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MESTRADO INTEGRADO EM MEDICINA

Efficacy of Ketamine-Assisted Psychotherapy in Treatment-Resistant Depression – a case series

Marlene Curralo da Cruz Pereira Teixeira

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Trabalho efetuado sob a Orientação de:

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E sob a Coorientação de:

Professora Doutora Maria Augusta Vieira Coelho

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Efficacy of Ketamine-Assisted Psychotherapy in Treatment-Resistant Depression - a case series

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UC Dissertação - DECLARAÇÃO DE TRANSPARÊNCIA
RELATIVAMENTE À UTILIZAÇÃO DE FERRAMENTAS DE CHATBOT GENERATIVO BASEADAS EM LARGE LANGUAGE MODELS

Eu, Marlene Cunado da Cruz Pereira Teixeira, abaixo assinado, nº mecanográfico 201907336, estudante do 6º ano do Ciclo de Estudos Integrado em Medicina, na Faculdade de Medicina da Universidade do Porto, declaro que:

☒ Não procedi à utilização de ferramentas de *chatbox* generativo baseadas em *large language models* para nenhuma das tarefas no contexto do meu trabalho de Dissertação ou Monografia

☐ Procedi à utilização de ferramentas de *chatbox* generativo baseadas em *large language models* no contexto do meu trabalho de Dissertação ou Monografia, encontrando-se todas as interacções (*prompts* e respostas) transcritas em anexo bem como a indicação das aplicações utilizadas.

Neste sentido, confirmo que a eventual utilização de ferramentas de *chatbox* generativo baseadas em *large language models* no contexto do meu trabalho de Dissertação ou Monografia foi exclusivamente descrita na sequência de *prompts* e respostas transcritos em anexo e nas aplicações indicadas.

Faculdade de Medicina da Universidade do Porto, 21/03/2025

Assinatura conforme cartão de identificação:
Marlene Cunado da Cruz Pereira Teixeira

Dedicatória

À curiosidade, à vontade de descobrir novas coisas, à minha família que me apoia em todos os momentos, aos meus amigos que me acompanharam nestes anos de faculdade e que levo para o resto da vida, às incansáveis viagens semanais de domingo à noite para o Porto, às viagens de metro para casa, a todos os momentos passados no salão de alunos, a cada estágio do curso, às videochamadas longas, às conversas com os meus amigos, à minha Lucy por se deitar aos meus pés sempre que me sento para estudar ou escrever, às minhas playlists de Spotify que me acompanharam na escrita desta dissertação e nestes anos, à Marlene que decidiu seguir este caminho há 6 anos e que cresceu tanto e que continua a crescer, à incerteza que me assustava quando era mais nova e que encaro agora com naturalidade, a todas as oportunidades que tive nestes 6 anos, a cada decisão que tomei,

OBRIGADA!

"- Qual é um dos teus sonhos?"

"- Quero descobrir a cura de alguma doença". Foi o que disse quando tinha 15 anos.

Mãe, pai, irmã,

Está feito!

Title: Efficacy of Ketamine-Assisted Psychotherapy in Treatment-Resistant Depression – a case series

(Original Article)

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Abstract
Ketamine-assisted psychotherapy (KAP) has emerged as a potential approach for patients with Treatment-Resistant Depression (TRD). However, several questions regarding the optimal implementation protocol and efficacy have yet to be thoroughly studied. We conducted a case series involving 31 patients diagnosed with TRD. Our KAP protocol, supervised by a physician, consisted of two preparation sessions, followed by a minimum of four weekly sessions of intravenous ketamine administration, starting with an initial dose of 0.5 mg/kg. Each ketamine session was followed by an integration psychotherapy session the next day. A follow-up reassessment was held one month after the final intervention to evaluate whether the antidepressant benefits were sustained. Depressive and anxiety symptoms were assessed using the Patient Health Questionnaire-9 (PHQ-9) and the Generalized Anxiety Disorder 7-item (GAD-7), respectively. The evaluations occurred during the second preparation session, the last integration session, and the reassessment consultation. There was significant improvement ($p < 0.05$) in PHQ-9 scores following the KAP intervention and at the reassessment evaluation, with mean scores decreasing from 17.68 (SD = 0.81, 95% CI = 16.03;19.32) at baseline to 6.87 (SD = 0.86, 95% CI = 5.11;8.63) in the last integration session, and to 7.71 (SD = 1.19, 95% CI = 5.24;10.17) at reassessment. Importantly, 38.70% of patients remitted from depression immediately after KAP, with an increase to 41.70% at reassessment. This study suggests psychotherapy may sustain ketamine's antidepressant effects, but further research is needed to assess the long-term impact and identify the most effective psychotherapy for patients with TRD.

Keywords: Case Series; Treatment-Resistant Depression; Ketamine-Assisted Psychotherapy; Ketamine; Remission.

Introduction

(R, S)-Ketamine (hereafter called ketamine) is a noncompetitive N-methyl-D-aspartate receptor (NMDAR) antagonist that has been approved by the FDA for general anesthesia since the 1970s.[1] In 2000, Berman *et al.* published the first double-blind, placebo-controlled trial demonstrating the rapid antidepressant effects of ketamine in patients with Major Depressive Disorder (MDD), highlighting its potential use in the treatment of depression.[2] Ketamine can be administered via intravenous (IV) infusion, intramuscular and subcutaneous injections, or intranasal and oral routes. Among these, the intravenous and intranasal routes are associated with a swift alleviation of depressive symptoms.[3] The effects of ketamine are dose-dependent, with IV doses of 1-2 mg/kg being used for the induction of anesthesia, 0.25-0.5 mg/kg in pain management, and subanesthetic doses of 0.5 mg/kg in the treatment of psychiatric conditions, including depressive and Post-Traumatic Stress Disorder (PTSD) symptoms.[4] Mood disorders are associated with the loss of glial cells in the frontal cortex, which are crucial for glutamate metabolism and signaling. Chronic stress appears to exacerbate this dysfunction by damaging astrocytes and impairing extracellular glutamate degradation, leading to the overactivation of NMDA receptors and resulting in synaptic loss and apoptosis.[5] Ketamine preferentially inhibits NMDARs on GABAergic interneurons, leading to the disinhibition of pyramidal neurons and enhancing excitatory glutamatergic signaling in the medial prefrontal cortex.[6] This glutamate release theoretically stimulates several pathways, including AMPA receptor activation, BDNF secretion, and mTOR signaling, resulting in synaptic growth.[7,8] An alternative hypothesis suggests that ketamine's antidepressant effects arise from eEF2K inhibition due to Ca^{2+} influx blockade, along with increased BDNF release, promoting synaptic potentiation and restoring depression-disrupted neural circuits.[8]

A single subanesthetic dose of ketamine (0.5 mg/kg, IV infusion for 40 min) can relieve depressive symptoms within hours, peaking at 24 hours,[4,9] unlike monoaminergic antidepressants that take 4 to 6 weeks.[10] In Treatment-Resistant Depression (TRD) patients, ketamine shows response rates of over 50% and remission rates of 30%-50%.[11] However, its effects usually last around 7 days,[12] requiring multiple doses for sustained benefits, though repeated infusions may not produce significantly greater effects than a single infusion, as the initial dose tends to induce the most substantial improvement.[13] One possible approach to extending ketamine's effects is through psychotherapy, particularly Psychedelic-Assisted Psychotherapy (PAP).[14] Although ketamine is not a traditional psychedelic, it induces similar dissociative effects that enhance emotional learning and neuroplasticity.[15,16] This altered state, when combined with psychotherapy, fosters meaningful emotional experiences, increases openness, and promotes treatment adherence.[17] Ketamine-Assisted Psychotherapy (KAP) has been tested for various conditions, including depression, PTSD, and bipolar II disorder.[15] Despite variability in study protocols, KAP has consistently shown effectiveness in reducing anxiety and depressive symptoms.[17] With approximately 33% of MDD cases progressing to TRD,[12] it is crucial to explore promising therapeutic approaches to enhance treatment efficacy. In this context, KAP is presented as an optional treatment for patients with TRD. Despite the growing body of literature on KAP, research regarding its true effectiveness in TRD remains limited. We present a case series in which we have administered a KAP protocol aimed at providing new insights into the potential of ketamine when combined with psychotherapy. This approach seeks to investigate whether the antidepressant effects of ketamine can be enhanced through psychotherapy and to evaluate the overall effectiveness of the KAP protocol in promoting sustained remission in patients with TRD.

Methods

The study protocol was approved by the Ethics Committee of Casa de Saúde Santa Catarina Hospital in Porto, Portugal. Prior to enrollment, all participants provided written Informed Consent. The study was conducted at the same institution.

Study Design

A retrospective, single-center case series was conducted on a population of patients with a clinical diagnosis of TRD, selected according to predefined inclusion criteria, between August 2023 and December 2024. Patients underwent intervention using a KAP protocol, detailed as follows.

Medical Team

The intervention was conducted by a medical team of two consultant psychiatrists, each of whom went through a 3-month KAP intervention course.

Procedures

Participants

The main criterion for participation in the study was a clinical diagnosis of TRD. Patients could seek treatment spontaneously or be referred by their attending psychiatrist or psychologist. To initiate the request, the patient's attending clinician or the patient themselves in cases where treatment was sought independently, had to complete a designated form. Each application was reviewed by the psychiatrists involved in the therapeutic approach. The physicians then determined whether to schedule a pre-treatment assessment, request further information from the attending clinician or decline the request due to the absence of inclusion criteria.

Pre-Treatment Assessment

The pre-treatment evaluation consisted of a session conducted by one of the psychiatrists participating in the study, followed by a team discussion to reach a final decision. During this process, an extensive clinical history was obtained, addressing the current illness, personal and family medical history, personality traits, a mental state examination, the formulation of a primary diagnostic hypothesis, and the identification of any comorbid psychiatric diagnoses. In this first session, the patient was comprehensively informed about KAP, and any initial questions or concerns were clarified. The main purpose of this assessment was to identify the presence of both inclusion and exclusion criteria, which are outlined as follows:

Inclusion Criteria

Moderate to severe TRD, defined by:

- **a.** Duration of current episode longer than six months.
- **b.** Lack of clinical response after:
    - **I.** At least two antidepressant regimens, in adequate doses and duration, including:
        - (i) A selective serotonin reuptake inhibitor (SSRI)
        - (ii) A combination of antidepressants (e.g., venlafaxine and mirtazapine)
        - (iii) A potentiation strategy (e.g., atypical antipsychotic, lithium, thyroid hormone)

II. Psychotherapy (cognitive behavioral, interpersonal, psychodynamic or other)

c. An abstract reasoning and symbolic thinking that constitutes an indication for psychotherapy.

Exclusion Criteria

1. Psychotic symptoms or psychomotor impairment.
2. Current abuse of or addiction to psychoactive substances.
3. Personal history of schizophrenia, bipolar I disorder or other psychotic disorder.
4. Severe impulsivity or antisocial behavior.
5. Severe personality disorder.
6. Intellectual development disorder or low level of education.
7. Family history (first-degree relatives) of psychotic symptoms in the context of schizophrenia or bipolar disorder.
8. Uncontrolled hypertension; unstable angina; high-risk coronary vascular disease; hyperthyroidism; pheochromocytoma; uncontrolled epilepsy; glaucoma; severe liver disease; sleep apnea syndrome.
9. Pregnancy or breastfeeding.

Intervention

The KAP protocol included two preparation sessions, followed by a minimum of four weekly ketamine administration sessions, each accompanied by integration psychotherapy sessions on the following day. The intervention concluded with a reassessment and therapeutic decision consultation one month after the final integration

session, ensuring follow-up, continuity of care, and the patient's transition back to their attending clinician.

