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Research Paper

A qualitative study of patients' experience of ketamine treatment for depression: The 'Ketamine and me' project

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ABSTRACT

Background: There has been a lack of in-depth interviews investigating patient experience of ketamine treatment for depression. We examined participants' pathways to receiving ketamine infusion to treat their depression, and their responses to, lived experiences of, and attitudes towards ketamine treatment.

Methods: Qualitative methods were used to conduct in-depth interviews with 13 patients (6 male; 7 female) diagnosed with treatment resistant depression (TRD) with experience of receiving ketamine treatment for depression. Interpretative phenomenological analysis (IPA) was employed.

Results: For the majority of participants ketamine infusion causes a reported initial 'high', enhanced perception, and dissociative experience; followed by a lifting of mood and a reduction in or removal of suicidal ideation and depression symptoms lasting around 3–6 days. This leads to a reported increase in motivation, socialisation, and activity. All participants valued the therapeutic alliance with clinicians which enhanced the treatment experience and all advocated treatment access for those with depression who have not responded to other treatments.

Limitations: Small numbers, purposive sample, participant self-selection, and single site recruitment limit generalisability.

Conclusions: Ketamine for depression can have many beneficial effects, and it is potentially life-transforming for some. Ketamine may be a source of hope for patients for whom other treatments have not been effective. For some, ketamine is not tolerated or does not have anti-depressive effects. Further qualitative in-depth exploration of patient experience and consideration of how ketamine depression treatment access can be appropriately made available are warranted.

1. Introduction

Some people diagnosed with major depressive disorder (MDD) are poor or non-responders to widely used antidepressant medication, such as selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs) (Henkel et al., 2009). These drugs are often not fast-acting, having a typical time lag of 2–4 weeks initially, and 6–12 weeks for maximum effect (Niciu et al., 2015). Over 50% of people do not experience remission after first-line antidepressant medication, and one-third do not after four different courses (Rush et al., 2006); and many experience negative side effects (Anderson et al., 2012). Non-response rate to psychotherapy (typically cognitive behavioural therapy [CBT]), has been reported at around 62–70% (Gyani et al., 2013; Griffiths and Griffiths, 2015).

Treatment resistant depression (TRD) may be defined as no response to at least two consecutive courses of antidepressant medication (Berlim and Turecki, 2007). Between 12% and 30% of depressed patients have TRD (Rush et al., 2006; Nemeroff, 2007; Eaton et al., 2008;). TRD is associated with higher rates of psychosocial dysfunction, morbidity, mortality, suicide, and health service costs (McCrone et al., 2008; Niciu et al., 2015; Balestri et al., 2016). Effective treatment options for TRD include: electroconvulsive therapy (ECT) (reported remission rates of around 50% (Jevolac et al., 2013); side effects include short and long term memory loss (Mohn and Rund, 2016; Griffiths and O'Neill-Kerr, 2019)) and transcranial magnetic stimulation (TMS) (reported remission rates of 21–50%) (Griffiths et al., 2019). Some people do not respond to, are excluded from (due to e.g. metal head implants, epilepsy), or prefer not to try either ECT or TMS.

Ketamine (N-methyl-D-aspartate receptor antagonist) is a rapid-acting antidepressant (Fond et al., 2014; Coyle and Laws, 2015;

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Kishimoto et al., 2016; Grady et al., 2017) and may decrease suicidal ideation (Canuso et al., 2018; Lascelles et al., 2019). Ketamine has maximal antidepressant effects at 24 hours which abates within 7 days (varies between individuals) (Phillips et al., 2019). Examining 10 systematic reviews, Lent et al. (2019) concluded ketamine significantly reduces depression severity in the short term. Adverse effects include psychotic and dissociative effects, blood pressure and heart rate fluctuations, blurred vision and drowsiness (Grady et al., 2017). Although there is a lack of evidence examining the longer-term effects, repeated weekly ketamine infusions may have cumulative and sustained antidepressant effects (Phillips et al., 2019). Increasingly, ketamine is prescribed for people with TRD (Krystal et al., 2019).

Qualitative research investigating patient experience of ketamine is lacking. Using focus group and survey data, Jilka et al. (2019) considered carers' and patients' attitudes towards and experience of ketamine. Participants thought ketamine was an effective antidepressant, wanted better long-term evidence (effect, safety and side effects), stated practical issues of accessing treatment were important (cost, travel for infusions), and felt clinicians need to know about ketamine treatment. However, only a minority (39%) of participants had experience of ketamine for depression and their opinions were not consistently separately reported. Van Schalkwyk et al. (2018) interviewed 10 participants who had received ketamine for depression, and reported four prominent themes: unusual bodily sensations, a sense of peace, disinhibition, and a sense of altered perception. Finally, interviewing 14 depressed patients with suicidal ideation, Lascelles et al. (2019) found following ketamine, they reported reduced suicidal ideation, associated with improved mood, clarity of thought, focus, concentration, and ability to function, and reduced anxiety; and indicated further studies of patients' experiences are warranted. The aim of this current paper is to examine participants' pathways to trying, lived experiences of and responses to ketamine treatment for depression through the use of in-depth interviews.

