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Maintenance Intramuscular Ketamine-Assisted Psychotherapy, a Retrospective Chart Review of Efficacy, Adverse Events, and Dropouts from a Community Practice

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ABSTRACT

The use of ketamine and ketamine-assisted psychotherapy (KAP) for treatment of depression has grown dramatically, though much of these data are short term. The clinical profile of maintenance treatment remains poorly characterized. We assessed maintenance KAP for efficacy, tolerability, and reasons for dropout. This observational study retrospectively analyzed electronic health records from an addiction psychiatry practice offering intramuscular ketamine with contemporaneous psychotherapy for the treatment of depression. All patients receiving treatment between January 2016 and September 2022 were included, yielding 1,114 sessions from 70 patients. The response was quantified via the clinical global impression-severity scale. Side effects and reasons for dropout were extracted from charts. Comorbidities include an anxiety disorder (79%) or substance use disorder (49%). The induction yielded 82% response, maintained above 80% after six months (sessions q21 days, 1.13 mg/kg mean dose). Many (38%) remained in treatment for at least one year. Nausea management accounted for nearly all as-needed medication use. Antihypertensives were seldom utilized. Chronic side effects were notable for one case of ketamine use disorder, resulting in residential treatment. Dropouts cited logistical reasons half the time and side effects only 9.7% of the time. KAP yielded robust improvements in mood, anxiety, and substance use. Maintenance sessions effectively extended benefit and were largely well tolerated.

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Ketamine; ketamine-assisted psychotherapy; psychedelic-assisted psychotherapy; depression; addiction; maintenance

Introduction

Ketamine was originally approved by the FDA in 1970 as an anesthetic; however, a large body of evidence now supports its use as a rapid-acting antidepressant (Berman et al. 2000; McIntyre et al. 2021; Zarate et al. 2006). Escalating mental health needs during the COVID-19 pandemic and concomitant regulatory changes allowing tele-mental health providers to remote-prescribe scheduled substances has led to a proliferation of ketamine use for psychiatric indications (Chen et al. 2020; Hull et al. 2022). Clinical practice models vary widely: ketamine is often offered in-office as an IV infusion or for take-home sublingual use, with or without accompanying psychotherapy. There are limited data on repeat use over months—and ample concern for side effects that may emerge with chronic use. Clinical evidence has not kept pace with the rapid expansion of ketamine access. Adverse events and benefits from treatment, particularly in this longer time course, are, so far, poorly characterized. Several recent real-world evidence studies from a variety of practice settings (Ahuja et al. 2022; Hietamies et al. 2023; Hull et al. 2022; McInnes et al. 2022; Sakurai et al. 2020) have used self-reported antidepressant efficacy measures in patient samples with high rates of attrition over time and limited descriptive data, which hampers the assessment of efficacy and adverse events during maintenance treatment. Comparing outcomes among these studies is further complicated by the lack of detailed information about clinical practice models, especially the psychotherapeutic component.

Particularly for the treatment of substance use disorders, psychotherapy has been utilized as a key component alongside ketamine; this combination, variously termed ketamine psychedelic therapy or ketamine-assisted psychotherapy (KAP) (Krupitsky and Grinenko 1997), has been studied in the context of treating alcohol use disorder (Dakwar et al. 2020; Das et al. 2019; Krupitsky and Grinenko 1997), heroin use disorder (Krupitsky et al. 2007), and cocaine use disorder (Dakwar et al. 2019). Similar to other psychedelic-assisted psychotherapies, such as with methylenedioxymethamphetamine and psilocybin, KAP seeks to

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leverage acute drug effects and insights in a longitudinal psychotherapeutic relationship before, during, and after the drug session. Careful control of context, or "set and setting" (Carhart-Harris et al. 2018), furthers clinical benefit (Reiff et al. 2020). For ongoing maintenance therapy, KAP may be associated with improved safety outcomes and more durable treatment responses (Dore et al. 2019; Joneborg et al. 2022), though there are little published data evaluating the safety and efficacy of this practice model.

With maintenance dosing, much concern exists over side effects, particularly those that may become apparent with chronic use. Existing literature from populations abusing ketamine suggests problematic outcomes in terms of lower urinary tract symptoms, such as abdominal pain, frequency, urgency, dysuria, and hematuria (Pal et al. 2013; Schep et al. 2023), as well as neurocognitive impairments (McIntyre et al. 2021), but it is unclear if this extends to more moderate dosages and frequencies utilized clinically. While ketamine is recognized as a drug of abuse, it is unclear how different the risk profile may be between unsupervised illicit use versus that of in-office use; existing data suggest the latter setting greatly mitigates such potential (Le et al. 2022). The few reports on repeat clinical use of ketamine are retrospective and naturalistic but suggest a relatively benign safety profile (Ahuja et al. 2022; Dore et al. 2019; Maudlin, Gibson, and Aggarwal 2022; Wilkinson et al. 2018).

Here we performed a retrospective chart review including 70 individuals and 1,114 intramuscular KAP sessions from a community general and addiction psychiatry practice over six years of operation.

Methods

Ethics, design

All clinical interventions were performed in compliance with relevant laws and institutional guidelines. The plan for retrospective analysis was approved by the Stanford institutional review board (#65771). Electronic medical records between January 2016 through September 2022 were extracted and deidentified. Patients who received intramuscular KAP were included.

Clinical procedures

Patient care took place in a single community practice via a physician board certified in psychiatry and addiction psychiatry, who also provided psychotherapy (WCR). Initial evaluation was performed during an hour-long structured psychiatric intake, which included primary complaints, current symptoms, history of prior symptoms, psychiatric history (including that of prior traumas), family history, substance use history, social history, past medical history, medications, and allergies. Diagnoses were made using DSM-5 criteria. KAP was integrated alongside medication management and psychotherapy. Laboratory testing was typically recommended as part of the workup for depression, but this was not required. Exclusion criteria included recent major cardiovascular events (that is, myocardial infarction, cerebrovascular accident), untreated hypertension, severe COPD, pregnancy, schizophrenia, and bipolar 1 disorder without adequate mania prophylaxis. Those with bipolar II disorder were not required to take prophylactic medication but were offered as-needed oral antipsychotics to abort a precipitated hypomanic episode. Inclusion criteria included signed written informed consent, agreement to restrict driving until the day after ketamine administration, and agreement to fasting for the preceding several hours. The primary indication for KAP was major depressive disorder or bipolar affective disorder; only one patient of 70, who was not in the efficacy cohort, did not meet DSM-5 criteria but rather had depressed mood with a diagnosis of generalized anxiety disorder and chronic pain. Antidepressant treatment refractoriness, including failed medication trials, was not strictly required, and those with suicidality, personality disorders, or limited psychotic symptoms (that is, vague delusions or odd beliefs, as may exist in schizotypal personality) were not excluded; preliminary data indicate use of ketamine in patient populations with psychotic symptomatology is safe and effective (Veraart et al. 2021).

