depression: a randomized clinical trial. *JAMA Psychiatry.* (2018) 75:139–48. doi: 10.1001/jamapsychiatry.2017.3739

51. Memon RI, Naveed S, Faquih AE, Fida A, Abbas N, Chaudhary AMD, et al. Effectiveness and safety of ketamine for unipolar depression: a systematic review. *Psychiatr Q.* (2020) 91:1147–92. doi: 10.1007/s11126-020-09830-6

52. Murrough JW, Perez AM, Pillemer S, Stern J, Parides MK, aan het Rot M, et al. Rapid and longer-term antidepressant effects of repeated ketamine infusions in treatment-resistant major depression. *Biol Psychiatry.* (2013) 74:250–6. doi: 10.1016/j.biopsych.2012.06.022

53. McIntyre RS, Rosenblat JD, Nemeroff CB, Sanacora G, Murrough JW, Berk M, et al. Synthesizing the evidence for ketamine and esketamine in treatment-resistant depression: an international expert opinion on the available evidence and implementation. *Am J Psychiatry.* (2021) 178:383–99. doi: 10.1176/appi.ajp.2020.20081251

54. Lapidus KA, Levitch CF, Perez AM, Brallier JW, Parides MK, Soleimani L, et al. A randomized controlled trial of intranasal ketamine in major depressive disorder. *Biol Psychiatry.* (2014) 76:970–6. doi: 10.1016/j.biopsych.2014.03.026

55. Arabzadeh S, Hakkikazazi E, Shahmansouri N, Tafakhori A, Ghajar A, Jafarinia M, et al. Does oral administration of ketamine accelerate response to treatment in major depressive disorder? Results of a double-blind controlled trial. *J Affect Disord.* (2018) 235:236–41. doi: 10.1016/j.jad.2018.02.056

56. Cavenaghi VB, da Costa LP, Lacerda ALT, Hirata ES, Miguel EC, Fraguas R. Subcutaneous ketamine in depression: a systematic review. *Front Psychiatry.* (2021) 12:513068. doi: 10.3389/fpsyt.2021.513068

57. Grant IS, Nimmo WS, Clements JA. Pharmacokinetics and analgesic effects of im and oral ketamine. *Br J Anaesth.* (1981) 53:805–10. doi: 10.1093/bja/53.8.805

58. Loo CK, Gálvez V, O'Keefe E, Mitchell PB, Hadzi-Pavlovic D, Leyden J, et al. Placebo-controlled pilot trial testing dose titration and intravenous, intramuscular and subcutaneous routes for ketamine in depression. *Acta Psychiatr Scand.* (2016) 134:48–56. doi: 10.1111/acps.12572

59. Zanicotti CG, Perez D, Glue P. Mood and pain responses to repeat dose intramuscular ketamine in a depressed patient with advanced cancer. *J Palliat Med.* (2012) 15:400–3. doi: 10.1089/jpm.2011.0314

60. Grott Zanicotti C, Perez D, Glue P. Case report: long-term mood response to repeat dose intramuscular ketamine in a depressed patient with advanced cancer. *J Palliat Med.* (2013) 16:719–20. doi: 10.1089/jpm.2013.0057

61. Cigognini MA, Moreno RA. Intramuscular ketamine in depression, suicidal thoughts and anxiety: a report on two case. *Eur Psychiatry.* (2017) 41:S420. doi: 10.1016/j.eurpsy.2017.01.378

62. Chilukuri H, Reddy NP, Pathapati RM, Manu AN, Jollu S, Shaik AB. Acute antidepressant effects of intramuscular versus intravenous ketamine. *Indian J Psychol Med.* (2014) 36:71–6. doi: 10.4103/0253-7176.127258

63. Kheirabadi D, Kheirabadi GR, Mirlohi Z, Tarrahi MJ, Norbaksh A. Comparison of Rapid antidepressant and antisuicidal effects of intramuscular ketamine, oral ketamine, and electroconvulsive therapy in patients with major depressive disorder: a pilot study. *J Clin Psychopharmacol.* (2020) 40:588–93. doi: 10.1097/JCP.0000000000001289

64. Harihar H, Dasari P, Srinivas JS. Intramuscular ketamine in acute depression: a report on two cases. *Indian J Psychiatry.* (2013) 55:186–8. doi: 10.4103/0019-5545.111461

65. Moher D, Schulz KF, Altman DG. The CONSORT statement: revised recommendations for improving the quality of reports of parallel-group randomized trials. *Lancet.* (2001) 357:1191–4. doi: 10.1016/S0140-6736(00)04337-3

66. European Medicines Agency. *Guideline for Good Clinical Practice E6(R2).* London: European Medicines Agency (2018). p. 1–68.

67. Del-Ben CM, Vilela JAA, Crippa JADS, et al. Confiabilidade da Entrevista Clínica Estruturada para o DSM-IV: versão clínica traduzida para o português. *Braz J Psychiatry.* (2001) 23:156–9. doi: 10.1590/S1516-44462001000300008

68. Schulz KF Grimes DA. Allocation concealment in randomized trials: defending against deciphering. Lancet 2002; 359: 614–618. doi: 10.1016/S0140-6736(02)07750-4

69. Hamilton M. A rating scale for depression. *J Neurol Neurosurg Psychiatry.* (1960) 23:56–62. doi: 10.1136/jnnp.23.1.56

70. Montgomery SA, Asberg M. A new depression scale designed to be sensitive to change. *Br J Psychiatry.* (1979) 134:382–9. doi: 10.1192/bjp.134.4.382

71. Fernandes F, Carneiro A, Campos RN. Soeiro-de-Souza MG, Barros VB, Moreno RA. SIGMA-VB: validity and reliability of the Brazilian Portuguese version of the Montgomery-Åsberg Depression Rating Scale using the Structured Interview Guide for the MADRS. *Braz J Psychiatry.* (2019) 41:297–302. doi: 10.1590/1516-4446-2018-0105

72. Freire MA, de Figueiredo VLM, Gomide A, et al. Hamilton Scale: a study of the psychometric characteristics in a sample from Southern Brazil. *J Bras Psiquiatr.* (2014) 63:281–9. doi: 10.1590/0047-20850000 00036

73. Carneiro AM, Fernandes F, Moreno RA. Hamilton depression rating scale and montgomery-asberg depression rating scale in depressed and bipolar I patients: psychometric properties in a Brazilian sample. *Health Qual Life Outcomes.* (2015) 13:1–8. doi: 10.1186/s12955-015-0235-3

74. Busner J. Targum SD. The clinical global impressions scale: applying a research tool in clinical practice. *Psychiatry.* (2007) 4:28–37.

75. Carneiro AM, e Baptista MN. Desenvolvimento e propriedades psicométricas da Escala de Pensamentos Depressivos – EPD. *Revista Brasileira de Terapias Cognitivas.* (2012) 8:74–84. doi: 10.5935/1808-5687.20120012

76. Carneiro AM, Baptista MN, Moreno RA. Depression thoughts scale: association with depression rating scales. *J Depress Anxiety.* (2014) 3:1–6.