Preparation Sessions

In the weeks preceding the first ketamine session, two two-hour preparation sessions were conducted. The main objectives were to establish a trust-based therapeutic relationship and to inform the patient about the expected experiences during and after ketamine administration. Additionally, these sessions aimed to deepen the understanding of the patient, focusing on their interpersonal relationships, biographical history, defense mechanisms, behavioral habits, dreams, and spiritual beliefs.

The preparation sessions took place in the same room where ketamine was administered, helping the patient become familiar with the environment and other components of the experience, such as music and the use of a blindfold.

During these sessions, patients were introduced to the treatment paradigm, including the potential therapeutic benefits of altered states of consciousness and the importance of integrative psychotherapy. Patients were encouraged to approach the experience with curiosity and acceptance while minimizing fear or resistance to the thoughts and emotions that might emerge. Furthermore, aspects related to the safety of the procedure were also discussed, to reassure patients about potential side effects, clarifying that while ketamine's psychological effects could be intense, its physiological risks at the administered doses were minimal.

At the end of the second preparation session, patients reviewed and signed the Informed Consent form. In this session, the medical team also administered the Patient Health Questionnaire-9 (PHQ-9) and the Generalized Anxiety Disorder 7-item (GAD-7) scales to assess depressive and anxiety symptoms.

The clinicians provided patients with dietary and lifestyle guidelines to follow before each ketamine session. These included fasting for 4 hours before drug administration, abstaining from alcohol and psychoactive substances for 48 hours beforehand, and continuing regular medications, including psychotropic drugs. Tobacco/nicotine use was permitted. Lastly, a designated individual was assigned to accompany the patient home after each session.

Ketamine Administration Sessions

The ketamine administration sessions were conducted in a room designed to provide optimal lighting, comfort, and safety, under the supervision of one of the team's physicians. During the sessions, patients lay on a hospital bed, with their eyes shielded by a blindfold to minimize external distractions. They listened to pre-selected music, chosen in collaboration with the patient, through headphones. This approach is believed to enhance tolerance to potential dissociation, alleviate associated anxiety, lower blood pressure, and facilitate the acceptance of higher ketamine doses.[18]

Ketamine was administered intravenously under the continuous presence and supervision of the doctor, using subanesthetic doses that varied across sessions based on the patient's response. The initial dose was 0.5 mg/kg, with adjustments made in subsequent sessions (up to a maximum of 1.2 mg/kg) according to the antidepressant effects observed after each session. Intravenous ketamine infusion was delivered over 40 minutes, requiring venous access, ideally placed in one of the upper limbs. The standard ketamine ampoule, with an initial concentration of 50 mg/mL, was diluted to a final concentration of 2 mg/mL for continuous infusion via syringe. The preparation involved drawing 2 mL of ketamine (50 mg/mL) into a 50 mL syringe and adding 48 mL of 0.9%

saline solution, resulting in a total volume of 50 mL. Excess ketamine was disposed of following established guidelines for the disposal of narcotics and controlled substances.

Each ketamine session lasted 2 hours and 30 minutes, with the most intense mental state changes occurring during the first 40 minutes, followed by a recovery phase and content recall. During this time, the clinician adopted a posture of attentiveness while maintaining a minimally intrusive presence, avoiding psychotherapeutic intervention during drug administration. Interaction with the patient was generally limited to situations where the patient explicitly requested it or exhibited significant distress, at which point reassurance and support were provided. Additionally, the doctor was also responsible for managing any adverse effects, according to established protocols (outlined in the annex) and for performing regular monitoring. This included measuring blood pressure, heart rate, respiratory rate, and peripheral oxygen saturation, upon the patient's arrival, every 30 minutes during the session, and at discharge.

The patient remained under observation for at least 90 minutes post-ketamine administration, until the doctor deemed them fit for discharge. This decision was based on vital sign measurements, mental state examination, and assessment of gait and balance. The patient was then discharged accompanied by their caregiver.

Integration Sessions

The integration sessions, which lasted one hour, took place the day after each drug administration session. A key aspect of this protocol was its combination of pharmacological and psychotherapeutic methods, requiring a more active role from patients compared to traditional antidepressant treatments. This approach was based on Acceptance and Commitment Therapy (ACT).

These sessions aimed to enhance psychological flexibility, foster insight, improve mentalization, encourage curiosity and develop strategies for coping with suffering and frustration. The objectives were personalized to address dysfunctional beliefs, behavioral changes or traumatic memories. In all patients, strengthening the therapeutic relationship and ensuring long-term benefits were core goals.

In the final integration psychotherapy session, the same assessment instruments used during the initial preparation sessions (PHQ-9 and GAD-7) were administered to evaluate symptom severity.

Decisions regarding the number of drug administration and integration sessions, as well as the transition to follow-up care in Psychiatry or Psychology, or discharge, were made collaboratively with the patient after team discussions.

Reassessment and Therapeutic Decision Consultation

At the reassessment appointment, held one month after the final integration psychotherapy session, the physicians conducted a clinical interview and administered the PHQ-9 and GAD-7 scales again. This process aimed to evaluate the patient's response to the KAP protocol and assess any changes in symptom severity since the last integration session.

Measures and Data Collection

Participant's data were collected through an extensive clinical history, which included sociodemographic information (age, gender, residence), aspects related to the current illness (regular medication, past psychotherapy, and current or past follow-up with psychiatrists and psychologists), and personal and family medical history. Depressive symptoms and anxiety disorders were assessed using the PHQ-9 and GAD-7 scales, respectively.

The nine-item PHQ-9 is a self-reported screening test for depression. This questionnaire assesses symptom severity across various domains, including anhedonia, depressed mood, sleep disturbances, fatigue, appetite changes, feelings of guilt or worthlessness, trouble concentrating, psychomotor agitation or retardation, and suicidal ideation.[19] Scores range from 0 to 27, as each of the nine items is rated on a scale from 0 ("not at all") to 3 ("nearly every day"). A total score of 0-4 indicates no depression, 5-9 indicates mild depression, 10-14 indicates moderate depression, 15-19 indicates moderately severe depression, and 20-27 reflects severe depression. A score of ≥10 is the standard cut-off value for detecting major depression.[20]

The GAD-7 scale is a self-administered seven-item tool widely employed for assessing the severity of anxiety disorders. In addition to generalized anxiety disorder (GAD), it is also effective in identifying other anxiety disorders, such as panic disorder, social anxiety disorder, and PTSD.[21] Scores range from 0 to 21, with 0-4 reflecting no anxiety, 5-9 mild anxiety, 10-14 moderate anxiety, and 15-21 severe anxiety. The standard cut-off value for screening GAD is 9 or above.[22]

Statistical Analysis

All statistical analyses were conducted using *Statistical Package for the Social Sciences* (SPSS), version 30.0. A significance level of 0.05 was applied for all statistical tests.

A descriptive analysis was performed to summarize the sample characteristics. For continuous variables (Age, Number of ketamine sessions, PHQ-9, and GAD-7 scores), the mean, standard deviation, and 95% Confidence Interval were reported. For categorical variables (Gender, and Ongoing psychotherapy), percentages were calculated to represent the distribution across the sample.

Depression and anxiety severity were classified into distinct categories based on the PHQ-9 and GAD-7 scales, respectively. Depression levels were categorized as “no depression”, “mild depression”, “moderate depression”, “moderately severe depression”, and “severe depression”, while anxiety levels were classified as **“**no anxiety”, “mild anxiety”, “moderate anxiety”, and “severe anxiety”. The distribution of patients across these categories was expressed in percentages at three assessment stages: before the KAP treatment, at the final integration session, and at the reassessment appointment. To determine whether the distribution of patients across severity classifications underwent significant changes over time, the Friedman test was applied. A p-value < 0.05 was considered indicative of statistically significant changes in the distribution across the assessment stages.

To evaluate changes in depressive and anxiety symptoms, the PHQ-9 and GAD-7 questionnaires were administered at three time points: prior to the KAP treatment, at the final integration psychotherapy session following the last ketamine administration, and at the reassessment appointment one month after the final integration session. Data normality was assessed using the Shapiro-Wilk test, with variables considered non-normally distributed if $p < 0.05$. Based on this, the Wilcoxon signed-rank test was applied to analyze differences in PHQ-9 and GAD-7 scores before and after KAP treatment, while the paired t-test was employed to compare baseline scores with those obtained at reassessment.

The response to KAP treatment for depression and anxiety was classified into five categories based on changes in the PHQ-9 and GAD-7 scores. “No response” was defined as cases where the pre-treatment scores were the same as those at the reassessment or final integration session. “Partial response” was considered when the difference between the pre-treatment score and the score at the last integration session or reassessment was

less than half of the pre-treatment score. A “response” was defined as cases where the difference between the pre-treatment score and the score at the last integration session or reassessment was equal to or greater than half of the pre-treatment score. “Remission” was defined as cases where the scores at the reassessment or final integration session were ≤ 4. “Progression” referred to an increase in scores compared to pre-treatment values. This classification was performed at two time points: at the conclusion of KAP treatment and at the reassessment session. To evaluate whether there were statistically significant differences in the distribution of patients across these categories of response and remission, Fisher’s exact test was applied, with a significance level set at $p < 0.05$ to determine statistical significance.

Quality Control

The protocol was implemented by the medical team composed of consultant psychiatrists, while the statistical analysis was conducted by an independent observer, a medical student, who had no prior knowledge of the patients and was not directly involved in implementing the protocol.

This case series has been reported in line with the PROCESS Guideline.[23]

Results

The protocol was implemented as planned, without any changes to the intended intervention.

Population

This study included 31 participants at baseline, with 24 completing the reassessment appointment. The same 31 patients were assessed before and after treatment, with 7 patients lost to follow-up during the reassessment phase: 2 of them returned to their home country, while the other 5 missed the reassessment consultation. The mean age of our baseline population was 45.71 years. The sample was 54.80% female, and 48.40% of participants were engaged in ongoing psychotherapy. Furthermore, the average number of ketamine sessions per patient was 4.32. Table 1 summarizes these findings.

Depression and Anxiety outcomes

Following KAP, PHQ-9 scores showed a significant decrease. The mean score dropped from 17.68 (SD = 0.81, 95% CI = 16.03;19.32) before treatment to 6.87 (SD = 0.86, 95% CI = 5.11;8.63) after treatment, with a slight increase to 7.71 (SD = 1.19, 95% CI = 5.24;10.17) at reassessment (Table 2).

The Wilcoxon signed-rank test was used for the full sample ($N = 31$), confirming a significant reduction in PHQ-9 scores after treatment ($p < 0.05$) (Table 3). For the 24 participants who completed the reassessment, the difference between baseline and reassessment scores was analyzed using a paired t-test, also showing a statistically significant difference ($p < 0.05$) (Table 4).

The severity levels of depression showed an important improvement. The percentage of participants identified as having “severe depression” decreased from 35.50% to 3.20% after treatment and reached 0% during the reassessment. Additionally, the proportion of patients experiencing “no depression” increased from 0% to 38.70% post-treatment and further to 41.70% at the time of reassessment (Table 2).

A similar pattern was observed for anxiety, with GAD-7 scores decreasing from 13.77 (SD = 0.70, 95% CI = 12.34;15.21) at baseline to 5.77 (SD = 0.79, 95% CI =

4.16;7.39) post-treatment, with a slight increase to 7.42 (SD = 0.99, 95% CI = 5.37;9.47) at reassessment (Table 2).

