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Standardized ketamine infusion protocol for chronic refractory pain: a retrospective study of preliminary effectiveness and treatment completion

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ABSTRACT

Background Chronic refractory pain presents limited treatment options and diminished quality of life. While ketamine treatment shows promise, protocol variations and safety concerns have hindered widespread adoption. This study evaluated preliminary effectiveness and rate of treatment completion for a standardized low-dose ketamine infusion therapy (KIT) protocol.

Methods This retrospective observational study examined adult patients with chronic refractory pain who received KIT between May 2021 and October 2024 at the Cleveland Clinic's outpatient multidisciplinary pain clinic. Patients received a standardized protocol of 0.5 mg/kg ketamine infused over 40 min for five consecutive days. We measured effectiveness using patient-reported outcomes (PROs) at baseline, last infusion, and 3-month and 6-month post-treatment, and rate of treatment completion. The primary outcome of interest was the proportion of patients achieving clinically meaningful improvement on validated measures.

Results Among 1034 patients (mean age 50.4±15.2 years; 71.8% female; 83.3% of white ethnicity), treatment completion was high, with 890 (86.1%) patients completing 5+ infusions. No adverse events were reported. Baseline measures reflected moderate impairment in pain interference, global physical health, fatigue, physical function, and depression. Between 20.3% and 46.4% of patients achieved clinically meaningful improvement on PROs from baseline to last infusion, with similar proportions maintained at 3-month and 6-month follow-up. Statistically significant mean improvements were observed across multiple domains; however, the majority of individual outcomes did not reach clinically meaningful thresholds. Patients demonstrated significant mean improvements in fatigue, pain interference, and social role satisfaction (mean change −2.1±7.7, −2.0±5.8, and 2.0±7.7, respectively), with improvements in depression, social role satisfaction, pain interference, self-efficacy, global health, and pain catastrophizing sustained through 6 months post-treatment.

Discussion This standardized low-dose ketamine protocol demonstrated therapeutic benefit and high completion rates within a multidisciplinary care model. Future randomized controlled trials are warranted to confirm findings and explore treatment response factors across pain conditions.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ While ketamine has shown promise as a therapeutic option for chronic refractory pain, variation in protocols and concerns about safety and effectiveness have hindered widespread adoption, with limited real-world data on its effectiveness.

WHAT THIS STUDY ADDS

⇒ This study demonstrates that patients with chronic refractory pain benefited from a standardized low-dose intravenous ketamine infusion protocol (0.5 mg/kg over 40 min for five consecutive days). We observed high completion rates (86.1% completing 5+ infusions), no serious adverse events, and sustained improvements in physical and mental health outcomes up to 6 months post-treatment.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Given the limited evidence base for ketamine infusion protocols in chronic pain and barriers to access—particularly for low-income populations—our findings add real-world data on treatment completion rates and safety profiles from a standardized low-dose ketamine infusion therapy (KIT) protocol. Importantly, our detailed protocol documentation (including dosing, monitoring procedures, staffing ratios, and safety measures) provides a reproducible framework that other healthcare systems can adapt for their own KIT programs, potentially accelerating broader implementation of evidence-based ketamine services. These results may help guide the design of future controlled trials, support informed clinical decision-making, and contribute to discussions around KIT's role in multidisciplinary pain care. The standardized protocol and outcome measures described here may serve as a framework for prospective comparative effectiveness research, which will be essential for generating the definitive evidence needed to inform policy and insurance coverage decisions.

INTRODUCTION

Chronic pain is a significant and costly public health issue, affecting more than 1 in 5 adults in the USA.[1] Despite increased healthcare, many continue to experience daily distressing pain.[2] Current evidence-based treatments, including medications (antidepressants, anticonvulsants, and opioids), interventional procedures, and surgery, provide meaningful relief for many. However, effectiveness is variable, with studies in conditions such as fibromyalgia and neuropathic pain demonstrating that 60% or more of patients may have suboptimal responses.[3–8] For patients with chronic refractory pain—pain lasting ≥6 months that has not responded adequately to conventional evidence-based therapies, as determined by the referring provider, patient report, and pain provider—alternative treatment approaches are warranted.