77. Bremner JD, Krystal JH, Putnam FW, Southwick SM, Marmar C, Charney DS, et al. Measurement of dissociative states with the Clinician-Administered Dissociative States Scale (CADSS). *J Trauma Stress.* (1998) 11:125–36. doi: 10.1023/A:1024465317902

78. Young RC, Biggs JT, Ziegler VE, Meyer DA. A rating scale for mania: reliability, validity and sensitivity. *Br J Psychiatry.* (1978) 133:429–35. doi: 10.1192/bjp.133.5.429

79. Overall JE Gorham DR. The brief psychiatry rating scale. *Psychol Rep.* (1962) 10:799–812. doi: 10.2466/pr0.1962.10.3.799

80. Fleck MP, Louzada S, Xavier M, Chachamovich E, Vieira G, Santos L, et al. Application of the Portuguese version of the abbreviated instrument of quality life WHOQOL-bref. *Rev Saude Publica.* (2000) 34:178–83. doi: 10.1590/S0034-89102000000200012

81. Sheehan DV, Harnett-Sheehan K, Raj BA. The measurement of disability. *Int Clin Psychopharmacol.* (1996) 11:89–95. doi: 10.1097/00004850-199606003-00015

82. StataCorp L. Stata data analysis and statistical Software. *Spec Ed Rel.* (2007) 10:733.

83. Soares I, Carneiro AV. Intention-to-treat analysis in clinical trials: principles and practical importance. *Rev Port Cardiol.* (2002) 21:1191–8.

84. Regard M. Cognitive rigidity and flexibility: a neuropsychological study. A Compendium of neuropsychological tests. Oxford: Oxford University Press (1998).

85. Wechsler D. *Wechsler Abbreviated Scale of Intelligence*. New York, NY: Psychological Corporation (1999).

86. Spreen O, Strauss E. *A Compendium of Neuropsychological Tests*. Oxford: Oxford University Press (1998).

87. Rey A. *Figuras Complexas de Rey - Teste de Cópia e de reprodução de memória de figuras Geométricas Complexas: Manual - Revisão técnica e tradução Terezinha Rey e Lucia Fleury Franco; adaptação brasileira de Margareth da Silva Oliveira*. São Paulo: Casa do Psicólogo (1998/1999).

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Ketamine as a prophylactic resilience-enhancing agent

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Stress exposure is one of the greatest risk factors for psychiatric illnesses, including major depressive disorder (MDD) and posttraumatic stress disorder (PTSD). Enhancing stress resilience could potentially protect against the development of stress-induced psychiatric disorders, yet no resilience-enhancing pharmaceuticals have been developed to date. This review serves to consider the existing evidence for a potential pro-resilience effect of ketamine in rodents as well as the preliminary evidence of ketamine as a prophylactic treatment for postpartum depression (PPD) in humans. Several animal studies have demonstrated that ketamine administered 1 week prior to a stressor (e.g., chronic social defeat and learned helplessness) may protect against depressive-like behavior. A similar protective effect has been demonstrated against PTSD-like behavior following Contextual Fear Conditioning (CFC). Recent work has sought to explore if the administration of ketamine prevented the development of postpartum depression (PPD) in humans. Researchers administered ketamine immediately following caesarian-section and found a significantly reduced prevalence of PPD in the ketamine-treated groups compared to the control groups. Utilizing ketamine as a resilience-enhancing treatment may have unique applications, including leading to a deeper understanding of the neurobiological mechanism underlying resilience. Future trials aiming to translate and replicate these findings with humans are warranted.

KEYWORDS

ketamine, prophylactic, resilience, stress, prevention

Introduction

Stress exposure is one of the greatest risk factors for psychiatric illnesses, including major depressive disorder (MDD) and posttraumatic stress disorder (PTSD). MDD is a pervasive condition affecting more than 300 million people and is a leading cause of disability worldwide (1). Currently available treatments for MDD and PTSD include lifestyle changes, psychological therapies, antidepressants, and other medications. The glutamate N-methyl-D-aspartate (NMDA) receptor antagonist ketamine has been associated with rapid antidepressant and anti-suicidal effects in several clinical trials

on patients with treatment-resistant depression [TRD; (2–5)] and also appears to be effective for the treatment of PTSD (6, 7). Ketamine trials with PTSD have found improved overall PTSD symptom severity and specifically improved symptom clusters of intrusion, avoidance, and negative mood and cognitions. In 2019, esketamine nasal spray (SPRAVATO) was FDA approved for the treatment of Treatment Resistant MDD (TRD) and in 2020, the label was updated to include MDD with suicidal ideation or behavior (8). Due to its novel mechanism of action, ketamine's use as an antidepressant is considered one of the biggest developments in psychiatry and psychopharmacology in decades (9).

Enhancing stress resilience in at-risk populations could potentially protect against the development of stress-induced psychiatric disorders, yet no resilience-enhancing pharmaceuticals have been identified to date. Stress resilience is a multidimensional construct with a variety of definitions. Stress resilience has been defined as the ability to experience stress without developing psychopathology but has also been associated with the concept of adaptation (or the ability to "bounce back"), the ability to quickly recover after a stressor, or the capacity to maintain functioning following adversity (40). In recent years, there is emerging evidence from preclinical data that the administration of ketamine prior to an acute stressor prevents the development of depressive-like or PTSD-like behavior in animals (see Table 1). In addition, recent human clinical trials suggest that the administration of ketamine immediately following cesarean section may reduce the incidence of postpartum depression (PPD). These results are reported in Table 2. This manuscript serves to summarize the current evidence on the potential of ketamine as a protective agent for the development of stress-related disorders. If confirmed by clinical trials in humans, this may represent a significant paradigm shift in the prevention of disorders such as MDD, PTSD, and PPD and provide a novel understanding of the neurobiological mechanism of resilience.

Ketamine as a prophylactic agent for depressive-like behavior

Several models have reliably induced pro-depressive behaviors in rodents, including Chronic Social Defeat (SD), Learned Helplessness (LH), Inescapable Shock (IS), Chronic Unpredictability Stress (CUS), and chronic corticosterone (CORT). In recent years, several authors have demonstrated a single administration of ketamine exerts a protective effect against the depressive-like behavior induced by these models. In 2016, Brachman et al. treated male mice with ketamine (10, 30, or 90 mg/kg) or saline 1 week prior to a 2-week SD and assessed behavior using the Forced Swim Test (FST) 1 day post-SD along with the Dominant Interaction (DI) social interaction test 2 days post-SD. The FST is commonly used to assess depressive-like behavior: immobility time during the FST has been used as a marker of negative mood, hopelessness, or despair (10). Similarly, DI is a robust way to test the induction of depressive-like behavior by SD: time spent investigating an empty enclosure (increased time indicates a depressive-like behavior) and willingness to interact with the dominant mouse (reduced willingness indicates depressive-like behavior) can be measured. Ketamine-treated mice (30 mg/kg, but not 10 or 90 mg/kg) showed significantly reduced immobility time during the FST and significantly increased time exploring a social target mouse compared to saline-treated mice during the DI, consistent with a reduction in the pro-depressive effects of SD and enhancement of stress resilience (11). In 2018, Mastrodonato et al. replicated these results after treating male mice with ketamine (30 mg/kg) 1 week prior to SD followed by the FST. Mice treated with ketamine exhibited significantly less immobility time compared with saline-treated mice on day 2 of the FST (12). Furthermore, Amat et al. (13) administered ketamine 10 mg/kg to male rats at varying times (2 h, 1 week, and 2 weeks) before IS, a laboratory inducing anxiety procedure in rodents. Ketamine blocked the behavioral impairment of IS at all time intervals compared to saline-treated rats on the Juvenile Social Interaction (JSI), which has been used to test social interest and motivation in rats (13).

