Instituto Universitário de Ciências Psicológicas, Sociais e da Vida

Ketamine-Assisted Psychotherapy in Real-World Setting: A Retrospective Observational Cohort Study

Mónica Sofia Ramalho Lopes Galo

Master Thesis Supervisor:

Professor Vitor Amorim Rodrigues

Master Thesis Co-Supervisor:

Professor Suzete Costa Duarte

Master Thesis Seminar Professor:

Professor Doctor Vitor José Amorim Rodrigues

Submitted as a partial requirement for obtaining the Master Degree:
Master in Clinical Psychology

2025

Master's Thesis submitted under Professor Victor Amorim Rodrigues supervision and Professor Suzete Costa co-supervision, presented at ISPA – Instituto Universitário to obtain the degree of Master in Psychology, specialization of Clinical Psychology.

Acknowledgements

I would like to express my heartfelt gratitude to my supervisors. To Professor Victor Amorim Rodrigues for his encouragement, trust and teachings that will remain far beyond this work is concluded. To Professor Suzete Costa Duarte for her invaluable guidance, thoughtful insights and continuous support that shaped this dissertation and helped me grow as a researcher.

To my dear friends, thank you for the laughter, the late-night talks, the music and (almost) loving the subject of this dissertation as much as I do. Your curiosity and willingness to learn and share added to the excitement of pursuing this work. Your cheering up and companionship made this experience lighter.

To my colleagues who made this academic journey more meaningful and richer. Your collaboration, shared experiences and words of encouragement created a fruitful learning environment I will always cherish. Thank you for reaching out and always being supportive.

To my family, to whom I am profoundly grateful for their love, patience, and understanding in the face of my absences. I am forever indebted to my life partner Paulo, my son António and my mother Aida. Your unwavering support has long been the foundation that lifts the weight through the most challenging moments. Your relentless optimism is the greatest gift facing the odds, and my endless source of courage. To my dear baby Tiago, who we are expecting within the next few days and has been the sweetest presence, a source of love and wonder, a delightful reminder of the spark of hope we all carry inside.

This work is as much yours as it is mine — thank you all for being part of it.

Abstract

Introduction: Despite ketamine-assisted therapy (KAP) becoming a promising intervention for depression, anxiety and other mental health conditions, empirical evidence from routine real-world settings remains limited.

Objectives: This study examines the effectiveness of a KAP program delivered in an outpatient clinic in Lisbon, by evaluating therapeutic primary and secondary patient outcomes measures (PROs).

Method: A real-world retrospective observational study was conducted to analyse data from 98 patients, to whom a KAP protocol was delivered as part of routine care for more than 2 years. Primary outcomes assessed changes in depressive symptoms, anxiety, and the patient's progress in psychotherapy, while secondary outcomes measured the overall daily functioning.

Results: Wilcoxon signed-rank test revealed that all primary and secondary outcomes were significantly lower at EoT when compared to the baseline ($p < .001$), with effect sizes between medium ($r = .386$) and large ($r = .585$). Multiple linear regression showed that age was the only factor predicting the PHQ-9 EoT scores ($p = .007$), while GAD-7 and OQ®-45.2 at EoT were influenced by the respective baseline scores ($p = .032$ and $p = .003$). Among the 68 (69.4%) patients who completed KAP protocol, *responder analysis* showed a clinically meaningful change of each primary outcome EoT score compared to the baseline, and *recovery* revealed reductions below clinical thresholds in depression, anxiety, and psychotherapy outcomes, alongside improvements in daily functioning.

Discussion: This study provides real-world evidence supporting the therapeutic value of a KAP in managing unmet clinical needs in depression and anxiety, and contributes to refine best practices, and inform treatment personalization of KAP interventions.

Keywords: ketamine, psychotherapy, depression, anxiety, real-world.

Resumo

Introdução: Apesar da psicoterapia assistida por cetamina (PAC) constituir uma intervenção promissora na depressão, ansiedade e outras condições em saúde mental, a evidência empírica de setting em contexto real mantém-se limitada.

Objetivos: Este estudo analisou a eficácia de um programa de PAC realizado numa clínica psiquiátrica em Lisboa, através da avaliação de outcomes terapêuticos primários e secundários.

Métodos: Foi realizado um estudo observacional retrospectivo em contexto naturalístico, no qual se analisaram os dados de 98 pacientes, aos quais foi aplicado um protocolo KAP como parte da intervenção de rotina realizada durante mais de 2 anos. Os outcomes primários avaliaram alterações nos sintomas depressivos, na ansiedade e na evolução da psicoterapia do paciente, enquanto os outcomes secundários avaliaram o funcionamento diário geral.

Resultados: O teste Wilcoxon signed rank revelou que todos os outcomes primários e secundários foram significativamente menores no final do tratamento (EoT) em comparação com a baseline ($p < .001$), com tamanhos de efeito entre médio ($r = .386$) e elevado ($r = .585$). A regressão linear múltipla mostrou que a idade foi o único fator que previu os pontuações de PHQ-9 no EoT ($p = .007$), enquanto o GAD-7 e o OQ®-45.2 no EoT foram influenciados pelas respectivas pontuações na baseline ($p = .032$ e $p = .003$). Entre os 68 (69,4%) pacientes que completaram o protocolo KAP, a *responder analysis* mostrou uma mudança clinicamente significativa em cada outcome primário no EoT em comparação com a baseline, e a *recovery* revelou reduções abaixo dos limiares clínicos de depressão, ansiedade e evolução da psicoterapia, juntamente com melhorias no funcionamento diário.

Discussão: Este estudo oferece evidências em contexto de *real-world* que apoiam o valor terapêutico de um PAC na gestão de necessidades clínicas não atendidas, na depressão e na ansiedade, e contribui para a definição de boas práticas e para a personalização do tratamento com psicoterapia assistida por cetamina.

Palavras-chave: cetamina, psicoterapia, depressão, ansiedade, real-world.

Table of Contents

Abbreviations

BMI: Body Mass Index

GAD: Generalized Anxiety Disorder

GAD-7: Generalised Anxiety Disorder Scale

ICE: Intercurrent events

IM: Intramuscular

IMA: Initial Medical Assessment

QR: Inter quartile range.

KAP: Ketamine-Assisted Psychotherapy

KSET: Ketamine Side Effect Tool

M: Mean

Mdn: Median

MDD: Major Depressive Disorder

RWE: Real World Evidence

OQ®-45.2: Outcomes Questionnaire 45.2

PHQ-9: Patient Health Questionnaire 9

PRO: Patient-Reported Outcomes

PROM: Patient-Reported Outcomes Measure

PTSD: Post-Traumatic Stress Disorder

SD: Standard deviation

TRDD: Treatment Resistant Depressive Disorder

WSAS: Work and Social Adjustment Scale

List of Tables

List of Figures

Introduction

Ketamine-assisted psychotherapy (KAP) represents an emerging and promising intervention, at the intersection of psychopharmacology and psychotherapy, as a new paradigm to manage complex and treatment-resistant mental health conditions. Understanding how KAP functions in real-world therapeutic contexts is essential for evaluating its clinical utility, optimizing treatment delivery, patient safety and efficacy.

Although ketamine is increasingly used in clinical practice, there remains a substantial gap in real-world evidence regarding its effectiveness, the most appropriate delivery models, and strategies for tailoring treatment to individual patients. This study aims to bring a significant contribution to fill in some of these gaps by systematically examining treatment outcomes within a naturalistic setting.

After years of use as an dissociative anaesthetic and analgesic, there is growing evidence of ketamine, a nonselective NMDA receptor antagonist, as a promising therapeutic option for treatment-resistant depressive disorder (TRDD; Gomes & Novais, 2025; Gregoire, 2025; Batievsky et al, 2023; Kew et al., 2023; Kopelman et al., 2023; Alnefeesi et al., 2022; Drozdz et al., 2022; Alnefeesi et al., 2022; Phillips, et al, 2019), including suicidal risk associated with major depressive disorder (MDD; Hartelius et al., 2023; Freind et al., 2024), recentely expanding to include conditions such as anxiety disorders, post-traumatic stress disorder (PTSD; Kew et al., 2023; Drozdz et al., 2022; Walsh et al., 2022; Greenway et al., 2020; Philipp-Muller et al., 2023; Albuquerque et al., 2022; Norbury et al., 2021; Feder et al., 2021; Halstead et al., 2021), eating disorders (Ragnhildstveit et al., 2022; Drozdz et al., 2022; Walsh et al., 2022), and alcohol addiction (Kew et al., 2023; Drozdz et al., 2022; Walsh et al., 2022; Kelson et al., 2023; Grabski et al., 2022; Dakwar et al., 2020), obsessive–compulsive disorder (OCD;) unresponsive to current treatments, while its application continues to expand, such as in substance use (Almog et al., 2025; Ware, 2024) or in postpartum depression disorder (Daghmouri et al., 2025).

These mental conditions are major health concerns with a severe burden of disease affecting the quality of life and productivity in Europe, as well as in Portugal (GBD, 2023; Sousa et al., 2022; Gonçalves-Pinho et al., 2022; Santos & Rachadell, 2022), requiring “Decisive, coordinated action is needed to address long-standing yet growing health challenges, including depressive and anxiety disorders” (GBD, 2023).

Different models have arisen with regards to ketamine use in mental health (Garet et al., 2025): i) biomedical model, where ketamine is administered at subanesthetic dosages (0.5 - 1-0 mg/kg), as a single or multiple dosage (often IM or IV), psychoactive effects are minimized and no accompaniment is required; ii) psychedelic model, where psychoactive effects determines the dosages (up to 4.0 mg/kg) and ketamine is administered in the presence of guides; iii) Montreal model, also with subanesthetic dosages (0.5 - 1-0 mg/kg), but where ketamine is administered with clinicians present as a psychotherapy enhancement agent with the framework of KAP (Nutt, 2024; Teixeira, 2024; Garet et al., 2025). While most pharmacological applications of ketamine fall under the framework of the biomedical model, in ketamine-assisted therapy (KAP) the subjective experiences of patients that arise from the ketamine use will be valued as psychotherapeutic elements (Figueiredo et al., 2023).

A KAP processes will typically consist of the following phases: preparation phase, when patient and therapist will meet to start co-constructing a therapeutic relationship; dosage administration, when ketamine is applied by an healthcare professional in a psychological safe setting; and integration phase, when the patient experiences and insights are reviewed with the therapists support and translated into psychological positive changes (Figueiredo et al., 2023); the pharmacological intervention is combined with the psychological support or the psychotherapy to enhance the therapeutic effects of ketamine (Muscat et al., 2021; Khalifian et al., 2024).

Study background

There is substantial research about the ketamine-assisted psychotherapy (KAP), including systematic reviews and clinical trials, in treatment-resistant depression (TRD; Gomes & Novais, 2025; Batievsky et al, 2023; Kew et al., 2023; Alnefeesi et al., 2022; Drozdz et al., 2022; Schimmers et al., 2022; Walsh et al., 2022; Conley et al., 2021; Greenway et al., 2020; Kopelman et al., 2023; Ahmed et al., 2023; Wilkinson et al., 2021; Basso et al., 2020; Phillips et al., 2020 Phillips et al., 2019), anxiety (Drozdz et al., 2022; Schimmers et al., 2022; Walsh et al., 2022; Greenway et al., 2020; Glue et al., 2020; Taylor et al., 2018), post-traumatic stress disorder (PTSD; Kew et al., 2023; Drozdz et al., 2022; Walsh et al., 2022; Greenway et al., 2020; Philipp-Muller et al., 2023; Albuquerque et al., 2022; Norbury et al., 2021; Feder et al., 2021; Halstead et al., 2021) eating disorders (Ragnhildstveit et al., 2022; Drozdz et al., 2022; Walsh et al., 2022) and alcohol addiction

(Kew et al., 2023; Drozdz et al., 2022; Walsh et al., 2022; Kelson et al., 2023; Grabski et al., 2022; Dakwar et al., 2020) unresponsive to current treatments.

The combined effect of ketamine and psychotherapy seems to enhance the benefits of the therapy for these conditions. A systematic review by Kew et al. (2023) outlined the heterogeneity of the published studies, impeding standardized report outcomes from these studies; nevertheless it suggested that the combination of psychotherapy and ketamine offers promise for the treatment of psychiatric disorders. The findings of a Phase II trial suggest a possible beneficial effect of adding psychological therapy alongside ketamine treatment (Grabski et al., 2022). Currently a Phase III clinical trial is ongoing for KAP use to reduce alcohol relapse (Kaar et al., 2023).

In Portugal, ketamine has also been used off-label in national health public-funded hospitals and private clinics (Figueiredo et al., 2023). Ketamine has also been prescribed and administered with psychotherapy for treatment-resistant depression, anxiety, post-traumatic stress disorder, eating disorders, and addiction, including alcohol use disorder, since July 2023, at a private clinic in Lisbon (The Clinic of Change), in patients who provided informed consent for off-label use. Off-label prescribing refers to the legally authorized prescription of an approved medicine for unlabeled use (e.g., indication, dose, population), which occurs almost without exception in an intended manner. Some of the most important reasons are related to the unmet medical needs in a certain therapeutic area, or for cases where the conventional therapy has failed (Rusz et al., 2021). It is also worth mentioning that off-label prescribing does not represent clinical research or experiments on humans of any kind (Rusz et al., 2021).

Regardless of the extensive research within clinical trials settings, real-world evidence (RWE) on ketamine-assisted psychotherapy is still rather scarce. Despite being used in Portugal under off-label use (Figueiredo et al., 2023), it is unknown that any KAP protocol has been studied within a naturalistic setting, treatment protocols have not been published and the outcomes from the application of these protocols remain unknown. We expect that this retrospective database cohort observational study may contribute to such evidence generation using secondary and anonymous (de-identified) patient data already collected in real-world routine clinical practice at a private outpatient psychiatric clinic in Portugal.

It is therefore the aim of this study to characterize a group of patients treated with a KAP protocol in a psychiatric outpatient clinic and evaluate the therapeutic outcomes following the treatment in this real-world/naturalistic setting.

The increasing relevance of patients' experiences at the core of the health care strategies, justifies the choice for focusing on patient-reported outcomes (PROs) and patient-reported outcomes measures (PROMs) in the present research (Weldring & Smith, 2013). A PRO is "directly reported by the patient without interpretation of the patient's response by a clinician or anyone else and pertains to the patient's health, quality of life, or functional status associated with health care or treatment" (*Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0*, 2011, cited by Weldring & Smith, 2013), while PROMs are "the tools and/or instruments that have been developed to ensure both a valid and reliable measurement of these patients-reported outcomes, such as quality of life measures." (Weldring & Smith, 2013). Including both PROs and PROMs in clinical research as well as in clinical practice offer a thorough comprehension about the impact of the treatment under evaluation on the patients.

The existing literature has been reviewed, and is presented in Appendix A, to identify key evidence about KAP programs, patient profiles and treatment outcomes, within the context of fast-moving psychedelic therapeutic application, especially those studies involving ketamine-assisted therapies in clinical trials and naturalistic settings.

Research Aims, Objectives and Questions

This study aims to investigate the effectiveness of a KAP program, when applied in an outpatient clinic in Lisbon (real-world setting), in reducing depression, anxiety and improving overall functioning, by evaluating therapeutic primary and secondary outcomes.

The findings from this study may provide valuable contributions to the evidence base regarding the efficacy of ketamine-assisted psychotherapy programs and support the development of refined clinical guidelines designed to optimize patient outcomes.

Considering the limited real-world investigation with ketamine assisted psychotherapy interventions, the following objectives are defined for this study: 1) To characterize the group of patients who underwent the KAP program at an outpatients psychiatric clinic in Lisbon, by describing their socio-demography and clinical characteristics, including primary and additional indications and symptoms severity; 2) To

describe the KAP program; 3) To evaluate patients' response to the KAP treatment for primary and secondary outcomes, before and after treatment; 4) To explore potential explanatory variables, age, sex at birth and baseline score, to predict the outcome of the KAP program at the end-of-treatment; 5) To assess the clinical significance of primary and secondary outcomes.

The research questions (Q), analytical approaches (A) and hypothesis (H) are:

Q1: What is the profile - demographic and clinical - of the patients who sought or underwent treatment with the KAP program at the Clinic of Change facilities?

A1: Descriptive statistics were applied to the full sample, consisting of means, medians, standard deviations, inter quartile ranges, minimum and maximum values, and percentiles were calculated for the quantitative variables; absolute and relative frequencies were calculated for categorical variables.

H1: Due to the exploratory nature of this objective, no hypothesis was anticipated.

Q2: How is the overall response of the patients to the KAP treatment protocol, both for primary and secondary outcomes. Primary outcomes include changes in scores from baseline to end-of-treatment (EoT) in depression symptoms using the Patient Health Questionnaire (PHQ-9), anxiety symptoms using the Generalized Anxiety Disorder (GAD-7) questionnaire, and psychotherapy outcomes using the Outcome-Questionnaire (OQ®-45.2) for all patients. Secondary outcomes include a change in score from baseline to EoT in work and social-related impairment using the Work and Social Adjustment Scale (WSAS).

