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Perceived Benefits of MDMA-Assisted Psychotherapy beyond Symptom Reduction: Qualitative Follow-Up Study of a Clinical Trial for Individuals with Treatment-Resistant PTSD

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ABSTRACT

We present select findings from a long-term follow-up qualitative study of MDMA-assisted psychotherapy for veterans, firefighters, and police officers suffering from chronic, treatment-resistant PTSD. Semi-structured qualitative interviews were conducted at participants' one-year follow-up after a recently completed phase 2 clinical trial. Available interviews from 19 of 24 participants were analyzed. This qualitative analysis sought to complement, clarify, and expand upon the quantitative findings obtained from the Clinician Administered PTSD Scale (CAPS-IV) and supported by the Long-Term Follow-Up (LTFU) Questionnaire. Pertinent data from interview transcripts were coded and analyzed using an interpretative phenomenological analysis (IPA) methodological framework. We explore prominent thematic elements from participant accounts to better understand the outcomes experienced in this trial. All participants reported experiencing lasting personal benefits and enhanced quality of life that extend beyond quantifiable symptom reduction. We explore a range of treatment benefits beyond symptom reduction to highlight the utility of qualitative investigations of the process and effects of MDMA-assisted psychotherapy. Limitations and challenges encountered in conducting this study are discussed along with recommendations for improved qualitative research protocols in future clinical trials.

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Introduction

Post-traumatic stress disorder (PTSD) is a growing public health concern associated with increased occupational, relationship, and other psychological dysfunction, as well as decreased quality of life and enhanced risk of suicide (Sareen et al. 2007). Of particular concern is the much higher prevalence observed among military veterans and first responders compared with the general population (Mithoefer et al. 2018). While a wide spectrum of pharmacotherapies and psychotherapies are available, there remains a large population with chronic PTSD that has gained little benefit from currently approved treatment approaches (Hamner, Robert, and Frueh 2004; Mithoefer et al. 2011).

The non-profit Multidisciplinary Association for Psychedelic Studies (MAPS, 2013) has sponsored multiple FDA-regulated phase 2 clinical trials in evaluating the therapeutic potential of MDMA-assisted psychotherapy for individuals suffering from treatment-resistant PTSD. The clinical trial examined here has applied this therapeutic approach to military veterans and first responders, who comprise a population of growing concern and unique challenges. The other studies have focused on sexual abuse and assault victims (Mithoefer et al. 2011; Oehen et al. 2013) and individuals with a variety of traumatic backgrounds (Ot'alora et al. 2018) who were suffering from treatment-resistant PTSD.

Each of the trials has focused on collecting data from the quantitatively oriented clinical measures necessary for documenting the safety and efficacy required for gaining eventual approval of MDMA-assisted psychotherapy. The Clinician Administered PTSD Scale (CAPS-IV), which served as the primary outcome measure, is widely accepted as the gold standard for evaluating PTSD in clinical trials and provides a measure of efficacy. However, PTSD symptom scores alone do not fully capture the potential benefits that manifest from this treatment. The CAPS-IV assesses the frequency and intensity of PTSD symptoms, but cannot measure changes in essential areas that supplant a diagnosis of PTSD or arise alongside symptoms (Weathers, Keane, and Davidson 2001).

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Clinicians recognize the value of efforts to gain a deeper phenomenological understanding of the process and outcomes of the treatment (Belser et al. 2017; Mithoefer, Grob, and Brewerton 2016; Passie 2012). Qualitative research provides a means for evaluating these nuances and other objectives. To date, qualitative research with psychedelic-assisted therapies has largely focused on studies investigating the therapeutic potential of LSD (Gasser, Kirchner, and Passie 2015) and psilocybin (Belser et al. 2017; Swift et al. 2017) for anxiety related to life-threatening illness, as well as psilocybin for depression (Watts et al. 2017) and smoking cessation (Noorani et al. 2018).