In another experiment, Brachman et al. (11) treated male mice with ketamine (30 mg/kg) 1 week prior to a 2-week LH protocol where mice were delivered repeated, inescapable shocks. Ketamine-treated mice had a decreased latency to escape the shock escape protocol during LH testing and the session length was significantly shorter in the ketamine-treated group, suggesting a blunting of the depressive effect of LH (11).

Anhedonia, a common symptom of depression, is characterized by a reduced ability to feel pleasure. CUS has been shown to cause anhedonia-like behavior in rodent models as measured by the Sucrose Preference Test (SPT). Krzystyniak et al. (14) administered ketamine (3 mg/kg) or saline to male mice 1 h before the CUS protocol, followed by an 8-day SPT, except on day 2, when the FST was administered. They reported an increase in anhedonic behaviors in mice treated with saline (60%) compared to the ones treated with ketamine (37%), as quantified by an impaired sucrose preference over water 24 h after the CUS protocol. They also found that ketamine (3 mg/kg) administration improved anhedonia recovery during the 8-day SPT in ketamine-treated mice exhibiting anhedonia-like behavior. However, inconsistent with previously mentioned findings, no difference between groups in immobility time during the FST was reported (14). Of note, the different dosage of ketamine, 3 mg/kg rather than 30 mg/kg used in previous findings (11, 12) as well as the different timing employed (2 days post ketamine rather than 1 week), may suggest that the prophylactic effect of ketamine against depressive-like symptoms is dose and time-dependent.

TABLE 1 The prophylactic effect of ketamine in rodent models on behavioral outcomes.

Paper	Drug and dose	Animal used	Stress paradigm	Outcome	Time	Behavioral results
Ketamine as a prophylactic against stress-induced depressive-like behavior (11)	Ketamine 10, 30, and 90 mg/kg	Male 129S6/SvEvTac mice (8–10 weeks old)	SD (2 weeks)	FST +1 day, DI +2 days, EPM +4 days	1 week between dose and stress	Ketamine (30 mg/kg, but not 10 or 90 mg/kg) significantly decreased behavioral despair (immobility time in the FST) following the SD when compared with saline. SD-ketamine mice exhibited a significantly increased willingness to interact with the dominant mouse when compared with SD-Sal mice. No effect on EPM: unclear if ketamine is an anxiolytic.
	Ketamine 30 mg/kg	Male 129S6/SvEvTac mice (8–10 weeks old)	LH (2 weeks)	LH Testing (Shock Escape Protocol)	1 week between dose and stress	Mice injected with ketamine (30 mg/kg) had a decreased latency to escape and the session length was significantly shorter in the ketamine group. Ketamine protection may not be limited to just SD stress.
	Ketamine 10, 30, and 90 mg/kg	Male C57BL/6NTac mice (8 weeks old)	21-day CORT	FST, ST, NSF	1 week between dose and stress	Ketamine (90 mg/kg, but not 10 or 30 mg/kg) was the most effective at preventing the chronic CORT-induced depressive-like phenotype and ketamine treated-mice showed significantly decreased immobility time on the FST, demonstrating the protective effect of ketamine at a higher dose.
Previous ketamine produces an enduring blockade of neurochemical and behavioral effects of uncontrollable stress (13)	Ketamine 10 mg/kg	Male Sprague Dawley rats (64–69 days old)	IS	JSI 24 h post-IS	2 h, 1 week, or 2 weeks between dose and stress	Ketamine (10 mg/kg) blocked behavioral effects of IS at all intervals (2 h, 1 week, and 2 weeks) at $p < 0.01$ compared to saline.
Prophylactic ketamine attenuates learned fear (17)	Ketamine 30 mg/kg	Male 129S6/SvEvTac mice (8 weeks old)	3-shock CFC	E and R	24 h, 1 week, or 1 month between dose and stress	Ketamine (30 mg/kg) treated mice exhibited significantly less freezing behavior during extinction exposure 5 days after CFC: ketamine attenuated fear response 1 week before CFC, but not 1 month or 24 h.
Prophylactic ketamine alters nucleotide and neurotransmitter metabolism in brain and plasma following stress (18)	Ketamine 30 mg/kg	Male 129S6/SvEvTac mice (8 weeks old)	3-shock CFC	Context Re-exposure	1 week between dose and stress	Ketamine (30 mg/kg) compared to saline attenuated fear response during context re-exposure.
Ventral CA3 activation mediates prophylactic ketamine efficacy against stress-induced depressive-like behavior (12)	Ketamine 30 mg/kg	Male 129S6/SvEvTac mice (8 weeks old)	SD and 3-shock CFC	FST	1 week between dose and stress	Mice treated with ketamine (30 mg/kg) exhibited attenuated fear compared with saline treated mice. On day 2 of the FST (6 days after CFC), ketamine-treated (30 mg/kg) mice exhibited decreased immobility compared with saline.

(Continued)

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TABLE 1 Continued

Paper	Drug and dose	Animal used	Stress paradigm	Outcome	Time	Behavioral results
Prophylactic ketamine treatment promotes resilience to chronic stress and accelerates recovery: correlation with changes in synaptic plasticity in the CA3 subregion of the hippocampus (14)	Ketamine 3 mg/kg	Male C57BL6J mice (3 months old)	CUS	FST 2 days after CUS and 8-day SPT	1 h between dose and stress	More anhedonic mice (based on sucrose preference over water) in saline group (60%) compared to ketamine group (37%) 24 h after CUS. Ketamine administration improved anhedonia recovery during an 8-day recovery period ($p = 0.022$). No difference between ketamine and saline groups on FST.
Sex-specific neurobiological actions of prophylactic (R,S)-ketamine, (2R,6R)-hydroxynorketamine, and (2S,6S)-hydroxynorketamine (23)	(R,S)-ketamine, (2R,6R)-HNK, (2S,6S)-HNK	Male 129S6/SvEv mice (8 weeks old)	3-shock CFC	FST	1 week between dose and stress	(R,S)-ketamine (30 mg/kg) and (2S,6S)-HNK (0.025, 0.075, 0.1, 0.3, 10, and 30 mg/kg), but not (2R,6R)-HNK attenuated learned fear on day 1 of the FST. On day 2, (R,S)-ketamine (30 mg/kg) and (2R,6R)-HNK (0.075 mg/kg), but not (2S,6S)-HNK, reduced depressive-like behavior compared to saline.
	(R,S)-ketamine, (2R,6R)-HNK, (2S,6S)-HNK	Female 129S6/SvEv mice (8 weeks old)	3-shock CFC	FST	1 week between dose and stress	(R,S)-ketamine and metabolites do not attenuate learned fear in female mice. On FST day 2, (R,S)-ketamine (10 mg/kg) and (2R,6R)-HNK (0.025 mg/kg) significantly reduced depressive-like behavior compared to saline.
	(R,S)-ketamine, (2R,6R)-HNK	Female 129S6/SvEv mice (8 weeks old) OVX and sham	CFC	FST	1 week between dose and stress	Ovarian hormones mediate the prophylactic effect of (R,S)-ketamine and (2R,6R)-HNK in female mice as the drugs did not affect immobility time during the FST in the OVX groups.
	(R,S)-ketamine, (2R,6R)-HNK, (2S,6S)-HNK	Female 129S6/SvEv mice (8 weeks old)	LH	FST and EPM	1 week between dose and stress	(R,S)-ketamine and (2R,6R)-HNK prevent LH induced depressive-like behavior in female mice. Both drugs significantly reduced immobility time in FST. Unlike in male mice, (R,S)-ketamine and (2R,6R)-HNK do not alter helplessness behavior in female mice.
Sex differences in the sustained effects of ketamine on resilience to chronic stress (22)	Ketamine 10 mg/kg	Male and Female C57Bl/6 mice (8 weeks old)	UCMS (4 week)	FST	1 week between dose and stress	Ketamine (10 mg/kg) administered prior to 4 weeks of UCMS significantly reduced immobility time on the FST in male mice, but not female mice.
Ketamine, but not guanosine, as a prophylactic agent against corticosterone-induced depressive-like behavior: possible role of long-lasting pro-synaptogenic signaling pathway (15)	Ketamine (1 or 5 mg/kg) or Guanosine (1 or 5 mg/kg)	Male C57BL/6NTac Swiss mice (55–60 days old)	21 day CORT (20 mg/kg)	TST and SPT	1 week between dose and stress	Ketamine (5 mg/kg, but not 1 mg/kg) significantly prevented increase in immobility time, grooming latency, and reduced total time grooming ($p < 0.01$) compared to saline. Unlike ketamine, guanosine did not prevent any behavioral changes induced by CORT administration.

