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Research paper

At-home, sublingual ketamine telehealth is a safe and effective treatment for moderate to severe anxiety and depression: Findings from a large, prospective, open-label effectiveness trial

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ABSTRACT

Background: At-home Ketamine-assisted therapy (KAT) with psychosocial support and remote monitoring through telehealth platforms addresses access barriers, including the COVID-19 pandemic. Large-scale evaluation of this approach is needed for questions regarding safety and effectiveness for depression and anxiety.

Methods: In this prospective study, a large outpatient sample received KAT over four weeks through a telehealth provider. Symptoms were assessed using the Patient Health Questionnaire (PHQ-9) for depression, and the Generalized Anxiety Disorder scale (GAD-7) for anxiety. Demographics, adverse events, and patient-reported dissociation were also analyzed. Symptom trajectories were identified using Growth Mixture Modeling, along with outcome predictors.

Results: A sample of 1247 completed treatment with sufficient data, 62.8 % reported a 50 % or greater improvement on the PHQ-9, $d = 1.61$, and 62.9 % on the GAD-7, $d = 1.56$. Remission rates were 32.6 % for PHQ-9 and 31.3 % for GAD-7, with 0.9 % deteriorating on the PHQ-9, and 0.6 % on the GAD-7. Four patients left treatment early due to side effects or clinician disqualification, and two more due to adverse events. Three patient subpopulations emerged, characterized by Improvement (79.3 %), Chronic (11.4 %), and Delayed Improvement (9.3 %) for PHQ-9 and GAD-7. Endorsing side effects at Session 2 was associated with delayed symptom improvement, and Chronic patients were more likely than the other two groups to report dissociation at Session 4.

Conclusion: At-home KAT response and remission rates indicated rapid and significant antidepressant and anxiolytic effects. Rates were consistent with laboratory- and clinic-administered ketamine treatment. Patient screening and remote monitoring maintained low levels of adverse events. Future research should assess durability of effects.

1. Background

Anxiety and depression are a leading cause of disability in the United States (SAMHSA, 2019), with nearly one in three people meeting criteria for diagnosable depression in their lifetime and one in four people for anxiety diagnoses (Kessler et al., 2012). Incidence rates of these disorders are increasing in most countries (Liu et al., 2020) and are over-represented among minorities and the economically vulnerable (Miranda et al., 2008). This growth is outpacing the number of clinicians available to provide care (Hoge et al., 2019) and lack of treatment availability is increasingly burdening healthcare systems with preventable mental and physical health concerns (Figueroa et al., 2020),

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especially following the onset of the global COVID-19 pandemic (Gruber et al., 2021). Clinicians, researchers, and national agencies are attempting to address these challenges by 1) overcoming access obstacles through technology and 2) by exploring novel treatments and research agendas (Holmes et al., 2018).

Research has documented significant growth in digital offerings and the promise of telecommunications for increasing treatment access (Bucci et al., 2019; Mohr et al., 2006). Mobile and desktop devices offer a variety of potential access solutions from automated, self-guided care delivery to messaging a provider or speaking with a clinician through video (Imel et al., 2017). Data to date suggest that the provision of care through digital media does not diminish the effectiveness of evidence-based treatments in most cases (Cuijpers et al., 2019). Accordingly, telemedicine presents an opportunity to expand access to effective mental health care by reducing travel and cost, and the pandemic has increased patient and provider comfort with and utilization of telehealth (Guinart et al., 2021).

Despite advances in access, the impact of mental health intervention has been dampened somewhat by the weaknesses of current treatment options. Patient response to psychiatric treatment, whether traditional or digital, is weaker than desired (Kilbourne et al., 2018), with 30 % to 40 % taking a chronic course despite available psychosocial and pharmacological treatments (Kennedy and Giacobbe, 2007; McLachlan, 2018; Rush et al., 2006; Akiki and Abdallah, 2019), and effects for well-accepted mental health interventions appear to be decreasing over time (Friborg and Johnsen, n.d.). As a result, new approaches are needed that both expand access and improve outcomes relative to traditional delivery models and treatments.

One such approach is treatment utilizing compounds with dissociative or psychedelic properties that have demonstrated rapid treatment effects for depression and anxiety, post-traumatic stress disorder (PTSD), substance-related disorders, end of life care, and other conditions (Reiff et al., 2020) that so far seem to go beyond those reported for available treatments. Of these compounds, ketamine, an *N*-methyl-D-aspartate receptor antagonist and glutamatergic modulator, is the only medication available for therapeutic use outside of a research setting and has received considerable research and clinical attention in the last decade (Sanacora et al., 2017). Intravenous (IV) and intramuscular (IM) administration have been dominant, with intranasal and sublingual forms becoming increasingly common due to their ease of administration and viability for improving treatment access (Lara et al., 2013). Remarkably, IV ketamine has consistently demonstrated rare onset of persistent adverse events when administered in subanesthetic doses in both laboratory (Katalinic et al., 2013; for a meta-analysis, Lee et al., 2015; for a review, Short et al., 2017) and real-world (McInnes et al., 2022) settings, and low risk of ongoing misuse (Glue et al., 2018). Clinical reports (Swainson and Khullar, 2020) and early laboratory work (Lara et al., 2013) show a similar low-risk profile for sublingual ketamine studied here.