The Wilcoxon signed-rank test was performed on the full sample (N = 31), confirming a significant reduction in GAD-7 scores from baseline to post-treatment ($p < 0.05$) (Table 3). For the 24 participants who completed the reassessment, a paired t-test was conducted to compare baseline and reassessment scores, also revealing a statistically significant difference ($p < 0.05$) (Table 4).

The proportion of participants with "severe anxiety" decreased from 35.50% to 6.50% post-treatment and remained at 12.50% at reassessment. Meanwhile, those experiencing "no anxiety" increased from 3.20% to 58.10% post-treatment, with a slight decrease to 33.30% at reassessment (Table 2).

Treatment Response

Regarding depression, 38.70% of participants achieved remission after KAP, which increased to 41.70% at reassessment. Additionally, 38.70% initially showed a treatment response, although this proportion declined to 20.80% at reassessment. The partial response rate increased from 12.90% to 37.50%. Notably, 3.20% of participants, corresponding to one patient, exhibited disease progression post-treatment. However, no cases of disease progression were observed at the final follow-up assessment.

For anxiety, remission was observed in 58.10% of participants following KAP treatment, though this decreased to 33.30% at reassessment. The proportion of individuals classified as treatment responders increased significantly from 19.40% post-treatment to 58.30% at reassessment. Additionally, 6.50% of participants demonstrated disease progression following KAP treatment. In contrast to depression, 8.30% of patients exhibited symptom progression at reassessment.

Table 2 summarizes these findings.

Analysis of Severity Distribution

To account for the differences in sample size at various assessment stages, we re-evaluated the percentages reflecting treatment response and the severity of depression and anxiety based on the 24 participants who attended the reassessment appointment. This adjustment allowed for accurate comparisons at three time points: before the KAP intervention, immediately after KAP, and during the reassessment.

For both depression and anxiety severity**,** there was a significant shift in distribution over time ($p < 0.05$, Friedman test). In contrast, the overall change in treatment response distribution for depression and anxiety was not statistically significant ($p = 0.22$ and $p = 0.15$, respectively, Fisher's exact test).

These findings are summarized in Table 5.

Safety and Tolerability

The ketamine administration was well tolerated by all participants, with no serious or unexpected adverse events reported. However, some adverse effects were observed. The most common was nausea, which required administration of oral ondansetron, 8 mg, in some cases for symptom control. Additionally, some patients experienced transient increases in blood pressure, requiring the use of oral captopril, 25 mg. These effects were generally mild, transient, and consistent with those previously described in the literature for subanesthetic doses of ketamine,[24] reinforcing the safety of the protocol used.

Patient perspective

During the integration psychotherapy sessions, physicians collected patients' perspectives on the intervention. Participants generally described their experiences as positive and meaningful. Many reported feeling a sense of fluctuation during the ketamine administration sessions, while others expressed a feeling of fusion with the surrounding space.

Discussion

Summary of Findings and Literature Review

In recent years, KAP has gained recognition as a promising therapeutic approach for TRD, integrating ketamine's rapid antidepressant effects with the theoretically sustained benefits of psychotherapy. As previously mentioned, ketamine enhances neuroplasticity and promotes synaptogenesis, potentially facilitating adaptative neural remodeling and optimizing cognitive and affective processing.[7,8,25] Furthermore, its dissociative effects may stimulate greater disinhibition and cognitive flexibility, allowing patients to engage more effectively in therapy sessions.[17,26] This interaction may help attenuate maladaptive thought patterns and ultimately enhance the efficacy of psychotherapeutic interventions in mood disorders, such as depression.[26]

Our study demonstrated significant improvements in depression and anxiety outcomes following the implementation of the KAP protocol. Specifically, depressive symptoms showed a substantial reduction, with PHQ-9 scores decreasing significantly from baseline to post-treatment, reflecting a clinically meaningful improvement. Although a slight increase in PHQ-9 scores was observed at reassessment, both post-treatment and reassessment scores remained significantly lower than baseline, indicating a sustained therapeutic effect. Anxiety symptoms followed a similar trajectory, as

measured by the GAD-7, with significant overall improvement after treatment and at reassessment. These findings suggest that the KAP protocol was effective in alleviating depressive and anxiety symptoms, with benefits persisting beyond the acute treatment phase.

Regarding treatment response, remission was observed in 58.10% of participants for anxiety post-treatment, although this outcome declined to 33.30% at reassessment. In contrast, depressive outcomes were more stable, with 38.70% of participants achieving remission from depression following KAP, and this proportion slightly increased to 41.70% at reassessment. Additionally, only one participant exhibited disease progression in depression immediately following treatment; however, no progression was observed at reassessment, suggesting a potential delayed benefit for some individuals. Notably, 8.30% of participants exhibited symptom progression in anxiety at reassessment.

This case series aligns with previous studies investigating KAP across various clinical contexts, including its use in TRD, PTSD, and anxiety disorders. In a 2017 open-label trial, Wilkinson *et al.* explored whether combining ketamine with Cognitive Behavioral Therapy (CBT) could extend ketamine's antidepressant effects in TRD. Of the 16 patients enrolled, 7 (43.8%) achieved remission, with 3 maintaining remission one month after the last ketamine administration and 2 remaining in remission at the two-month follow-up.[27] In their 2021 randomized controlled trial, Wilkinson *et al.* demonstrated that CBT, when provided after a course of ketamine infusions, helped sustain antidepressant effects over a 14-week follow-up period. While the improvement in Montgomery-Åsberg Depression Rating Scale (MADRS) scores was moderate, it did not reach statistical significance; however, the Quick Inventory of Depressive Symptomatology (QIDS) scores showed a statistically significant difference, suggesting that CBT played a meaningful role in prolonging ketamine's effects.[28] In comparison, our

study shows even more promising outcomes, with a higher proportion of patients remaining in remission after treatment cessation.

Similarly, other studies investigating KAP have highlighted its potential in alleviating depressive symptoms. In a 2022 cohort-based case study of 94 patients, Dames *et al.* found that 79% experienced clinical improvements after completing a 12-week KAP treatment.[29] Also in 2022, Robinson *et al.* conducted a case series in which small groups of participants underwent a four-week KAP protocol, reporting substantial reductions in depressive symptoms, with four out of five participants achieving clinical improvement.[30] In 2023, Robinson *et al.* examined KAP in individuals experiencing burnout and PTSD, finding a 58% reduction in PHQ-9 scores following the intervention.[31]

Electroconvulsive therapy (ECT) remains the gold standard treatment for TRD,[32] with remission rates ranging from 60% to 90%[33] and a longer-lasting treatment response, extending up to three months.[34] However, despite its efficacy, ECT continues to be an unpopular treatment option, partly due to its cognitive side effects (SEs), including anterograde and retrograde amnesia.[35] Many patients with TRD experience relapse after the initial treatment, often requiring more ECT sessions, potentially worsening these SEs over time.[36] These concerns emphasize the need to explore alternative therapeutic approaches. While our study demonstrated a lower remission rate (41.70% at reassessment) compared to ECT, the results remain promising. Additionally, this case series highlighted that the acute effects of ketamine were generally well-tolerated, with no serious or unexpected adverse events reported. Most adverse effects observed were mild, transient, and infrequent, with no significant cognitive impairments reported, further supporting the feasibility of integrating KAP into clinical practice for TRD. These findings align with previous studies demonstrating ketamine's tolerability.[37,38] Furthermore, the literature identifies nausea, dizziness, dissociation, blurred vision,

anxiety, tachycardia, and transient increases in blood pressure as among the most commonly reported SEs, which is consistent with the adverse effects identified in our study.[24]

We also analyzed treatment response distribution, revealing no statistically significant differences between the post-treatment and reassessment time points for either depression (p = 0.22) or anxiety (p = 0.15). This suggests that the therapeutic effects observed immediately after treatment were largely sustained at the 1-month follow-up, supporting the possibility of a prolonged benefit of this protocol. While the rapid antidepressant effects of ketamine are typically seen within hours[4,9] and can last up to 7 days,[12] the sustained response at reassessment raises the question of whether adjunctive psychotherapy played a role in extending the benefits of ketamine treatment.

Implications for clinical practice

The Canadian Network for Mood and Anxiety Treatments (CANMAT) 2023 updated guidelines already recognize ketamine as a suitable adjunctive agent for TRD, with IV racemic ketamine receiving a Level 1 recommendation based on evidence of its antidepressant effects. However, it remains a second-line option due to its potential for adverse effects.[39] In contrast, despite the growing interest in Psychedelic-assisted psychotherapy, namely KAP, its implementation as a standard therapeutic approach to TRD is currently restricted because of limited research.[39] In this context, developing real-world studies, such as our case series, is crucial to provide clinically relevant information on KAP's effectiveness and applicability.

This is one of the largest published studies investigating the use of KAP in TRD, with 31 patients enrolled. Our results suggest that combining psychotherapy with ketamine may contribute to longer-lasting effects, possibly improving treatment efficacy

in TRD. However, limited prior research exists on implementing a structured and well-defined psychotherapeutic approach alongside the use of ketamine. Most existing studies focus extensively on the pharmacological potential of ketamine in TRD, which has already shown proven results. Yet, there is a lack of evidence regarding its adverse effects in long-term use. Exploring psychotherapeutic approaches to extend the benefits of ketamine is an important area that requires further investigation, as it may serve as an alternative to repeated infusions of subanesthetic doses of this drug to sustain its antidepressant effects.

Limitations

While the study yielded relevant results, it has limitations that must be acknowledged. Its case series design, although providing valuable insights into real-world scenarios, restricts the ability to generalize findings. A RCT would provide a higher level of evidence, allowing for direct comparisons between KAP and alternative treatments or placebo. Another limitation is the 1-month follow-up period. While our findings show a sustained remission rate at this time point, suggesting short-term efficacy, the long-term benefits of this treatment remain uncertain. Additionally, seven patients were lost to follow-up during reassessment, which could have affected our results, particularly if the losses were not random. We emphasize the importance of cautious interpretation of our findings in light of these limitations.

Future Research

This case series offers insights into the short-term effects of KAP; however further research is needed to evaluate its long-term safety profile, including potential cognitive effects and addiction risk, that could be associated with repeated ketamine exposure.

Moreover, studies should be designed to investigate the long-term sustained benefits of KAP in TRD, particularly in comparison to ECT, as our follow-up period was limited to one month. There were no significant concerns regarding the implementation of KAP that would prevent larger feasibility or pilot studies from being conducted.

Furthermore, while our findings indicate psychotherapy may enhance the therapeutic effects of ketamine, it is crucial to assess its specific role in maintaining these benefits over time. A study comparing KAP with ketamine-alone treatments could help clarify the independent contribution of psychotherapy in sustaining symptom relief. Additionally, the most effective psychotherapeutic modality for TRD patients to integrate into KAP remains an open question. While we employed an ACT-based approach, Interpersonal Psychotherapy (IPT), Behavioral Activation (BA), and CBT have also been studied alongside ketamine, with evidence already suggesting CBT might extend its antidepressant effects.[40] For instance, BA appears to play a role in alleviating depressive symptoms by boosting environmental reinforcement, which is particularly promising for individuals with pronounced anhedonia, as the resulting behavioral changes could potentially outlast ketamine's transient effects.[41] To better identify the most suitable psychotherapeutic approach, future research should conduct comparative studies, evaluating the efficacy of CBT, ACT, BA, and IPT in combination with ketamine. Identifying the most effective therapeutic combination could help optimize the KAP protocol, leading to improved outcomes for individuals with TRD.