(Continued)

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TABLE 1 Continued

Paper	Drug and dose	Animal used	Stress paradigm	Outcome	Time	Behavioral results
Inhibition of a descending prefrontal circuit prevents ketamine-induced stress resilience in females (21)	Ketamine 10 mg/kg, 40 mg/kg	Female Sprague Dawley rats (57–70 days old)	IS	JSE +24 h from IS	1 week between dose and stress	Ketamine (10 mg/kg, but not 40 mg/kg) given 1 week prior to IS completely blocked the effect of IS on JSE in female rats.

FST, Forced Swim Test; LH, Learned Helplessness; CFC, Contextual Fear Conditioning; CUS, Chronic Unpredictability Stress; E, Extinction; R, Reinstatement; DI, Dominant Interaction; EMP, Elevated Maze Plus; TST, Tail Suspension Test; SPT, Splash Test; SD, Chronic Social Defeat; CORT, Chronic Corticosterone; SPT, Sucrose Preference Test; IS, Inescapable Shock; JSI, Juvenile Social Investigation; OVX, Ovariectomized; ST, Sucrose Splash Test; NSF, Novelty Suppressed Feeding; UCMS, Unpredictable Chronic Mild Stress; JSE, Juvenile Social Exploration.

Brachman et al. (11) also tested the effect of ketamine (90 mg/kg) on male mice prior to a 21-day CORT treatment. CORT administration has been shown to induce depressive-like behavior in mice as measured with the Tail Suspension Test (TST), Splash Test (SPT), and FST (11, 15). Ketamine (90 mg/kg) prevented the chronic CORT-induced depressive-like phenotype and treated mice showed significantly decreased immobility time on the FST, demonstrating the protective effect of ketamine also at a higher dose (11). Similarly, Camargo et al. (15) treated male mice with ketamine (5 mg/kg or 1 mg/kg) 1 week prior to 21-day CORT (20 mg/kg) treatment. Ketamine-treated (5 mg/kg, but not 1 mg/kg) mice showed significantly less immobility time on the TST, grooming latency, and reduced total time grooming on the SPT. Grooming during the Splash Test is considered a self-care behavior and a marker of anhedonia in mice (15). To investigate whether ketamine exerted a similar effect when administered after stress rather than before, ketamine (30 mg/kg) was administered 1 day after a 28-day CORT treatment. However, post-stress treatment with ketamine did not affect immobility time in the FST (11).

Ketamine as a prophylactic agent for PTSD-like behavior

Contextual Fear Conditioning (CFC) has reliably shown to produce PTSD- and depressive-like behavior in mice. The CFC utilizes shocks, most commonly one or three shocks, context re-exposure (R) and extinction (E) to assess the ability of mice to learn and associate environmental cues and aversive experiences. PTSD is characterized by the persistence of intrusive and debilitating traumatic memories (16). In rodents, PTSD-like behavior is associated with learned fear when re-exposed to aversive contexts. During re-exposure tests, freezing behavior is often measured as an index of fear memory. McGowan et al. (17) treated mice with 30 mg/kg of ketamine or saline at different time points (24 h, 1 week, or 1 month) before a 3-shock CFC protocol. Mice treated with ketamine (30 mg/kg) 1 week prior to CFC showed significantly less freezing behavior during extinction exposure 5 days after CFC, while mice treated 24 h or 1 month before CFC did not differ from the control group (17). Of note, ketamine administered after the CFC at various time points did not alter fear expression (17). Interestingly, there was no effect of ketamine on fear expression or depressive-like behavior in the FST when administered 1 week before a "stronger" re-exposure. This may suggest that ketamine's prophylactic effect is dependent on the severity of the stressor (17). McGowan et al. (18) replicated these findings while investigating markers associated with the prophylactic effect of ketamine. Ketamine appeared to significantly alter metabolites in the prefrontal cortex (PFC) and in the hippocampus (HPC) following CFC. Additionally, amino acid derived neurotransmitters and precursors significantly

changed following ketamine and stress in PFC and HPC tissue and plasma. These changes were durable (detectable at 2 weeks post ketamine administration) and observable in the PFC, HPC, and plasma. Interestingly, these alterations were not found in ketamine-treated mice that did not undergo the CFC stress, suggesting that the interaction between stress and ketamine may be key to creating long-lasting metabolic changes that affect stress-related behavior (18).

In 2018, Mastrodonato et al. treated mice with ketamine (30 mg/kg) or saline 1 week prior to a 3-shock CFC protocol and showed that mice treated with ketamine exhibited significantly attenuated fear compared to saline-treated mice on day 2 of the FST, suggesting that the prophylactic effect ketamine can be extended also to the PTSD-like behavior induced by CFC (12). Furthermore, the authors sought to explore the neural mechanisms associated with the pro-resilient effect of ketamine. Through the use of viral vectors, the authors were able to test the hypothesis that the mice that received ketamine prior to a stressor (CFC) showed an alteration of stress-related memories (CFC-related) in the hippocampus (12). Overall, these findings suggest that ketamine may impact the encoding of negative memories. While ketamine has been studied in cue-specific fear conditioning models (19, 20) wherein it appeared to disrupt contextual fear reconsolidation, it has not yet been studied when administered prophylactically prior to CFC.

Ketamine as a prophylactic agent for anxiety-like behavior

The Elevated Plus Maze (EPM) test is widely used to assess anxiety-related behavior in rodents. In the previously discussed study from Brachman et al. (11), the EPM was conducted 4 days after SD and no effect of ketamine was found on the EPM results. Dolzani et al. (21) sought to replicate the findings of Amat et al. (13) in a population of female rats. Ketamine (10 mg/kg) was administered 1 week prior to IS and the effect of ketamine was assessed 24 h after on the Juvenile Social Exploration (JSE) test, which is a measure of anxiety-like behavior. Another group was given 40 mg/kg (high dose) of ketamine. Low-dose ketamine (10 mg/kg) given 1 week prior to IS completely blocked the effect of IS on JSE, but high-dose ketamine (40 mg/kg) behaved the same as control. It remains unclear if ketamine prevents the development of anxiety-related behaviors in mice, but it appears it could be dose-dependent.