Patient selection, clinical experience and training, treatment setting, and follow-up assessments are also critical components of ensuring patient safety and effective care in this treatment (Sanacora et al., 2017). Important physical criteria include allergies, heart health, urological health, and presence of any serious physical illnesses. Psychological criteria include trauma history, substance use history, and suicide history. For a detailed list of considerations, we refer the reader to the Participants, Patients section below. Relatedly, empirical work on predictors of outcome suggested a more favorable response for higher body mass index, family history of alcohol use, and no previous suicide attempts (Niciu et al., 2014), though these findings are no replacement for selection criteria designed to ensure the safety of the patient.

Following the careful selection of patients with the criteria mentioned, ketamine treatment varies in the use of complementary behavioral intervention (Schenberg, 2018). Ketamine-infusion therapy (KIT) typically denotes a medication-only treatment with support from the prescribing clinician as needed. Ketamine-assisted psychotherapy (KAP) utilizes licensed behavioral health providers to deliver psychotherapy during and in conjunction with medication sessions. Ketamine-assisted therapy (KAT), the treatment approach used in this study, utilized certified behavioral coaches to assist patients in establishing set and setting, and to provide behavioral support in-between medication sessions (more detail is offered below in Procedures-Intervention). Evidence suggests that both exploratory (Krupitsky et al., 2007) and behavioral (Wilkinson et al., 2017) models enhance the effectiveness of ketamine treatment over no behavioral support, but data to date have not determined whether the effectiveness of behavioral intervention is dependent upon therapeutic model or licensure of the provider. Advances in telecommunications have made it less burdensome and more convenient to integrate remote methods of psychosocial care into models of ketamine treatment that emphasize treatment access and safety in a properly selected patient population.

While the reported effects of ketamine for mental and emotional disorders from research settings are promising (Schenberg, 2018), important differences between laboratory and clinical settings make observational and quality management data from clinical practices critical for evaluating the ecological validity and safety of the treatment due to smaller effect sizes observed for disseminated treatments relative to clinical trials (Johnsen and Friborg, 2015). To this end, this study undertakes an evaluation of sublingual ketamine treatment administered at-home with prescribing psychiatric clinician and behavioral coach support offered through a secure, HIPAA-compliant telehealth and remote monitoring platform. Patterns of response to this treatment approach were investigated utilizing a prospective, longitudinal open-label effectiveness design, enabling predictors of patient improvement, utilizing observational, quality management data and electronic medical records for a large patient population. Adverse events were also gathered and reported to establish safety benchmarks for ketamine-assisted therapy delivered among a large and diverse population.

2. Methods

2.1. Setting

Data was for a service offering ketamine-assisted therapy (KAT) through a telemedicine platform (www.mindbloom.com) used by independently practicing, licensed psychiatric clinicians in 15 of the United States. The platform is accessible through internet search or external physician/provider referral. Patients first complete an eligibility questionnaire, followed by intake paperwork if they are eligible, in preparation to hold a standardized medical and psychiatric evaluation with their selected psychiatric clinician through live video conference. The psychiatric clinician walks them through the informed consent and emergency contact process and determines whether the patient is suitable for at-home ketamine treatment. Observations included data collected as part of organizational quality assurance and program management processes between January 21, 2021 and November 30, 2021. All patients and clinicians gave consent to the use of their data in a de-identified, aggregate format for research purposes as part of the user agreement before using the platform. Study analytic procedures were approved as exempt by the institutional review board at New York University (i21-01533).

2.2. Participants

2.2.1. Patients

Participants were individuals who presented with a chief complaint of anxiety or depression, were seeking treatment through the service, and who completed at least two PHQ-9 and/or GAD-7. Inclusion criteria consisted of: (1) being 18 years old or older, (2) having regular internet or cell phone access, (3) receiving a depression or anxiety diagnosis from their selected licensed clinician based on a video-based clinical intake interview, (4) scoring 10 or higher on the PHQ-9 and/or GAD-7 at

baseline.

Exclusion criteria consisted of: (1) ketamine allergy, (2) ongoing alcohol or substance use dependence, (3) history of opioid use disorder, (4) active psychotic, manic or mixed symptoms or history of psychotic symptoms, (5) untreated high blood pressure, (6) congestive heart failure or other serious cardiac problems, (7) severe breathing problems (e.g., COPD), (8) unstable thyroid disease, (9) elevated intraocular pressure/glaucoma, (10) elevated intracranial pressure, (11) other serious medical illnesses, (12) pregnancy, nursing, or currently trying to become pregnant, (13) active suicidal ideation with method, intent, or plan within the past month, or suicide attempt within the past year, or (14) any other aspect of the patient's psychiatric history, outpatient support system or home environment that would render at-home treatment psychologically unsafe in the opinion of the prescribing psychiatric clinician, including a history of severe and unresolved trauma. When necessary, clinicians require labs, EKG, coordination with external mental health providers, and clearance from medical providers following a physical examination as appropriate to ensure the patient is fit for treatment.

Patient records totaling 2848 were reviewed with these criteria. Of these, 28 dropped from treatment prior to the first medication session, and 1247 of the remaining sample had two outcome measure completions sufficient for follow-up data analysis. Supplementary Table 1 reports sensitivity analyses and Fig. 1 is a participant flow diagram.