Substance use disorder and active substance use were not contraindications to ketamine or KAP, as the available data on the use of ketamine in patients with these comorbidities, while limited, suggest efficacy in treatment of alcohol, heroin, and cocaine use disorders (Dakwar et al. 2019, 2020; Das et al. 2019; Krupitsky and Grinenko 1997; Krupitsky et al. 2007). Urine toxicology was not required prior to KAP but rather was used selectively as part of typical addiction psychiatry practice. Patients were required to present to ketamine sessions as not overtly intoxicated to minimize the risk of acute side effects as well as be able to participate in psychotherapy. Dependence and risk of withdrawal were assessed as part of the initial evaluation; those deemed to be medically unstable or at risk of complicated withdrawal were referred out or first stabilized. Recent illicit substance use in and of itself was not a contraindication, even in substances with a well-defined withdrawal syndrome, such as with opioids,

alcohol, and benzodiazepines. Patients were encouraged but not required to discontinue use of prescribed benzodiazepines, especially on days surrounding a KAP session, and those consenting were tapered off prior to induction.

While initially not mandatory, the majority of patients ($n = 41$) received preparatory sessions prior to ketamine administration, consisting of an hour-long visit to provide psychoeducation, discuss expected psychedelic drug effects, facilitate informed consent, build rapport, and identify topics of psychotherapeutic inquiry (that is, interpersonal relationships, patterns of behavior, thought feeling behavior interactions, behavioral activation). Patients were subsequently scheduled for an initial series (induction) consisting of six KAP sessions over three to four-weeks, at a frequency of one to two sessions per week on nonconsecutive days, and an intersession interval of no more than one week. Induction could be extended by patient request up to eight sessions. Completers were defined as having attended at least four sessions. A minority ($n = 11$) were accepted directly into maintenance, typically after receiving ketamine treatment elsewhere (with or without psychotherapy).

KAP sessions ranged from one and a half to two-hours. The initial 20–30 minutes included evaluation and management, and establishing more specific psychotherapeutic goals or topics of inquiry for the session (that is, "intention setting"). Ketamine was then administered, followed shortly by the onset of acute drug effects, which typically peaked in intensity over the next 20 minutes. Patients were largely unable to communicate coherently during the peak, and so were instructed ahead of time to attend to their sensory experience rather than engage in dialogue and were offered a blindfold to facilitate this process. During this time, the clinician provided support to offer reassurance, comfort, and encouragement to resist avoidance. Physical touch, in the form of hand holding, was offered when patients expressed anxiety or feeling overwhelmed. By around 30 minutes post dosing, patients typically became spontaneously conversational, describing gradual diminution of drug effects, and were engaged in dialogue about their experience. Patients were helped to construct a narrative of their experience, reflect on any spiritual or mystical experiences that may have occurred, explore associated meaning, and relate this to longitudinal conflicts or potential insights. As with other psychedelic psychotherapies, set and setting were important considerations (Carhart-Harris et al. 2018), with efforts made to make the environment aesthetically pleasing and comfortable. Patients reclined on a couch, and music was offered, typically ambient electronic in style.

Ketamine was provided via intramuscular bolus injection, starting at 0.5 mg/kg (actual body weight); over the course of this observational case series, the initial dose was modified to allow up to 0.75 mg/kg on initial dosing for those with suicidal ideation, based on a report that an induction of IV infusions at this dose yielded more rapid relief from suicidal ideation (Calabrese 2019). Subsequent visits allowed for 10 mg increases, to a target of 1 mg/kg and maximum of 1.5 mg/kg. Dose increases were patient-led but could be held by the physician, similar to protocols at opioid treatment programs. Lower initial doses allowed patients to gain mastery over potentially distressing psychedelic effects.

The physician remained with patients throughout each session to provide psychological support during peak drug effects, provide psychotherapy, and intervene in the event of emergent cardiorespiratory issues. Blood pressure and heart rate measurements were taken at baseline and again at discharge. Those with nausea were treated with ondansetron, which in cases of failure was replaced with promethazine or scopolamine patch applied at least several hours prior to the session; in refractory cases, a combination was used.

Ketamine was administered within the first 30 minutes of a session to allow at least 60 minutes for recovery from acute drug effects. Subsequent to the injection, patients agreed to not attempt to stand or ambulate. Immediately prior to the end of the session, patients were assessed for gait impairment; if present, they were asked to remain at least 15 more minutes in an ancillary unsupervised room on-site, leaving only once they felt this had resolved. Dosages for future sessions could be reduced in cases of excessive sedation, nausea, emesis, or gait imbalance. Initially patients were asked to have a friend or family member provide transportation to and from the office; this policy was later relaxed to allow the use of rideshare services.

Maintenance sessions were offered to patients after completion of induction as a strategy to sustain clinical benefit. They were largely identical to induction sessions in structure, monitoring, and ongoing psychotherapy, but typically utilized higher ketamine dosages given that such sessions followed an induction consisting of several sessions with gradual upward adjustment in dose. Maintenance sessions were typically recommended to begin three to four weeks after completion of induction, and less commonly began one to two weeks after; intersession intervals were subsequently adjusted in one-to-two-week increments, up to a maximum frequency of

weekly. Timing of sessions was based on the severity of remaining post-induction psychopathology as well as patient preference. Logistical impacts (that is, work absence, pre-session fasting, post-session driving restrictions, greater financial burden from more frequent sessions), the presence of side effects, and the magnitude of benefit were balanced against the greater risk of decompensation with longer intersession intervals. Recommendations for timing were made based on clinician judgment and patient report. Often patients could identify a relatively consistent trajectory of their symptomatology after each maintenance session until the next, with optimal functioning at first, proceeding to mild decompensation, and then full decompensation after enough time had elapsed without a subsequent maintenance session (that is, months).