2. Methods

2.1. Design

A qualitative design was employed using semi-structured interviews. Interpretative phenomenological analysis (IPA) allowed: exploration of how participants made sense of their lives; nuanced analysis of particular instances and experiential phenomenon; and an examination of the meaning of experiences, events, states and contexts held for each participant (Smith and Osborn, 2003; Smith et al., 2012).

2.2. Recruitment

Ethical approval gained from UK Health Department's Health Research Authority (HRA) (project ID: 2707478). The sample was recruited purposefully from those who have received ketamine infusion treatment within an NHS trust. Participants were included if they were aged 18 or over, had experienced ketamine depression treatment (at least 3 sessions), had the capacity to consent, and the ability to understand English.

2.3. Procedure

Two of the interviews took place face-to-face at the treatment centre. The rest were carried out over the phone, participants taking the calls at home. Areas covered in the interview schedule: (i) decisions around using ketamine; (ii) experience of ketamine during and following treatment; (iii) effects of ketamine treatment; (iv) impact ketamine treatment had on life, mood, cognition, wellbeing, motivation, social life, sleep; (v) changes experienced through ketamine treatment; (vi) feedback on service provision; (vii) any other comments.

Thirteen interviews were conducted. In eleven just the patient and the interviewer were present; for two of the interviews, the patients' partners were present and participated in the interview process, as the patients requested guidance from partners to prompt and assist with memory issues. Interview length ranged from 16 to 62 minutes (M = 43.53, SD = 13.24). All interviews were digitally recorded and fully transcribed.

2.4. Analysis

The analysis followed an iterative and inductive cycle strategy (Smith, 2007). All transcripts were individually read and re-read, and initial codes were developed by two researchers. These codes were shared with the third researcher, where emergent themes were structured, and provisional titles agreed upon. Charting and mapping themes was undertaken where connections across emergent themes were identified and initial super-ordinate and associated themes were developed. Once completed on an individual participant basis, patterns were identified through comparisons across the whole dataset. Following the synthesising of the patterns and themes across all datasets, key themes were refined and relabelled. The themes were grounded in the data, and consensus of patterns across participants were identified and exceptions noted.

To ensure trustworthiness of the data, strategies were employed to promote credibility, transferability, dependability and confirmability of the research, as informed by Shenton (2004). This comprised several processes: (a) the utilisation of well-established research methods in qualitative investigation; (b) frequent debriefing sessions; (c) use of transparent and in-depth protocol for data collection and analysis; (d) keeping detailed logbook, memos, notes, and extensive records throughout the analytical process; (e) construction of a data orientated audit trail; and (f) examination and verification by three researchers of analysis undertaken and the conclusions drawn.

3. Results

3.1. Participants

All 13 participants (6 male; 7 female) identified as 'White British'. The age range was 30.19–59.65 years (M = 46.05, SD = 10.69). All participants had TRD, other recorded diagnoses included: bipolar affective disorder (n = 2), mixed anxiety depressive disorder (n = 1), schizoaffective disorder (n = 1).

The number of ketamine sessions ranged from 3 to 112 (M = 34.69, SD = 39.61). The individual dose of ketamine was calculated by factors such as height and weight. Doses given ranged from 25 mg/40 mls to 75 mg/40 mls, all infused over 40 min (M = 48.61, SD = 14.52). There were no gender differences in doses; however, ketamine treatment sessions were significantly higher for women (U = 6, p = .035), 56.57 sessions (SD = 43.76) compared to 9.17 sessions in men (SD = 3.87).

3.2. Findings

The themes identified are in Table 1. They correspond to a chronological flow through the treatment pathway, from the decision-making processes pre-treatment, to experience of ketamine treatment, the enhancers of or barriers to treatment, and participants' advocacy of treatment.

3.3. Treatment decision influences

This theme represents how and why patients decided to try ketamine. The decision-making processes are divided into three themes that capture participants' thought processes, motivations and sources of knowledge that influenced and led to their decision.

Table 1
Table of themes.