Conclusion

This study suggests that KAP may offer short-term benefits for TRD, with remission rates remaining stable at the 1-month follow-up appointment. This reinforces its potential as a possible adjunctive treatment. However, while psychotherapy appears to

sustain the antidepressant effects of ketamine better, further research is needed to clarify its contribution and identify the optimal type of psychotherapy. Additionally, studies with longer-term follow-up periods are crucial to investigate whether KAP provides sustainable benefits in TRD beyond the acute phase of treatment.

Conflicts of Interest

The authors report there are no conflicts of interest to declare.

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Tables

Table 1. Baseline Characteristics

	Baseline			
Sample Characteristic	***N* = 31**			
	Mean	**SD**	**95% CI**	
Age	45.71	2.15	41.32	50.10
Gender (% female)	54.80			
Ongoing Psychotherapy (%)	48.40			
Ketamine Sessions	4.32	0.11	4.10	4.54

SD, standard deviation; 95% CI, 95 percent confidence interval.

Table 2. Depression and Anxiety Outcomes

	Population											
	Before KAP				After KAP				Reassessment appointment			
Characteristic	***N* = 31**				***N* = 31**				***N* = 24**			
	Mean	**SD**	**95% CI**		**Mean**	**SD**	**95% CI**		**Mean**	**SD**	**95% CI**	
PHQ-9 scale	17.68	0.81	16.03	19.32	6.87	0.86	5.11	8.63	7.71	1.19	5.24	10.17
Depression Severity (%)												
No depression	0,00				38.70				41.70			
Mild depression	3,20				41.90				25.00			
Moderate depression	19.4				9.70				20.80			
Moderately severe depression	41.9				6.50				12.50			
Severe depression	35.5				3.20				0.00			
GAD-7 scale	13.77	0.70	12.34	15.21	5.77	0.79	4.16	7.39	7.42	0.99	5.37	9.47
Anxiety Severity (%)												
No anxiety	3.20				58.10				33.30			
Mild anxiety	9.70				19.40				37.50			
Moderate anxiety	51.60				16.10				16.70			
Severe anxiety	35.50				6.50				12.50			
Depression - Response (%)												
No response					6.50				0.00			
Partial response					12.90				37.50			
Response					38.70				20.80			
Remission					38.70				41.70			
Progression					3.20				0.00			
Anxiety - Response (%)												
No response					0.00				0.00			
Partial response					16.10				0.00			
Response					19.40				58.30			
Remission					58.10				33.30			
Progression					6.50				8.30			

KAP, Ketamine-Assisted Psychotherapy; PHQ-9, Patient Health Questionnaire-9; GAD-7, Generalized Anxiety Disorder 7-item; SD, standard deviation; 95% CI, 95 percent confidence interval.

Legend: This table presents PHQ-9 and GAD-7 mean scores before and immediately after the intervention, and at the reassessment appointment. The percentage distribution of participants across different severity levels for both Depression and Anxiety was calculated. The treatment response for Depression and Anxiety was measured as a percentage and evaluated at 2 time points: at the end of the treatment and during the reassessment appointment.

Table 3. Changes in Depression and Anxiety scores before and after the intervention

Related-Samples Wilcoxon Signed-Rank Test Summary

***N* = 31**

Measure	Test Statistic	Std. Error	Standardized Test Statistic	*p*-value (2-sided test)
PHQ-9 Before KAP - PHQ-9 After KAP	1.50	46.21	-4.67	<0.05
GAD-7 Before KAP - GAD-7 After KAP	10.00	50.98	-4.67	<0.05

KAP, Ketamine-Assisted Psychotherapy; PHQ-9, Patient Health Questionnaire-9; GAD-7, Generalized Anxiety Disorder 7-item; Std. Error, standard error.

Legend: The differences in PHQ-9 and GAD-7 scores before and after KAP treatment were assessed using the Wilcoxon signed-rank test. *p*-value was considered statistically significant if it was ≤ 0.05.

Table 4. Changes in Depression and Anxiety scores from baseline to reassessment

Paired Samples T-Test Summary

***N* = 24**

Measure	Mean	Std. Deviation	Std. Error Mean	95% CI	t	df	*p*-value (2-sided test)
PHQ-9 Before KAP - PHQ-9 Reassessment appointment	10.54	7.50	1.53	7.37 ; 13.71	6.89	23.00	< 0.05
GAD-7 Before KAP - GAD-7 Reassessment appointment	6.33	5.87	1.20	4.37 ; 9.31	5.71	23.00	< 0.05

KAP, Ketamine-Assisted Psychotherapy; PHQ-9, Patient Health Questionnaire-9; GAD-7, Generalized Anxiety Disorder 7-item; Std. Deviation, standard deviation; Std. Error Mean, standard error mean; df, degrees of freedom.

Legend: The differences in PHQ-9 and GAD-7 scores between baseline and the reassessment appointment were tested using a paired t-test for the subset of patients who completed the reassessment ($N = 24$). *p*-value was considered statistically significant if it was ≤ 0.05.

A higher t-value indicates a more significant difference between the groups in comparison

Table 5. Severity Distribution and Treatment Response Over Time

Characteristic	Population									Friedman	Fisher
	Before KAP			After KAP			Reassessment appointment				
	N = 24										
	Mean	SD	95% CI	Mean	SD	95% CI	Mean	SD	95% CI	*p*-value	*p*-value
Depression Severity (%)											
No depression	0,00			37.50			41.70				
Mild depression	0,00			37.50			25.00				
Moderate depression	20.80			12.50			20.80			< 0.05	
Moderately severe depression	37.50			8.30			12.50				
Severe depression	41.70			4.20			0.00				
Anxiety Severity (%)											
No anxiety	0.00			54.20			33.30				
Mild anxiety	12.50			20.80			37.50			< 0.05	
Moderate anxiety	45.80			16.70			16.70				
Severe anxiety	41.70			8.30			12.50				
Depression - Response (%)											
No response				6.50			0.00				
Partial response				12.90			37.50				
Response				38.70			20.80				0.22
Remission				38.70			41.70				
Progression				3.20			0.00				
Anxiety - Response (%)											
No response				0.00			0.00				
Partial response				16.10			0.00				
Response				19.40			58.30				0.15
Remission				58.10			33.30				
Progression				6.50			8.30				

KAP, Ketamine-Assisted Psychotherapy; SD, standard deviation; 95% CI, 95 percent confidence interval.

Legend: To account for differences in sample size at each assessment stage, the percentages for treatment response and severity distribution were recalculated based only on the 24 patients who attended the reassessment appointment. Friedman test and Fisher's exact test were applied to evaluate the differences between measurements. *p*-value was considered statistically significant if it was ≤ 0.05.

Annex

The following safety procedures will be complied with, which are the responsibility of the medical team present at the dosing sessions:

I. If Hypertension:

Pre-treatment:

a) Systolic Blood Pressure (SBP) > 180 mmHg:
   i. Reassess after rest;
   ii. Do not start ketamine until SBP < 160 mmHg;
   iii. Consider referral to Family Medicine and delay administration of ketamine until hypertension is under control.

b) SBP > 160 mmHg and Diastolic Blood Pressure (DBP) > 100 mmHg:
   i. Reassess after rest;
   ii. Consider referral to Family Medicine and delay administration of ketamine until hypertension is under control.

In the event of a hypertensive crisis during the session, signs/symptoms of organ dysfunction (chest pain; shortness of breath; severe headache; signs of stroke [facial paralysis, unilateral hemiparesis, dysarthria, aphasia]; loss of consciousness; peripheral O2 saturation < 90%; severe arrhythmia), an emergency medical team should be contacted immediately.

II. If hypotension occurs (SBP < 90 mmHg):

i. Include oximetry in the vital parameters until stabilization;

ii. If SBP < 90, check the other arm.

iii. If symptomatic, contact the emergency medical team.

III. If tachycardia (HR > 150 bpm):

i. If HR > 150 bpm without symptoms or signs of organ dysfunction, assess again; if symptomatic: contact the medical prevention team;

ii. If HR > 120 bpm without symptoms or signs of organ dysfunction:

Reassess vital parameters every 5 minutes until stabilization;

Recommend that the patient perform slow, deep abdominal breathing.

IV. If nausea and vomiting:

a) Pre-treatment:

i. Ondansetron 8 mg PO ~30 minutes before the session;

ii. If ondansetron is insufficient, consider domperidone on the day of the session.

b) During the session:

i. Most nausea and vomiting is self-limiting;

ii. Ensure that the patient is sitting or lying on their side (or stomach) to prevent aspiration;

iii. Provide a sheet;

iv. Provide napkins;

v. Provide water, but recommend small sips or just mouthwash

V. If respiratory problems:

i. Take extra care in patients with a personal history of asthma and/or sleep apnea. Ensure that patients with asthma bring their inhalers to ketamine administration sessions.

ii. If decreased respiratory rate without signs of breathing difficulty:

Wake the patient with a voice or touch to stimulate respiratory drive.

iii. If airway obstruction due to vomiting or sialorrhea:

Ensure that the patient is lying on their side or stomach to allow fluid drainage and prevent aspiration.

iv. If breathing difficulty is NOT due to vomiting/sialorrhea and there is a risk of airway collapse (especially in obese patients with a history of sleep apnea) OR laryngospasm:

Place the patient on their side and perform a jaw traction/elevation maneuver;

If symptoms persist, liaise with the emergency medical team.

VI. If chest pain or pressure (with or without shortness of breath):

Assess vital parameters including oximetry;

If symptoms persist, contact the emergency medical team.

VII. If headaches (during or after the session):

Assess vital parameters and ensure BP < 160/90 mmHg;

If hypertension, follow corresponding protocol;

Medicate with paracetamol 1000 mg PO;

Alternatively, ibuprofen 400 mg can be used, according to the patient's preference, or as an add-on if there is no response to paracetamol.

VIII. If seizures:

Signal the time of onset;

Assess vital parameters including oximetry every 5 minutes until stabilization;

Place the patient in a safe lateral position and protect the airway;

Ensure that the patient does not injure themselves;

Consider administering diazepam 10 mg IM if the seizure does not end spontaneously after 1-2 minutes;

If the seizure ends before 5 minutes, keep the patient in a safe lateral position and reassess vital parameters.

IX. If symptoms of hypoglycemia occur (in patients with diabetes mellitus):

Watch for sweating, hunger, fainting, light headedness, tremors, nausea, marked mental confusion, dry mouth, headache, dysarthria, seizures, or impaired consciousness (some symptoms may be similar to the expected response to ketamine);

Assess capillary blood glucose;

Reassess vital parameters including oximetry until stabilized;

If glucose >400 mg/dL, contact Internal Medicine;

If glucose <70 mg/dL, offer fruit juice or sugar, and reassess blood glucose after 5 minutes;

If blood glucose <50 mg/dL (or 'low' reading), offer sugar and contact Internal Medicine (reassess capillary blood glucose after 15 minutes);

If hypoglycemia does not respond to intervention and remains <70 mg/dL but the patient is stable and not convulsing: offer sugar again and Reassess.

Questionnaires

PATIENT HEALTH QUESTIONNAIRE-9 (PHQ-9)

Over the last 2 weeks, how often have you been bothered by any of the following problems? *(Use "✔" to indicate your answer)*	Not at all	Several days	More than half the days	Nearly every day
1. Little interest or pleasure in doing things	0	1	2	3
2. Feeling down, depressed, or hopeless	0	1	2	3
3. Trouble falling or staying asleep, or sleeping too much	0	1	2	3
4. Feeling tired or having little energy	0	1	2	3
5. Poor appetite or overeating	0	1	2	3
6. Feeling bad about yourself — or that you are a failure or have let yourself or your family down	0	1	2	3
7. Trouble concentrating on things, such as reading the newspaper or watching television	0	1	2	3
8. Moving or speaking so slowly that other people could have noticed? Or the opposite — being so fidgety or restless that you have been moving around a lot more than usual	0	1	2	3
9. Thoughts that you would be better off dead or of hurting yourself in some way	0	1	2	3

FOR OFFICE CODING 0 + _____ + _____ + _____

=Total Score: _____

If you checked off any problems, how difficult have these problems made it for you to do your work, take care of things at home, or get along with other people?