Ketamine infusion therapy (KIT) has gained attention as a potentially effective adjunct treatment for chronic refractory pain.[9–11] Unlike conventional treatments (eg, opioids and beta-blockers) that focus primarily on pain relief, KIT has been found to relieve pain and distress while also improving daily function. Importantly, patients report that this relief persists for what they personally consider to be a clinically meaningful duration.[10] Although some side effects may occur even at subanesthetic doses, including perceptual disturbance (eg, hallucinations), dizziness, and nausea,[12] effective mitigation strategies are available.[9] Additionally, KIT has no known contraindications when combined with antidepressants, benzodiazepines, or other psychotropic medications.[9]

Although prior studies demonstrate KIT benefits for chronic pain, published protocols vary widely in dosage,[10] frequency,[10] setting (inpatient[13 14] vs outpatient[10 11]), route of administration,[10] and duration (ranging from single 2-hour infusions to continuous multi-day treatment).[14] Additionally, observational studies of KIT integrated into real-world practice are lacking. Most existing studies are randomized controlled trials (RCTs) with small sample sizes, a narrow focus on specific conditions, like Complex Regional Pain Syndrome and fibromyalgia, and effects lasting only 2 weeks.[11 12 15] The literature presents mixed findings regarding ketamine dose-response relationships. While some studies suggest potential benefits of higher doses (>400 mg),[16 17] other research has not demonstrated statistically significant superiority of higher doses over lower doses, and high doses may also carry increased risk of adverse effects.[15] Given this uncertainty, more research is needed to evaluate low-dose KIT protocols and identify optimal patient populations.[16] The diversity of existing protocols has made treatment optimization and meaningful comparisons difficult, highlighting the need for standardized approaches that balance efficacy with safety considerations.[9]

The Cleveland Clinic's Center for Comprehensive Pain Recovery (CCPR), located within the Neurological Institute, is a multidisciplinary program treating a large number of individuals with complex, refractory pain conditions. Our team developed a standardized low-dose ketamine protocol (0.5 mg/kg infused over 40 min for five consecutive days) offered in conjunction with behavioral and physical therapies. The goals of this study are to evaluate KIT completion rates and the effectiveness of our KIT protocol in the real-world setting of a busy multidisciplinary pain clinic.

METHODS

Study design and study sample

This retrospective observational study included patients who received KIT between May 2021 and October 2024 within CCPR. We extracted demographics, pain diagnoses, ketamine infusion dates, and the number of infusions from electronic health records. Patients were categorized into seven pain categories based on the International Association for the Study of Pain classifications.[18]

Ketamine protocol

The KIT protocol consisted of five 40-min infusions of 0.5 mg/kg (actual body weight; no ceiling dose) over five consecutive days. This standardized dosing protocol was developed based on clinical experience, safety considerations, and clinical feasibility. It represents a systematic approach to ketamine administration for chronic pain, while acknowledging that optimal outpatient dosing parameters remain an area of ongoing study, as noted in the current American Society of Regional Anesthesia and Pain Medicine chronic pain guidelines.[16]

One week before the first infusion, patients and their support person attended a shared medical appointment (SMA) co-led by a pain physician and a pain psychologist. During this visit, biometrics were recorded, overall health was assessed for KIT safety, and patients received ketamine education. Patients also received pain neuroscience education and behavioral strategies (eg, relaxation techniques) for use during infusions. On the day of the first infusion, baseline data, including pain levels, functional status, and analgesic use, were recorded. Premenopausal women underwent a pregnancy test if indicated.