Master Theme	Themes	Subthemes
1. Treatment decision influencers		
	⇒ Desperation	
	⇒ Risk-rewards, pros-cons evaluation	
	⇒ Trusted advice and recommendations	
2. Responses experienced taking ketamine		
	⇒ Physiological	⇒ Dissociation, a high
		⇒ Relaxed and sleepy
		⇒ Heightened sensory perception
		⇒ Adverse side effects
	⇒ Emotional	⇒ Happy and laughing
		⇒ Uplifted feeling, brightened mood
		⇒ Feeling 'normal' and like 'true self'
	⇒ Behavioural	⇒ Actively undertake activities
		⇒ Sociable and communicative with others
	⇒ Cognitive	⇒ Positive thoughts increased, negative thoughts decreased
		⇒ Reduced suicidal ideation
		⇒ Reframing thoughts and reprogramming mindset
		⇒ Motivated thinking and a want to take action
	⇒ Life-changing, a profound impact	
3.Treatment enhancers		
	⇒ Conducive and safe environment	
	⇒ Medical expertise and professionalism	
	⇒ Therapeutic alliance with caring staff	
4. Barriers to treatment efficacy and success		
	⇒ Being a non-responder to ketamine	
	⇒ Loss of ketamine effects over time	
	⇒ Negative external & environmental factors	
5. Advocate for treatment		

3.3.1. Desperation

Being desperate for 'something' that would help their depression was apparent across all narratives. Seven participants used the word 'desperate': '*desperate is a good summation'* (P10). Participants had tried many treatment options without enduring success, and were experiencing prolonged, severe depression; they were seeking new forms of treatment:

> P9: *in absolute honesty…I had reached a point where I was willing to try almost anything to get my mental health back to a level where I felt I could function as a human being again.*

Participants suggested this was a last resort for them; they had run out of options:

> P13: *it was a last-ditch attempt at… jump-starting… any kind of recovery…I was getting desperate*

3.3.2. Risks-rewards, pros-cons evaluation

The majority of participants made an assessment of the costs/risks/benefits of ketamine:

> P1: *It was very well documented, on how it worked …it was very quick acting…I don't know about lasting too long, it very quickly had the benefit that I wanted which was to feel better, yes and it just made sense to just try it.*

Even following a negative reaction a participant felt the benefits outweighed the risks:

> P6: *I'd try it again… am I nervous? …Yes I am, totally, absolutely…. Would I have it done? Yes, because I, I know that the rewards outweigh the risk… I've had a turn; I'm prepared to take that risk, or calculated risk, to have it done again.*

3.3.3. Trusted advice and recommendations

Ketamine treatment was relatively unknown to the majority of participants prior to description by medical professionals. The participants reported a good relationship and rapport with the psychiatrists and nursing staff, and as a result trusted their opinion and advice. This influenced their decision to try ketamine:

P10: *The fact that I really trusted [psychiatrist's name]. Because he knew me inside and out, he's an expert in his field, I put myself in his hands and I was willing to go with what he felt.*

3.4. Responses experienced taking ketamine

This theme is made up of five sub-themes, which collate the participants' experiences of responses to ketamine, in the immediate, short and longer term.

3.4.1. Physiological

This theme is divided into four subthemes, generally experienced during the infusion or shortly following.

3.4.1.1. Dissociation, a high. Participants revealed during infusions they experienced dissociation, or out of body experiences: '*So the dissociation was, was definitely there'* (P13), and '*the dissociation, I feel that very much'* (P10), others described how this felt:

P12: *it was almost like an out of body experience… I tried to lift up my arm, it was almost like it wasn't me, I was like watching my arm being lifted up.*

For some there was a feeling of being high, a '*trippy experience*' (P12); with several participants describing the physiological responses similar to taking psychoactive drugs or alcohol:

P4: *You've got no controls, you know, everything seems a bit funny, it, it makes you a bit high.*
P1: *arms and legs feel quite heavy, you might start feeling a little giddy.*

3.4.1.2. Relaxed and sleepy. Participants described a relaxed, sleepy, floaty feeling that was pleasant in nature during the infusion:

P1: *kind of like just floaty, in and out state of kind of sleep.*
P3: *well I used to nod off!*

3.4.1.3. Heightened sensory perception. During the infusion and for a short period afterwards, participants described how they experienced heightened senses and perceptions, particularly in relation to noise and vision. Several participants described how colours were more vibrant and brighter:

P12: *Certain colours like I had never seen them as they were before…things like the colour red, so like brake lights and cars and just things like that, that I had never seen a brake light as vibrant before.*

Participants recalled how noises became '*like almost amplified'* (P12), vividly recalling '*clippy-cloppy heels, banging of doors*' (P3), '*birds tweeting'* (P8), and '*lorries reversing*' (P6).

3.4.1.4. Adverse side effects. Some physiological responses were not pleasant experiences. These varied in type and severity, including nausea, headaches, and adverse physiological reactions:

P1: *During the treatment…I would always have low blood pressure…so a few times I had to be laid down flat very quickly.*

Some of the adverse effects included an outpouring of grief and crying, whilst another participant experienced panic:

P12: *It was almost like an impending doom, like I was panicking.*

For the majority these unpleasant experiences were manageable, and they were able to continue with treatment. However, for three of the participants the adverse side effects, such as horrific hallucinations or exceptionally high temperature, meant that treatment was stopped.

3.4.2. Emotional

This theme is represented by three subthemes, which describe different emotional responses during the infusion and following.

