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Ketamine-Assisted Group Psychotherapy for Frontline Healthcare Workers with COVID-19-Related Burnout and PTSD: A Case Series of Effectiveness/Safety for 10 Participants

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ABSTRACT

This study reports on 10 frontline healthcare workers, employed during the COVID-19 pandemic and experiencing symptoms of burnout and PTSD, treated with group ketamine-assisted psychotherapy (KAP) in a private outpatient clinic setting. Participants attended 6 sessions once weekly. These included 1 preparation session, 3 ketamine sessions (2 sublingual, 1 intramuscular), 2 integration sessions. Measures of PTSD (PCL-5), depression (PHQ-9), and anxiety (GAD-7) were administered at baseline and post-treatment. During ketamine sessions, the Emotional Breakthrough Inventory (EBI) and the 30-item Mystical Experience Questionnaire (MEQ-30) were recorded. Participant feedback was gathered 1-month post-treatment. We observed improvements in participants' average PCL-5 (59% reduction), PHQ-9 (58% reduction), and GAD-7 (36% reduction) scores from pre- to post-treatment. At post-treatment, 100% of participants screened negative for PTSD, 90% had minimal/mild depression or clinically significant improvement, and 60% had minimal/mild anxiety or clinically significant improvement. MEQ and EBI scores had large variations among participants at each ketamine session. Ketamine was well tolerated, and no significant adverse events were reported. Participant feedback corroborated findings of improvements observed in mental health symptoms. We found immediate improvements treating 10 frontline healthcare workers experiencing burnout, PTSD, depression, and anxiety using weekly group KAP and integration.

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Introduction

Burnout and Post-Traumatic Stress Disorder (PTSD) among nurses and physicians are widely known to inhibit the provision of adequate care and have been alarmingly increasing since the start of the COVID-19 pandemic (Pereira-Lima et al. 2019; Tawfik et al. 2019). Prior to the pandemic, burnout had reached levels often exceeding 40% of surveyed populations (Medscape 2019). There has since been an alarming increase in burnout and isolation as noted in a Medscape survey conducted in 2020 of 12,339 physicians in more than 29 specialties (Medscape 2021). Among the physicians surveyed, 42% reported experiences of burnout, and over 70% of physicians who reported burnout considered it serious enough to have at least a moderate impact on their life. Other studies have found similar effects. A systematic review and meta-analysis published in July 2021 found that there were high levels of psychiatric symptoms among healthcare workers during the COVID-19 pandemic (Marvaldi et al. 2021). Prevalence of acute stress and post-traumatic stress were found to be 56.5% and 20.2%, respectively (Marvaldi et al. 2021). A study conducted in 2020 surveyed 1,122 healthcare workers across the United States (US) and found that almost a third of respondents reported elevated symptoms of psychological trauma (Hagerty and Williams 2022). Additionally, the level of suicidal ideation was approximately three times greater among the surveyed healthcare workers than that of the general population (Hagerty and Williams 2022).

The impact of the difficulties faced by frontline health workers, including social isolation, COVID-19 mortality, and extreme workload, potentially limited the effective response to the COVID-19 pandemic. Furthermore, these difficulties may have detrimental effects on not only the healthcare workers' professional responsibilities, but on their personal lives, relationships, and overall well-being. It is critical that frontline healthcare workers impacted by the overburdening of

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healthcare resources due to the pandemic (i.e., nurses and physicians working in emergency departments and intensive care units; first responders such as emergency medical technicians and paramedics; mental health care workers suffering vicarious trauma) receive access to effective mental health treatment to support their ability to remain engaged and effective in their work.

Current models of care for depression and PTSD often fail to provide successful treatment. In the last two decades, there have only been two medications (i.e., paroxetine and sertraline) approved for treating PTSD, both of which have limited efficacy (Hoskins et al. 2015). Due to the limited efficacy of PTSD pharmacotherapy, current treatment guidelines promote psychotherapy including cognitive behavioral therapy and prolonged exposure therapy (APA 2020). However, even when combining multiple modalities of treatment, resistance to treatment remains high, coupled with significant functional impairment and psychiatric and medical comorbidities (Krediet et al. 2020; Rodriguez, Holowka, and Marx 2012; Sessa 2017). Thus, there is a significant unmet need for novel and effective treatment for PTSD, particularly among frontline healthcare workers.

Ketamine was approved by the US Food and Drug Administration (FDA) in 1970 as an anesthetic and has been observed to improve symptoms of depression and other mood disorders at low doses in several studies (Kim et al. 2019; McIntyre et al. 2020; Moghaddam 2021). Ketamine is a noncompetitive antagonist of N-methyl-D-aspartate (NMDA) glutamate receptors, which is a novel mechanism of action for mood disorder pharmacotherapy (Hough 2019; Kim et al. 2019; Sanacora et al. 2017). Ketamine is delivered through several routes of administration including intravenous (IV), intramuscular (IM), intranasal (IN), oral, sublingual (SL), rectal, and subcutaneous (SQ). The benefits of ketamine for depression have been shown to be rapid-acting and transient, peaking on post infusion day one and diminishing by day seven (Newport et al. 2015; Sanacora et al. 2017; Walsh et al. 2022). However, there is growing evidence of prolonging the antidepressant and anxiolytic effects with the combination of ketamine treatment and psychotherapy, hereafter called ketamine-assisted psychotherapy (KAP) (Dore et al. 2019). Ketamine leads to changes in synaptic function and neuroplasticity, thus having the potential to enhance psychotherapy effects (Hasler 2020). KAP can refer to the administration of ketamine as a therapy aid by administering ketamine at low doses prior to a psychotherapy session to decrease fear and resistance to the exploration of psychological material, which is typically termed as a psycholytic experience (Dore et al. 2019). KAP can also refer to administering moderate doses to induce psychedelic effects which is then followed by psychotherapy sessions (Dore et al. 2019). In terms of safety, common adverse events of ketamine include dissociation, sedation, and slight increases in blood pressure. However, these are transient effects and have been observed to resolve quickly once ketamine is eliminated from the system (Kim et al. 2019; McIntyre et al. 2020; Szarmach et al. 2019).