The outpatient infusion suite is an 8-chair room located within the CCPR, staffed with specialized infusion nurses trained in ketamine administration and side-effect management. KIT is prescribed by pain management providers (anesthesiologists and psychiatrists who completed pain medicine fellowships), with one provider always on site for consultation. Dedicated ketamine-trained infusion nurses maintain a 1:2 nurse-to-patient ratio to ensure close monitoring and rapid response to any adverse effects. On arrival, peripheral intravenous access is obtained, and patients are placed on standard monitoring: ECG, pulse oximetry, and blood pressure assessment every 15 min. The infusion suite is equipped with full resuscitation equipment. Nurses proactively address potential side effects by preemptively administering ondansetron 8 mg intravenously for nausea prevention (unless contraindicated), with one additional dose available as needed based on real-time patient assessment. Throughout the infusion, nurses continuously monitor for perceptual disturbances, hemodynamic changes, or respiratory concerns, intervening immediately at the onset of symptoms. Following the infusion, patients are monitored for 30 min and then discharged home with a known driver (ie, rideshare services or public transportation are not permitted).

Outcome measures

Treatment completion and safety

Treatment completion was assessed by tracking infusion attendance. Safety was monitored through adverse events requiring KIT discontinuation and/or a medical emergency team response, including abnormal ECG findings (new-onset bradycardia, tachycardia, and atrial fibrillation), symptomatic hypertension, or hypotension (or changes>20% from baseline). Manageable side effects, such as dizziness, nausea, and hallucinations, were not tracked as adverse events.

Effectiveness

Our primary effectiveness outcome of interest was achievement of minimal clinically important difference (MCID) in the

Patient-Reported Outcomes (PROs) Measurement Information System (PROMIS) Scales, with secondary outcomes of interest, including group mean changes across time. Patients completed previsit questionnaires shared via tablets or electronic patient portal (MyChart and Epic Systems). Standard questionnaires included the following PROs:

PROMIS measures

Six computer adaptive tests evaluated relevant domains, including Fatigue (V.1.0), Satisfaction with Social Roles and Activities (V.1.0), PROMIS Sleep Disturbance (V.1.0), PROMIS Pain Interference (V.1.1), PROMIS Physical Function (V.2.0), and PROMIS Self-Efficacy for Managing Symptoms (V.1.0). The 10-item PROMIS Global Health Short Form (V.1.0) yielded global mental and physical health scores. PROMIS scores were calibrated to the general population (T-score: mean=50, SD=10). Higher scores indicate a greater level of the domain being measured. A change of 5+ points (one-half SD) represents an MCID.[19] These PROMIS domains have been established to be valid and reliable in chronic pain populations.[20]

Patient Health Questionnaire-9 (PHQ-9)

9-item depression screen, with higher scores reflecting greater depressive symptoms. A change of 5 points indicates MCID.[21]

Generalized Anxiety Disorder-7

7-item anxiety screen, with higher scores reflecting greater anxiety. A change of 4 points indicates MCID.[22]

Pain Catastrophizing Scale (PCS)

13-item questionnaire assessing maladaptive cognitive and emotional responses to pain. Higher scores reflect greater pain catastrophizing, with a change of 5 points indicating MCID.[23]

Data were extracted for preketamine (baseline within 100 days prior), last infusion (within 30 days after), 3-month (31–135 days after), and 6-month (136–240 days after) follow-up timepoints. If multiple PROs were completed in the time windows of 3 and 6 months, the PROs closest to 90 days and 180 days after the last ketamine infusion were selected, respectively.

Statistical analysis

To address our primary outcome of interest, we calculated the proportion of patients who achieved MCID for each PRO. Demographics and baseline PROs were summarized by mean with SD or median with IQR for continuous variables and count with percentage for categorical variables. Mixed-effects linear regression models evaluated PROs over time and adjusted for covariates, including age, sex, race, Charlson Comorbidity Index (predicted mortality based on comorbid conditions), and the number of ketamine infusion days. Subject random effects were included in the models.

A selection bias analysis compared characteristics between patients who completed PROs versus those who did not. Characteristics were compared using the χ^2 test for categorical variables and the t-test or Wilcoxon rank-sum test for continuous variables. All analyses were conducted using SAS Enterprise Guide V.8.2 at a significance level of 0.05. As our study is hypothesis-generating, we did not adjust for multiple comparisons.