A2: To compare the baseline and EoT scores, a parametric Paired T-Test or non-parametric Wilcoxon Signed Rank Test was planned as the statistical test, respectively, if the assumptions were or not met; in either cases, the effect size would also be estimated and Cohen's (1988) guidelines will be applied ($r = 0.10$, $r = 0.30$, and $r = 0.50$ to be considered small, medium, and large in magnitude, respectively; Gignac & Szodorai, 2016).

H2: It was hypothesized that there would be a statistically significant improvement of the primary - PHQ-9, GAD-7, and OQ®-45.2 - and secondary outcome - WSAS - at the EoT, when compared to the respective scores at the baseline, for a 95% significance level.

Q3: Can age, sex or the symptom severity from baseline score predict the patient's response to KAP treatment?

A3: A multiple linear regression analysis was conducted to examine whether age, sex at birth, and baseline score for each primary outcome - GAD-7, PHQ-9, and OQ®-45.2 - predicted the respective outcome score at the end-of-treatment (EoT).

H3: It was hypothesized that the symptom severity measured at the baseline would have a statistically significant influence on the symptom severity measured at the end of the KAP program, for a significance level of 95%. Due to the exploratory nature of this analytic approach, there were no specific hypotheses as to the pattern of change for age and sex.

Q4: Are there clinically meaningful changes in the treatment response for depression (PHQ-9), anxiety (GAD-9) and patients' overall functioning (OQ®-45.2)?

A4: To assess the meaningfulness of the changes between baseline and EoT scores, *responder analysis* and *recovery* were calculated. *Responder analysis*, defined by the proportion of patients with improvement at the EoT for each outcome, was examined using the meaningful change threshold (MCT), or an equivalent measure of the clinical significance, for each PRO: 6 or more points for PHQ-9 (Hudgens et al., 2021); 4 or more points for GAD-7 (Toussaint et al., 2020); 14 or more points for OQ®-45.2 (Beckstead et al., 2003); 8 or more points for WSAS (Zahra et al., 2014). Meaningful change thresholds (MCTs) are used to define what constitutes a clinically important difference in scores, signifying that an observed change is meaningful from the patient's perspective (Griffiths et al., 2021). *Recovery* is defined by the proportion of patients moving below the clinical threshold established for each PRO measure (Porter et al., 2024): PHQ-9<10 (Kroenke et al., 2001); GAD-7<8 (Spitzer et al., 2006); OQ®-45.2<64 (Beckstead et al., 2003); WSAS<20 (Zahra et al., 2014).

H4: It was hypothesized that, after the treatment completion (EoT), there would be a clinically significant improvement of the PROM, both using the responder analysis and the recovery criteria, for each of the primary and secondary outcomes.

Research significance

This research aims to generate practice-based insights to bridge the gap between experimental findings and applied psychological practice, strengthening the evidence surrounding the real-world application of KAP programs. The findings can inform evidence-based clinical guidelines, enhance practitioner competence, and support an ethical and effective integration of KAP into psychotherapeutic frameworks.

Methods

Study design

A non-interventional, retrospective database observational cohort study was performed using secondary data collection from a real-world routine clinical practice, at a private psychiatric outpatient clinic in Portugal, where a KAP program is offered to treat treatment-resistant health conditions, such as Depression and Anxiety. Patient-Reported Outcomes Measures (PROMs), used at the clinic as part of the standardized treatment protocols, were used to measure patients' mental health status at the baseline and end-of-treatment (EoT), as detailed in the variables section below. Additional information collected at the baseline during the intake procedures of the KAP program, were also used for the present study, to carry out a detailed demographic and clinical characterisation of the patients who sought treatment at the clinic.

Participants and eligibility criteria

The target population included all adult participants who provided written informed consent for the treatment and research purposes and were enrolled in the KAP program at the Clinic of Change (Lisbon), from July 2023 until database lock in October 2025 (cut-off date on 13-Oct-2015). As a retrospective secondary data collection study, from a naturalistic setting, no exclusion criteria were applied to the present study, in addition to those already resulting from the initial medical assessment (IMA), as part of the KAP protocol.

Clinical setting and KAP Protocol

The treatment protocol at the Clinic of Change, a private psychiatric outpatient facility located in Lisbon has been licensed by Awakn™, currently Solvonis Therapeutic Company, to use their proprietary copyright treatment protocols. Awakn™ clinical staff also trained and certified the clinical staff at The Clinic of Change to ensure standard procedures were applied. The program has operated since July 2023 under off-label use. At the Clinic of Change, generic ketamine is acquired, stored, prescribed and administered as part of KAP, to eligible and consenting patients previously diagnosed with treatment-resistant depression, anxiety, eating disorders, alcohol or other substance use disorders and post-traumatic stress disorder (PTSD). The exclusion criteria defined for KAP protocol are: patients under 18, reporting any active substance abuse, symptoms of psychosis, bipolar disorder, severe

personality disorder, schizophrenia, suicidal risk, or other severe psychiatric disorders, patients with serious comorbidities, uncontrolled hypertension or other severe cardiac disorders, previous negative reaction to ketamine, BMI <16 or >35 Kg/m2, currently pregnant or breastfeeding, intention of becoming pregnant in the following months, with compromised listening, reading or speech comprehension, or who could not or refused to provide written informed consent to the treatment and research.

The KAP protocol comprises 11 sessions (two for preparation, four ketamine treatment, four psychotherapy, and one final session), over the course of eight weeks; end-of-treatment (EoT) is defined as the date of visit 11 (V11) for KAP or intercurrent events (ICEs), defined by treatment discontinuation, disease progression, or death; the protocol also includes follow-up assessments at 3, 6, 9 and 12 months post-end of treatment, however these are out of scope of this study.

During the intake process, several data is collected as part of routine clinical care: socio-demographics and clinical information, medical and psychological history, and Patient-Reported Outcome Measures (PROMs) from validated public domain or licensed psychometric instruments which are then recorded in the electronic medical record via a licensed clinical software (iMED®). The intake involves pre-screening, a battery of patient self-reported measures, and an Initial Medical Assessment (IMA), performed by a psychiatrist, which includes the medical, physical and psychological present data and history, diagnosis, prescription of ketamine, and informed consent. This assessment process is used in the clinical decision-making and treatment planning (e.g. ketamine dosage), as well as a data setting at the baseline for comparison with EoT scores after the KAP program. Acquisition and storage of generic ketamine is in charge of a responsible pharmacist as per legislation. Ketamine is administered by a nurse.

During the sessions where ketamine is administered, patients are supported in a safe and comfortable environment while the medication is active. Following each ketamine session (preferably in the same week), where patients meet with their assigned psychotherapist for an integration session, discuss their ketamine experience, further explore and elaborate on the insights gained. A final session (session 11) should take place at the end of the program, expected around the 8th week, where self-reported measures are again solicited to patients, including the primary and secondary outcomes of the current study.

Variables

To describe the patients who were treated, the demographic variables used were age, sex at birth and body-mass index (BMI, calculated from weight and height), as well as the variables available from the clinical profile, such as, the primary and secondary psychiatric diagnosis, past psychiatric history, previous psychedelic-type adverse events, previous use of ketamine, substance abuse, suicidal ideation, at baseline.

To assess the KAP treatment outcomes, primary outcomes include changes in scores from baseline to EoT in depression symptoms using the *Patient Health Questionnaire* 9 (PHQ-9), in anxiety symptoms using the *Generalized Anxiety Disorder 7* (GAD-7) scale, and in psychotherapy outcomes using the *Outcomes Questionnaire®-45.2* (OQ®-45.2) scale. Secondary outcomes include a change in score from baseline to EoT in work and social-related impairment using the *Work and Social Adjustment Scale* (WSAS).

Materials

The following psychological instruments were applied as PROMs to measure PROs, before and after treatment with the KAP program: *Patient Health Questionnaire 9* (PHQ-9, Kroenke et al., 2001); *Generalized Anxiety Disorder 7* (GAD-7, Spitzer et al., 2006); *Outcomes Questionnaire®-45.2* (OQ®-45.2; Lambert et al., 1996); *Work and Social Adjustment Scale* (WSAS; Mundt at al., 2002). Additional instruments were part of the study, as they are applied at the baseline of the KAP program and will be assessed as part of the demographic and clinical characterization of patients who were treated at the clinic: *Montgomery-Åsberg Depression Rating Scale* (MADRS; Montgomery & Åsberg, 1979); *Ketamine Side Effect Tool - Screening and Baseline* (KSET; Short et al., 2020); *Alcohol Use Disorders Identification Test* (AUDIT; Babor et al., 1989).

The *Patient Health Questionnaire 9* (PHQ-9; Kroenke et al., 2001), also a self-reported questionnaire, consists of nine items measuring depressive symptoms corresponding to the diagnostic criteria for major depressive disorder, over the last 14 days. Each item is scored on a four-point Likert scale (from 0 “not at all to 3 “nearly everyday”), with total scores ranging from 0 to 27, with higher scores reflecting greater depression severity, representing mild 0–4, moderate 5–9, moderately severe 10–14, and severe 15–21 depression, respectively (Kroenke et al., 2001). PHQ-9 has shown good psychometric properties, with excellent internal consistency (Cronbach’s α = 0.86 - 0.89, Kroenke et al., 2001), confirmed by Monteiro et al. (2013) for the Portuguese PHQ-9 scale (Cronbach’s α =

0.86). Hudgens et al. (2021) estimated the meaningful change threshold (MCT) for PHQ-9 at 6 points.

The *Generalized Anxiety Disorder 7* (GAD-7; Spitzer et al., 2006) is a self-reported Lykert-type questionnaire, consisting of seven items used as a screening tool and a severity measure for patients with generalized anxiety disorder (Sousa et al., 2015). Each item asks patients how often they were bothered by each symptom, during the last 2 weeks, with response options from "not at all," "several days," "more than half the days," and "nearly every day," scored respectively as 0, 1, 2, and 3. With an excellent internal consistency (Cronbach's $\alpha = 0.92$), total scores range from 0 to 21, with higher scores reflecting greater anxiety severity, classified as none/normal 0–4, mild 5–9, moderate 10–14, and severe 15–21 (Spitzer et al., 2006). Sousa et al. (2015) confirmed the cultural adaptation into the Portuguese GAD-7 scale, allowing an early detection and treatment of affected patients (Cronbach's $\alpha = 0.88$). The minimal clinically important difference (MCID) was estimated at 4 points on the GAD-7 total score (Toussaint et al., 2020).

The *Outcomes Questionnaire-45.2* (OQ®-45.2; Lambert et al., 1996) is a 45-item self-report scale, designed to track and measure the client's progress in psychotherapy (e.g., pre- and post-treatment), and it is considered the gold standard for adult outcome assessment in global psychology research. It comprised three subscales (social role, symptom distress, and interpersonal relationships with items addressing common symptoms and problems (mostly depressive and anxiety-based) occurring in psychiatric disorders. Each item questions about the past 7 days and is rated using a 5-point Likert-type scale (from 0 "never" to 4 "always), with a total score from 0 to 180 (Beckstead et al., 2003). Stress levels are classified as low <64, moderate 64-82, moderately high 83-105 and high >105. Internal consistency values were found to be high for the original scale (Cronbach's $\alpha = 0.93$; Lambert et al., 1996), and good for the Portuguese version (Cronbach's $\alpha = 0.86$; Monteiro et al., 2013). The reliable change was estimated at 14 or more points (Beckstead et al., 2003).

The *Work and Social Adjustment Scale* (WSAS; Marks, 1986, cited by Mundt et al., 2002) consists of a 5 items self-report scale of functional impairment which can be attributed to a specific problem. It has been used in patients with depression and anxiety, to complement PHQ-9 and GAD-7 PROMs, due to WSAS distinct social component (Zahra et al., 2014). It is a Likert type scale on a 9-points (from 0 "not at all", to 8 "very severely"), with a total score from 0 to 40, below 20 scores being associated with subclinical population, 10-20 with significant functional impairment but less severe clinical symptoms, whereas above 20

suggests moderately severe or worse psychopathology. WSAS has shown a good internal consistency (Cronbach's α from 0.79 to 0.94; Mundt at al., 2002). Zahra et al. (2014) consider the minimum clinically significant change to be 8 points.

The *Montgomery-Åsberg Depression Rating Scale* (MADRS; Montgomery & Åsberg, 1979) is recurrently used in clinical trials as an outcome measure for depression, which is available in a 10 items clinician-rated version (MADRS; Montgomery & Åsberg, 1979) and 9 items patient-rated version (MADRS-S; Wikberg et al., 2016), measured on a 7-point Likert-scale, scored from 0 "absence of symptoms" to 6 "maximum presence of symptoms". Total scores ranging from 0 to 60 for MADRS version and 0 to 54 for MADRS-S, classified into 0-6 as normal/symptom-free, 7-19 as mild depression, 20-34 as moderate depression and 35-60 as severe depression. The KAP protocol only applies one specific item from the clinician version, questioning about suicidal thoughts, with a score ranging from 0 "enjoys life" to 6 "explicit plans for suicide; active preparations".

The *Adverse Childhood Experiences (ACE) Study Questionnaire* (ACE-Q; Felitti et al., 1998) is a 10-item measure originally developed by physicians from Kaiser Permanente from several previously researched assessment tools (Zarse et al., 2019). This 10-item questionnaire checks for the subject's recall of the first 18 years exposure to psychological, physical, and sexual abuse, as well as household dysfunction including domestic violence, substance use, and incarceration (Zarse et al., 2019). In 1996, surveys assessing current medical symptoms and past adverse experience were sent to a large sample of Kaiser patients. It was from this sample that the seminal ACE-Q study was published. The results from this questionnaire will only be used in the present study as a measure to characterise the patients who were treated with the KAP program (but not as a PRO nor assessment of KAP).

The *Ketamine Side Effect Tool* (KSET; Short et al., 2020) was developed to capture baseline acute and longer-term side effects associated with repeated ketamine (or its derivatives) treatments and standardizes safety monitoring in psychiatry. A set of forms were developed by Short et al. (2020) to monitor side effects across a course of treatment, at different time points: screening, baseline, immediately after a single treatment (acute), and longer-term follow-up (none of these replaces a thorough patients' psychiatric and physical examination). It has two main components, implemented across the four modules: a set of questions relating to potential side effects (SEs) from a ketamine treatment course (clinician or self-rated) and a safety framework including cardiovascular monitoring, orientation and discharge checklists, investigations (e.g. urinalysis) and recommendations for use of

additional validated scales (e.g. cognitive measures). The KAP protocol applies the KSET Screening and Baseline modules at the IMA, which examines symptoms prior to ketamine commencement and vital signs (e.g., blood pressure, pulse, oxygen saturation). The screening module presents 14 Yes/No items enquiring patients about medical conditions that are known to increase the risk of adverse effects with ketamine treatment plus two additional items for female patients assessing pregnancy and breastfeeding status. It also elicits information about prior experience with ketamine. The baseline module presents 19 Likert-type items to be completed by the clinicians as the patient is asked about potential symptoms which may emerge during ketamine treatment experienced in the previous month before commencing ketamine treatment. Each item is scored from 0 "never" to 3 "severe", with a total score from 0 to 57. It also includes one additional item to record other symptoms, not scored. In the present study, results from the KSET screening and KSET baseline have been used as a measure to characterise patients at baseline.

The *Alcohol Use Disorders Identification Test* (AUDIT; Babor et al., 1989) is a 10-item screening tool developed by the World Health Organization (WHO) to assess alcohol consumption, drinking behaviors, and alcohol-related problems. It comprises a clinician-administered version and a self-report version of the AUDIT. Each question is scored from 0 to 4, with the exception of questions 9 and 10 which have possible responses of 0, 2 and 4. The total score ranges from 0 to 40, where 0 indicates an abstainer who has never had any problems from alcohol, 1 to 7 suggests low-risk consumption, 8 to 14 suggests hazardous or harmful alcohol consumption and 15 or more indicates the likelihood of alcohol dependence (moderate-severe alcohol use disorder). Results from the AUDIT at baseline, already available from KAP protocol records, have been used as a measure to characterise patients at baseline.

Blood pressure, pulse, oxygen saturation, adverse event monitoring, and overall status are measured pre, during and post each ketamine session and recorded by the nurse in the nurse paper-based record, not available in time for the current study.

Procedure

Data collection

Ethics approval for this study was obtained from The Clinic of Change Ethics Committee on the 8th August 2025, to perform secondary data collection on de-identified patient data extracted from the electronic medical records (iMED© V4.27.0, license no.

6/2011 by ACSS, certified ISO 9001 and ISO 27001, and compliant with the General Data Protection Regulation (GDPR)). De-identified data was extracted under supervision of the Data Protection Officer, exported to MS Excel file and included demographics (age, sex at birth), clinical and psychological history, Initial Medical Assessment (IMA) including KSET Screening, KSET Baseline score and MADRS suicidal question score, AUDIT baseline score, ACE-Q baseline score, treatment status, baseline date for all patients, and end of treatment date for those patients who have completed the KAP treatment, as well as baseline and treatment primary and secondary outcomes scores - PHQ-9, GAD-7, OQ®-45.2 and WSAS - for patients who have provided the questionnaires at the end-of-treatment..

Data management and quality control

After receiving the anonymized patient data, where needed, data was recoded (e.g. Female = 0 and Male = 1), transformed (e.g. calculations made for BMI, duration of treatment), and quality control was performed for completeness (checking for missing values, and performing calculation where such as number of sessions, when missing). Data were also reviewed for accuracy (verifying accurate representation of the described parameter), consistency (checking for formatting synchronization across data sets), validity (checking for impossible values), and uniqueness (identifying duplicates or overlaps) in collaboration with the clinical staff and supervisor and cosupervisor. After completion and corrections, the final database was imported to a data analysis software (IBM® SPSS® Statistics v30.0).