Generalizability of prophylactic effect of ketamine: Is it the same for female rodents?

Along with Dolzani et al. (21), other researchers have sought to test if the prophylactic effects of ketamine and its metabolites (2R,6R)-hydroxynorketamine and (2S,6S)-hydroxynorketamine extend to female animals and to explore the potential contribution of sex hormones. Okine et al. (22) administered ketamine (10 mg/kg) to male and female mice 1 week prior to a 4-week Unpredictable Chronic Mild Stress (UCMS) protocol. They tested the effect of the UCMS with the FST and found that ketamine promoted resilience in male mice, but not in female mice. More recently, Chen et al. (23) used the LH protocol and three-shock CFC to test the prophylactic effect of ketamine in female rodents. In this work, ketamine and (2R,6R)-HNK prevented LH-induced depressive-like behavior in female mice along with reducing immobility time during the FST, suggesting that the stress resilience enhancement of ketamine applies to both male and female mice. Furthermore, ketamine (30 mg/kg) and (2R,6R)-HNK (0.075 mg/kg), but not (2S,6S)-HNK, administered 1 week prior to a three-shock CFC reduced depressive-like behavior in male mice on day 2 of the FST. Similarly, ketamine (10 mg/kg), (2R,6R)-HNK (0.025 mg/kg), and (2R,6R)-HNK (0.025 mg/kg) administered 1 week prior to the three-shock CFC significantly reduced depressive-like behavior in female mice on day 2 of the FST, providing evidence for a protective effect of ketamine following an acute stressor also on female rodents. Both ketamine (30 mg/kg) and (2S,6S)-HNK at a variety of doses, but not (2R,6R)-HNK, when administered 1 week prior to a three-shock CFC induced attenuated learned fear on day 1 of the FST. Unlike male mice, ketamine and its metabolites did not attenuate learned fear in female mice. To further explore the timing of administration in the stress resilience model, ketamine and its metabolites were administered 3 days or 24 h prior to the CFC rather than 1 week. (2R,6R)-HNK, but not ketamine, was prophylactic when administered 3 days, but not 24 h, before stress in female mice, suggesting a prominent role of the timing of ketamine administration in mediating the stress resilience effect. Although it is possible that the lower dose of ketamine in Okine et al. (10 mg/kg rather than 30 mg/kg used by Chen et al.) may explain some of the variations in the prophylactic effect of ketamine, the lack of available data on higher dose of ketamine using the UCMS protocol limits the possibility to draw definite conclusions.

Ketamine as a prophylactic agent for postpartum depression

Recent studies have explored the potential of ketamine for the prevention of postpartum depression (PPD) in humans. Despite not representing translational trials of the aforementioned animal models, these studies also investigated the effect of ketamine ahead of the development of psychopathology and specifically tested if ketamine exerts a protective effect against the development of mood and anxiety disorders following childbirth. PPD affects an estimated 10–20%

TABLE 2 Effect of ketamine on prevention postpartum depression (PPD).

Paper	Drug and dose	Sample	Control used	Outcome measure	Primary outcome	Secondary outcomes	Exploratory findings
Prophylactic use of ketamine reduces postpartum depression in Chinese women undergoing cesarean section (27)	Ketamine 0.5 mg/kg +10 minutes after c-section + PCIA device: sufentanil (100 ug), ketamine (160mg), and palonosetron hydrochloride (0.25 mg)	$n = 654$ ($n = 343$ in each group)	0.9% saline + PCIA device: sufentanil (100 ug) and palonosetron hydrochloride (0.25 mg)	EPDS +1 day, +2 days, +4–6 days (Secondary Outcome), and +6–8 weeks (Primary Outcome) post c-section	PPD prevalence in ketamine group significantly lower (12.8%) than control group (19.6%) ($p = 0.02$) at 6–8 weeks post c-section.	EPDS score at days 4–6 was significantly lower in the ketamine group ($p = 0.007$). Prevalence of postpartum blues significantly lower in ketamine group (11.9%) than control (18.3%) ($p = 0.022$). Reduction in suicidal ideation was significantly higher in the ketamine group ($p = 0.017$).	Stronger effect in those with a history of moderate stress during pregnancy ($p = 0.003$), antenatal depressive symptoms ($p = 0.05$) and antenatal suicidal ideation ($p = 0.02$).
The effect of ketamine on preventing postpartum depression (30)	Ketamine 0.5 mg/kg + Nesdonal 1–2 mg/kg	$n = 134$ ($n = 67$ in each group)	Nesdonal 3–5 mg/kg of body weight intravenously injected during induction of anesthesia	EPDS +2 weeks and +4 weeks post c-section	PPD prevalence in ketamine group was significantly lower than control ($p < 0.001$) at 4 weeks postpartum. The mean EPDS score in the ketamine group (10.84) was significantly less than the control group (13.09; $p < 0.001$) at 4 weeks postpartum.	PPD prevalence in ketamine group significantly lower than control ($p < 0.001$) at 2 weeks postpartum. EPDS score in the ketamine group (11.82) was significantly less than the control group (14.34; $p < 0.001$) at 2 weeks postpartum.	In the control group, the mean EPDS score was increased 2-weeks after the c-section compared to before and the mean EPDS score was significantly decreased 4 weeks after the c-section in comparison to two weeks after ($p < 0.001$).
S-ketamine as an adjuvant in patient controlled intravenous analgesia for preventing postpartum depression: a randomized controlled trial (31)	PCIA device containing: S-ketamine (0.5 mg/kg), sufentanil (2 μg/kg), and tropisetron (10 mg)	$n = 380$ ($n = 190$ in each group)	PCIA device containing: sufentanil (2 μg/kg), and tropisetron (10 mg)	Incidence of PPD, EPDS scores before surgery, +3, +14, and +28	PPD prevalence in the S-ketamine group was significantly lower than the control group ($p < 0.05$) at 3 days and 14 days post-c-section (17.6 and 8.2% vs. 24.2 and 9.8%)	EPDS score intergroup differences were significant at 3 days ($p < 0.001$) and 14 days ($p < 0.001$) postpartum.	VAS scores were significantly lower in the S-ketamine group at 4, 8, 12, and 24 h post-c-section.

PCIA, Patient Controlled Intravenous Analgesia Device; EPDS, Edinburgh Postnatal Depression Scale; PPD, Postpartum Depression.

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of mothers (24, 25) and unique challenges face providers in the treatment of PPD, including the potential exposure of the newborn to medications during pregnancy and/or breastfeeding. Currently, only one medication, brexanolone, is available and received Food and Drug Administration approval for the treatment of PPD (26).