Table 1 Demographics, clinical characteristics, and baseline PROs, n=1034

	Overall (n=1034)	
	N	Statistics
Age, mean±SD	1034	50.4±15.2
Gender, n (%)	1034	
Female		742 (71.8)
Male		290 (28.0)
Nonbinary		2 (0.19)
Ethnic group, n (%)	1034	
White		861 (83.3)
Black		91 (8.8)
Other/unknown		82 (7.9)
Marital status, n (%)	1034	
Married		533 (51.5)
Single		343 (33.2)
Divorced		91 (8.8)
Other/unknown		67 (6.5)
Body Mass Index, mean±SD	1026	30.5±7.9
Charlson Comorbidity Index, mean±SD	1034	2.3±2.8
Ketamine infusion days, median (Q1, Q3)	1034	5 (5, 14)
Diagnosis, n (%)	1034	
Chronic primary pain		651 (63.0)
Chronic primary widespread pain		371 (35.9)
CRPS (chronic primary)		71 (6.9)
Chronic primary headache or orofacial pain		78 (7.5)
Chronic primary visceral pain		40 (3.9)
Chronic primary musculoskeletal pain		91 (8.8)
Chronic cancer pain		2 (0.19)
Chronic neuropathic pain		108 (10.4)
Chronic post-traumatic or postsurgical pain		41 (4.0)
Chronic secondary musculoskeletal pain		49 (4.7)
Chronic secondary visceral pain		6 (0.58)
Chronic secondary headache or orofacial pain		0 (0.00)
Multiple pain diagnosis categories		147 (14.2)
Other		30 (2.9)
Baseline PROs, mean±SD		
PHQ-9 (range: 0–27)*	849	11.7±6.8
PROMIS Fatigue*	807	65.5±8.5
PROMIS Social Role Satisfaction†	793	36.4±7.8
PROMIS Sleep Disturbance*	361	60.3±8.9
PROMIS Pain Interference*	814	68.7±5.8
PROMIS Physical Function†	795	34.6±6.4
PROMIS Self-Efficacy for Managing Symptoms†	784	38.4±5.9
PROMIS Global Mental Health†	812	37.2±9.0
PROMIS Global Physical Health†	808	33.7±6.8
GAD-7 (range: 0–21)*	408	13.3±5.3
PCS total (range 0–52)*	728	25.0±13.8

Note: all PROMIS measure outcomes are reported as T-scores with a mean of 50 and SD of 10.
*Lower score indicates better function.
†Higher score indicates better function.
CRPS, Complex Regional Pain Syndrome; GAD-7, Generalized Anxiety Disorder-7; PCS, Pain Catastrophizing Scale; PHQ-9, Patient Health Questionnaire-9; PRO, patient-reported outcome; PROMIS, Patient-Reported Outcomes Measurement Information System.

RESULTS

Sample description and baseline characteristics

The study included 1034 patients (mean age 50.4±15.2 years; 71.8% female; 83.3% white; table 1). At baseline, patients reported significantly worse scores across all PROMIS domains compared with the general population. Pain interference was most affected (M=68.7±5.8), followed by global physical health

(M=33.7±6.8), fatigue (M=65.5±8.5), and physical function (M=34.6±6.4). The average PHQ-9 score was 11.7±6.8, indicating moderate depressive symptoms.

Treatment completion and safety

A total of 890 patients (86.1%) completed 5+ infusion sessions, demonstrating high rates of treatment completion. Of these, 420 patients (47.2%) completed only the initial five-session sequence, while 470 patients (52.8%) voluntarily returned for additional infusion sequences. A small number of patients did not complete the five-session infusion sequence: 80 patients (7.7%) completed 4 out of 5 sessions, 32 (3.1%) completed 3, 18 (1.7%) completed 2, and 12 (1.2%) completed 1. Treatment non-completion was primarily due to scheduling constraints (holidays reducing clinic availability to 4 days), transportation challenges, and illness unrelated to KIT (eg, COVID-19); complete reasons are documented in online supplemental material. Total infusions ranged from 1 to 64. There were no adverse medical events requiring emergency team response or safety event reporting.