Recent evidence has shown ketamine's efficacy in protecting against the detrimental effects of excessive stress while preventing a depressive response (Albott et al. 2018; Feder et al. 2014, 2020, 2021; Liriano, Hatten, and Schwartz 2019). A clinical trial published in February of 2021 showed efficacy for ketamine treatment of chronic PTSD, where 67% of participants in the ketamine group were treatment responders compared to 20% in the midazolam group (Feder et al. 2021). Midazolam is a short-acting injectable benzodiazepine with rapid onset and sedative, anxiolytic, amnestic, muscle relaxant, and hypnotic activities (FDA 2022). Additionally, an open-label study of repeated ketamine infusions for comorbid PTSD and treatment-resistant depression (TRD) found that the remission rate for PTSD was 80% and the response rate for TRD was 93% (Albott et al. 2018). Another study reinforced the benefits of KAP in addressing the psychiatric issues most likely to result from a COVID-19 work environment including anxiety, depression, and PTSD (Dore et al. 2019). Thus, working with ketamine provides an opportunity to address comorbid depression and PTSD symptoms.

Perhaps, even more importantly, ketamine appears to rapidly reduce suicidal ideation. Healthcare workers exhibit elevated suicide risk (Hagerty and Williams 2022). Suicide risk is larger in female physicians than male physicians, with a standardized mortality ratio estimated at 1.9 (p-value<.0001) for females compared to males (Dutheil et al. 2019). Ketamine is unique in modern psychopharmacology in that the reduction in suicide risk is often rapid and may occur within hours of treatment (Phillips et al. 2020). A review of ketamine and suicidal ideation found that 4 of 5 RCTs assessing ketamine demonstrated a significant benefit for ketamine treatment over controls to reduce suicidal ideation (Hochschild, Grunebaum, and Mann 2021). Thus, ketamine treatment may be an effective tool to reduce completed suicide, the most devastating outcome of depression and burnout in healthcare workers.

In this case series, we present results on a series of 3 cohorts, with 3–4 participants each, of frontline healthcare workers experiencing significant burnout and/or PTSD symptomology during to the COVID-19

pandemic who received group KAP. The group setting provided a platform for processing trauma with peers, more effectively building community and reducing feelings of isolation compared to individual treatment. All participants received the standard of care clinical treatment protocol for KAP as outlined in the procedures.

Methods

This case series study presents 10 frontline healthcare workers employed during the COVID-19 pandemic treated with group KAP in a private outpatient psychiatric clinic setting. Participants were screened for appropriateness of inclusion in the study, and once screening was complete, they received a psychiatric intake performed by a licensed mental health professional to determine the candidate's suitability for ketamine treatment and group cohesion. Each participant was experiencing burnout as measured by the Copenhagen Burnout Inventory (CBI) and psychiatric evaluation (Table 1) (Kristensen et al. 2005). Scores of < 50 are considered "low," 50–74 are considered "moderate," 75–99 are considered "high," and a score of 100 on the CBI is considered "severe" burnout. Exclusion criteria included the following: bipolar I disorder with current mixed or manic episode; unstable complex PTSD; dissociative identity disorder; severe and/or recent substance dependence; and uncontrolled hypertension, tachycardia, or unstable cardiopulmonary disease.

Participants attended 6 group sessions 1 week apart that were designed to create a safe environment for healing in which participants could gather, process, and provide one another with support as they navigated continued stressors related to COVID-19. The length of the intervention was chosen based on a combination of the clinic's experience treatment patients with ketamine and an attempt to limit the cost of this intervention and time commitment for the participants. The total number of participants ranged from 3 to 4 for each group depending upon the mental health status, availability of program applicants, and perceived group cohesion by study investigators. Group psychotherapy outcome research data show strong correlations between group cohesion (i.e., sense of connection or closeness among group members) and therapeutic outcome (Rosendahl et al. 2021). In an effort to increase the likelihood of healthy cohesion among group members, investigators screened out participants who demonstrated characteristics antithetical to group cohesion (e.g., irritability, hostility, preoccupation with self, contrary). The 6 sessions included the following: preparation session, ketamine dosing session 1 (SL), integration session 1, ketamine dosing session 2 (SL), ketamine dosing session 3 (IM), and integration session 2. The dose range of ketamine for each of the three dosing sessions was chosen to deliver mild, moderate, and significant dissociation in the typical participant, leaving flexibility for personalization and medication sensitivity (Dore et al. 2019; McIntyre et al. 2020, 2021). The psychotherapy provided at each dosing session was similar to the Multidisciplinary Association for Psychedelic Studies (MAPS) approach to 3,4-Methylenedioxymethamphetamine (MDMA)-assisted psychotherapy in the phase 3 trial for PTSD (Mitchell et al. 2021). This approach uses a psychedelic framework of providing music, eye shades, and individual direction with non-directive provider support for the personal journey which follows.

Participants completed mental health assessments prior to the beginning of the 6-week program (i.e., pre-treatment) and upon completion of the program (i.e., post-treatment) to provide baseline and follow-up measurements for changes in mental health symptoms. These assessments included the Post-Traumatic Stress

Table 1. Individual participant characteristics, ketamine dose for sessions 1–3, baseline CBI score, and pre- and post-ketamine treatment PCL-5, PHQ-9, and GAD-7 scores.