While a number of qualitative studies have explored MDMA as a cultural phenomenon (Beck and Rosenbaum 1994; Ditton, Hammersley, and Khan 2002; Leneghan 2011; Perrone 2010) and its use in therapeutic contexts (Corey, Pisano, and Halpern 2016; Passie 2012; Sola 2017), this is the first to examine MDMA-assisted psychotherapy in a long-term follow-up context. In so doing, we seek to complement, clarify, and expand upon the quantitative findings obtained from the CAPS-IV and self-reported outcomes described in the Long-Term Follow-Up (LTFU) Questionnaire.[1]We identify key themes in participant experiences from before, during, and after the trial to better understand the scope of outcomes resulting from this treatment.[2]

Methods

This retrospective qualitative follow-up study was approved by the John F. Kennedy University Institutional Review Board as well as the Western-Copernicus Group Institutional Review Board that oversees the MAPS phase 2 clinical trials. The 19 individuals interviewed for our study were participants in a phase 2 clinical trial investigating the safety and efficacy of MDMA-assisted psychotherapy for military veterans and first responders with treatment-resistant PTSD (Mithoefer et al. 2018). All of the semi-structured qualitative interviews were conducted during participants' LTFU session, one year after the end of the trial. This provided participants with a rich opportunity to reflect on the nature and meaning of their experience within a safe and supportive context. It also allowed us to compare our data with results from the CAPS-IV and LTFU Questionnaire completed as part of that visit.

The original phase 2 clinical trial followed a randomized, double-blind, crossover protocol where, after unblinding, each of the participants in the low-dose (active control) and medium-dose groups was offered three open-label full-dose sessions of MDMA-assisted psychotherapy to match those in the full-dose group. Additionally, participants took part in weekly non-drug therapy sessions throughout the study period. Experimental sessions were administered at monthly intervals, and involved six- to eight-hour sessions of manualized MDMA-assisted psychotherapy with a male and female co-therapy team using a relatively non-directive or client-directed therapeutic approach (Mithoefer et al. 2018). A full description of the therapeutic process is provided in the treatment manual (Mithoefer 2017).

A member of our research team (JB) worked closely with MAPS staff and the principal investigator of the trial in helping to revise the LTFU Questionnaire completed by participants for their one-year site visit. Modeled on this, he then designed the LTFU Qualitative Interview instrument and annotated guide employed in this study. Each of the qualitative interviews was conducted by one or both of the trial therapists at the time of each participant's one-year follow-up site visit. The semi-structured interview format closely followed the LTFU Questionnaire, which participants completed prior to the site visit. This format allowed for open discussion of certain aspects of the experience that individuals deemed significant, while also allowing the conversation to be steered towards important topics. In this way, essential themes could emerge organically while key topics were also addressed.

Coding and analysis

Nineteen of these interviews were recorded, transcribed, and made available to the research team via encrypted software. These interviews underwent thematic analysis by the four-member research team. The two original researchers (WB and JB) created an initial codebook based on their review of the first three available transcripts. Codes were derived top-down from interview questions and bottom-up from patterns found in the interviews. Where appropriate, codes were expanded to account for descriptions of time frame, including before, during, and after treatment, to better understand how participants' experiences and perceptions evolved throughout the process. The full research team then discussed and finalized the codebook before completing the coding process. The codebook was applied to each interview transcript by a minimum of two researchers using standard practices (Berends and Johnston 2005; Merrick 1999; Smith 2004), and concurrent coded transcripts were submitted to a pooled Cohen's kappa test (≥ 0.75) for inter-rater reliability (Cohen 1960; De Vries et al. 2008). Codes and themes were discussed among the team at weekly research meetings to maintain continuity among coders, and any alterations to codes were then applied to previous interviews.

Our decision to employ an Interpretative Phenomenological Analysis (IPA) methodological approach was

informed by New York University (NYU) researchers studying psilocybin-assisted psychotherapy for anxiety associated with life-threatening illnesses (Belser et al. 2017; Swift et al. 2017). We found the IPA framework to be optimal for conceptualizing participants' personal experiences and perceptions of the treatment process. IPA is concerned with inquiry rather than hypothesis (Willig 2008), emphasizing the analysis of experience in its own terms instead of narrowing it into preestablished categories (Pietkiewicz and Smith 2014). This framework is particularly relevant for evaluating novel treatments such as MDMA-assisted psychotherapy because it illuminates the meaning participants make of their experiences in the trial (Biggerstaff and Thompson 2008).