PROs at last infusion and at 3-month and 6-month follow-up

Between 15.7% and 46.4% of patients demonstrated clinically meaningful improvement from baseline to last infusion (table 2, figure 1). The highest proportions of improvements were observed in pain catastrophizing (46.4%), fatigue (32.7%), pain interference (31.2%), and social role satisfaction (30.2%). Seven of the eight PROMIS measures demonstrated clinically meaningful improvement rates exceeding 20% at last infusion. These proportions remained generally consistent at 3-month and 6-month follow-up.

Mean change analysis

Patients reported statistically significant mean improvements across all PROs from baseline to last infusion (table 3). The most notable improvements were in pain catastrophizing, fatigue, pain interference, and social role satisfaction (mean change −5.2±9.6, −2.1±7.7, −2.0±5.8, and 2.0±7.7, respectively). Similar findings were observed at 3 months, although changes in sleep disturbance did not reach significance. At 6 months, statistically significant improvements were sustained in most domains, except fatigue, sleep disturbance, physical function, and anxiety. Overall, the magnitude of change was smaller at 6 months, with the greatest improvements in social role satisfaction and global mental health (1.7±8.3 and 1.1±6.6, respectively).

The selection bias analysis demonstrated that the majority of characteristics were similar between patients who did and did not complete PROs (see online supplemental data tables 1–3). Non-completers were younger (48.6±15.6 vs 52.2±14.5, p<0.01) and had a lower Charlson Comorbidity Index (2.1±2.6 vs 2.5±3.1, p<0.01). Differences were similar for those with 3-month and 6-month follow-up, with those missing 6-month follow-up also being more likely to have more ketamine visits (median (q1, q3) 5 (5, 15) vs 5 (5, 9), p<0.01) and worse baseline fatigue scores (66.0±8.2 vs 64.0±9.3, p<0.01) compared with PRO completers.

Table 2 Frequency and percentage of patients with clinically meaningful improvement from baseline to last infusion, 3-month, and 6-month follow-up

	Improvement from baseline to last infusion*	Improvement from baseline to 3-month follow-up†	Improvement from baseline to 6-month follow-up‡
PHQ-9	93/439 (21.2)	104/493 (21.1)	42/172 (24.4)
PROMIS Fatigue	118/361 (32.7)	136/396 (34.3)	26/108 (24.1)
PROMIS Social Role Satisfaction	104/344 (30.2)	126/373 (33.8)	31/93 (33.3)
PROMIS Sleep Disturbance	16/72 (22.2)	22/75 (29.3)	8/33 (24.2)
PROMIS Pain Interference	116/372 (31.2)	123/436 (28.2)	24/132 (18.2)
PROMIS Physical Function	62/395 (15.7)	76/442 (17.2)	20/139 (14.4)
PROMIS Self-Efficacy for Managing Symptoms	87/361 (24.1)	104/371 (28.0)	22/89 (24.7)
PROMIS Global Mental Health	55/234 (23.5)	100/413 (24.2)	59/204 (28.9)
PROMIS Global Physical Health	54/237 (22.8)	97/408 (23.8)	47/200 (23.5)
GAD-7	26/128 (20.3)	28/141 (19.9)	9/44 (20.5)
PCS total	136/293 (46.4)	145/304 (47.7)	30/58 (51.7)

Statistics presented as N/total N (%); the denominator is the number of patients with available data, not the total sample. Meaningful improvement was defined as the absolute value of the change scores≥MCID. For PROMIS domains, PHQ-9, and PCS, a 5-point change was used as MCID. For GAD-7, a 4-point change was used as an MCID.
*The last infusion follow-up was defined as the closest score within 30 days after the last ketamine infusion.
†The 3-month follow-up was defined as 31–135 days after the last ketamine infusion.
‡The 6-month follow-up was defined as 136–240 days after the last ketamine infusion.
.GAD-7, Generalized Anxiety Disorder-7; MCID, minimal clinically important difference; PCS, Pain Catastrophizing Scale; PHQ-9, Patient Health Questionnaire-9; PROMIS, Patient-Reported Outcomes Measurement Information System.