Ma et al. (27) reported the results of 654 women undergoing cesarean section (c-section) that were randomized to either 0.5 mg/kg of ketamine or saline *via* epidural bolus 10 min after c-section. Following initial administration of ketamine or saline, participants were provided with a Patient Controlled Intravenous Analgesia (PCIA) device. Patients undergoing c-section were enrolled because the procedure involves the use of anesthesia regardless of study participation. Further, ketamine has been commonly used as a general anesthetic in patients undergoing planned c-section since its safety profile in pregnant patients is well-established (28). Participants that were randomized to ketamine received a PCIA device of sufentanil (100 μg), palonosetron hydrochloride (0.25 mg), and ketamine (160 mg). Control subjects were provided the same PCIA device without the addition of ketamine. Participants were assessed with the Edinburgh Postnatal Depression Scale [EPDS; (29)] at various time points postpartum. The primary outcome at 6–8 weeks postpartum showed a significantly lower prevalence of PPD in the ketamine group (12.8%) than in the control group (19.6%). The secondary outcome on days 4–6 postpartum showed a significantly lower mean EPDS score and lower prevalence of postpartum blues in the ketamine group (11.9%) than in the control group (18.3%). Notably, a reduction in suicidal ideation 4–6 days postpartum was also significantly higher in the ketamine group compared to the control group. Finally, the effect of ketamine appeared more pronounced in women with a history of moderate stress during pregnancy, antenatal depressive symptoms, and suicidal ideation.

A similar study by Alipoor et al. (30) was conducted on 134 women undergoing c-section randomized to either ketamine (0.5 mg/kg) plus nesdonal (1–2 mg/kg) or nesdonal (3–5 mg/kg) alone administered intravenously during the induction phase of anesthesia. Participants were assessed with the EPDS at 2 and 4 weeks postpartum. The primary outcome at 4 weeks postpartum showed that PPD prevalence (EPDS score > 9) in the ketamine group was significantly lower compared to the control group and that the mean EPDS score in the ketamine group (10.84) was significantly lower than the control group (12.09). The secondary outcome at 2 weeks postpartum showed a significantly lower prevalence of PPD in the ketamine group and a mean EPDS in the ketamine group (11.82) significantly lower than the control group (14.34). A third randomized trial from Han et al. (31) explored the effect of a PCIA device with S-ketamine (0.5 mg/kg) given to patients immediately following c-section delivery. Patients randomized to receive the PCIA device with S-ketamine had significantly less prevalence of PPD at 3 and 14 days postpartum. However, these findings must be interpreted with caution, as the results reported reflect the mean difference and prevalence difference between groups drawn from uncorrected *t*-tests at the pre-determined time points.

Discussion

Current evidence suggests a potential for ketamine as a pharmacological agent for the prevention of stress-related behavior in animal models of stress-related disorders and recent findings from Ma et al. (27) and Alipoor et al. (30) provide encouraging evidence that this prophylactic effect may apply to humans. Ketamine as a treatment for psychiatric disorders was discovered as early as 2000 and evidence has grown over the years to support its treatment efficacy for MDD, TRD, suicidality, and PTSD (2–6, 32). However, there has not yet been any study published testing the potentially pro-resilient effect of ketamine in humans with the exception of studies on postpartum depression.

Current evidence-based methods for enhancing resilience are limited to therapeutic lifestyle changes (TLC) focused on smoking habits, alcohol use, diet, physical exercise, obesity, and stress management (33). Successful lifestyle changes are often dependent on psychotherapy and motivational interviewing, which can be expensive and inaccessible (34). While treating the population with ketamine to prevent psychopathology is unrealistic, the implementation of ketamine as a prophylactic treatment may have a potential application for individuals who are at risk of being exposed to a high level of stress within a specific time frame, such as soldiers prior to military deployment or first responders. Interestingly, the preclinical data discussed in the current review (17, 23) suggests that the timing of ketamine administration plays a key role in its stress resilience action and further research is required to optimize administration timing in humans. More broadly, however, the results of these data may inform about the neurobiological mechanisms underpinning resilience. Current practice in psychiatry is focused on the treatment of symptoms, while resilience is generally conceptualized as the absence of disease. Considering resilience as an active state rather than simply as the absence of illness may allow a more in-depth understanding of the neurobiological mechanisms involved, leading to a deeper understanding of resilience-related neural mechanisms and ultimately to the identification of novel target for the prevention of stress-related disorders. Evidence from rodent models discussed in this review may point to the glutamatergic system, the PFC, and the HPC as potential mediators of resilience.

These findings are seemingly consistent with previous work underscoring the neurobiological underpinnings of resilience. In a 2019 review, Cathomas et al. (41) described resilience

as an active mechanism rooted in the PFC, HPC, locus coeruleus (LC), ventral tegmental area (VTA), and nucleus accumbens (NAc) as well as peripherally in the body in the innate and adaptive immune systems and the gut microbiota. Consistent with McGowan et al. (18) and Mastrodonato et al. (12), the PFC and HPC are key regions for processing stress and for resilience. Of note, the HPC is highly reactive to hypothalamic-pituitary-adrenal (HPA) axis activation and hippocampal neurogenesis appears foundational to a resilient phenotype (42, 43). However, Brachman et al. (11) found no effect of prophylactic ketamine on hippocampus neurogenesis, and similarly later work from the same animal cohort (35) found no effect of prophylactic ketamine on neurogenesis. At the current time, the neurobiological mechanism underpinning the prophylactic effect of ketamine remains largely unknown. However, the PFC and HPC are also relevant regions within the mesolimbic dopamine pathway, part of a discrete reward circuit, where dopamine neurons projections from the VTA reach the NAc, HPC, and PFC. Relevantly, resilient mice display normal projections of dopamine neurons while susceptible mice display hyperactivity of dopamine neurons (36). The NAc also integrates glutamatergic inputs from the HPC, PFC, and other brain regions—further supporting the hypothesis that resilience may be related to the modulation of glutamatergic transmission (37). Further, psychosocial stress has also repeatedly been shown to be associated with a pro-inflammatory status and current evidence suggests that ketamine may reduce levels of pro-inflammatory cytokines (38, 39). Whether this plays a role in the pro-resilient effect of ketamine is yet to be determined.

This does not serve as a comprehensive review and is primarily focused on the behavioral outcomes showing a pro-resilient effect of ketamine. The implementation of ketamine as a resilience-enhancing agent represents a novel approach to the treatment and prevention of stress-related psychiatric disorders such as MDD or PTSD. The preclinical data discussed in this review suggests that ketamine and its metabolites can be effective at preventing depression, PTSD, and possibly anxiety-like behaviors in animals. In humans, initial evidence from the use of ketamine for the prevention of postpartum depression appears encouraging. Further trials aiming at exploring if the potential stress-preventative effect of ketamine applies also to humans are warranted. Future studies aiming to translate these results into humans should consider the different doses of ketamine and its metabolites used in these rodent models. Although a dose between 10 and 30 mg/kg administered intraperitoneally has been widely accepted as a translational animal model to study the antidepressant effect of ketamine, a variety of factors like the route of administration, metabolism of the drug, and side effect profiles should be accounted for. Substantial uncertainty remains around a standardized prophylactic ketamine protocol including timing, mouse strain, and the optimal prophylactic dosing for animal models and for humans.

Author contributions

All authors devised the article. SC, AE, and JM conceived the paper. AE wrote the first draft of the article and drafted the tables. All authors commented on drafts of the article. All authors contributed to the article and approved the submitted version.