Not difficult at all	Somewhat difficult	Very difficult	Extremely difficult
☐	☐	☐	☐

Developed by Drs. Robert L. Spitzer, Janet B.W. Williams, Kurt Kroenke and colleagues, with an educational grant from Pfizer Inc. No permission required to reproduce, translate, display or distribute.

GAD-7 Anxiety

Over the last two weeks, how often have you been bothered by the following problems?	Not at all	Several days	More than half the days	Nearly every day
1. Feeling nervous, anxious, or on edge	0	1	2	3
2. Not being able to stop or control worrying	0	1	2	3
3. Worrying too much about different things	0	1	2	3
4. Trouble relaxing	0	1	2	3
5. Being so restless that it is hard to sit still	0	1	2	3
6. Becoming easily annoyed or irritable	0	1	2	3
7. Feeling afraid, as if something awful might happen	0	1	2	3

Column totals _____ + _____ + _____ + _____ =

Total score _____

If you checked any problems, how difficult have they made it for you to do your work, take care of things at home, or get along with other people?

Not difficult at all	Somewhat difficult	Very difficult	Extremely difficult
☐	☐	☐	☐

Source: Primary Care Evaluation of Mental Disorders Patient Health Questionnaire (PRIME-MD-PHQ). The PHQ was developed by Drs. Robert L. Spitzer, Janet B.W. Williams, Kurt Kroenke, and colleagues. For research information, contact Dr. Spitzer at ris8@columbia.edu. PRIME-MD® is a trademark of Pfizer Inc.

Scoring GAD-7 Anxiety Severity

This is calculated by assigning scores of 0, 1, 2, and 3 to the response categories, respectively, of "not at all," "several days," "more than half the days," and "nearly every day."
GAD-7 total score for the seven items ranges from 0 to 21.

0–4: minimal anxiety

5–9: mild anxiety

10–14: moderate anxiety

15–21: severe anxiety

PROCESS 2020 Checklist			
Topic	**Item**	**Checklist Item Description**	**Page Number**
Title	**1**	- The phrase 'case series' and the area of focus should appear in the title (e.g. patient population, diagnosis, intervention or outcome).	Pg.1 – "Efficacy of Ketamine-Assisted Psychotherapy in Treatment-Resistant Depression – a case series"
Key Words	**2**	- Include three to six keywords that identify what is covered in the case series (e.g. patient population, diagnosis, intervention or outcome). - Include 'case series' as one of the keywords.	Pg.2 – "Case Series; Treatment-Resistant Depression; Ketamine-Assisted Psychotherapy; Ketamine; Remission."
Abstract	**3a**	Introduction and Importance - Describe what is unique or educational. - What is the overarching theme of the case series?	Pg.2 – "Ketamine-assisted psychotherapy (KAP) has emerged as a potential approach for patients with Treatment-Resistant Depression (TRD). However, several questions regarding the optimal implementation protocol and efficacy have yet to be thoroughly studied."
	3b	Methods - Describe what was done, how and when was it done and by whom.	Pg.2 – "We conducted a case series involving 31 patients diagnosed with TRD. Our KAP protocol, supervised by a physician, consisted of two preparation sessions, followed by a minimum of four weekly sessions of intravenous ketamine administration, starting with an initial dose of 0.5 mg/kg. Each ketamine session was followed by an

			integration psychotherapy session the next day. A follow-up reassessment was held one month after the final intervention to evaluate whether the antidepressant benefits were sustained."
	3c	Outcomes - Describe the outcomes of the intervention and management strategy.	Pg.2 – "Depressive and anxiety symptoms were assessed using the Patient Health Questionnaire-9 (PHQ-9) and the Generalized Anxiety Disorder 7-item (GAD-7), respectively. The evaluations occurred during the second preparation session, the last integration session, and the reassessment consultation. There was significant improvement ($p < 0.05$) in PHQ-9 scores following the KAP intervention and at the reassessment evaluation, with mean scores decreasing from 17.68 (SD = 0.81, 95% CI = 16.03;19.32) at baseline to 6.87 (SD = 0.86, 95% CI = 5.11;8.63) in the last integration session, and to 7.71 (SD = 1.19, 95% CI = 5.24;10.17) at reassessment. Importantly, 38.70% of patients remitted from depression immediately after KAP, with an increase to 41.70% at reassessment."
	3d	Conclusion - Describe the take home message(s), including what has been learnt? - How will this impact future clinical practice?	Pg.2 – "This study suggests psychotherapy may sustain ketamine's antidepressant effects, but further research is needed to assess the long-term impact and identify the most effective psychotherapy for patients with TRD."

Introduction	**4**	- Describe the background of the case series and specify the overarching theme (e.g. common disease, intervention, or outcome). - The introduction should explain what is unique or educational about the case series. - Relevant scientific literature should be referenced. - Introduction should be 1-2 paragraphs in length.	Pg.3, Pg.4 – “Despite variability in study protocols, KAP has consistently shown effectiveness in reducing anxiety and depressive symptoms. With approximately 33% of MDD cases progressing to TRD, it is crucial to explore promising therapeutic approaches to enhance treatment efficacy. In this context, KAP is presented as an optional treatment for patients with TRD. Despite the growing body of literature on KAP, research regarding its true effectiveness in TRD remains limited. We present a case series in which we have administered a KAP protocol aimed at providing new insights into the potential of ketamine when combined with psychotherapy. This approach seeks to investigate whether the antidepressant effects of ketamine can be enhanced through psychotherapy and to evaluate the overall effectiveness of the KAP protocol in promoting sustained remission in patients with TRD.”
Methods	**5a**	Registration - State the research registry number in accordance with the Declaration of Helsinki - "Every research study involving human subjects must be registered in a publicly accessible database". This can be obtained	Not applicable.

		from, for example, ResearchRegistry.com, ClinicalTrials.gov, or ISRCTN. - If a protocol already exists, state the corresponding registration number and access directions (e.g. website or journal, and include a hyperlink that is publicly accessible). It must be written in the English language.	
	5b	Study Design - State that the study is a case series. - State whether the case series is: (1) prospective/ retrospective, (2) single/multi-centre, and if (3) cases are consecutive/non-consecutive.	Pg.5 – "A retrospective, single-center case series was conducted on a population of patients with a clinical diagnosis of TRD (…)."
	5c	Settings and Time-Frames - Describe the setting(s) in which the patient was managed (e.g. research institution, teaching/district general hospital, community, or private practice).	Pg.5 – "The study protocol was approved by the Ethics Committee of Casa de Saúde Santa Catarina Hospital in Porto, Portugal. (…) The study was conducted at the same institution." Pg.5 – "A retrospective, single-center case series was conducted on a population of patients with a clinical diagnosis of TRD, selected according to predefined inclusion

		- Document any relevant dates (e.g. recruitment, intervention, follow-up, and data collection time-frames).	criteria, between August 2023 and December 2024.”
	5d	Participants - Describe the relevant characteristics (e.g. demographics, comorbidities, tumour staging, smoking status) and if relevant, exposure(s) of the participants. - Describe the method of participant recruitment, if relevant. - State any subsequent inclusion or exclusion criteria, and how the participants were selected. - Methods used to ensure the de-identification of patient information.	Pg.5 – “The main criterion for participation in the study was a clinical diagnosis of TRD. Patients could seek treatment spontaneously or be referred by their attending psychiatrist or psychologist.” Pg.5, Pg.6 – “To initiate the request, the patient's attending clinician or the patient themselves in cases where treatment was sought independently, had to complete a designated form. Each application was reviewed by the psychiatrists involved in the therapeutic approach. The physicians then determined whether to schedule a pre-treatment assessment, request further information from the attending clinician or decline the request due to the absence of inclusion criteria. (…) The pre-treatment evaluation consisted of a session conducted by one of the psychiatrists participating in the study, followed by a team discussion to reach a final decision. (…) The main purpose of this assessment was to identify the presence of both inclusion and exclusion criteria” Pg.6, Pg.7 – “*Inclusion Criteria* Moderate to severe TRD, defined by: Duration of current episode longer than six months.

			Lack of clinical response after: At least two antidepressant regimens, in adequate doses and duration, including: A selective serotonin reuptake inhibitor (SSRI) A combination of antidepressants (e.g., venlafaxine and mirtazapine) A potentiation strategy (e.g., atypical antipsychotic, lithium, thyroid hormone) Psychotherapy (cognitive behavioral, interpersonal, psychodynamic or other) An abstract reasoning and symbolic thinking that constitutes an indication for psychotherapy.

			Exclusion Criteria Psychotic symptoms or psychomotor impairment. Current abuse of or addiction to psychoactive substances. Personal history of schizophrenia, bipolar I disorder or other psychotic disorder. Severe impulsivity or antisocial behavior. Severe personality disorder. Intellectual development disorder or low level of education. Family history (first-degree relatives) of psychotic symptoms in the context of schizophrenia or bipolar disorder. Uncontrolled hypertension; unstable angina; high-risk coronary vascular disease; hyperthyroidism; pheochromocytoma; uncontrolled epilepsy; glaucoma; severe liver disease; sleep apnea syndrome. Pregnancy or breastfeeding.”
	5e	Pre-Intervention Patient Optimisation - Lifestyle (e.g. weight loss). - Medication review (e.g. anticoagulation, oral hypoglycemics/insulin).	Pg.8, Pg.9 – “In the weeks preceding the first ketamine session, two two-hour preparation sessions were conducted. (…) The clinicians provided patients with dietary and lifestyle guidelines to follow before each ketamine session. These included fasting for 4 hours before drug administration, abstaining from alcohol and psychoactive substances for 48

		- Pre-surgical stabilisation/preparation (e.g. treating hypothermia/hypovolemia/hypotension, ICU care for sepsis, nil by mouth, or enema). - Other (e.g. psychological support).	hours beforehand, and continuing regular medications, including psychotropic drugs. Tobacco/nicotine use was permitted. Lastly, a designated individual was assigned to accompany the patient home after each session."
	5f	Interventions - Describe the type(s) of intervention(s) used (e.g. pharmacological, surgical, physiotherapy, psychological, preventative). - Describe any concurrent treatments (e.g. antibiotics, analgesia, antiemetics, venous thromboembolism prophylaxis).	Pg.7, Pg.8 – "The KAP protocol included two preparation sessions, followed by a minimum of four weekly ketamine administration sessions, each accompanied by integration psychotherapy sessions on the following day. The intervention concluded with a reassessment and therapeutic decision consultation one month after the final integration session, ensuring follow-up, continuity of care, and the patient's transition back to their attending clinician."
	5g	Intervention Details - Describe the rationale behind the treatment offered, how it was performed and time to intervention. - For pharmacological therapies, include information on the formulation, dosage,	Pg.9 – "The ketamine administration sessions were conducted in a room designed to provide optimal lighting, comfort, and safety, under the supervision of one of the team's physicians. During the sessions, patients lay on a hospital bed, with their eyes shielded by a blindfold to minimize external distractions. They listened to pre-selected music, chosen in collaboration with the patient, through headphones."

		strength, route, and duration. - For surgery, include details such as anaesthesia, patient position, preparation used, use of other relevant equipment, sutures, devices, and surgical stage. - The degree of novelty for a surgical technique/device should be mentioned (e.g. 'first in human' or 'first in this context'). - Medical devices should have manufacturer and model specifically mentioned.	Pg.9, Pg.10 – “Ketamine was administered intravenously under the continuous presence and supervision of the doctor (…) The initial dose was 0.5 mg/kg, with adjustments made in subsequent sessions (up to a maximum of 1.2 mg/kg) according to the antidepressant effects observed after each session. Intravenous ketamine infusion was delivered over 40 minutes, requiring venous access, ideally placed in one of the upper limbs. The standard ketamine ampoule, with an initial concentration of 50 mg/mL, was diluted to a final concentration of 2 mg/mL for continuous infusion via syringe. The preparation involved drawing 2 mL of ketamine (50 mg/mL) into a 50 mL syringe and adding 48 mL of 0.9% saline solution, resulting in a total volume of 50 mL. Excess ketamine was disposed of following established guidelines for the disposal of narcotics and controlled substances. Each ketamine session lasted 2 hours and 30 minutes, with the most intense mental state changes occurring during the first 40 minutes, followed by a recovery phase and content recall.” Pg.10 – “The integration sessions, which lasted one hour, took place the day after each drug administration session. (…) This approach was based on Acceptance and Commitment Therapy (ACT).”