DISCUSSION

In this retrospective observational study of 1034 adults with chronic refractory pain, we demonstrated high treatment completion (86.1%) with a standardized low-dose KIT protocol within a multidisciplinary pain clinic. From baseline to last infusion, between 16% and 46% of patients achieved clinically meaningful improvements, and these proportions remained relatively consistent at 3 and 6 months postinfusion. While statistically significant mean changes were observed across multiple physical and mental health outcomes over 6 months, the majority of outcomes did not reach clinically meaningful thresholds. No adverse events requiring emergency response occurred.

Our observed treatment completion rates compare favorably to high dropout rates commonly seen in chronic pain populations.[24] There are two possible explanations for these findings. First, we adopted a standardized protocol across all patients, an approach essential for successful implementation in our high-volume clinical setting (>1000 infusions monthly, >200 patients per month). Fixed protocols streamline clinical procedures, minimize treatment variability, and reduce errors, ensuring consistent quality treatment implementation at this scale. Second, we adopt a multidisciplinary approach guided by a biopsychosocial framework with the goal of establishing a strong therapeutic alliance with patients. All patients attended an SMA that emphasizes the multidimensional nature of chronic pain, helps patients and families form realistic treatment expectations, addresses concerns, and teaches coping strategies to be used

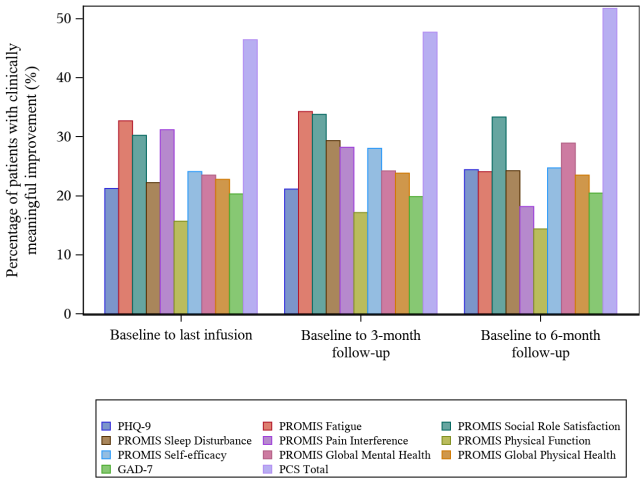

Figure 1 Percentage of patients with clinically meaningful improvement from baseline to last infusion, 3-month, and 6-month follow-up. Meaningful improvement was defined as the absolute value of the change scores ≥MCID. For PROMIS domains, PHQ-9, and PCS, a 5-point change was used as MCID. For GAD-7, a 4-point change was used as MCID. The last infusion follow-up was defined as the closest score within 30 days after the last ketamine infusion. The 3-month follow-up was defined as 31–135 days after the last ketamine infusion. The 6-month follow-up was defined as 136–240 days after the last ketamine infusion. GAD-7, Generalized Anxiety Disorder-7; MCID, minimal clinically important difference; PCS, Pain Catastrophizing Scale; PHQ-9, Patient Health Questionnaire-9; and PROMIS, Patient-Reported Outcomes Measurement Information System.

during treatment, thereby reducing safety risks and promoting the completion of the treatment protocol.

While several RCTs have examined ketamine's effectiveness in chronic pain,[15 25] our pragmatic design precludes direct comparison. To our knowledge, only one group has reported real-world effectiveness data.[10 11] Their initial study[11] followed 298 patients receiving KIT every 3 months and found that repeated administration was associated with decreased pain and improved physical and mental well-being over 1 year. A subsequent study[10] of 256 patients receiving a single ketamine administration was associated with decreased pain that was maintained for 1 year. However, the protocols in these studies varied in dosage, duration, frequency, and route of administration, with higher rates of adverse effects. The physical and mental health improvements observed in our study align with these real-world findings, though direct protocol comparison remains limited. Our standardized protocol and 1034-patient cohort represent one of the largest pragmatic studies conducted to date.