A computer-assisted qualitative data analysis software package, ATLAS.ti 8.2.4, was used to assist in data analysis of the interview transcripts (Muhr 2014). Atlas.ti helped organize data to identify emerging themes, develop tables of co-occurring codes, and provide an opportunity to easily search codes by participant or groups of participants. Our qualitative analysis also benefited from the rich comparative data provided by the LTFU questionnaire and CAPS-IV.

Participants

Eligible participants were military veterans, police, and firefighters over 18 years old who had a confirmed diagnosis of PTSD as measured by a CAPS-IV total score of 50 or higher, indicating moderate to severe PTSD symptoms. Participants were also considered treatment-resistant; they must have previously failed to respond or been unable to tolerate more than one psychotherapeutic or psychopharmacological treatment for PTSD of adequate dose/duration.

Of the 26 original phase 2 study participants, 24 completed the study along with the LTFU interview and CAPS-IV assessment one year after the end of treatment. One participant dropped out after significant improvement of symptoms in the first stage of treatment; the other dropped out after one session in the blinded low-dose group. Of the 24 participants, we were able to analyze qualitative interviews from 19 (Figure 1). The 19 participants interviewed for our qualitative study included 16 military veterans, two firefighters, and one police officer. They included 13 men and six women who ranged from 24 to 56 years old (Table 1).

Results

For a detailed report of quantitative long-term outcomes of the phase 2 trial, see Mithoefer et al. (2018). In our sample, 15 participants (79%) showed clinically significant decreases in PTSD symptoms at one-year follow-up (>30% reduction in CAPS-IV total scores from baseline), with average change in CAPS-IV total scores of 68% from baseline (Table 2).

Benefits of MDMA-assisted psychotherapy beyond symptom reduction

The phase 2 clinical trials have found significant and durable reductions in PTSD symptoms that persist more than one year following the treatment (Mithoefer et al. 2018, 2013; Ot'alora et al. 2018). Our qualitative analysis illuminated a range of additional outcomes from the treatment that are often difficult to discern from PTSD symptom scores alone. Exemplifying this was the only participant in our sample (819) whose CAPS-IV total scores improved less than 10% from baseline to the first-year follow-up. Despite this modest change, he nevertheless insisted that "there is improvement from every one of my problems I had when I first came here. Definitely improvement."

Participants described qualitative improvement in their self-awareness (n = 19), relationships and social skills (n = 12), problem substance use (n = 13), and openness to continued therapy (n = 14). Preparatory and integrative therapy sessions, strong rapport with the therapy team, and the beneficial effects of MDMA in the treatment process were perceived as factors in aiding long-term benefit.

The number of participants who described experiences with various qualitative themes and their ratings of perceived benefits from treatment are shown in Figure 2. While our complete qualitative analysis explored a range of experiential themes, the following categories were chosen to demonstrate the most common, essential elements of participants' experience of the treatment and changes reported. Some quotes have been edited to remove filler words.

Improved self-awareness

Many participants (n = 8) expressed how their experiences with trauma and PTSD before the study limited their ability to understand themselves or their issues. Participant 811 reflected that before the study he felt "something is seriously wrong with me. And you don't know what's causing it because you don't know that there's triggers." All participants (n = 19) reported valuable insights into their personal experiences and shared some of the ways in which they gained deeper self-understanding during their LTFU interviews. For instance, Participant 819, who showed the smallest change in CAPS-IV total scores among the sample,