Data analysis

The full data set included all patients who provided informed consent, with Initial Medical Assessment, demographic data, and who had initiated the KAP treatment protocol, defined by having at least one primary or secondary outcome variable at baseline. This full data set was used for descriptive analysis.

The subset of individuals who completed the 11 KAP sessions and provided both baseline and end of treatment scores for at least one primary outcome was used to assess mean change from baseline and is referred to as “paired data set”.

The subset of individuals from the full sample size who included eligible patients, that is, patients with an end of treatment date completed or planned before database lock and with at least one score, regardless of whether completing treatment, withdrawing, or lost to follow up (intention to treat approach) was used to conduct a multiple linear regression, following

the intention-to-treat approach. This subset excluded patients who were still ongoing treatment at database lock date.

Descriptive analysis at baseline was used to summarize: 1) patient disposition (defined as the number (n) and proportion (%) of patients in treatment flow, from eligible patients to patients completing the end of treatment); 2) completion rates (defined as the ratio of patients with a PROM score, who are expected to have a PRO at the time point); 3) patient demographics and clinical data at baseline, including primary and secondary diagnosis, KSET Screening, prior history of drug use, 4) mean (and SD) duration of treatment, 5) baseline scores for AUDIT, ACE-Q, KSET Baseline, and MADRS suicidal question, and 6) baseline and end of treatment scores for PHQ-9, GAD-7, OQ®-45.2, and WSAS. Descriptive analysis included statistical measures as mean (*M*), standard deviation (*SD*), median (*Mdn*), inter-quartile range (*IQR*), maximum, and minimum for numerical data, and absolute (n) and relative (%) frequencies for categorical data.

Group-level analysis was used to test the primary hypothesis (H2): a comparative within-subject analysis was performed between the baseline PRO and the End-of-Treatment (EoT) scores for GAD-7, PHQ-9, OQ®-45.2, and WSAS, using non-parametric Wilcoxon signed-rank test due to the non continuous nature of the PRO scales (Wu & Leung, 2017; Jamieson, 2024).

We also conducted multiple linear regression analyses to confirm significance while controlling for covariates, after assessing all standard assumptions - linearity, multicollinearity, independence of residues, homoscedasticity, normality of residuals - and the presence of outliers - either by visual inspection (from scatterplots, residual plots, and P–P plotS) or diagnostic statistics in SPSS (Variance Inflation Factor values and tolerance levels to check for the absence of multicollinearity; Durbin–Watson statistic).

We handled missing values by comparing multiple linear regression results using pairwise deletion (using all available cases for analysis) and listwise deletion (using complete cases only for analysis).

Individual-level analyses included the estimation of *Responder analysis and Recovery*. *Responder analysis* is defined by the proportion of patients with improvement at the EoT (having MCT as the reference of a reliable improvement) and was examined by comparing the mean change from baseline scores with the meaningful change threshold (MCT), or an equivalent measure of the clinical significance, for each PRO (for PHQ-9 defined by Hudgens et al., 2021; for GAD-7 estimated as the minimal clinically important

difference by Toussaint et al., 2020; for OQ®-45.2 estimated as the reliable change by Beckstead et al., 2003; for WSAS estimated as the minimum clinically significant change by Zahra et al., 2014). *Recovery* is defined by The National Health Service (NHS) England's Improving Access to Psychological Therapies (IAPT) programme, cited by Porter et al. (2024), as the proportion of patients moving from caseness (PHQ-9≥10; GAD-7≥8; OQ®-45.2≥64; WSAS≥ 20) to recovered (PHQ-9<10; GAD-7<8; OQ®-45.2<64; WSAS<20) for each PRO measures; *Recovery* was examined by comparing the EoT score for each PRO with the respective scale clinical threshold (for PHQ-9 defined by Kroenke et al., 2001; for GAD-7 defined by Spitzer et al., 2006; for OQ®-45.2 defined by Lambert et al., 1996; for WSAS defined by Mundt at al., 2002).

All statistical tests were two-tailed, considering a significance level of 0.05. IBM® SPSS® Statistics v30.0 was used for statistical analyses.

Results

Descriptive statistics

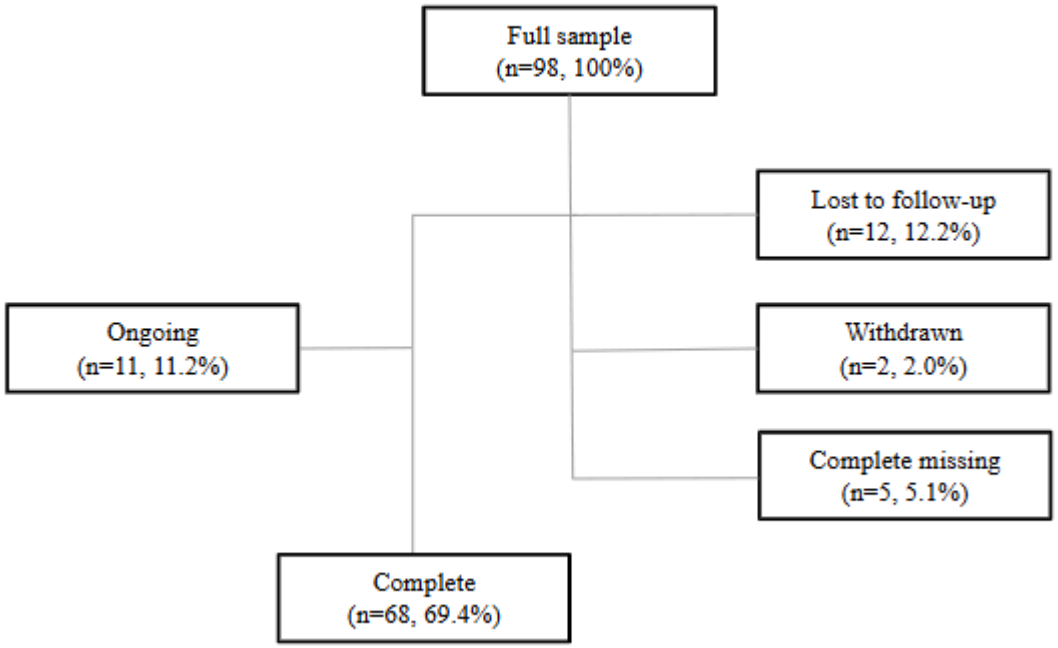
Patient disposition.

Disposition refers to adherence, attrition, and loss to follow up, including reasons for missingness. Figure 1 presents the flow of patients treated with the KAP program, since treatment eligibility was confirmed and informed consent signed, corresponding to the original dataset and full sample size (N=98, 100%) for this study.

Complete status refers to patients who completed the 11 sessions included in the full KAP program. Ongoing refers to patients who initiated the treatment but had not completed at database lock date. Lost to follow-up refers to patients who repeatedly fail to return for scheduled appointments.Withdrawn refers to patients withdrawn from the treatment at any time at the discretion of the psychiatrist for safety, behavioral, or compliance reasons or to patients who withdraw consent from the treatment at any time at request. Complete missing refers to patients who completed the KAP program but have not completed the questionnaires at baseline and at the end-of-treatment.

Figure 1

Diagram with the flow of patients treated with the KAP program.



Note. Initial sample size (n=98) used as the denominator for all relative frequencies.

Completion rate

Completion rate is defined by the ratio of patients with a PRO score who are expected to have a PRO at the time point. The completion rates for the PRO measures used at the practice is presented in Table 1. This includes completion rates at baseline for PRO measures used at baseline only, as well as completion rates for both baseline and end of treatment for PRO measures capturing primary outcomes.

From the group of patients who started the KAP program, 88 (89.8%) have completed all PRO measures at the baseline. Regarding completion of PRO measures at the EoT, 54 patients have completed, corresponding to 79.4% of the patients who completed the KAP program; overall completion rates of PRO measures at both baseline and EoT was 51 patients, corresponding to 75.0% of the patients who completed the KAP program.

Baseline scores for primary outcomes demonstrate the severity of patients when initiating treatment with PHQ-9 moderately severe, GAD-7 moderate, OQ®-45.2 moderately high; and WSAS moderately severe scores. Patients enrolled in KAP also present a mean low risk score for alcohol-related problems (AUDIT), low to moderate adversity score for adverse childhood experiences (ACE-Q), low risk (0.3, 17 of 57) for potential symptoms which may emerge during ketamine treatment experienced in the previous month before commencing ketamine treatment, and a low risk for suicide.

Table 1

Completion rates and summary of descriptive statistics of the questionnaire measures.

Outcomes measure	Completion rate *(%)*[a]	Count (*n*)	*M (SD)*	*Mdn (IQR)*
Baseline				
PHQ9_Baseline	99.0%	97	16.67 (6.342)	17.00 (11.00 - 22.00)
GAD7_Baseline	99.0%	97	14.22 (5.506)	15.00 (11.00 - 19.00)
OQ®45.2_Baseline	92.9%	91	96.60 (24.906)	99.00 (86.00 - 111.00)
WSAS_Baseline	96.9%	95	24.01 (10.859)	26.00 (16.00 - 33.00)
AUDIT_Baseline	93.9%	92	6.29 (7.878)	3.00 (1.00 - 10.00)
ACE_Baseline	80.6%	79	2.81 (2.293)	2.00 (1.00 - 4.00)
KSET_Baseline	83.7%	82	17.11 (8.000)	17.00 (11.00 - 21.25)
MADRS_Baseline[b]	96.7%	85	1.41 (1.408)	1.00 (0.00 - 2.00)

End-of-Treatment (EoT)				
PHQ9_EoT	89.7%	61	7.43 (6,187)	6.00 (2.00 - 11.50)
GAD7_EoT	83.8%	63	6.54 (5,722)	5.00 (2.00 - 11.00)
OQ®45.2_EoT	86.8%	59	56,73 (29,052)	60.00 (29.00 - 79.00)
WSAS_EoT	83.8%	57	15,12 (11,193)	14.00 (5.00 - 24.00)

Note. *M*=mean; *Mdn*=median; *SD*=standard deviation; *IQR*=inter quartile range.

[a] Completion rate was determined using the initial sample size (n=98) as the denominator to calculate completion at the baseline; for end-of-treatment, the denominator used was the subset of patients who completed KAP (n=68).

[b] MADRS_Baseline only refers to the question about suicidal thoughts.

Demographic and Clinical characteristics

The original cohort consisted of 98 patients, aged between 19 and 76 years old, with a mean of 43.2 years (SD=11.46), with equally distributed sex at birth (n=50; 51.0% females and n=48; 49.0% males). The two most common psychiatric diagnoses within the full dataset of patients were depression disorders (n=62; 63.3%) and anxiety disorders (n=29; 29.6%), followed by eating disorders (n=3; 3.1%) and others (n=4; 4.0%). KSET screening indicates a low proportion of patients with medical conditions that are known to increase the risk of adverse effects with ketamine treatment. MADRS score (for suicidal question) shows >68% patients with low risk (0-2) for suicide. A detailed demographic and clinical characterization of the patients who were treated with the KAP program is described in Table 2.

Table 2

Demographic and clinical characteristics of patients treated with the KAP program.

	N (%)	***M (SD)***	***Mdn (IQR)***
Demographic characteristics			
Age	98 (100%)	43.15 (11.455)	44.00 (34.00 - 52.00)
Sex at birth - female	50 (51.0%)		
BMI	74 (75.5%)	32,449 (14,577)	31,08 (21.611 - 40.960)
Clinical characteristics			
Primary psychiatric indication			
Depression disorder	62 (63.3%)		
Anxiety disorder	29 (29.6%)		
Eating disorder	3 (3.1%)		

Anxiety and depression disorder	1 (1.0%)
Substance use disorder	1 (1.0%)
Alcohol use disorder	1 (1.0%)
PTSD	1 (1.0%)
Secondary psychiatric indication	
None	40 (40.8%)
Depression disorder	19 (19.4%)
Anxiety	16 (16.3%)
Anxiety co-morbid with eating disorder, burnout, PTSD, substance use disorder	5 (5.1%)
PTSD	5 (5.1%)
Alcohol use disorder alone or co-morbid with depression, anxiety, substance use disorders	5 (5.1%)
Eating disorder	3 (3.1%)
Substance use disorder	3 (3.1%)
Depression co-morbid with OCD	1 (1.0%)
KSET Screening	
Hallucinations	13 (13.3%)
High irritable mood	31 (31.6%)
Dissociation induced by drug substances	13 (13.3%)
Dissociation NOT induced by drug substances	17 (17.3%)
Hypertension	6 (6.1%)
Heart/Cardiovascular disease	2 (2.0%)
Convulsion, stroke, head trauma or neurological pathology	2 (2.0%)
Glaucoma	1 (1.0%)
Liver disease	5 (5.1%)
Kidney disease	2 (2.0%)
Bladder urinary problems	9 (9.2%)
Alcohol or substance abuse	31 (31.6%)
Chronic pain	23 (23.%)
Memory and/or concentration problems	67 (58.4%)
Experience with clinical ketamine	4 (4.1%)
Substance use in the previous 30 days[a]	66 (67.3%)
History of dependence to drugs (other than ketamine)	24 (24.5%)
History of IV drug use	2 (2.0%)
History of service entries due to use of substances	4 (4.1%)

MADRS - clinical assessment of suicidality (suicidal thoughts risk score 0-6)[b]	
0	31 (31.6%)
1 - 2	36 (36.7%)
3 - 4	16 (16.3%)
5 - 6	2 (2.0%)

Note. *M*=mean; *Mdn*=median; *SD*=standard deviation; *IQR*=inter quartile range.

[a]Substances reported include alcohol, amphetamines, benzodiazepines, cannabinoids, cocaine, MDMA, opiates, psilocybin.

[b] Suicidal risk score for 54 (55.1%) patients was 1 or above.

Patient treatment characteristics

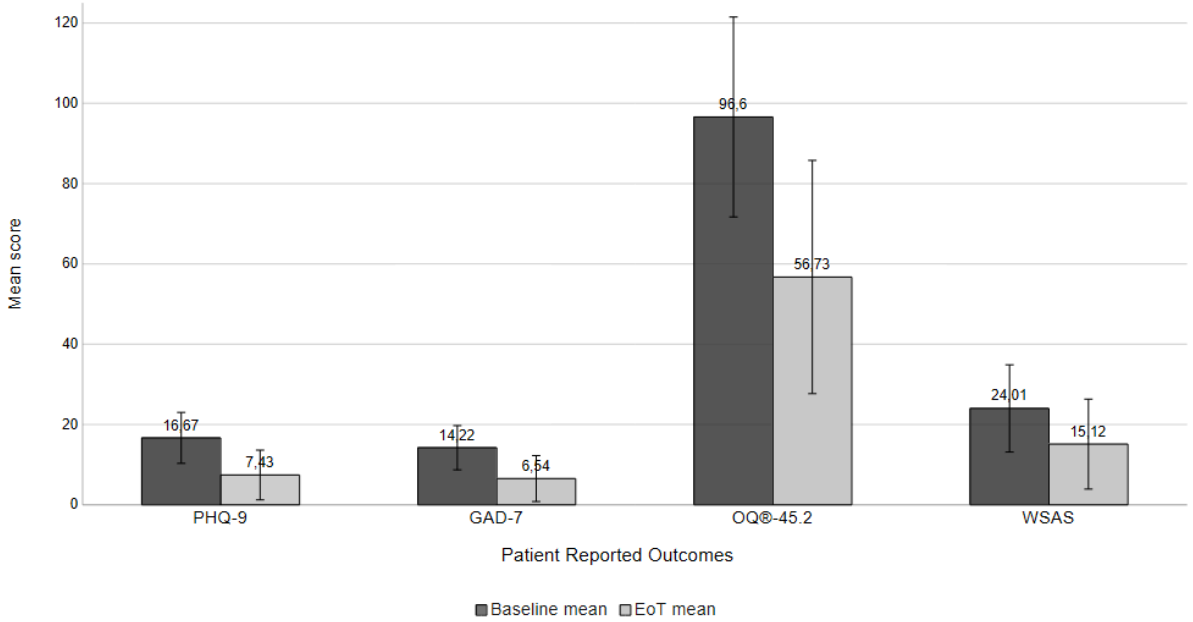
The treatment duration and the number of the sessions undertaken by each patient, for the full data set of patients (*n*=98; 100%), had a mean duration of 66.74 days (*SD*=37.890), which varied between 14 and 229 days; the total number of sessions had a mean of 10.18 (*SD*=2.049), which varied between 3 and 11. When considering the subset of patients who completed the program (*n*=68; 69.4%), the duration of treatment and the number of sessions slightly increases to 67 days (*SD*=37.563) and 11 sessions (*SD*=0.000), respectively.