3.4.2.5. Happy and laughing. For many this feeling started during the infusion, where they talk about laughing. This was a therapeutic part of the process making it an enjoyable experience:

P1: *I do think laughter is the best, best drug…..with the nurse tending me today…I had tears of laughter and she did as we, we were laughing so much.*

Happiness was something that some participants felt continued through the following days. Several participants used the word '*happy/happier*', in contrast to previously seeing themselves as unhappy:

P3: *And Mum [P3] was happy! And Mum hadn't been happy for many years, and seriously not happy….they [family] were really pleased because I was so happy. I mean I would bounce off the walls over the weekend.*

3.4.2.6. Uplifted feeling, brightened mood. Participants experienced an overall lift in their mood:

P2: *It gives me space, so lifts me, my emotions, my feelings, my mind, my spirit, my well-being.*

This lifted mood was something that was experienced during and after the infusion, and for some was sustained over a few days or longer. Participants described themselves as '*elated*' (P2), that their '*mood is lifted*' (P8), they '*felt bright*' (P7), and had '*fire in their belly*' (P6). These feelings were a stark comparison to feelings when depressed:

P2: *It just lifts darkness away.*
P3: *It brightened my mood and it, it lightened it. Again, until the Tuesday, and I'd start to slip down into depressive mode and suicidal mode and have dark thoughts.*

3.4.2.7. Feeling 'normal' and like 'true self'. Participants explained how they felt normal, a person without symptoms of depression:

P6: *I felt normal. Or I seemed to feel like just a normal person, just functioning.*

Ketamine enabled them to be their real and true self:

P7: *I just felt like myself again…I used to just, it was like putting a front on for people just to be what they wanted me to be, not what I really was. But after the ketamine, it was me, it was me. I really felt, it was real.*

3.4.3. Behavioural

Participants described noticeable and concrete positive changes in their behaviours following ketamine, some maintained over longer periods of time. For example, improved night-time sleep: *'instead of your brain whirring away with stuff that does not matter, I'd go to bed… shut me eyes, my eyes would be open in the morning… I'd be ready to go again'* (P6). This theme comprises two subthemes.

3.4.3.8. Actively undertake activities. Participants described how they were able to undertake activities such as: cooking, showering, visiting friends, cleaning the house, going to the gym, work, sport, and walking the dog. Participants explained they had the motivation to undertake these activities and implement them:

P3: *I wanted to do things. I wanted to have a shower and doing my housework, walking the dog, just normal things that everybody takes for granted, I couldn't do. But once I'd had a ketamine, I could do all those things.*

P10: *I joined a running club*
P11: *Guitar… I started having lessons again. Go to classes at the gym… go running*
P7: *I had an interview… I would never have… even thought about work… it was successful… I have been working ever since.*

3.4.3.9. Sociable and communicative with others. Participants found that their ability and desire to socialise and communicate improved greatly, and for some this lasted longer term. Individuals expressed: '*I was a lot more sociable'* (P8); for some this meant improved relationships: '*The relationship we [with daughter] have got [now] is amazing, it's lovely*' (P7). Many identified this as a radical change:

P3: *I was quite happy to see people and entertain people and ask people to come back to my home, which is unheard of. But again, since I've been off the ketamine, I don't, nobody comes into my home.*

3.4.4. Cognitive

This theme is about a change in cognitive focus: '*it just enables be to think*' (P10), '*definitely concentrate more*' (P11), '*I can rationalise'* (P7), '*I was much sharper'* (P3), and shifts in thinking patterns and mindset. This theme is made up of 4 subthemes.

3.4.4.10. Positive thoughts increased, negative thoughts decreased. The participants described a two-way process: negative thoughts diminished, replaced by positive thoughts:

P1: *I could see a future, I could see that I was capable of doing things…I didn't kind of feel the sort of the negative person sitting on your shoulder telling you that you can't do this there's a problem here…. It was almost as if…the angel and the demon on your shoulder, and all you could hear was the angel.*

There was a shift to less anxiety, looking forward to things, being motivated and generally feeling good.

3.4.4.11. Reduced suicidal ideation. This radical change occurred for around half of the participants: '*before the treatment I was really quite suicidal, that's all but disappeared*' (P1), '*I haven't been suicidal for three years'* (P2). The participants described how previous dark, suicidal thoughts were replaced with positive thoughts about improved self-worth, an ability to see a future and a renewed desire to live:

P10: My zest for life has returned, my outlook is back in terms of I have an outlook, instead of thinking, I, you know there is no point and optimism is gone. Like the thought of leaving life is, I just can't comprehend that that was me who thought that.