							CBI	PCL-5		PHQ-9		GAD-7	
Participant	Age	Sex	Occupation	SL dose 1 (mg)	SL dose 2 (mg)	IM dose (mg)	Pre	Pre	Post	Pre	Post	Pre	Post
1	28	F	Therapist	125	250	70	58	50	11	15	0	16	12
2	32	M	Nurse Practitioner	125	250	70	65	34	25	9	3	4	6
3	25	F	Medical Assistant/Project Coordinator	125	250	70	74	39	17	20	8	15	17
4	31	F	Therapist	125	250	70	49	45	14	15	4	8	3
5	41	M	Freighter/AEMT	125	250	85	54	14	18	8	10	10	9
6	40	M	Physician, Emergency Room	125	250	70	43	21	5	7	3	8	3
7	38	F	Medical assistant	200	250	80	71	31	28	21	12	13	12
8	33	M	Paramedic	200	250	80	62	41	11	8	2	15	4
9	49	F	Therapist	200	250	75	51	22	9	8	3	9	1
10	53	M	CNA/Director of environmental services	200	275	100	49	44	1	9	1	8	1

Abbreviations: AEMT: advanced emergency medical technician; CBI: Copenhagen Burnout Inventory; CNA: certified nursing assistant; GAD-7: Generalized Anxiety Disorder Assessment; mg: milligrams; IM: intramuscular; PCL-5: Post-Traumatic Stress Disorder Checklist; PHQ-9: Patient Health Questionnaire; SL: sublingual.

Disorder Checklist (PCL-5) (score range 0–80), the Patient Health Questionnaire (PHQ-9) depression survey (score range 0–27), and the Generalized Anxiety Disorder Assessment (GAD-7) (score range 0–21) (Kroenke, Spitzer, and Williams 2001; Spitzer et al. 2006; Zuromski et al. 2019). Higher scores on each assessment indicate more severe symptomatology. Clinically significant improvement on the PHQ-9 or GAD-7 was defined as a reduction of 5 or greater in the total score (Kurt Kroenke 2012; Toussaint et al. 2020). A cut-point score of 31 was used to determine if the patient met criteria for PTSD (VA 2022). During each ketamine dosing session, participants completed the Emotional Breakthrough Inventory (EBI) and the 30-item Mystical Experience Questionnaire (MEQ-30) (both with score ranges 0–100) to assess emotional release or breakthrough during a psychedelic experience and to assess mystical or profound transpersonal experiences occasioned by a psychedelic substance, respectively (Barrett, Johnson, and Griffiths 2015; Maclean et al. 2012; Roseman et al. 2019). Higher scores on the MEQ-30 indicate a higher intensity mystical experience. Previous research has shown a dose-response relationship of the mystical effects occasioned by psychedelic medicines as measured by the MEQ-30 (Barsuglia et al. 2018). Similarly, higher scores on the EBI indicate a higher intensity emotional breakthrough or release, and EBI scores are dose-dependent, as shown in previous research on psychedelic medicines (Roseman et al. 2019). Both the MEQ-30 and EBI have been shown to significantly predict post-psychedelic changes in well-being (Roseman et al. 2019). Additionally, participants completed satisfaction questionnaires approximately 1 month after completion of the final session to evaluate individual experiences in the program and for quality improvement purposes.

The preparation session introduced the process of KAP and aimed to promote a sense of connection and security among participants and therapy facilitators. At the first ketamine dosing session, each participant was administered a low dose (125–200 mg) of liquid ketamine held sublingually for 12 minutes. This session was mildly consciousness-altering to gently familiarize participants with ketamine and its effects including reduction in defenses and negative thinking while still allowing for awareness, reflection, and dialogue. The first integration session, held 1 week after the initial ketamine dosing session, did not involve the administration of medicine and provided participants with a platform for integrating their SL ketamine experience. This session centered around bonding, support, and sharing of personal stories, especially in relation to trauma and work-related stress. The second ketamine dosing session involved higher dose (250–275 mg) SL ketamine administration during which participants were encouraged to "go inside," allowing for the induction of dissociative, psychedelic, or transformative experiences. Participants were given the option to listen to pre-determined playlists of music for the second and third dosing sessions, as music is a central part of the inward process with ketamine, and it facilitates greater openness to the inner process. Participants had the opportunity to process the experience with one another toward the end of this psychedelic session. The third and last ketamine dosing session involved a high dose (70–100 mg) IM ketamine administration, providing an alternative way to benefit from the psychedelic properties of this medicine. Similar to the previous dosing session, participants were encouraged to "journey inward" by exploring and embracing the insights, sensations, and feelings induced by ketamine. This session again concluded with time for group processing and sharing. The sixth and final session was aimed to support participants as they integrated their ketamine dosing experiential sessions into everyday life. This included processing insights gained about themselves, their practice, or their relationships. Participants also explored ways in which they could continue to promote resiliency and sustain positive behavioral change during times of destabilization and uncertainty in the future. At the start of the final session, participants completed post-treatment assessments to assess change in mental health symptoms as measured by the PCL-5, PHQ-9, and GAD-7 survey instruments (Table 1).

Tolerability of ketamine dosing was assessed by measuring vital signs (i.e., heart rate, blood pressure) prior to administration and one hour post administration, as well as recording of treatment-emergent adverse events (i.e., dissociation, sedation, nausea, and vomiting).

Participation in the study was voluntary. The University of Utah's Institutional Review Board deemed this case series to be service evaluation and did not require ethical approval. Patients were informed their clinical data would be de-identified and used confidentially for clinical evaluation purposes. Written publication consent was received from all participants.

Descriptive statistics were used to present and estimate individual and mean change in PCL-5, PHQ-9, and GAD-7 scores pre- and post-ketamine treatment. Descriptive statistics were also used to summarize MEQ and EBI scores for ketamine dosing sessions 1–3.