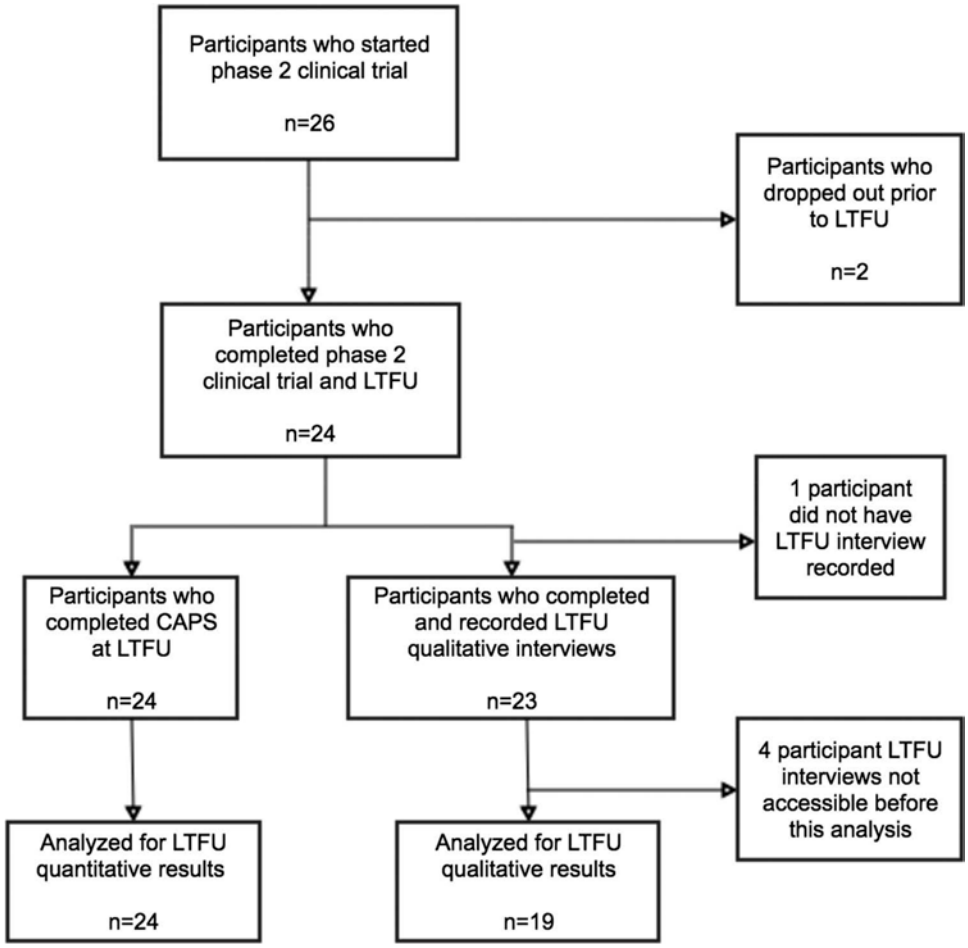

Figure 1. Flow chart denoting the movement of participants from the phase 2 clinical trial to the LTFU qualitative study.

Table 1. Demographic data for 19 participants in the LTFU qualitative study.

Subject ID	Gender	Age	Ethnicity	Cause of PTSD
801	Female	27	White/Caucasian	Sexual Assault
803	Male	24	White/Caucasian	War
804	Male	25	White/Caucasian	War
805	Female	34	White/Caucasian	War
806	Male	25	White/Caucasian	War
808	Male	30	White/Caucasian	War
809	Male	56	White/Caucasian	War
810	Female	48	White/Caucasian	Sexual Assault
811	Male	45	White/Caucasian	Firefighting
812	Male	34	Half Caucasian, Half Native American	War
813	Male	39	White/Caucasian	Firefighting
814	Male	35	White/Caucasian	War
815	Male	33	White/Caucasian	War
817	Male	30	White/Caucasian	War
819	Male	46	White/Caucasian	War
820	Female	51	White/Caucasian	Sexual Assault
821	Female	30	Native American	War
822	Female	43	White/Caucasian	Job as police officer
823	Male	38	White/Caucasian	War

described how the treatment allowed him to step back and reflect upon his inherent beliefs and actions:

> *I learned a lot. I learned a lot about myself. I'd gotten to the point of questioning myself, my own morals, and for someone who hasn't done this stuff, they're not going to understand. You can see yourself like you can read a book and see everything that you stand for and kind of analyze your own self, your own thought, your own reasoning.*

A number of participants described how the treatment altered their perception of self and brought about more self-compassion. Participant 804 explained how he had

Table 2. CAPS-IV total scores of each participant, taken by independent raters at multiple points of treatment.