3.4.4.12. Reframing thoughts and reprogramming mindset. Participants experienced a complete change in their mindset and the ability to reframe their thinking:

P1: *Almost as if it rewired the brain very quickly and it kind of just matched things up the way they should be, rather than what they felt they were.*
P2: *It is the treatment that has… helped me to re-programme myself or play a different record. You'd see the bigger picture… you realise that there is more to life than worrying over stuff you cannot change. If you can change it, brilliant, go ahead and change it.*

This encapsulated new positive, future-focused thinking experienced:

P10: *I drive there [treatment centre] and everything is grey and black, and I come out and it is technicolour. It really is… that powerful.*

3.4.4.13. Motivated thinking and a want to take action. Related to behavioural motivation and implementation of activities, this theme is differentiated as a cognitive response; participants talked about motivated thoughts and thinking without examples of implementation:

P2: [after treatment] *I'm still thinking I want to do something, I want to be more active with my life, I want to get on with life.*

Participants expressed motivated thinking and a desire to do a range of things including developing their career, going out to visit places, taking up a hobby, painting the house and everyday chores:

P10: *So I start thinking …my brain then starts working overtime and I start thinking about the things I really want to do…so it's a real turnaround.*

3.4.5. Life-changing, a profound impact

This theme represents a powerful response and impact following ketamine. One participant commented the difference was like '*day and night how I behaved, functioned and acted*' (P6). All the participants, for whom the treatment had an antidepressive effect, commented it was life changing:

P13: *It just, it, it had a knock-on effect with everything especially anxiety, it was almost like a wonder drug for it to act so quickly, and to see such huge change that I'd never seen before and haven't really seen since.*

The enormity or profoundness of the effect was apparent in the language used: '*major impact…a drastic change*' (P1), *'discharged from mental health team'* (P7), '*a profound effect'* (P8), *'ketamine breathes life back into me'* (P10), *'erased… negativity'* (P12).

3.5. Treatment enhancers

Participants identified environmental and psychological factors they felt enhanced their treatment experience. Although a biological treatment, ketamine is administered in a psychological and environmental context. This theme is represented through three subthemes.

3.5.1. Conducive and safe environment

The participants discussed how important the environment was for enhancing their experience, several referring to feeling safe: '*I knew that I was safe, I always felt safe'* (P6). Being able to relax facilitated a positive ketamine experience: *'I was able to relax'* (P12).

The patients described how the psychological environment augmented their treatment experience:

P9: *It's a very nice, nice environment as well, not clinical and that, that really helps to put your mind at ease.*

3.5.2. Medical expertise and professionalism

This theme reflects how participants trusted the medical staff to administer procedures safely and support any medical needs during treatment. This reduced anxiety, improving the experience:

P11: *Cannula in your hand, you know I was a bit anxious about that, but they did it so well really didn't feel much, and then, the doctors, you know, just very efficient and doing their job.*

Many of the participants felt staff were very professional in the way they interacted:

P9: *…very professional so she was supporting and looking at my notes and checking the doses.*

3.5.3. Therapeutic alliance with caring staff

Across all narratives the therapeutic alliance formed with the staff, who participants felt were caring and compassionate towards them, was a strong enhancer of treatment experience. Staff were described as: '*caring*' (P2), '*lovely, they really looked after us*' (P4), '*so friendly and reassuring*' (P6) and '*really kind*' (P9). The feeling was that each patient was treated as an individual and staff connected effectively:

P2: *They are very, very caring they speak, they talk to you with your first name, they treat you as an individual they read your notes, but they also remember you and care for you and they connect with you.*

The participants emphasised the value of psychological support through informal therapeutic input:

P1: *Talking with the nurses in the breakfast room is a huge benefit. …they are so nice and easy to talk to, although it is a clinical procedure, it doesn't feel clinical….I would say it's almost 50% the benefit you get is that.*

3.6. Barriers to treatment efficacy and success

Some participants experienced barriers to treatment efficacy. For a minority, they did not respond to the ketamine infusions, others finding the effects lacked longevity. This theme is represented by 3 subthemes.

3.6.1. Being a non-responder to ketamine

Three participants reported no antidepressive effects:

P9: *I was not a responder after three treatments and I think that was, that was sort of clear after one to be honest in terms of my reaction.*

When asked if he felt the treatment impacted on factors such as mood, ability to think, engaging socially, sleep, and ability to cope, he responded: '*no effect on any of these whatsoever*' (P4).

3.6.2. Loss of ketamine effects over time

The patterns of treatment effect longevity differed, some experiencing longer-term benefits, while for others benefits were sustained over a few days only:

P11: *Mood-wise, it does elevate me. Say I was having* [treatment] *on Friday… my mood is fine and good. But by Monday, it's gone.*

Having to manage and live with this cyclical pattern:

P8: *…you are climbing a mountain and you get to the top and then you fall down the hill again. And you are back to square one and you, look forward to Fridays again* [another infusion] *just to feel that a lot, feel a lot different than you normally do.*

3.6.3. Negative external and environmental factors

Participants reported that if they experienced negative external factors, this could affect treatment experience and act as a barrier to treatment success:

P3: *I had a young girl with me in the room, she was having treatment. It was her first time of having ketamine and she freaked…. Screaming like a banshee. And I just, it sent me on one…. I was screaming 'just get me out of this room' …that week, ketamine had no effect on me whatsoever.*

Other external factors impacted on treatment effect, for example: death in the family, events such as Christmas, unfamiliar and inexperienced staff, or just having a bad day:

P1: *There is always the risk if you are having a bad day on the treatment day, and this happened to me… I found that if I felt very negatively on the treatment day, the effect actually doesn't last as well.*

3.7. Advocate for treatment

All participants recommended that others should try and have access to the treatment, regardless of whether the treatment was effective or not for them.