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Conflict of interest

DC (Dean of Icahn School of Medicine at Mount Sinai) is a named co-inventor on several issued U.S. patents and several pending U.S. patent applications filed by the Icahn School of Medicine at Mount Sinai (ISMMS) related to ketamine and esketamine for treatment-resistant depression, suicidal ideation, and other disorders. ISMMS has entered into a licensing agreement with Janssen Pharmaceuticals, Inc. and it has and will receive payments from Janssen under the license agreement related to these patents. As a co-inventor, DC is entitled to a portion of the payments received by the ISMMS. Since SPRAVATO (esketamine) has received regulatory approval for treatment-resistant depression, ISMMS and DC as its employee and a co-inventor, will be entitled to additional payments, under the license agreement. SC has provided consultation services for Guidepoint and TCG Crossover. In the past 5 years, JM has provided consultation services and/or served on advisory boards for Allergan, Boehreinger Ingelheim, Clexio Biosciences, Fortress Biotech, FSV7, Global Medical Education (GME), Otsuka, and Sage Therapeutics. JM is named on a patent pending for neuropeptide Y as a treatment for mood and anxiety disorders and on a patent pending for the use of ezogabine and other KCNQ channel openers to treat depression and related conditions.

Publisher's note

References

1. Hasin DS, Sarvet AL, Meyers JL, Saha TD, Ruan WJ, Stohl M, et al. Epidemiology of adult DSM-5 major depressive disorder and its specifiers in the United States. *J Am Med Assoc Psychiatry*. (2018) 75:336–46. doi: 10.1001/jamapsychiatry.2017.4602

2. Berman RM, Cappiello A, Anand A, Oren DA, Heninger GR, Charney DS, et al. Antidepressant effects of ketamine in depressed patients. *Biol Psychiatry*. (2000) 47:351–4. doi: 10.1016/S0006-3223(99)00230-9

3. Zarate CAJr, Singh JB, Carlson PJ, Brutsche NE, Ameli R, Luckenbaugh DA, et al. A randomized trial of an N-methyl-D-aspartate antagonist in treatment-resistant major depression. *Arch Gen Psychiatry*. (2006) 63:856–64. doi: 10.1001/archpsyc.63.8.856

4. Murrough JW, Iosifescu DV, Chang LC, Al Jurdi RK, Green CE, Perez AM, et al. Antidepressant efficacy of ketamine in treatment-resistant major depression: a two-site randomized controlled trial. *Am J Psychiatry*. (2013) 170:1134–42. doi: 10.1176/appi.ajp.2013.13030392

5. Murrough JW, Soleimani L, DeWilde KE, Collins KA, Lapidus KA, Iacoviello BM, et al. Ketamine for rapid reduction of suicidal ideation: a randomized controlled trial. *Psychol Med*. (2015) 45:3571–80. doi: 10.1017/S0033291715001506

6. Feder A, Parides MK, Murrough JW, Perez AM, Morgan JE, Saxena S, et al. Efficacy of intravenous ketamine for treatment of chronic posttraumatic stress disorder: a randomized clinical trial. *J Am Med Assoc Psychiatry*. (2014) 71:681–8. doi: 10.1001/jamapsychiatry.2014.62

7. Feder A, Costi S, Rutter SB, Collins AB, Govindarajulu U, Jha MK, et al. A Randomized controlled trial of repeated ketamine administration for chronic posttraumatic stress disorder. *Am J Psychiatry*. (2021) 178:193–202. doi: 10.1176/appi.ajp.2020.20050596

8. Janssen Pharmaceuticals Inc. *SPRAVATO: Esketamine Nasal Spray*. Beerse: Janssen Pharmaceuticals Inc (2020) .

9. Krystal JH, Abdallah CG, Sanacora G, Charney DS, Duman RS. Ketamine: a paradigm shift for depression research and treatment. *Neuron*. (2019) 101:774–8. doi: 10.1016/j.neuron.2019.02.005

10. Porsolt RD, Le Pichon M, Jalfre M. Depression: a new animal model sensitive to antidepressant treatments. *Nature*. (1977) 266:730–2. doi: 10.1038/266730a0

11. Brachman RA, McGowan JC, Perusini JN, Lim SC, Pham TH, Faye C, et al. Ketamine as a prophylactic against stress-induced depressive-like behavior. *Biol Psychiatry*. (2016) 79:776–86. doi: 10.1016/j.biopsych.2015.04.022

12. Mastrodonato A, Martinez R, Pavlova IP, LaGamma CT, Brachman RA, Robison AJ, et al. Ventral CA3 activation mediates prophylactic ketamine efficacy against stress-induced depressive-like behavior. *Biol Psychiatry*. (2018) 84:846–56. doi: 10.1016/j.biopsych.2018.02.011

13. Amat J, Dolzani SD, Tilden S, Christianson JP, Kubala KH, Bartholomay K, et al. Previous ketamine produces an enduring blockade of neurochemical and behavioral effects of uncontrollable stress. *J Neurosci*. (2016) 36:153–61. doi: 10.1523/JNEUROSCI.3114-15.2016

14. Krzystyniak A, Baczynska E, Magnowska M, Antoniuk S, Roszkowska M, Zareba-Koziol M, et al. Prophylactic ketamine treatment promotes resilience to chronic stress and accelerates recovery: correlation with changes in synaptic plasticity in the CA3 subregion of the hippocampus. *Int J Mol Sci*. (2019) 20:1726. doi: 10.3390/ijms20071726

15. Camargo A, Dalmagro AP, de Souza MM, Zeni A, Rodrigues A. Ketamine, but not guanosine, as a prophylactic agent against corticosterone-induced depressive-like behavior: possible role of long-lasting pro-synaptogenic signaling pathway. *Exp Neurol*. (2020) 334:113459. doi: 10.1016/j.expneurol.2020.113459

16. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders, 5th Edn*. Arlington, VA: American Psychiatric Association (2013). doi: 10.1176/appi.books.9780890425596

17. McGowan JC, LaGamma CT, Lim SC, Tsitsiklis M, Neria Y, Brachman RA, et al. Prophylactic ketamine attenuates learned fear. *Neuropsychopharmacology*. (2017) 42:1577–89. doi: 10.1038/npp.2017.19

18. McGowan JC, Hill C, Mastrodonato A, LaGamma CT, Kitayev A, Brachman RA, et al. Prophylactic ketamine alters nucleotide and neurotransmitter metabolism in brain and plasma following stress. *Neuropsychopharmacology*. (2018) 43:1813–21. doi: 10.1038/s41386-018-0043-7

19. Duclot F, Perez-Taboada I, Wright KN, Kabbaj M. Prediction of individual differences in fear response by novelty seeking, and disruption of contextual fear memory reconsolidation by ketamine. *Neuropharmacology*. (2016) 109:293–305. doi: 10.1016/j.neuropharm.2016.06.022

20. Philippens I, Draaisma L, Baarends G, Krugers HJ, Vermetten E. Ketamine treatment upon memory retrieval reduces fear memory in marmoset monkeys. *Eur Neuropsychopharmacol*. (2021) 50:1–11. doi: 10.1016/j.euroneuro.2021.04.004

21. Dolzani SD, Baratta MV, Moss JM, Leslie NL, Tilden SG, Sørensen AT, et al. Inhibition of a descending prefrontal circuit prevents ketamine-induced stress resilience in females. *eNeuro*. (2018) 5:ENEURO.0025-18.2018. doi: 10.1523/ENEURO.0025-18.2018

22. Okine T, Shepard R, Lemanski E, Coutellier L. Sex differences in the sustained effects of ketamine on resilience to chronic stress. *Front Behav Neurosci*. (2020) 14:581360. doi: 10.3389/fnbeh.2020.581360