Psychotherapy combined elements from psycholytic and psychedelic peak therapy (Kishon et al. 2024), framing acute drug effects not as side effects (that is, thought disorder, dissociation) but rather as goals of the treatment, where defenses are transiently reduced, and manifestations of the subconscious can be explored and leveraged for clinical benefit. Direct drug effects that often manifested with improved mood and motivation were directed toward behavioral activation, ideally regarding unhealthy lifestyle choices or patterns of behavior. Psychotherapy drew from several modalities:

- MDMA-assisted psychotherapy (Mithoefer 2017), which invites attention, inquiry, and acceptance of drug induced psychedelic experience and provides support for approaching and processing difficult psychological material.
- Psychodynamic psychotherapy, including exploration of transference/countertransference phenomena, to gain awareness of patterns of behavior as they relate to prior relationships.
- Motivational interviewing to encourage change in those with substance use disorders or change more globally.
- Mindfulness-based cognitive therapy to foster awareness of thoughts and body sensations.
- Cognitive behavioral therapy to build insight into cognitive distortions and facilitate behavioral activation.

Integration, the longitudinal process of transforming psychedelic experiences and insights into actionable change, was carried out over subsequent KAP sessions as well as additional non-drug psychotherapy sessions.

Outcome measures

Efficacy was assessed via the clinical global impressions-severity (CGI-S) scale, a transdiagnostic scale of psychopathology ranging 1–7 (Guy 1976), at the start of each visit prior to dosing. Response was defined as a CGI-S reduction of 2 or more points from baseline, or an absolute CGI-S of 3 or less (Morrens et al. 2022; Turkoz et al. 2021). Excluded from efficacy analysis were patients whose baseline CGI-S was below 4 ("moderately ill") and those whose treatment plan did not include induction.

Tolerability analysis, in contrast, was performed on the entire dataset. Adverse events and use of as-needed medications were extracted from medical records, along with reasons for dropout.

Statistical analysis

Aggregated continuous variables (for example, age) are reported as mean (SD). Aggregated ordinal data (for example, number of prior treatments) are reported as median (interquartile range [IQR]). CGI-S during treatment was compared to baseline using a mixed model ANOVA with time as the factor. Missing values were not imputed. Multiple comparison correction was performed using Dunnett's multiple comparisons test. All analyses were conducted in GraphPad Prism 9.5.1.

Results

Demographics and baseline characteristics

A total of $n = 70$ patients and 1,114 sessions were identified (Figure 1). Fewer sessions were carried out over the initial two years (126 sessions), with an overall mean of 159.14 sessions per year (SD 69.75). Excluded from efficacy analysis were $n = 11$ (71 sessions), for lack of induction in their treatment plan, and $n = 4$ (27 sessions), for insufficient baseline morbidity (CGI-S = 3). The induction cohort had high symptom severity at baseline, as evidenced by a mean CGI-S of 4.56 (SD 0.73) and the presence of suicidality in 70% of the cohort (Table 1). Patients in the overall cohort had a median age of 36.5, ranging from 19–72. Most were employed (61%), had at least some college education (93%), and lived with family or their partner (50%). Only a minority had used illicit ketamine previously (31%), and the majority regularly used alcohol (66%) or cannabis (61%). Nearly all had a history of prior psychotherapy (91%), and a minority had histories of psychiatric hospitalization (23%), suicide attempt (20%), self-injurious behavior (24%), or residential addiction treatment (17%). Patients had a median of

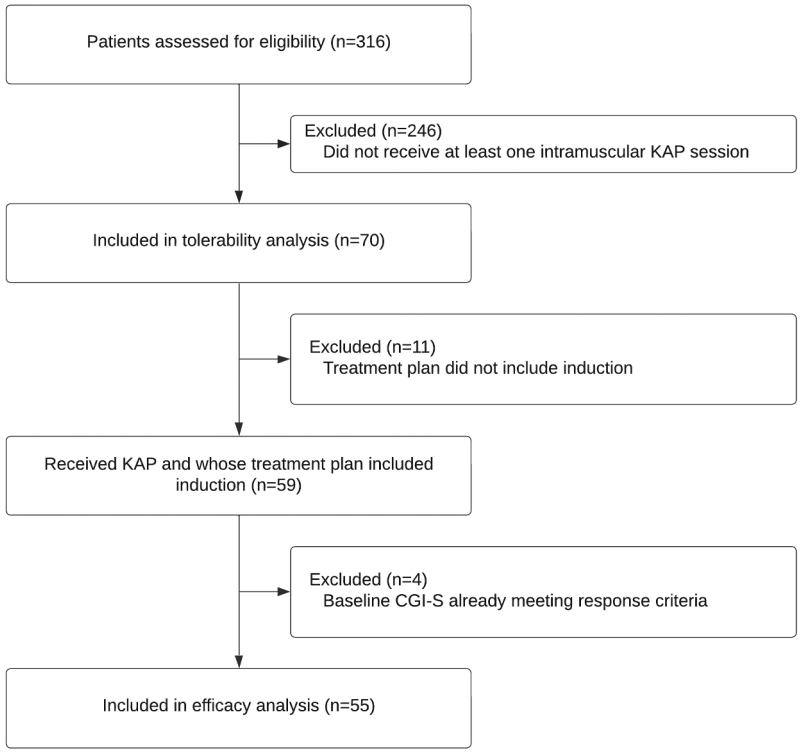

Figure 1. STROBE flow chart. A total of n=70 received at least one intramuscular injection. Of these, two groups were excluded from efficacy analysis: n=11 due totheir treatment plan not including an induction, and n=4 due to insufficient baseline morbidity.

four psychiatric diagnoses (IQR 3–5), with frequent comorbidities being anxiety or substance use disorders. Patients entered treatment with a median of 2.5 psychiatric medications (IQR 1.25–4) (Table 2). The majority were taking serotonergic antidepressant medication.