P11: *It really works; I would recommend it…without a shadow of a doubt… to anyone with long term, severe depression who's tried lots of other options.*

The advocacy was linked to the high quality of service provision:

P2: *I tell everyone wherever we go, whoever asked about such things I just can't stop talking about this place. What they provide here, it's a goldmine…it is getting the word out about this place.*

4. Discussion

For the majority of participants a consistent story emerges. Ketamine infusion causes some initial 'high', enhanced perception, and dissociation experience, followed by a lifting of mood, a reduction in or removal of suicidal ideation and depression, improved ability to concentrate and sleep, lasting from around 3 to 6 days; these factors lead to an increase in motivation, socialisation, and activity. People on maintenance ketamine are in a cycle of reduced or no depression symptoms (a return to 'normal') and then a decline over a period of 5-7 days until their next ketamine infusion. Some participants were able to use ketamine to experience longer remission and return to a socially engaged, active and purposeful life. Some participants report ketamine has a profound effect and is transformational; however, for others ketamine does not have an antidepressive effect, while others experience adverse effects preventing them from further treatment. All participants valued the therapeutic alliance with the clinic's staff which enhanced the treatment experience, and all advocated ketamine treatment access for those who had not responded to other forms of antidepressant treatment.

This study's results add to other interview analysis results that ketamine causes an initial 'high', enhanced perception, and dissociation experience (van Schalkwyk et al., 2018; Lascelles et al., 2019; Phillips et al., 2019). Most people tolerate adverse effects, and these effects may reduce over a course of treatment (Sakurai et al., 2020), people engage in a risk/benefit analysis and most choose to have ketamine (Fairchild et al., 2020). As has been found in other studies, the antidepressive effect is rapid, trails off, and longevity of effect varies between individuals (Sakurai et al., 2020). Neurocognitive function improvement, reduction or removal of suicidal ideation and depression symptoms, elevated mood, and improved functioning and sociability are all patient-reported beneficial effects (van Schalkwyk et al., 2018; Jilka et al., 2019; Lascelles et al., 2019; Phillips et al., 2019; Shiroma et al., 2020).

Ketamine is a biological treatment; however, the holistic view of treatment delivery is that psychological (mind) and biological (brain) interventions interact to affect outcomes and treatment efficacy (Rosendale, 2009). Ketamine is administered within a psychological and environmental context, in this study the treatment environment was perceived as safe and relaxing: one that augmented, enriched, and enabled a positive treatment experience. The therapeutic alliance between patients and staff was also identified as a contributory factor for enhancing treatment experience. This is in line with research which suggests a positive relationship between the therapeutic alliance and outcomes (Flückiger et al., 2018).

Study limitations include the small sample size, the potential lack of generalisability associated with the qualitative methodology, people who agreed to participate were self-selected and there may be some bias in terms of those agreeing to participate having a more positive experience and to be currently experiencing fewer depression symptoms. The participant group is quite small at 13 but a good number for a qualitative in-depth interview study as saturation often occurs at around 12

participants in relatively homogeneous groups (Guest et al., 2006). Although some participants had additional diagnosis to TRD, it is quite often the case in a TRD population. The participants all attended a single clinic and all identified as 'White British' reducing generalisability. Although, we only recruited patients from one ketamine clinic for depression, there are only two in the UK so this clinic represents 50% of the UKs service provision and it draws patients from a national population. The interviews were conducted retrospectively and at varying time periods following initiation of treatment.

In conclusion, ketamine has risks, adverse side effects, and, for some, is not tolerated and does not have antidepressive effects. It has beneficial effects for others and life transforming for some. It is imporatnt to have a treatment environment where patients feel supported, safe and relaxed to maximise the chance of a positive and mimimise chance of a negative expereince. There is some evidence of sustained antidepressant effects with once-weekly maintenance treatment (Phillips et al., 2019). People with TRD continue with maintenance ketamine treatment due to perceived significant improvement (Sakurai et al., 2020). Ketamine may be a source of hope for patients for whom other treatments have not been effective (Krystal et al., 2019). People who experience depression have expressed hope for acceptance of ketamine as a drug that improves people's lives, reduces symptoms of depression and improves functioning (Jilka et al., 2019). This present study adds value in providing a first-hand patient perspective of ketamine for depression. Further research could investigate if people who received ketamine developed habitational effects, while positive and negative effects of ketamine declined or increased, and if doses needed to be subsequently escalated. Larger sample surveys of ketamine experience and further exploration of topics raised with qualitative methods such as in-depth interviews are warranted.