2.2.2. Clinicians and guides

Clinicians in the provider network had current prescription privileges in their state of licensure and had demonstrated psychiatric training (e.g., Psychiatrist, Psychiatric-Mental Health Nurse Practitioner, or Physician Assistant with psychiatry experience, and a supervising psychiatrist if required by the state for the NP/PA). 33 % of providers reported one or more additional certifications. Guides were required to have prior behavioral coaching experience and/or relevant certifications. 74.6 % of guides reported 2+ certifications and 46.5 % reported 3+ certifications.

2.3. Procedures

2.3.1. Intervention

Clinicians and patients met by video for a 40 to 60 min intake session to determine suitability for and safety of the treatment. Individuals meeting criteria, with no contraindications, are sent a single 300 mg to 450 mg dose of sublingual, rapidly dissolving ketamine tablets to establish ongoing dosing. Ondansetron for nausea and materials to ensure safe and proper administration of the medication, such as a digital blood pressure cuff, a journal, and eye mask, and instructions for treatment are mailed along with the medication. Ketamine dosing is based on a combination of bioavailability studies and clinical experience with this route of administration. Prior to the pandemic and transition to full telemedicine, Mindbloom clinicians treated over 100 patients in-person at a clinic in New York City. Initially, dosing was developed referencing the standard IV ketamine dosing of 0.5 mg/kg, which was then adjusted up to account for the lower bioavailability of sublingual administration. The initial adjustment assumed a 20 % bioavailability based on sublingual bioavailability studies (Chong et al., 2009; Clements et al., 1982; Yanagihara et al., 2003) and the observed effects of Mindbloom's administration protocol described in this section below that involved spitting instead of swallowing saliva. Dosing was slowly adjusted to 5 mg/kg for the initial dose to more closely achieve clinician-observed levels of patient dissociation seen in their prior experience with 0.5 mg/kg for IV and IM treatments, and in accordance with the reported observations of others that greater levels of dissociation predict stronger and more durable antidepressant effects (Luckenbaugh et al., 2014). The extension of this approach to fully at-home care with telehealth support and remote monitoring post-pandemic was designed to overcome commonly observed access, transportation, and affordability barriers, as well as to reduce risk of COVID-19 infection, while maintaining treatment safety and outcomes.

To prepare for treatment, patients login to their web portal to review written and video materials and are also paired with a specially trained “guide” who is available for as-needed support by text message throughout treatment. Directly prior to the first medication session, patients met with their guide for 30 min by video to reinforce education provided by the clinician and to help the patient establish a positive set and setting for their medication session, where ‘set’ refers to the patient's mindset entering the at-home medication session, and ‘setting’ refers to the physical environment in which the session takes place. During this meeting, guides confirmed that patients had a “peer monitor,” a trusted friend or family member, physically with them, and provided training to the peer monitor on how to support the patient and how to contact staff

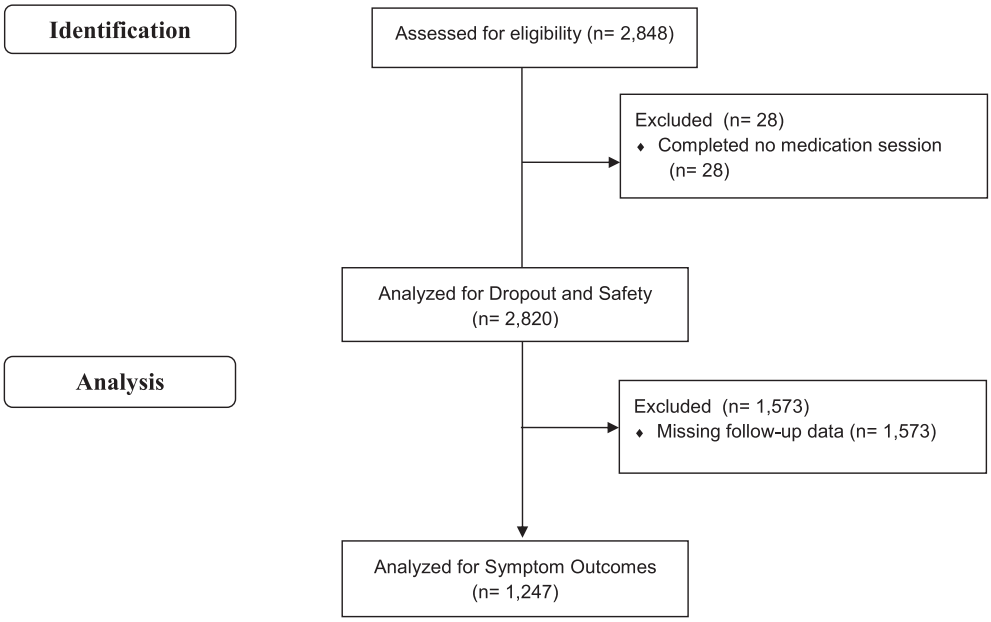

Fig. 1. Flowchart of patient selection and analysis.

members if necessary. Guides also confirmed that the blood pressure cuff provided was used properly. Absence of a physically present peer monitor, blood pressure >150/100, or a heart rate in excess of 100 blocked treatment from proceeding. Abstinence from food for 3 h, fluids for 1 h, and alcohol, stimulants, and benzodiazepines on the day of treatment were also checked prior to treatment commencement.