Results

Table 1 summarizes the demographic characteristics, ketamine dose information, baseline CBI scores, and

PCL-5, PHQ-9, and GAD-7 survey scores pre- and post-treatment for the 10 frontline healthcare workers that participated in group KAP. The mean age of the participants was 37 years (SD 8.5), and 50% were male. The participants were employed in a diverse range of healthcare occupations including therapist, nurse practitioner, certified nursing assistant, firefighter, emergency room physician, paramedic, and medical assistant/project coordinator.

Over the course of the 6 group sessions, we observed improvements in the participants' average PCL-5, PHQ-9, and GAD-7 scores (Table 2, Figure 1). In terms of aggregate PTSD symptom improvement, the average PCL-5 score reduced by 59% from pre- to post-treatment for the 10 participants (Table 2). Similarly, we observed improvements in depression and anxiety symptoms. The average PHQ-9 score reduced by 58% while the average GAD-7 score reduced by 36% from pre- to post-treatment. In terms of individual participant improvement, all but one participant showed improvement in the PCL-5 from pre- to post-treatment; however, 100% of participants did not meet criteria for PTSD post-treatment. The single participant with an increase in their PCL-5 score did not meet criteria for PTSD at pre- or post-treatment. Similarly, all but one participant improved on the PHQ-9 from pre- to post-treatment, and 90% of participants were in the minimal to mild depression range or had clinically significant improvement post-treatment. The participant that experienced an increase in PHQ-9 score increased their score by 2 and went from the mild depression category to the moderate depression category at post-treatment. Eight of the 10 participants improved their score on the GAD-7, and 60% of participants were in the minimal to mild anxiety range or had clinically significant improvement at post-treatment. Two participants increased their GAD-7 score by 2 from pre- to post-treatment. One of these participants went from the minimal to mild anxiety category and one participant stayed in the severe anxiety category.

Table 3 and Figure 2 presents MEQ and EBI scores for ketamine dosing sessions 1–3. The MEQ and EBI had large variations among the participants at each session (Table 3). We observed an increase in average MEQ during the third ketamine dosing session delivered IM compared to the first two ketamine dosing sessions where ketamine was delivered SL (dose 1: mean = 46 (SD 27); dose 2: mean = 37 (SD 21); dose 3: mean = 75 (SD 19)) (Figure 2). The average EBI score decreased from ketamine dosing session 1 to session 2 and increased from session 2 to session 3 (dose 1: mean = 42 (SD 28); dose 2: mean = 28 (SD 21); dose 3: mean = 41 (SD 32)) (Figure 2).

In terms of safety, the ketamine treatments were well tolerated by all participants. There were no emergent or significant adverse events or dropouts due to adverse events.

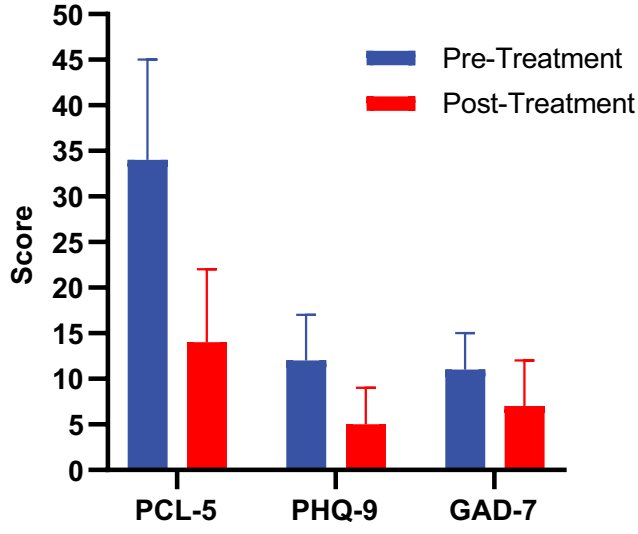

Figure 1. Mean PCL-5, PHQ-9, and GAD-7 scores for KAP participants ($n = 10$) pre- and post-ketamine treatment. Higher scores indicate more severe PTSD, depression, or anxiety symptoms. Error bars represent standard deviation.

Table 2. Pre- and post-ketamine treatment PTSD, depression, and anxiety scores (individual and mean).

	Pre Individual n (%)	Post Individual n (%)	Pre-Treatment score Mean (SD)	Post-Treatment score Mean (SD)	Percent Change
PTSD (PCL-5)	6 (60%) screened positive	10 (100%) screened negative	34 (11)	14 (8)	−59%
Depression (PHQ-9)	4 (40%) with moderate to severe depression	9 (90%) with minimal to mild depression or had clinically significant improvement (>5)	12 (5)	5 (4)	−58%
Anxiety (GAD-7)	5 (50%) with moderate to severe anxiety	6 (60%) with minimal to mild anxiety or had clinically significant improvement (>5)	11 (4)	7 (5)	−36%

Abbreviations: GAD-7: Generalized Anxiety Disorder Assessment; PCL-5: Post-Traumatic Stress Disorder Checklist; PHQ-9: Patient Health Questionnaire; SD: standard deviation.

Table 3. Individual MEQ and EBI scores for ketamine treatment sessions 1–3. Scores range 0–100.

	MEQ			EBI		
Participant	SL dose 1	SL dose 2	IM dose	SL dose 1	SL dose 2	IM dose
1	63	33	94	57	53	87
2	59	55	90	38	22	42
3	50	61	93	72	73	95
4	17	17	58	22	10	0
5	6	15	65	0	2	15
6	3	6	81	25	7	38
7	57	27	31	62	43	68
8	93	77	63	97	25	5
9	45	31	81	25	23	13
10	69	47	89	25	17	45

Abbreviations: EBI: Emotional Breakthrough Inventory; IM: intramuscular MEQ: 30-item Mystical Experience Questionnaire; SL: sublingual.