Subject ID	Baseline	End of Treatment	Long-Term Follow-Up (LTFU)	% Change from Baseline to LTFU
801	107	93	57	46.72%
803	87	25	30	65.51%
804	74	4	20	72.97%
805	105	54	87	17.14%
806	111	33	39	64.86%
808	105	8	10	90.47%
809	90	32	59	34.44%
810	73	44	58	20.54%
811	106	78	92	13.20%
812	85	11	7	91.76%
813	108	74	21	80.56%
814	79	3	2	97.47%
815	74	3	0	100%
817	111	32	27	75.68%
819	92	81	89	3.26%
820	85	60	46	45.88%
821	100	50	58	42%
822	100	11	35	65%
823	94	52	50	46.81%
Avg.	93.2	36.3	40.5	56.54%

Baseline scores assessed at study enrollment; *End of Treatment* scores assessed within two months of final MDMA session; *Long-Term Follow-Up* scores assessed one year following final treatment session.

Degree of Overall Benefit	**n**	**Percentage (%) of participants endorsing**
1 (slight)	0	0
2	1	5.3
3	1	5.3
4	4	21.1
5 (large)	13	68.4
Degree the Benefit Lasted		
1 Only a small amount of the benefit has lasted	0	0
2 Some but not most of the benefit has lasted	0	0
3 Most but not all of the benefit has lasted	4	21.1
4 Virtually all the benefit has lasted	4	21.1
5 It has lasted and continues to grow	9	47.4
Other: Unsure	1	5.3
Other: The benefit lasted 3 months	1	5.3
Effects of MDMA-Assisted Psychotherapy	**n**	**% participants**
Lasting Benefits Mentioned		
Improved Friendships	11	57.9
Improved Family Relationships	12	63.2
Reduced Problem Substance Use	13	68.4
Openness to Further Therapy	14	73.6
Improved Self-Awareness	19	100
Engagement in New Activities	19	100
Enhanced Quality of Life	19	100
Reduction in PTSD Symptoms	19	100

Degree of Overall Benefit and *Degree the Benefit Lasted*: participant responses on a 1-5 Likert scale from LTFU Questionnaire. *Effects of MDMA-Assisted Psychotherapy*: themes garnered from participant qualitative interviews.

Figure 2. Perceived benefits endorsed by participants at long-term follow-up.

Degree of Overall Benefit and *Degree the Benefit Lasted*: participant responses on a 1–5 Likert scale from LTFU Questionnaire. *Effects of MDMA-Assisted Psychotherapy*: themes garnered from participant qualitative interviews.

become more in touch with his "inner self." He was now able to reality-test more effectively to avoid irrational negative thoughts:

> *I feel like I understand a little differently now…. It's like my inner self is asking me, "How many times have you actually done something so horrific that it just… that it would turn people away from you?" I can't think of a single thing.*

Similarly, Participant 801 explained how improved self-awareness gained in the treatment helped her better understand and manage her PTSD symptoms:

> *I'm just better at recognizing and managing. And I recognize that it's not something that I have to blame myself for. There's actually an underlying medical condition that's affected the way that my brain has been wired, and I'm working on rewiring, but for me, because I think if the trauma is such, you know, it was, like, stuck in the 10 years of consistent trauma…. I feel like I had to unravel it first.*

Improved relationships and social skills

All participants described the ways their PTSD symptoms had impacted their social functioning. The majority of our sample (n = 12) reported improved relationships and social functioning as a benefit from participating in the treatment. For example, Participant 808 described how a "breakthrough" in his first session helped him communicate with friends and family in ways that were not possible before the treatment:

> *[An improvement is] just being able to communicate what I'm going through with people. Up until I finished the MDMA therapy, or maybe it was sometime in the middle of it, I was never able to communicate with anybody in my day-to-day life about any of the issues that I was going through. Really not friends, not family…. I feel like I can be more open with people now. It was really that first MDMA session that we had, where I had that, I consider it a breakthrough, where I was able to clearly see that I had a big disconnect in compassion for myself.*

Participant 809 described improvements in his family relationships as well as an increased sense of empathy for all people:

> *[I feel] love, compassion, and it's not just for family, it's for everyone… [my parents and I] have a much better relationship now, no doubt… the study helped me really get there.*

Engagement in new activities

Many participants expressed how their PTSD symptoms led to isolation and limited participation in activities, sometimes for years at a time. All participants (n = 19) reported that they were able to take more healthy and rewarding action in their life after the study, regardless of the degree to which their symptoms changed. Many credited their experience in the study as the primary source of a newfound feeling of motivation to try new things. As Participant 808 observed:

> *Looking back, I really didn't start getting into recording music or anything like that at all until I started the study…. And I've got hundreds of hours of original music, and painting.*

Participant 806 reflected on how his isolation and lack of motivation to engage in society before the study had shifted into a sense of urgency to live life to the fullest:

> *I went from not living life and locked myself in my house to getting out and living in overdrive actually, almost like I am trying to catch up for all of those lost years…. I don't watch TV anymore, I don't want to sit stagnant any more, like I have until I die to get a lot of things done.*

Similarly, Participant 823 described a renewed enthusiastic drive to engage with life:

> *I've done some really weird and amazing stuff since I've come out of this study. I had this drive before, but I had this thing holding me back. And it's like the gates were opened and I just… ran. So I do end up butting up against triggers and stuff like that occasionally. But it's because I'm doing way more.*

Reduced medication and problem substance use

Medications have shown limited efficacy in treating certain symptoms and comorbid presentations associated with PTSD (Foa et al. 2009; Stein et al. 2006). While our entire sample had been prescribed a variety of medications for their PTSD, most had reduced their reliance on medications over the course of treatment. Thirteen of the 19 participants reported that reduction in PTSD symptoms and meaningful experiences from the study contributed to a decrease in their reliance on medication and problematic substance use. This change was particularly noteworthy for Participant 814:

> *When I first started [the study] I was taking 10 different things. And now no blood pressure medicine, no anxiety pills, no pain pills.*

In addition to prescription medication, alcohol and illicit substances are commonly used to manage PTSD symptoms (Najt, Fusar-Poli, and Brambilla 2011; Norman et al. 2010; Stein et al. 2006). Nine of our participants recalled extensive substance use in attempting to cope with their PTSD. Participant 808 explained his former reliance on alcohol:

[I was] probably just trying to self-medicate or something. I started drinking a lot in the Marines and it was just kind of this way of turning off from what was going on around me and in me and I think it was something that I kept doing for the same reasons. Just a way to disconnect, just to dull myself.

He then went on to observe how markedly this urge had changed in the year since completing the trial: "Before it was 15–20 drinks. And now it's down to three a week."

Participant 809 reflected on how the treatment helped him appreciate the value of more enduring changes over the short-term relief afforded by substance use:

I think what pushed me away from the alcohol was that the MDMA proved to me that if you want something to help you, it helps you continuously, not just for a moment and then the next moment you are feeling bad. The study helped me see that.

Participant 821 elaborated on how the lessons from the therapy helped her reduce her reliance on substances:

I've started learning the tools to where I don't need to depend or rely upon medicine or alcohol or even deviant behavior to feel better or get through things like that. So I think that's been the most valuable.

Openness to future therapies

Prior to involvement in the phase 2 trial, all participants had engaged in multiple pharmacological and psychotherapeutic PTSD treatments that provided little or no improvement, and some reported perceiving harms. Despite these past failures, most participants (n = 14) described how their experience with the MDMA-assisted psychotherapy had helped them feel more open to exploring other treatment modalities. As Participant 808 explained it:

I had a lot of defenses going up into the therapies that I had previous to the MDMA, and it made accomplishing any substantial breakthroughs in what I was going through pretty impossible. So with the MDMA, it broke this hard, outer shell that was up that kept me from being able to connect with the therapies I was going through. So now, when I go through and I'm doing the [cognitive processing therapy], I understand the material and how it is beneficial.