During medication sessions, patients are asked to hold the ketamine tablets under the tongue or between the cheek and gums, without swallowing for 7 min, at which time they spit out all saliva. This approach is designed to substantially reduce swallowing, which can increase ketamine metabolites, such as norketamine, that have side effects such as nausea and prolonged sedation (Lara et al., 2013). Patients then lie down, put on their eye mask and headphones, and listen to music provided for their session. After an hour, patients journal for 30 min and then join a 30 min video meeting with their guide. One to two days following the first medication session, patients meet again with their prescribing clinician by video for 20 to 30 min to assess the initial reaction and establish a treatment plan, including dosage and timing, for the remaining medication sessions. A 45 min integration session with the guide is held after the second medication dose, and patients communicate with their guide by text daily after that. Symptoms and side effects are monitored by guides daily and by patient-reported surveys every other week. Guides assess ongoing tolerability of the medication and any adverse events, as well as to provide time for the patient to reflect on their experience and receive any support as needed. Guides are not licensed professionals and do not provide psychotherapy. They do however provide an empathetic and warm response to the patient's experience, utilizing active listening and reflective techniques. The prescribing clinician is available for 15 min consults as requested by the patient. Finally, a 30 min exit meeting is offered by the guide to review progress and to discuss next steps for integration and treatment. In the event that a patient fails to show for a scheduled meeting, attempts are made to contact them by phone and by text. If this is unsuccessful, guides attempt to reach the patient's emergency contact and/or peer monitor. Patients and peer monitors can contact the guide during medication sessions using the provided phone number, and guides can contact clinicians through internal messaging or an emergency contact line. The cost was between $193 and $250 per treatment dose during the evaluation period, which is 28 % to 83 % of the reported cost of a single ketamine infusion (cf. McInnes et al., 2022 for IV price ranges across a large number of practices). Insurer and employer coverage for ketamine treatment is unavailable for the vast majority of treatment seekers, so reducing the cost of out-of-pocket care is an important aim for increasing accessibility.

2.3.2. Assessments

Patients completed screeners for suicide, alcohol use, substance use, and depression and anxiety symptoms at baseline. Follow-up symptom measures were administered along with measures for side effects, adverse events and dissociation after the second and fourth medication sessions, two weeks and four weeks after baseline, respectively. Assessments are introduced to patients as an important aspect of their care that facilitates goal setting and to track progress.

The 9-item Patient Health Questionnaire (Kroenke and Spitzer, 2002) was used for depression symptomatology. Responses were given on a 4-point Likert scale (0 = Not at all to 3 = Nearly every day) with a total maximum score of 27. Scores greater than or equal to 10 have been shown to have high sensitivity and specificity as a threshold for clinical depression (Kroenke and Spitzer, 2002; Kroenke et al., 2001a, 2001b).

Anxiety symptoms were assessed with the 7-item Generalized Anxiety Disorder questionnaire (Spitzer et al., 2006). Responses were given on a 4-point Likert scale (0 = Not at all to 3 = Nearly every day) with a total maximum score of 21. Scores of 10 or above have been shown to have high sensitivity and specificity for moderate anxiety (Kroenke et al., 2007).

The Columbia Suicide Severity Rating Scale (C-SSRS; Posner et al., 2011) is a 5-item yes-no scale assessing suicidal ideation from passive up to active with specific plan and intent, along with suicidal behavior, and was used to determine suitability for treatment. Only positive indication of method, intent, or plan within the past month or a suicide attempt within the past year prevented individuals from continuing with treatment, and these were provided appropriate referrals.

Alcohol use was assessed with the Alcohol Use Disorders Identification Test (AUDIT; Bush et al., 1998), a 10-item screening tool for problematic alcohol use. The assessment asks about habitual drinking patterns over various timescale, with responses ranging from 0 (“Never”) to 4 (Daily or Almost daily).

Substance use was assessed by the Drug Abuse Screening Test 10-item (DAST-10; Villalobos-Gallegos et al., 2015). Items refer to drug use in the last 12 months and offer yes-no responses.

Side effects and adverse events were assessed through a single-item self-report measure administered after session 2 and again after session 4, that said, “Have you noticed any issues with your physical or mental health since beginning treatment?” Response options included; chest pain, lower abdominal pain, increased blood pressure, shortness of breath, cravings for ketamine, memory loss, pain urinating, suicidal thoughts, none of the above, and a field to specify anything else. Any adverse events reported to the clinician or guide outside of this measure were recorded in the electronic health record (EHR) and were identified for inclusion in analysis as well.

Dissociative symptoms in response to ketamine administration were measured with 3-items adapted from the Clinician Administered Dissociative States Scale (Bremner et al., 1998): “Did things seem to be unreal to you, as if you were in a dream?”; “Did you feel disconnected from your own body?”; and “Did you space out, or in some other way lose track of what was going on?”. Response options were on a 5 point Likert scale with anchors: “no,” “slightly,” “moderately,” “definitely,” and “Yes, completely”.

Dropout was measured by the number of individuals who canceled ongoing treatment prior to Session 4, or who were removed from treatment by the clinician due to adverse events or noncompliance.