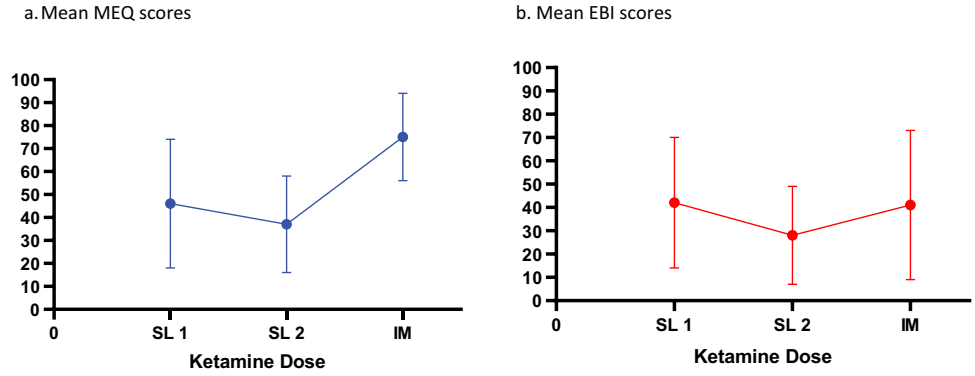

Figure 2. Mean MEQ and EBI scores recorded during ketamine dosing sessions 1–3 for KAP participants ($n = 10$). Error bars represent standard deviation. Abbreviations: SL: sublingual, IM: intramuscular. a. Mean MEQ scores. b. Mean EBI scores.

Participant feedback

All participants were sent a satisfaction survey approximately 1 month after completion of the final session that included questions regarding the degree of benefit and harms, improvement in burnout, depression, PTSD, and anxiety symptoms, and the appropriateness of dose and number of ketamine and non-dosing sessions. We received responses from 9 of the 10 participants.

Of the participants that responded to the satisfaction survey, all participants (100%) reported they benefited from participation in ketamine treatments, and no participants (0%) reported that they felt they were harmed by participation in these treatments. The average degree of benefit from participation in ketamine treatments was 4.4 (SD 1.3) on a scale of 1 to 5. Eight (89%) participants reported they experienced improvement in burnout and PTSD symptoms as a result of participation. The average degree of burnout and PTSD improvement on a scale of 1 to 5 was 4.1 (SD 0.6) and 4.0 (SD 1.2), respectively. All participants (100%) reported they experienced a decrease in symptoms of depression and anxiety as a result of their participation. The average degree of depression and anxiety improvement on a scale of 1 to 5 were 4.0 (SD 0.9) and 3.9 (SD 1.0), respectively. Additionally, participants were asked to describe their overall improvement, including improvements in burnout, depression, PTSD, anxiety, or other. Participant feedback included the following:

> I experienced an immense improvement in my depression and PTSD. I feel as though my views and feelings towards others and how they treat me/have treated me has come to a sense of understanding that I did not feel this way previously. I feel an overall sense of forgiveness and sense of security in who I am and my future. There were many fears of abandonment when I first entered the study and by the end this had immensely improved.

> The greatest improvement has been in my PTSD symptoms. I feel less "hooked" by things that used to hook me into responses. Even when I do feel myself reacting I feel I have more awareness and I am able to better re-regulate.

> Directly following the treatments I had huge improvement to my overall mental health. I felt a great sense of joy in the world. This has decreased over time but I still believe I am better off now than I was before.

Participants were surveyed regarding the appropriateness of the treatment schedule and ketamine doses received. Eight of the nine participants reported that additional ketamine sessions would have been helpful, and one participant reported that the number of

sessions was adequate. The number of additional ketamine sessions that the participants thought would be helpful ranged from 1–6 sessions or on an "as needed" basis. All participants reported that the once-a-week program was appropriate and allowed time in-between sessions to integrate and reflect upon the group experiences. In terms of dose of ketamine received, 4 (44%) participants reported that the SL doses of ketamine were too low. All participants stated that they thought the ketamine doses were both safe and effective. Participant feedback regarding safety and effectiveness included the following:

> For such a vulnerable experience, I have to say I felt extremely safe, both physically and emotionally.

> I think I will carry my IM dosage experience with me for the rest of my life. It is one of the things that helps tether me to "the truth." I gauge how open and in "higher self" I am by reflecting on that experience. It is a reminder of my true essence and when I am reminded of that, life seems to flow more easily.

Discussion

This case series provides evidence of employing a psychedelic medicine framework for the treatment of trauma and burnout related to the COVID-19 pandemic experienced by frontline healthcare workers. The results of this study show the immediate benefits using SL and IM ketamine combined with psychotherapy in a group setting for 10 participants. With respect to PTSD outcome measures, participants showed an average improvement in symptoms post-KAP treatment (PCL-5: 59% reduction), and all participants screened negative for PTSD at the post-treatment timepoint. Similarly, participants showed an average improvement in symptoms of depression and anxiety at the post-treatment timepoint (PHQ-9: 58% reduction; GAD-7: 36% reduction). The participant feedback corroborated these findings. Although 3 participants experienced an increase in their PHQ-9 or GAD-7 scores, these participants reported in the satisfaction survey that they experienced improvement in their anxiety, depression, and PTSD symptoms as a result of participation in the program and that additional IM ketamine sessions would have been helpful.