Frequency, dosing, and efficacy

The $n = 55$ analyzed for efficacy received a median of 12 KAP sessions (IQR 5.5–22), engaging over a median of 133 days (IQR 29–672), with 38% for a year or more (Figure 2(a)). Treatment started at a mean dose of 0.53 mg/kg (SD 0.08), increasing to 0.90 mg/kg (SD 0.28) by session 6 (Figure 2(b)). The majority ($n = 46$, 84%) completed induction, and $n = 45$ (82%) achieved response (Figure 2(c)), corresponding to a final mean CGI-S of 2.64 (SD 1.03). Induction consisted of six sessions for most ($n = 32$), while fewer had four to five sessions ($n = 10$) or seven to eight sessions ($n = 4$). Completed inductions spanned a median of 16 days (IQR 14–21) with a session q2days (IQR 2–5).

The majority ($n = 39$, 71%) proceeded with maintenance treatment; 715 sessions took place a median of q21days (IQR 8–35), utilizing a mean dose of 1.13 mg/kg (SD 0.32). Response rates remained above 80% at the three- and six-month time points, dropping to 57% at 12 months (Table 3). A mixed effects model comparing CGI-S during treatment versus baseline indicated statistically significant improvements at the following time points (mean, mean difference [95% CI of difference], p value): after induction (2.64, 1.93 [1.55–2.30], $p < .0001$), 3 months (2.91, 1.66 [1.23–2.08], $p < .0001$), 6 months (2.74, 1.82 [1.36–2.29], $p < .0001$), 12 months (3.14, 1.42 [0.77–2.07] $p < .0001$), and 24 months (3.42, 1.15 [0.31–1.99], $p < .01$).

Side effects, adverse events

Side effects and adverse events, acute and chronic, were noted at each session (Table 4). Nearly all reported dissociation (96%) and acute mood improvement (94%). Others included sedation (31%), dizziness (17%), unsteadiness (11%), nausea (8.8%), anxiety (5.5%), headache (5.2%), emesis (1.6%), diplopia (2.2%), amnesia (1.9%), insomnia (0.9%), or worsened mood (0.3%). Patients typically laid calmly on the couch, but in a handful of sessions exhibited psychomotor agitation (0.3%) or yelling (0.3%), often with concomitant amnesia. Ketamine misuse, including seeking out illicit ketamine, occurred rarely (0.3%). Tinnitus or epistaxis occurred once each (0.1%). One patient received treatment in an emergency department for

Table 1. Demographic and baseline characteristics.

Characteristics	Overall (*n*=70)		Efficacy (*n*=55)	
Age in years, median (IQR)	36.5 (30.3–51)		35 (30–51)	
Sex, *n* %				
Female	29	41%	22	40%
Male	39	56%	31	56%
Transexual, female to male	2	3%	2	4%
Race/ethnicity, *n* %				
White European	58	83%	47	85%
Jewish	8	11%	5	9%
Arabic	2	3%	1	2%
Southern Asian	1	1%	1	2%
Hispanic	1	1%	1	2%
Employment, *n* %				
Employed	43	61%	31	56%
Disabled or medical leave	5	7%	4	7%
Student (full time)	5	7%	4	7%
Unemployed	16	23%	15	27%
Retired	1	1%	1	2%
Education completed, *n* %				
High school or equivalent degree	5	7%	3	5%
Some college	19	27%	15	27%
Undergraduate degree	36	51%	28	51%
Graduate degree, masters	7	10%	6	11%
Graduate degree, doctoral	3	4%	3	5%
Living status, *n* %				
Alone	28	40%	20	36%
Roommates	5	7%	4	7%
Family, partner, or parents	35	50%	30	55%
Homeless, in vehicle	2	3%	1	2%
Current substance use, *n* %				
Alcohol	46	66%	35	64%
Tobacco	16	23%	14	25%
Cannabis	43	61%	33	60%
Other substances	18	26%	14	25%
History of use, *n* %				
Classical psychedelics	45	64%	36	65%
Ketamine	22	31%	13	24%
3,4-methylenedioxymethamphetamine	21	30%	15	27%
History of arrest or legal charges, *n* %	8	11%	5	9%
Psychiatric hospitalization, history of, *n* %	16	23%	11	20%
Psychotherapy, history of, *n* %	64	91%	52	95%
Suicide attempt, history of, n %	14	20%	11	20%
Self-injurious behavior, history of, *n* %	17	24%	14	25%
Residential addiction treatment, history of, *n* %	12	17%	9	16%
Suicidality, *n* %				
None, C-SSRS-SI=0	21	30%	12	22%
Passive, C-SSRS-SI=1	25	36%	22	40%
Active, C-SSRS-SI≥2	24	34%	21	38%
Psychopathology (CGI-S), mean ± SD	4.33 ± 0.89		4.56 ± 0.73	
Diagnoses, number of, median (IQR)	4 (3–5)		4 (3–5.5)	

refractory nausea, dizziness, and vertigo but was discharged later that day.

While formal cognitive testing was not performed, cognitive complaints were rarely endorsed (0.6%) and tended to be intermittent, typically described by patients as transient mental fogginess or reduction in attention resolving within one to two days. One patient described symptoms that persisted for a week, but only after their first session and not subsequently. There were no cases of hallucinogen persisting perception disorder, and more broadly, no cases of "enduring adverse experiences" (Evans et al. 2023). No patients had worsening or onset of psychotic symptoms, and no patients experienced a manic or hypomanic episode.

Urinary complaints occurred in 1.7% of sessions. Causes independent of ketamine were often identified (that is, urinary tract infection diagnosed via urinalysis), while in other cases symptoms were minor and transient (polyuria or urgency, resolving over days despite ongoing ketamine treatment). One patient receiving weekly KAP was evaluated by a urologist for new onset, persistent dysuria; the specialist opined it was unrelated to ketamine, and continuing treatment was not contraindicated. Another patient receiving weekly treatments, a male in

Table 2. Additional baseline characteristics.