PRO mean scores and severity at baseline and end of treatment

Figure 2 represents the mean score (and respective SDs) at baseline and at EoT for each PROM - PHQ-9, GAD-7, OQ®-45.2, and WSAS. For all PROMs, there was a decrease in the measured score. Regarding primary and secondary outcomes, all scores have decreased in severity: PHQ-9 from moderately severe (*M*=16.67; *SD*=6.342) to mild score (*M*=7.43; *SD*=6.187), GAD-7 from moderate (*M*=14.22; *SD*=5.506) to mild score (*M*=6.54; *SD*=5.722), OQ®-45.2 from moderately high (*M*=96.6; *SD*=24.906) to low score (*M*=56.73; *SD*=29.052); and WSAS from moderately severe (*M*=4.01; *SD*=10.859) to significant functional impairment score (*M*=15.12; *SD*=11.193).

Figure 2

Patient Reported Outcome mean scores at baseline and end of treatment.



Note. Bars represent mean scores of the PHQ-9, GAD-7, OQ®-45.2, and WSAS at baseline which decrease at the end of treatment. Error bars indicate the standard deviation.

Group-level analysis

Longitudinal analysis of change from baseline PRO scores.

Changes in PRO score, from baseline to EoT, were analysed with a 95% confidence interval, using the non-parametric Wilcoxon's Signed Rank Test. The results, described in Table 3 and 4, show that there is a statistically significant change from the score at baseline and EoT, for all PROs.

Table 3

Descriptive statistics of the paired scores from baseline to end of treatment scores.

Outcomes measure	Count (n)	*M (SD)*	*Mdn (IQR)*
PHQ-9			
PHQ9_Baseline	61	16.56 (6.331)	17.00 (11.00 - 21.50)
PHQ9_EoT	61	7.43 (6,187)	6.00 (2.00 - 11.50)
GAD-7			
GAD7_Baseline	62	14.37 (5.837)	16.00 (10.75 - 20.00)

GAD7_EoT	62	6.60 (5,750)	5.00 (2.00 - 11.00)
OQ®-45.2			
OQ®45.2_Baseline	55	97.91 (23.194)	102.00 (91.00 - 111.00)
OQ®45.2_EoT	55	56,89 (29,736)	60.00 (29.00 - 82.00)
WSAS			
WSAS_Baseline	57	22.91 (11.107)	25.00 (16.50 - 31.50)
WSAS_EoT	57	15,12 (11,193)	14.00 (5.00 - 24.00)

Note. *M*=mean; *Mdn*=median; *SD*=standard deviation; *IQR*=inter quartile range.

Table 4

Wilcoxon signed rank test statistics of the paired scores from baseline to end of treatment.

Outcomes measure	**Count (n)**	**z**[a]	**p-value**[b]	**Effect size**[c] **(*r*)**
PHQ9_EoT - PHQ9_Baseline	61	-6.092	< .001	.553
GAD7_EoT - GAD7_Baseline	62	-5.935	< .001	.533
OQ®45.42_EoT - OQ®45.42_Baseline	55	-6.138	< .001	.585
WSAS_EoT - WSAS_Baseline	57	-4.125	< .001	.386

Note. [a] z: standardized test statistics; [b] Asymp. Sig. (2-tailed); [c]Effect size calculated as $z/\sqrt{N}$ (Pallant, 2007).

A comparative *within-subject analysis,* performed using Wilcoxon signed rank test, revealed that primary outcomes - PHQ9, GAD7, OQ®45.2 - scores were significantly lower at the end of the KAP treatment (PHQ9_EoT: *Mdn* = 7.43, *n* = 61; GAD7_EoT: *Mdn* = 6.64, *n* = 62; OQ®45_EoT: *Mdn* = 56.89, *n* = 55), when compared to the respective pair before KAP treatment, (PHQ9_Baseline: *Mdn* = 16.56, *n* =61; GAD7_Baseline: *Mdn* = 14.37, *n* = 62; OQ45_Baseline: *Mdn* = 97.91, *n* = 55), being the respective test statistics, p values and effect sizes: PHQ-9 z = -6.092, p <.001, with a large effect size, r = .553; GAD-7 z = -5.935, p < .001, with a large effect size, r = .533; OQ®45.2 z = -6.138, p < .001, with a large effect size, r = .583 (Cohen, 1988; Gignac & Szodorai, 2016).

Similarly, the secondary outcomes variable score - WSAS - was also significantly lower at the end of the KAP treatment (WSAS_EoT: *Mdn* = 15.12, n = 57), when compared to the baseline (WSAS_baseline: *Mdn* = 22.91, *n* =57), with z = -4.125, p < .001, with a medium effect size, r = .386 (Cohen, 1988; Gignac & Szodorai, 2016).

The statistical significance observed using the bivariate analysis indicates improvement for all outcome measures.

Multiple linear regression predicting EoT PRO scores

A multiple linear regression model was conducted to confirm statistical significance while controlling for covariates, including baseline primary outcome scores and assess whether age, sex at birth and the baseline score of a primary outcomes variable could predict or explain a significant amount of the variance of the outcome variable at the end-of-treatment.

Prior to conducting the multiple linear regression analyses, all relevant statistical assumptions were examined: **i) Linearity.** Inspection of scatterplots and partial regression plots indicated that continuous predictors (age and score at the end-of-treatment) demonstrated linear relationships with the dependent variable (respective score at the baseline). Categorical predictors were dummy coded (sex female=0; male=1), and thus the linearity assumption did not apply. **ii) No multicollinearity.** Pearson's correlation matrix showed that correlations between any of the tested independent variables were low (ranging from r = .25 - .354), Variance Inflation Factors (VIFs) were below 10 (ranging from 1.000 to 1.179), and all tolerance values were above 0.6 (ranging from .848 to 1.000), suggesting that multicollinearity was not a concern. **iii) Independence of residuals.** The Durbin–Watson statistics values for each test were around 2 (between 1.964 and 2.129), suggesting that residuals were independent and that the assumption of independence was satisfied. **iv) Outliers and Influential Cases.** Standardised residuals were within ±3 (ranging from a minimum of -1.581 and a maximum of to 2.185), suggesting no influential outliers were present. **v) Homoscedasticity.** Visual inspection of standardized residuals plotted against predicted values (scatter plots) revealed no clear pattern or funnel shape, indicating that the assumption of homoscedasticity was met. **vi) Normality of Residuals.** Examination of the histogram and normal P–P plot of standardized residuals showed an approximately normal distribution of residuals, for each outcome variable.

The multiple linear regressions conducted to determine whether age, sex and each baseline score predicted each EoT score, showed that the three predictors jointly not always explain a significant portion of the respective outcome score at the EoT.

To explore better adjusted models, a multiple linear regression using the stepwise method was performed for each outcome, choosing the best predictor(s) and removing the ones that did not show a significant contribution to the model. Adjusted models are shown to be statistically significant, as presented in Tables 5-7.

Age is the only factor significantly influencing the PHQ-9 EoT score. The other variables in the model (sex and baseline score) do not have any significant influence in explaining the PHQ-9 EoT score. The regression coefficient (*B*) for age is -0.181 (95% CI: -0.310 to -0.053). This indicates that the average decrease in PHQ-9 EOT score is 0.18, if the age increases by 1 after adjusting for all other variables (PHQ-9 baseline score, age and sex) in the model. The R-square value of 0.119 indicates that the independent variable age alone explains 11.9% variation in PHQ-9 EOT score, which is statistically significant (p = .007). See Table 5.

The GAD-7 baseline score is the only factor significantly influencing the GAD-7 EoT score. The other variables in the model (age and sex) do not have any significant influence in explaining the GAD-7 EoT score. The regression coefficient (*B*) for GAD-7 baseline score is 0.276 (95% CI: 0.025-0.527). This indicates that the average decrease in GAD-7 EOT score is 0.28, if the GAD-7 baseline score decreases by 1 after adjusting for all other variables (GAD-7 baseline score, age and sex) in the model. The R-square value of 0.074 indicates that the independent variable GAD-7 baseline score alone explains 7.4% variation in GAD-7 EOT score, which is statistically significant (p = .032). See Table 6.

Similarly, the OQ®-45.2 baseline score is the only factor significantly influencing the OQ®-45.2 EoT score. The other variables in the model (age and sex) do not have a significant influence in explaining the OQ®-45.2 EoT score. The regression coefficient (*B*) for OQ®-45.2 baseline score is 0.462 (95% CI: 0.168-0.755). This indicates that the average decrease in OQ®-45.2 EOT score is 0.46, if the OQ®-45.2 baseline score decreases by 1 after adjusting for all other variables (OQ®-45.2 baseline score, age and sex) in the model. The R-square value of .158 indicates that the independent variable OQ®-45.2 baseline score alone explains 15.8% variation in OQ®-45.2 score, which is statistically significant (p = .003). See Table 7.

The results presented used the pairwise deletion method. When using listwise deletion, the regression coefficients (*B*) for primary outcomes baseline score (PHQ-9, GAD-7 and OQ®-45.2) are similar. Since both methods yield similar results, we used the pairwise

deletion to minimize the loss incurred by listwise deletion and increase the power of regression analysis. These results confirm statistical significance in the improvement of EoT primary outcomes when controlling for covariates and indicate that, within the KAP program, the respective baseline scores contributed significantly to treatment outcomes for GAD-7 and OQ®-45.2, while age significantly contributed to treatment outcomes for PHQ-9. However, sex alone did not appear to be a relevant predictor for any of the considered primary outcomes.

Table 5

Summary of the adjusted multiple linear regression predicting PHQ-9 EoT score.

Variables	Regression coefficient (*B*)[a]	Coefficient *SE*[b]	95% CI[c]	p-value[d]
Constant	15.274	2.882	[9.508, 21.040]	<.001
Age	-0.181	.064	[-.310, -.053]	.007

Note. R^2 = .119, $F(1,59)$ =7.957, N = 60.

[a]B=Unstandardized coefficient; [b]SE=Standard error; [c]CI=Confidence interval; [d]95% significance.

Table 6

Summary of the adjusted multiple linear regression predicting GAD-7 EoT score.

Variables	Regression coefficient (*B*)[a]	Coefficient *SE*[b]	95% CI[c]	p-value[d]
Constant	2.581	1.936	[-1.293, 6.454]	.188
GAD-7 Baseline score	0.276	.126	[.025, .527]	.032

Note. R^2 = .074, $F(1,60)$ = 4.819, N = 61.

[a]B=Unstandardized coefficient; [b]SE=Standard error; [c]CI=Confidence interval; [d]95% significance.

Table 7

Summary of the adjusted multiple linear regression predicting OQ®-45.2 EoT score.

Variables	Regression coefficient (*B*)[a]	Coefficient *SE*[b]	95% CI[c]	p-value [d]
Constant	12.603	14.447	[16.374, 41.580]	.387
OQ®-45.2 Baseline score	0.462	.146	[.168, .755]	.003

Note. R^2 = .158, $F(1,53)$ = 9.957. N = 54.

[a]B=Unstandardized coefficient; [b]SE=Standard error; [c]CI=Confidence interval; [d]95% significance.

Individual-level analysis

Responder analysis, defined by the proportion of patients with improvement at the EoT for each outcome, was examined using the meaningful change threshold (MCT), or an equivalent measure of the clinical significance, for each PRO, as presented in Table 8. The mean change from baseline largely exceeds the meaningful change threshold (or equivalent measure) for each primary outcome; for secondary outcome WSAS, the mean change was close to the MCT.

Additionally, responder ratios for all primary outcomes combined was estimated at 61.8% (n=34), meaning that more than half of the patients who completed the KAP program improved in all primary measures (GAD-7, PHQ-9 and OQ®-45.2); the responder ratio for all PROMs, primary and secondary combined, was 38.2% (n=21).

Table 8

Mean change score versus meaningful change threshold (or equivalent) and respective Responder analysis.

Outcomes measure	Count (n)	Mean (SD)	MCT	Responder analysis[e]
PHQ9_Change	61	-9,13 (7.743)	6 or more[a]	68.9%
GAD7_Change	62	-7.77 (6.988)	4 or more[b]	67.7%
OQ®-45.2_Change	55	-41,02 (29.558)	14 or more[c]	81.8%
WSAS_Change	57	-7.79 (13.437)	8 or more[d]	49.1%

Note. SD=standard deviation; MCT meaningful change threshold or an equivalent measure of the clinical significance of an outcome score change.

[a]Estimated by Hudgens et al. (2021); [b]Estimated as the minimal clinically important difference (MCID) by Toussaint et al.(2020); [c]Estimated as the reliable change by Beckstead et al.(2003); [d]Estimated as the minimum clinically significant change by Zahra et al. (2014); [e]Count as denominator.

Recovery, defined by The National Health Service (NHS) England's Improving Access to Psychological Therapies (IAPT) programme cited by Porter et al. (2024) as the proportion of patients moving from caseness (PHQ-9≥10; GAD-7≥8; OQ®-45.2≥64; WSAS≥

20) to recovered (PHQ-9<10; GAD-7<8; OQ®-45.2<64; WSAS<20) for each PRO measures, was examined using the respective scale clinical threshold (Kroenke et al., 2001; Spitzer et al., 2006; Lambert et al., 1996; Mundt at al., 2002), as presented in Table 9. The mean EoT score was below the recovery threshold score for each primary and secondary outcome.

Additionally, recovery for all primary outcomes combined was estimated at 54.5% (n=55), meaning that more than half of the patients who completed the KAP program improved in all primary measures (GAD-7, PHQ-9 and OQ®-45.2); the recovery for all PROMs, primary and secondary combined, was 32.7% (n=55).

Table 9

Mean EoT score versus recovery threshold and respective Recovery.

Outcomes measure	Count (n)	Mean (SD)	Recovery	Recovery[e]
PHQ9_EoT	61	7.43 (6,187)	<10[a]	63.5%
GAD7_EoT	63	6.54 (5,722)	<10[b]	72.1%
OQ®-45.2_EoT	59	56,73 (29,052)	>64[c]	57.6%
WSAS_EoT	57	15,12 (11,193)	>20[d]	42.1%

Note. SD=standard deviation; MCT meaningful change threshold or an equivalent measure of the clinical significance of an outcome score change.

[a]Estimated by Kroenke et al. (2001); [b]Estimated by Spitzer et al. (2006); [c]Estimated by; Lambert et al.1996); [d]Estimated by Mundt at al. (2002); [e]Count as denominator.

Discussion

The present study examined the real-world effectiveness of a ketamine-assisted psychotherapy (KAP) program delivered within an outpatient clinic in Lisbon, focusing on patient-reported outcomes to assess depressive and anxiety, as well as psychotherapy progress, as the primary outcomes and daily functioning as the secondary outcome. We started by describing the socio-demographic (age, sex and BMI) and clinical characteristics psychiatric indications, medical history, etc.) of patients who underwent the KAP program, as well as their treatment patterns (patient disposition, completion rates, treatment duration, baseline scores). Data analysis was performed on *group-level*, by comparing the within-subject PRO scores at baseline with the EoT and conducting predicting models to explore explanatory variables of the treatment outcomes, as well as *individual-level* by calculating the responder analysis and recovery rates.

Patients characteristics and Treatment patterns

From descriptive analysis, we noted that the patient group was homogenous regarding sex (50 female, 51.0%), but heterogenous in age with a median age of 44.0 years (IQR 34.0 - 52.0), median BMI of 31.1 (IQR 21.6 - 49.9), and depression (63.3%) and anxiety (29.6%) disorders were the most frequent primary diagnoses at the baseline, also being the most common secondary indication (respectively, 19.4% and 16.3%), not divergent from other KAP treatment research groups, reflecting typical clinical populations seeking treatment for treatment-resistant conditions (Ahuja et al., 2022; Dore et al., 2019; Jobnah et al., 2024). Due to the exploratory nature of this study, no hypothesis was anticipated (**H1**).

Patient disposition (number and proportion of patients in treatment flow, from eligible patients to completing the EoT) revealed that, from initial full sample of 98 (100%) patients, 68 (69.4%) completed the KAP program, corresponding to an attrition rate of 30 (30.6%) patients, equivalent or below the rates observed for other ketamine protocols, when reported (Wilkinson et al., 2021; Dakwar et al., 2020; Wilkinson et al., 2017; Jobnah et al., 2024). Nevertheless, attrition rate found for this KAP protocol can be potentially reduced, if we take into account that drop-out rates reported amongst diverse psychotherapeutic treatments are situated around 20% (Leichsenring et al., 2019).

Baseline scores for PHQ-9, GAD-7, OQ®-45.2, and WSAS had a high completion rate (ratio of patients with a PRO score who were expected to have a PRO at the time point), averaging between 91 - 97 (91% - 99% from the initial full data set of 98 patients) of patients,

contrasting with the not so high completion rates in the EoT measures, averaging between 57 - 63 (83.8% - 89.7% from the 68 patients who completed the KAP program), probably as a consequence of less patients being willing or available to comply with the clinic's requirement to complete the requested questionnaires as PROs.

Clinical efficacy and significance of KAP Treatment Outcomes

Overall, the results from the comparative *within-subject analysis* demonstrated that, as hypothesized (**H2**) using Wilcoxon signed rank test, there was a statistically significant improvement in the primary outcomes and the secondary outcomes. The primary outcomes scores - PHQ9, GAD7, and OQ®45.2 - were significantly lower at the end of the KAP treatment versus baseline scores, with all p-value < .001 and large effect sizes (varying between r = .533 - .585). Therefore, the KAP program at The Clinic of Change resulted in significant improvement in depression (measured by PHQ-9), anxiety (measured by PHQ-9), and the outcomes of psychotherapy (measured by OQ®-45.2).