The large variations in individual MEQ and EBI scores recorded during each ketamine dosing session are reflective of the variations in individual ketamine experiences. However, it is important to note that the MEQ scores recorded at dosing session 3 were higher than dosing session 1 scores for 8 of the 10 participants. The increase in MEQ scores recorded during the ketamine dosing session 3 are indicative of increased intensity of mystical experiences where the participants received the medicine IM compared to the first 2 doses that were administered SL. The bioavailability of SL ketamine is estimated between 20–30% while IM ketamine has a near 100% bioavailability (R. S. McIntyre et al. 2021). Therefore, although a higher dose was used for SL administration, the increase in MEQ scores seen at session 3 are likely due the effects of ketamine being more profound with IM administration compared to SL. This was reflected in participant feedback where participants reported the SL ketamine dose to be too low, and that additional IM ketamine sessions would have been helpful. The EBI scores recorded at each ketamine dosing session were highly variable within the group, and the scores did not increase substantially at session 3. However, the third session EBI score was higher than the first session score for 7 of the 10 participants, indicating an increased emotional release or breakthrough for these participants with IM ketamine.

The promising response among these 10 participants aligns with a recently published study of ketamine for PTSD among healthcare workers (Dames, Kryskow, and Watler 2022). Dames, Kryskow, and Watler (2022) reported on a cohort of healthcare providers with PTSD and depression treated with ketamine-assisted therapy over a 12-week program that consisted of weekly virtual large group meetings with small breakout groups of 6–9 participants and 3 IM ketamine injections ranging from 1 to 1.5 mg/kg. Their results showed a 91% improvement in GAD, 79% improvement in depression, and 86% remission for PTSD for 94 participants across 3 cohorts. These results from a large cohort along with this case series provide evidence for ketamine as a pharmacotherapy, delivered in a group setting, for frontline healthcare workers experiencing symptoms of burnout, PTSD, depression, and anxiety.

Importantly, group therapy is cost-effective and addresses a core limitation found in the psychedelic framework around affordability. Access to KAP treatment in the US is limited due to cost and availability of therapists. Using a group-based model for KAP, we reduced costs and increased the capacity of therapists to deliver treatment. Furthermore, participants reported they appreciated the shared experience, similar to the therapeutic factors observed in conventional group therapy settings (Yalom 1995). Participants noted an enhanced sense of connection and community, elements that are lacking in our current culture. Ketamine appeared to speed the sense of connection within the group and reduce the isolation magnified by the COVID-19 epidemic. Group therapy may represent an underutilized tool that may be synergistic with

the beneficial effects of psychedelic-like agents such as ketamine.

Limitations

The contents of this report must be interpreted in the context of its limitations. This was a case series without a placebo control. Therefore, firm conclusions about the effectiveness of the intervention cannot be drawn due to the nature of the study. Implementing the group KAP protocol in a larger cohort with a placebo control would promote future understanding of this treatment regimen and modifying factors for treating various types of healthcare workers. Additionally, we did not assess durability of the ketamine intervention after the last integration session, which occurred one week after the third ketamine session. However, we assessed participant feedback one month following the last integration session.

Conclusion

Frontline healthcare workers require adequate mental health treatment to address symptoms of burnout, PTSD, depression, and anxiety resulting from the COVID-19 pandemic. We found immediate benefits using SL and IM ketamine administered with psychotherapy in a group setting, in combination with integration sessions, on a weekly basis. The results presented in this case series can lead to the development of programs to answer an alarming need of our healthcare system. Based on the positive outcomes of this program, we foresee an increase in demand for community-based group ketamine treatment programs and integration support for frontline healthcare workers in need of mental health treatment.

Disclosure statement

No potential conflict of interest was reported by the authors.

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Authors' contributions

SS and RR conceptualized and designed the study and/or retrospective data analysis plan. CM provided administrative oversight at the psychiatric clinic. MB extracted and analyzed data and completed the manuscript writeup. RR and SS reviewed the data analysis and critically reviewed/revised the manuscript writeup. All authors have read and approved the final article.

Data availability statement

The data that support the findings of this study are available from the corresponding author, MB, upon reasonable request.

References

Albott, C. S., K. O. Lim, M. K. Forbes, C. Erbes, S. J. Tye, J. G. Grabowski, P. Thuras, Y. C. T. M. Batres, J. Wels, and P. R. Shiroma. 2018. Efficacy, safety, and durability of repeated ketamine infusions for comorbid posttraumatic stress disorder and treatment-resistant depression. *The Journal of Clinical Psychiatry* 79 (3). doi:10.4088/JCP.17m11634.

APA. 2020. Summary of recommendations of the APA guideline development panel for the treatment of PTSD https://www.apa.org/ptsd-guideline/treatments/recommendations-summary-table.pdf

Barrett, F. S., M. W. Johnson, and R. R. Griffiths. 2015. Validation of the revised mystical experience questionnaire in experimental sessions with psilocybin. *Journal of Psychopharmacology (Oxford, England)* 29 (11):1182–90. doi:10.1177/0269881115609019.

Barsuglia, J., A. K. Davis, R. Palmer, R. Lancelotta, A. -M. Windham-Herman, K. Peterson, M. Polanco, R. Grant, and R. R. Griffiths. 2018. Intensity of mystical experiences occasioned by 5-MeO-DMT and comparison with a prior psilocybin study [Brief Research Report]. *Frontiers in Psychology* 9:9. doi:10.3389/fpsyg.2018.02459.

Dames, S., P. Kryskow, and C. Watler. 2022. 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 [Case Report]. *Frontiers in Psychiatry* 12:12. doi:10.3389/fpsyt.2021.803279.

Dore, J., B. Turnipseed, S. Dwyer, A. Turnipseed, J. Andries, G. Ascani, C. Monnette, A. Huidekoper, N. Strauss, and P. Wolfson. 2019. Ketamine Assisted Psychotherapy (KAP): Patient demographics, clinical data and outcomes in three large practices administering ketamine with psychotherapy. *Journal of Psychoactive Drugs* 51 (2):189–98. doi:10.1080/02791072.2019.1587556.