The greatest proportion of responders and the largest mean improvements were seen at the last infusion and 3 months, with many outcomes sustained at 6 months, demonstrating the durability of our protocol. Our findings show statistically significant mean improvements in physical functioning over 3 months, with 17.2% of our sample reaching MCID. Pain catastrophizing and physical global health demonstrated statistically significant mean improvements through 6 months, with 51.7% and 23.5% of patients reaching MCID, respectively. As such, this study contributes to the evidence base by documenting low-dose KIT's potential to reduce pain catastrophizing and improve physical functioning with sustained benefits.

This study highlights ketamine's benefits in improving psychiatric outcomes, including global mental health and depression, with continued improvement over time. Given the well-established interconnection between chronic pain, depression, and suicide risk,[26] addressing mental health remains essential in comprehensive pain management. For example, by alleviating depressive symptoms, ketamine may enhance motivation to engage in other therapies. Our findings support a cumulative mood-enhancing effect consistent with research suggesting that ketamine's modulation of pain's affective-motivational component, such as pain-related unpleasantness and low mood, may contribute to sustained benefits following KIT.[9 25]

A key strength of our study is the large sample size and use of a standardized, low-dose, weight-based ketamine protocol across a diverse range of chronic pain conditions, enhancing generalizability beyond previous studies that focus primarily on specific pain conditions.[25 27] Our data are derived from a ketamine clinic embedded within a multidisciplinary pain program, providing a snapshot of clinical practice. This pragmatic approach in a high-volume setting (>1000 infusions monthly) demonstrates how KIT can be effectively delivered in busy clinical environments while maintaining safety and high rates of treatment completion. Our study was conducted within a well-resourced multidisciplinary program at a large academic medical center as a part of routine clinical practice rather than under controlled trial conditions. Our hospital system is characterized by a population that is diverse in terms of socioeconomic status, and patients were not recruited for ketamine; rather, they were referred to our pain clinic for a full evaluation, and KIT was recommended only if the patients were deemed to be appropriate candidates. Therefore, our study reflects real-world patient populations and clinical workflows, with the potential to scale to other systems. While the Cleveland Clinic's CCPR is supported by institutional resources, the standardized low-dose ketamine infusion protocol we implemented relies on widely available medications, standard infusion equipment, routine monitoring procedures, and staffing models consistent with many outpatient infusion centers. With appropriate training and safety protocols, these elements could be adapted in health systems with varying levels of resources. Future studies should evaluate the feasibility, cost-effectiveness, and outcomes of implementing this protocol in community-based and resource-limited settings to ensure broader accessibility.

This study has several limitations. The lack of a control group limits comparison with other interventions and prevents accounting for placebo effects. Our pragmatic design resulted in variable PRO collection timeframes and suboptimal response rates (<50%), a common finding in clinical research.[28] The broad time windows for the 3-month and 6-month follow-up assessments (31–135 days and 136–240 days, respectively) may have reduced the accuracy of outcomes at these time points. Analyses revealed minimal differences between PRO completers and non-completers. To improve response rates in future studies, implementing reminder systems may be beneficial, as prior research has shown they can boost response rates to over 60%.[28] Self-report assessments introduce potential bias, and patients with positive outcomes may have been more likely to return for additional infusions, potentially overestimating ketamine's long-term effectiveness. While our study was large, 83.3% of participants were white, limiting generalizability. Integrating KIT within our multidisciplinary pain program makes it difficult to isolate ketamine's independent effects from concurrent therapies (physical therapy, psychology, preketamine SMA), though this may more accurately reflect real-world practice. Mixed-effects models adjusted for some factors (age, sex, race, comorbidities), but findings do not account for other potential confounders, including concurrent medications, psychological

Table 3 Changes in PROs from baseline to last infusion, 3-month, and 6-month follow-up