Participant 809 reflected that while he benefited from the study, he feels that the treatment was not a silver bullet, but rather the start of a healing process:

I'm definitely better, but I've got to continue on. This isn't something that you take a pill or push a button and say "I'm well." [It is something I] will be working on for a long time. [But] I have definitely moved light years ahead in a short period of time.

Similarly, Participant 806 observed how traumas processed in the study had previously blocked him from working on other issues in his life. He now felt more capable of working through difficult memories:

I feel like all of this was just like getting that taken care of so I could start the work on my childhood stuff. Now that the worst stuff is done, I feel like I can just work on my other issues.

Perceived therapeutic factors of the treatment

Our study also sought to explore the therapeutic factors of MDMA-assisted psychotherapy in the treatment of PTSD through participant descriptions of their experience. Participants described factors they felt were integral to the therapy process, including the effects of MDMA on the therapy process, rapport with the therapy team, and preparatory/integration sessions. Participant 815 explained how the combination of these factors contributed to healing and set the experience apart from past treatment attempts:

I think that the MDMA gave me the ability to feel as though I was capable and safe of tackling the issues. Whereas before I feared those thoughts and I tried to avoid them at all times, and avoid things that reminded me of those thoughts, I think it allowed me to feel safe in my space. Of being able to fight it. I felt like I had the ability and tools, whereas before I was unarmed, unarmored, and had no support. And this type of environment, with [the therapists], the catalyst drug, and everything else, it felt as though I had backup. Now it was safe and I had my tools and weapons to be able to tackle the obstacles that I never had before.

In recounting why this clinical trial may have produced improved outcomes from previous therapeutic and pharmacological trials, participants described how these factors created an environment for healing. Participant 809 described:

When I did the MDMA study it was exactly what they were trying to get me to do (in other therapies)… but I guess in such a slow pace… and then I got on the rocket ship (of) the MDMA. I'm not a very patient person… I want to get better now. I want to push the button and get better now. I mean it doesn't always happen; now I still got a ways to go, but I definitely accelerated from where I was, no doubt.

Participant 810 described that the improved ability to process traumatic memories, due to the physiological effects of MDMA in conjunction with the safe therapeutic setting, was an integral factor in her long-term improvement:

It can't hurt you physically anymore. It's not happening right then, it's not happening again, you've already experienced it and it can't hurt you anymore than it already has, and it's just a memory and it's not happening right now. And that's important.

A common factor among participants was the belief that this treatment provided them healing beyond what they could find in traditional modalities. Participant 821 exemplified this in stating:

> *I just think it would have been several more years of painful maybe terrible therapy that went nowhere. I feel like this therapy really helped me get past the tears and get right to the problem and several other problems I didn't know were related to the feeling.*

Discussion

The quantitative findings from multiple trials of MDMA-assisted psychotherapy for treatment-resistant PTSD have shown robust and reliable reduction of symptoms on the CAPS-IV and other clinical measures. This long-term follow-up qualitative analysis of a recently completed phase 2 trial illuminates the benefits to the treatment beyond what can be measured by quantitative instruments alone. Participant depictions of their experience before, during, and in the year after the treatment provide a context to more fully understand outcome data. These results demonstrate how MDMA-assisted psychotherapy can impact a range of important areas of functioning as well as overall quality of life, regardless of changes to PTSD symptoms.

All clinical trials of MDMA-assisted psychotherapy for PTSD employ the widely accepted CAPS-IV as their primary outcome measure (Mithoefer 2017). The durable improvement in CAPS-IV scores observed in the phase 2 trials has helped inform the FDA's decision to allow MAPS to move forward with phase 3 clinical trials. However, this measure can only assess the frequency and intensity of symptoms and does not elucidate other factors that affect quality of life as a function of having PTSD, such as impacted relationships or increased substance use.