Dutheil, F., C. Aubert, B. Pereira, M. Dambrun, F. Moustafa, M. Mermillod, J. S. Baker, M. Trousselard, F. X. Lesage, and V. Navel. 2019. Suicide among physicians and health-care workers: A systematic review and meta-analysis. *Plos One* 14 (12):e0226361. doi:10.1371/journal.pone.0226361.

FDA. 2022. Intravenous Midazolam FDA Label https://s3-us-west-2.amazonaws.com/drugbank/cite_this/attachments/files/000/002/434/original/Intraveous_Midazolam_FDA_label.pdf?1545435299

Feder, A., S. Costi, S. B. Rutter, A. B. Collins, U. Govindarajulu, M. K. Jha, S. R. Horn, M. Kautz, M. Corniquel, K. A. Collins, et al. 2021. A randomized controlled trial of repeated ketamine administration for

chronic posttraumatic stress disorder. *The American Journal of Psychiatry* 178 (2):193–202. doi:10.1176/appi.ajp.2020.20050596.

Feder, A., M. K. Parides, J. W. Murrough, A. M. Perez, J. E. Morgan, S. Saxena, K. Kirkwood, M. Aan Het Rot, K. A. Lapidus, L. B. Wan, et al. 2014. Efficacy of intravenous ketamine for treatment of chronic posttraumatic stress disorder: A randomized clinical trial. *JAMA Psychiatry* 71 (6):681–88. doi:10.1001/jamapsychiatry.2014.62.

Feder, A., S. B. Rutter, D. Schiller, and D. S. Charney. 2020. The emergence of ketamine as a novel treatment for post-traumatic stress disorder. *Advances in Pharmacology* 89:261–86. doi:10.1016/bs.apha.2020.05.004.

Hagerty, S. L., and L. M. Williams. 2022. Moral injury, traumatic stress, and threats to core human needs in health-care workers: The COVID-19 pandemic as a dehumanizing experience. *Clinical Psychological Science* 21677026211057554. doi:10.1177/21677026211057554.

Hasler, G. 2020. Toward specific ways to combine ketamine and psychotherapy in treating depression. *CNS Spectrums* 25 (3):445–47. doi:10.1017/S1092852919001007.

Hochschild, A., M. F. Grunebaum, and J. J. Mann. 2021. The rapid anti-suicidal ideation effect of ketamine: A systematic review. *Preventive Medicine* 152 (Pt 1):106524. doi:10.1016/j.ypmed.2021.106524.

Hoskins, M., J. Pearce, A. Bethell, L. Dankova, C. Barbui, W. A. Tol, M. van Ommeren, J. de Jong, S. Seedat, H. Chen, et al. 2015. Pharmacotherapy for post-traumatic stress disorder: Systematic review and meta-analysis. *British Journal of Psychiatry* 206 (2):93–100. doi:10.1192/bjp.bp.114.148551.

Hough, D. 2019. Esketamine. https://www.fda.gov/media/121379/download

Kim, J., T. Farchione, A. Potter, Q. Chen, and R. Temple. 2019. Esketamine for treatment-resistant depression - First FDA-Approved antidepressant in a new class. *The New England Journal of Medicine* 381 (1):1–4. doi:10.1056/NEJMp1903305.

Krediet, E., T. Bostoen, J. Breeksema, A. van Schagen, T. Passie, and E. Vermetten. 2020. Reviewing the potential of psychedelics for the treatment of PTSD. *The International Journal of Neuropsychopharmacology* 23 (6):385–400. doi:10.1093/ijnp/pyaa018.

Kristensen, T., M. Borritz, E. Villadsen, and K. Christensen. 2005. The Copenhagen burnout inventory: A new tool for the assessment of burnout. *Work and Stress* 19:192–207. doi:10.1080/02678370500297720.

Kroenke, K. 2012. Enhancing the clinical utility of depression screening. *Canadian Medical Association Journal* 184 (3):281–82. doi:10.1503/cmaj.112004.

Kroenke, K., R. L. Spitzer, and J. B. Williams. 2001. The PHQ-9: Validity of a brief depression severity measure. *Journal of General Internal Medicine* 16 (9):606–13. doi:10.1046/j.1525-1497.2001.016009606.x.

Liriano, F., C. Hatten, and T. L. Schwartz. 2019. Ketamine as treatment for post-traumatic stress disorder: A review. *Drugs Context* 8:212305. doi:10.7573/dic.212305.

Maclean, K. A., J. -M.S. Leoutsakos, M. W. Johnson, and R. R. Griffiths. 2012. Factor analysis of the mystical experience questionnaire: A study of experiences occasioned by the hallucinogen psilocybin. *Journal for the Scientific Study of Religion* 51 (4):721–37. doi:10.1111/j.1468-5906.2012.01685.x.

Marvaldi, M., J. Mallet, C. Dubertret, M. R. Moro, and S. B. Guessoum. 2021. Anxiety, depression, trauma-related, and sleep disorders among healthcare workers during the COVID-19 pandemic: A systematic review and meta-analysis. *Neuroscience and Biobehavioral Reviews* 126:252–64. doi:10.1016/j.neubiorev.2021.03.024.

McIntyre, R. S., I. P. Carvalho, L. M. W. Lui, A. Majeed, P. S. Masand, H. Gill, N. B. Rodrigues, O. Lipsitz, A. C. Coles, Y. Lee, et al. 2020. The effect of intravenous, intranasal, and oral ketamine in mood disorders: A meta-analysis. *Journal of Affective Disorders* 276:576–84. doi:10.1016/j.jad.2020.06.050.

McIntyre, J. D. Rosenblat, C. B. Nemeroff, G. Sanacora, J. W. Murrough, M. Berk, E. Brietzke, S. Dodd, P. Gorwood, R. Ho, et al. 2021. Synthesizing the evidence for ketamine and esketamine in treatment-resistant depression: An international expert opinion on the available evidence and implementation. *The American Journal of Psychiatry* 178 (5):383–99. doi:10.1176/appi.ajp.2020.20081251.