2.4. Statistical analyses

Changes in symptoms from baseline to session 4 of treatment (week 0–4) were monitored for patients meeting criteria for Depression (diagnosis + PHQ $\geq$ 10) and Anxiety (diagnosis + GAD-7 $\geq$ 10). Response rate was defined as a 50 % or more reduction in symptom score on the respective measure. Clinically significant change (Jacobson and Truax, 1991) was defined as a reduction of 5 or more points and a score that began above the clinical threshold of 10 and fell below it at follow-up. Remission was defined as beginning above the clinical threshold at baseline and having a follow-up score of <5 (Coley et al., 2020). Deterioration was defined as a reliable increase of 5 points or more (Jacobson and Truax, 1991) from the previous measure. Sensitivity analyses examined survey non-response. All analyses were performed in R 4.1 (Team R Core, 2021).

Outcome trajectories of anxiety and depression symptoms over the 4 weeks of treatment were analyzed using Growth Mixture Modeling (GMM) in Mplus 8 (Muthén and Muthén, 1998-2019). GMM is an unsupervised machine learning method that identifies subgroups with heterogeneous outcomes (such as responders and non-responders) within a larger population. To capture changes in both anxiety and depression outcomes, the GMM modeled concurrent changes of PHQ-9 and GAD-7 scores as parallel processes (Muthén and Muthén, 1998–2019). The optimal number of trajectories was determined based on model fit statistics, relative entropy, and theoretical parsimony (Nylund et al., 2007). Technical specifications and model fit information are reported in the supplementary materials.

After identifying the best fitting solution, patients' baseline characteristics were nested into a conditional GMM as covariates to inform prediction of trajectory membership. Dissociative symptoms and side

effects from ketamine administration were analyzed as trajectory predictors using 3-step multinomial logistic regression analyses (Asparouhov and Muthén, 2012). Prior to the analyses, missing values were iteratively imputed using the R package missForest (Stekhoven and Bühlmann, 2012) by random forest (100 trees, 10 iterations). Examined predictors were imputed while masking outcome variables to prevent information leakage. Continuous variables were centered, scaled, and normalized using min-max transformations prior to modeling.

3. Results

3.1. Sample characteristics

Patients were between the ages of 19 and 76, with a mean 40.0 (SD = 9.1) years of age. Women were 54.6 % of the patient sample, and 5.0 % of patients had zipcodes in Center for Medicare and Medicaid Services classified rural areas. Six (0.5 %) patients dropped out or were removed from treatment by the clinician due to events described further below. Table 1 provides the full distribution of demographic characteristics.

3.2. Clinical outcomes

Table 2 describes the clinical outcomes and characteristics for the full sample. Suicide ideation (SI) was defined as a score of 1 or higher on PHQ item 9, and we report results tracking cohorts reporting any amount of ideation at each session and remitting ideation for each cohort at each time point in Table 2. Any indication of suicide ideation was reviewed and escalated to the clinician to perform a safety assessment and intervene as needed for safety.

Baseline severity scale score mean for the C-SSRS was 0.54 (range 0 to 5, SD = 0.92), with 408 (33.4 %) patients reporting some amount of suicide ideation. Mean for the DAST-10 was 0.83 (range 0 to 10, SD = 1.18), 624 (51.2 %) reporting some drug use in the previous 12 months, and mean scores for the AUDIT were 3.54 (range 0 to 40, SD = 4.24), 1014 (80.9 %) reporting some alcohol use. Dissociation mean after session 2 was 3.4 (range 0 to 12, SD = 2.8), with 1034 of 1247 responses (82.9 %) reporting any amount, and 3.7 (SD = 2.9) after session 4, with 618 of 708 responses (87.3 %) reporting any amount.

Side effects were reported by 59 (4.7 %) patients after session 2, and by 27 (3.8 %) patients after session 4. Four of these individuals had their treatment discontinued due to adverse events: one due to elevated heart rate, one due to worsening symptoms of depression, one needing to visit a urologist for follow-up on increased urinary pressure, including hematuria 24 h after the fourth medication session, which resolved with confirmatory CT and ultrasound, and a final who presented to the ER for worsening anxiety and depression who was then admitted for ongoing psychiatric services. Two others were removed from treatment by the clinician due to noncompliance.

Table 1
Demographic characteristics for full sample ($N = 1247$).

Variable	# missing	Valid %
Relational status:	27	
Partnered	813	66.6 %
Single	257	21.1 %
Divorced or separated	145	11.9 %
Widowed	5	0.4 %
Gender:	37	
Female	661	54.6 %
Male	549	45.4 %
Rurality:	28	
Urban	1158	95.0 %
Rural	61	5.0 %
Dropout	0	
After 1st session	2	0.16 %
After 2nd session	1	0.08 %
After 3rd session	3	0.24 %

3.3. Trajectory patterns and predictors

Fig. 2 presents symptom trajectories for anxiety and depression from baseline (week 0) to session 4 (week 4) of ketamine assisted treatment. GMM model fit information is reported in Supplementary Table 2. Three classes of patients emerged, characterized by distinct patterns of GAD-7 and PHQ-9 scores over treatment.