Author statement

All authors have materially participated in the research and/or article preparation

Chris Griffiths was the chief investigator on the project, gained HRA ethics approval, designed the project, part of analysis team, lead writing of introduction, and discussion/conclusion/abstract

Kate Walker conducted all interviews, led the analysis and interpretation team, and assisted in paper preparation

Isabel Reid was part of analysis and interpretation team

Ksenija Maravic da Silva led the patient data analysis and reporting

Alex O'Neill-Kerr provided permission to access patients, contributed to HRA ethics application, and provided information on treatment

All authors have inputted into writing of the paper and approved the final article

Declaration of Competing Interest

None of the authors have any actual or potential conflict of interest to disclose including any financial, personal or other relationships with other people or organizations within three (3) years of beginning the work submitted that could inappropriately influence, or be perceived to influence, their work.

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References

Anderson, H.D., Pace, W.D., Libby, A.M., West, D.R., Valuck, R.J., 2012. Rates of 5 common antidepressant side effects among new adult and adolescent cases of depression: a retrospective US claims study. Clin. Ther. 34 (1), 113–123. doi:10.1016/j.clinthera.2011.11.024.

Balestri, M., Calati, R., Souery, D., Kautzky, A., Kasper, S., Montgomery, S., … Serretti, A., 2016. Socio-demographic and clinical predictors of treatment resistant depression: a prospective European multicenter study. Journal of Affective Disorders 189, 224–232.

Berlim, M.T., Turecki, G., 2007. Definition, assessment, and staging of treatment—resistant refractory major depression: a review of current concepts and methods. Can. J. Psychiatry 52 (1), 46–54. doi:10.1177/070674370705200108.

Canuso, C.M., Singh, J.B., Fedgchin, M., Alphs, L., Lane, R., Lim, P., … Drevets, W.C., 2018. 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. American Journal of Psychiatry 175 (7), 620–630. doi:10.1176/appi.ajp.2018.17060720.

Coyle, C.M., Laws, K.R., 2015. The use of ketamine as an antidepressant: a systematic review and meta-analysis. Hum. Psychopharmacol. 30 (3), 152–163.

Eaton, W.W., Shao, H., Nestadt, G., Lee, B.H., Bienvenu, O.J., Zandi, P., 2008. Population-based study of first onset and chronicity in major depressive disorder. Arch. Gen. Psychiatry 65 (5), 513–520.

Fairchild, A.O., Katz, E.G., Reed, S.D., Johnson, F.R., DiBernardo, A., Hough, D., … Levitan, B., 2020. Patient preferences for ketamine-based antidepressant treatments in treatment-resistant depression: Results from a clinical trial and panel. Neurology, Psychiatry and Brain Research 37, 67–78.

Fond, G., Loundou, A., Rabu, C., Macgregor, A., Lançon, C., Brittner, M., … Roger, M., 2014. Ketamine administration in depressive disorders: a systematic review and meta–analysis. Psychopharmacology 231 (18), 3663–3676.

Flückiger, C., Del Re, A.C., Wampold, B.E., Horvat, A.O., 2018. The alliance in adult psychotherapy: a meta-analytic synthesis. Psychotherapy 55 (4), 316–340. doi:10.1037/pst0000172316.

Grady, S.E., Marsh, T.A., Tenhouse, A., Klein, K., 2017. Ketamine for the treatment of major depressive disorder and bipolar depression: a review of the literature. Ment. Health Clin. 7 (1), 16–23.

Griffiths, C.A., Griffiths, L.J., 2015. Recovery and reliable change rates for patients scoring severe on depression, anxiety or impaired functioning in a psychological therapies service: IAPT. Ment. Health Rev. J. doi:10.1108/MHRJ-06-2014-0022.

Griffiths, C., O'Neill-Kerr, A., 2019. Patients', carers' and the public's perspectives on electroconvulsive therapy. Front. Psychiatry 10, 304.

Griffiths, C., O'Neill-Kerr, A., Millward, T., Da Silva, K., 2019. Repetitive Transcranial Magnetic Stimulation (rTMS) for depression: outcomes in a United Kingdom (UK) clinical practice. Int. J. Psychiatry Clin. Pract. 23 (2), 122–127.

Gyani, A., Shafran, R., Layard, R., Clark, D.M., 2013. Enhancing recovery rates: lessons from year one of IAPT. Behav. Res. Ther. 51 (9), 597–606. doi:10.1016/j.brat.2013.06.004.

Guest, G., Bunce, A., Johnson, L., 2006. How many interviews are enough? An experiment with data saturation and variability. Field Methods 18 (1), 59–82.