The secondary outcomes score - WSAS - was also significantly lower at the end of the KAP treatment compared to the baseline scores, with p-value < .001 and a medium effect size (r = .386). This improvement extends the clinical significance beyond symptom reduction to meaningful changes in daily functioning, addressing the practical concerns patients face in maintaining employment and social relationships.

The results from the *responder analysis* and *recovery* also confirmed, as hypothesized (**H4**), that after the treatment completion (EoT), there was a clinically significant improvement of each PROM, either for each of the primary and secondary outcomes. Clinical significance was rigorously established using meaningful change thresholds (MCT) as a reference, which provides assessment beyond statistical significance alone by measuring what constitutes a clinically important difference in scores, signifying that an observed change is meaningful from the patient's perspective (Griffiths et al., 2021). This methodological approach aligns with NHS recommendations (Porter et al., 2024) for evaluating treatment outcomes, strengthening the evidence for real-world applicability of KAP interventions in contemporary clinical practice. The integration of both statistical and clinical significance metrics demonstrates that KAP produces improvements that are not only statistically robust but also meaningfully impact patient symptomatology and functioning.

After examining the change of the PRO scores from baseline to the EoT, using the *responder analysis* criteria - meaningful change threshold (MCT; Griffiths et al., 2021; NHS Talking Therapies, 2025), or an equivalent measure of the clinical significance, - results showed that, after the treatment completion (EoT), there was a clinically significant improvement of each one of the the patient's outcomes measures, translated by the scores reduction of the respective scale (6 or more points for PHQ-9 (Hudgens et al., 2021); 4 or more points for GAD-7 (Toussaint et al., 2020); 14 or more points for OQ®-45.2 (Beckstead et al., 2003); 8 or more points for WSAS (Zahra et al., 2014); when using the *recovery* criteria, it was also noted that for the majority of the patients had primary and secondary outcomes scores lower that the the clinical threshold established for each PRO measure (Porter et al., 2024): PHQ-9<10 (Kroenke et al., 2001); GAD-7<8 (Spitzer et al., 2006); OQ®-45.2<64 (Beckstead et al., 2003); WSAS<20 (Zahra et al., 2014). Nearly half of patients who completed KAP program had reliable improvements (considering the MCT) cumulatively in depression, anxiety and psychotherapy outcomes - all primary outcomes measures. This ratio was higher than 60% when considering the reliable improvement for depression or anxiety individually.

The combination of these findings suggests KAP addresses core functions shared across depression and anxiety, positioning ketamine as a potential transdiagnostic treatment effective across diverse patient groups.

These results seem to be consistent with the outcomes found in the several systematic reviews and meta-analysis research (Gomes & Novais, 2025; Joneborg et al., 2022), adding to the existing research (Gregoire, 2025; Drozdz et al., 2022; Wilkinson et al., 2021; Dore et al., 2019), which yielded similar results regarding the statistically significant reduction of depressive symptoms. However it is noteworthy that previous research of KAP protocols has often used diverse variables, instruments or analysis, which results in a challenge to have more straightforward comparisons (Aday et al., 2024).

Predictors of Treatment Response and Heterogeneity in Patient Outcomes

Multiple linear regression analysis revealed differential predictive patterns across primary outcomes. As hypothesized (**H3**), for anxiety (GAD-7) and psychotherapy outcomes (OQ®-45.2), the respective symptom severity measured at the baseline had a statistically significant influence on the symptom severity measured at the end of the KAP program:

patients who started the treatment protocol with higher symptom severity tended to retain higher scores at the end of treatment, despite showing significant improvement overall.

However, and contrary to what has been hypothesized (**H3**), the analysis conducted to determine whether age, sex and each baseline score predicted each EoT score, revealed that the three predictors jointly not always explain a significant portion of the respective outcome score at the EoT. The tested model also revealed that the depression (PHQ-9) EoT scores were not influenced by the respective baseline scores but rather by age as a significant predictor. This age-related effect on depression outcomes suggests that older patients may benefit from modified treatment approaches or require closer monitoring during KAP protocols to optimize therapeutic response. Sex at birth did not emerge as a significant predictor for any primary outcome, supporting the premise that ketamine's antidepressant and anxiolytic effects are equally effective across diverse demographic populations. Lack of variation in treatment responses across different demographic characteristics (sex) suggests that ketamine antidepressant and anxiolytic effects are effective for diverse patient populations, positioning ketamine as a potential transdiagnostic treatment across diverse patients subgroups (Gregoire, 2025).

The adjusted regression models explained limited variance in treatment outcomes, with R-squared values ranging from 10.4% for PHQ-9 to 17.1% for OQ®-45.2. This indicates that while baseline symptom severity and demographic variables contribute meaningfully to predicting treatment response, substantial heterogeneity in treatment outcomes remains unexplained by these conventional predictors.

Taken together, these results sustain the existing evidence of the clinical relevance of structured KAP protocol that integrate ketamine administration with psychotherapy integration sessions, in achieving significant therapeutic effects, aligned with previous research about KAP programs' effectiveness both in clinical trials settings (Kew et al., 2023; Dames et al., 2022; Joneborg et al., 2022; Wilkinson et al., 2021; Zydb & Hart, 2021; Dore et al., 2019; Wilkinson et al., 2017) as in real-world settings (Yermus et al., 2024; Dore et al., 2019; Alnefeesi et al., 2022; Drozdz et al., 2022; McInnes et al., 2022; McInnes et al., 2025), supporting the effectiveness of implementing KAP in a real-world outpatient setting. Consistent with prior research, these patterns of results underline the importance of considering the initial clinical severity when setting treatment expectations, tailoring interventions, and interpreting outcomes.

Strengths and limitations of the present study

Strengths. The present study was performed in a real-world setting, therefore and to the best of our knowledge being the first study to be conducted in Portugal outside clinical trials, despite the already existing programs based on the off-label use of ketamine (Teixeira, 2024). It should be noted that the KAP protocol under study was based on the outcomes from the application of psychometric validated instruments. These PRO measures were collected during the routine care for ketamine-assisted psychotherapy and included the effectiveness measures - PHQ-9, GAD-7, OQ®45.2 and WSAS - as well as other safety measures - KSET Screening and Baseline and MADRS suicidal question.

Employing a real-world observational retrospective methodology has many advantages. By examining outcomes in a naturalistic environment, this study adds ecological validity to the existing literature, demonstrating that significant improvements observed in controlled trials can translate into everyday clinical practice. It also provides a richer context for considering the participants' greater variability and enhances the external validity of the findings. Additionally, allows application of the MCT, a clinical relevant index used as a reference to assess clinical outcomes over time, instead of only assessing the statistical significance. (Porter et al. 2024; Welding et al., 2013).

The heterogeneous sample reflects the complexity encountered in community mental health settings, thereby validating the clinical applicability of findings and strengthening the evidence surrounding development of clinical guidelines and practitioner competence in integrating KAP into psychotherapeutic frameworks. By avoiding the artificial constraints imposed by rigid study protocols, this methodology provides valuable empirical contributions regarding KAP efficacy and supports development of refined clinical guidelines designed to optimize patient outcomes across diverse demographic and diagnostic presentations in contemporary practice.

Limitations. A real world study, as any other research, also warrants several limitations. The observational and retrospective nature of the study design methodology has limited the control over potentially confounding variables (e.g. concurrent changes in medication, variability in KAP program adherence) that may have influenced the outcome. Significant variability between studies posed a difficulty to compare the results with previous research or use standardized metrics to compare the reported outcomes.

Further, without an interventional design with a randomized controlled group (with a standard of care treatment or a placebo control group) it limits the possibility of any causal inferences of ketamine-assisted psychotherapy. The absence of a comparison or control group also limits the ability to differentiate the effects of ketamine itself from those of psychotherapy, or those effects from the expectancy levels, or concurrent treatments.

Furthermore, although follow-up measures are part of the KAP protocol, this study did not include follow-up assessments, limiting the analysis and into long-term effects of KAP treatment. Several patients are still under follow-up under KAP protocol and the retrieved database had limited values for follow-up sessions, even though these scores may be available in paper or tablet format at the clinic. The same reason of having several missings values in between baseline and end-of-treatment sessions, limited the application of a generalized linear mixed models (GLMM) statistical test.

While being an advantage to collect information based on patient reports, it can also be a limitation as self-reporting measures where patients may tend to provide biased responses.

Another limitation may have resulted from the limited number of data points which may have influenced some statistical analysis such as the multiple linear regression model using stepwise regression (Maroco & Bispo, 2005), not negligible missing values (even though we had minimized impact by re-running the model with pairwise approach) and the lack of other relevant variables, such as the psychotherapy modalities applied into the KAP protocol (as investigated by Drozdz et al., 2022).

It should also be noted that this research and its findings are limited to the studied patients group and not generalizable to the Portuguese or other population.

Future research

Future research should prioritize examining long-term outcomes beyond the end of treatment, to include PRO data from follow-up assessments - post end-of-treatment - at 12 months, as the number of patients with available data at this point is increasing. With the same rationale, of an increasing number of available data, other measures can be subject to future research, such as the PCL-5 to assess PTSD symptoms and a complete version of MADRS.

Considering the relevance of the patients expectations and the psychotherapy component of the KAP program (Aday et al., 2024), further characterization of both these variables would also enrich a future study. Incorporating clinician-reported outcomes and biological markers may also broaden understanding of the mechanisms underlying therapeutic change in a KAP program, even though it may pose an additional burden (both financial as to the already high number of questionnaires to manage) as part of a real-world context.

The significant unexplained variance of the treatment outcomes requires investigation of additional variables, while considering the need to balance all participants' efforts in managing the collection of data in a complete and sustainable manner.

Future research employing generalized linear mixed models with session-by-session data collection may better elucidate the mechanisms underlying variable treatment response and identify optimal treatment trajectories. Although a substantial proportion of patients completed the KAP protocol, a nontrivial percentage discontinued treatment, and understanding their perspectives and potential barriers to treatment continuation remains an important direction for future research. These could also contribute to improving the quality and cost-effectiveness of these mental health interventions.

Finally, qualitative inquiry to patients' experience, by adding qualitative PROs, could provide a holistic perspective of the impact of KAP on individuals suffering from mental health challenges (Gregoire, 2025).

Conclusion

This research aimed at generating practice-based insights to support real-world evidence of effectiveness of ketamine-assisted psychotherapy for depression, anxiety and other mental health conditions. The findings reinforce the potential of KAP to produce substantial symptom reduction, even when delivered outside a controlled research environment, bridging the gap between experimental findings and applied psychological practice and strengthening the evidence surrounding the real-world application of KAP programs. The improvements in depressive and anxiety symptoms, as well as in daily functioning further highlight the wider impact of KAP, suggesting that symptom relief is translated into tangible gains in patients' overall quality of life, and sustaining the potential of

KAP to address unmet needs in the treatment of depressive and anxiety disorders in clinical real-world contexts. It also outlines the value of integrating ketamine with psychotherapeutic support in outpatient settings and emphasizes the importance of treatment personalization based on baseline symptom severity and patient characteristics. As interest in KAP continues to grow, these results offer timely insights that may inform clinical guidelines, contribute to defining best practices, enhance practitioner competence, and optimize the delivery of this emerging therapeutic modality, towards an ethical and effective integration of KAP into psychotherapeutic frameworks. Hopefully, it may help to understand how innovative interventions such as KAP can be harnessed to improve therapeutic processes and patient outcomes in contemporary clinical psychology.

References

Aday, J. S., Horton, D., Fernandes-Osterhold, G., O'Donovan, A., Bradley, E. R., Rosen, R. C., & Woolley, J. D. (2024). Psychedelic-assisted psychotherapy: where is the psychotherapy research?. *Psychopharmacology, 241*(8), 1517–1526. https://doi.org/10.1007/s00213-024-06620-x

Ali, N. M., & Viqar, U. (2024). Treatment-Resistant depression: A comprehensive insight of ketamine infusion therapy, transcranial magnetic stimulation (TMS), and Psychedelic-Assisted psychotherapy. *Annals of Punjab Medical College*, *18*(4), 357–361. https://doi.org/10.29054/apmc/2024.1658

Albuquerque, T. R., Macedo, L. F. R., Delmondes, G. A., Rolim Neto, M. L., Almeida, T. M., Uchida, R. R., Cordeiro, Q., Lisboa, K. W. S. C., & Menezes, I. R. A. (2022). Evidence for the beneficial effect of ketamine in the treatment of patients with post-traumatic stress disorder: A systematic review and meta-analysis. *Journal of cerebral blood flow and metabolism: official journal of the International Society of Cerebral Blood Flow and Metabolism, 42*(12), 2175–2187. https://doi.org/10.1177/0271678X221116477

Almog, S., Rodriguez Perez, M., Varma, D. S., Obrochta, A. N., Weiner, M., Cheong, J., & Berry, M. S. (2025). Self-reported changes and experiences with substance use among real-world patients treated with medical ketamine. *Experimental and Clinical Psychopharmacology, 33*(5), 448–458. https://doi.org/10.1037/pha0000788

Alnefeesi, Y., Chen-Li, D., Krane, E., Jawad, M. Y., Rodrigues, N. B., Ceban, F., Di Vincenzo, J. D., Meshkat, S., Ho, R. C. M., Gill, H., Teopiz, K. M., Cao, B., Lee, Y.,

McIntyre, R. S., & Rosenblat, J. D. (2022). Real-world effectiveness of ketamine in treatment-resistant depression: A systematic review & meta-analysis. *Journal of psychiatric research, 151*, 693–709. https://doi.org/10.1016/j.jpsychires.2022.04.037

Argento, E., Petker, T., Vig, J., Robertson, C., Jaeger, A., Necyk, C., Thielking, P., & Walsh, Z. (2024). "This is you teaching you:" Exploring providers' perspectives on experiential learning and enhancing patient safety and outcomes in ketamine-assisted therapy. *PLoS ONE, 19*(8), 1–14. https://doi.org/10.1371/journal.pone.0306381

Babor, T.F., de la Fuente, J.R., Saunders, J. and Grant, M. (1989) *AUDIT The alcohol use disorders identification test: Guidelines for use in primary health care*. WHO/MNH/DAT 89.4, World Health Organization.

Basso, L., Bönke, L., Aust, S., Gärtner, M., Heuser-Collier, I., Otte, C., Wingenfeld, K., Bajbouj, M., & Grimm, S. (2020). Antidepressant and neurocognitive effects of serial ketamine administration versus ECT in depressed patients. *Journal of psychiatric research, 123*, 1–8. https://doi.org/10.1016/j.jpsychires.2020.01.002

Batievsky, D., Weiner, M., Kaplan, S. B., Thase, M. E., Maglione, D. N., & Vidot, D. C. (2023). Ketamine-assisted psychotherapy treatment of chronic pain and comorbid depression: a pilot study of two approaches. *Frontiers in pain research (Lausanne, Switzerland), 4,* 1127863. https://doi.org/10.3389/fpain.2023.1127863

Beckstead, D. J., Hatch, A. L., Lambert, M. J., Eggett, D. L., Goates, M. K., & Vermeersch, D. A. (2003). Clinical significance of the Outcome Questionnaire (OQ-45.2). *The*

Behavior Analyst Today, 4(1), 86–97. https://doi.org/10.1037/h0100015

Campolina, A. G., & De Oliveira, M. a. T. (2025). Unfolding States of Mind: A Dissociative-Psychedelic model of Ketamine-Assisted Psychotherapy in Palliative care. *Healthcare, 13*(21), 2714. https://doi.org/10.3390/healthcare13212714

Cohen, J. (1988). *Statistical Power Analysis for the Behavioral Sciences* (2nd ed.). Routledge. https://doi.org/10.4324/9780203771587

Cohen, J., 1992. Statistical power analysis. *Curr. Dir. Psychol. Sci. 1*, 98–101. https://doi.org/10.1111/1467-8721.ep10768783

Conley, A. A., Norwood, A. E. Q., Hatvany, T. C., Griffith, J. D., & Barber, K. E. (2021). Efficacy of ketamine for major depressive episodes at 2, 4, and 6-weeks post-treatment: A meta-analysis. *Psychopharmacology, 238*(7), 1737–1752. https://doi.org/10.1007/s00213-021-05825-8

Cuijpers, P., Sijbrandij, M., Koole, S. L., Andersson, G., Beekman, A. T., & Reynolds, C. F., 3rd (2014). Adding psychotherapy to antidepressant medication in depression and anxiety disorders: a meta-analysis. *World psychiatry : official journal of the World Psychiatric Association (WPA), 13(*1), 56–67. https://doi.org/10.1002/wps.20089

Daghmouri, M. A., Chaouch, M. A., Ben Ayoun, L., Gouader, A., Chatzistergiou, K., Mion, G., Cheurfa, C., & Camby, M. (2025). Intravenous ketamine to prevent post-partum depression following cesarean under neuraxial anesthesia: A systematic review and meta-analysis of randomized controlled trials. *International Journal of Gynaecology and Obstetrics: The Official Organ of the International Federation of Gynaecology and Obstetrics, 17*1(1), 94–105.

https://doi.org/10.1002/ijgo.70190

Dakwar, E., Levin, F., Hart, C. L., Basaraba, C., Choi, J., Pavlicova, M., & Nunes, E. V. (2019). A single ketamine infusion combined with motivational enhancement therapy for alcohol use disorder: a randomized Midazolam-Controlled pilot trial. *American Journal of Psychiatry*, *177*(2), 125–133. https://doi.org/10.1176/appi.ajp.2019.19070684

Dames, S., Kryskow, P., & Watler, C. (2022). A Cohort-Based Case Report: The Impact of Ketamine-Assisted therapy embedded in a Community of Practice Framework for healthcare providers with PTSD and Depression. *Frontiers in Psychiatry, 12,* 803279. https://doi.org/10.3389/fpsyt.2021.803279

Dworkin, R. H., McDermott, M. P., Nayak, S. M., & Strain, E. C. (2023). Psychedelics and Psychotherapy: Is the Whole Greater than the Sum of its Parts? *Clinical Pharmacology & Therapeutics*, *114*(6), 1166–1169. https://doi.org/10.1002/cpt.3050

Drozdz, S. J., Goel, A., McGarr, M. W., Katz, J., Ritvo, P., Mattina, G. F., Bhat, V., Diep, C., & Ladha, K. S. (2022). Ketamine Assisted Psychotherapy: A systematic narrative review of the literature. *Journal of pain research, 15*, 1691–1706. https://doi.org/10.2147/JPR.S360733

Feder, A., Costi, S., Rutter, S. B., Collins, A. B., Govindarajulu, U., Jha, M. K., Horn, S. R., Kautz, M., Corniquel, M., Collins, K. A., Bevilacqua, L., Glasgow, A. M., Brallier, J., Pietrzak, R. H., Murrough, J. W., & Charney, D. S. (2021). A randomized controlled trial of repeated ketamine administration for chronic posttraumatic stress disorder. *American Journal of Psychiatry*, *178*(2), 193–202. https://doi.org/10.1176/appi.ajp.2020.20050596

Felitti, V. J., Anda, R. F., Nordenberg, D., Williamson, D. F., Spitz, A. M., Edwards, V., Koss, M. P., & Marks, J. S. (1998). Adverse Childhood Experiences Study questionnaire [Dataset]. In *PsycTESTS Dataset*. https://doi.org/10.1037/t26957-000

Figueiredo, I. C., Corvacho, M., & Mota, P. (2023). *Psicadélicos em saúde mental.* Lidel.