	5h	Operator Details - Where applicable, include operator experience and position on the learning curve, any relevant training, and specialisation (e.g. 'junior trainee with three years of surgical specialty training in Plastic Surgery and seven similar cases completed previously under direct supervision').	Pg.5 – "The intervention was conducted by a medical team of two consultant psychiatrists, each of whom went through a 3-month KAP intervention course."
	5i	Quality Control - What measures were taken to reduce inter- or intra-operator/operation variation, to ensure quality, and to maintain consistency between cases (e.g. independent observers, lymph node counts, standard surgical technique). - State any specific disparities between cases.	Pg.14 – "The protocol was implemented by the medical team composed of consultant psychiatrists, while the statistical analysis was conducted by an independent observer, a medical student, who had no prior knowledge of the patients and was not directly involved in the implementation of the protocol."

	5j	Follow-Up - When (e.g. how long after discharge, frequency, maximum follow-up length at the time of submission). - Where (e.g. home via video consultation, primary care, secondary care). - How (e.g. telephone consultation, clinical examination, blood tests, imaging). - Any specific long-term surveillance requirements (e.g. imaging surveillance of endovascular aneurysm repair or clinical exam/ultrasound of regional lymph nodes for skin cancer). - Any specific post-operative instructions (e.g. post-operative medications, targeted physiotherapy, psychological therapy). - State if any participants were lost to follow-up and why.	Pg.11 - “At the reassessment appointment, held one month after the final integration psychotherapy session, the physicians conducted a clinical interview and administered the PHQ-9 and GAD-7 scales again. This process aimed to evaluate the patient’s response to the KAP protocol and assess any changes in symptom severity since the last integration session.” Pg.15 – “The same 31 patients were assessed before and after treatment, with 7 patients lost to follow-up during the reassessment phase: 2 of them returned to their home country, while the other 5 missed the reassessment consultation.”

Results	**6a**	Participants - Please state the number of patients involved, the patient characteristics (e.g. demographics, comorbidities, smoking status, and if applicable, tumour staging (e.g. TNM)).	Pg.15– "This study included 31 participants at baseline, with 24 completing the reassessment appointment. (…) The mean age of our baseline population was 45.71 years. The sample was 54.80% female, and 48.40% of participants were engaged in ongoing psychotherapy. Furthermore, the average number of ketamine sessions per patient was 4.32."
	6b	Deviation from the Initial Management Plan - State if there were any changes in the planned intervention(s) (e.g. what was changed and why). - Please include a suitable schematic diagram if appropriate.	Pg.14 – "The protocol was implemented as planned, without any changes to the intended intervention"
	6c	Outcomes and Follow-Up - Expected versus attained clinical outcome as assessed by the clinician. Reference literature used to inform expected outcomes. - When appropriate, include patient-reported measures (e.g. questionnaires including quality-of-life scales).	Pg.15, Pg.16 (assessed by the clinician)– "Following KAP, PHQ-9 scores showed a significant decrease. The mean score dropped from 17.68 (SD = 0.81, 95% CI = 16.03;19.32) before treatment to 6.87 (SD = 0.86, 95% CI = 5.11;8.63) after treatment, with a slight increase to 7.71 (SD = 1.19, 95% CI = 5.24;10.17) at reassessment (…) a significant reduction in PHQ-9 scores after treatment ($p < 0.05$) (…) The severity levels of depression showed an important improvement. The percentage of participants identified as having "severe depression" decreased from 35.50%

		- Describe and explain the percentage of patients lost to follow-up.	to 3.20% after treatment and reached 0% during the reassessment. Additionally, the proportion of patients experiencing “no depression” increased from 0% to 38.70% post-treatment and further to 41.70% at the time of reassessment (…) A similar pattern was observed for anxiety (…) Regarding depression, 38.70% of participants achieved remission after KAP, which increased to 41.70% at reassessment. Additionally, 38.70% initially showed a treatment response, although this proportion declined to 20.80% at reassessment. The partial response rate increased from 12.90% to 37.50%. Notably, 3.20% of participants, corresponding to one patient, exhibited disease progression post-treatment. However, no cases of disease progression were observed at the final follow-up assessment. For anxiety, remission was observed in 58.10% of participants following KAP treatment, though this decreased to 33.30% at reassessment. The proportion of individuals classified as treatment responders increased significantly from 19.40% post-treatment to 58.30% at reassessment. Additionally, 6.50% of participants demonstrated disease progression following KAP treatment. In contrast to depression, 8.30% of patients exhibited symptom progression at reassessment.” Pg.19 (expected outcomes) – “This case series aligns with previous studies investigating KAP across various clinical

			contexts (…) In a 2017 open-label trial, Wilkinson *et al.* explored whether combining ketamine with Cognitive Behavioral Therapy (CBT) could extend ketamine's antidepressant effects in TRD. Of the 16 patients enrolled, 7 (43.8%) achieved remission, with 3 maintaining remission one month after the last ketamine administration and 2 remaining in remission at the two-month follow-up. In their 2021 randomized controlled trial, Wilkinson *et al.* demonstrated that CBT, when provided after a course of ketamine infusions, helped sustain antidepressant effects over a 14-week follow-up period." Pg.15 – "The same 31 patients were assessed before and after treatment, with 7 patients lost to follow-up during the reassessment phase: 2 of them returned to their home country, while the other 5 missed the reassessment consultation."
	6d	Intervention Adherence and Compliance - Where relevant, detail how well the patient adhered to and tolerated the advice provided (e.g. avoiding heavy lifting for abdominal surgery, or tolerance of chemotherapy and	Pg.23 – "The ketamine administration was well tolerated by all participants, with no serious or unexpected adverse events reported." Patients showed excellent adherence to the intervention, as confirmed by their consistent presence for both ketamine administration and psychotherapy sessions in the institution where our study took place. However, it's worth noting that 7 patients missed their reassessment evaluations.

		pharmacological agents). - Explain how adherence and tolerance were measured.	
	6e	Complications and Adverse Events - Precautionary measures taken to prevent complications (e.g. antibiotic or venous thromboembolism prophylaxis). - All complications and adverse or unanticipated events should be described in detail and ideally categorised in accordance with the Clavien-Dindo Classification (e.g. blood loss, length of operative time, wound complications, re-exploration or revision surgery, impact on length of stay). - If relevant, was the complication reported to the relevant national agency or	Pg.17 – "The ketamine administration was well tolerated by all participants, with no serious or unexpected adverse events reported. However, some adverse effects were observed. The most common was nausea, which required administration of oral ondansetron, 8 mg, in some cases for symptom control. Additionally, some patients experienced transient increases in blood pressure, requiring the use of oral captopril, 25 mg. These effects were generally mild, transient, and consistent with those previously described in the literature for subanesthetic doses of ketamine, reinforcing the safety of the protocol used."

		pharmaceutical company. - Specify the duration of time between completion of the intervention and discharge, and whether this was within the expected timeframe (if not, why not). - Where applicable, the 30-day post-operative and long-term morbidity/mortality may need to be specified. - State if there were no complications or adverse outcomes.	
Discussion	**7a**	- Summarise the key results.	Pg.18, Pg.19 – "Our study demonstrated significant improvements in depression and anxiety outcomes following the implementation of the KAP protocol. Specifically, depressive symptoms showed a substantial reduction, with PHQ-9 scores decreasing significantly from baseline to post-treatment, reflecting a clinically meaningful improvement. Although a slight increase in PHQ-9 scores was observed at reassessment, both post-treatment and reassessment scores remained significantly lower than baseline, indicating a sustained therapeutic effect. Anxiety symptoms followed a similar trajectory, as measured by the GAD-7, with significant overall improvement after

			treatment and at reassessment. These findings suggest that the KAP protocol was effective in alleviating depressive and anxiety symptoms, with benefits persisting beyond the acute treatment phase. Regarding treatment response, remission was observed in 58.1% of participants for anxiety post-treatment, although this outcome declined to 33.3% at reassessment. In contrast, depressive outcomes were more stable, with 38.7% of participants achieving remission from depression following KAP, and this proportion slightly increased to 41.7% at reassessment. Additionally, only one participant exhibited disease progression in depression immediately following treatment; however, no progression was observed at reassessment, suggesting a potential delayed benefit for some individuals. Notably, 8.3% of participants exhibited symptom progression in anxiety at reassessment."
	7b	Relevant Literature and Placing the Results in Context - Include a discussion of the relevant literature and, if appropriate, similar published studies. - Describe the implications for clinical practice guidelines (e.g.	Pg.19, Pg.20 – "This case series aligns with previous studies investigating KAP across various clinical contexts, including its use in TRD, PTSD, and anxiety disorders. In a 2017 open-label trial, Wilkinson *et al.* explored whether combining ketamine with Cognitive Behavioral Therapy (CBT) could extend ketamine's antidepressant effects in TRD. Of the 16 patients enrolled, 7 (43.8%) achieved remission, with 3 maintaining remission one month after the last ketamine administration

		NICE) and any relevant hypotheses generated.	and 2 remaining in remission at the two-month follow-up. In their 2021 randomized controlled trial, Wilkinson *et al.* demonstrated that CBT, when provided after a course of ketamine infusions, helped sustain antidepressant effects over a 14-week follow-up period. While the improvement in Montgomery-Åsberg Depression Rating Scale (MADRS) scores was moderate, it did not reach statistical significance; however, the Quick Inventory of Depressive Symptomatology (QIDS) scores showed a statistically significant difference, suggesting that CBT played a meaningful role in prolonging ketamine's effects.[28]In comparison, our study shows even more promising outcomes, with a higher proportion of patients remaining in remission after treatment cessation. Similarly, other studies investigating KAP have highlighted its potential in alleviating depressive symptoms. In a 2022 cohort-based case study of 94 patients, Dames *et al.* found that 79% experienced clinical improvements after completing a 12-week KAP treatment. Also in 2022, Robinson *et al.* conducted a case series in which small groups of participants underwent a four-week KAP protocol, reporting substantial reductions in depressive symptoms, with four out of five participants achieving clinical improvement. In 2023, Robinson *et al.* examined KAP in individuals experiencing burnout and PTSD, finding a 58% reduction in PHQ-9 scores following the intervention."