Henkel, V., Seemüller, F., Obermeier, M., Adli, M., Bauer, M., Mundt, C., … Riedel, M., 2009. Does early improvement triggered by antidepressants predict response/remission? analysis of data from a naturalistic study on a large sample of inpatients with major depression. Journal of Affective Disorders 115 (3), 439–449. doi:10.1016/j.jad.2008.10.011.

Jelovac, A., Kolshus, E., McLoughlin, D.M., 2013. Relapse following successful electroconvulsive therapy for major depression: a meta-analysis. Neuropsychopharmacology 38 (12), 2467–2474. doi:10.1038/npp.2013.149.

Jilka, S., Murray, C., Wieczorek, A., Griffiths, H., Wykes, T., McShane, R., 2019. Exploring patients' and carers' views about the clinical use of ketamine to inform policy and practical decisions: mixed-methods study. BJPsych Open 5 (5), e62. doi:10.1192/bjo.2019.52.

Kishimoto, T., Chawla, J.M., Hagi, K., Zarate, C.A., Kane, J.M., Bauer, M., Correll, C.U., 2016. 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. 46 (7), 1459–1472.

Krystal, J.H., Abdallah, C.G., Sanacora, G., Charney, D.S., Duman, R.S., 2019. Ketamine: a paradigm shift for depression research and treatment. Neuron 101 (5), 774–778.

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

Lent, J.K., 2019. Ketamine and treatment-resistant depression. AANA J. 87 (5), 411–419.

McCrone, P.R., Dhanasiri, S., Patel, A., Knapp, M., Lawton-Smith, S., 2008. Paying the Price: the Cost of Mental Health Care in England to 2026. King's Fund.

Mohn, C., Rund, B.R., 2016. Significantly improved neurocognitive function in major depressive disorders 6 weeks after ECT. J. Affect. Disord. 202, 10–15.

Nemeroff, C.B., 2007. Prevalence and management of treatment-resistant depression. J. Clin. Psychiatry 68 (8), 17.

Niciu, M.J., Luckenbaugh, D.A., Ionescu, D.F., Richards, E.M., Vande Voort, J.L., Ballard, E.D., … Zarate, C.A.J., 2015. Ketamine's antidepressant efficacy is extended for at least four weeks in subjects with a family history of an alcohol use disorder. International Journal of Neuropsychopharmacology 18 (1), 1–7. doi:10.1093/ijnp/pyu039.

Phillips, J.L., Norris, S., Talbot, J., Birmingham, M., Hatchard, T., Ortiz, A., … Blier, P., 2019. Single, repeated, and maintenance ketamine infusions for treatment-resistant depression: a randomized controlled trial. American Journal of Psychiatry 176 (5), 401–409.

Rosedale, M., Lisanby, S.H., Malaspina, D., 2009. The structure of the lived experience for

persons having undergone rTMS for depression treatment. J. Am. Psychiatr. Nurses Assoc. 15, 333–337. doi:10.1177/1078390309350773.

Rush, A.J., Trivedi, M.H., Wisniewski, S.R., Nierenberg, A.A., Stewart, J.W., Warden, D., … McGrath, P.J., 2006. Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: a STAR* D report. American Journal of Psychiatry 163 (11), 1905–1917. doi:10.1176/appi.ajp.163.11.1905.

Sakurai, H., Jain, F., Foster, S., Pedrelli, P., Mischoulon, D., Fava, M., Cusin, C., 2020. Long-term outcome in outpatients with depression treated with acute and maintenance intravenous ketamine: a retrospective chart review. J. Affect. Disord. 276, 660–666.

Shenton, A., 2004. Strategies for ensuring trustworthiness in qualitative research projects. Educ. Inf. 22, 63–75. doi:10.3233/EFI-2004-22201.

Shiroma, P.R., Thuras, P., Wels, J., Albott, C.S., Erbes, C., Tye, S., Lim, K.O., 2020. Neurocognitive performance of repeated versus single intravenous subanesthetic ketamine in treatment resistant depression. J. Affect. Disord..

Smith, J.A., 2007. Hermeneutics, human science and health: Linking theory and practice. Int. J. Qual. Stud. Health Well-being 21, 3–11. doi:10.1080/17482620601016120.

Smith, J.A., Flowers, P., Larkin, M., 2012. Interpretative Phenomenological Analysis Theory, Method and Research. Sage, London.

Smith, J.A., Osborn, M., 2003. Interpretative phenomenological analysis. In: Smith, J.A. (Ed.), Qualitative Psychology: a Practical Guide to Research Methods. Sage, London, pp. 51–80.

van Schalkwyk, G.I., Wilkinson, S.T., Davidson, L., Silverman, W.K., Sanacora, G., 2018. Acute psychoactive effects of intravenous ketamine during treatment of mood disorders: analysis of the clinician administered dissociative state scale. J. Affect. Disord. 227, 11–16. doi:10.1016/j.jad.2017.09.023.