Characteristics	Overall (*n*=70)		Efficacy (*n*=55)	
Diagnoses, presence of, *n* %				
Mood disorder	69	99%	55	100%
Major depressive disorder	62	89%	52	95%
Bipolar 2 disorder	4	6%	2	4%
Bipolar 1 disorder	3	4%	1	2%
Anxiety disorder	55	79%	44	80%
Generalized anxiety disorder	25	36%	19	35%
Panic disorder	16	23%	15	27%
Post traumatic stress disorder	18	26%	16	29%
Social phobia	9	13%	6	11%
Obsessive compulsive disorder	7	10%	5	9%
Substance use disorder	33	47%	28	51%
Cannabis	17	24%	15	27%
Alcohol	16	23%	14	25%
Tobacco	11	16%	9	16%
Opioid	7	10%	6	11%
Benzodiazepine	5	7%	4	7%
Cocaine	3	4%	3	5%
Eating disorder	7	10%	6	11%
Binge eating disorder	5	7%	4	7%
Anorexia	1	1%	1	2%
Insomnia	21	30%	15	27%
Chronic pain	18	26%	14	25%
Attention deficit hyperactivity disorder	9	13%	6	11%
Thyroiditis	7	10%	4	7%
Migraine, or other headache	8	11%	6	11%
Personality disorder	5	7%	5	9%
Histrionic	1	1%	1	2%
Borderline	4	6%	4	7%
Fibromyalgia	4	6%	3	5%
Premenstrual dysphoric disorder	3	4%	3	5%
Traumatic brain injury	3	4%	3	5%
Gender dysphoria	2	3%	2	4%
Behavioral addiction	4	6%	3	5%
Compulsive sexual behavior	3	4%	2	4%
Internet gaming disorder	1	1%	1	2%
MTHFR mutation	2	3%	2	4%
Intermittent explosive disorder	2	3%	2	4%
Somatic symptom disorder	1	1%	1	2%
Trichotilomania	2	3%	2	4%
Complex regional pain syndrome	2	3%	1	2%
Psychotic disorder, not otherwise specified	1	1%	0	0%
Body dysmorphia	1	1%	1	2%
Dissociative identity disorder	1	1%	1	2%
Psychiatric medications, number of, *n* %				
None	10	14%	9	16%
1	8	11%	5	9%
2	17	24%	12	22%
3	13	19%	11	20%
4	9	13%	7	13%
5 or more	13	19%	11	20%
Psychiatric medications, categories, *n* %				
SSRI, SNRI, SMS, or SARI (at least one)	37	53%	33	60%
SSRI	21	30%	18	33%
SNRI	10	14%	9	16%
SMS (i.e., vortioxetine, vilazodone)	6	9%	6	11%
SARI (i.e., trazodone)	6	9%	6	11%
Stimulant	24	34%	19	35%
Benzodiazepine	21	30%	14	25%
Antipsychotic	15	21%	13	24%
Thyroid hormone	12	17%	8	15%
Norepinephrine–dopamine reuptake inhibitor (i.e., buproprion)	12	17%	10	18%
Mood stabilizer	15	21%	9	16%
Gabapentinoid	10	14%	8	15%
Opioid agonist (i.e., methadone, suboxone)	10	14%	9	16%
Z-hypnotic drug	7	10%	4	7%
Beta blocker (i.e., propranolol)	8	11%	5	9%
Opioid antagonist (i.e., naltrexone)	5	7%	5	9%
Methylfolate	3	4%	3	5%
Monoamine oxidase inhibitor	2	3%	1	2%
Antihistamine (i.e., hydroxyzine)	2	3%	2	4%
Tetracyclic antidepressant (i.e., mirtazapine)	2	3%	2	4%

(*Continued*)

Table 2. (Continued).

Characteristics	Overall (*n*=70)		Efficacy (*n*=55)	
Serotonin 5-HT1A receptor agonist (i.e., buspirone)	2	3%	2	4%
Norepinephrine reuptake inhibitor (i.e., atomoxetine)	1	1%	1	2%
Alpha-2 agonist (i.e., clonidine)	1	1%	1	2%
Melatonin agonist (i.e., ramelteon)	1	1%	1	2%
N-acetyl cysteine	1	1%	1	2%

Note. C-SSRS-SI, Columbia Suicide Severity Rating Scale, suicidal ideation subscale; CGI-S, Clinical Global Impressions-Severity scale; SD, standard deviation; IQR, interquartile range, SSRI, selective serotonin reuptake inhibitor; SNRI, serotonin-norepinephrine reuptake inhibitor; SMS, serotonin modulator and stimulator; SARI, serotonin antagonist and reuptake inhibitor.