The modal group of patients (*Improvement*, 79.3 %) was characterized by lower baseline levels of PHQ-9 and GAD-7 scores, which steadily decreased over the course of the four weeks in KAT treatment. The second largest group (*Chronic*, 11.4 %) was composed of patients with higher GAD-7 and PHQ-9 scores at baseline that, despite some reduction, maintained clinically elevated levels of symptoms throughout treatment. The final group (*Delayed Improvement*, 9.3 %) began with elevated symptoms (similar to the *Chronic* group) that were relatively stable in the first two sessions, and then showed sharp decreases in PHQ-9 and GAD-7 scores in the final two weeks of treatment.

Logistic regression analyses were performed to identify baseline and treatment-related predictors of symptom trajectories. Results indicated that the *Delayed Improvement* group (which experienced the least initial symptom reduction) were more likely to report side effects at session 2 than the *Chronic* and *Improvement* groups. *Chronic* patients were more likely to experience dissociation at Session 4 compared to the other groups. *Chronic* patients also endorsed more suicidal ideation or behavior at baseline than the *Improvement* trajectory, which reported more dissociative experiences than the *Delayed Improvement* group at Session 4. No other significant differences emerged, and full odds ratio estimates are reported in Table 3.

4. Discussion

This is the largest study to date on real world safety and effectiveness of any type of ketamine treatment, and specifically for sublingual, at-home administration of ketamine-assisted therapy (KAT) for depression and anxiety. From a chart review of 4334 cases, 1247 individuals had sufficient data to evaluate baseline characteristics, adverse events, dissociation, and clinical outcomes. These data suggested that KAT offered clinically meaningful improvement and demonstrated a desirable safety and risk mitigation profile.

Baseline PHQ-9 scores suggested that this sample was predominantly in the moderately-severe category for depression, and baseline GAD-7 scores suggested participants were predominantly in the severe category for anxiety. These baseline means are two to three points lower than those reported for depression in ketamine lab studies (Fava et al., 2020; Phillips et al., 2019) and in a real world effectiveness study (McInnes et al., 2022) for KIT, however, response and remission rates for this sample are similar to, if slightly stronger than, those previously reported (aan het Rot et al., 2010; Fava et al., 2020; Lara et al., 2013; Lener et al., 2017; McInnes et al., 2022; Phillips et al., 2019). This is in keeping with studies showing that individuals with lower baseline scores are more likely to meet the criteria set for response and remission. The effect sizes reported here for sublingual ketamine are comparable to the higher end of those reported for KIT in lab settings (see Lee et al., 2015 for a meta-analysis) and just above those in real-world KIT settings (McInnes et al., 2022). The critical factor here appears to be ongoing administration of treatment. Lab studies have tended to deploy a smaller number of infusions, often just one, in a short period of time, whereas the data here and for real-world KIT is based on repeated administrations. Deterioration rates reported here are also lower than those previously reported, particularly for KIT. There is insufficient data to draw conclusions regarding this difference, but we offer several possibilities for future research. These include aspects of the at-home and needle-free setting that may help reduce anxious responses to IV ketamine administration (Aust et al., 2019; McLenon and Rogers, 2019), the addition of psychosocial support to maximize the benefit of increased plasticity (Krupitsky et al., 2007; Wilkinson et al., 2017; Wilkinson et al., 2019)

Table 2
Clinical characteristics for full sample.

	Available	Mean (SD)	Cohen's d (95 % CI)	Response rate	Remission rate	Clin. sig. change	Deteriorated
PHQ-9 observations							
Baseline	989	15.3 (3.9)	–	–	–	–	–
Session 2	989	8.9 (4.9)	1.29 (1.20–1.37)	45.7 %	16.7 %	53.9 %	0.6 %
Session 4	553	7.3 (4.8)	1.61 (1.48–1.73)	62.8 %	32.6 %	63.1 %	0.9 %
GAD-7 Observations							
Baseline	937	14.8 (3.3)	–	–	–	–	–
Session 2	937	8.2 (4.8)	1.34 (1.25–1.42)	50.9 %	24.0 %	57.5 %	1.0 %
Session 4	501	7.1 (4.6)	1.56 (1.43–1.69)	62.9 %	31.3 %	63.9 %	0.6 %

PHQ Item 9 observations	Available	At baseline N score > 0 (%)	Mean baseline (SD)	By Session 2 N score > 0 (%)	Mean Session 2 (SD)	By Session 4 N score > 0 (%)	Mean Session 4 (SD)
SI at Baseline	1247	295 (23.7 %)	1.36 (0.64)	152 (12.2 %)	1.28 (0.56)	67 (5.4 %)	1.30 (0.55)
First SI at Session 2	952	0 (0 %)	0 (0)	36 (3.8 %)	1.17 (0.38)	10 (1.1 %)	1.30 (0.48)
First SI at Session 4	918	0 (0 %)	0 (0)	0 (0 %)	0 (0)	16 (1.7 %)	1.13 (0.50)

NOTES: Response rate defined as 50 % or larger reduction in symptoms. Remission defined as final symptom score below 5. Clinically significant change as moving below the clinical threshold (score of <10) AND improving at least 5 points. Deterioration as worsening of symptoms by 5 or more points. SI = Suicide ideation measured by PHQ item 9.