	Last infusion*		3-month follow-up†		6-month follow-up‡		P value from mixed-effects model§		
	N	Change scores mean±SD	N	Change scores mean±SD	N	Change scores mean±SD	Last infusion compared with baseline	3-month follow-up compared with baseline	6-month follow-up compared with baseline
PHQ-9¶	438	−1.3±4.8	492	−1.04±5.3	172	−0.87±4.9	*<0.001*	*<0.001*	*<0.001*
PROMIS Fatigue¶	361	−2.1±7.7	397	−1.9±8.1	108	0.07±7.7	*<0.001*	*<0.001*	0.32
PROMIS Social Role Satisfaction**	344	2.0±7.7	373	2.1±7.7	93	1.7±8.3	*<0.001*	*<0.001*	*0.002*
PROMIS Sleep Disturbance¶	72	−0.69±7.0	75	−0.09±9.5	33	3.0±9.4	*0.026*	0.20	0.95
PROMIS Pain Interference¶	372	−2.0±5.8	436	−2.0±6.6	132	−0.46±5.9	*<0.001*	*<0.001*	*0.027*
PROMIS Physical Function**	395	0.84±5.0	443	0.53±4.6	139	0.29±4.3	*<0.001*	*<0.001*	0.17
PROMIS Self-Efficacy for Managing Symptoms**	361	1.6±5.9	371	1.4±5.8	89	0.89±6.2	*<0.001*	*<0.001*	*0.018*
PROMIS Global Mental Health**	234	0.98±6.8	413	1.08±6.7	204	1.1±6.6	*0.004*	*<0.001*	*0.002*
PROMIS Global Physical Health**	237	1.2±5.3	407	1.3±5.5	200	0.93±5.9	*<0.001*	*<0.001*	*<0.001*
GAD-7¶	128	−1.04±4.4	141	−1.01±4.3	44	−0.14±5.2	*0.003*	*0.004*	0.34
PCS total¶	293	−5.2±9.6††	304	−3.8±9.5	58	−3.9±10.6	*<0.001*	*<0.001*	*<0.001*

Italics indicate statistical significance at $p < .05$.
*The last infusion follow-up was defined as the closest score within 30 days after the last ketamine infusion.
†The 3-month follow-up was defined as 31–135 days after the last ketamine infusion.
‡The 6-month follow-up was defined as 136–240 days after the last ketamine infusion.
§P values from mixed-effects linear regression models where time point was the independent variable, adjusted for age, sex, race, Charlson Comorbidity Index, and the number of ketamine infusion days.
¶The negative change score indicates improvement.
**The positive change score indicates improvement.
††Achieved an MCID.
.GAD-7, Generalized Anxiety Disorder-7; MCID, minimal clinically important difference; PCS, Pain Catastrophizing Scale; PHQ-9, Patient Health Questionnaire-9; PRO, patient-reported outcome; PROMIS, Patient-Reported Outcomes Measurement Information System.

comorbidities, or socioeconomic factors. Finally, the majority of outcome measures did not reach clinically meaningful thresholds despite statistical significance, though the high proportion reporting meaningful change in pain catastrophizing is promising given its predictive value of treatment response.[29] Future studies should examine outcomes by specific pain diagnoses, incorporate patient-reported impression of change measures, explore the synergistic contributions of behavioral interventions, and include diverse populations in controlled trial designs.

CONCLUSIONS

This is the first study to evaluate a standardized KIT protocol within a high-volume multidisciplinary pain center, demonstrating high treatment completion rates and sustained benefits lasting up to 6 months. Given the limited evidence for ketamine infusion protocols in chronic pain and existing access barriers, these real-world findings may help inform patients, payers, and healthcare systems about the potential of standardized KIT. Our detailed protocol provides a reproducible framework, with standardized dosing, monitoring, and safety measures serving as a blueprint for evidence-based program development. Our findings support integration into multidisciplinary pain centers and lay the groundwork for generating evidence needed for policy and coverage decisions. Further research should explore the biological, psychological, and mechanistic factors influencing ketamine's effects, as well as pretreatment predictors of response across pain subgroups. The implementation strategies described here also provide a foundation for comparative effectiveness research and randomized trials in diverse populations to further validate our protocol.

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