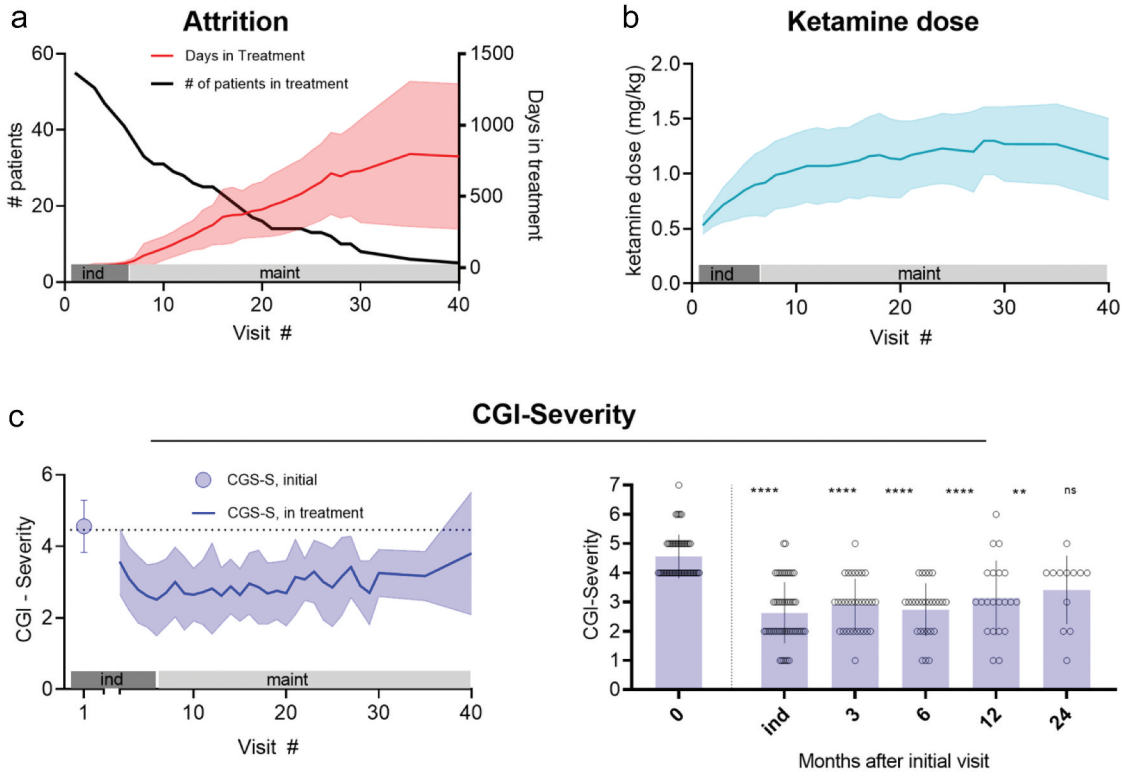

Figure 2. A. Attrition. Patients remaining in treatment by visit number as well as days in treatment. **B. Ketamine dose.** Ketamine dose in mg/kg by visit number. **C. CGI-Severity.** CGI-Severity by visit number as well as baseline, post-induction, 3 months after, 6 months after, 12 months after, and 24 months after.

Table 3. Response rates over time.

Timepoint	CGI-S, mean ± SD	Responders, n (%)	n	ITT response
Baseline	4.56 ± 0.73	n/a	55	n/a
After induction	2.64 ± 1.03	45 (82%)	55	82%
3 months	2.91 ± 0.88	27 (84%)	32	49%
6 months	2.74 ± 0.89	23 (85%)	27	42%
12 months	3.14 ± 1.25	14 (67%)	21	25%
24 months	3.42 ± 1.11	8 (67%)	12	15%

Table 4. Adverse events and as needed medications.

	Sessions (*n*=1114)		Patients (*n*=70)	
Adverse events, n %	N	%	N	%
Dissociation	1,071	96.1%	66	94%
Mood improvement (in the session, or soon after)	1,048	94.1%	63	90%
Any, except dissociation or mood improvement	737	66.2%	58	83%
Sedation	342	30.7%	34	49%
Dizziness	194	17.4%	21	30%
Unsteadiness	126	11.3%	13	19%
Nausea (in session or on ride back home from last)	98	8.8%	25	36%
Anxiety	61	5.5%	26	37%
Headache	58	5.2%	15	21%
Diplopia	24	2.2%	8	11%
Amnesia	21	1.9%	9	13%
Urinary	19	1.7%	8	11%
Emesis	18	1.6%	6	9%
Insomnia	10	0.9%	5	7%
Cognitive	7	0.6%	3	4%
Worse mood	3	0.3%	3	4%
Yelling/screaming	3	0.3%	2	3%
Movement, rolling on floor	3	0.3%	2	3%
Ketamine misuse	3	0.3%	2	3%
Tinnitis	1	0.1%	1	1%
Epistaxis (nosebleed)	1	0.1%	1	1%
As needed medications, *n* %				
Any as needed medication	346	31.1%	25	36%
Any antinausea medication	342	30.7%	23	33%
Ondansetron	241	21.6%	22	31%
Promethazine	156	14.0%	8	11%
Ondansetron and promethazine	59	5.3%	5	7%
Scopalamine	24	2.2%	2	3%
Ondansetron, promethazine, and scopalamine	15	1.3%	2	3%
Olanzapine	1	0.1%	1	1%
Lorazepam	16	1.4%	1	1%
Clonidine	4	0.4%	3	4%
Propranolol	1	0.1%	1	1%

his 40s with alcohol use disorder, endorsed chronic nocturia without other impairment, noting resolution with cessation of binge drinking; his urinary complaints accounted for an additional 8.1% of session-related adverse urinary system complaints and were not included in our event rate calculation.

Serious adverse events

Two patients completed suicide after their last KAP session: 71 and 432 days later, respectively. The former aborted induction after their fourth session, having insignificant improvement, and was later lost to follow up. Both suicides were judged unrelated to KAP given the temporal delay and presence of suicidality at baseline.

One patient was admitted to residential addiction treatment for relapse to polysubstance abuse and new onset ketamine use disorder, occurring in maintenance treatment a month after induction. He reported euphoria from the acute effects of in-office ketamine, subsequently seeking out and binging on illicit ketamine immediately after the session, leading to job loss.

As needed medications

As needed medications (Table 4) were utilized in a minority of sessions (31%), most often antiemetics (31%). Lorazepam (1.4%) was seldom used and from an existing outside prescription. Antihypertensives, including clonidine (0.4%) and propranolol (0.1%), were used a handful of times in cases of higher-than-expected pre-dose blood pressures.

Dropout analysis

Sixty-two dropouts were identified, defined as cancellation of a session without rescheduling or being eligible for maintenance treatment but not proceeding (Figure 3). The most common reasons for dropping out were logistical (37%), lost to follow up (24%), insufficient benefit (19%), and side effects (9.7%). Logistical reasons included: transportation (as patients were restricted from driving the rest of the day), inability to secure time off from work, financial, relocation to another city, and acute COVID-19 illness. Physical side effects accounted for 4.8% (fall later in the day,