	7c	Strengths - Describe the relevant strengths of the study. - Detail any multidisciplinary or cross-speciality relevance. Weaknesses and Limitations - Describe the relevant weaknesses or limitations of the study. - For novel techniques or devices, outline any contraindications and alternatives, potential risks and possible complications if applied to a larger population.	Pg.21, Pg.22 – "The Canadian Network for Mood and Anxiety Treatments (CANMAT) 2023 updated guidelines already recognize ketamine as a suitable adjunctive agent for TRD, with IV racemic ketamine receiving a Level 1 recommendation based on evidence of its antidepressant effects. However, it remains a second-line option due to its potential for adverse effects. In contrast, despite the growing interest in Psychedelic-assisted psychotherapy, namely KAP, its implementation as a standard therapeutic approach to TRD is currently restricted because of limited research. In this context, developing real-world studies, such as our case series, is crucial to provide clinically relevant information on KAP's effectiveness and applicability. This is one of the largest published studies investigating the use of KAP in TRD, with 31 patients enrolled. Our results suggest that combining psychotherapy with ketamine may contribute to longer-lasting effects, possibly improving treatment efficacy in TRD. However, limited prior research exists on implementing a structured and well-defined psychotherapeutic approach alongside the use of ketamine. Most existing studies focus extensively on the pharmacological potential of ketamine in TRD, which has already shown proven results. Yet, there is a lack of evidence regarding its adverse effects in long-term use. Exploring psychotherapeutic approaches to extend the benefits of ketamine is an important

			area that requires further investigation, as it may serve as an alternative to repeated infusions of subanesthetic doses of this drug to sustain its antidepressant effects." Pg.22 – "While the study yielded relevant results, it has limitations that must be acknowledged. Its case series design, although providing valuable insights into real-world scenarios, restricts the ability to generalize findings. A RCT would provide a higher level of evidence, allowing for direct comparisons between KAP and alternative treatments or placebo. Another limitation is the 1-month follow-up period. While our findings show a sustained remission rate at this time point, suggesting short-term efficacy, the long-term benefits of this treatment remain uncertain. Additionally, seven patients were lost to follow-up during reassessment, which could have affected our results, particularly if the losses were not random. We emphasize the importance of cautious interpretation of our findings in light of these limitations"
	7d	Directions for Future Research - State how the methodology and findings discussed can impact future research and clinical practice. Describe the questions that have arisen as a result of this study.	Pg.22, Pg.23 – "This case series offers insights into the short-term effects of KAP; however further research is needed to evaluate its long-term safety profile, including potential cognitive effects and addiction risk, that could be associated with repeated ketamine exposure. Moreover, studies should be designed to investigate the long-term sustained benefits of KAP in TRD, particularly in comparison to ECT,

		- State the alternative study design(s) best suited to address these questions.	as our follow-up period was limited to one month. There were no significant concerns regarding the implementation of KAP that would prevent larger feasibility or pilot studies from being conducted. Furthermore, while our findings indicate psychotherapy may enhance the therapeutic effects of ketamine, it is crucial to assess its specific role in maintaining these benefits over time. A study comparing KAP with ketamine-alone treatments could help clarify the independent contribution of psychotherapy in sustaining symptom relief. Additionally, the most effective psychotherapeutic modality for TRD patients to integrate into KAP remains an open question. While we employed an ACT-based approach, Interpersonal Psychotherapy (IPT), Behavioral Activation (BA), and CBT have also been studied alongside ketamine, with evidence already suggesting CBT might extend its antidepressant effects. For instance, BA appears to play a role in alleviating depressive symptoms by boosting environmental reinforcement, which is particularly promising for individuals with pronounced anhedonia, as the resulting behavioral changes could potentially outlast ketamine's transient effects. To better identify the most suitable psychotherapeutic approach, future research should conduct comparative studies, evaluating the efficacy of CBT, ACT, BA, and IPT in combination with ketamine. Identifying the most effective therapeutic combination

			could help optimize the KAP protocol, leading to improved outcomes for individuals with TRD."
Conclusions	**8a**	Key Conclusions - Outline the key conclusions from this study.	Pg.23 – "This study suggests that KAP may offer short-term benefits for TRD, with remission rates remaining stable at the 1-month follow-up appointment. This reinforces its potential as a possible adjunctive treatment."
	8b	Rationale - Ensure that any of the conclusions made are supported by a strong rationale.	Pg.19 – "In contrast, depressive outcomes were more stable, with 38.7% of participants achieving remission from depression following KAP, and this proportion slightly increased to 41.7% at reassessment."
	8c	Future Work - Briefly discuss any questions arisen from this study and any differences in approach to patient diagnosis or management which the authors might adopt in future similar studies.	Pg.23, Pg.24 - "However, while psychotherapy appears to sustain the antidepressant effects of ketamine better, further research is needed to clarify its contribution and identify the optimal type of psychotherapy. Additionally, studies with longer-term follow-up periods are crucial to investigate whether KAP provides sustainable benefits in TRD beyond the acute phase of treatment."
Patient Perspective	**9**	- Where appropriate, the patients should be given the opportunity to share their perspective on the	Pg.18 – "During the integration psychotherapy sessions, physicians collected patients' perspectives on the intervention. Participants generally described their experiences as

		intervention(s) they received (e.g. sharing quotes from a consented, anonymised interview, or questionnaire).	positive and meaningful. Many reported feeling a sense of fluctuation during the ketamine administration sessions, while others expressed a feeling of fusion with the surrounding space."
Informed Consent	**10**	- The authors must provide evidence of consent, where applicable, and if requested by the journal. - State the method of consent at the end of the article (e.g. verbal or written). - If not provided by the patients, explain why (e.g. death of patient and consent provided by next of kin). If the patients or family members were untraceable then document the tracing efforts undertaken.	Pg.5 - "all participants provided written Informed Consent" (the journal requires Informed Consent to be mentioned in the Methods section and not at the end of the article)
Additional Information	**11a**	- State any conflicts of interest.	Pg.24 – "The authors report there are no conflicts of interest to declare."
	11b	- State any sources of funding.	Pg.24 – "Funding – none declared".

	11c	Other Relevant Disclosures - Please state any author contributions, acknowledgments, and where required, institutional review board and ethical committee approval. - Disclose whether the case has been presented at a conference or regional meeting.	Pg.5 – “The study protocol was approved by the Ethics Committee of Casa de Saúde Santa Catarina Hospital in Porto, Portugal.”
Clinical Images and Videos	**12**	- Where relevant and available, include clinical images to help demonstrate the cases pre-, peri-, and post-intervention (e.g. radiological, histopathological, patient photographs, intraoperative images). - Where relevant and available, include a link (e.g. Google Drive, YouTube) to the narrated operative video to highlight specific techniques or operative findings.	Not applicable.

		- Ensure all media files are appropriately captioned and indicate points of interest to allow for easy interpretation.	
Referencing the Checklist	**13**	- Include reference to the PROCESS 2020 publication by stating: 'This case series has been reported in line with the PROCESS Guideline' at the end of the methods section (and include citation in the references section).	Pg.14 – “This case series has been reported in line with the PROCESS Guideline”

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For guidance on how to prepare, write and submit a manuscript to any journal, please follow this link: http://www.mpip-initiative.org/mpip-authorship-activities/authors-submission-toolkit

Page Charges: *JCP* has no page charges for publication.

Please Note: These instructions must be followed for manuscript submission to *JCP*. Manuscripts will be returned without review if the instructions are not followed.

Equality, Diversity and Inclusion

JCP aims to foster inclusive research that reflects the disciplinary, human, and geographic diversity of scientists, clinicians and other health professionals working in this area. Submissions are welcomed from authors of all ethnicities, races, colors, religions, sexes, sexual orientations, gender identities, national origins, disabilities, ages, or other individual status.

Editorial Content

JCP is a publication dedicated to clinical (human) pharmacology. **Manuscripts are invited that deal with the effects of drugs in humans. Animal research and *in vitro* research will not be considered.** These include, but are not limited to, the general categories of pharmacokinetics (PK) and drug disposition, drug metabolism, pharmacodynamics (PD), clinical trials and design issues, pharmacogenomics and pharmacogenetics, pharmacometrics and population PK/PD, pharmacoepidemiology, pharmacovigilance, PBPK, and human pharmacology. In addition, another area of emphasis for submissions is the validation and use of biomarkers in drug development. Manuscripts should be clearly written and well organized. Priority will be given to new developments in the field along with manuscripts dealing with PK/PD relationships of drug response in humans.

Article Types (limits should be strictly followed)

Original Articles

Up to 6500 words, 8 tables/figures total, and up to 150 references. **An unstructured abstract is required.**

Reviews

Both narrative and systematic reviews are considered for publication. All narrative reviews must critically evaluate the literature and should not cite other reviews in the reference list. Reviews that are just a restatement of the literature will be rejected. Additionally, all reviews must have tables and/or figures and not be solely text.

Up to 7000 words, 10 tables/figures total, and up to 200 references. **An unstructured abstract is required.**

Meta-Analyses

All meta-analyses to be published in the Journal should have clear objectives regarding drug effects and be based on thorough, systematic and recent review of the literature. Usually, a meta-analysis is done to determine the general and more specific effects on the basis of various small or large studies investigating the same research questions. The search strategy, selection process and statistical methods used should be described in detail in the manuscript. Beyond the type and design of selected studies, authors should provide details on exposure regarding the drug(s) to be examined, i.e., substance, dose, route of administration, and duration of treatment. Relevant patient characteristics, e.g., demographics, disease state and co-medication, should be described in sufficient detail. Meta-analysis of clinical trials should be accompanied by the PRISMA flow diagram and checklist (Liberati et al., PLoS Med. 2009 Jul 21;6(7):e1000100), those of observational studies of clinical trials should be accompanied by the MOOSE checklist (Stroup et al., JAMA. 2000; 283(15):2008-12). Extensive tables on the characteristics of included or excluded studies should be submitted as Online Supplementary Material.

Meta-analyses reports should follow the guidelines above for Full Original Research Articles.

Commentaries

These are invited or unsolicited to give a scientific opinion on a topic pertinent to clinical pharmacology or to comment on an article that will appear in the same

issue of the Journal. **Commentaries do not require an abstract.**

The suggested length is 1500 words with no more than 15 references.

Letters to the Editor

Letters for consideration should address articles previously published in *JCP* or issues felt to be of importance to *JCP* readers. Letters must be 500 words or less and **no abstract is required.**

Announcements

JCP will publish official notices of interest to the members of the American College of Clinical Pharmacology.

Supplements

Supplement issues are published yearly. Submissions must undergo peer review, and final approval rests with the Editor. More information can be obtained by contacting the editorial office.

Preprint Policy

The Journal of Clinical Pharmacology will consider for review articles previously available as preprints, on a case-by-case basis, where the author has retained copyright of their work. We ask that you disclose this fact upon submission. You may also post the submitted version of a manuscript to a preprint server at any time. If your manuscript is accepted, you must update any pre-publication versions with a link to the final published article.

JCP does not allow authors to cite preprint articles in the reference list of submissions unless the preprint has undergone peer review (for example Accepted Articles from other journals).

Refer and Transfer Program

Wiley believes that no valuable research should go unshared. This journal participates in Wiley's Refer & Transfer program. If your manuscript is not accepted, you may receive a recommendation to transfer your manuscript to

another suitable Wiley journal, either through a referral from the journal's editor or through our Transfer Desk Assistant.

General Manuscript Style and Submission Guidelines

Manuscripts not following these general manuscript style guidelines will be returned for correction before peer review.

Please follow the AMA Manual of Style: A Guide for Authors and Editors, 11th edition, 2020. This guide provides specifics for style, data analysis and presentation and terminology to be used. Additionally, these guidelines outline authorship criteria for manuscripts.

We require that manuscripts submitted to *JCP* be reviewed for grammar and spelling by a native speaker of English or preferably an English language editing service for our non-English speaking authors before submission. Please visit https://bmchealthservres.biomedcentral.com/submission-guidelines/language-editing-services for more information on the use of English Language Editing services.