This was exemplified in our interviews with the two participants (811 and 819) who experienced the least positive change in their CAPS-IV scores from baseline to the one-year follow-up (only 13.2% and 3.26% reductions, respectively). Contrary to expectations, both participants detailed significant areas of improvement in their quality of life, relationships, and self-awareness. These findings confirm that CAPS-IV total scores alone can miss vital measures of the treatment benefits (Mithoefer et al. 2013). While CAPS-IV total score improvement is a desired outcome of treatment, the descriptions of additional quality-of-life benefits from participants in our sample warrant further qualitative exploration to more thoroughly understand the full impetus of MDMA-assisted psychotherapy for PTSD.

There are limitations and challenges inherent in conducting a qualitative study after the clinical trial was underway. Consequently, our protocol was necessarily tailored to fit within existing study parameters. The decision to have one of the trial therapists conduct the interviews with each of the participants during their one-year follow-up visit was clearly beneficial for rapport, safety, and economic reasons. Although the relationship between the therapists and participants appears to be very strong, it can nevertheless be anticipated that discussion of certain topics could be more constrained than speaking to an independent interviewer. Additionally, their longstanding familiarity with each other may have shaped or limited the conversation in particular directions. While this provided some unique opportunities for memories that may have otherwise been lost, this structure did undoubtedly alter the nature of the interviews. Additionally, five participant LTFU interviews were not used because they were not recorded or not available to the study team at time of analysis. Although we included six of the seven women who participated in this phase 2 trial, this cohort was largely male and identified almost entirely as White/Caucasian. Responses to this modality could vary, depending on demographic factors which include race, gender, age, ability, and socioeconomic status (Mithoefer et al. 2011).

Lessons from this study provide opportunities to improve future qualitative protocols of MDMA-assisted psychotherapy. First, performing the qualitative interviews at the one-year follow-up session provided a powerful perspective on the treatment after some time has passed, but it also may have lost some of the nuances that participants might have been able to describe closer to their sessions. A better design might include a qualitative interview prior to the study, at the end of the treatment period, and at long-term follow-up intervals. This could provide an array of perspectives and more rich detail that may be lost with time. In this context, targeted semi-structured interviews could be developed for each timeframe to garner the most pertinent data.

Also, using an independent interviewer with no prior contact with participants could allow the participants to speak more freely on concerns they had about the study or the therapists, as there may be less concern with limiting negative feedback to the therapy team. This would also decrease instances where the interviewer primes the participant for a certain answer, or provides an answer for them based on previous discussions. It is clear the relationship participants developed with the therapy team had a profound effect on their experiences. It is therefore important to assess

outcomes in future studies with other therapy teams to understand the impact of the therapeutic relationship aside from the medication.

In terms of future clinical trials, it is critical for those interested in qualitative research to begin networking with MAPS and clinical trial teams from the outset to help ensure success. It is important to recognize the potential value offered by diverse qualitative approaches that strive in alternate ways to better understand the therapeutic process from the participant (as well as clinician) point of view.

The reemergence of psychedelic-assisted psychotherapy has allowed for more research to present evidence of safety and efficacy for these treatments. Based on the quantitative outcomes, the FDA designated MDMA-assisted psychotherapy for PTSD as a "Breakthrough Therapy." Findings from this retrospective qualitative analysis of a phase 2 MDMA-assisted psychotherapy trial illuminate a range of outcomes from the treatment that are not fully covered in quantitative explorations.

This article highlights the value of qualitative research in the investigation of psychedelic-assisted therapies by exploring the nuance of experience often missed by quantitative measures. Our findings also serve to honor the experience and perspective of those most affected by the therapy, the veterans and first responders themselves. Giving voice to participant experience is essential in order to thoroughly understand the full benefits of treatments, particularly as multi-site phase 3 trials begin.

Notes

1. The Long-Term Follow-Up (LTFU) Qualitative Interview Guide is available upon request to the authors.
2. The finalized codebook is available upon request to the authors.

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Disclosure statement

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