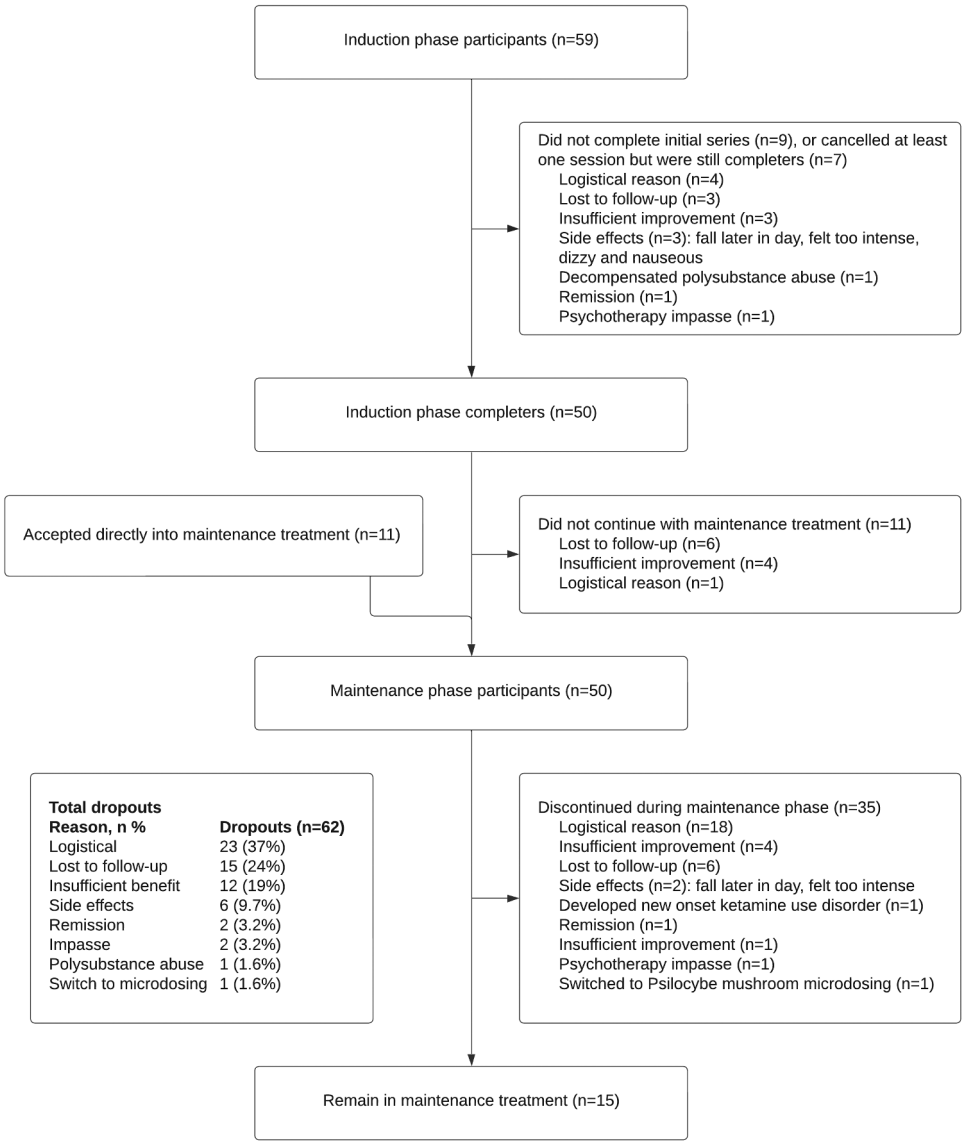

Figure 3. Patientflow and dropouts. Of the n=59 induction phase participants, n=9 did not complete their induction, and a further n=7 completed their induction but canceled at least one session. Of the n=50 induction phase completers, n=11 did not continue with maintenance treatment, and another n=11 were accepted into maintenance treatment, yielding n=50 maintenance phase participants. With n=35 discontinuing, n=15 remained in ongoing maintenance treatment. Reasons for dropout were varied, but most ften logistical, lost to follow-up, and insufficient benefit.

persistent dizziness and nausea), while psychological effects accounted for 3.2% ("felt too intense"). Others stopped due to remission (3.2%), psychotherapy impasse (3.2%), decompensated polysubstance abuse (1.6%), or switching to microdosed psilocybin-containing mushrooms (1.6%).

Discussion

In this retrospective chart review of long-term in-office intramuscular KAP, we analyzed 70 individuals over 1,114 sessions. Due to the high patient retention of this real-world study (38% at one year), this dataset allows for detailed longitudinal assessments, not only of clinician-rated symptom scores and dosing but also of adverse events, tolerability, and reasons for dropout. Symptom assessments demonstrate robust initial and long-term efficacy in the treatment of depression. We found that maintaining patients in long-term treatment with intramuscular ketamine was not associated with ongoing dose escalation. Tolerability was generally favorable, with nausea treatment and anti-emetic

prophylaxis accounting for the vast majority of as-needed medication used. Patient dropouts most frequently cited logistical reasons rather than overt treatment failure, highlighting the greater patient burden this treatment entails over standard pharmacotherapy.

Several real-world datasets have been published that report on efficacy of ketamine for depression (Ahuja et al. 2022; Dore et al. 2019; Hassan et al. 2022; Hietamies et al. 2023; Hull et al. 2022; Li et al. 2022; McInnes et al. 2022; McIntyre, Rodrigues et al. 2020; Oliver et al. 2022; Sakurai et al. 2020; Tsang et al. 2023). A subset of these studies have examined outcomes in the maintenance phase of treatment (Ahuja et al. 2022; Hietamies et al. 2023; Oliver et al. 2022; Sakurai et al. 2020), none of which reported the use of KAP, and only one of which studied intramuscular administration (Ahuja et al. 2022). Among real world studies of maintenance phase ketamine, studied outcomes are biased by the exclusion of large segments (~70%) of patient data (Hietamies et al. 2023), high attrition rates (50–80%) after induction (Ahuja et al. 2022; Sakurai et al. 2020), and limited data on patient demographics, comorbid disorders, ketamine dosage, and adverse events (Hietamies et al. 2023; Oliver et al. 2022). These limitations have prevented generalizable inferences about efficacy and adverse event frequency. The present dataset, in contrast, reports adverse events data in the entire sample, and efficacy analysis in 84% of patients.

Efficacy

Consistent with other studies, we saw rapid and robust initial response after induction (De Gregorio et al. 2021). Our 82% response rate exceeds that reported in most other studies, perhaps due to the high acuity in our population, evidenced by high baseline CGI-S and CSSR-S. The CGI-S, a clinician-assessed measure, has been shown to be a practical and reliable alternative to "gold standard" instruments such as the Montgomery-Åsberg depression rating scale (Morrens et al. 2022; Turkoz et al. 2021). Our relatively high response rate may be explained by the combined offering of medication management, ketamine administration, and psychotherapy, consistent with the superiority of psychotherapy plus conventional antidepressants for treating depression compared to medication alone (Cuijpers et al. 2020).

Response rates in our sample declined over time, consistent with other studies, with intention to treat analysis showing 42% remaining in response at six months, and 22% at 12 months. There are few other datasets to compare with: Li et al. described a 24.1% intention to treat response rate at nine months after an induction, but in the absence of any maintenance treatment. In contrast, Sakurai et al. reported 18.3% response after completion of induction, which reduced to 7.3% over less than year.