Fletcher, K., Ezard, N., Siefried, K. J., MacDonald, H., Acheson, L., Bedi, G., Guerin, A., Knock, E., Millard, M., May, R., Brett, J., Doumany, J., Morgan, C., & Clifford, B. (2025). Protocol of an open-label safety and feasibility pilot study of ketamine-assisted psychotherapy for methamphetamine use disorder (the KAPPA trial). *BMJ Open, 15*(2), e092504. https://doi.org/10.1136/bmjopen-2024-092504

Flynn, L., Krsak, M., Rondeau, M., McCarty, D., Walker, M., Horan, D., Forstner, S., & Shannon, S. (2025). Treating job-related stress with psychedelic group therapy: a case series on group ketamine-assisted psychotherapy for healthcare workers and first responders. *Therapeutic Advances in Psychopharmacology, 15,* 20451253251383415. https://doi.org/10.1177/20451253251383415

Garel, N., Drury, J., Thibault Lévesque, J., Goyette, N., Lehmann, A., Looper, K., Erritzoe, D., Dames, S., Turecki, G., Rej, S., Richard-Devantoy, S., & Greenway, K. T. (2023). The Montreal model: an integrative biomedical-psychedelic approach to ketamine for severe treatment-resistant depression. *Frontiers in Psychiatry, 14*, 1268832. https://doi.org/10.3389/fpsyt.2023.1268832

GBD 2023 Disease and Injury and Risk Factor Collaborators (2025). Burden of 375 diseases and injuries, risk-attributable burden of 88 risk factors, and healthy life expectancy

in 204 countries and territories, including 660 subnational locations, 1990-2023: a systematic analysis for the Global Burden of Disease Study 2023. *Lancet (London, England), 406*(10513), 1873–1922. https://doi.org/10.1016/S0140-6736(25)01637-X

Gignac, G. E., & Szodorai, E. T. (2016). Effect size guidelines for individual differences researchers. *Personality and Individual Differences, 102,* 74–78. https://doi.org/10.1016/j.paid.2016.06.069

Glue, P., Neehoff, S., Sabadel, A., Broughton, L., Le Nedelec, M., Shadli, S., McNaughton, N., & Medlicott, N. J. (2020). Effects of ketamine in patients with treatment-refractory generalized anxiety and social anxiety disorders: Exploratory double-blind psychoactive-controlled replication study. *Journal of psychopharmacology (Oxford, England), 34*(3), 267–272. https://doi.org/10.1177/0269881119874457

Gomes, A. M., & Novais, F. (2025). Ketamine-Assisted Psychotherapy for Treatment-Resistant Depression: a Systematic Review. *Current Treatment Options in Psychiatry, 12*(1), 1–9. https://doi.org/10.1007/s40501-025-00346-z

Gonçalves-Pinho, M., Ribeiro, J. P., Fernandes, L., & Freitas, A. (2022). Depressive Disorder Related Hospitalizations in Portugal Between 2008–2015: a Nationwide Observational Study. *Psychiatric Quarterly*, *93*(3), 791–802. https://doi.org/10.1007/s11126-022-09996-1

Grabski, M., McAndrew, A., Lawn, W., Marsh, B., Raymen, L., Stevens, T., Hardy, L., Warren, F., Bloomfield, M., Borissova, A., Maschauer, E., Broomby, R., Price, R., Coathup, R., Gilhooly, D., Palmer, E., Gordon-Williams, R., Hill, R., Harris, J., . . . Morgan, C. J. (2022). Adjunctive Ketamine with Relapse Prevention–Based

Psychological therapy in the treatment of alcohol use Disorder. *American Journal of Psychiatry*, *179*(2), 152–162. https://doi.org/10.1176/appi.ajp.2021.21030277

Greenway, K. T., Garel, N., Jerome, L., & Feduccia, A. A. (2020). Integrating psychotherapy and psychopharmacology: psychedelic-assisted psychotherapy and other combined treatments. *Expert review of clinical pharmacology, 13*(6), 655–670. https://doi.org/10.1080/17512433.2020.1772054

Gregoire, N. H. D. (2025). Personalized approaches to mental health interventions : effectiveness of ketamine-assisted therapy for treatment-resistant psychological conditions (T). University of British Columbia. Retrieved from https://open.library.ubc.ca/collections/ubctheses/24/items/1.0448342

Griffiths, P., Sims, J., Williams, A., Williamson, N., Cella, D., Brohan, E., & Cocks, K. (2021). How Strong Should My Anchor Be For Estimating Group And Individual Level Meaningful Change? A Simulation Study Assessing Anchor Correlation Strength And The Impact of Sample Size, Distribution of Change Scores And Methodology On Establishing A True Meaningful Change Threshold. Research Square (Research Square). https://doi.org/10.21203/rs.3.rs-384605/v1

Halstead, M., Reed, S., Krause, R., & Williams, M. T. (2021). Ketamine-Assisted Psychotherapy for PTSD Related to Racial Discrimination. *Clinical Case Studies, 20*(4), 310-330. https://doi.org/10.1177/1534650121990894

Harris, C. P., Jones, B., Walker, K., & Berry, M. S. (2024). Case report: Adult with bipolar disorder and autism treated with ketamine assisted psychotherapy. *Frontiers in*

Psychiatry, 15, 1322679. https://doi.org/10.3389/fpsyt.2024.1322679

Hartelius, G., Muscat, S.-A., & Bartova, L. (2023). Editorial: Bridging the gap: an interdisciplinary perspective on ketamine in psychiatric disorders. *Frontiers in Psychiatry, 14*. https://doi.org/10.3389/fpsyt.2023.1246891

Hicks, M. R., Zwickey, H., & Bradley, R. (2025). Ketamine-Assisted Psychotherapy for Antisocial Personality Disorder: A Case Report. *Journal of Psychoactive Drugs, 1*–7. https://doi.org/10.1080/02791072.2025.2449911

Hudgens, S., Floden, L., Blackowicz, M., Jamieson, C., Popova, V., Fedgchin, M., Drevets, W. C., Cooper, K., Lane, R., & Singh, J. (2021). Meaningful Change in Depression Symptoms Assessed with the Patient Health Questionnaire (PHQ-9) and Montgomery-Åsberg Depression Rating Scale (MADRS) Among Patients with Treatment Resistant Depression in Two, Randomized, Double-blind, Active-controlled Trials of Esketamine Nasal Spray Combined With a New Oral Antidepressant. *Journal of affective disorders, 281*, 767–775. https://doi.org/10.1016/j.jad.2020.11.066

Jamieson, S. (2004). Likert scales: how to (ab)use them. *Medical Education, 38*(12), 1217–1218. https://doi.org/10.1111/j.1365-2929.2004.02012.x

Johnston, J. N., Bashkim Kadriu, Kraus, C., Henter, I. D., & Zarate, C. A. (2023). Ketamine in neuropsychiatric disorders: an update. *Neuropsychopharmacology, 49*(1), 23–40. https://doi.org/10.1038/s41386-023-01632-1

Joneborg, I., Lee, Y., Di Vincenzo, J. D., Ceban, F., Meshkat, S., Lui, L. M., Fancy, F., Rosenblat, J. D., & McIntyre, R. S. (2022). Active mechanisms of ketamine-assisted

psychotherapy: A systematic review. *Journal of Affective Disorders, 315,* 105–112. https://doi.org/10.1016/j.jad.2022.07.030

Kamilar-Britt, P., Gordis, E. B., & Earleywine, M. (2023). The Therapeutic Alliance in Psychedelic-Assisted Psychotherapy: a novel target for research and interventions. *Psychedelic Medicine*, *1*(4), 262–266. https://doi.org/10.1089/psymed.2023.0020

Khalifian, C., Rashkovsky, K., Mitchell, E., Bismark, A., Wagner, A. C., & Knopp, K. C. (2024). A novel framework for ketamine-assisted couple therapy. *Frontiers in Psychiatry, 15,* 1376646. https://doi.org/10.3389/fpsyt.2024.1376646

Kelson, M., Burnett, J. M., Matthews, A., & Juneja, T. (2023). Ketamine Treatment for Alcohol Use Disorder: A Systematic Review. *Cureus, 15*(5), e38498. https://doi.org/10.7759/cureus.38498

Kew, B. M., Porter, R. J., Douglas, K. M., Glue, P., Mentzel, C. L., & Beaglehole, B. (2023). Ketamine and psychotherapy for the treatment of psychiatric disorders: systematic review. *BJPsych open, 9*(3), e79. https://doi.org/10.1192/bjo.2023.53

Kopelman, J., Keller, T. A., Panny, B., Griffo, A., Degutis, M., Spotts, C., Cruz, N., Bell, E., Do-Nguyen, K., Wallace, M. L., Mathew, S. J., Howland, R. H., & Price, R. B. (2023). Rapid neuroplasticity changes and response to intravenous ketamine: a randomized controlled trial in treatment-resistant depression. *Translational psychiatry, 13*(1), 159. https://doi.org/10.1038/s41398-023-02451-0

Kroenke K., Spitzer R. L., Williams J. B. (2001). The PHQ-9: Validity of a brief depression severity measure. *Journal of General Internal Medicine, 16*(9), 606–613.

Lambert, M. J., Burlingame, G. M., Umphress, V., Hansen, N. B., Vermeersch, D. A., Clouse, G. C., & Yanchar, S. C. (1996). The Reliability and Validity of the Outcome Questionnaire. *Clinical Psychology & Psychotherapy, 3*(4), 249–258. https://doi.org/10.1002/(SICI)1099-0879(199612)3:4<249::AID-CPP106>3.0.CO;2-S

Leichsenring, F., Sarrar, L., & Steinert, C. (2019). Drop-outs in psychotherapy: a change of perspective. *World psychiatry: official journal of the World Psychiatric Association (WPA), 18*(1), 32–33. https://doi.org/10.1002/wps.20588

Mathai, D. S., Mora, V., & Garcia-Romeu, A. (2022). Toward Synergies of Ketamine and Psychotherapy. *Frontiers in psychology, 13*, 868103. https://doi.org/10.3389/fpsyg.2022.868103

Maroco, J., & Bispo, R. (2005). *Estatística aplicada às ciências sociais e humanas* (2nd ed.). Climepsi Editores. (Original work published 2003)

Mathai, D. S., Mora, V., & Garcia-Romeu, A. (2022). Toward Synergies of Ketamine and Psychotherapy. *Frontiers in psychology, 13*, 868103. https://doi.org/10.3389/fpsyg.2022.868103

MacConnel, H. A., Earleywine, M., & Radowitz, S. (2024). Rapid and sustained reduction of treatment-resistant PTSD symptoms after intravenous ketamine in a real-world, psychedelic paradigm. *Journal of Psychopharmacology, 39*(1), 29–37. https://doi.org/10.1177/02698811241286726

Marguilho, M., Figueiredo, I., & Castro-Rodrigues, P. (2022). A unified model of ketamine's dissociative and psychedelic properties. *Journal of Psychopharmacology*, *37*(1), 14–32. https://doi.org/10.1177/02698811221140011

McInnes, L. A., Qian, J. J., Gargeya, R. S., DeBattista, C., & Heifets, B. D. (2022). A retrospective analysis of ketamine intravenous therapy for depression in real-world care settings. *Journal of affective disorders, 301*, 486–495. https://doi.org/10.1016/j.jad.2021.12.097

McInnes, L. A., Berman, R. M., Worley, M., & Shih, E. (2025). A Retrospective analysis of ketamine intravenous therapy for Post-Traumatic Stress Disorder in Real-World care settings. *Psychiatry Research, 352*, 116689. https://doi.org/10.1016/j.psychres.2025.116689

Miller, C., Lopes, B., & McCurdy, A. (2025). The collective lie in ketamine therapy: a call to realign clinical practice with neurobiology. *Frontiers in Psychiatry*, *16*, 1610335. https://doi.org/10.3389/fpsyt.2025.1610335

Mollaahmetoglu, O. M., Keeler, J., Ashbullby, K. J., Ketzitzidou-Argyri, E., Grabski, M., & Morgan, C. J. A. (2021). "This is something that changed my life": A qualitative study of patients' experiences in a clinical trial of ketamine treatment for alcohol use disorders. *Frontiers in Psychiatry*, *12*, 695335. https://doi.org/10.3389/fpsyt.2021.695335

Monteiro, S., Torres, A., Pereira, A., Albuquerque, E., & Morgadinho, R. (2013). 2077 – Preliminary Validation Study Of a Portuguese Version Of The Patient Health Questionnaire (phq-9). *European Psychiatry, 28*(S1), 28-E1270. https://10.1016/S0924-9338(13)76982-7

Monteiro, S., Bártolo, A., Torres, A., Pereira, A., & Albuquerque, E. (2019). Examinando a validade de construto da versão Portuguesa do Patient Health Questionnaire-9 entre estudantes universitários. *Psicologia, 33*(2), 1–8. https://doi.org/10.17575/rpsicol.v33i2.1421

Montgomery, S. A., & Åsberg, M. A. R. I. E. (1979). A new depression scale designed to be sensitive to change. *The British journal of psychiatry, 134*(4), 382-389. http://doi.org/10.1192/bjp.134.4.382

Mundt, J. C., Marks, I. M., Shear, M. K., & Greist, J. M. (2002). The Work and Social Adjustment Scale: a simple measure of impairment in functioning. British Journal of Psychiatry, 180(5), 461–464. http://doi.org/10.1192/bjp.180.5.461

Muscat, S.-A., Hartelius, G., Crouch, C. R., & Morin, K. W. (2021). An Integrative Approach to Ketamine Therapy May Enhance Multiple Dimensions of Efficacy: Improving Therapeutic Outcomes With Treatment Resistant Depression. *Frontiers in Psychiatry, 12*. https://doi.org/10.3389/fpsyt.2021.710338

NHS Talking Therapies: Monthly statistics including Employment Advisors, performance January 2025. (2025, March 13). *NHS Digital*. Retrieved October 25, 2025, from https://digital.nhs.uk/data-and-information/publications/statistical/nhs-talking-therapies-monthly-statistics-including-employment-advisors/performance-january-2025/outcomes

Norbury, A., Rutter, S. B., Collins, A. B., Costi, S., Jha, M. K., Horn, S. R., Kautz, M., Corniquel, M., Collins, K. A., Glasgow, A. M., Brallier, J., Shin, L. M., Charney, D. S., Murrough, J. W., & Feder, A. (2021). Neuroimaging correlates and predictors of response to repeated-dose intravenous ketamine in PTSD: preliminary evidence. *Neuropsychopharmacology: official publication of the American College of Neuropsychopharmacology, 46*(13), 2266–2277. https://doi.org/10.1038/s41386-021-01104-4

Nutt, D. (2024). *Psicadélicos: Um guia completo sobre as substâncias revolucionárias que podem mudar a sua vida.* Nascente.