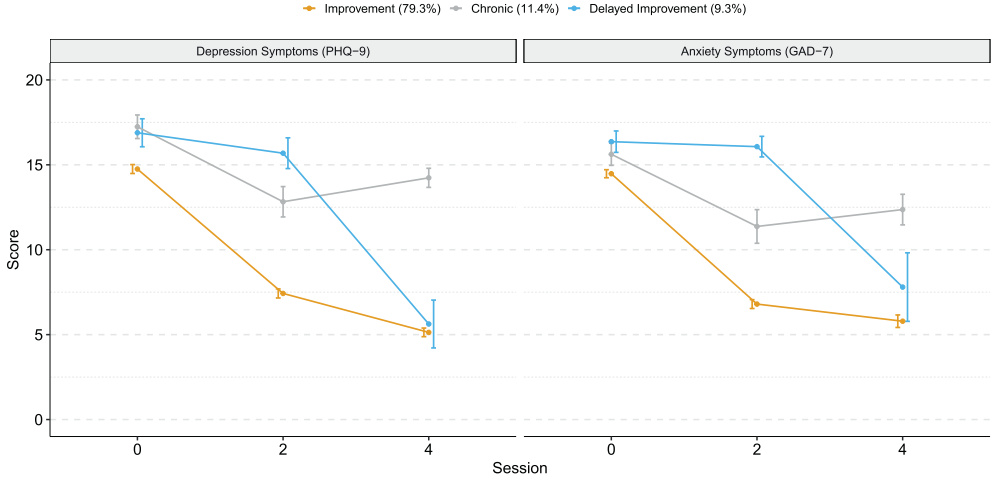

Fig. 2. Latent Growth Mixture Model Outcome Trajectories.

Table 3
Multinomial logistic regression for predictors of PHQ-9 and GAD-7 trajectories (n = 1247).

Variable	Reference: Improvement						Reference: Delayed improvement		
	Delayed improvement			Chronic			Chronic		
	OR	[95 % CI]	p	OR	[95 % CI]	p	OR	[95 % CI]	p
Age	0.99	[0.97–1.02]	0.675	1.00	[0.98–1.02]	0.827	1.00	[0.97–1.03]	0.843
Gender: Male	0.82	[0.50–1.35]	0.440	0.97	[0.67–1.41]	0.885	1.18	[0.67–2.10]	0.567
Rural zip code	0.64	[0.18–2.28]	0.488	1.56	[0.75–3.22]	0.231	2.45	[0.61–9.86]	0.208
AUDIT	0.98	[0.91–1.05]	0.526	0.96	[0.92–1.01]	0.125	0.99	[0.91–1.07]	0.720
DAST-10	0.80	[0.56–1.15]	0.228	1.04	[0.87–1.24]	0.680	1.30	[0.90–1.87]	0.158
CSSRS (ideation + behavior)	1.30	[0.88–1.91]	0.193	1.39	[1.16–1.65]	<0.001	1.07	[0.73–1.57]	0.734
Dissociation: Session 2	1.03	[0.94–1.14]	0.511	0.93	[0.86–1.00]	0.041	0.90	[0.80–1.00]	0.060
Dissociation: Session 4	0.70	[0.62–0.79]	<0.001	1.21	[1.13–1.30]	<0.001	1.73	[1.51–1.98]	<0.001
Side effects: Session 2	4.42	[2.02–9.67]	<0.001	1.26	[0.55–2.86]	0.582	0.28	[0.11–0.75]	0.011
Side effects: Session 4	0.97	[0.40–2.39]	0.952	1.11	[0.24–5.16]	0.898	1.14	[0.19–6.92]	0.890

Note. OR = Odd Ratio; 95 % CI = 95 % Confidence Interval; *P* = *P*-value; AUDIT = Alcohol Use Disorder Identification Test; DAST-10 = Drug Abuse Screening Test; CSSRS = Columbia Suicide Severity Rating Scale.

and to reduce uncertainty and anxiety concerning the treatment, and finally, having a higher proportion of patients in the sample without a history of treatment resistance, which may reduce the likelihood of individuals with complex comorbidities (Bhatt et al., 2021).

Of note is the association between KAT and reduction in anxiety symptoms in this study, an area with very few clinical or effectiveness studies (but see Glue et al., 2018; Lener et al., 2017). These results suggest that sublingual ketamine administration is a promising, but

understudied approach for this condition (Swainson and Khullar, 2020). Also of interest is the higher proportion of men seeking KAT (45.4 %) relative to those who seek other forms of mental healthcare, including digital (about 20 %; Hull et al., 2020; Titov et al., 2017) and in-person (between 20 % and 35 %; Cook et al., 2010) options, suggesting that some aspect of KAT may be helpful in overcoming attitudinal and structural barriers for men (Mojtabai et al., 2011). Conditional models showed no difference in outcomes for men relative to women. Real-world evidence studies are critical for determining the acceptability of particular treatments among certain populations given the recruitment criteria for clinical trials designed to enhance generalizability. Gender information was missing from the only large real-world study of KIT (cf. McInnes et al., 2022), so it is impossible to disentangle the possible appeal of ketamine in general from the sublingual administration specifically, however a possible area for future research is the higher utilization of pharmacological treatments by men. For example, whereas women outnumber men 4 to 1 in psychosocial treatments, women outnumber men just 2 to 1 for antidepressant use (NCHS, 2020), suggesting that men are more likely to utilize medication-based care over psychosocial care.