Dosing

A frequent cited concern with ketamine is tolerance and dose escalation, potentially with associated abuse liability (Le et al. 2022; Schatzberg 2014). Our data clearly demonstrate that maintaining treatment efficacy is compatible with stable maintenance dosage. Doses tended to rapidly increase through the induction phase in accordance with treatment protocol and then stabilize over subsequent maintenance treatment, suggesting limited tachyphylaxis. There is little known about optimal intramuscular dosage, and available dose-response data for intravenous ketamine are inconsistent (Fava et al. 2018; Kheirkhah et al. 2018).

The intramuscular route of administration utilized here differs from most other studies; many trials have substantiated the efficacy of intravenous infusions (McIntyre, Carvalho et al. 2020), and while less data exist to support other routes of administration, intramuscular and subcutaneous routes appear to be effective (Ahuja et al. 2022; Loo et al. 2016) and comparable to intravenous administration. The chief advantage of intramuscular administration lies in its simpler administration, decreased cost and greater patient comfort, and comparable efficacy (Ahuja et al. 2022; Dore et al. 2019).

Tolerability

KAP demonstrated a favorable side effect profile, in terms of both physical and psychological effects, with expected in-session effects of dissociation and mood improvement. Dizziness (17%), nausea (8.8%), and emesis (1.6%) were most disruptive to patient engagement with psychotherapy, well managed with antiemetics, and cited as a reason for dropout in only one individual. In the few sessions where antihypertensives were administered, this occurred prior to treatment, and there were no incidents of hypertensive emergency. Similarly, no respiratory issues were noted, though individuals with severe cardiorespiratory disease were excluded from treatment. These data suggest KAP, at least at such dosages of 1.5 mg/kg and under, can safely be carried out in outpatient settings with lower levels of monitoring in well selected patients.

Other in-session effects included anxiety (5.5%), amnesia (1.9%), agitation (0.3%), and yelling (0.3%). Anxiety was typically transient and tended to respond to a combination of verbal reassurance, physical contact (hand holding), and reorientation. The infrequency of benzodiazepine use (1.4%) suggests non-pharmacological techniques are effective for most individuals. Evidence suggesting benzodiazepines hamper antidepressant response (Andrashko et al. 2020) are a compelling reason to avoid use, and our low use may further explain the superior observed response rates.

Higher doses of ketamine tended to be disorienting and elicit a loss of sense of self, which some framed as a death and rebirth experience, consistent with psychedelic peak therapy. Such complex psychological experiences are not necessarily "adverse events," though are framed as such by some and may indeed occasion anxiety. Patients often reported such intense experiences preceded a catharsis and relief from existential anxiety and depressive symptoms, consistent with other reports (Karl Jansen, personal communication, November 4, 2017), and suggest psychotherapy is a particularly important component of the overall treatment.

Adverse events

Serious chronic sequelae have been identified in populations with excessive use of illicit ketamine, including addiction, urinary tract symptoms, and cognitive deficits (Bonnet 2015; Pal et al. 2013; Sassano-Higgins et al. 2016; Schep et al. 2023; Zhang et al. 2020; Zhu et al. 2016), but it has been unclear if these generalize to clinical use. The several incidents of misuse in our sample, including decompensated polysubstance abuse and new onset ketamine use disorder, indicate the importance of monitoring for ketamine misuse, but may also reflect higher risk in our patient population that has considerable baseline substance use disorders. Conversely, cognitive complaints in our sample were rare, inconsistent, and more often attributed to other causes such as underlying chronic depressive symptomatology arguing against neurotoxicity. We similarly did not find evidence for overt urinary toxicity, finding such complaints to be uncommon, and either unrelated to ketamine treatment, or transient and minor. The toxicity noted in abuse populations is likely due to excessive doses and frequency, or perhaps greater bladder load due to lower bioavailability of non-parenteral administration.

Suicide has been generally associated with treatments for severe depression. While two suicides occurred in our cohort, they took place months to years after last contact and in those with baseline suicidality, and so are unlikely to have been caused by KAP. Evidence instead points to robust anti-suicidal effects of ketamine (Abbar et al. 2022).

Dropouts

Dropout analysis shows logistical considerations were the biggest barriers to treatment in about half the sample where a reason was found, while, surprisingly, side effects (13%) were a much smaller contributor. While median patient engagement spanned several months, many did so for years, and so the attrition over time is unsurprising. KAP is a time-consuming intervention, requiring at minimum 90-minute visits two times per week during the induction, though this is comparable to electroconvulsive therapy. This time burden is compounded by restriction against driving the rest of the day, which is particularly impactful in metropolitan areas, with many individuals reporting commutes of more than an hour each way. Financial considerations, another factor included under logistics, is exacerbated by lack of insurance coverage for this off-label intervention and the high out-of-pocket cost; clinic pricing was $550 per session, and all patients paid for services outside of insurance. FDA approval for mental health indications with racemic ketamine would facilitate insurance coverage and improved patient retention.

Limitations

This analysis has several important limitations, most notably in that it is retrospective, without a control group, unblinded, and from a single community clinic. Such naturalistic treatment analyses also may conflate benefits from different interventions, such as medication management—via other antidepressant medications—that was provided in many cases. It is also difficult to distinguish the benefit of KAP in terms of component psychotherapy and direct drug effects; both are effective treatment options for depression. Potential studies comparing ketamine to KAP are hampered by the unanswered challenge of how to blind a psychotherapy arm, let alone the challenges with blinding the psychedelic itself. Finally, treatment outcomes as measured here by the transdiagnostic

CGI, while correlating well with treatment outcome in other studies, do not offer the level of granularity and specificity of depression scales.

Conclusion

Our findings suggest intramuscular KAP is an effective and well-tolerated long-term treatment option for mood disorders, particularly for those with comorbid anxiety and substance use disorders, as were heavily represented in this sample. This study provides greater generalizability than many prospective clinical trials in the broader recruitment here of individuals with suicidality, psychotic disorders, and substance use disorders. Treatment gains appeared to be reliably maintained with ongoing repeated intramuscular administration at stable maintenance doses, suggesting this route of administration is effective. Psychotherapy appears to be a crucial component, with acute psychedelic drug effects being a desired outcome rather than side effect. Future prospective, masked, controlled, long-term trials testing KAP versus intravenous infusion in outpatient settings are warranted.

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Data availability statement

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

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