Pallant, J. (2020). *SPSS Survival Manual.* https://doi.org/10.4324/9781003117445

Philipp-Muller, A. E., Stephenson, C. J., Moghimi, E., Shirazi, A. H., Milev, R., Vazquez, G., Reshetukha, T., & Alavi, N. (2023). Combining Ketamine and Psychotherapy for the Treatment of Posttraumatic Stress Disorder: A Systematic Review and Meta-Analysis. *The Journal of clinical psychiatry, 84*(2), 22br14564. https://doi.org/10.4088/JCP.22br14564

Phillips, J. L., Norris, S., Talbot, J., Hatchard, T., Ortiz, A., Birmingham, M., Owoeye, O., Batten, L. A., & Blier, P. (2020). Single and repeated ketamine infusions for reduction of suicidal ideation in treatment-resistant depression. *Neuropsychopharmacology: official publication of the American College of Neuropsychopharmacology, 45*(4), 606–612. https://doi.org/10.1038/s41386-019-0570-x

Porter, A., Franklin, M., De Vocht, F., d'Apice, K., Curtin, E., Albers, P., & Kidger, J. (2024). Estimating the effectiveness of an enhanced 'Improving Access to Psychological Therapies' (IAPT) service addressing the wider determinants of mental health: a real-world evaluation. *BMJ open, 14*(1), e077220. https://doi.org/10.1136/bmjopen-2023-077220

Ragnhildstveit, A., Jackson, L. K., Cunningham, S., Good, L., Tanner, Q., Roughan, M., & Henrie-Barrus, P. (2021). Case report: Unexpected remission from extreme and enduring bulimia nervosa with repeated ketamine assisted psychotherapy. *Frontiers in Psychiatry*, *12*, 764112. https://doi.org/10.3389/fpsyt.2021.764112

Ragnhildstveit, A., Slayton, M., Jackson, L. K., Brendle, M., Ahuja, S., Holle, W., Moore, C., Sollars, K., Seli, P., & Robison, R. (2022). Ketamine as a Novel

Psychopharmacotherapy for Eating Disorders: Evidence and Future Directions. *Brain sciences, 12*(3), 382. https://doi.org/10.3390/brainsci12030382

Robison, R., Brendle, M., Moore, C., Cross, H., Helm, L., Darling, S., … Shannon, S. (2024). Ketamine-Assisted Group Psychotherapy for Frontline Healthcare Workers with COVID-19-Related Burnout and PTSD: A Case Series of Effectiveness/Safety for 10 Participants. *Journal of Psychoactive Drugs, 56*(1), 23–32. https://doi.org/10.1080/02791072.2023.2186285

Rojas, D., Zelman, D. C., Hauson, A. O., & Alexander, I. (2025). Exploring Cultural Competence, Inclusivity, and Diversity in Ketamine Assisted Psychotherapy: A Phenomenological Study. *Journal of Psychoactive Drugs, 57*(3), 243–253. https://doi.org/10.1080/02791072.2024.2341811

Ryan, W. C., & Heifets, B. D. (2025). Maintenance Intramuscular Ketamine-Assisted Psychotherapy, a Retrospective Chart Review of Efficacy, Adverse Events, and Dropouts from a Community Practice. *Journal of Psychoactive Drugs, 57*(5), 525–539. https://doi.org/10.1080/02791072.2024.2421895

Rusz, C., Ősz, B., Jîtcă, G., Miklos, A., Bătrînu, M., & Imre, S. (2021). Off-Label medication: from a simple concept to complex practical aspects. *International Journal of Environmental Research and Public Health*, *18*(19), 10447. https://doi.org/10.3390/ijerph181910447

Santos, A., & Rachadell, J. (2022). Anxiety and depression disorders in Portugal during the COVID-19 pandemic: Juan Rachadell. *The European Journal of Public Health, 32*(Suppl 3), ckac131.486. https://doi.org/10.1093/eurpub/ckac131.486

Saunders, J. B., Aasland, O. G., Babor, T. F., De La Fuente, J. R., & Grant, M. (1993). Development of the Alcohol Use Disorders Identification Test (AUDIT): WHO Collaborative Project on Early Detection of Persons with Harmful Alcohol Consumption‐II. *Addiction, 88*(6), 791–804. https://doi.org/10.1111/j.1360-0443.1993.tb02093.x

Schenberg, E. E. (2018). Psychedelic-Assisted Psychotherapy: A paradigm shift in psychiatric research and development. *Frontiers in Pharmacology, 9*, 733. https://doi.org/10.3389/fphar.2018.00733

Schimmers, N., Breeksema, J. J., Smith-Apeldoorn, S. Y., Veraart, J., van den Brink, W., & Schoevers, R. A. (2022). Psychedelics for the treatment of depression, anxiety, and existential distress in patients with a terminal illness: a systematic review. *Psychopharmacology, 239*(1), 15–33. https://doi.org/10.1007/s00213-021-06027-y

Short, B., Dong, V., Gálvez, V., Vulovic, V., Martin, D., Bayes, A. J., Zarate, C. A., Murrough, J. W., McLoughlin, D. M., Riva-Posse, P., Schoevers, R., Fraguas, R., Glue, P., Fam, J., McShane, R., & Loo, C. K. (2020). Development of the Ketamine Side Effect Tool (KSET). *Journal of Affective Disorders, 266*, 615–620. https://doi.org/10.1016/j.jad.2020.01.120

Singh, J. B., Fedgchin, M., Daly, E. J., De Boer, P., Cooper, K., Lim, P., Pinter, C., Murrough, J. W., Sanacora, G., Shelton, R. C., Kurian, B., Winokur, A., Fava, M., Manji, H., Drevets, W. C., & Van Nueten, L. (2016). A Double-Blind, Randomized, Placebo-Controlled, Dose-Frequency Study of Intravenous Ketamine in Patients With Treatment-Resistant Depression. *The American journal of psychiatry, 173*(8), 816–826. https://doi.org/10.1176/appi.ajp.2016.16010037

Sousa, T. V., Viveiros, V., Chai, M. V., Vicente, F. L., Jesus, G., Carnot, M. J., Gordo, A. C., & Ferreira, P. L. (2015). Reliability and validity of the Portuguese version of the Generalized Anxiety Disorder (GAD-7) scale. *Health and quality of life outcomes, 13,* 50. https://doi.org/10.1186/s12955-015-0244-2

Sousa, R. D., Gouveia, M., Da Silva, C. N., Rodrigues, A. M., Cardoso, G., Antunes, A. F., Canhao, H., & De Almeida, J. M. C. (2022). Treatment-resistant depression and major depression with suicide risk—The cost of illness and burden of disease. *Frontiers in Public Health*, *10*, 898491. https://doi.org/10.3389/fpubh.2022.898491

Spitzer, R. L., Kroenke, K., Williams, J. B., & Löwe, B. (2006). A brief measure for assessing generalized anxiety disorder: the GAD-7. *Archives of internal medicine, 166*(10), 1092–1097. https://doi.org/10.1001/archinte.166.10.1092

Taylor, J. H., Landeros-Weisenberger, A., Coughlin, C., Mulqueen, J., Johnson, J. A., Gabriel, D., Reed, M. O., Jakubovski, E., & Bloch, M. H. (2018). Ketamine for Social Anxiety Disorder: A Randomized, Placebo-Controlled Crossover Trial. *Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology, 43*(2), 325–333. https://doi.org/10.1038/npp.2017.194

Teixeira, P. (2024). *Psicadélicos em português*. Fundação Francisco Manuel dos Santos.

Thomas, A., & Chambers, R. A. (2025). Ketamine's Therapeutic Role in Substance Use Disorders: A Narrative review. *NeuroSci, 6*(3), 83. https://doi.org/10.3390/neurosci6030083

Toussaint, A., Hüsing, P., Gumz, A., Wingenfeld, K., Härter, M., Schramm, E., & Löwe, B. (2020). Sensitivity to change and minimal clinically important difference of the

7-item Generalized Anxiety Disorder Questionnaire (GAD-7). *Journal of affective disorders, 265*, 395–401. https://doi.org/10.1016/j.jad.2020.01.032

Tsang, V. W., Tao, B., Dames, S., Walsh, Z., & Kryskow, P. (2023). Safety and tolerability of intramuscular and sublingual ketamine for psychiatric treatment in the Roots To Thrive ketamine-assisted therapy program: a retrospective chart review. *Therapeutic Advances in Psychopharmacology*, *13*, 20451253231171512. https://doi.org/10.1177/20451253231171512

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

Ware, O. D. (2024). Mental health facilities with ketamine infusion therapy in the United States in 2020: Co-location of dual diagnosis mental health and substance use disorder treatment. *Experimental and Clinical Psychopharmacology, 32*(3), 263–269. https://doi.org/10.1037/pha0000686

Weldring, T., & Smith, S. M. (2013). Patient-Reported Outcomes (PROs) and Patient-Reported Outcome Measures (PROMs). *Health services insights, 6,* 61–68. https://doi.org/10.4137/HSI.S11093

Wikberg, C., Pettersson, A., Westman, J., Björkelund, C., & Petersson, E. L. (2016). Patients' perspectives on the use of the Montgomery-Asberg depression rating scale self-assessment version in primary care. *Scandinavian Journal of Primary Health Care, 34*(4), 434–442. https://doi.org/10.1080/02813432.2016.1248635

Wilkinson, S. T., Wright, D., Fasula, M. K., Fenton, L., Griepp, M., Ostroff, R. B., & Sanacora, G. (2017). Cognitive Behavior Therapy May Sustain Antidepressant Effects of Intravenous Ketamine in Treatment-Resistant Depression. *Psychotherapy and psychosomatics, 86*(3), 162–167. https://doi.org/10.1159/000457960

Wilkinson, S. T., Rhee, T. G., Joormann, J., Webler, R., Ortiz Lopez, M., Kitay, B., Fasula, M., Elder, C., Fenton, L., & Sanacora, G. (2021). Cognitive Behavioral Therapy to Sustain the Antidepressant Effects of Ketamine in Treatment-Resistant Depression: A Randomized Clinical Trial. *Psychotherapy and psychosomatics, 90*(5), 318–327. https://doi.org/10.1159/000517074

Wolfson, P. E., Andries, J., Ahlers, D., & Whippo, M. (2023). Ketamine-assisted psychotherapy in adolescents with multiple psychiatric diagnoses. *Frontiers in Psychiatry, 14,* 1141988. https://doi.org/10.3389/fpsyt.2023.1141988

Wu, H., & Leung, S. O. (2017). Can Likert Scales be Treated as Interval Scales?—A Simulation Study. *Journal of Social Service Research, 43*(4), 527–532. https://doi.org/10.1080/01488376.2017.1329775

Yermus, R., Bottos, J., Bryson, N., De Leo, J. A., Earleywine, M., Hackenburg, E., Kennedy, S., Kezemidis, M., Kratina, S., McMaster, R., Medrano, B., Mina, M., Morisano, D., Muench, M., Pillai, S., Scharlach, R., Setlur, V., Verbora, M., Wolfson, E., . . . Lo, C. (2024). Ketamine-Assisted Psychotherapy Provides Lasting and Effective Results in the Treatment of Depression, Anxiety, and Post-Traumatic Stress Disorder at 3 and 6 Months: Findings from a Large Retrospective Effectiveness Study. *Psychedelic Medicine, 2*(2), 87–95. https://doi.org/10.1089/psymed.2023.002

Zahra, D., Qureshi, A., Henley, W., Taylor, R., Quinn, C., Pooler, J., Hardy, G., Newbold, A., & Byng, R. (2014). The work and social adjustment scale: reliability, sensitivity and value. *International Journal of Psychiatry in Clinical Practice, 18*(2), 131–138. https://doi.org/10.3109/13651501.2014.894072

Zarse, E. M., Neff, M. R., Yoder, R., Hulvershorn, L., Chambers, J. E., & Chambers, R. A. (2019). The adverse childhood experiences questionnaire: Two decades of research on childhood trauma as a primary cause of adult mental illness, addiction, and medical diseases. *Cogent Medicine*, *6*(1), 1581447. https://doi.org/10.1080/2331205x.2019.1581447

Appendix A - Literature Review

Introduction

Ketamine-assisted psychotherapy (KAP) represents a convergence of rapid-acting pharmacological intervention with structured psychological treatment. As a novel therapeutic paradigm, KAP integrates the antidepressant properties of ketamine - a non-selective N-methyl-D-aspartate (NMDA) receptor antagonist - with concurrent and sequential psychotherapeutic support (Garet et al., 2025; Wolfson & Vaid, 2024; Figueiredo et al., 2023; Nutt, 2024; Teixeira, 2024; Drozdz et al., 2022).

This combination model has gained significant clinical and research attention over the past decade as traditional psychiatric interventions continue to demonstrate limited efficacy in treatment-resistant populations (Figueiredo et al., 2023; Nutt, 2024; Teixeira, 2024). The emergence of KAP reflects a broader paradigm shift in psychedelic-assisted therapy, challenging conventional approaches to mental illness treatment and offering hope for patients who have failed multiple pharmacological and psychological interventions.

This review synthesizes current evidence on KAP's research, focusing its clinical applications, treatment protocols, efficacy, and implementation considerations.

Historical Context and Development

Ketamine's therapeutic potential for psychiatric conditions emerged from observations during its use as an anesthetic agent. Early research in the 1960s recognized the dissociative and psychedelic properties of ketamine, which were initially characterized as adverse side effects (Wolfson & Vaid, 2024; Figueiredo et al., 2023; Nutt, 2024; Teixeira, 2024; Walsh, 2022). However, contemporary research has reframed these altered states of consciousness as potentially integral to therapeutic outcomes rather than undesirable complications (Wolfson & Vaid, 2024; Figueiredo et al., 2023; Nutt, 2024).

The definition of KAP as a structured treatment modality represents a relatively recent development . While ketamine monotherapy for depression has established evidence dating back several decades, systematic integration with psychotherapy protocols has accelerated only in recent years (Schenberg, 2018). This represents a paradigm shift recognizing that the temporal coordination of pharmacological and psychological interventions may produce

synergistic effects superior to either modality alone (Figueiredo et al., 2023; Nutt, 2024; Drozdz et al., 2022; Mathai et al., 2022).

Neurobiological Mechanisms

NMDA Receptor Antagonism and Neuroplasticity

Ketamine's primary mechanism involves antagonism of N-methyl-D-aspartic acid (NMDA) glutamate receptors, which promotes rapid increases in neuroplasticity and synaptic connectivity (Wolfson & Vaid, 2024; Nutt, 2024; Figueiredo et al., 2023; Johnston et al., 2023). Due to the high density of glutamate receptors in the cortex area of the brain, ketamine distorts and disturbs the rigidified thought patterns, characteristic in depression, and other mental health disorders (Nutt, 2024). At subanesthetic doses, ketamine increases dendritic spine density and stimulates synaptogenesis, particularly in the prefrontal cortex and limbic regions (Miller at al., 2025; Figueiredo et al., 2023; Johnston et al., 2023). These neurobiological changes create a critical window of heightened neural malleability lasting approximately 24-48 hours following administration (Figueiredo et al., 2023).

Brain-derived neurotrophic factor (BDNF), a crucial protein supporting neuronal survival and growth, increases substantially following ketamine administration. This upregulation of neuroplasticity markers facilitates the consolidation of new learning and memory patterns, which psychotherapy seeks to establish (Fletcher et al., 2025; Miller et al., 2025; Wolfson & Vaid, 2024; Figueiredo et al., 2023). The enhanced neuroplasticity induced by ketamine theoretically allows psychotherapeutic interventions to establish more durable cognitive and behavioral changes than psychotherapy alone (Figueiredo et al., 2023; Johnston et al., 2023).

Dissociation and Ego-Dissolution

A critical conceptual distinction in KAP involves understanding ketamine's dissociative properties. Traditionally, dissociation has been viewed as a side effect, but emerging evidence suggests that carefully contextualized dissociative experiences may contribute meaningfully to therapeutic outcomes (Wolfson & Vaid, 2024). In supportive therapeutic environments, ego-dissolution experiences—characterized by temporary dissolution of self-referential boundaries—may facilitate psychological reorganization and reduction of rigid maladaptive cognitions (Wolfson & Vaid, 2024; Figueiredo et al., 2023).

Research examining the relationship between psychedelic-type experiences and outcomes reveals significant correlations between mystical-type experiences and clinical improvement (Dakwar et al., 2014, 2018 cit. by Figueiredo et al., 2023). These experiences, characterized by feelings of interconnectedness, transcendence, and meaning, appear linked to sustained symptom reduction extending well beyond the duration of acute pharmacological effects (Figueiredo et al., 2023).

Default Mode Network and Salience Network

Contemporary neuroimaging research distinguishes ketamine's differential effects on large-scale brain networks. The Default Mode Network (DMN), associated with self-referential processing and narrative identity construction, shows characteristic changes following ketamine administration (Muscat et al., 2021). Simultaneously, the Salience Network (SN), related to embodied self-awareness and attention to significant stimuli, responds distinctly to ketamine's effects (Muscat et al., 2021). This dual-network perspective has informed novel treatment models proposing sequential dosing strategies to address both narrative and embodied dimensions of psychological distress (Muscat et al., 2021).

Clinical Efficacy and Treatment Outcomes

Treatment-Resistant Depression

Ketamine-assisted psychotherapy shows substantial efficacy in treatment-resistant depression (TRD), defined as inadequate response to at least two antidepressant trials at adequate doses and durations. A large retrospective effectiveness study of KAP across 11 clinics documented large treatment effects at three months (effect sizes: d = 0.75–0.86) that sustained at six months (d = 0.61–0.73) (Yermus et al., 2024). Notably, symptom improvements persisted for approximately five months following the final ketamine dose, suggesting enduring psychological reorganization rather than temporary biochemical symptom suppression.