The rapid, consistent, and large effects of KAT contrast with those of monoaminergic treatments (Trivedi et al., 2006), which can take up to 10 to 14 weeks to produce similar remission rates and have highly variable effect sizes between 0.2 and 0.5 depending on baseline severity (Fournier et al., 2010). Similarly, evidence-based psychotherapies typically require 12 to 16 weeks to achieve a 61 % clinically significant change rate (Layard et al., 2007), a slower and slightly weaker rate of change than that reported here and in other ketamine treatments for depression. Ongoing medication sessions seem to enhance therapeutic benefit by preventing the 90 % relapse rate at two weeks observed for single ketamine infusions (Kryst et al., 2020). The large reductions in suicide ideation for KAT replicate those in more controlled settings (Abbar et al., 2022; Zeifman et al., 2022) and reiterate the potential utility of dissociative and psychedelic compounds for rapidly reducing suicide ideation and behavior.

While adverse events for psychotherapy are very rare and mild, though less rare or mild for pharmacotherapy (Vaughan et al., 2014), the adverse events for KAT reported here and for other ketamine treatments are remarkably low, which is especially notable given the large and diverse sample reported on here. We suspect that the relative lack of adverse reactions and the convenience offered by at-home ketamine administration and monitoring via telehealth account for the high treatment completion rates in this study. However, relying on cancellation as a measure of dropout could under-estimate true dropout as some patients may stop treatment without initiating a cancellation or requesting a refund.

There was strong and consistent evidence that experiencing greater dissociation at the end of treatment decreased the likelihood of symptom improvement for both depression and anxiety. Side effects mid-treatment were also associated with delayed symptom improvement. In addition to documenting temporal differences between dissociation, side effects and treatment outcome, these findings add to the complex picture emerging on the role of dissociation in ketamine treatment (Luckenbaugh et al., 2014; Valentine et al., 2011). The interplay between baseline severity, non-dissociative side effects, and dissociation reported here is an important area for future research and clinical practice and adds to findings that highlight the role of individual differences (Mello et al., 2021), timing of dissociation (Niciu et al., 2018), and durability of the treatment (Pennybaker et al., 2017).

4.1. Limitations

While this study demonstrates the promising potential of KAT for treating anxiety and depression and using telehealth for overcoming treatment access barriers and ensuring safety through remote monitoring, there are limitations of this study. The first is the drop in symptom survey completions at week 4 for around half of the records reviewed. While sensitivity analyses suggested no systematic differences between those completing week 4 measures and those who did not, there could be differences on a number of unobserved variables. This may suggest that the clinical outcomes reported after Session 4 are biased upwards due to the particular enthusiasm reflected by the full completion of all measures by those patients. A review of the EHR for those excluded due to missing follow-up measures did not reveal any differences in rates of cancellation, dropout, or adverse events, which is an important finding of this study, however it is impossible to characterize their pattern of clinical outcomes. While data missingness is a challenge, investigating naturalistic outcomes where measure completion is not compensated avoids the artificial increase of engagement (Baumel et al., 2019). This study found that trials offering incentives for measure completion artificially inflate engagement over four times compared to real-world usage data. Since safety, dropout and engagement were important metrics for this study, the loss of follow-up outcomes for a portion of the sample may be an acceptable trade-off for more accurate measures of safety and engagement. The lack of comparison or control group data for other types of ketamine treatment or for non-ketamine therapies for depression and anxiety also limits the claims that can be made from this study, as does the self-selection of the patients enrolled in the study. Lastly, the lack of follow-up data beyond 4 weeks makes it difficult in this study to assess the long-term durability of this approach to KAT. Efforts are underway to gather this data for future cohorts.

5. Conclusions

We found large and persistent clinical effects for four at-home sublingual KAT sessions carried out over four weeks for 62.8 % of depressed patients and 62.9 % of anxious patients, with effect sizes of 1.61 and 1.56, respectively. Less than 1 % of patients deteriorated, and 6 patients dropped out due to adverse events, suggesting that this form of ketamine treatment has an exceedingly desirable safety profile. The combination of strong and rapid effects with very small numbers of adverse events suggest that at-home sublingual ketamine therapy is an important avenue for overcoming long-standing barriers to depression and anxiety treatment, safely and conveniently. Evaluating the durability of these effects will be important for future research.

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CRediT authorship contribution statement

Design and conduct of the study: TDH, MM.

Collection, management, analysis, and interpretation of the data: TDH, MM.

Preparation, review, or approval of the manuscript: TDH, MM, LV, AM, AG, TJA, KA, MK, JS, CP.

Decision to submit the manuscript for publication: TDH, MM, LV, AM, AG, TJA, KA, MK, JS, CP.

Declaration of competing interest

LV, KA, JS, and MK are employees of the service providing the data. AM and TDH received minor consulting fees from the service. CP and TJA are on the scientific advisory board of the service. TJA also receives compensation for editorial work for Data in Brief (Elsevier, Inc.). MM and AG declare no competing interests.

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Data sharing statement

Data can be made available upon reasonable request to the corresponding author, with a statistical analysis plan, and a fully executed data use agreement.

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