23. Chen BK, Luna VM, LaGamma CT, Xu X, Deng SX, Suckow RF, et al. Sex-specific neurobiological actions of prophylactic (R,S)-ketamine, (2R,6R)-hydroxynorketamine, and (2S,6S)-hydroxynorketamine. *Neuropsychopharmacology*. (2020) 45:1545–56. doi: 10.1038/s41386-020-0714-z

24. Hansotte E, Payne SI, Babich SM. Positive postpartum depression screening practices and subsequent mental health treatment for low-income women in Western countries: a systematic literature review. *Public Health Rev*. (2017) 38:3. doi: 10.1186/s40985-017-0050-y

25. Meltzer-Brody S, Howard LM, Bergink V, Vigod S, Jones I, Munk-Olsen T, et al. Postpartum psychiatric disorders. *Nat Rev Dis Primers*. (2018) 4:18022. doi: 10.1038/nrdp.2018.22

26. Powell JG, Garland S, Preston K, Piszczatoski C. Brexanolone (Zulresso): finally, an FDA-approved treatment for postpartum depression. *Ann Pharmacother*. (2020) 54:157–63. doi: 10.1177/1060028019873320

27. Ma JH, Wang SY, Yu HY, Li DY, Luo SC, Zheng SS, et al. Prophylactic use of ketamine reduces postpartum depression in Chinese women undergoing cesarean section. *Psychiatry Res*. (2019) 279:252–8. doi: 10.1016/j.psychres.2019.03.026

28. Lema GF, Gebremedhn EG, Gebregzi AH, Desta YT, Kassa AA. Efficacy of intravenous tramadol and low-dose ketamine in the prevention of post-spinal anesthesia shivering following cesarean section: a double-blinded, randomized control trial. *Int J Women's Health*. (2017) 9:681–8. doi: 10.2147/IJWH.S139655

29. Cox JL, Holden JM, Sagovsky R. Detection of postnatal depression. Development of the 10-item Edinburgh postnatal depression scale. *Br J Psychiatry*. (1987) 150:782–6. doi: 10.1192/bjp.150.6.782

30. Alipoor M, Loripoor M, Kazemi M, Farahbakhsh F, Sarkoohi A. The effect of ketamine on preventing postpartum depression. *J Med Life*. (2021) 14:87–92. doi: 10.25122/jml-2020-0116

31. Han Y, Li P, Miao M, Tao Y, Kang X, Zhang J. S-ketamine as an adjuvant in patient-controlled intravenous analgesia for preventing postpartum depression: a randomized controlled trial. *BMC Anesthesiol*. (2022) 22:49. doi: 10.1186/s12871-022-01588-7

32. Witt K, Potts J, Hubers A, Grunebaum MF, Murrough JW, Loo C, et al. Ketamine for suicidal ideation in adults with psychiatric disorders: a systematic review and meta-analysis of treatment trials. *Aust N Z J Psychiatry*. (2020) 54:29–45. doi: 10.1177/0004867419883341

33. Marques A, Bordado J, Peralta M, Gouveia ER, Tesler R, Demetriou Y, et al. Cross-sectional and prospective relationship between physical activity and depression symptoms. *Sci Rep*. (2020) 10:16114. doi: 10.1038/s41598-020-72987-4

34. Min JA, Lee CU, Lee C. Mental health promotion and illness prevention: a challenge for psychiatrists. *Psychiatry Investig*. (2013) 10:307–16. doi: 10.4306/pi.2013.10.4.307

35. LaGamma CT, Tang WW, Morgan AA, McGowan JC, Brachman RA, Denny CA. Antidepressant but not prophylactic ketamine administration alters calretinin and calbindin expression in the ventral hippocampus. *Front Mol Neurosci*. (2018) 11:404. doi: 10.3389/fnmol.2018.00404

36. Friedman AK, Walsh JJ, Juarez B, Ku SM, Chaudhury D, Wang J, et al. Enhancing depression mechanisms in midbrain dopamine neurons achieves homeostatic resilience. *Science*. (2014) 344:313–9. doi: 10.1126/science.1249240

37. Christoffel DJ, Golden SA, Russo SJ. Structural and synaptic plasticity in stress-related disorders. *Rev Neurosci*. (2011) 22:535–49. doi: 10.1515/RNS.2011.044

38. Tan S, Wang Y, Chen K, Long Z, Zou J. Ketamine alleviates depressive-like behaviors *via* down-regulating inflammatory cytokines induced by chronic restraint stress in mice. *Biol Pharmaceut Bulle*. (2017) 40:1260–7. doi: 10.1248/bpb.b17-00131

39. Chen MH, Li CT, Lin WC, Hong CJ, Tu PC, Bai YM, et al. Rapid inflammation modulation and antidepressant efficacy of a low-dose ketamine infusion in treatment-resistant depression: a randomized, double-blind control study. *Psychiatry Res*. (2018) 269:207–11. doi: 10.1016/j.psychres.2018.08.078

40. American Psychological Association. *The Road to Resilience*. (2018). Available online at: https://www.apa.org/helpcenter/road-resilience (accessed December 1, 2021).

41. Cathomas F, Murrough JW, Nestler EJ, Han MH, Russo SJ. Neurobiology of resilience: interface between mind and body. *Biol Psychiatry*. (2019) 86:410–20. doi: 10.1016/j.biopsych.2019.04.011

42. Jankord R, Herman JP. Limbic regulation of hypothalamo-pituitary-adrenocortical function during acute and chronic stress. *Ann N Y Acad Sci*. (2008) 1148:64–73. doi: 10.1196/annals.1410.012

43. Levone BR, Cryan JF, O'Leary OF. Role of adult hippocampal neurogenesis in stress resilience. *Neurobiol Stress*. (2014) 1:147–55. doi: 10.1016/j.ynstr.2014.11.003

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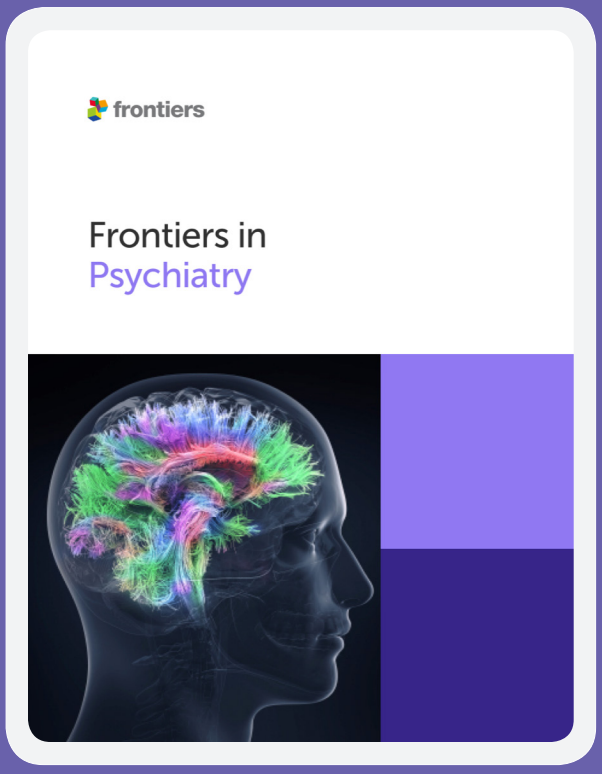

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