Please use Western English.

Cover letter

For initial submission of a manuscript, a cover letter detailing originality of the manuscript and agreement of all authors and also identifying the Principal Investigator who undertook any human studies reported is required.

Plagiarism Screen

All manuscripts submitted are screened by Crossref Similarity Check powered by iThenticate service, which is a web-crawling software that can compare the current manuscript with multiple published sources.

Authorship

The ICMJE recommends that authorship be based on the following 4 criteria:

1. Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND

2. Drafting the work or revising it critically for important intellectual content; AND
3. Final approval of the version to be published; AND
4. Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

In addition to being accountable for the parts of the work he or she has done, an author should be able to identify which co-authors are responsible for specific other parts ofthe work.In addition, authorsshould have confidence in the integrity of the contributions of their co-authors.

All those designated as authors should meet all four criteria for authorship, and all who meet the four criteria should be identified as authors. Those who do not meet all four criteria should be listed in Acknowledgements at the end of the manuscript.

Authorship on a manuscript should follow the 2023 ICMJE and GPP3 guidelines as noted below.

Appendix Table 1. Authorship Criteria

ICMJE 2023 Criteria	**GPP3 Guidance**
Substantial contributions to the conception or design of the work; or the acquisition. analysis, or interpretation of data for the work; AND	"A substantial contribution is an important intellectual contribution, rather than technical assistance. without which the work, or an important part of the work, could not have been completed or the manuscript could not have been written and submitted for publication- (19). Simply collecting data (e.g., enrolling many patients) would not necessarily be considered a qualifying criterion for authorship. Some examples of what might represent a substantial intellectual contribution include actively guiding the scientific or medical content of the publication or presentation, statistical analysis and interpretation, crafting of the discussion, and developing the protocol.
Drafting the work or reviewing it critically for important intellectual content; AND	This criterion refers to revisions beyond minor corrections for grammar, language, formatting, or layout. The key is sustained intellectual contribution, the provision of substantial comments, and approval of the final version. Although preferred, it is not always feasible or

	necessary for authors to comment on every stage of manuscript development.
Final approval of the version to be published; AND	To give final approval, it is necessary to have carefully read the entire manuscript from start to finish.
Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved	Each author is accountable for the work and should have confidence in the integrity of the other authors' contributions. Each author should be able to identify who wrote each section.

GPP3 = Good Publication Practice 3 guideline; ICMJE = International Committee of Medical Journal Editors.

Corresponding Author

One author should be designated as the corresponding author to communicate with the editorial staff, receive and check galley proofs, and handle reprint requests. That author's primary affiliation, complete mailing address, and e-mail address should be included on the title page.

Artificial Intelligence Generated Content

Artificial Intelligence Generated Content (AIGC) tools—such as ChatGPT and others based on large language models (LLMs)—cannot be considered capable of initiating an original piece of research without direction by human authors. They also cannot be accountable for a published work or for research design, which is a generally held requirement of authorship (as discussed in the previous section), nor do they have legal standing or the ability to hold or assign copyright. Therefore—in accordance with COPE's position statement on AI tools—these tools cannot fulfill the role of, nor be listed as, an author of an article. If an author has used this kind of tool to develop any portion of a manuscript, its use must be described, transparently and in detail, in the Methods or Acknowledgements section. The authors are fully responsible for the accuracy of any information in the manuscript including the information provided by the tool and for correctly referencing any supporting work on which that information depends. The final decision about whether use of an AIGC tool is appropriate or permissible in the circumstances of a submitted manuscript or a published article lies with the journal's editor or other party responsible for the publication's editorial policy.

Manuscript formatting

- Manuscripts should be submitted in Word not PDF format.
- Please double space the body of the manuscript (not the abstract).
- Use a normal, plain font (12 pt Times Roman) for text. Use italics for emphasis.
- **Do not add line numbering** to your Word document. When ScholarOne generates a PDF review proof, it automatically adds line numbering to the file.
- Use tab stops or other commands for indents, not the space bar.
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- Please do not include a list of abbreviations. Keep abbreviations to a minimum.
- Do not number your sections. We do not use the international format for manuscripts.
- Do not embed tables/figures or use table/figure placeholders in the manuscript.

Title Page

Please include the following on the first page of your submitted manuscript:

- Title
- Full names, with terminal academic degrees listed, and affiliations of all authors
- Name, address, and email of corresponding author
- Indicate which authors, if any, are Fellows of the American College of Clinical Pharmacology (FCP)
- Word count for the body of the manuscript, the aggregate number of figures and tables, and the number of References

Abstract

Please provide an **unstructured** abstract of up to 250 words for all manuscripts except Commentaries and Letters to the Editor.

Keywords

Please provide 4 to 6 keywords, which can be used for indexing purposes.

Headings

Please do not enumerate or place letters before headings or subheadings. Headings should be as follows:

- Introduction
- Methods
- Results
- Discussion
- Conclusions

Introduction

This should be short with the majority of information in the Discussion section.

Methods

Methodology is the most important section of a manuscript as it determines if the results and conclusions of the study were validly derived. Methods should be concise and clear such that the study could be reproduced by another investigator. Please read carefully the requirements for Methods.

Human Subject Protection

In the first sentence of the Methods section, it must be explicitly stated that an investigational review board (IRB) or human subjects committee approved the study protocol, and the specific IRB and location of the IRB should be named first in the "Methods" section.

An informed consent statement must also be placed in the the Methods section right after the IRB information. The name and location of the actual study site or sites must be named. For studies with large numbers of sites, such as population pharmacokinetic studies, the Editor may at his discretion append the specific sites as Online Supporting Information because of space considerations. In those cases, a notation to that effect will be included in the "Methods" section of the paper.

Drug Nomenclature

All drugs and therapeutic agents must be referred to by their accepted generic or chemical name. The name should not be abbreviated. Code numbers should be used only when a generic name is not yet available. In that case, the chemical name and a figure giving the chemical structure of the drug are required. **A proprietary/trade name may be used one time in the "Abstract" and one time in the "Introduction" of a report to designate a particular preparation used in a study.** In Editorials or Commentaries, the Editor may elect to allow 1 parenthetical use of a trade name following the first mention of the generic name, if this is felt to be scientifically pertinent and not promotional.

Laboratory Results

Laboratory values may be expressed in SI units or U.S. Conventional Units with normal ranges for the laboratory in use supplied. Normal ranges for the laboratory that did the testing should be provided with the name of the laboratory test in every table/figure. For example:

Bilirubin	(4-23	umol/L)
Creatinine	(49-82	umol/L)
Creatinine	(0.5-1.3	mg/dL)

Erythrocyte Sedimentation Rate (<12 mm/h)

Pharmacokinetic Terminology

Please refer to the following link for pharmacokinetic terminology to use for *JCP*:

https://accp1.onlinelibrary.wiley.com/hub/journal/10.1002(issn)1552-4604/BJCP_PK_and_other_symbols.pdf

Other Abbreviations and Standard Terminology

Standard accepted abbreviations and terminology should be used in the manuscript. **Abbreviations that are developed to save word space are not acceptable (abbreviations developed for example such as: glucagon releasing muscle building factor or GRMBF) cannot be used unless they are standard accepted abbreviations in the medical literature**. Manuscripts with excessive abbreviations will be returned to the author for correction. In addition, changing standard terminology (i.e., drug phenotyping cocktails being referred to as drug phenotyping cassettes) is not acceptable and results in confusion to the reader.

Do not provide a list of abbreviations used in the manuscript. Any abbreviations must be defined the first time they are used only.

Requirements for Referencing Analytic Methods in Original Reports

Analytic methods that are not referenced to archived peer-reviewed publications must include specific core information, such as the detector and monitoring settings, internal standards, and assay performance parameters. Specific sample preparation details are not required, but a general synopsis is requested. A complete description of the analytic assay methods is essential, unless the assay procedure has been previously published. Required items are: internal standard(s), method of extraction, HPLC column and mobile phase, MS instrument settings, m/z monitored, within- and between-day variability, limits of sensitivity. It is not sufficient to state only that a validated method was used.

Requirements for Data Analysis

Statistical, pharmacokinetic, pharmacodynamic, pharmacometric , PBPK or other types of analysis must be performed using validated programs that are available to other investigators either free of charge or for a fee to acquire from the developer. **The specific program(s) used must be specified in the manuscript.**

Data Citation

Please review Wiley's Data Citation policy.

Results

All data should be expressed as ONE significant figure (following AMA guidelines) unless there are "special" circumstances or otherwise accepted convention.

Statistical results should be expressed as significant ($p \leq 0.05$) or not significant ($p > 0.05$).

Terminology such as "trends to significance" or the like should not be used if the *p*value does not reach the 0.05 level.

Equivalence tests are not significance tests and thus the term "significant or not significant" should not be used to describe the results of these tests.

Discussion and Conclusions

Each manuscript should have a discussion of the pertinent results with a review and interpretation of appropriate literature along with a brief conclusion.

Acknowledgements

Acknowledgements are optional. Please use this section to thank or note anyone who contributed to the manuscript but did not meet the criteria for authorship. Also use this section to acknowledge any medical writing assistance.

Author Contributions

Statements of author contribution are allowed but optional.

Conflicts of Interest

All authors must disclose any competing or conflicts of interest in a COI statement. In revision, authors are also asked to submit ICMJE COI forms. The information listed on those forms should match the COI statement which will be published at the end of the manuscript. If there are no conflicts of interest to disclose, the statement should read: The authors declare no conflicts of interest.

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We urge authors to provide as TXT files the code used for data analysis. While this is not an absolute requirement, some readers may find it helpful to have. This should be provided as supplemental material.

References

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References should appear at the end of the manuscript, after all end-matter statements but before tables/figures. JCP references follow the format of the American Medical Association Manual of Style (11th edition). They should be listed numerically, in the order they are cited in the text. They should contain all authors of the original report unless there are more than 6 authors, in which case the first 3 authors should be listed, followed by "et al." Italicize and abbreviate the names of journals according to the listing in PubMed. DOIs are optional.

Example:
Author(s). Title. *Abbreviated Journal Name*. Year;vol(issue #):inclusive pages.

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All figures and tables should be cited in the manuscript text, in sequential order. Tables and figures should not be embedded in the text. They should be numbered using Arabic numbers. All abbreviations used in each table/figure must be defined in each table/figure. Tables/figures from other publications should be referenced with the corresponding number of the reference in the reference list and include a credit line. Each figure and table must be able to "stand on its own," that is be interpreted without reading the entire manuscript.

Tables should be uploaded in Word format, either at the end of the reference list on the manuscript file itself or as a separate file or files. Data should be expressed to ONE significant figure.

Figures may be submitted in a variety of formats, but figure legends should always be submitted in Word format, either after the reference list on the manuscript file or as a separately uploaded file. There is no charge for color figures, as JCP is an online-only journal.

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Excess illustrations may be provided as online supplementary material (see the next section).

Supplementary Online Material

Excess illustrations or other materials, including long tables, may be provided to publish online only. Because supplementary material is not copyedited or typeset,

it should be submitted exactly as it is to be viewed, in PDF or Word document. List the manuscript. List article title and authors (or lead author) at the top of the page and include captions for any tables and figures. Supplementary tables and figures should be numbered beginning with an "S" (Supplemental Table S1) to distinguish them from regular tables/figures; references to supplemental materials within the main manuscript should also follow this numbering system. Please see our full guidelines for Supporting Information at https://authorservices.wiley.com/author-resources/Journal-Authors/Prepare/supporting-information.html

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