Response rates in systematic reviews demonstrate that KAP may enhance ketamine's antidepressant effects compared to ketamine monotherapy alone (Gomes & Novais, 2025). In maintenance treatment studies, initial induction response rates of 82% were maintained above 80% after six months with periodic dosing schedules (Ryan et al., 2024), indicating sustained therapeutic benefit with ongoing structured treatment.

Anxiety Disorders and Post-Traumatic Stress Disorder

KAP demonstrates efficacy across anxiety spectrum disorders. In first responders and healthcare workers receiving group KAP for work-related stress, significant reductions occurred in anxiety symptoms, as Generalized Anxiety Disorder-7 scores declined from median 9.5 to 6, $p = 0.003$ (Flynn et al., 2025). Treatment effects extended to complex trauma presentations, with one intravenous ketamine protocol in a psychedelic paradigm producing large reductions in PTSD symptoms , as mean PCL-5 changed from 52.54 to 28.78, $d = 1.64$ (MacConnel et al., 2024).

Integration of ketamine with trauma-focused psychotherapy, such as Eye Movement Desensitization and Reprocessing (EMDR), shows particular promise. Ketamine-assisted EMDR for PTSD demonstrated significant PTSD symptom reductions (baseline mean 15.50 to post-treatment mean 9.88, large effect size $g = 1.01$) with functional improvements sustained across follow-up (Topel & Ciccone, 2025). The proposed mechanism involves ketamine's facilitation of adaptive memory reconsolidation, allowing trauma memories to undergo therapeutic updating without overwhelming the client's emotional regulation capacity.

Substance Use Disorders

Emerging evidence supports KAP's application to substance use disorders, though methodological limitations restrict definitive conclusions. Ketamine-assisted psychotherapy demonstrates signal for efficacy in alcohol use disorder, cocaine use disorder, and opioid use disorder, with several studies reporting increased abstinence rates and reduced cravings (Fletcher et al., 2025). A pilot study combining ketamine with motivational enhancement therapy for methamphetamine use disorder is currently underway, investigating both feasibility and mechanism through assessment of neuroplasticity markers.

The theoretical rationale involves ketamine's proposed ability to increase neuroplasticity and reduce withdrawal-associated dysphoria, thereby enhancing engagement with concurrent psychotherapy and facilitating more adaptive learning patterns incompatible with substance-seeking behavior (Thomas & Chambers, 2025).

Additional Clinical Applications

KAP shows emerging utility in eating disorders, with one case study documenting complete remission of severe bulimia nervosa following three treatment courses (Ragnhildstveit et al., 2021). In adolescent populations, early published cases document rapid symptomatic improvement in adolescents aged 14-19 with comorbid treatment-resistant depression, bipolar disorder, eating disorders, and trauma-related symptoms (Wolfson et al., 2023). Individuals with bipolar disorder and autism spectrum disorder demonstrated significant reductions in anger outbursts, anxiety, and suicidality (Harris et al., 2024).

In palliative care settings, a novel dissociative-psychedelic KAP model addresses end-of-life existential distress through structured protocol incorporating preparatory sessions, dual-dosing (low-dose and moderate-dose ketamine), and goals-of-care discussions, with emphasis on meaning-making and psychological safety (Campolina & De Oliveira, 2025).

Treatment Protocols and Procedural Variation

Dosing Strategies

Substantial heterogeneity characterizes KAP protocols across clinical settings. Ketamine may be administered intravenously (IV), intramuscularly (IM), sublingually (SL), or intranasally, with doses typically ranging from 0.5 to 1.5 mg/kg depending on route and clinical context (Drozdz et al., 2022). Two distinct dosing approaches emerge: psychedelic dosing (higher doses administered 24 hours before psychotherapy sessions) and psycholytic dosing (lower doses administered during psychotherapy sessions). A pilot study comparing these approaches found all participants showed symptom decline, with psychedelic approach participants showing larger, more consistent improvements (Batievsky et al, 2023). This distinction reflects different therapeutic models: psychedelic dosing prioritizes the altered conscious state and subsequent integration, while psycholytic dosing emphasizes dissociative facilitation during direct therapeutic work.

Sequential or tiered dosing protocols have been proposed and implemented, with some models utilizing low-dose ketamine in initial sessions followed by moderate-dose in subsequent sessions to address distinct psychological dimensions (Campolina & De Oliveira, 2025). Maintenance protocols typically employ dosing intervals of 2-3 weeks following the initial induction phase, with mean maintenance doses of approximately 1.13 mg/kg intramuscularly (Ryan et al., 2024).

Psychotherapy Integration

Critical to KAP's theoretical foundation is integration of psychotherapy before, during, and after ketamine administration. Pre-treatment psychotherapy establishes therapeutic alliance, clarifies treatment goals, and prepares patients for subjective ketamine experiences. Sessions preceding ketamine sessions typically employ psychoeducation regarding expected effects and anxiety management strategies (Drozdz et al., 2022; Figueiredo et al., 2023).

During ketamine administration, therapeutic presence - either passive presence or active therapeutic engagement of a therapist - varies across protocols. Some models emphasize minimal intervention during acute effects, providing eye shades and curated music to facilitate internal exploration. Others incorporate active psychotherapeutic guidance during the experience (Wolfson & Vaid, 2024). Concurrent psychotherapy during ketamine effects remains controversial regarding potential to enhance versus interfere with therapeutic process (Figueiredo et al., 2023).

Integration sessions occurring 24-48 hours post-administration represent a consistent protocol element. These sessions facilitate processing of subjective ketamine experiences, cognitive restructuring of insights generated during altered states, and consolidation of therapeutic gains into daily functioning. The timing capitalizes on peak neuroplasticity window while allowing sufficient time for acute dissociative effects to resolve (Miller et al., 2025).

Therapeutic Modalities

Diverse psychotherapeutic approaches have been incorporated into KAP protocols, including cognitive-behavioral therapy, acceptance and commitment therapy, somatic therapies, motivational enhancement therapy, functional analytic psychotherapy, and psychodynamic approaches (Kew et al., 2023). A systematic review identified considerable heterogeneity in psychotherapy type, with no clear superiority emerging for specific modalities. Integration appears more important than specific theoretical orientation, with emphasis on therapeutic alliance, safety, and meaning-making (Dworkin et al., 2023).

Group psychotherapy models of KAP have demonstrated efficacy, reducing treatment costs and potentially enhancing collective therapeutic factors (Robinson et al., 2023; Flynn et al., 2025).

Acute Subjective Experiences and Therapeutic Mechanisms

Phenomenology of Ketamine Experiences

Qualitative research examining subjective ketamine experiences reveals complex, often contradictory phenomenological features. Participants report simultaneous experiences of dissociation and connection, ego-dissolution and enhanced self-awareness, and profound meaningfulness amid sensory disorientation (Mollaahmetoglu et al., 2021). These paradoxical experiences appear contextualized substantially by treatment setting and therapeutic frame.

Set and setting—participants' expectations and the physical/social environment—significantly influence acute experiences and subsequent outcomes (Wolfson & Vaid, 2024). Professional, supportive environments with trained clinicians present correlate with more therapeutically oriented experiences compared to unstructured settings. Psychedelic-type experiences characterized by a sense of unity, transcendence, and ego-dissolution show stronger associations with clinical improvement than purely dissociative experiences (MacConnel et al., 2024).

Belief-Updating and Cognitive Restructuring

Ketamine appears to facilitate adaptive belief updating distinct from depression-related negative bias. This selective cognitive flexibility may represent a mechanism by which ketamine facilitates psychotherapy by increasing receptivity to alternative perspectives and reducing automatic negative thought patterns (Nutt, 2024; Figueiredo et al., 2023).

The window of enhanced neuroplasticity following ketamine administration seems to create an opportunity for psychotherapy to establish new neural pathways supporting adaptive cognition and behavior. Integration sessions during this neuroplastic window theoretically allow therapeutic insights and behavioral learning to become more deeply encoded compared to psychotherapy alone (Muscat et al., 2021; Nutt, 2024; Figueiredo et al., 2023).

Safety and Tolerability

Adverse Events

Safety data from retrospective chart reviews and clinical trials consistently document good tolerability of KAP when administered in professional settings with appropriate screening and monitoring. In a review of 128 participants across 448 ketamine-assisted therapy sessions, adverse events included elevated blood pressure in 49.16% of sessions (transient), nausea in 12.05%, vomiting in 2.52%, headache in 3.35%, and dizziness in seven sessions (Tsang et al., 2023). No participants dropped out due to adverse events in this cohort, and serious adverse events were not reported.

Acute dissociative and perceptual effects are intrinsic to ketamine administration at therapeutic doses but typically resolve within hours. When occurring in supportive professional settings with experienced clinicians, these experiences are generally not clinically problematic and may contribute to therapeutic effect (Wolfson & Vaid, 2024). Transient increases in blood pressure and heart rate occur predictably and can be managed with standard medical monitoring.

Ketamine Use Disorder

Long-term risks of ketamine treatment include potential for problematic use patterns. In a maintenance ketamine-assisted psychotherapy study of 70 patients over six years, one participant developed ketamine use disorder requiring residential treatment (Ryan & Heifets, 2024). This represents approximately 1.4% of the maintenance treatment cohort, suggesting that problematic ketamine use remains a genuine but uncommon risk requiring careful patient selection and monitoring.

Risk factors for problematic ketamine use include personal or family history of substance use disorders, though individuals with history of substance abuse have been successfully treated with KAP when appropriate precautions are implemented. Combination with behavioral interventions addressing substance use patterns and psychoeducation regarding ketamine's abuse potential appear protective (Fletcher et al., 2025).

Contraindications and Special Populations

Absolute contraindications include uncontrolled hypertension, cardiovascular instability, and active untreated psychosis. Relative contraindications include history of

dissociative disorders, active substance use, and certain personality pathologies, though emerging evidence suggests some previously contraindicated populations may benefit from carefully structured KAP (Hicks et al., 2025).

Adolescent populations appear to tolerate KAP well, though studies remain limited. Early case series in adolescents aged 14-19 documented good tolerability with no serious adverse events (Wolfson et al., 2023). Family involvement appears important for adolescent treatment success, reflecting developmental considerations distinct from adult KAP implementation.

Integration into Clinical Practice

Treatment Setting and Infrastructure

KAP has been implemented across diverse clinical settings, from university research centers to community mental health clinics to private practices. A 2023 national survey of U.S. mental health facilities with ketamine infusion therapy identified 134 programs, with approximately 63% offering dual diagnosis treatment for mental health and substance use disorders (Ware, 2024). Infrastructure requirements include medical monitoring capability, trained clinicians skilled in both ketamine administration and psychotherapy, and structured integration protocols. To date, no study or any other form of inventory was found for Portugal, on the use of KAP, even though there are references in published literature as ketamine has been used within off-label framework (Figueiredo et al, 2023; Teixeira, 2024).

The therapeutic alliance—the collaborative relationship between clinician and patient—emerges as critical for KAP outcomes (Kamilar-Britt et al., 2023; Figueiredo et al., 2023). Despite decades of research establishing alliance's importance in psychotherapy, few publications to date were found to address therapeutic alliance in KAP contexts. Enhanced attention to alliance measurement and cultivation could enhance KAP's impact, though this remains underexplored relative to medication-specific factors.

Cultural Considerations and Equity

Emerging research has shown some significant cultural and socioeconomic barriers to KAP access. A phenomenological study of culturally diverse individuals (Hispanic, African American, Asian, Native American, biracial, LGBTQIA+) at a sliding-scale community clinic identified four major themes: insufficient financial resources, race/ethnicity-related

concerns, perceived stigma, and importance of culture and ritual (Rojas et al., 2025). Results demonstrate that cultural context substantially influences KAP experience, suggesting need for culturally attuned treatment planning and trauma-informed approaches responsive to historical and ongoing discrimination, in particular considering culturally-informed trauma treatments. Such approaches recognize ketamine's consciousness-altering properties as compatible with healing traditions present in many cultures, potentially enhancing acceptability and efficacy in underserved populations.

Cost-Effectiveness

Economic analyses suggest KAP may offer favorable cost-effectiveness despite higher per-session costs compared to conventional psychotherapy, as improving the outcomes may reduce overall healthcare utilization, offsetting higher treatment costs. A cost-effectiveness analysis comparing a ketamine-assisted therapy program to standard group psychotherapy in British Columbia found KAP produced better outcomes at lower cost, saving $14,481 per individual while producing 0.94 additional quality-adjusted life years over five years (Tsang, 2024).

Research Gaps and Future Directions

Methodological Limitations

Current KAP literature reveals substantial methodological constraints limiting definitive efficacy conclusions. Small sample sizes, heterogeneous protocols, high attrition rates, and limited long-term follow-up characterize many studies. Many investigations employ retrospective designs without control groups, restricting causal inference regarding KAP versus placebo or active comparison conditions (Dworkin et al., 2023).

The distinction between ketamine's pharmacological effects and contextual/psychotherapeutic factors remains inadequately investigated. Few factorial design studies isolating drug effects from psychotherapy components have been conducted, limiting understanding of synergistic mechanisms (Dworkin et al., 2023). Future research requires larger randomized controlled trials with standardized protocols enabling comparison across sites.

Mechanistic Understanding

While neurobiological mechanisms have been increasingly characterized, psychological mechanisms of change remain incompletely understood. The relative contribution of acute dissociative experience versus post-administration neuroplasticity to clinical outcomes requires clarification. Some researchers propose that subjective experience during ketamine administration may be neither necessary nor sufficient for therapeutic benefit, with meaningful improvement instead reflecting post-treatment neuroplastic reorganization (Miller et al., 2025).

Standardization and Accessibility

Development of standardized KAP protocols through consensus-building among researchers and clinicians remains urgently needed. Variability in dosing, administration routes, psychotherapy modalities, and treatment duration poses challenges to the efficacy evaluation and clinical implementation (Kew et al., 2023). Professional guidelines and training standards could improve consistency while allowing appropriate clinical flexibility.

Accessibility barriers related to cost, geographic availability, and specialized training requirements limit KAP's reach. Community-based models and telepsychiatry integration represent emerging directions potentially expanding access to underserved populations (Rojas et al., 2023). Integration with digital mental health platforms could further enhance accessibility and treatment consistency.

Comparison with Psychedelic-Assisted Therapies

Unique Characteristics of Ketamine

Ketamine's position within the psychedelic-assisted therapy landscape differs meaningfully from classical psychedelics like psilocybin. Ketamine's rapid onset of action, briefer duration of acute effects, and legal prescriptibility in many jurisdictions distinguish it from Schedule I substances currently limited to research contexts. These practical differences have positioned ketamine as the first psychedelic-assisted therapy approaching clinical implementation in mainstream mental health settings (Nutt, 2024; Teixeira, 2024).

Mechanistically, ketamine's NMDA antagonism differs from classical psychedelics' serotonin 2A agonism (Nutt, 2024; Teixeira, 2024; Figueiredo et al., 2023). While both appear to enhance neuroplasticity and reduce default mode network activity, the specific

neurobiological pathways and subjective phenomenology differ. Ketamine produces dissociative effects alongside psychedelic-type experiences, whereas classical psychedelics typically produce primarily psychedelic (perceptual alteration and ego-dissolution) effects (Marguilho et al., 2022).

Integration with Other Modalities

KAP can be integrated with other evidence-based interventions. Combination of ketamine with transcranial magnetic stimulation, electroconvulsive therapy, and pharmacological augmentation strategies has shown promise in preliminary reports (Ali & Viqar, 2024).

Some research explores synergistic effects of combining ketamine-assisted psychotherapy with couple or family modalities, recognizing that relationship distress often accompanies individual mental illness (Khalifian et al., 2024). These integrative approaches remain early in development but suggest broader applicability of the KAP framework beyond individual treatment.

Conclusion

Ketamine-assisted psychotherapy represents a promising emerging intervention for treatment-resistant psychiatric conditions, supported by growing empirical evidence of efficacy and generally favorable safety profiles when implemented in professional settings. The integration of ketamine's rapid neuroplasticity-enhancing effects with structured psychotherapy creates a treatment model addressing limitations of either modality alone.

Clinical efficacy has been documented across treatment-resistant depression, anxiety disorders, post-traumatic stress disorder, substance use disorders, and additional psychiatric conditions. Effect sizes generally exceed those of conventional psychiatric treatments, with improvements sustained well beyond the period of active pharmacological effects, suggesting durable psychological reorganization.

However, substantial research gaps constrain definitive efficacy conclusions. Methodological limitations, heterogeneous protocols, and inadequate mechanistic understanding highlight the need for larger, better-controlled trials with standardized procedures, as well as other research approaches such as qualitative. Professional consensus

regarding optimal protocols, training standards, and accessibility approaches would facilitate responsible implementation in mainstream clinical practice.

Future development should prioritize rigorous investigation of synergistic mechanisms, standardization of evidence-based protocols, equitable access in underserved populations, and investigation of long-term sustainability and relapse prevention. With continued research and thoughtful clinical implementation, KAP may substantially expand treatment options for psychiatric disorders that have resisted conventional interventions, reducing suffering in vulnerable populations and catalyzing broader paradigm shifts in psychiatric treatment.