Medscape. 2019. Medscape national physician burnout and suicide report 2020.

Medscape. 2021. Death by 1,000 cuts: Medscape national physician burnout and suicide Report 2021.

Mitchell, J. M., M. Bogenschutz, A. Lilienstein, C. Harrison, S. Kleiman, K. Parker-Guilbert, G. M. Ot'alora, W. Garas, C. Paleos, I. Gorman, et al. 2021. MDMA-assisted therapy for severe PTSD: A randomized, double-blind, placebo-controlled phase 3 study. *Nature Medicine* 27 (6):1025–33. doi:10.1038/s41591-021-01336-3.

Moghaddam, B. 2021. *Ketamine*. MIT Press. https://books.google.com/books?id=QP5gzQEACAAJ.

Newport, D. J., L. L. Carpenter, W. M. McDonald, J. B. Potash, M. Tohen, and C. B. Nemeroff. 2015. Ketamine and other NMDA antagonists: Early clinical trials and possible mechanisms in depression. *The American Journal of Psychiatry* 172 (10):950–66. doi:10.1176/appi.ajp.2015.15040465.

Pereira-Lima, K., D. A. Mata, S. R. Loureiro, J. A. Crippa, L. M. Bolsoni, and S. Sen. 2019 e1916097-e1916097. Association between physician depressive symptoms and medical errors: a systematic review and meta-analysis. *JAMA Network Open*. 2 (11). doi:10.1001/jamanetworkopen.2019.16097.

Phillips, J. L., S. Norris, J. Talbot, T. Hatchard, A. Ortiz, M. Birmingham, O. Owoeye, L. A. Batten, and P. Blier. 2020. Single and repeated ketamine infusions for reduction of suicidal ideation in treatment-resistant depression. *Neuropsychopharmacology* 45 (4):606–12. doi:10.1038/s41386-019-0570-x.

Rodriguez, P., D. W. Holowka, and B. P. Marx. 2012. Assessment of posttraumatic stress disorder-related functional impairment: A review. *Journal of Rehabilitation Research and Development* 49 (5):649–65. doi:10.1682/jrrd.2011.09.0162.

Roseman, L., E. Haijen, K. Idialu-Ikato, M. Kaelen, R. Watts, and R. Carhart-Harris. 2019. Emotional breakthrough and psychedelics: Validation of the emotional breakthrough inventory. *Journal of Psychopharmacology* 33 (9):1076–87. doi:10.1177/0269881119855974.

Rosendahl, J., C. T. Alldredge, G. M. Burlingame, and B. Strauss. 2021. Recent developments in group psychotherapy research. *American Journal of Psychotherapy* 74 (2):52–59. doi:10.1176/appi.psychotherapy.20200031.

Sanacora, G., M. A. Frye, W. McDonald, S. J. Mathew, M. S. Turner, A. F. Schatzberg, P. Summergrad, and C. B. Nemeroff. 2017. A consensus statement on the use of ketamine in the treatment of mood disorders. *JAMA Psychiatry* 74 (4):399–405. doi:10.1001/jamapsychiatry.2017.0080.

Sessa, B. 2017. MDMA and PTSD treatment: "PTSD: From novel pathophysiology to innovative therapeutics". *Neuroscience Letters* 649:176–80. doi:10.1016/j.neulet.2016.07.004.

Spitzer, R. L., K. Kroenke, J. B. W. Williams, and B. Löwe. 2006. A brief measure for assessing generalized anxiety disorder: The GAD-7. *Archives of Internal Medicine* 166 (10):1092–97. doi:10.1001/archinte.166.10.1092.

Szarmach, J., W. J. Cubała, A. Włodarczyk, and M. S. Wiglusz. 2019. Short-term ketamine administration in treatment-resistant depression: Focus on cardiovascular safety. *Psychiatria Danubina* 31 (Suppl 3):585–90.

Tawfik, D. S., A. Scheid, J. Profit, T. Shanafelt, M. Trockel, K. C. Adair, J. B. Sexton, and J. P. A. Ioannidis. 2019. Evidence relating health care provider burnout and quality of care. *Annals of Internal Medicine* 171 (8):555–67. doi:10.7326/M19-1152.

Toussaint, A., P. Hüsing, A. Gumz, K. Wingenfeld, M. Härter, E. Schramm, and B. Löwe. 2020. Sensitivity to change and minimal clinically important difference of the 7-item Generalized Anxiety Disorder questionnaire (GAD-7). *Journal of Affective Disorders* 265:395–401. doi:10.1016/j.jad.2020.01.032.

VA. 2022. Using the PTSD Checklist for DSM-5 (PCL-5) https://www.ptsd.va.gov/professional/assessment/documents/using-PCL5.pdf

Walsh, Z., O. M. Mollaahmetoglu, J. Rootman, S. Golsof, J. Keeler, B. Marsh, D. J. Nutt, and C. J. A. Morgan. 2022. Ketamine for the treatment of mental health and substance use disorders: Comprehensive systematic review. *BJPsych Open* 8 (1):e19. Article e19. doi:10.1192/bjo.2021.1061.

Yalom, I. D. 1995. *The theory and practice of group psychotherapy*. 4th. New York, NY: Basic Books.

Zuromski, K. L., B. Ustun, I. Hwang, T. M. Keane, B. P. Marx, M. B. Stein, R. J. Ursano, and R. C. Kessler. 2019. Developing an optimal short-form of the PTSD checklist for DSM-5 (PCL-5). *Depression and Anxiety* 36 (9):790–800. doi:10.1002/da.22942.